

Bupropion and alopecia

Introduction

Bupropion (Wellbutrin® or Zyban®) is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit monoamine oxidase A or B. It is indicated for *the treatment of depression* (Wellbutrin®) and as *an aid to smoking cessation in combination with motivational support in nicotine-dependent patients* (Zyban®). The mechanism of action as an antidepressant and the mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion was granted market authorisation in the Netherlands in 1999 (Zyban®) and 2007 (Wellbutrin®)[1;2].

Hair loss is a common clinical complaint, resulting from a wide variety of causes. The human scalp contains approximately 100,000 to 150,000 hair follicles. Once formed, hair follicles undergo lifelong cycling characterized by periods of growth (anagen), transformation (catagen), and rest (telogen). At any given time, 90 percent of hair follicles on the scalp are in the anagen phase. The duration of the anagen phase determines the maximum length of hair growth. Hair loss may occur due to disorders of hair cycling, inflammatory conditions that damage hair follicles, or inherited or acquired abnormalities in hair shafts. Hair loss can occur diffuse or localized and be acute or chronic. It can be caused by drugs by interference of the normal cycle of scalp hair growth. This can lead to two types of hair loss: a telogen effluvium (most common and usually appearing two to four months after start of drug intake) or an anagen effluvium (usually after a few days to weeks after drug initiation)[3].

Reports

From February 2003 until July 2019 the Netherlands Pharmacovigilance centre Lareb received 13 reports of alopecia associated with the use of bupropion.

Table 1. Reports of bupropion associated with alopecia in the Lareb database

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
NL-LRB-38976, F, 30-40, Pharmacist	bupropion tablet mga 150mg for smoking cessation		1: Adjustment disorder with depressed mood, 2: Affect lability, 3: Alopecia, 4: Dry mouth, 5: Dysgeusia, 6: Headache, 7: Hyperhidrosis, 8: Pollakiuria, 9: Sleep disorder	3: TTO unknown Drug withdrawn Recovered/resolved
NL-LRB-89048, F, 50-60, Pharmacist	bupropion tablet mga 150mg for unspecified psychiatric symptoms	rabeprazole, mebeverine, acetylsalicylic acid, furosemide, nifedipine, losartan, rosuvastatin, allopurinol, levomepromazine, quetiapine, risperidone, oxazepam, lormetazepam, escitalopram	1: Alopecia	1: 5 Days Dose not changed Not recovered/not resolved/ongoing
NL-LRB-92662, M, 30-40, Specialist doctor	bupropion tablet mga 150mg for attention deficit-hyperactivity disorder		1: Alopecia	1: 2 Weeks Drug withdrawn Not recovered/not resolved/ongoing

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
NL-LRB-141749, M, 30-40, Consumer	bupropion tablet mga 300mg for attention deficit/hyperactivity disorder		1: Alopecia	1: 4 Weeks Dose not changed Not recovered/not resolved/ongoing
NL-LRB-156197, F, 50-60, Consumer	bupropion tablet mga 150mg for attention deficit/hyperactivity disorder	nifedipine	1: Alopecia	1: 0 Days Drug withdrawn Recovering/resolving
NL-LRB-157758, F, 50-60, Pharmacist	bupropion tablet mga 150mg for psychiatric disorder NOS	pantoprazole, simvastatin, hepatitis a vaccination, DTP vaccination, clonidine, quetiapine, desloratadine	1: Alopecia	1: 2 Months Drug withdrawn Outcome unknown
NL-LRB-164773, M, 40-50, Specialist doctor	bupropion tablet mga 300mg for attention deficit/hyperactivity disorder		1: Alopecia	1: 6 Months Drug withdrawn Recovered/resolved
NL-LRB-188540, M, 20-30, Pharmacist	bupropion tablet mga 300mg for depression	magnesiumoxide	1: Alopecia,2: Presyncope,3: Sleep disorder	1: 2 Years Dose not changed Not recovered/not resolved/ongoing
NL-LRB-249677, M, 20-30, Consumer	bupropion tablet mga 300mg for depression		1: Alopecia	1: 5 Hours Dose reduced Recovering/resolving
NL-LRB-249882, M, 30-40, Specialist doctor	bupropion tablet mga 150mg for anxiety disorder		1: Alopecia	1: 3 Months Drug withdrawn Recovering/resolving
NL-LRB-250436, F, 40-50, Consumer	bupropion tablet mga 150mg for depressed mood		1: Alopecia,2: Arthralgia,3: Constipation,4: Coordination abnormal	1: 2 Days Drug withdrawn Recovering/resolving
NL-LRB-00306368, F, 20-30, Psychiatrist	bupropion tablet mga 150mg for anxiety and mood swings	quetiapine	1: Alopecia	1: 24 Days Dose not changed Outcome unknown
NL-LRB-00343160, F, 20-30, Psychologist	bupropion tablet mga 150mg for attention deficit/hyperactivity disorder and depressed mood	zolpidem	1: Alopecia	1: 4 Months Drug withdrawn Recovering/resolving

Additional information on the cases is given below:

Case NL-LRB-249677: hair loss following dose increase from 150 mg to 300 mg. After dose reduction the hair loss improved. Another factor that could have contributed in this patient is a family history of hair loss.

Case NL-LRB-250436: hair loss following dose decrease from 300 mg to 150 mg. Blood tests revealed no abnormalities besides a slightly low vitamin D level.

Case NL-LRB-249882: previous use also resulted in hair loss after three months. Blood tests revealed no abnormalities.

Case NL-LRB-00343160: the patient also had a vitamin D deficiency.

Other sources of information

SmPC

The Dutch SmPC of bupropion does not mention alopecia as an adverse reaction[1;2]. However, the US SmPCs of Zyban as well as Wellbutrin mentions alopecia as an adverse event identified during postmarketing experience with bupropion[4;5].

Literature

A retrospective cohort study by Etminan et al.[6] aimed to quantify the risk of hair loss with different antidepressants. They used a large health claims database in the USA from 2006 to 2014. A cohort of new user and mutually exclusive users of fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, desvenlafaxine, and bupropion were followed to the first diagnosis of alopecia. The cohort was comprised of 1,025,140 new users of fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, desvenlafaxine, and bupropion. Compared with bupropion, all other antidepressants had a lower risk of hair loss, with fluoxetine and paroxetine having the lowest risk. The results of this large population-based cohort study suggest an increase in the risk of hair loss with bupropion (HR=1.46, 95% CI: 1.35-1.58) compared with selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors.

Databases

Table 2. Reports of alopecia associated with the use of bupropion in the Lareb, WHO and Eudravigilance database[7;8]

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	bupropion	alopecia	13	1.0 [0.6-1.7]
WHO	bupropion	alopecia	720	1.5 [1.4-1.6]
Eudravigilance	bupropion	alopecia	80	0.7 [0.6-0.9]

Prescription data[9].

Drug	2013	2014	2015	2016	2017
bupropion	15,433	19,944	21,768	24,479	25,039

Mechanism

The mechanism by which bupropion is linked to hair loss is likely because of its dopaminergic pharmacology. Dopamine has been shown to play an important role in hair follicle cycling. Several cases of hair loss have been reported with dopamine agonists[10]. Furthermore, prolactin receptors are present in human hair follicles and a decrease in prolactin levels by dopamine agonists might lead to alopecia[6;11].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received thirteen reports of alopecia associated with the use of bupropion. Bupropion was used as an aid to smoking cessation in one patient and for depression and attention deficit/hyperactivity disorder in the other patients. These reports concerned both women and men, with ages varying from 23 to 58 years. Although time to onset was short in some reports (hours and days), the median latency was 6 weeks. A latency of two to four months would suggest a telogen effluvium which is most common. The causal link between bupropion and alopecia is further supported by a positive dechallenge in half of the patients and a positive rechallenge in one patient.

Alopecia is labelled in the US SmPC of bupropion. A retrospective cohort study showed that, compared with other antidepressants, bupropion had an increased risk of hair loss. The association of bupropion and alopecia is supported by a statistically significant disproportionality in the database of WHO.

Reference List

- (1) Dutch SmPC Wellbutrin. https://www.geneesmiddeleninformatiebank.nl/smpc/h33668_smpc.pdf (last updated 2017 September 18, cited 2019 Sep 25).
- (2) Dutch SmPC Zyban. https://www.geneesmiddeleninformatiebank.nl/smpc/h24160_smpc.pdf (last updated 2017 September 18, cited 2019 Sep 25).
- (3) Shapiro J, Hordinsky M. Evaluation and diagnosis of hair loss. Up to Date® 2019 April 17 [cited 2019 Sep 25]; Available from: URL: <http://www.uptodate.com/>
- (4) US SmPC Wellbutrin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20358s27lbl.pdf (last updated 2017 August 11, cited 2019 Sep 25).
- (5) US SmPC Zyban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020711s048lbl.pdf (last updated 2019 July 19, cited 2019 Sep 25).
- (6) Etminan M, Sodhi M, Procyshyn RM, Guo M, Carleton BC. Risk of hair loss with different antidepressants: a comparative retrospective cohort study. *Int Clin Psychopharmacol* 2018 Jan;33(1):44-8.
- (7) Eudravigilance database. <http://bi.eudra.org> (access restricted) 2019.
- (8) WHO database Vigilyze. <https://vigilyze.who-umc.org/#/> 2019.
- (9) GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board. <http://www.gipdatabank.nl> (last updated 2019 June 27, cited 2019 Sep 25).
- (10) Miwa H, Kondo T. Hair loss induced by dopamine agonist: case report and review of the literature. *Parkinsonism Relat Disord* 2003 Oct;10(1):51-2.
- (11) Foitzik K, Krause K, Conrad F, Nakamura M, Funk W, Paus R. Human scalp hair follicles are both a target and a source of prolactin, which serves as an autocrine and/or paracrine promoter of apoptosis-driven hair follicle regression. *Am J Pathol* 2006 Mar;168(3):748-56.

This signal has been raised on November 21, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl