

# Zyban: an effective treatment for nicotine addiction

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**Recent research has identified nicotine as a powerfully addictive substance. This article outlines how the new non-nicotine smoking cessation drug, Zyban, can help people to break the cycle of addiction and stop smoking.**

In the UK it is estimated that one in three adults aged 16 years of age and over are smokers, which equates to a total of approximately 13 million adult smokers in Britain (Department of Health, 1998).

The recent Royal College of Physicians report (Britten, 2000) on nicotine addiction states 'tobacco dependence is a serious form of drug addiction', emphasizing that tobacco addiction is as powerful as addiction to hard drugs such as heroin and cocaine. The World Health Organization's *International Classification of Diseases* (ICD-10; World Health Organization, 1992) lists tobacco dependence as a disease, and the American Psychiatric Association's (1987) *Diagnostic and Statistical Manual*, which classifies mental and behavioural disorders, supports this view and lists tobacco use as a dependence disorder.

Recent literature has demonstrated that: 'As an active substance, nicotine, on a milligram for milligram basis is 10 times more potent than heroin...' (Sachs, 1991).

Research indicates that willpower alone is usually not enough to break the cycle of nicotine addiction. Only 3% of unaided quit attempts succeed in the long term (Arnsten, 1996). Nicotine, like other drugs of addiction, stimulates the release of brain neurotransmitters dopamine, noradrenaline and acetylcholine (Benowitz, 1999). The cravings and withdrawal symptoms on stopping smoking are considered the major barrier to quitting.

Evidence shows that giving pharmacological treatment in combination with advice and support is the most effective way of helping smokers to quit (Thompson and Hunter, 1998), and the current smoking cessation guidelines emphasize that support and pharmacotherapy have

been shown to be the most effective strategy (Raw et al, 1998). It is also recognized that smoking cessation is one of the most cost-effective health interventions that can be made, £174 per life-year saved compared to statin therapy which costs £11 440 per life-year saved (Parrott et al, 1998) (*Tables 1 and 2*). Nicotine replacement therapy has helped many patients stop smoking; however, the introduction of Zyban (bupropion hydrochloride sustained release, Glaxo Wellcome, North Carolina) represents a unique approach to smoking cessation.

### ZYBAN

Zyban was initially discovered when researchers noticed that some of the patients who were taking a different formulation of the drug (Wellbutrin, Glaxo Wellcome, North Carolina) for depression were spontaneously giving up smoking. This was a surprising outcome, as smoking cessation in non-depressed patients is very difficult. Clinical evaluations have since revealed that administered at a lower dose in a slow release formulation, Zyban can be effective in smoking cessation (Jorenby et al, 1999) (*Figure 1*).

Zyban is a selective inhibitor of the neuronal uptake of noradrenaline and dopamine. It is suggested that the drug works by modifying dopamine levels in the mesolimbic system and affects the noradrenergic pathways in the locus coeruleus, to reduce the nicotine craving and withdrawal symptoms. Zyban is not nicotine based or a nicotine-related drug. Zyban is available on NHS prescription, and is licensed for use in adults over the age of 18 years to help in smoking cessation in nicotine dependent patients who are motivated to quit smoking. The patient starts treatment while smoking, setting a target day to quit within the first 2 weeks, usually day

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eight. The initial dose is one 150 mg tablet daily for 3 days, increasing to 150 mg twice daily (allow 8 hours between doses) for the remainder of the 8-week treatment course. Zyban is not licensed for the treatment of any other drug dependency.

### EFFICACY

Two studies published in the *New England Journal of Medicine* have shown that Zyban is an effective aid to smoking cessation.

Hurt (1997) compared sustained release bupropion and placebo for smoking cessation. In a double-blind, placebo-controlled trial Zyban was found to be effective in smoking cessation, with some patients experiencing the benefit of less weight gain compared to placebo.

A more recent comparative study published in *New England Journal of Medicine* (Jorenby et al, 1999) involved nearly 900 chronic smokers. The double-blind, placebo-controlled study compared Zyban 150 mg twice a day with placebo, a nicotine replacement patch and, a combination of Zyban plus patch. The study consisted of a 9-week treatment period, with fol-

low-up to 1 year. Patients also received brief counselling on smoking cessation. In the Zyban group 30.3% of patients were not smoking at 1 year (nearly one in three) compared with 15.6% in a placebo group and 16.4% in patients prescribed a nicotine patch. In the group given Zyban and nicotine patch in combination, 35.5% were found not to be smoking after 1 year, although no significant statistical difference was found between patients taking Zyban alone and Zyban in combination with nicotine patch ( $P=0.61$ ) (Jorenby et al, 1999). This single study showed that patients treated with Zyban have a significantly greater chance of quitting smoking than patients treated with placebo or nicotine patch.

In addition, Ferry concluded that Zyban can reduce cravings for nicotine and withdrawal symptoms, helping nearly one-third of smokers to maintain complete abstinence at 1 year follow-up (Ferry, 1999).

Research has shown that Zyban is generally well-tolerated. The commonest side-effects reported were dry mouth, headache and insomnia, which are mild and transient. These effects can also be associated with quitting

**TABLE 1.**  
Cost effectiveness estimates (health authority)

|                                 |   | Costs per life-year saved |            |
|---------------------------------|---|---------------------------|------------|
|                                 |   | Undiscounted              | Discounted |
| Face-to-face interventions      | Brief advice  | £112                      | £174       |
|                                 | Brief advice + self-help                                      | £142                      | £221       |
|                                 | Brief advice + self-help + NRT                                | £173                      | £269       |
|                                 | Brief advice + self-help + NRT + specialist cessation service | £164                      | £255       |
| Community interventions         | Quit and win  | Low                       | £562       |
|                                 |   | Medium                    | £542       |
|                                 |   | High                      | £735       |
|                                 | No smoking day  | £22                       | £34        |
| Broader community interventions | Low   | £328                      | £509       |
|                                 | Medium  | £164                      | £252       |
|                                 | High  | £33                       | £51        |

NRT = nicotine replacement therapy. From Parrott et al (1998)

**TABLE 2.**  
Cost effectiveness estimates (society)

|                            |   | Costs per life-year saved |            |
|----------------------------|---|---------------------------|------------|
|                            |   | Undiscounted              | Discounted |
| Face-to-face interventions | Brief advice  | £136                      | £212       |
|                            | Brief advice + self-help                                      | £167                      | £259       |
|                            | Brief advice + self-help + NRT                                | £448                      | £696       |
|                            | Brief advice + self-help + NRT + specialist cessation service | £562                      | £873       |

NRT = nicotine replacement therapy. No estimates of the total costs to society could be made for the community interventions as the costs are highly dependent upon the exact nature of the programme. From Parrott et al (1998)

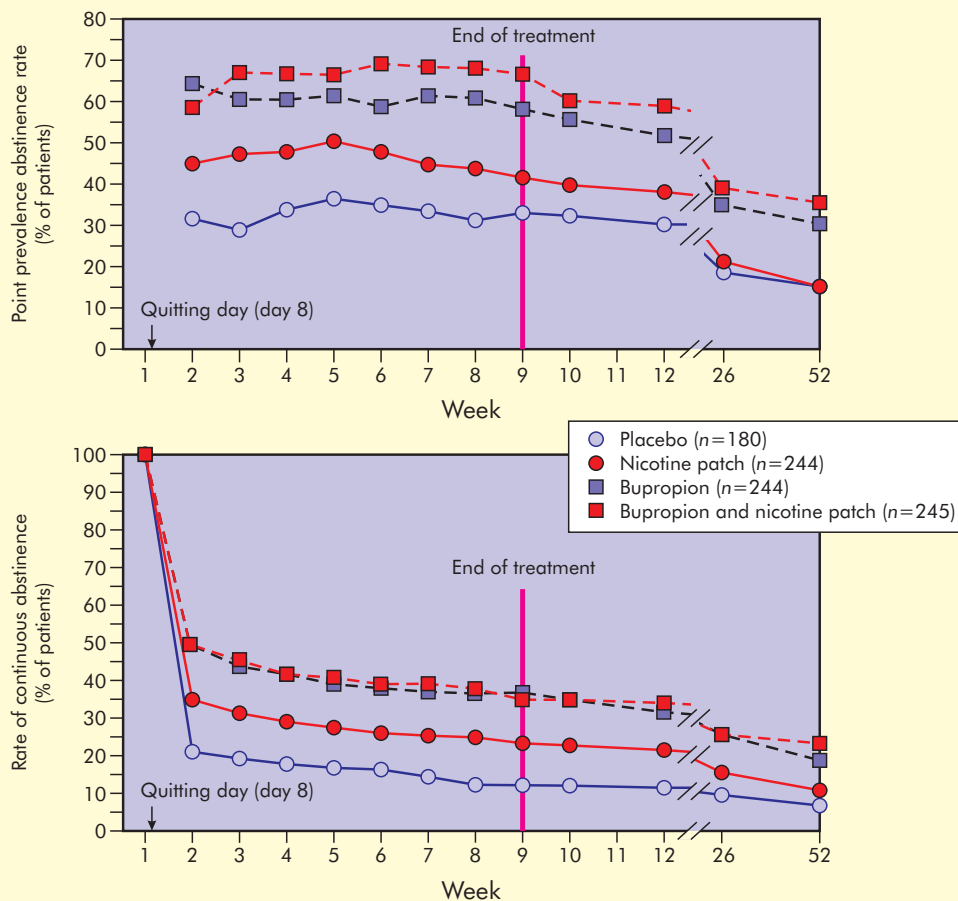


Figure 1. Point-prevalence rates of abstinence (A) and rates of continuous abstinence (B) during treatment (weeks 1–9) and follow-up (weeks 10–52) (from Jorenby et al., 1999). The point-prevalence rates of abstinence at 4 weeks were significantly higher in all three treatment groups than in the placebo group ( $P=0.005$  for the comparison with the nicotine-patch group,  $P<0.001$  for the comparison with the bupropion group, and  $P<0.001$  for the comparison with the group given the nicotine patch and bupropion). For continuous abstinence, all three active treatments were superior to placebo ( $P<0.001$ ), and there was no significant difference between bupropion alone and bupropion in combination with the nicotine patch ( $P=0.61$ ). Error bars indicate standard errors.

smoking without any pharmacological aid (Hughes et al., 1990).

## MANAGEMENT

Experts in smoking cessation agree that a smoker's level of commitment to quit is a key determinant of success. Zyban is therefore intended for those smokers who have demonstrated their motivation to quit. As a guide, motivated patients should respond positively to the following questions:

- Do you really want to stop smoking?
- Would you be prepared to stop smoking in the next 2 weeks?

To achieve quitting success, it is crucial that patients remain motivated to quit. For patients who have been prescribed Zyban, a personalized

patient support programme, called 'The Right Time Programme' is available. It consists of motivational materials such as a stop smoking action plan and a health benefit chart. This programme also includes follow-up support with mailings at critical times during the quitting process and a dedicated telephone helpline with trained smoking cessation counsellors for support 7 days a week.

Providing support improves the success rate for any patient trying to give up smoking and it can be beneficial for patients to be followed up, initially within 1 week of their quit date and then at regular intervals during the 2-month treatment cycle. Patients could also be contacted at 6 months and 1 year to ensure continuing abstinence.

## SIDE-EFFECTS AND CONTRAINDICATIONS

As already mentioned, common side-effects include dry mouth, insomnia, and headaches. Zyban can cause dizziness and light-headedness, so patients should be warned to exercise caution while driving or operating machinery until their response to the drug has been established. As with most drugs, there is also a possibility of hypersensitivity and anaphylactic reactions.

Zyban should not be used in patients with a current or previous history of seizure disorder, such as epilepsy. At doses up to the maximum recommended daily dose, the incidence of seizures is approximately 0.1% (1/1000) and caution should be exercised in patients with conditions or drugs lowering the seizure threshold, e.g. alcoholism, unstable diabetes. Other contraindications include current or previous diagnosis of bulimia or anorexia, severe hepatic cirrhosis, a history of bipolar disorder, or hypersensitivity to bupropion. Zyban is also contraindicated in pregnancy and lactation.

Use in patients under 18 years of age is not recommended as the safety and efficacy of the drug has not been evaluated in these patients. Zyban should be used with caution in elderly patients and they should only be prescribed a lower dose of 150 mg, once a day.

## PHARMACOKINETIC PROPERTIES

Zyban is well absorbed. After oral dosing its peak plasma concentration of 100 ng/ml ( $C_{max}$ ) is observed after about 2.5–3 hours. Zyban is metabolized to hydroxybupropion by the CYP2B6 enzyme pathway. It is extensively metabolized and the fraction of the dose of Zyban excreted unchanged was less than 0.5%. Clinical experiences have not identified differences in tolerability between elderly and younger patients, but greater sensitivity in older patients cannot be ruled out.

## KEY POINTS

- Zyban is the only non-nicotine prescription-only medication licensed in the UK to treat nicotine addiction.
- A recent study concluded that Zyban has been shown to reduce cravings for nicotine and withdrawal symptoms, helping nearly one third of smokers to maintain complete abstinence at 1 year follow-up.
- Zyban has been shown to be highly effective in smoking cessation, helping people to break the cycle of nicotine cessation.

## COST EFFECTIVENESS

Thorax has published guidance to commissioners on the cost effectiveness of smoking cessation interventions and reported that smoking cessation is one of the most cost-effective health-care interventions (Parrott et al, 1998).

Zyban is taken as a 2-month treatment course at the basic NHS price of £85.70 for 60 tablets, £42.85 per month, and it is competitively priced with respect to nicotine replacement patches when used at recommended doses (Browning et al, 2000).

## CONCLUSION

Evidence shows that giving pharmacological treatment in combination with advice and support is the most effective way of helping smokers to stop smoking. Zyban represents a unique approach to smoking cessation and the treatment offers new hope to smokers trying to quit. **HM**

*Conflict of interest: Dr Steele has received honoraria from GlaxoWellcome for postgraduate lectures on smoking cessation.*

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