CNS demyelination after treatment with bupropion
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Citation

Abstract
We present a case of presumed inflammatory central nervous system demyelination in association with the use of bupropion for smoking cessation. The patient developed paraesthesias and Lhermitte's phenomenon shortly after starting the drug. There were oligoclonal bands in cerebrospinal fluid and white matter lesions in the cerebral hemispheres and cervical spinal cord. The case is discussed in the light of the known side effects of the drug.

INTRODUCTION
Bupropion is an antidepressant of the aminoketone class, chemically unrelated to the tricyclics or SSRIs, and has been available in the USA for almost 20 years. It was licensed in the UK in 2000 under the trade name Zyban specifically as an aid for smoking cessation. It acts by relatively weak but selective inhibition of both noradrenaline and dopamine reuptake in the CNS and is presumed to facilitate smoking cessation by modulating pathways involved in addiction and withdrawal. Recognised neurological side effects of bupropion include insomnia and seizures. However as far as we can ascertain from the literature, this is first reported association with demyelination.

CASE PRESENTATION
A 45 year-old right-handed practice manager was prescribed Zyban 150 mg daily by her General Practitioner for smoking cessation. After the first dose she was aware of numbness in her lower abdomen and on the following day her right leg began to tingle. This worsened over the next two days and by day four had spread to her right hand and forearm at which point she stopped taking the drug and sought medical advice. Over the next four weeks the symptoms resolved in her abdomen and leg resolved, but an unpleasant ice-like sensation and clumsiness in her right hand and forearm persisted and Lhermitte phenomenon developed. No motor or sphincter disturbance occurred. There was no preceding illness and she was systemically well throughout. Her past medical history was unremarkable apart from an episode of viral meningitis six years previously and she was not taking any other medication.

On examination three weeks after the onset of symptoms, she had reduced sensation in the right hand and forearm to light touch, and altered sensation to light touch at T12 on the right thorax. The motor and cranial nerve examinations were normal.

MRI four weeks after her first symptoms revealed multiple abnormal foci of increased T2 signal within the periventricular and subcortical white matter of both cerebral hemispheres (figure 1). The cervical cord also contained a focus of increased T2 signal at the level of C4 (figure 2). Oligoclonal bands were present in cerebrospinal fluid, but negative in serum, with a white count of less than 1, glucose ratio 3.1/4.3 mmol/l (csf/serum), and protein 0.24 g/l. Other screening blood test including ESR, FBC, U&E, LFT, Ca, P04, B12, folate, RPR, ANCA, ENA, ANA were negative or normal.

She was empirically treated with a reducing dose of oral prednisolone, for a putative inflammatory process, on the basis of both the MRI appearances and oligoclonal band status, starting at 60 mg per day for three weeks. MRI three months after onset showed no new lesions and, although the original lesions in the brain and cervical spine persisted, the appearances were those of a resolving inflammatory lesion.

Eleven months after the onset, altered sensation persisted in the right hand but the other symptoms, including Lhermitte's phenomenon, had resolved.
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Figure 1
Figure 1: T2 weighted MRI brain.

Figure 2
Figure 2: T2 weighted MRI cervical spine.

DISCUSSION
The following is based on information gathered by searching Medline 1950 to date, Embase 1980 to date, Psychinfo 1985 to date, Cochrane Database of Systematic Reviews, DARE, HTA, EED, TRIP database, as well as general web searching. We also communicated personally with the Medicines and Healthcare products Regulatory Authority (MHRA), the UK equivalent of the USA's Food and Drug Administration (FDA).

Bupropion is known to have CNS side effects. In fact shortly after its first release in the USA it had to be reformulated owing to an unacceptably high incidence of seizures2 (approximately 0.4% at 300 – 450 mg daily rising to 10 times this risk at doses over 600 mg daily3). It was subsequently re-released as the currently available lower dose sustained release preparation. The risk of seizures in clinical practice today is approximately 0.1%2,3.

Around the time of bupropion's re-formulation GlaxoSmithKline (the maker) funded two large trials that reported relatively low rates of adverse reactions. In these studies only 6%-8%4 and 11.9%5 of patients discontinued the drug because of adverse reactions. However, despite fears about inadequate reporting of adverse reactions in some countries6, as experience with the drug grew some investigators suggested significantly more frequent adverse reactions occur in clinical practice than were reported in the initial trials. In one study 31% of patients taking 300mg and 26% on 150mg bupropion discontinued the drug8.

The MHRA, which keeps a database of adverse drug reactions in the UK, received 7,360 reports of suspected adverse reactions in the first two years after the drug was licensed there9. Among the most frequent were insomnia, headache, dizziness, tremor and agitation. However some of these symptoms may relate to nicotine withdrawal given that the patients were being treated for smoking cessation.

The MHRA has only received four reports (not including our case) since 2000 mentioning demyelination in association with the use of bupropion10. However, three of these were exacerbations of the symptoms of pre-existing multiple sclerosis. The fourth patient had been well before starting the drug and experienced shakiness, falls, visual disturbance and hearing impairment after 5 months of treatment for depression. The patient was not admitted to hospital for investigation until a further five months later and was subsequently diagnosed with multiple sclerosis.

Whether or not bupropion was responsible for our patient's illness is debatable. However, the clear temporal relationship between the drug and both the onset and resolution of symptoms is suspicious. Furthermore bupropion is known to be immunogenic. Rash, pruritus and angioedema are
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relatively common, and symptoms of delayed hypersensitivity and serum sickness-like reactions have also been reported. Thus it is conceivable that in a susceptible individual the drug might trigger autoimmune destruction of CNS myelin. We must continue to monitor the drug, and to be diligent in reporting adverse reactions.

References
10. MHRA Personal communication.
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