Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Bupropion and suicidality

Introduction

In December 1999 bupropion (Zyban®) was granted a marketing authorization as *an aid to smoking cessation treatment*. The Netherlands is reference member state in the European Mutual Recognition Procedure. In several countries bupropion had been admitted long before as an antidepressant. Bupropion is a relatively weak selective inhibitor of the neuronal re-uptake of dopamine, serotonin and noradrenalin, but it is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors or other known anti-depressants. The mechanism by which bupoprion is effective in smoking cessation treatment is not entirely understood.
Several neuropsychiatric adverse reactions are listed in section 4.8 'undesirable effects' of the Dutch SPC of Zyban® including *depression in 0.1 – 1% of patients with reference to section 4.4*. In section 4.4 'Special warnings and special precautions for use' it is stated that *depression can be a symptom of nicotine abstinence. Depression, rarely accompanied by suicidal ideation, has been reported in patients trying to quit smoking. These symptoms have also been reported during treatment with Zyban® and in general occur early during treatment* [1].

Reports

Until 1 March 2006, the Netherlands Pharmacovigilance Centre Lareb received in total 518 reports of suspected adverse reactions on bupropion. In 134 reports on bupropion an ADR belonging to the 'system organ class Psychiatric Disorders' was present of which in 37 reports depression was diagnosed.
Suicidality, including attempted suicide, was explicitly reported in 15 of these 37 reports (table 1).

Table 1. Reports of suicidality associated with the use of bupropion

Patient, sex, age	latency	Suspected adverse drug reaction	Concomitant medication	Dechallenge
A, F, 80	5 weeks	thoughts of self harm depression	diazepam enalapril hydrochlorothiazide furosemide	positive (2 weeks)
B, F, 34	2 weeks	suicidal tendency nausea insomnia, emotional lability	microgynon 30	positive (?)
C, M, 59	unknown	suicidal tendency depression agitated	flixotide ventolin serevent	positive (?)
D, F, 49	4 day	suicidal tendency depression aggravated	seroxat seretide orgametril naproxen	positive (2 weeks)
E, M, 47	unknown	suicidal tendency depression paraesthesia palpitation	selektine acenocoumarol lisinopril oxazepam	negative (5 months)

F, F, 46	unknown	suicidal tendency depression paraesthesia palpitation	-	negative (5 months)
G, F, 31	3 day	suicidal tendency depression	ibuprofen flixonase	positive (10 days)
H, M, 50	unknown	suicidal tendency depressed reaction	-	positive (? days)
I, M, 49	12 day	suicidal tendency depression	risperidon	unknown
J, F, 53	unknown	thoughts of selfharm, depression, emotional lability, agitation	oxazepam zolpidem	negative (1 day)
K, M, 42	11 weeks	suicide attempt	temazepam	unknown
L, M, 40	9 day	suicidal ideation hallucination visual panic reaction	-	negative
N, F, 50	4 day	suicidal tendency depression	-	positive (12 days)
O, M, 40	unknown	suicidal tendency depressed state, muscle spasm, anxiety	-	
P, F, 33	6 day	suicidal ideation depression, crying	-	positive (17 days) after dose reduction

Patients D and I had a previous medical history of depression

It is important to distinguish between nicotine withdrawal symptoms and adverse reactions caused by concomitant smoking-cessation treatment with bupropion, especially when neuropsychiatric symptoms and signs are concerned. Nicotine withdrawal can cause agitation, depression, irritability, impairment of concentration and of memory, sweating, insomnia and weight increase.

Since instructions for use indicate smoking to be stopped in the second week of treatment with bupropion, a short latency of symptoms suggests an adverse reaction to bupropion rather than nicotine withdrawal symptoms [2]. This applies to cases D, G, N and P in which also a positive dechallenge with a latency of 10-17 days was reported after dose reduction or discontinuation of bupropion treatment. It must be stated however, that exact data on smoking cessation in these particular patients are lacking.

Other sources of information

Literature

In a recent Cochrane review of antidepressant medications to alternative therapies for smoking cessation it is concluded from data of the MHRA in 2004 and the TGA in 2004 that the concerns that bupropion may increase suicide risk are currently still not conclusive [3].

Databases

In the Lareb database, suicide or suicide attempt is reported in 40% (15 out of 37) of the reports of depression on bupropion. In reports on other drugs, suicide

(attempt) is reported only in 5% of the reports concerning depression (ROR 13.4; 95% CI 6.5 – 28).

In 11 out of the 15 above mentioned reports, suicidality is the only other psychiatric symptom that was reported in addition to depression. This is remarkable because suicidality is just one of the 9 possible symptoms used to diagnose depression according to DSM-IV and to the Dutch College of General Practitioners Guideline Depressive disorder [NHG Standaard Depressieve stoornis (depressie) M44] [4]. To our reporters suicidality seems to be a distinguishing addition to the diagnosis depression, indicating increased severity or unexpectedness.

Disproportionality data of the database of the WHO is of limited value since the indication for use of bupropion – either smoking cessation or depression - is not always listed.

Mechanism

There are two mechanisms by which antidepressants might help in smoking cessation. First, depression may be a symptom of nicotine withdrawal, and smoking cessation sometimes precipitates depression. This depression is treated by the antidepressant. Second, nicotine may have an antidepressant effect that maintains smoking for some smokers. Antidepressants may substitute for this effect. Noradrenalin and dopamine play an important role in nicotine addiction. Nicotine stimulates the release of these neurotransmitters in various parts of the brain [3]. Antidepressants that affect these neurotransmitters may be beneficial in smoking cessation.

Discussion

Bupropion is an antidepressant but for the indication ‘smoking cessation’ it is prescribed to individuals who are not diagnosed as depressed. Suicidality was explicitly reported in 40% of the reports on depression associated with use of bupropion. In 4 out of 15 reports to Lareb suicidality occurred during the first week of treatment when smoking was not yet stopped. Therefore there is no confounding by nicotine withdrawal symptoms. More over in these 4 instances a positive dechallenge was also reported. One of these 4 individuals had a previous medical history of depression.
The text in the Dutch SPC under section 4.8 ‘warnings and precautions’ states that psychotic and manic symptomatology have been reported mainly in patients with a history of psychiatric illness[1]. This suggest that this particular subgroup is more prone to develop serious psychiatric reactions.

The Marketing Authorisation holder reviewed reports of suicidality (suicidal ideation, suicide attempts and completed suicides) during the European Article 36 referral in 2002, which resulted in a positive benefit-risk of bupropion at that time. However, based on the aforementioned reports, the Netherlands Pharmacovigilance Centre Lareb has the opinion that vigilance for this possible adverse drug reaction in warranted.

References
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2. Graaf L de, Monster-Simons MH Stoppen met roken induceert neveneffecten. Neuropsychiatrische bijwerkingen tijdens gebruik van bupropion Pharm Weekbl 2003; 32: 1126-28
3. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD000031.pub2. DOI: 10.1002/14651858.CD000031.pub2.
4. NHG Standaard Depressieve stoornis (depressie) M44 (oktober 2003) http://nhg.artsennet.nl/upload/104/standaarden/M44/start.htm