Quetiapine-Induced Thyroid Dysfunction: A Systematic Review

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Abstract
Thyroid abnormalities are documented consequences of quetiapine treatment. This may have clinical implications as changes in thyroid hormones may deteriorate a person’s affective state. Yet less is known about the clinical factors and underlying mechanisms associated with thyroid hormones on quetiapine therapy. We therefore systematically reviewed the published literature of evidence of quetiapine-induced thyroid abnormalities. We searched MEDLINE, PsycINFO, Google Scholar, and EMBASE for articles in which individuals developed biochemically confirmed thyroid abnormalities (with or without clinical symptoms) while on quetiapine treatment. We included case reports, case series, observational, and experimental studies. We included 32 studies, 20 of which were observational and experimental studies. There were 10 case reports and 1 case series. All the research designs suggested an association between quetiapine and hypothyroidism. However, these findings were limited by the quality of the included studies and the general lack of either a clear temporal relationship or dose response. Quetiapine has been associated with thyroid abnormalities, mainly with hypothyroidism. Drug imputability in these abnormalities is not always clear, and the underlying pathophysiology may include immunological and nonimmunological mechanisms. Large prospective studies are required to clarify this association and to further inform the management of patients treated with quetiapine where hypothyroidism occurs.

Keywords
adverse effects, antipsychotic, hypothyroid, psychopharmacology, quetiapine, seroquel, systematic review, thyroid, thyroid gland

The systematic review protocol was registered with the Open Science Framework (OSF) on January 2, 2021 (osf.io/uqgwz).

The hypothalamic-pituitary-thyroid axis (Figure 1) has long been an area of interest in mental health research, as altered thyroid states can manifest with psychiatric symptoms such as depression, anxiety, mood swings, and psychosis. The symptoms of hypothyroidism often resemble those of depression, whereas those of hyperthyroidism include anxiety, dysphoria, emotional lability, intellectual dysfunction, mania, or depression. In clinical practice, drug-induced thyroid dysfunctions are not uncommon, targeting at various pathways of synthesis, secretion, transport, metabolism, and absorption of thyroid hormones. In this context, certain antipsychotics have been associated with lower concentrations of serum-free thyroxine (FT4). In particular, quetiapine, a widely used second-generation antipsychotic with a broad receptor profile, has been associated with lower levels of FT4, variable changes in thyroid-stimulating hormone (TSH), total thyroxine (TT4), and total triiodothyronine (TT3). Several factors might contribute in generating thyroid abnormalities in patients treated with quetiapine. These factors may include the nature of the mental illness, sex, age group, duration of treatment, positive antithyroperoxidase antibodies (anti-TPOs) and whether quetiapine was used as monotherapy or in combination with other drugs. It is also important to highlight that the drug manufacturer reported that quetiapine was associated with a dose-related decrease in TT4 and FT4. However, the underlying mechanism was not mentioned.

In this systematic review, we investigated (1) the incidence or risk of thyroid abnormalities in patients on quetiapine; (2) the clinical factors associated with thyroid abnormalities on quetiapine, including the underlying psychiatric diagnosis, sex, age group, duration of treatment, and whether quetiapine was used as monotherapy or combination therapy; and (3) the underlying mechanisms of quetiapine-induced thyroid dysfunction.

The clinical implications of the present review about thyroid abnormalities in patients on quetiapine can be of importance to mental health professionals. Indeed,

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Figure 1. Regulation of the hypothalamic-pituitary-thyroid axis. The paraventricular nucleus (PVN) in the hypothalamus releases TRH, which acts on pituitary thyrotropes to stimulate TSH synthesis. TSH acts on thyrocytes to stimulate all steps of thyroid hormone synthesis. The thyroid hormones T4 and T3 act on PVN neurons and on the thyrocytes to inhibit TRH and TSH synthesis and release and this feedback regulation is the main regulatory mechanism of thyroid function. The pituitary thyrotropes are also regulated by local factors in through autocrine and paracrine pathways. Green arrows represent stimulation, and red arrows represent inhibition. T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

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Methods

Our protocol was registered on OSF (osf.io/uqgwz) and is reported following the items outlined in Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data guidelines.\(^1\)

Information Sources and Search Strategy

We conducted a search on the MEDLINE, PsycINFO, Google Scholar, and EMBASE databases for studies indexed from inception to December 31, 2020. We used Google Scholar as a gray literature database for this project. The search query used for each of the databases was “Quetiapine AND (thyroid OR FT4 OR TSH or FT3 OR TT4 or TT3 or TRH).”

We used filters to restrict the search to articles in English, French, Spanish, German, Italian, Portuguese, or Arabic.

Inclusion and Exclusion Criteria

We included observational or experimental studies, case reports, case series, and conference or meeting abstracts about thyroid abnormalities associated with quetiapine, in any age group, and for any indication of quetiapine.

We excluded narrative and systematic reviews, clinical guidelines, and protocols, as well as articles in a language other than English, French, Spanish, German, Italian, Portuguese, or Arabic.

Data Management

All identified articles were imported into Rayyan software, where duplicates were removed by a reviewer (M.A.S.K.), with a double-check of this step conducted by another reviewer (S.O.).\(^1\) Two reviewers (M.A.S.K. and S.O.) independently conducted a multilevel screening on Rayyan software. To examine articles for inclusion/exclusion criteria, we first screened titles and abstracts of all articles. We then screened the included full text to select the relevant articles that were included in our systematic review. In the Title/Abstract screening step, we agreed that we would be inclusive: If one of the reviewers thought that the report needed to go through a full-text screening, we would include the report in this following step.

For the full-text screening step, reasons for exclusion in each screening step were recorded. One reviewer (M.A.S.K.) extracted data on Excel (Microsoft Corp., Redmond, Washington) for articles published in English. Another reviewer (S.O.) extracted data on Excel for articles published in French, Spanish, German, Italian, and Portuguese. A different reviewer (A.K.A.A.) extracted data on Excel for articles published in Arabic, and S.O. checked all of the extracted data.

We extracted articles’ characteristics such as authors, digital object identifier, language, demographic data, underlying mental illness, medical comorbidities, duration of treatment, mono- or combination therapy, incidence/prevalence of thyroid function test (TFT) abnormalities, type of alteration of the TFTs (increase or
decrease in TSH, FT4, FT3, TT4, TT3, or thyrotropin-releasing hormone), and the underlying mechanisms. Any disagreement during the extraction process was resolved by discussion and consensus between the reviewers.

Assessment of Methodological Quality of Included Articles
We assessed the quality of the articles by 2 independent reviewers. We used the Newcastle-Ottawa Scale to assess the quality of nonrandomized studies to be included in our systematic review.12 For case reports and case series, we used the framework for appraisal, synthesis, and application of evidence suggested by Murad et al13 based on the domains of selection, ascertainment, causality, and reporting.

Data Synthesis
Data were analyzed to evaluate (1) the incidence/prevalence of thyroid abnormalities in patients on quetiapine; (2) the degree of thyroid derangements based on the underlying mental illness, sex, age group, duration of treatment, and whether quetiapine was used as mono- or combination therapy; and (3) the underlying mechanisms of quetiapine-induced thyroid dysfunction. Tables were used to tabulate results of individual studies.

Results
A literature search yielded a total of 503 results (393 in Embase, 45 in PubMed, 35 in PsycINFO, and 30 in Google Scholar), with 6 additional studies found via screening of references or other sources (Figure 2). Following duplicate removal, title and abstract screening, then full-text screening, we included 32 studies, 20 of which were observational or experimental studies. There were 11 case reports and 1 case series.

Clinical and Sociodemographic Characteristics
The 11 case reports gave details on 15 patients (Table 1).14–24 Quetiapine was used for a range of psychiatric diagnoses including bipolar disorder (BD; n = 5), schizoaffective disorder bipolar subtype (n = 4), and schizophrenia (n = 2). The majority of patients were women (n = 12) and were between 18 and 65 years of age (n = 10). Ten patients were on combination therapy, mostly with selective serotonin reuptake inhibitors. Duration of treatment before diagnosing the thyroid abnormality varied between 3 weeks and 1.5 years. The dose of quetiapine ranged between 50 mg and 1500 mg.

One case series reported 23 adolescents (16 boys and 7 girls) with severe early-onset psychosis treated with quetiapine.25 Patients were stratified according to whether they were changed to quetiapine from another antipsychotic medication (change-over group, n = 12)
| No. | Author, Year | Age, y/Sex | Diagnosis | Quetiapine Dose/Duration | Mono- or Combination Therapy | Symptoms | Autoantibodies | TSH | T3 | T4 | Treatment |
|-----|--------------|------------|-----------|--------------------------|-----------------------------|----------|----------------|-----|----|----|-----------|
| 1   | Feret et al, 2000 | 46/F       | Schizoaffective disorder, bipolar type | 425 mg/1 y | CT (sertraline, VPA) | NR | NR | High = 8.45 μIU/L | NR | NR | LT4 50 μg/day |
| 2   | Dobbs et al, 2004 | 18/M       | Schizoaffective disorder, conduct disorder, moderate learning disability, features of borderline personality disorder | 1500 mg/1.5 years | CT (methylphenidate, fluoxetine, gabapentin, trazodone, benztropine) | NR | NR | 1.54 mIU/L | NR | Low = 3.5 μg/dL | QTP continued |
| 3   | Ramaswamy et al, 2005 | 43/F       | Schizoaffective disorder, bipolar type | 400 mg/5 months | MT | 20-kg weight gain, leg edema, hoarseness of voice, chronic constipation | NR | High = 9.01 mIU/L | NR | NR | QTP discontinued. LT4 50 μg/day |
| 4   | Liappas et al, 2006 | 49/F       | Dysthymia with 2 major depressive episodes | 800 mg/6 mo | CT (venlafaxine, paroxetine) | Modest weight gain, decline of appetite, hoarseness of voice, expressionless face, slowing of intellectual and motor activity, and constipation | High anti-TPO = 126.36 IU/mL | High = 6.78 μIU/mL | 0.77 ng/mL | 4.17 μg/dL | TFT normalized within 2 mo after QTP tapered off |
| 5   | Tor et al, 2007 | 72/F       | Bipolar disorder with psychotic features | 150 mg/6 mo | MT | Dry skin, hair loss | High anti-thyroglobulin = 2507 IU/mL | High = 79.4 mIU/L | Low FT3 = 1.9 pmol/L | Low FT4 = 2.7 pmol/L | Thyroxine 50 μg/d |
| 6   | Kontaxakis et al, 2009 | (a) 51/F | Schizophrenia | 300 mg/TFT at 3 weeks | MT | None | Normal range | High = 5.98 μIU/mL | 0.86 ng/mL | Low TT4 = 5.05 μg/dL | TFT normalized after 45 d on QTP |
|     |              | (b) 46/M | Bipolar disorder | 350 mg/3 wk | MT | None | Normal range | High = 5.58 μIU/mL | 1.13 ng/mL | Low TT4 = 3.93 μg/dL | TFT normalized after 45 d on QTP |

(Continued)
| No. | Author, Year | Age, y/Sex | Diagnosis | Quetiapine Dose/Duration | Mono- or Combination Therapy | Symptoms | Autoantibodies | TSH | T3 | T4 | Treatment |
|-----|-------------|------------|-----------|--------------------------|-----------------------------|----------|---------------|-----|-----|-----|-----------|
| 7   | Poutanen et al, 2010 | (a) 14/F Asperger syndrome | 600 mg long-acting/6 wk | MT | None | NR | High = 4.7 mU/L | NR | Low FT4 = 11.1 pmol/L | QTP discontinued; TFT normalized after 45 d |
|     |             | (b) 18/F Schizophrenia | 600 mg long-acting/unknown | CT (citalopram, lorazepam, levomepromazine) | Tiredness | High antithyroid antibody titres = 83 kU/L ≤ 6 kU/L | 2.8 mU/L | Low FT3 = 2.8 pmol/L | Low FT4 = 10 pmol/L | QTP discontinued; LT4 100 μg/d; TFT normalized in 3 mo |
|     |             | (c) 24/F Severe depressive episode with anxiety | 600 mg long-acting/13 wk | CT (citalopram, mirtazapine, lorazepam) | Depression | High = 5.4 mU/L | 4.5 pmol/L | Low FT4 = 7.9 pmol/L | QTP continued; LT4 150-200 μg/d; TFT normalized |
| 8   | Park et al, 2011 | (a) 21/F Both had bipolar disorder, admitted for manic symptoms | 500 mg/short-term | VPA and QTP – short-term | NR | NR | 1.78 μU/mL | Low = 0.68 ng/mL | Low = 4.0 ng/d | NR |
|     |             | (b) 29/F | 800 mg/long-term | VPA and QTP – long-term | NR | NR | High = 6.06 μU/mL | Low = 0.66 ng/d | Low = 4.8 ng/d | NR |
| 9   | Dreijerink et al, 2013 | 36/M Depression, psychosis, suicidal behavior, schizoaffective personality disorder | 600 mg/1.5 y | CT (venlafaxine, promethazine, lorazepam, temazepam) | Fatigue and weakness (especially while exercising), feeling cold, and a weight gain of ~50 kg during a period of 1.5 y | NR | NR | 2.4 mU/L | NR | Low = 0.68 ng/d | QTP discontinued; LT4 (dose NR); TFT normalized |
| 10  | Shoib et al, 2013 | 27/F Bipolar I disorder | 50 mg/3 months | CT (clonazepam) | Easy fatigability, generalized weakness, and cold intolerance | Antithyroid peroxidase normal | High = 8.8 mU/L | 3.2 pg/mL | FT4 = 1.4 ng/d | QTP discontinued; TFT normalized after 3 mo |
| 11  | Zenno et al, 2020 | 12/F Mood instability | 225 mg/1 y | CT (fluoxetine) | Fatigue | NR | 1.18 mU/L | Low FT3 = 3.1 pg/mL | Low FT4 = 0.8 ng/d | QTP discontinued; LT4 25 μg/d; TFT normalized after 8 wk |

CT, combination therapy; FT3, free triiodothyronine; FT4, free thyroxine; LT4, levothyroxine; MT, monotherapy; NR, not reported; QTP, quetiapine; T3, triiodothyronine; TFT, thyroid function test; TT4, total thyroxine; VPA, valproic acid.
or directly treated with quetiapine (acute high-dosage group, n = 11). Daily dosage ranged between 300 mg and 1200 mg.

There were twenty observational or experimental studies (Table 2) that included a total of 6880 patients who were treated with quetiapine.2,4,9,26–42 The number of participants on quetiapine was not reported in one study.41 Of these patients, the majority were women in the age group 18 to 65 years of age. Four studies investigated quetiapine in 134 children and adolescents.31,32,37,39 One study assessed the long-term tolerability, safety, and clinical benefit of quetiapine in 184 elderly patients with psychosis.30 Quetiapine was used mainly for schizophrenia and BD. Three studies specifically looked at treatment-resistant schizophrenia33 and bipolar depression.4,39 Quetiapine was used in combination with divalproex in 15 adolescents with BD32 and in combination with lithium or divalproex in 310 adult patients with BD.36 Two studies examined the dose-response relationship of quetiapine in patients with schizophrenia.27,29

Changes in Thyroid Function Tests
All 15 patients from case reports had hypothyroidism: 10 primary14,15,17–21,24 and 5 secondary,16,19,20,22,23 and of the 10 cases with primary hypothyroidism, 4 were subclinical.14,15,21,24 It is of note that mild or subclinical hypothyroidism, which is commonly regarded as a sign of early thyroid failure, is defined by TSH concentrations above the reference range and free thyroxine concentrations within the normal range.5 Eight were asymptomatic,14,16,18–20 while 7 were symptomatic.15,17,19,21–24 Weight gain and fatigue were common symptoms reported. Autoantibodies, namely anti-TPO, antithyroglobulin, and antithyroid antibody, were positive in 3 cases, respectively,18,19,23 and not reported in 8 cases.14,16,19,20,22–24 High anti-TPO was reported.

As for the case series, in the change-over and acute high-dosage groups, FT4 values were slightly below the norm in 67% and 33% of the cases, respectively. No significant changes in TSH or FT3 were observed.25

Thirteen observational or experimental studies showed a decrease in thyroxine levels.2,4,27–31,32,35,37,41,42 Among these, TSH level was increased, compared to baseline, in 6 studies.4,31,34,35,39,42 Three studies that only measured TSH showed no difference in TSH levels.26,32,38 Hypothyroidism was reported in 6.5% of patients on combination therapy (lithium or divalproex) and in 2.4% of patients on monotherapy, respectively.36,40 In another large study of 3798 patients on quetiapine for BD (of 24 574 patients treated for BD), the 4-year risk of hypothyroidism was estimated at 8.26%.9 Two studies reported a dose-dependent decrease in thyroxine levels.27,29 In terms of side effects, 12% in the quetiapine group reported sedation, somnolence, and constipation.35 Additionally, a lower level of FT4 was associated with self-reported weight gain.2 In pediatric patients on 150 to 300 mg of quetiapine extended release, TSH increased above 5 mIU/L in 4.7% of participants.39

Pathophysiology
Three female patients had positive autoantibodies, namely anti-TPO, antithyroglobulin, and antithyroid antibody, respectively, suggesting an autoimmune mechanism.15,17,19 In the case of a 49-year-old woman with mood disorder who developed symptomatic subclinical hypothyroidism, anti-TPO rose to 126.36 IU/mL 1 week after quetiapine discontinuation, and then decreased to 74/40 IU/mL 2 months after discontinuation.15 As for the elderly patient with BD with psychotic features who developed primary hypothyroidism, the endocrinology team suggested that quetiapine could have caused autoimmune thyroiditis in light of the hypothyroid state, elevated antithyroglobulin antibodies at 2507 IU/mL and antithyroid peroxidase antibodies at 50 IU/mL.17 Finally, antithyroid antibody titers were 83 kU/L (reference range, 0 to <6 kU/L) after discontinuing quetiapine because of symptomatic secondary hypothyroidism in an 18-year-old woman with schizophrenia.19 Another possible mechanism could be dysregulation of leptin and adiponectin.37

Assessment of Quality
The results of the quality assessment of the included studies are presented in Tables 3 and 4. Table 3 includes the leading explanatory questions used in all 4 areas. We made an overall judgment of the quality of the case reports and series included on the basis of the questions most critical. In the domain “selection,” the overall quality was assessed to be medium. For “ascertainment,” exposure and outcome should be sufficiently ascertained, which was deemed high by authors. As for the “causality,” the case reports could not rule out alternative causes that might explain the observations and no challenge/rechallenge was possible, which rendered a judgment of low quality. Finally, the cases described were of wide-ranging but mostly sufficient detail, rendering a medium quality in the domain “reporting.” In accordance with the Newcastle-Ottawa Scale quality assessment scale, half of the included observational and experimental studies were of high evidence quality. Of note, the assessment of outcome was generally of high quality in most case reports, series, and observational and experimental studies.

Management of Quetiapine-Induced Thyroid Abnormalities
Care guidance and approach can be summarized in 4 different ways: (1) continue quetiapine and monitor,16,18
Table 2. Characteristics of Included Observational and Experimental Studies

| No. | Author(s), Year | Study Design and Recruitment | Psychiatric Diagnosis | Outcome Measures | No. of Participants | Sex/Age, y | Duration of Quetiapine Therapy | Findings |
|-----|-----------------|------------------------------|-----------------------|------------------|--------------------|------------|------------------------------|----------|
| 1   | Wetzela et al, 1995 | Open clinical trial | Schizophrenia or schizophreniform disorder with predominantly positive symptomatology | TSH levels at days 0, 14, and 28 | 12 | 58.3% M; Age range, 19-61 | 12-28 days; 400-600 mg | No alteration is TSH levels |
| 2   | Arvanitis et al, 1997 | Double-blind, multicenter study to evaluate a dose-response relationship of quetiapine | Acute exacerbation of chronic schizophrenia | TFTs at baseline and 3, 4, 5, and 6 weeks | 361 | 76% M; mean age, 37 | 6 weeks; 5 fixed doses: 75, 150, 300, 600, or 750 mg | Dose-dependent decrease in TT4 and FT4; smaller decreases in TT3 and reverse T3 were seen at higher doses; TSH changes not seen; decreases in total T4 and free T4 were generally within 20% of the lower limit of normal, and clinical hypothyroidism did not occur |
| 3   | Peuskens et al, 1997 | Double-blind, randomized, multicenter, parallel-group study, QTP vs chlorpromazine | Hospitalized patients with acute exacerbation of subchronic or chronic schizophrenia, or schizophreniform disorder | TFTs at baseline and weekly | 101 | 63% M; mean age, 32 | 6 weeks; mean daily dose of 407 mg | Modest decrease in TT4 in both arms; small decrease in TT3 (QTP) vs modest increase in CPZ; no significant increase in TSH among 2 groups; clinically significant values were recorded for 10% patients on QTP and 5% of patients on CPZ; patients remained asymptomatic |
| 4   | Small et al, 1997 | A high- (≤ 750 mg/d) and low-dose (≤ 250 mg) double-blind comparison with placebo | Hospitalized with chronic or subchronic schizophrenia | TFTs weekly | 94 patients received low-dose quetiapine and 96 received high-dose | Low-dose group: 69% M Mean age, 36 High-dose group: 78% M Mean age, 37 | 6 weeks | Mean dose in low-dose group 209 mg Mean dose in high-dose group 360 mg | Decrease in TT3 and TT4 was significantly greater in high-dose group than low-dose group; decrease in TT4 in low-dose group greater than in placebo, suggesting a dose-response relationship; no statistically significant differences were found among treatment groups for change from baseline for TSH |

(Continued)
| No. | Author(s), Year | Study Design and Recruitment | Psychiatric Diagnosis | Outcome Measures | No. of Participants | Sex/Age, y | Duration of Quetiapine Therapy | Findings |
|-----|----------------|-----------------------------|-----------------------|------------------|---------------------|-----------|-------------------------------|----------|
| 5   | Tariot et al, 2000 | Open-label, multicenter, uncontrolled trial | Elderly patients with psychosis | TFT at week 36 | 184 | 53.3% F; mean age, 76.1 | 52 weeks; median daily dose, 137.5 mg | A small decrease in FT4 (within normal range) occurred without an increase in TSH |
| 6   | Shaw et al, 2001 | Open-label trial | Adolescents with psychotic disorders | TFT at baseline and at week 8 | 15 | 53% M; mean age, 15.1 | 8 weeks; 467 mg/d | FT4 levels decreased. TSH levels increased, nonsignificant findings |
| 7   | Delbello et al, 2002 | Randomized, double-blind, placebo-controlled study; QTP in combination with DVP | Adolescents with BD | TSH weekly | 15 | 53% M; mean age, 14.1 | 6 weeks; 432 mg/d | No alteration in TSH levels |
| 8   | Greenspan et al, 2005 | Randomized, double-blind, study with a total of 382 patients assigned to treatment with risperidone, QTP, or placebo in a 2:2:1 fashion | Schizophrenia | TFT at baseline and at week 6 | 79 | NR | NR | Statistically significant decrease in TT4 and TT3; TSH significantly increased |
| 9   | Kelly et al, 2005 | Randomized double-blind trial with 38 adults treated with QTP, risperidone, or fluphenazine | Treatment-resistant schizophrenia | TFT at baseline and week 6 | 10 | 80% M; mean age, 42.6 | 6 weeks; 400 mg/d | Mean TT4 levels decreased significantly; decrease in TSH level was not significant; no signs and symptoms of hypothyroidism |
| 10  | Potkin et al, 2006 | International, randomized, double-blind study included a 2-week monotherapy phase followed by a 4-week additive therapy phase; 382 patients were randomly assigned to risperidone, QTP, or placebo in a 2:2:1 fashion | Recently exacerbated patients with schizophrenia or schizoaffective disorder | TFT at baseline, 2 and 6 weeks | 156 | 64% M; mean age, 34.2 | 6 weeks; mean doses at days 14 and 42 were 523 mg and 556 mg, respectively | Statistically significant decrease in mean TT3 and TT4 levels observed in QTP group compared with risperidone and placebo groups; at the additive therapy phase endpoint a significant increase in TSH, compared with baseline, was also found in the QTP group; 12% reported sedation, somnolence, and constipation in QTP group |

(Continued)
| No. | Author(s), Year | Study Design and Recruitment | Psychiatric Diagnosis | Outcome Measures | No. of Participants | Sex/Age, y | Duration of Quetiapine Therapy | Findings |
|-----|-----------------|------------------------------|----------------------|------------------|---------------------|----------|-------------------------------|----------|
| 11  | Suppes et al., 2009 | Multicenter, randomized, parallel-group, double-blind study comparing quetiapine plus lithium or DVP and placebo plus lithium or DVP in the maintenance treatment of adult patients with bipolar I disorder for up to 104 wk | Bipolar I disorder | NR | 310 patients received QTP plus lithium (42.3%) or DVP (57.7%) | NR | 104 weeks; 400-800 mg | Hypothyroidism was reported in 6.5% patients in QTP + Li/DVP group vs 1.3% in placebo + Li/DVP; parameters were not mentioned |
| 12  | Pina-Camacho et al, 2012 | Longitudinal, observational, uncontrolled clinical study to observe the obesogenic capacity of antipsychotics (risperidone, OLZ, and QTP) in naïve adolescents | 87 antipsychotic-naive children and adolescent patients | TFT at baseline, 3 and 6 months | 12 received QTP | NR for QTP group | NR for QTP group | FT4 levels decreased significantly in the whole sample without significant differences among treatment groups |
| 13  | Radhakrishnan et al, 2013 | Retrospective hospital-based study on 468 inpatient samples; TFTs were obtained for 343 patients | Schizophrenia (31.49%), BD (35.57%), major depressive disorder (18.37%) | TFT on admission and on suspicion; TSH was done on almost all patients; T3, T4, FT3, FT4, and anti-TPO were done when TSH level was abnormal | 9 received QTP | NR for QTP group | NR for QTP group | There was no significant difference in TSH levels among the patients on different classes of antipsychotics, although levels of TSH were least with QTP and highest with OLZ |
| 14  | Findling et al, 2014 | Multicenter, double-blind, randomized, placebo-controlled study investigated quetiapine XR in pediatric outpatients | Pediatric bipolar depression | Baseline, weeks 4 and 8 | 70/92 completed the study in the QTP arm | 51.1% F; 27.2% and 72.8% were in the 10-12 and 13-17 age groups, respectively | 8 weeks; 150-300 mg QTP XR daily | 4.7% in QTP group had a shift in TSH >5 mIU/L |
Table 2. Continued

| No. | Author(s), Year | Study Design and Recruitment | Psychiatric Diagnosis | Outcome Measures | No. of Participants | Sex/Age, y | Duration of Quetiapine Therapy | Findings |
|-----|-----------------|------------------------------|-----------------------|------------------|---------------------|-----------|--------------------------------|----------|
| 15  | Lambert et al, 2016 | Administrative claims data on 24,574 patients with BD were analyzed with competing risk survival analysis | BD | At least 1 thyroid test during monotherapy | 3798 | 65.9% F; mean age, 40.1 | The duration of observation ranged from 1 day to 3255 days (8.9 years), with a mean of 269 days and median of 142 days | 8.26% 4-year estimated risk of hypothyroidism |
| 16  | Hayes et al, 2016 | Population-based cohort study on adverse endocrine events during maintenance mood stabilizer treatment for BD | BD | NR | 1376 | 69.69% F; median age, was 38.08 y | Median duration of treatment was 1.06 years | 33 and 6 events of hypo- and hyperthyroidism, respectively; the rate of thyroid disease was elevated in people taking lithium, compared to valproate and OLZ, but not QTP |
| 17  | Iversen et al, 2018 | Cross-sectional study looking at the differences in thyroid hormone levels between patients with severe mental illness and healthy controls | Schizophrenia and BD | TSH and FT4 were measures in patients and healthy controls | NR | Participants were between 18 and 65 | NR | Significant associations between lower FT4 level and QTP and OLZ, but no significant associations were found with TSH level |
| 18  | Vedal et al, 2018 | Naturalistic study investigating thyroid function associated with use of antipsychotics in patients with psychotic disorders compared with healthy controls | Psychotic and mood disorders | NR | 66 | NR | NR | Lower level of FT4 was associated with self-reported weight gain | (Continued) |
| No. | Author(s), Year | Study Design and Recruitment | Psychiatric Diagnosis | Outcome Measures | No. of Participants | Sex/Age, y | Duration of Quetiapine Therapy | Findings |
|-----|----------------|-----------------------------|----------------------|-----------------|-------------------|---------|-------------------------------|----------|
| 19  | Li et al, 2019  | Depressed BD                | TFT at 4 and 12 wk   | 58              | 53.4% M; mean age, 20.7 | 3-month treatment: 52 patients received 300 mg/d; the rest received 400-500 mg/d | TT4, FT4, FT3 decreased in posttreatment 1 month, whereas TSH increased 2 patients with subclinical hypothyroidism TT3 unchanged Subgroup of 13 patients followed for 3 months, serum level of TT4, TT3, FT4, and FT3 was significantly reduced compared to baseline, and serum level of TSH was not significantly changed | Depressed BD |
| 20  | Samawi et al, 2020 | Retrospective, cross-sectional observational study exploring the effect of QTP and OLZ on thyroid function | Schizophrenia         | TFT at baseline and 12 weeks | 36 | 75% M; | 3 months; 200-400 mg/day | TT3 and TT4 levels decreased, while TSH level increased |

Anti-TPO, antithyroid peroxidase antibodies; BD, bipolar disorder; CPZ, chlorpromazine; DVP, divalproex; NR, not reported; OLZ, olanzapine; QTP, quetiapine; TFT, thyroid function test; TSH, thyroid stimulating hormone; XR, extended release.
Table 3. Quality Assessment of Case Reports and Series

| Study                  | Selection | Ascertainment | Causality | Reporting |
|------------------------|-----------|---------------|-----------|-----------|
| 1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? | | | | |
| 2. Was the exposure adequately ascertained? | | | | |
| 3. Was the outcome adequately ascertained? | | | | |
| 4. Were other alternative causes that may explain the observation ruled out? | | | | |
| 5. Was there a challenge/rechallenge phenomenon? | | | | |
| 6. Was there a dose–response effect? | | | | |
| 7. Was follow-up long enough for outcomes to occur? | | | | |
| 8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice? | | | | |
| Feret et al             | 1         | 1             | 1         | 0         | 0         | 1         | 0         |
| Dobbs et al             | 1         | 1             | 1         | 0         | 0         | 1         | 1         |
| Liappas et al           | 1         | 1             | 1         | 1         | 0         | 0         | 1         |
| Tor et al               | 0         | 0             | 1         | 0         | 0         | 0         | 1         |
| Kontaxacis et al        | 1         | 1             | 1         | 0         | 0         | 0         | 1         |
| Poutanen et al          | 1         | 1             | 1         | 0         | 0         | 1         | 1         |
| Park et al              | 1         | 1             | 1         | 0         | 0         | 0         | 0         |
| Shoib et al             | 0         | 0             | 1         | 1         | 0         | 0         | 1         |
| Dreijerink et al        | 0         | 1             | 1         | 1         | 0         | 0         | 1         |
| Zenno et al             | 0         | 1             | 1         | 1         | 0         | 0         | 1         |
| Ramaswamy et al         | 1         | 1             | 1         | 0         | 0         | 0         | 1         |
| Beer et al              | 1         | 1             | 1         | 0         | 0         | 0         | 1         |

0 = no; 1 = yes.
Table 4. Quality Assessment of Observational and Experimental Studies

| Study                     | Selection | Comparability a | Outcome/Exposure | Evidence Quality b |
|--------------------------|-----------|-----------------|------------------|-------------------|
| Vedal et al              | ****      | **              | ***              | High              |
| Li et al                 | **        | *               | ***              | Low               |
| Wetzel et al             | ***       | ...             | ***              | Low               |
| Arvanitis et al          | ****      | **              | ***              | Low               |
| Peuskens et al           | ****      | *               | ***              | Moderate          |
| Small et al              | ****      | **              | ***              | High              |
| Tariot et al             | ***       | ...             | ***              | Low               |
| Shaw et al               | ***       | ...             | ***              | Low               |
| Delbello et al           | ****      | **              | ***              | High              |
| Greenspan et al          | ****      | *               | ***              | High              |
| Kelly and Conley         | ****      | **              | ***              | High              |
| Potkin et al             | ****      | **              | ***              | High              |
| Suppes et al             | ****      | **              | ***              | High              |
| Pina-Camacho et al       | ****      | **              | ***              | Moderate          |
| Radhakrishnan et al      | ***       | *               | **               | Low               |
| Findling et al           | ****      | **              | ***              | High              |
| Lambert et al            | ****      | **              | ***              | High              |
| Hayes et al              | ****      | **              | ***              | High              |
| Iversen et al            | ****      | *               | *                | Low               |
| Samawi et al             | ***       |                 |                 | Low               |

*Also includes controlling for potential confounders.

Evidence quality: low = downgrading from moderate to low based on design or lack of information in report; moderate = study met selection criteria (4 stars), comparability (1 star and upgraded level for 2 stars), and outcome assessment; high = upgrading from moderate to high based on comparability of 2 stars.

(2) continue quetiapine with thyroid replacement,\textsuperscript{14,19}
(3) stop quetiapine and monitor,\textsuperscript{15,19,21} and (4) stop quetiapine and add thyroid replacement.\textsuperscript{17,19,22–24} Management plan was not reported for 2 patients.\textsuperscript{20} Clinical and family history influenced the decision to continue or discontinue quetiapine in 3 cases.\textsuperscript{18,23} Thyroid replacement consisted of levothyroxine with a range of 25 to 200 μg/d. TFT normalized in 45 days to 3 months when quetiapine was continued.

**Discussion**

Quetiapine has been associated with thyroid dysfunction in clinical trials, and thyroid abnormalities were included in product labeling for the drug.\textsuperscript{5} To our knowledge, this is the first systematic review of all published reports of thyroid dysfunction associated with quetiapine. We found 32 studies, 20 of which were observational or experimental studies. There were 11 case reports and 1 case series. We applied the Newcastle-Ottawa Scale and the Murad et al\textsuperscript{13} framework for assessing quality of included studies.

The mechanisms by which quetiapine induces a hypothyroid state are unclear, with several different theories proposed by researchers. One explanation is an underlying autoimmune mechanism, especially in women. Hormonal and genetic factors that influence the female predominance of autoimmunity have been proposed to explain why women are more prone to develop autoimmune diseases.\textsuperscript{43} It is noteworthy that the antithyroid peroxidase antibodies (anti-TPOs), considered as the most sensitive and specific marker of thyroid autoimmunity, were initially greater than normal limits but within the reference range after quetiapine discontinuation in a female patient with symptomatic subclinical hypothyroidism treated for mood disorder.\textsuperscript{15} This may indicate an immune reaction due to quetiapine, similar to the one reported in patients who develop hypothyroidism with associated anti-TPOs during lithium therapy,\textsuperscript{44,45} or an accidental finding that mood and anxiety disorders frequently coexist with thyroid autoimmunity in the community.\textsuperscript{46,47} These findings suggest that thyroid autoantibodies, especially anti-TPOs could have potential utility as a biomarker for hypothyroidism in patients taking quetiapine and may even affect prognosis.\textsuperscript{7} Another plausible mechanism for the decrease of thyroid hormones during quetiapine treatment is competitive metabolism of thyroid hormones and quetiapine by uridine 5’-diphospho-glucuronyltransferase.\textsuperscript{33} Nonetheless, direct action of quetiapine on the hypothalamic-pituitary axis cannot also be excluded, although TSH levels have been reported to remain unaffected in context of decrease in thyroid hormones in some studies (Table 2). Moreover, leptin and adiponectin may be associated with development of quetiapine-related thyroid and metabolic side effects, especially in pediatric antipsychotic-naïve patients.\textsuperscript{37} One explanation could be the potential relationship between thyroid hormones and adipose tissue metabolism, as a study showed positive correlation between TSH and body mass index and leptin but negative correlation between TSH and adiponectin.\textsuperscript{48}
There are a number of important clinical considerations. For instance, sudden changes in thyroid hormone levels may precipitate a psychiatric relapse, while thyroid dysregulation in a patient with a mood disorder may mimic the symptoms of their psychiatric disorder and therefore be easily missed. This highlights the importance of checking thyroid function in acutely ill psychiatric patients, particularly if they are on quetiapine therapy, not responding to treatment, or in case of high quetiapine dosage (because of the potential dose-dependent decrease in thyroxine levels). It is well established that thyroid function tests should be routinely performed before initiating lithium therapy, then periodically repeated as long as the patients are on lithium. However, the recommendations regarding monitoring TFTs for patients on quetiapine remains less clear, possibly because of the lower incidence of thyroid abnormalities on quetiapine compared to lithium. Maudsley guidelines recommend that patients on quetiapine should have yearly TFTs, although the risk of abnormality is very small.

By systematically reviewing the literature, we report the largest collection to date of case reports, observational studies, and experimental studies on the association between quetiapine therapy and thyroid dysfunction. Our search was not limited to studies in English, and we used a database source of gray literature. However, there were several limitations to be acknowledged. Many of the papers were of variable quality. TFTs, autoantibodies, and symptoms of thyroid illness were inconsistently reported. There was heterogeneity in the reference ranges, study populations, and designs, limiting the possibility to carry out a meta-analysis. The limited number of prospective studies meant that a clear temporal relationship could not be established in most cases, although there was some evidence of dose response. A plausible alternative explanation for any association might be that patients on quetiapine in these studies are more likely to have their thyroid function monitored than in clinical practice; therefore, incident cases are more likely to be detected. In addition, it is possible that concomitant psychotropic medication could be responsible for changes in thyroid function. In fact, one study found that rates of thyroid disease were elevated in people taking lithium compared to valproate and olanzapine but not quetiapine. Therefore, these make it difficult to make any conclusions regarding the nature of the association between quetiapine and thyroid dysfunction. Large prospective studies using the most important and sensitive TSH test are required to clarify this association and to guide the clinical management of patients with quetiapine in whom thyroid abnormalities occur. Another limitation in terms of our search strategy was that we avoided using thyroxine as a search term since most search results including this term referred to the use of thyroxine as a treatment rather than endogenous thyroxine. We also checked that adding this term to the query did not yield additional articles that were not included in the review. Therefore, we preferred omitting this search term since this seemed to improve specificity without compromising sensitivity.

Nonetheless, after reviewing the highest quality papers, we can conclude that (1) there seems to be a decrease in TT3 and TT4 with an apparent dose-response relationship; (2) alterations in TSH levels in adolescents showed mixed results, that is, elevated TSH and no change in TSH in bipolar depression and manic/mixed affective states, respectively; and (3) the rate of thyroid disease remains higher in people taking lithium compared to quetiapine.

**Conclusion**

Quetiapine has been associated with thyroid abnormalities, mainly with hypothyroidism. Drug imputability in these abnormalities is not always clear, and the underlying pathophysiology may include immunological and nonimmunological mechanisms. These abnormalities seem to be more commonly reported in adult females. It seems wise to request TFTs in patients before starting quetiapine, especially when they are potentially at risk for hypothyroidism (young, female, family history of thyroid disease, high doses of quetiapine, use of other drugs that can affect the thyroid function). It is also recommended to monitor TFTs yearly and to work in partnership with family practitioners and endocrinologists. Thyroid abnormalities should be considered whenever a patient on quetiapine stops responding to the treatment or exhibits “new” mood, psychotic, or cognitive symptoms despite good adherence. When thyroid abnormalities on quetiapine are diagnosed, the pros and cons of continuing vs discontinuing quetiapine can be discussed with the patient in a case-by-case manner. If hypothyroidism persists after quetiapine is discontinued, or if the decision was to pursue treatment with quetiapine, it seems reasonable to prescribe levothyroxine targeting a normalization of the TSH levels in most cases.

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**Conflicts of Interest**

The authors declare no conflicts of interest.

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Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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