

Bipolar disorder, comorbid anxiety disorders, gynecomastia and dental pain: case analysis with literature review*

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Bipolar disorder with comorbid anxiety disorders frequently requires rational polypharmacy, including use of serotonergic psychotropics. These may result in adverse effects, influencing adherence, complicating treatment and confounding diagnoses. Serotonergic non-adherence is associated with discontinuation syndromes. In this complex case with an on/off/on/off design, both dose-dependent buspirone-induced gynecomastia and buspirone discontinuation syndrome with dental pain are reported. Clinicians and patients should consider these findings to maximise treatment adherence, minimise any unnecessary interventions and address unusual adverse effects. Since patients may not voluntarily disclose specific adverse effects and often do not acknowledge non-adherence, clinician-directed questions are required. This case further emphasises the importance of medication and symptom timelines to guide determination of causation for adverse effects. Although findings from this case cannot be generalised, they suggest the need for

continued clinician and patient education, as well as the benefit from detailed case reports.

Declaration of interest

None.

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Bipolar disorder psychiatric comorbidities are important in determining diagnosis, treatment and outcome. Anxiety disorder comorbidity in bipolar disorder patients is often underappreciated by clinicians. Recent systematic reviews and meta-analyses have noted lifetime comorbidity prevalence rates of 42.7% for any anxiety disorder, 15.1% for generalised anxiety disorder (GAD), 10.8% for post-traumatic stress disorder (PTSD), 16.8% for panic disorder, and 17.0% for obsessive-compulsive disorder (OCD).^{1–3} Comorbid anxiety disorders may be associated with an earlier age at onset for bipolar disorder,⁴ as well as poorer acute treatment of the disorder and longitudinal course outcomes.^{5,6} Similarly, substance use disorders (SUD) are commonly comorbid with bipolar disorder (combining all SUD ~35–40%, with alcohol > cannabis > other illicit drugs)^{7,8} and may be associated with early age at onset (child and adolescent populations) for bipolar disorder.⁴ SUD, in particular, cannabis use disorder (CUD), may also be associated with self-medication of comorbid anxiety disorders.⁹ Further, attention-deficit hyperactivity disorder (ADHD) has been reported in >20% of patients with bipolar disorder and may be associated with earlier age at onset for bipolar disorder with poorer outcome.¹⁰

Treatment of bipolar disorders with comorbid anxiety disorders and SUD may be complex and often requires rational polypharmacy, including combined mood-stabilising agents (lithium, anti-epileptic drugs and second-generation antipsychotics) and serotonergic psychotropics (selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors).^{11,12} Optimal care for all medical conditions, and bipolar disorder with psychiatric comorbidities in particular, is premised on maximising therapeutic response and minimising adverse effects.¹³ The key to positive treatment outcomes in mood disorders is psychotropic adherence, which has frequently been reported to be <50%.^{14–18} A recent review emphasised that strategies for treatment adherence remain an unmet need for bipolar disorder.¹⁸

Adverse effects associated with serotonergic psychotropics influence general treatment adherence and psychotropic adherence, complicate treatment and may even confound diagnoses. In treating bipolar disorders with comorbid anxiety disorders, specific adverse effects may be related to both serotonergic agents and mood stabilisers, requiring an accurate timeline of psychotropic initiation, dosing and development of adverse effects to determine causation in the presence of polypharmacy. As adverse effects are a common factor leading to psychotropic non-adherence, consideration of all adverse effects is paramount to ensure adherence to pharmacotherapy.¹⁶ Often, specific adverse effects that might lead to non-adherence, including sexual dysfunction and mammoplasia or gynecomastia, are neither voluntarily reported by patients nor directly questioned by clinicians.^{19–22}

When considering the influence of adverse effects on adherence and treatment outcome, it is also important to consider the effects of rapid or abrupt discontinuation of the purported offending agent and the development of psychotropic discontinuation syndromes, which can cause diagnostic dilemmas, treatment mismanagement and increased morbidity.²³ Specifically, the antidepressant discontinuation syndrome associated with serotonergic agents includes a *pot pourri* of symptoms including, but not limited to, depression, anxiety, hallucinations, confusion, fatigue, tremors, paraesthesia, insomnia, dizziness, vertigo, vivid dreams, labile mood, irritability or anger, suicidal ideation, and hypomania or mania.^{23–25}

This case report describes both a previously unreported discontinuation symptom (dental pain) and gynecomastia in a patient with bipolar disorder and multiple psychiatric comorbidities (GAD, panic disorder, PTSD, OCD, ADHD and SUD) treated with rational polypharmacy including serotonergic psychotropics.

Method

The study consisted of a case analysis with a PubMed literature review.

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Results

A 21-year-old male college student presented with a major depressive episode (MDE), GAD of sixth month duration, CUD, and alcohol use disorder (AUD). The patient was in excellent medical health and denied any historical or active medical diagnoses; his body mass index (BMI) was 23.14 kg/m². During the psychiatric evaluation, this patient acknowledged chronic depressive features since age 16, but masked other psychopathology beyond GAD, CUD and AUD. Initial psychotropic treatments included escitalopram 5 mg q.a.m. and buspirone 7.5 mg b.i.d. which were titrated to 20 mg q.d. and 15 mg t.i.d., respectively, with the addition of lorazepam 0.5 mg b.i.d. p.r.n. to address situational exacerbation of the patient's anxiety. After a 4-month therapeutic escitalopram trial with persistent complete neurovegetative-affective cluster, bupropion 150 mg q.a.m. was added to his psychotropic regimen.

Shortly thereafter, the patient abruptly decreased both escitalopram to 10 mg q.a.m. and buspirone to 7.5 mg t.i.d. for 2 days and described the following psychotropic discontinuation features – agitation, restlessness, fogginess, word-finding difficulties, memory loss, diaphoresis, diarrhoea, headache, shivering, goose bumps, fever and 'feeling glass shards in my bones'. To address the new-onset discontinuation features, escitalopram was increased to 15 mg q.a.m. followed by a gradual taper (2.5 mg/week) with resolution of all discontinuation features over the course of 3 weeks. Buspirone was returned to the prior 15 mg t.i.d. dosing. Further, the patient commented on using cannabis both to treat anxiety and to diminish the discontinuation features. At this time, the patient acknowledged panic attacks that were independent of situational stressors, and he was diagnosed with panic disorder without agoraphobia. Lorazepam was increased to 0.5–1 mg t.i.d. p.r.n.. To better treat the patient's ongoing depression, bupropion was titrated to 200 mg q.a.m. and then 300 mg q.a.m..

All standard blood chemistries, including thyroid function tests, lipid profile and vitamin D, were within normal limits; however, the patient's total testosterone level of 313 ng/dL (laboratory reference range 348–1197 ng/dL) led to treatment with topical testosterone 50 mg/5 g gel q.a.m. on the right upper extremity. Within 2 weeks of initiation of testosterone and the increased bupropion, the patient reported new-onset left breast (contralateral to testosterone gel) gynecomastia with tenderness, which was confirmed by mammography – testosterone was discontinued with total treatment course of 3 weeks only. At the same session, the patient presented with continuing depressive features, as well as intermittent brief hypomanic/manic features. Historical bipolar features were reassessed, and he acknowledged not having previously shared their presence since age 13 – these brief hypomanic/manic features never lasted beyond 1–2 days. The patient's mood disorder diagnosis was changed to bipolar disorder not otherwise specified (NOS). Further, with acknowledgment of compulsive counting and folding from youth with obsessive thoughts, the patient was diagnosed with OCD. Lurasidone 40 mg q. dinner was initiated to address his bipolar features, but discontinued within 2 days secondary to marked akathisia which responded to a brief course of benzotropine mesylate 0.5 mg b.i.d. p.r.n.. Subsequently, lithium 600 mg q.h.s. was initiated but discontinued within 2 weeks secondary to polyuria, polydipsia and new-onset tremor.

Given the continuing depressive features and adverse effects with both lurasidone and lithium, alternative interventions for bipolar depression were reviewed; however, the patient initially declined both anti-epileptic drugs and other second-generation antipsychotics. As attention issues were a key concern to his studies, ADHD criteria were re-assessed. Whereas previously he denied meeting criteria for ADHD, he now admitted full criteria which

dated back to elementary school and further commented that testing for ADHD had been recommended but had not been pursued. Amphetamine–dextroamphetamine extended release 10 mg q.a.m. was initiated for the newly diagnosed ADHD. Since there was no reduction in gynecomastia with continuing tenderness and pain during the 3 weeks following testosterone and escitalopram discontinuation, buspirone was reduced to 15 mg b.i.d..

With amphetamine–dextroamphetamine extended release titrated to 20 mg q.a.m., ADHD further resolved. Aripiprazole 2 mg q.h.s. was added to address limited paranoia and hypersexuality and to serve as an anxiolytic agent, permitting further reduction in buspirone to 7.5 mg t.i.d.. When aripiprazole was increased to 4 mg q.h.s., the patient presented with akathisia, which responded to a brief course of benzotropine mesylate 0.5 mg b.i.d. p.r.n., and aripiprazole was discontinued. Nonetheless, the patient gradually tapered buspirone over 1 month (22.5 mg/day, 20 mg/day, 17.5 mg/day and then 15 mg/day). With buspirone tapering, the patient reported a dose-dependent resolution of gynecomastia; on buspirone 15 mg q.d., the patient described very minimal gynecomastia – 'almost unnoticeable and no pain'. Further, during buspirone tapering, the patient reported recurrent discontinuation features, as previously described, and new-onset dental pain. A dental consultation with full assessment found no pathology, including bruxism, associated with this dental pain with non-response to antibiotics. On low-dose buspirone, significantly increased generalised anxiety was noted, and buspirone was directly increased to 15 mg b.i.d.. Within 7–10 days, the patient reported increased unilateral gynecomastia with recurrent tenderness and pain ('breast silhouette with B-size cup'). With buspirone increased to 15 mg b.i.d., all discontinuation features including dental pain resolved.

Although the patient noted improvement of multiple features on his combined bupropion 300 mg q.a.m., amphetamine–dextroamphetamine extended release 20 mg q.a.m., and buspirone 15 mg b.i.d. regimen, lamotrigine was initiated to better treat his bipolar disorder. The patient responded well to lamotrigine slow titration with resolution of remaining depressive features. At this juncture, with continuing stabilisation, the patient acknowledged long-standing PTSD, which he felt could finally be addressed in his ongoing CBT (this patient was in therapy prior to and throughout treatment by the psychiatrist).

Concomitantly, the patient was evaluated by a breast surgical oncologist, who concluded that the patient had drug-induced gynecomastia. A repeat testosterone level was 413 ng/dL. Buspirone was again titrated down to 15 mg q.d. with minimal gynecomastia compared with higher doses and no tenderness; however, he also had recurrent discontinuation features and dental pain. Thereafter, buspirone was gradually discontinued (10 mg/day, 7.5 mg/day, 5 mg/day and 2.5 mg/day). With each step, the patient noted dental pain which persisted for 1 week. Of note, the other discontinuation features lasted for several weeks after final titration. Off buspirone, the patient commented on subjective total resolution of gynecomastia; however, a repeat mammogram revealed minimal bilateral gynecomastia. The patient was again evaluated by the same breast oncologist, who noted no gynecomastia on physical examination and considered the current mammogram to be benign.

The patient remains stabilised with the following psychotropic regimen: bupropion 300 mg q.a.m., amphetamine–dextroamphetamine extended release 20 mg q.a.m., lamotrigine 150 mg q.h.s. and lorazepam 1 mg t.i.d. p.r.n..

Discussion

This unique case permits discussion of different aspects of patient symptom reporting, early-onset bipolar disorder with delayed

treatment/diagnosis, bipolar disorder with comorbidities, rational polypharmacy, gynecomastia, discontinuation syndrome and determination of possible/probable adverse effect causation.

First, this case is consistent with general clinical practice, wherein historical symptoms and even prior diagnoses may not be reported during an appropriate comprehensive initial evaluation and are only retrospectively acknowledged over a naturalistic treatment course. Specifically, this patient described an MDE consistent with a major depressive disorder during his evaluation; he only later revealed earlier onset of bipolar features resulting in the corrected mood disorder diagnosis: bipolar disorder NOS. Delay in reporting both current and historical symptoms may result in inappropriate treatments. Thus, it is important for clinicians to periodically reassess symptom history and review potential alternative diagnoses in treatment-refractory patients, as well as those patients with only partial response to adequate pharmacotherapy.

Second, bipolar disorder outcome is premised on timely and appropriate treatments; however, early-onset bipolar disorders often have both delayed treatment intervention and delayed diagnosis which lead to poorer outcomes, including increased rates of suicidal behaviours.^{26–28} Even in the context of care by specialised mental health services, such delays have been reported for initial presentation with SUD, depression and anxiety disorders.²⁹ In this case, initial psychiatric features dated to childhood, bipolar features had been present since age 13, and depressive features since age 16 – the delay to any psychiatric treatment from bipolar disorder onset was 8.5 years, and the delay to appropriate diagnosis and treatment was 9 years.

Third, bipolar disorder is commonly associated with multiple comorbidities.^{1–10} Comorbidity is the rule rather than the exception, as >75% of patients with bipolar disorder have at least one lifetime comorbid psychiatric condition, and >50% have multiple lifetime comorbid psychiatric conditions.³⁰ The findings in this case are consistent with the literature; a summary of all psychiatric comorbidities acknowledged at the time of initial evaluation of this patient and during ensuing treatment over the course of 12 months included GAD, SUD, panic disorder, OCD, ADHD and PTSD. Prevalence rates for comorbid conditions may be similar and/or increased in patients with childhood onset of bipolar disorder compared with lifetime prevalence rates.^{1–3,7–8,10,31} The Course and Outcome of Bipolar Youth (COBY) study noted the following comorbidity prevalence rates: 47.2% any anxiety disorder, 33.9% GAD, 16.9% panic disorder, 67.8% ADHD and 37.3% any SUD.³¹ The COBY study also confirmed the negative effects of anxiety disorders, SUD and ADHD on acute and longitudinal outcomes for bipolar disorder.³¹

Fourth, rational polypharmacy is frequently required for patients with bipolar disorders with comorbidities.^{11,12,32} As in the present case, when the patient does not present with or acknowledge historical bipolar features, such psychotropic treatment may begin with antidepressants which could worsen acute and longitudinal outcomes; however, the effect on ‘switching’ and increased mood episodes may be dependent on multiple factors, including antidepressant class, antidepressant treatment duration, bipolar disorder subtype (bipolar I, bipolar II or bipolar NOS) and the presence of rapid cycling.^{33–35} Treatment guidelines recommend initial treatment with standard mood-stabilising psychotropics (lithium, anti-epileptic drugs and second-generation antipsychotics), to which would then be added, as required, specific psychotropics to address individual comorbidities.^{11,12,32,35} Non-adherence to psychotropic treatment is multifactorial; however, polypharmacy has an increased risk for drug–drug interactions and adverse effects which may lead to decreased adherence.^{14,16,36,37} Consider that this patient decreased both escitalopram and buspirone by 50% simply to see whether he would feel better on a lower dose and, by so doing, precipitated a discontinuation syndrome. Since bipolar disorder management requires an appreciation of acute

and long-term psychotropic efficacy, safety and tolerability, when treating patients with bipolar disorder with comorbidities, clinicians should also consider which psychotropics may effectively treat multiple conditions while considering both acute and long-term number needed to treat/number needed to harm ratios.^{12,13,33,35,38}

Fifth, gynecomastia is a frequent benign finding in men (prevalence range 32–65%) that significantly increases with BMI >25 kg/m².³⁹ Although gynecomastia is predominantly idiopathic, other aetiologies include medication, systemic illness (hepatic, renal, hormonal) and tumors.^{21,22,39–41} This patient had normal standard laboratories and BMI; only his testosterone level was borderline low, for which he briefly received testosterone gel that was discontinued upon development of contralateral gynecomastia – this level returned to normal later in the treatment course. Pertinent to the findings in this case, a PubMed literature review noted the following classes of medications, specific medications and substances as potential factors in the development of gynecomastia – selective serotonin reuptake inhibitors, benzodiazepines, bupropion, marijuana, testosterone, amphetamines and second-generation antipsychotics (aripiprazole has been utilised to reverse gynecomastia).^{21,22,40–46} There are no reported cases of gynecomastia induced by buspirone, lurasidone, lithium, aripiprazole or lamotrigine. One case report describes gynecomastia induced by the anxiolytic tandoospirone, a 5-HT_{1A} partial agonist related to buspirone.⁴⁷

Sixth, determination of causation for gynecomastia and mammaplasia in psychiatric patients is especially difficult, as patients rarely volunteer this condition.^{21,22,40} This patient openly addressed his gynecomastia at each session, permitting the development of a timeline based on alterations in psychotropics.

- Unilateral gynecomastia first reported – bupropion 300 mg q.a.m., escitalopram 7.5 mg q.a.m., buspirone 15 mg t.i.d., lorazepam 0.5–1.0 mg t.i.d. p.r.n., topical testosterone (3 week course with discontinuation secondary to gynecomastia) and self-medication with daily marijuana
- Persistent gynecomastia – bupropion 300 mg q.a.m., buspirone 15 mg b.i.d., lorazepam 0.5–1.0 mg t.i.d. p.r.n., amphetamine–dextroamphetamine extended release 10 mg q.a.m. and self-medication with daily marijuana (lurasidone and lithium both utilised briefly with discontinuation secondary to adverse effects)
- Minimal gynecomastia without tenderness – buspirone tapered to 15 mg q.a.m., bupropion 300 mg q.a.m., lorazepam 0.5–1.0 mg t.i.d. p.r.n., amphetamine–dextroamphetamine extended release 20 mg q.a.m. and self-medication with daily marijuana (aripiprazole utilised briefly with discontinuation secondary to adverse effects)
- Recurrent gynecomastia with tenderness and pain – buspirone increased to 15 mg b.i.d., bupropion 300 mg q.a.m., lorazepam 0.5–1.0 mg t.i.d. p.r.n., amphetamine–dextroamphetamine extended release 20 mg q.a.m. and self-medication with daily marijuana
- Persistent gynecomastia – buspirone 15 mg b.i.d., bupropion 300 mg q.a.m., lorazepam 0.5–1.0 mg t.i.d. p.r.n., amphetamine–dextroamphetamine extended release 20 mg q.a.m., lamotrigine 100 mg q.d. and self-medication with daily marijuana
- Resolved gynecomastia on physical exam by breast specialist – buspirone discontinued, bupropion 300 mg q.a.m., lorazepam 1 mg t.i.d. p.r.n., amphetamine–dextroamphetamine extended release 20 mg q.a.m., lamotrigine 150 mg q.d. and self-medication with daily marijuana

This medication timeline revealed an on/off/on/off titration of buspirone directly correlated to the degree of gynecomastia, with

ultimate resolution of observable/palpable gynecomastia with total discontinuation of buspirone (a repeat mammogram noted mild bilateral gynecomastia). Although other medications or substances or even hormonal imbalance may have played an additive part in this patient's gynecomastia, buspirone-induced gynecomastia is considered probable by the Naranjo probability scale.⁴⁸

Seventh, antidepressant discontinuation syndromes occur with all classes of antidepressants, with a broad range of symptoms, present even with gradual psychotropic tapering, can be precipitated by psychotropic non-adherence, and may have varying time duration including different durations for specific symptoms.^{23–25,49}

In this case, symptoms associated with gradual escitalopram discontinuation are consistent with the above principles. Buspirone withdrawal/discontinuation syndrome has not been previously reported.^{50–52} Further, dental pain has not been previously reported in any psychotropic discontinuation or withdrawal syndrome. As such, buspirone discontinuation syndrome with dental pain represents a case of first impression. Similar to antidepressant discontinuation syndromes, the dental pain had a different time duration compared with other discontinuation features. Based on the medication timeline and the on/off/on/off buspirone titration, the buspirone discontinuation syndrome with dental pain is considered probable by the Naranjo probability scale.⁴⁸

This case has multiple limitations. (a) As a case report ($N = 1$), the findings cannot be generalised. (b) Comprehensive hormonal panels were not assessed during the treatment course beyond thyroid function tests and testosterone levels. Oestrogen balance and hyperprolactinemia are associated with gynecomastia. Baseline hormonal values and assessments throughout the treatment course might have suggested both predisposing hormonal factors and the influence of psychotropic titrations on hormones influencing gynecomastia. (c) No psychotropic blood levels were obtained to address concentration-dependent as opposed to dose-dependent effects of buspirone on gynecomastia. (d) Breast biopsies were not considered clinically indicated and there was no histopathology confirmation of benign gynecomastia. (e) Urine/serum toxicology for cannabinoids and active metabolites was not obtained, which precluded determining whether there was a correlation with gynecomastia. (f) Psychometric scales were not utilized, though such scales can be of benefit in monitoring symptom severity, especially when patients are seen infrequently in follow-up (this patient was followed every 1–3 weeks based on symptom severity and development of adverse effects). (g) As a naturalistic clinical case, for ethical reasons this patient could not be re-challenged or retested for further determinations.

Conclusions

This case summarises some of the important complexities associated with bipolar disorder treatment: incomplete patient symptom reporting requiring reassessment of historical symptoms during treatment course to ensure appropriate diagnoses; early onset with delayed treatment/diagnosis; frequent comorbidities; rational polypharmacy with adverse effects; and psychotropic non-adherence.

Rational polypharmacy in bipolar disorder with comorbid psychiatric conditions may reveal unusual adverse effects. This report presents a case of first impression for both dose-dependent buspirone-induced gynecomastia and buspirone discontinuation syndrome with a new discontinuation symptom, dental pain. Clinicians and patients should consider these findings to maximise treatment adherence, minimise any unnecessary interventions and address unusual adverse effects. Since patients may not voluntarily disclose specific adverse effects and often do not acknowledge

non-adherence, clinician-directed questions are required.^{16,20,22} This case further emphasises the importance of medication and symptom timelines to guide determination of causation for adverse effects. Although findings from this case cannot be generalised, they suggest the need for continued clinician and patient education, as well as the benefit from detailed case reports.

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