mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Delayed allergic reaction from bupropion in a 27-year-old male with MDD: A case report and literature review

Ana Anghel, BSc(Psych)[1]
G. Lucy Wilkening, PharmD[2]

How to cite: Anghel A, Wilkening GL. Delayed allergic reaction from bupropion in a 27-year-old male with MDD: a case report and literature review. Ment Health Clin [internet]. 2024;14(5):293-7. DOI: 10.9740/mhc.2024.10.293.

Submitted for Publication: August 22, 2023; **Accepted for Publication:** July 2, 2024

Abstract

Introduction: Bupropion is an antidepressant approved for the treatment of major depressive disorder (MDD), seasonal affective disorder, and smoking cessation. Nausea, headache, tremor, and insomnia are well-known adverse effects of this medication. Less well-recognized adverse effects include delayed allergic reactions, which, in some cases, can appear 2 or more weeks after bupropion initiation.

Case Report: A 27-year-old male with recurrent MDD was referred for medication treatment at an outpatient mental health clinic and prescribed bupropion XL. On day 28 of treatment, he reported significant improvement in depressive symptoms and the development of itchiness and urticaria on his extremities and back. Bupropion was tapered over the course of 7 days, and he was given cetirizine 10 mg daily. He was transitioned to venlafaxine treatment and experienced complete resolution of hives and pruritus.

Discussion: Despite published reports on bupropion causing delayed hypersensitivity reactions, there remains limited clinical recognition of this side effect, and the risk of underrecognition may be greater when the onset of the reaction is more than 2 weeks after bupropion initiation.

Conclusion: Bupropion can cause delayed hypersensitivity reactions, including delayed pruritis and urticaria. The risk may be highest in males aged 17 to 40 years and those with a history of allergic reactions.

Keywords: bupropion, delayed allergic reaction, delayed hypersensitivity reaction, delayed urticaria

[1] Bachelor of Science in Psychology, Boise State University, Boise, Idaho, ORCID: https://orcid.org/0009-0001-6267-3062; [2] (Corresponding author) Clinical Associate Professor, Department of Clinical Psychopharmacology, Idaho State University, Meridian, Idaho, g.lucy.wilkening@gmail.com, ORCID: https://orcid.org/0000-0002-2247-1466

Disclosures: The authors have no conflicts of interest to disclose.

Introduction

Bupropion is a commonly used antidepressant primarily prescribed to treat major depressive disorder (MDD) and aid in smoking cessation. It belongs to the norepinephrine-dopamine reuptake inhibitor antidepressant class. The most commonly reported side effects of bupropion include upset stomach, tremors, headache, anxiety, nausea, insomnia, and dizziness. However, a lesser-recognized side effect involves the development of delayed urticaria, including onset more than 2 weeks after bupropion initiation.

Allergic reactions, or hypersensitivity reactions, can be categorized by timeline of symptoms and cell/protein involvement. There are 4 types of allergic reactions as follows: Type I (anaphylactic), Type II (cytotoxic), Type III (immunocomplex) and Type IV (cell-mediated). Types I to III hypersensitivity reactions are classified as immediate and occur within 24 hours of allergen exposure. Type IV reactions are delayed and occur more than 24 hours after allergen exposure; however, it is important to consider that the preponderance of these delayed reactions onset within 48 to 72 hours.[1] Immediate allergic reactions result in rapid-onset symptoms such as hives, itching, and difficulty breathing. In contrast, delayed hypersensitivity reactions involve immune system responses that can occur

days after allergen exposure.[2] While immediate-type reactions are well-documented with numerous medications, including bupropion, the relationship between specific medications and delayed hypersensitivity reactions is not well understood. In this report, we present a case of a 27-year-old patient with MDD who developed self-reported urticaria and pruritis 3 weeks into bupropion treatment. A comprehensive literature review of bupropion-induced allergic reactions occurring greater than 2 weeks after drug initiation is also included in this report. Verbal consent for this report was obtained from the patient.

Case Report

A 27-year-old male with recurrent, moderate MDD presented to an outpatient mental health clinic. The patient denied prior psychopharmacological trials and reported no significant medical history except for a climbing accident 5 years ago. No formal diagnosis of concussion or traumatic brain injury was documented. The patient's chief complaints included concentration problems, low mood, insomnia, appetite changes, and loss of interest and pleasure in activities (PHQ-9 = 13, moderate depression). He denied any history of allergic reactions to any medications or substances.

The patient was prescribed bupropion XL 150 mg daily. After 21 days of treatment, he requested to titrate the dosage to 300 mg and 150 mg every other day to continue working on a response but minimize the risk of upset stomach. On day 28, the patient reported significant improvement in depressive symptoms (PHQ-9 = 1). However, he also reported that he had developed hives and severe itchiness over the prior 7 days. His physical exam revealed considerable scratch marks on both deltoids and the lumbar region of his back and diffuse erythema across his back and bilaterally on both arms. The patient had taken 10 mg of cetirizine before his appointment, which he reported had helped him control the hives and itching while he was at home. The patient associated the rash with a recent change in detergent and was prescribed cetirizine 10 mg daily and switched back to his regular soap. He was advised to notify the clinic if the rash persisted.

Despite this intervention, on day 32, the patient called the clinic and reported continued urticaria and itching. A bupropion XL taper at 150 mg daily for 7 days with continued cetirizine 10 mg daily treatment was ordered. The patient's pruritus had resolved within a week after the completion of the taper. Additionally, the patient could resume using the new detergent without issue and no longer required cetirizine. The patient was transitioned to venlafaxine ER, which he tolerated. A Naranjo Adverse Drug Reaction Probability Scale[3] score of 7 was calculated based on previous documentation of this adverse reaction, appearance after administration of bupropion, resolution after discontinuation of bupropion, no other potential causes of the reaction, and confirmation of the reaction on physical examination.

Methods

A literature search was conducted on May 27, 2023, to review other cases of delayed-onset allergic reactions from bupropion. *Delayed* was defined as the onset of hypersensitivity reaction more than 2 weeks after bupropion initiation based on our patient case, other published reports, and the increased likelihood of clinical misdiagnoses with a hypersensitivity delay of this type. A literature search was conducted on PubMed using the keywords *bupropion* and *allergic reaction*. Results were limited to articles available in full text and the English language. Citations within these publications were reviewed for relevance. Papers reporting hypersensitivity reactions that started less than 2 weeks after initiation of bupropion were not included in the review but are included in the discussion of this work.

Results

The PubMed advanced search yielded 37 results. Thirteen articles were selected for inclusion in our review, including 9 case reports, 2 case series, 1 meta-analysis, and 1 population-based study.

Bupropion and Delayed Urticarial Reactions

The literature review revealed 3 case reports and 1 cohort study regarding delayed urticarial reactions with bupropion. Gutiérrez and colleagues[4] published a case of a healthy 20-year-old male who presented with a severe, itchy rash 3 weeks after starting extended-release bupropion for a mood disorder. The rash improved with oral cetirizine and diphenhydramine, and complete resolution was achieved within a week after discontinuing bupropion. The patient refused a medication rechallenge.[4] Peri et al[5] published another report of a case of a 17-year-old male who was started on bupropion for depressive symptoms during psychiatric hospitalization. Eighteen days after starting bupropion, he presented to the emergency department (ED) with diffuse urticaria on his extremities. The patient had a history of severe urticarial reactions to mangoes but no reported reactions to medications. He was switched to escitalopram and tolerated it well.[5] Another case by Benson[6] reported a 35-year-old male who presented to the ED for urticarial rash and joint pain and swelling 17 days after starting bupropion. The patient required discontinuation of bupropion, hospitalization, and 2 weeks of corticosteroid treatment.[6]

A large, nationwide population-based study that aimed to investigate the incidence of bupropion-induced urticaria and delayed onset was published using Taiwan's National Health Insurance Dataset. A cohort study was conducted between 2000 and 2009 involving 65 988 patients diagnosed with depressive disorder. The findings from this study demonstrated a heightened risk of urticaria among bupropion users, particularly within the first 4 weeks of treatment initiation; specifically, delayed onset (defined as days 15-28) accounted for

72% (34 of 47 cases) of bupropion urticaria cases and occurred significantly more frequently in this timeframe compared with match controls ($P < .001$). The cumulative incidence of urticaria was 16.56 per 1000 patients in the bupropion cohort, while it was 9.16 per 1000 patients in the comparison cohort (risk ratio 1.81; 95% confidence interval [CI] 1.28, 2.54, $P = .001$). Further analysis was conducted by stratifying patients based on age and sex. Bupropion use was associated with a higher risk of urticaria in patients under 40 years old (risk ratio 2.25, 95% CI 1.41, 3.60, $P < .001$), and researchers found that history of urticaria (hazard ratio 3.03, 95% CI 1.7, 5.4, $P < .001$) was the only independent risk factor for bupropion-associated urticaria.[7]

Bupropion and Other Delayed Skin Reactions

One case study reported a 31-year-old female with MDD who developed erythema multiforme 20 days after starting sustained-release bupropion; bupropion was discontinued, and rechallenge was deemed inappropriate.[8] In another case, a 33-year-old male was prescribed bupropion for smoking cessation. The patient developed a rash on his extremities 18 days after initiation of bupropion and then self-discontinued bupropion on day 22 and had total resolution of symptoms by day 25.[9] In another case, a 25-year-old male experienced urticarial eruption and angioedema 2 weeks after initiating bupropion for smoking cessation. Bupropion was promptly discontinued, and no mention of rechallenge was made in the report.[10] A case series by Tuman and colleagues[11] reported 3 patients who developed urticarial plaques and facial swelling after taking bupropion for smoking cessation and MDD. In the case of a 33-year-old male, he presented to the ED for 3 days of facial swelling and generalized erupted hyperemic plaques. He had been taking bupropion 300 mg daily for 15 days for smoking cessation before presenting to the ED. The same case series reported another case of a 31-year-old female who presented to the ED with generalized erupted plaques and periocular swelling after 3 weeks of treatment with bupropion 300 mg daily for MDD. In all cases, bupropion was discontinued, and patients showed regression of lesions and improvement with prednisolone and pheniramine treatment.[11] Another case by Singh and colleagues[12] reported a case of a 55-year-old female who developed erythrodermic pustular psoriasis 3 weeks after initiation of bupropion/naltrexone. The patient required a 2-week hospitalization, and bupropion/naltrexone was not restarted. Thurman and colleagues[13] also reported the case of a 29-year-old female who presented to the ED for an evaluation of a diffuse pustular rash that started 2 weeks after she started taking bupropion. The patient was not on any other prescription medications.[13]

Bupropion and Serum Sickness Reactions

A number of serum sickness–like (SSL) reactions to bupropion have been reported in the literature. One report is of a 25-year-old female who developed SSL symptoms 21 days after bupropion initiation. The patient required treatment with corticosteroids, and bupropion was discontinued.[14] Similarly, Nguyen and colleagues[15] also reported a case of SSL reactions with neutrophilic urticarial pattern. The patient was a 24-year-old Caucasian male who was admitted to the hospital for painful urticarial plaques and arthralgia 1 month after starting bupropion. Histologic confirmation was included in their report.[15]

Bupropion and Serious Allergic Reactions

A meta-analysis using data from the French pharmacovigilance database evaluated a total of 698 000 patients taking bupropion for smoking cessation. A total of 1682 adverse reactions were reported, and 28% ($n = 475$) were classified as serious allergic reactions (SARs); 148 of these SARs were dermatologic reactions, including urticaria, angioedema, and serum sickness. Patients who reported angioedema and SSL reactions were significantly younger than the entire exposed population (37.5 years, ±10.4; $P = .008$; 35.2 years [±8.4], $P < .0001$, respectively). Male patients accounted for 55.1% ($n = 27$) of angioedema cases and 61.5% ($n = 24$) of SSL reaction cases. The median time to onset for these SARs ranged from 12 to 14 days.[16]

Discussion

Bupropion is generally well-tolerated and is used frequently in primary care and mental health settings. It is known to carry warnings in those with histories of eating disorders and seizure disorders, and a preponderance of its adverse effects is logically associated with its stimulant-like properties. Similarly, bupropion is well-documented to cause a variety of hypersensitivity reactions, especially dermatologic in nature. Several reports of various hypersensitivity reactions, including SSL reactions, Stevens-Johnson syndrome, pityriasis rosea–like reaction, and psoriasis, were captured by our search but not included, given their more immediate onset.[17-20] There remains more limited information about delayed allergic reactions associated with bupropion, particularly with onset more than 2 weeks from the time of bupropion initiation.

The emphasis of this review involved patients who experienced delayed hypersensitivity reactions more than 2 weeks after initiating bupropion. The precise mechanism by which bupropion may induce delayed reactions is not well understood and is likely influenced by several factors. Bupropion is known to modulate norepinephrine and dopamine, which may influence immune responses.[21] It is also hypothesized that bupropion and/or its metabolites could act as haptens. Haptens are protein-drug-linked complexes that can trigger an immune response, including the production of antibodies.[22] These complexes may accumulate gradually over

time until reaching a threshold that triggers an immune and/or inflammatory response and could explain why this reaction takes longer to manifest.[22] Other factors, such as preexisting allergic conditions, may contribute to the development of delayed allergic reactions to bupropion. Several patients included in the literature review had a history of allergic reactions to other drugs and/or foods. The findings from our case and the reviewed literature suggest a potential risk profile for bupropion-induced delayed allergic reactions as follows: male individuals aged 17 to 40 and those with a history of allergic reactions. The meta-analysis from our review reported younger patients as being more prone to experiencing angioedema and SSL reactions.[16] Additionally, Hu and colleagues[7] reported that bupropion use was associated with a higher risk of urticaria in patients under 40 years old, and history of urticaria was the only independent risk factor for bupropion-associated urticaria. Given these findings, it is important for healthcare professionals to remain vigilant in monitoring patients during the first 6 weeks of bupropion treatment, especially in younger patients (<40 years) with a history of allergies.

In all cases reviewed, adverse reactions led to the discontinuation of bupropion and often the use of antihistamines and/or corticosteroids. Early recognition and prompt discontinuation of bupropion is vital to prevent further complications and improve patient outcomes. A salient limitation of our report includes the absence of objective laboratory tests to confirm urticaria or hypersensitivity. The patient in our case was managed in a manner consistent with most typical outpatient allergic drug reactions (ie, suggestive findings on exam, including scratch marks, diffuse erythema, scratching during the exam; evaluating worsening, remitting, and confounding factors; use of antihistamines; reliance on a patient report) but visual observation of urticaria by the provider did not occur, likely because the patient self-administered antihistamines immediately before the visit. The number of published cases on this topic remains somewhat limited, and larger prospective studies are needed to better understand risk factors and mechanisms underlying delayed allergic reactions to bupropion. Despite these limitations, healthcare professionals should consider bupropion as a potential cause of unexplained skin reactions. Further research is warranted to better understand the pathophysiology and identify susceptible populations for targeted risk assessment and management strategies.

Conclusion

Bupropion is associated with delayed hypersensitivity reactions, including delayed urticaria and pruritis. The risk for this reaction may be highest in male patients aged 17 to 40 and those with a history of allergic reactions. Clinicians should be vigilant in monitoring this reaction as its delayed onset may increase the risk of attributing hypersensitivity to other causes.

References

1. Pichler WJ. Drug Allergy: Pathogenesis [Internet]. Pocatello (ID): UpToDate; [cited 2024 Jun 13]. Available from: https://www-uptodate-com.libpublic3.library.isu.edu/contents/drug-allergy-pathogenesis?search=types%20of%20allergic%20reactions&source=search_result&selectedTitle=3%7E150&usage_type=default&display_rank=3#references
2. Abbas M, Moussa M, Akel H. Type I Hypersensitivity Reaction. *StatPearls*. StatPearls Publishing; 2023.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharacol Ther. 1981;30:239-45. DOI: 10.1038/clpt.1981.154
4. Gutierrez N, Malik S, Cohen PR, Winn AE. Bupropion-associated delayed onset urticaria. Cureus. 2021;13:e18297. DOI: 10.7759/cureus.18297
5. Puri S, Coplan BM, McGuire PR. Delayed onset of bupropion-induced urticaria. Prim Care Companion CNS Disord. 2020;22:19l02508. DOI: 10.4088/PCC.19l02508
6. Benson E. Bupropion-induced hypersensitivity reactions. Med J Aust. 2001;174:650-1. DOI: 10.5694/j.1326-5377.2001.tb143479.x11480688
7. Hu LY, Liu CJ, Lu T, Hu T-M, Tsai C-F, Hu Y-W, et al. Delayed onset urticaria in depressive patients with bupropion prescription: a nationwide population-based study. PLoS One. 2013;8:e80064. DOI: 10.1371/journal.pone.0080064
8. Lineberry TW, Peters GE Jr, Bostwick JM. Bupropion-induced erythema multiforme. Mayo Clin Proc. 2001;76:664-6. DOI: 10.5021/ad.2015.27.3.334
9. Tackett AE, Smith KM. Bupropion-induced angioedema. Am J Health Syst Pharm. 2008;65:1627-30. DOI: 10.2146/ajhp070575
10. Loo WJ, Alexandroff A, Flanagan N. Bupropion and generalized acute urticaria: a further case. *Br J Dermatol*. 2003;149:660. DOI: 10.1046/j.1365-2133.2003.05509.x
11. Tuman TC, Tuman BA, Göksügür N, Kayka N, Yıldırım O. Urticaria and angioedema associated with bupropion: three cases. Prim Care Companion CNS Disord. 2016;18. DOI: 10.4088/PCC.15l01916
12. Singh PA, Cassel KP, Moscati RM, Eckersley D. Acute generalized erythrodermic pustular psoriasis associated with bupropion/naltrexone (Contrave®). J Emerg Med. 2017;52:e111-3. DOI: 10.1016/j.jemermed.2016.11.034
13. Thurman RJ, Hadley ED 3rd. Young woman with diffuse pustular rash. Ann Emerg Med. 2016;67:576-87. DOI: 10.1016/j.annemergmed.2015.11.001
14. Cartwright AM, Shaw JT, Traiger D. Bupropion-induced delayed hypersensitivity serum sickness-like reaction. Cureus. 2023;15:e36158. DOI: 10.7759/cureus.36158
15. Nguyen CV, Miller DD. Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern. J Cutan Pathol. 2017;44(2):177-82. DOI: 10.1111/cup.12863
16. Beyens MN, Guy C, Mounier G, Laporte S, Ollagnier M. Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. Drug Saf. 2008;31:1017-26. DOI: 10.2165/00002018-200831110-00006
17. Caldas R, Campos-Lopes S, Guimarães MJ, Areal J, Alves M, Pereira T. Patch test-proven delayed-type hypersensitivity from naltrexone/bupropion possibly eliciting psoriasis. Contact Dermatitis. 2021;85:456-8. DOI: 10.1111/cod.13875

18. Polat M, Uzun Ö, Örs I, Boran Ç. Pityriasis rosea-like drug eruption due to bupropion: a case report. Hum Exp Toxicol. 2014;33(12):1294-6. DOI: 10.1177/0960327113478444
19. Surovik J, Riddel C, Chon SY. A case of bupropion-induced Stevens-Johnson syndrome with acute psoriatic exacerbation. J Drugs Dermatol. 2010;9(8):1010-2. PMID: 20684153
20. Peloso PM, Baillie C. Serum sickness-like reaction with bupropion. JAMA. 1999;282:1817. DOI: 10.1001/jama.282.19.1817
21. Channer B, Matt SM, Nickoloff-Bybel EA, Pappa V, Agarwal Y, Wickman J, et al. Dopamine, immunity, and disease. Pharmacol Rev. 2023;75:62-158. DOI: 10.1124/pharmrev.122.000618
22. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009;7:911-8. DOI: 10.1111/j.1538-7836.2009.03360.x