Thyroid Adverse Effects of Psychotropic Drugs: A Review

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Objectives: Because many patients with mental illness take more than one psychotropic drug, an understanding of the effects of every class of these drugs is very important to manage any thyroid abnormalities that can happen with these patients.

Methods: A systematic review of all the published literature was made via Medline. Keywords used for the search were “thyroid side effects” in association with one of the following: “antipsychotics,” “antidepressants,” “lithium,” “anticonvulsants,” “benzodiazepines,” “anticholinergics,” “antihistaminergics,” “cholinesterase inhibitors,” “stimulants,” “methadone,” and “naltrexone.”

Results: Phenothiazines, which are antipsychotics, mainly alter iodine capture, complex, and deactivate it, as well as decrease thyroid-stimulating hormone’s (TSH’s) response to thyroid-releasing hormone (TRH). Nonphenothiazines, typical antipsychotics, can induce the formation of thyroid autoantibodies and can elevate TSH levels. Atypical antipsychotics may decrease TRH-stimulated TSH. Trecyclic antidepressant drugs complex with iodine and thyroid peroxidase and deactivate them, induce deiodinase activity and interfere with the hypothalamic-pituitary-thyroid (HPT) axis by decreasing TSH response to TRH. The main effect with other antidepressant drugs is a decrease in circulating thyroid hormone levels. Lithium inhibits thyroid hormone release and increases TRH-stimulated TSH, inducing goiter, clinical and subclinical hypothyroidism, and hyperthyroidism. Carbamazepine mainly reversibly decreases serum thyroid hormone levels. Other psychotropic drugs such as valproic acid, benzodiazepines, opiates, anticholinergic and antihistaminergic drugs, and stimulants have minor interferences with thyroid functions.

Conclusion: Patients receiving lithium, phenothiazines, and tricyclic antidepressants TCA should be closely monitored for the development of thyroid function abnormalities. Only patients at risk for developing thyroid function abnormalities should be monitored when they receive typical or atypical antipsychotic drugs, nontricyclic antidepressant drugs, and carbamazepine. No specific recommendations are proposed as toward thyroid function monitoring for patients receiving any other psychopharmacologic drug.

Key Words: thyroid function, side effects, antipsychotic drugs, antidepressant drugs, mood stabilizers

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According to many studies, patients with mental illness, especially those with mood disorders, frequently present thyroid function abnormalities. In 2 important reviews considering the relationship between thyroid function and mental disorders, it has been considered that most patients with mental illness are euthyroid. However, most adults with thyroid dysfunction will develop mental symptoms. In addition, hyperthyroidism-related adrenergic hyperactivity is a major cause of psychiatric symptoms. Most patients with severe hypothyroidism will also demonstrate psychiatric symptoms. Affective disorders seem to be, by far, the most represented psychopathology related to thyroid abnormalities. Many psychotropic drugs also interfere with the thyroid physiology as a result of their action on many levels of the thyroid hormone synthesis. Because many patients with mental illness take more than one psychotropic drug, an understanding of the effects of every class of these drugs is very important to manage any thyroid abnormalities that can happen with these patients. The purpose of this article was to review published preclinical and clinical studies dealing with the adverse effects on the thyroid of all classes of psychotropic drugs without reviewing thyroid function abnormalities related to the psychiatric illness itself.

MATERIALS AND METHODS

A systematic review of all the published literature was made via Medline. All published articles in English or French between January 1956 and May 2010 were considered. Keywords used for the search were “thyroid side effects” in association with one of the following: “antipsychotics,” “antidepressants,” “lithium,” “anticonvulsants,” “benzodiazepines,” “anticholinergics,” “antihistaminergics,” “cholinesterase inhibitors,” “stimulants,” and “opiate substitution drugs.”

RESULTS

Our literature review findings are summarized in Table 1.

Effect of Antipsychotic Drugs on Thyroid Function

Effects of Phenothiazines on Thyroid Function

At the thyroid gland and circulation level, phenothiazines interfere with iodine capture by thyroid cells, increase protein-bound iodine, and exert immunogenic effect on thyroid tissue. Incubation of thyroid cells with chlorpromazine decreases iodine uptake. In humans, an iodine uptake increase and a decrease in renal clearance of iodide were observed after a 6-week treatment with 300 to 1200 mg/d of chlorpromazine administered in a double-blind study. Phenothiazines complex and deactivate thyroid hormone. Drug-iodine complexes have formation constants, Kc, that estimate the electron-donating potential of the drug. Phenothiazines with high Kc (alimemazine and chlorpromazine) may lead to iatrogenic hypothyroidism or hyperthyroidism. Phenothiazines without high Kc, such as perphenazine, can also exert a peripheral effect by increasing T4 blood levels and protein-bound iodine in 50 patients receiving the drug for periods ranging from 8 to 50 months.

Phenothiazine drugs may exert immunogenic effects. Chlorpromazine is able to induce systemic lupus erythematosus. Phenothiazines induce experimentally the production of antithyroglobulin antibodies. Phenothiazines can induce and perpetuate thyroid autoimmune disorders through induction of class II major histocompatibility complex antigen.
Phenothiazines have also an effect on the hypothalamo-pituitary-thyroid (HPT) axis. Thioridazine and chlorpromazine were shown to decrease thyroid-stimulating hormone (TSH) response to thyroid-releasing hormone (TRH) stimulation by inhibiting α-adrenergic receptors without altering basal TSH levels in a sample of 75 subjects.21

In conclusion, phenothiazines can induce a hypothyroid state through either their deiodination effect or their thyroid autoimmune-inducing activity. Infrequently, they may induce a hyperthyroid state if they induce a thyroiditis. Other central and peripheral actions do not seem to have major clinical implications. In all patients receiving phenothiazines, regular monitoring of thyroid function parameters is recommended owing to the direct interference of these drugs with thyroid functioning.

Effect of Typical Antipsychotic Drugs on Thyroid Function

Typical antipsychotic drugs may exert an effect on thyroid functioning through a central activity on tuberoinfundibular dopaminergic pathway. The antagonism of dopamine receptors in this pathway results in hyperprolactinemia. This pathway also plays an important role in the regulation of various anterior pituitary hormones. Changes of TSH levels after dopamine antagonism due to typical antipsychotic drug administration is rather small or demonstrable only in female or hypothyroid patients.22

In a cross-sectional study, increased prolactinemia was associated with an increased prevalence of thyroid autoantibodies (P = 0.039) in 74 schizophrenic outpatients.23 This effect is similar to autoimmune thyroid abnormalities observed in patients with prolactinomas.24

Accordingly, typical antipsychotic drugs, whether they were phenothiazines or not, can induce autoimmune thyroid abnormalities (anti-thyroid peroxidase [anti-TPO] and antithyroglobulin increment) via their dopamine antagonism and subsequent induced hyperprolactinemia. Precautionary monitoring of thyroid function parameters is recommended in case these drugs were accompanied with high blood prolactin level.

Effect of Atypical Antipsychotic Drugs on Thyroid Function

Thyroid effects of atypical antipsychotic drugs can be either central or peripheral. Aripiprazole, quetiapine, and clozapine are the most atypical antipsychotic drugs studied in this domain. Dopamine 2 (D2) receptor blockade can increase TRH-stimulated TSH levels. In a placebo-controlled study, 8 men were administered intravenous amisulpride and had their TSH levels significantly elevated compared to their TSH levels after placebo administration (P < 0.01).25 In another randomized comparative double-blind clinical trial, a sample of 32 patients with schizophrenia were given amisulpride or fluphenazine and showed a significant elevation in TRH-stimulated TSH secretion in male patients receiving amisulpride.25 The non-D2 antagonist atypical antipsychotic drug clozapine shows an inverse effect. In a comparative clinical study, 13 patients treated with 150 to 250 mg/d of clozapine had their TRH-stimulated TSH secretion significantly decreased after 1 week of treatment compared with 13 patients treated with 20 to 40 mg/d of haloperidol (P < 0.01).26

Patients with compromised thyroid function who receive treatment with atypical antipsychotic drugs may develop hypothyroidism probably through a peripheral effect that involves a...
competition, with thyroid hormones, in the glucuronidation process in the liver. Cyclic tertiary amines such as piperidine and piperazines are most frequently incriminated in this process. Many case reports describe cases of hypothyroidism in patients receiving drugs such as quetiapine and aripiprazole.\textsuperscript{27,28} In a prospective double-blind study, a group of 30 schizophrenic patients taking quetiapine (n = 10), risperidone (n = 11), or fluphenazine (n = 9) showed a significant decrease in T\textsubscript{4} levels after 6 weeks of treatment in the group receiving quetiapine, whereas other patients receiving risperidone and fluphenazine had no change in their thyroid hormones levels (P = 0.01).\textsuperscript{29}

In conclusion, atypical antipsychotic drugs can, according to their dopamine antagonism profile, moderately interfere with TSH response to TRH without provoking major disturbances to thyroid function. However, piperazine and piperidine compounds are incriminated in clinical hypothyroidism in predisposed patients receiving them. Precautions toward thyroid function should be taken only in patients predisposed to develop thyroid abnormalities and, as with typical antipsychotic drugs, in those that present high blood prolactin levels.

**Effect of Antidepressants on Thyroid Function**

**Effect of Tricyclic Antidepressants (TCA) on Thyroid Function**

Tricyclic antidepressants (TCA) may alter thyroid blood parameters via peripheral and central effects. Tricyclic antidepressants deactivate iodine by complexation. Molecules with a high Ke (desipramine, imipramine, or clomipramine) are incriminated in this process.\textsuperscript{12} Tricyclic antidepressants also deactivate TPO by binding covalently to its heme.\textsuperscript{14,30} In a double-blind study desipramine (up to 300 mg/d) effect on thyroid hormones was compared to fluoxetine in 39 patients with major depression and was found to induce a small and transient increase in total T\textsubscript{4} levels after 3 weeks of treatment with no changes occurring to TSH level.\textsuperscript{31}

Tricyclic antidepressants have also a central effect on HPT axis. In two clinical trials, patients with major depressive disorder (n = 13 and n = 28, respectively), treatment with TCA (eg, 2.5 mg/kg per day of desipramine) significantly decreased free T\textsubscript{4} (f T\textsubscript{4} P < 0.01) and TSH levels.\textsuperscript{32,33} Finally, many studies found no thyroid hormone alterations in patients taking TCA.\textsuperscript{34–37}

As for phenothiazines, TCA may induce a hypothyroid state via a deiodination process and deactivation of TPO. They may also moderately interfere with T\textsubscript{4} and TSH levels without causing significant clinical adverse effects to thyroid function. Regular monitoring of thyroid function parameters is recommended owing to this possible direct interference of TCA in thyroid functioning.

**Effect of Other Antidepressants on Thyroid Function**

With antidepressant treatment, the most common change in thyroid hormones is a decrease in T\textsubscript{4} and f T\textsubscript{4}.\textsuperscript{37,38} Many studies evaluated the effect of selective serotonin reuptake inhibitors (SSRI) and showed that their effect is mainly a decrease in T\textsubscript{3} and T\textsubscript{4} levels without any change in TSH level. In a prospective study where 17 patients were taking 200 mg/d of sertraline or 40 mg/d of fluoxetine over a 10-week period, T\textsubscript{3} and T\textsubscript{4} levels were significantly decreased (P = 0.05 and P = 0.02, respectively), whereas TSH levels did not change.\textsuperscript{40} In a previously mentioned study, no significant changes were found in TSH or total T\textsubscript{4} with fluoxetine treatment, but a significant reduction in T\textsubscript{3} levels was noted (after a six-week follow-up).\textsuperscript{31} In 25 depressed patients, treatment with 20 mg/d of paroxetine significantly decreased T\textsubscript{4} levels by 11.2%.\textsuperscript{41} In a prospective controlled interventional study, 67 patients (28 with depression and hypothyroidism, 29 with depression but without hypothyroidism, and 10 controls on levothyroxine) were administered either fluoxetine or sertraline, and the group of euthyroid depressed patients on fluoxetine showed a significant reduction in T\textsubscript{3} levels at 15 and 30 days of follow-up (P = 0.034 and P = 0.011, respectively) and a decrease in T\textsubscript{4} during the 90-day follow-up period (P = 0.029).\textsuperscript{42}

Other effects of non-SSRI antidepressant drugs on thyroid function were evaluated and showed that T\textsubscript{4} and TSH levels may change in all direction. In a prospective study evaluating the effect of mirtazapine on thyroid hormones in a small sample of 17 depressed outpatients, a significant increase in free T\textsubscript{3} (fT\textsubscript{3}) concentrations was found, whereas f T\textsubscript{4} concentrations decreased (P = 0.015 and P = 0.046, respectively) after a 6-month follow-up period. There were no significant changes in the TSH levels. The deiodination process was potentially incriminated.\textsuperscript{43}

In a prospective study, the differential effects of reboxetine (25 patients on 8 mg/d), sertraline (11 patients on 50 mg/d), and venlafaxine (26 on 150 mg/d) on thyroid hormones were evaluated in 62 depressed patients. After 10 weeks of follow-up, TSH levels were significantly increased (P = 0.033) and T\textsubscript{4} levels increased (P = 0.009) in the reboxetine group, and TSH levels were increased (P = 0.033) and T\textsubscript{4} levels decreased (P = 0.029) in the sertraline group.\textsuperscript{44} Finally, in a retrospective case-control study, Saint John’s wort was administered to 6 of 37 patients with elevated TSH levels in the 6 months preceding the survey and to 2 of 37 controls with normal TSH levels. The odds ratio for elevated TSH levels associated with taking Saint John’s wort was 2.12 (95% confidence interval, 0.36–12.36).\textsuperscript{45}

In conclusion, SSRI and non-SSRI antidepressant drugs may alter T\textsubscript{4} and TSH levels without having major clinical implications on thyroid function. Whereas SSRI seem to decrease T\textsubscript{4} levels, non-SSRI antidepressant drugs seem to change T\textsubscript{4} and TSH levels in both directions. Precautions should be taken only in patients at risk for thyroid function abnormalities.

**Effect of Lithium on Thyroid Function**

**Effect of Lithium on Thyroid Physiology and HPT Axis**

Many studies evaluated the effect of lithium on thyroid functioning and HPT axis. In a comparative case-control trial where 5 euthyroid patients and 6 thyrotoxic patients were administered lithium for 5 days, it was demonstrated that T\textsubscript{4} release was inhibited in both groups (P < 0.01).\textsuperscript{46} Lithium was also considered to be responsible for inhibiting type 1 5’-deiodinase activity in a prospective study where 18 schizophrenic inpatients were administered lithium carbonate during a follow-up period of 8 weeks.\textsuperscript{47} In one study, lithium therapy resulted in an increase in TRH-stimulated TSH in 49% of 73 patients who had been receiving lithium for at least 6 months.\textsuperscript{48} In a prospective study, 12 euthymic bipolar patients receiving lithium carbonate were followed for over 12 months (some of them were followed further); 10 (83%) of the 12 patients had their basal TSH levels increased, and 11 of the 12 patients had their TRH-stimulated TSH increased compared to baseline.\textsuperscript{49} In conclusion, lithium competes for iodide transport. It inhibits T\textsubscript{4} release to the blood circulation. It is responsible for inhibiting type 1 5’-deiodinase.
activity and inducing TSH secretion via the induction of a hypothyroid state.

**Lithium, Goiter, and Hypothyroidism**

Lithium inhibits thyroid hormone secretion and results in an increase in TSH and consequent thyroid enlargement. In a prospective study where 8 women and 8 men received 600 mg/d of lithium carbonate, thyroid volume increased in the women’s group after 28 days of lithium initiation (P < 0.005). In a case series reporting the occurrence of goiter in 330 bipolar patients, 12 patients were found to have goiter after a period of 5 months to 2 years. The incidence of goiter of 4 per 100 patients per year on continuous lithium therapy was calculated. A cross-sectional study using ultrasonic measurement of thyroid volume showed that goiter occurred in 40% of 100 bipolar patients treated for 1 to 5 years and in 50% of those treated for more than 10 years. In a cross-sectional controlled study including 96 patients with bipolar, major depressive, or schizoaffective disorders who had received lithium for at least 6 months, 55% of the subjects had increased thyroid volume compared to 20% of controls (P < 0.001). In conclusion, lithium is responsible of thyroid gland enlargement and goiter, especially in female patients shortly after the drug initiation.

Clinical and subclinical hypothyroidism may appear within weeks of starting lithium therapy. Studies evaluating this adverse effect of lithium therapy are mostly cross-sectional. In a cross-sectional case-control study where 68 bipolar patients receiving lithium therapy were included, women had thyroid abnormalities 5.9 times more frequently than men (P < 0.05), and clinical and subclinical hypothyroidism were present in 9% of the patients included. In a cross-sectional study including 207 patients treated with lithium for a period ranging from 1 to 30 years, prevalence of hypothyroidism was found to be 6%. In a retrospective study including 201 lithium-treated patients with mood disorders, 20 patients (0.099%) mainly females, developed hypothyroidism. In a cross-sectional case-control study, 132 patients with mood disorders were evaluated; T4 levels declined by 24% (P < 0.05) with lithium therapy, and clinical hypothyroidism was detected in 4 patients (0.03%). In a retrospective case-control review where 695 patients treated with lithium were included, the prevalence of clinical hypothyroidism was 10.4% with a prominent prevalence in women as compared to men (P < 0.05) and clinical and subclinical hypothyroidism were present in 9% of the patients included. In a cross-sectional and prospective study (n = 57) where 115 men and 159 women on lithium were evaluated, hypothyroidism rates calculated to range between 21.7 and 27.4 in 1000 survivor years. Data from a 15-year follow-up of 150 patients on long-term lithium therapy have shown that the annual rate of development of subclinical hypothyroidism was 1.5%. After 2 and 10 years of follow-up in the cohort of patients described previously, the incidence of subclinical hypothyroidism was higher in women and in patients with thyroid autoimmunity. A cross-sectional controlled study where 100 patients with affective disorders received lithium for at least 6 months did not support this finding. Accordingly, although the etiology of lithium-induced hypothyroidism is related to various pathophysiological mechanisms including the inhibition of thyroid hormone secretion (see “Effect of lithium on thyroid physiology and HPT axis” subsection) some data support that lithium accelerates the development of existing thyroiditis and can increase circulating anti-TPO antibody titer in patients who already had positive circulating antibodies at the beginning of the treatment.

In conclusion, clinical and subclinical hypothyroidisms are frequent adverse effects of lithium therapy occurring as shortly as few weeks after this drug initiation. Women seem to be more vulnerable to the drug’s adverse effect than men. Patients receiving lithium should be screened for thyroid function abnormalities before and regularly after this drug initiation. Thyroid function monitoring is also important for a short period after lithium withdrawal.

**Lithium and Hyperthyroidism**

Studies evaluating hyperthyroidism as a complication of lithium therapy are mainly retrospective. Hyperthyroidism occurs most probably after many years of lithium therapy. In a retrospective study, a case series of 14 patients with lithium thyrotoxicosis was described and the incidence rate was considered to be more than 3 times greater from lithium-unrelated incidence rates (P < 0.05). Etiologies of hyperthyroidism include toxic nodular goiter and silent thyroiditis. A retrospective epidemiological study showed that long-term lithium therapy is associated with an increased risk of thyrotoxicosis. Lithium-associated silent thyroiditis occurred with an incidence rate of approximately 1 to 3 cases per 1000 person-years, and lithium-associated thyrotoxicosis occurred with an incidence rate of approximately 2 to 7 cases per 1000 person-years, higher than the reported incidence rates of silent thyroiditis and of thyrotoxicosis in the general population. Lithium directly damages thyroid cells, with consequent release of thyroglobulin and thyroid hormones into the circulation. Lithium treatment could mask the underlying hyperthyroidism by reducing thyroid hormones so that when lithium therapy is stopped, hyperthyroidism will appear. Lithium incrimination in Graves’ disease therapy is not clear. In conclusion, patients receiving lithium therapy may develop hyperthyroidism many years after the initiation of this drug. The yearly incidence of this complication seems to be clearly lower than that of clinical and subclinical hypothyroidism. Specific monitoring for this complication is not necessary because it is the same as that for hypothyroidism in patients receiving lithium.

**Effect of Mood Stabilizer Anticonvulsants on Thyroid Function**

**Effect of Carbamazepine (CBZ) on Thyroid Function**

Decreases in T4 and fT4 concentrations, without TSH level changes during CBZ treatment, have been reported since 1978. In a cross-sectional controlled study evaluating thyroid function in 45 patients on chronic CBZ therapy, T4 and fT4 were decreased in 53.3% and 28.9% of patients, respectively. Serum T4 (P < 0.001), fT4 (P < 0.001), and T3 (P < 0.05) levels were lower than those of the control group. Carbamazepine interferes with thyroid function without exerting an effect on the HPT axis. Decreases in serum thyroid hormone levels can be detected as soon as 2 months after starting CBZ. This altered thyroid function is attributed to the induction of the hepatic cytochrome P450 enzyme system that increases the metabolism of thyroid hormones. In a prospective study, 20 epileptic patients on CBZ followed over a 5-year period, a decrease in fT4 was noted as early as 2 months after treatment initiation and normalized after switching to oxcarbazepine. Authors concluded that induction of cytochrome P450 liver enzymes resulted in the decrease in thyroxine levels. Although CBZ decreases thyroid hormone concentrations, it rarely causes hypothyroidism. In a prospective study, CBZ treatment was administered to 29 patients with or without thyroid dysfunction at baseline. After 7 weeks of follow-up, the patients without thyroid...
abnormalities showed decreased thyroxine levels \( (P < 0.001) \) with no TSH level changes, whereas the patients with thyroid dysfunction had thyroxine level reduction and TSH level elevation.\(^\text{72}\) However, data have demonstrated that the changes induced by this drug are reversible after the drug discontinuation. In a prospective, randomized, controlled double-blind study, a sample of 130 adult patients receiving CBZ showed, especially in the women group \( (P = 0.001) \), an increase in serum \( \Gamma T_4 \) when withdrawn from the drug.\(^\text{73}\) In conclusion, CBZ seems to be incriminated in thyroid hormones lowering without any effect on TSH.\(^\text{73}\) In vitro, hepatic enzyme induction mechanism. Clinical hypothyroidism may manifest only in patients predisposed to thyroid function abnormalities. Precautionary measures such as regular thyroid function monitoring should be taken only in these at risk patients.

### Effect of Valproic Acid (VPA) on Thyroid Function

Studies reporting altered thyroid function among valproic acid (VPA)-treated epileptic patients are controversial, showing elevated diminished, or even normal thyroid hormone levels.\(^\text{74,75}\) Most of the studies evaluating this adverse effect of VPA are cross-sectional studies. In a cross-sectional comparative controlled study, 21 epileptic men on VPA showed no abnormality in their thyroid function.\(^\text{74}\) In a cross-sectional comparative controlled study, 5 epileptic patients on VPA showed an increase in their \( T_3 \) and \( T_4 \) levels compared to controls \( (P = 0.05)\).\(^\text{75}\) In a prospective comparative study of adult patients on VPA \( (n = 8) \), a decrease in \( T_3 \) \( (P < 0.01) \), \( T_4 \) \( (P < 0.025) \), and \( \Gamma T_4 \) \( (P < 0.05) \) levels were noted after 3 months of follow-up.\(^\text{76}\) Subclinical hypothyroidism and increased TSH with normal \( \Gamma T_4 \) and \( T_4 \) were reported.\(^\text{77}\) In a controlled cross-sectional study described earlier, TSH levels were higher in the group of patients on VPA than in controls \( (P < 0.001)\).\(^\text{69}\) Other cross-sectional comparative studies \( (n = 11, n = 20, \text{and} n = 21, \text{respectively}) \) showed that thyroid hormones and TSH concentrations were normal and VPA did not affect thyroid function.\(^\text{4,78}\) In a prospective, randomized, controlled double-blind study, a group of adult female patients \( (n = 8) \) withdrawn from VPA had a decrease in their \( \Gamma T_3 \) levels compared to women in the group who had not been withdrawn from the drug \( (n = 7; P = 0.03)\).\(^\text{73}\) Coadministration of VPA with enzyme-inducing anticonvulsant such as CBZ was shown to decrease serum levels of \( T_3 \) and \( \Gamma T_3 \) and to increase serum levels of TSH \( (P < 0.001)\).\(^\text{69}\) In conclusion, although VPA may provoke some abnormalities in circulating thyroid hormones levels, these abnormalities do not seem to have major clinical implications. Precautionary measures in thyroid function monitoring should be restricted to patients who receive VPA with another enzyme-inducing anticonvulsant drug such as CBZ.

### Effect of Benzodiazepines on Thyroid Function

Since the report that diazepam may cause depression of iodine 131 \( (^{131}\text{I}) \) uptake, some studies tended to confirm this belief.\(^\text{78,79}\) Diazepam was shown to have no effect on TSH release or thyroid gland activity in a double-blind placebo controlled prospective study including 24 euthyroid adults followed for 12 weeks (and 11 followed for 6 weeks further).\(^\text{80}\) In another study, no effect on laboratory measurements was found in 3 patients with thyrotoxicosis.\(^\text{81}\) A competitive comparative study where 2 groups of 12 euthyroid patients and 6 patients with thyrotoxicosis received 15 mg/d of diazepam, an increase in the \( ^{131}\text{I} \) uptake 1 hour after the diazepam ingestion in the euthyroid patients’ group was noted \( (P < 0.05)\).\(^\text{82}\) In conclusion, benzodiazepines may interfere with \( ^{131}\text{I} \) uptake in both directions. This effect does not seem to interfere with thyroid function parameters. Accordingly, no monitoring precautions should be taken in patients receiving benzodiazepines.

### Effect of Opiates Substitution Drugs on Thyroid Function

Methadone is frequently included as a cause of euthyroid hyperthyroxinemia, although its initiation for heroin withdrawal was reported to normalize the high serum \( T_4 \) found in opiate addicts.\(^\text{83,84}\) Studies that were made in this domain are cross-sectional. In a cross-sectional study evaluating thyroid function in 285 male opiates addicts, 22% had their \( T_4 \) above the upper limits of normal, whereas 36 patients on methadone had normal thyroid function tests.\(^\text{85}\) In a controlled retrospective and cross-sectional study, 145 patients received methadone for a mean period of 5.8 weeks. In comparison to a euthyroid control group, the principal difference was an increase in the concentration of thyroxin-binding globulin in the serum, which augmented total \( T_3 \) and \( T_4 \) and diminished \( T_3 \) uptake \( (P < 0.001 \text{each})\).\(^\text{86}\) In a cross-sectional study, 24 euthyroid patients on naltrexone \((50 \text{mg/d})\) were evaluated. The duration of their naltrexone treatment was positively correlated with \( T_1 \) level and \( T_3 /T_4 \times 100 \) (a coefficient of peripheral conversion from \( T_4 \) to \( T_3 \) \( P < 0.001 \text{each})\).\(^\text{87}\) In conclusion, patients receiving opiate substitution drugs present higher \( T_3 \) and \( T_4 \) blood levels than controls. This effect is due to an increase in thyroxin-binding globulin in the serum and is devoid of any clinical repercussions and any effect on TSH level. Accordingly, no thyroid function monitoring is recommended in these patients.

### Effects of \( \beta \)-Blockers on Thyroid Function

Abnormalities seen in patients taking high doses of propranolol are known to be due to drug-induced blockade of \( T_4 \) deiodination resulting in euthyroid hyperthyroxinemia. Signs and symptoms of hyperthyroidism were lacking in a sample of 6 patients, on high doses of propranolol \((485 \pm 155 \text{mg/d})\) described in a cross-sectional study, although they manifested low \( T_3 \) and high \( T_4 \) levels.\(^\text{88}\) In one cross-sectional study, the prevalence of hyperthyroxinemia in patients with hypertension treated with high doses of propranolol \((320 \text{mg/d or more})\) was determined. Four of 14 patients had elevated serum \( T_4 \) levels. As a group, the patients on propranolol therapy had higher \( T_4 \), \( \Gamma T_4 \), and \( T_3 \) levels than had healthy controls.\(^\text{89}\) In prospective controlled studies considering small samples of alcoholic patients with liver cirrhosis \((n = 10; n = 20)\), no major thyroid function abnormalities were noticed after 2 weeks of propranolol administration, although in healthy controls, \( T_3 \) levels were lower \( (P < 0.001)\).\(^\text{90,91}\) In conclusion, patients receiving non-selective \( \beta \)-blockers such as propranolol may present a state of high \( T_4 \) and/or low \( T_3 \) levels, but these abnormalities do not seem to have any clinical repercussions as well as any effect on TSH level even at high doses of \( \beta \)-blockers. No monitoring is recommended for these patients.

### Effects of Anticholinergic and Antihistaminergic Drugs on Thyroid Function

In one retrospective study, 13 psychiatric patients taking orphenadrine or had recently stopped taking it showed an elevation of their \( T_3 \) levels. In the same study, thyroid function tests were compared in 15 pairs of matched psychiatric patients treated with orphenadrine or other anticholinergic drugs. Values of \( T_3 \) and free thyroxine index (FTI) were significantly higher among patients treated with orphenadrine. Also in this study, orphenadrine was instituted in four patients and withdrawn in six patients. \( T_3 \) levels and free thyroxine indices increased gradually over orphenadrine treatment had been initiated and
decreased gradually when it was withdrawn. No other adverse effects to thyroid function are described with anticholinergic and antihistaminergic drugs. Although orphenadrine seems to have an effect on thyroid hormones (increase in T3 levels), data emanating from one study are not sufficient to draw conclusions toward clinical impact and monitoring recommendations for patients receiving this drug.

Effects of Stimulants on Thyroid Function

Few studies have shown that stimulants such as methylphenidate and atomoxetine exert an effect on thyroid function. When methylphenidate was administered acutely to rats in a controlled study, serum T3 and T4 levels diminished significantly and TSH increased (P < 0.001). These changes were reversed after the drug was discontinued. In an open-label trial evaluating the effects and adverse effects of atomoxetine in 20 children with attention-deficit/hyperactivity disorder, raised serum levels of thyroid hormones were noted in one child, which normalized after the drug was stopped. Because further studies are needed in this domain, no specific recommendations for thyroid function monitoring are proposed for patients receiving stimulant drugs.

DISCUSSION

We have presented a unique review of all the studies that evaluated the thyroid adverse effects of all the psychopharmacologic agents. According to this review, major influence of psychopharmacologic drugs is correlated to the administration of lithium, phenothiazines, and TCA. Other psychotropic drugs such as CBZ, non-TCA antidepressant, and typical and atypical antipsychotic drugs can alter thyroid-function blood parameters without causing major dysthyroidism except in patients predisposed to thyroid abnormalities. Minor, clinically insignificant thyroid-function blood parameters can be found with treatments such as VPA, benzodiazepines, β-blockers, and opiate substitution drugs. Further studies are needed to better understand the effect of some antipsychotic drugs such as anticholinergic and antihistaminergic agents and stimulants on thyroid gland function.

Patients receiving lithium should be screened for thyroid function abnormalities before and regularly after this drug initiation. This monitoring should be continued as long as the drug is received and for a short period after its withdrawal. In addition, regular thyroid function parameter monitoring is recommended owing to the direct interference of phenothiazines and TCA with thyroid functioning.

Precautionous monitoring measures of thyroid function are recommended only in case typical or atypical antipsychotic drugs were accompanied with high blood prolactin level or when the concerned patient is at risk for development of thyroid function abnormalities. In addition, these precautions should be taken in patients receiving non-TCA antidepressant drugs and CBZ only when they are at risk for developing thyroid function abnormalities. Precautionous monitoring of thyroid function monitoring should be restricted to patients that receive VPA with another enzyme-inducing anticonvulsant drug such as CBZ. No specific recommendations are proposed as toward thyroid function monitoring for patients receiving benzodiazepines, β-blockers, opiates substitution drugs, anticholinergic, antihistaminergic, and stimulant drugs.

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