Bupropion and acute generalised exanthematous pustulosis (AGEP)

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].

Acute generalised exanthematous pustulosis (AGEP) is a rare, acute eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema. Fever and peripheral blood leukocytosis are usually present. In approximately 90 percent of cases, AGEP is caused by drugs, most often antibiotics (eg, aminopenicillins and macrolides), antifungals, the calcium channel blocker diltiazem, and antimalarials. The eruption develops within hours or days of drug exposure and resolves spontaneously in one to two weeks after drug discontinuation. A rough estimate of the incidence of AGEP is one to five cases per million persons per year. AGEP can occur at any age, although it most often affects adults. Both sexes are affected, with a slight female predominance. The diagnosis of AGEP is based upon the clinical presentation and histologic examination of a skin biopsy[3].

Reports
Until May 2020 the Netherlands Pharmacovigilance centre Lareb received one report of AGEP associated with the use of bupropion.

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This spontaneous report from a dermatologist concerns a male aged 70 years and older, with AGEP following administration of bupropion tablet 150mg for smoking cessation therapy. AGEP occurred two days after start. Bupropion was withdrawn and the patient was treated with clobetasol cream. He is recovering from AGEP. A skin biopsy was taken to confirm the diagnosis. Concomitant medication was omeprazole, aclidinium, simvastatin, hydrochlorothiazide, acetylsalicylic acid, triamcinolonacetonide, amlodipine, salmeterol/fluticasone and acetylcysteine.

Other sources of information

SmPC

The Dutch SmPC and the US SmPC of bupropion do not mention AGEP as an adverse reaction [1;2;4;5].

Literature

There are three case reports of AGEP associated with the use of bupropion:

Tak et al.[6] describe a 30-year-old woman who developed AGEP one day after start of bupropion for smoking cessation. A skin biopsy was taken to confirm the diagnosis. She discontinued the bupropion treatment after the eruption and fever appeared. Intravenous methylprednisolone (40 mg/day) was administered for four days. In addition, a topical corticosteroid and an oral analgesic and antihistamine were used. Within 10 days she recovered. The EuroSCAR validated scale* suggested that this case was definitely caused by bupropion.

*The AGEP validation score of the EuroSCAR study group can be used to establish the diagnosis of AGEP. This scoring system ranges from 0 to 12. A score between 8 and 12 for AGEP is a definitive diagnosis.

Thurman et al.[7] describe a 29-year-old woman who presented to the emergency department (ED) for evaluation of a diffuse pustular rash that started 3 days before arrival. The rash had progressed to include her back, abdomen, extremities, and torso, but she had no mucosal involvement. She noted some areas of skin desquamation as well. She reported subjective fevers and intense pruritus but

generally felt well. She had begun receiving bupropion 2 weeks before the onset of the rash and was receiving no other prescription medications. Laboratory study results were remarkable only for a mild leukocytosis. Because of the extent of the rash, a skin biopsy was performed and cultures of the pustular fluid were sent. Diagnosis was made: AGEP. The authors state that treatment of AGEP is generally supportive, and with removal of the offending agent symptoms typically resolve in 1 to 2 weeks.

Ray [8] report a 43-year-old female with AGEP starting 10 days after taking bupropion 100 mg orally twice daily for worsening of her depressive symptoms. She also had malaise and fever. A skin biopsy revealed AGEP. Discontinuation of the bupropion and supportive care resulted in significant improvement of all symptoms in four days. The EuroSCAR scale suggested that this case was definitely caused by bupropion.

Databases

Table 2. Reports of AGEP associated with the use of bupropion in the Lareb, WHO and Eudravigilance database[9;10]

Database	Drug	ADR	Number of reports	ROR (95% CI)
Lareb	bupropion	AGEP	1	-
WHO	bupropion	AGEP	15	0.9 [0.5-1.5]
Eudravigilance	bupropion	AGEP	7*	0.6 [0.3-1.3]

*See Addendum 1 for the cases from Eudravigilance.

The seven cases in Eudravigilance consist of four supportive cases, of which one is the Lareb case and two are literature cases (the cases described by Thurman et al[7] and Ray [8]). The other supportive case concerns a 47-year-old female who received bupropion for depression. Seven days after start of bupropion, AGEP developed. Bupropion was withdrawn and she was treated with an unspecified treatment at the hospital. She recovered from AGEP. Concomitant medication consisted of insulin, melatonin, omeprazole, alimemazine, amlodipine, metformin and venlafaxine.
The other cases are less supportive and concern a case that reported an aggravation of psoriasis which proved to be AGEP after a skin biopsy was taken, a case that is primarily about aripiprazole as suspect drug and a very brief case with little information.

Prescription data [11].

Drug	2014	2015	2016	2017	2018
Bupropion (Wellbutrin®)*	19,944	21,768	24,479	25,047	26,551

*Only prescription data from bupropion (Wellbutrin®) are available in the GIP databank and not of bupropion (Zyban®) due to the reimbursement status of this product.

Mechanism

There are several theories on the pathogenesis of AGEP. Britschgi et al [12] suggested a T-cell mediated mechanism, as evidenced by positive findings on patch tests and lymphocyte transformation tests. Moreau et al [13] proposed that AGEP is a delayed-type hypersensitivity reaction. Another possible mechanism is the production of antigen-antibody complexes induced by an infection or drug that activates the complement system, which in turn leads to neutrophil chemotaxis [14]. More recently, a new concept called pharmacological interaction has been developed to explain drug-induced hypersensitivity reactions. This concept implies direct, reversible interactions of the drug with T-cell receptors and is classified as a T-cell mediated reaction[15]. Tak et al proposes that bupropion caused AGEP in their patient probably through this pharmacological interaction [6].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received one report of AGEP associated with the use of bupropion from a dermatologist. Bupropion was used as an aid to smoking cessation in this patient. A skin biopsy confirmed the diagnosis of AGEP. The databank Eudravigilance contains seven cases. In

the literature three case reports have been described of which two can be found in Eudravigilance. Two literature cases determined the causation of AGEP by bupropion as definite according to the EuroSCAR validated scale. AGEP is not labelled in the Dutch or US SmPC of bupropion. AGEP induced by bupropion is probably rare, but can have a severe course. Prompt withdrawal of bupropion is necessary. Clinicians prescribing bupropion should be aware of this possible severe adverse reaction.

Reference List
(1) Dutch SmPC Wellbutrin. https://www.geneesmiddeleninformatiebank.nl/smpc/h33668_smpc pdf.
(2) Dutch SmPC Zyban. https://www.geneesmiddeleninformatiebank.nl/smpc/h24160_smpc pdf.
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(5) US SmPC Zyban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020711s048lbl pdf
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(7) Thurman RJ, Hadley ED. Young woman with diffuse pustular rash. Ann Emerg Med 2016 May;67(5):576-87.
(8) Ray AK, Wall GC. Bupropion-induced acute generalized exanthematous pustulosis. Pharmacotherapy 2011 June;31(6):621.
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(12) Britschgi M, Steiner UC, Schmid S et al. T-cell involvement in drug-induced acute generalized exanthematous pustulosis. J Clin Invest 2001;107(11):1433-1441.
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(14) Beylot C, Doutre MS, Beylot-Barry M. Acute generalized exanthematous pustulosis Semin Cutan Med Surg 1996;15(4):244-249.
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This signal has been raised on October 22, 2020. 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.cbg-meb.nl