BJPsych The British Journal of Psychiatry (2025)
1–3. doi: 10.1192/bjp.2025.50

Guest Editorial

Missing a trick? Bupropion for the pharmacological treatment of depression in the UK

Michael Browning and Philip J. Cowen

Bupropion is not licensed as an antidepressant in the UK, limiting its use. We highlight bupropion's distinct pharmacological profile and its potential benefits in treatment-resistant depression and people experiencing selective serotonin reuptake inhibitor-induced sexual dysfunction. The National Health Service repurposing medicines programme could improve equity of access for UK patients.

Keywords
Bupropion; depression; inflammation; licensing; sexual dysfunction.

Bupropion is a venerable molecule, first licensed for depression in the USA almost 40 years ago. Since then bupropion has been approved for the management of depression in several countries, including Australia, Canada, Germany, France and Italy. In the UK, however, as a result of a marketing decision, bupropion is licensed only for the treatment of smoking cessation. While there is some 'off-label' prescribing by specialists, generally bupropion is little used as an antidepressant in this country.

Does bupropion have distinct value as an antidepressant?

Bupropion is structurally and pharmacologically different from other available antidepressants, being a moderate (micromolar) dopamine and noradrenaline reuptake inhibitor. It has little or no effect on serotonin reuptake mechanisms or serotonin receptors (Table 1).[1] Bupropion also antagonises nicotinic acetylcholine receptors, at drug concentrations similar to those that inhibit the noradrenaline transporter; this may be relevant to its utility in smoking cessation (Table 1). Probably as a consequence of dopamine and noradrenaline reuptake inhibition, bupropion augments activity of the vesicular monoamine transporter (VMAT), which is involved in the storage and release of monoamine neurotransmitters from nerve terminals.

In the broad range of depressed patients included in short-term clinical trials, bupropion appears as effective as selective serotonin reuptake inhibitors (SSRIs).[2] However, its adverse effect profile contrasts with SSRIs in that it does not cause sexual dysfunction or weight gain.[1] Lack of sexual side-effects is an important feature of bupropion in view of the high frequency of sexual dysfunction associated with SSRIs and concerns about its possible persistence post-treatment.[3] In countries where bupropion is licensed for depression, it is seen as a useful option. For example in the USA, in 2022, bupropion was the fifth most prescribed antidepressant.

Matching bupropion to clinical symptomatology

Unlike SSRIs, bupropion is not thought to have useful activity in the range of anxiety disorders that are often comorbid with depression. Indeed, there is some evidence that SSRIs are superior to bupropion in depressed patients with high levels of anxiety.[4]

From the pharmacological profile of bupropion, its use would seem most appropriate in depressed patients with a significant degree of anhedonia and diminished motivation and energy, particularly where this is associated with increased appetite and hypersomnia. Consistent with this, in the USA, bupropion is licensed for the treatment of seasonal affective disorder.

The pharmacology of bupropion suggests potential efficacy in attention-deficit hyperactivity disorder (ADHD) and there is some evidence to support this possibility. Adult patients with depression are increasingly diagnosed with ADHD and there may be a role for bupropion in depressed patients with such comorbidity.[1]

In both animal and human studies, bupropion possesses anti-inflammatory actions, in particular lowering blood levels of tumour necrosis factor-α (TNF-α).[5] This makes it possible that bupropion could have utility in patients whose depression is associated with raised markers of peripheral inflammation. In the CO-MED study, depressed patients with higher blood levels of C-reactive protein (CRP) had a better outcome when treated with a combination of bupropion and a SSRI than with a SSRI alone.[5] Perhaps, raised CRP levels in depressed patients might be a useful predictor of bupropion response.

Bupropion in treatment-resistant depression

First-line pharmacological management of depression, usually with SSRIs such as citalopram, escitalopram or sertraline, is not particularly satisfactory with more than half of patients showing either a partial or minimal response to treatment. At this point, a switch in medication is usually considered. The STAR*D trial randomised over 700 depressed patients who had either failed to respond or been unable to tolerate treatment with citalopram to one of three medications; sertraline, bupropion or the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine. At the 14-week trial end-point, there was no difference in outcome among the three medications.[6] This study suggests that as a switch medication bupropion does not possess additional value over other antidepressants in unselected depressed patients who have not responded to first-line SSRI treatment.

When patients have failed to respond to two or more antidepressant treatments, they are conventionally regarded as experiencing treatment-resistant depression (TRD). Most patients under the care of specialist mental health teams in the UK will be suffering from TRD. At this stage it is common to consider 'augmentation' approaches, where other agents are added to ongoing SSRI or SNRI treatment. Frequently used options are the antidepressant drug, mirtazapine, or the atypical antipsychotic drugs, quetiapine and aripiprazole. The utility of the latter two agents is supported by a substantial body of randomised trial evidence; however, their tolerability is limited. Might there be a role for bupropion in this setting?

https://doi.org/10.1192/bjp.2025.50 Published online by Cambridge University Press

Table 1 Affinity of bupropion for selected transmitter binding sites

Receptor site/ion channel	Bupropion affinity (μM)
Dopamine transporter	0.57
Noradrenaline transporter	1.4
Serotonin transporter	19
Serotonin-1A receptor	>100
Serotonin-2C receptor	>100
Serotonin-3 receptor	87
α_3*-nAChR (nicotinic receptor)[a]	1.8

a. Functional antagonism of nicotinic ion channels. For additional references to pharmacological actions of bupropion, see the supplementary material.

In countries where bupropion is commonly used as an antidepressant, it is often added to ineffective SSRI or SNRI treatment. The combination is usually well tolerated and bupropion has the advantage that it can relieve SSRI-induced sexual dysfunction.[1] However, the evidence for its antidepressant efficacy for this indication is limited and there is no large, placebo-controlled trial to support this approach.

Ji et al[7] conducted a systematic review of five clinical trials that compared bupropion and aripiprazole augmentation with bupropion switching in 4480 depressed patients with inadequate response to SSRI or SNRI treatment. They found similar remission rates following addition of either aripiprazole or bupropion. In addition, both augmentation treatments produced superior outcomes compared to a switch to bupropion monotherapy.

Tolerance and safety of bupropion

In systematic reviews, the acceptability of bupropion as judged by drop-out rate from short-term clinical trials is similar to that of sertraline.[2] The most common side-effects experienced during bupropion treatment of depression are insomnia, dry mouth, headache and tremor. Gastro-intestinal disturbances such as nausea, vomiting and abdominal pain also occur. Anxiety may increase.

The most serious adverse effect of bupropion is seizure. This was particularly apparent with the original immediate release form of bupropion, especially when daily dosage exceeded 450 mg. The sustained release form of bupropion (available as 'Zyban' in the UK) carries a risk of seizure of about one in a thousand patients at dosages of less than 400 mg daily.[1] This is similar to that of most other licensed antidepressant drugs and less than that associated with some tricyclic antidepressants (TCAs), for example, amitriptyline and clomipramine.

People with a previous history of fits or head injury have a higher risk of seizure with bupropion. The risk of seizure is also reportedly increased by a history of clinical eating disorder. During bupropion treatment, patients should not withdraw from drugs with anticonvulsant properties such as benzodiazepines or gabapentinoids. For the same reason, the use of alcohol should be limited. Drugs with proconvulsant properties such as TCAs should not be co-administered with bupropion.

Bupropion can cause significant toxicity in overdose, with seizures a frequent complication. The mortality after bupropion overdose is greater than that with SSRIs and is similar to that seen with venlafaxine. Withdrawal symptoms can occur after abrupt cessation of bupropion. These include irritability, anxiety, sleep disturbances and fatigue. Dose tapering is recommended.

Bupropion and its active metabolite, hydroxybupropion, are effective inhibitors of hepatic CYP2D6 enzymes. Bupropion treatment therefore has the potential to increase plasma levels of the many drugs metabolised by this pathway. Such drugs include other antidepressants, for example, SSRIs and SNRIs, and antipsychotic drugs such as risperidone and aripiprazole.[8]

Dosing of bupropion in the treatment of depression

In the UK, bupropion is available in the sustained release form as 150 mg tablets. Dosing in depression should begin with 150 mg daily, which can be increased after about a week to 150 mg twice daily; this is the dose most commonly used to treat depression. The same dosing is used in augmentation treatment when bupropion is added to SSRIs or SNRIs but some patients may respond to the initial dose of 150 mg daily.

Bupropion sustained release doses should be separated by at least 8 h to minimise the risk of seizures. The second dose should not be given late in the evening because this increases the incidence of insomnia. The USA labelling of bupropion sustained release advises that doses of up to 400 mg daily can be given to depressed patients not responding to 300 mg; however, this is difficult to achieve with the 150 mg tablet formulation available in the UK. For a full summary of prescribing information of bupropion sustained release in depression, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020358s068lbl.pdf.

Is there a role for bupropion in the treatment of depression in the UK?

It seems incongruous that in the UK bupropion is available as a treatment for smoking cessation but not for major depression, where its use internationally is well established. However, there are many antidepressant medications available in the UK. Would bupropion add anything useful to our current treatments?

The clinical data outlined above suggest that SSRIs have a better safety profile than bupropion and are more straightforward to prescribe in depressed patients. SSRIs are also useful for treating comorbid anxiety disorders, which are particularly common in primary care settings. It therefore seems unlikely that bupropion would add to currently used first-line medications. Similarly, judging from the STAR*D study, where depressed patients have not responded to initial SSRI treatment, a switch to bupropion as a general second-line option would probably not have advantages over safer strategies, such as a switch to a second SSRI or a SNRI.

However, bupropion probably does have a role in some patients who do not respond to SSRIs or SNRIs or find them intolerable because of sexual dysfunction or weight gain. In addition, specialists working with TRD patients will be aware that some people with depression who have not been helped by many licensed antidepressants appear to respond well to bupropion; this likely reflects its distinct pharmacological profile.

Meta-analytic data suggest that bupropion augmentation of SSRIs and SNRIs is about as effective as aripiprazole addition.[7] Bupropion has advantages over atypical antipsychotic augmentation because of the absence of metabolic side-effects, weight gain and movement disorders. Also, bupropion has the potential ability to attenuate SSRI/SNRI-induced sexual dysfunction.[9] Indeed, it is sometimes used for this purpose in patients who have otherwise responded well to SSRIs and SNRIs.

Precision psychiatry and bupropion

The utility and safety of bupropion treatment in the management of depression would be substantially enhanced if effective treatment

https://doi.org/10.1192/bjp.2025.50 Published online by Cambridge University Press

predictors were available. As noted above, the ability of bupropion to facilitate dopamine neurotransmission would suggest a role in managing the anhedonia and diminished motivation that are core symptoms of more severe depression and are not well addressed by SSRI or SNRI treatment. However, this theoretical benefit of bupropion is yet to be established empirically.

Experimental medicine studies employing functional neuroimaging have identified potential neurobiological predictors of bupropion response in depression, but such work needs to be validated prospectively and is not readily transferrable to routine clinical settings. Computational approaches using psychological testing[1] are more likely to be scalable and are currently under study. Finally, raised peripheral inflammatory markers could predict an antidepressant response to bupropion. This intriguing suggestion requires prospective confirmation.

Licensing of bupropion as an antidepressant in the UK

For bupropion to be licensed as a treatment for depression in the UK a 'market authorisation holder', the company that holds the rights to sell and distribute the drug, must be identified. As bupropion is no longer under patent this may be a company that provides generic medication, rather than the pharmaceutical company that originally developed it. National Health Service (NHS) England hosts a scheme that supports the repurposing of drugs that facilitates this process (https://www.england.nhs.uk/medicines-2/medicines-repurposing-programme/). Also the Medicines and Healthcare products Regulatory Agency (MHRA) is able to take into account decisions from other 'trusted regulators' (such as the Food and Drug Administration (FDA) or European Medicines Agency (EMA)) to streamline assessment of drugs already approved in other territories. In our opinion, licensing bupropion for the treatment of depression in the UK would provide NHS patients with an additional, useful treatment option.

Michael Browning, Department of Psychiatry, University of Oxford, Oxford, UK; and Department of Psychiatry, Oxford Health NHS Foundation Trust, Oxford, UK; **Philip J. Cowen**, Department of Psychiatry, University of Oxford, Oxford, UK; and Department of Psychiatry, Oxford Health NHS Foundation Trust, Oxford, UK

Correspondence: Philip J. Cowen. Email: phil.cowen@psych.ox.ac.uk

First received 11 Nov 2024, final revision 4 Feb 2025, accepted 5 Feb 2025

Supplementary material

The supplementary material is available online at https://doi.org/10.1192/bjp.2025.50

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Acknowledgements

The views expressed are those of the authors and not necessarily those of the UK National Health Service, the National Institute for Health and Care Research (NIHR) or the UK Department of Health and Social Care.

Author contributions

M.B. and P.J.C. both contributed to the initial research, drafting and editing of this manuscript.

Funding

M.B. was supported by the Office for Life Sciences and the NIHR Mental Health Translational Research Collaboration, hosted by the NIHR Oxford Health Biomedical Research Centre and by the NIHR Oxford Health Biomedical Research Centre. P.J.C. is a Medical Research Council (MRC) Clinical Scientist.

Declaration of interest

M.B. has received consulting fees from J&J, Engrail Therapeutics and CHDR, and travel expenses from Lundbeck. None of the latter companies market bupropion. He was previously employed by P1vital Ltd. P.J.C. has none.

References

1 DeBattista C, Schatzberg AF. Antidepressants. In *Schatzberg's Manual of Clinical Psychopharmacology*: 47–203. American Psychiatric Association Publishing, 2024

2 Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa U, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network matter analysis. *Lancet* 2018; **391**: 1357–66.

3 Reisman Y. Post-SSRI sexual dysfunction. *BMJ* 2020; **368**: m754.

4 Papakostas GI, Stahl SM, Krishen A, Seifert CA, Tucker VL, Goodale EP, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. *J Clin Psychiatry* 2008; **69**: 1287–92.

5 Ja MK, Minhajuddin A, Gadad B, Greer T, Grannemann B, Soyombo A, et al. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* 2017; **78**: 105–13.

6 Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, sertraline or venlafaxine-XR after failure of SSRIs for depression. *New Eng J Med* 2006; **354**: 1231–42.

7 Ji M, Feng J, Liu G. Efficacy and safety of aripiprazole or bupropion augmentation and switching in patients with treatment-resistant depression or major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *PLOS ONE* 2024; **19**(4): e0299020.

8 Costa R, Oliveira NJ, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic bupropion: integrative overview of relevant clinical and forensic aspects. *Drug Metabol Rev* 2019; **51**: 293313.

9 Pereira VM, Arias-Carrion O, Machado S, Nardi AE, Silva AC. Bupropion in the depression-related sexual dysfunction: a systematic review. *CNS & Neurological Disorders – Drug Targets* 2014; **13**: 1079–88.

EXTRA CONTENT ONLINE

https://doi.org/10.1192/bjp.2025.50 Published online by Cambridge University Press