

Title page

Bupropion perceived as a stimulant by two patients with a previous history of cocaine misuse

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Abstract. *Background and objective.* Despite animal studies have shown a generalisation of the bupropion cue to cocaine, this drug has been used in cocaine abuse with mixed results. We here aimed at describing two cases which contradict current knowledge. *Case Reports.* We describe two cases of former cocaine abusers who reported a cocaine-like sensation upon taking bupropion. Bupropion improved patients' depression without any increase in cocaine craving. One of the patients increased without doctor consultation his dose on an as needed basis. *Conclusions.* The issue of bupropion cue generalisation to cocaine needs further elucidation. People with past cocaine addiction need to be informed on the potential of bupropion to elicit cocaine-like cues and be invited to adhere to medical prescription, because bupropion has been associated with fatalities in some cases.

Il bupropione percepito come uno psicostimolante da due pazienti con anamnesi pregressa di abuso di cocaina. Riassunto. *Contesto e obiettivo.* Sebbene studi su animali abbiano dimostrato una generalizzazione del *cue* del bupropione alla cocaina, tale farmaco è stato utilizzato nell'abuso di cocaina con risultati misti. Il nostro obiettivo è stato di descrivere due casi che contraddicono le conoscenze attuali. *Casi clinici.* Riportiamo due casi di pazienti che hanno riferito una sensazione cocaino simile in due ex-utilizzatori di cocaina. Il bupropione ha migliorato la depressione di questi pazienti senza aumentare il *craving* cocainico. Uno di questi pazienti ha aumentato la dose, *pro re nata*, senza consultarsi col medico. *Conclusioni.* La questione della generalizzazione del *cue* del bupropione alla cocaina va ulteriormente delucidata. Gli ex-cocainomani vanno informati sulla possibile associazione del bupropione con *cue* cocaino simili e invitati ad aderire alle prescrizioni mediche, perché l'assunzione di bupropione è stata associata in qualche caso con fatalità.

Key words: Bupropion; cocaine abuse; depression; internal stimulant cue; monoamine transporter inhibitors

Parole chiave: Bupropione; abuso di cocaina; depressione; *cue* interno da psicostimolanti; inibitori dei trasportatori delle mono ammine

Increased synaptic dopamine levels in the dorsal striatum appear to mediate cocaine craving in cocaine-experienced individuals [1]. Cocaine craving predicts relapse to subsequent cocaine use [2]. The dopamine transporter inhibitor, amineptine, which has been used for some time as an antidepressant, and which has been withdrawn due to its abuse/dependence potential, was shown to generalise its cue to other weakly dopaminergic antidepressants, like fluoxetine [3] and venlafaxine [4], hence inducing cross-abuse/dependence. The dopamine/noradrenaline-reuptake inhibitor bupropion has long been used in the US as an antidepressant, before receiving approval for nicotine dependence. Due to its mechanism, it could be expected to mimic other dopamine transporter inhibitors and generalise its cue to them. In fact, it is long known that bupropion produces cocaine-appropriate responses in the self-administration, lever pressing paradigm in several animals, including the pigeon [5], the rat [6,7], and baboon and *rhesus* monkeys [7,8], substituting completely for cocaine at the higher doses, although there has recently been a negative report in the rat, in which only amphetamine and nicotine were found to substitute for the bupropion cue [9]. Bupropion has been used for cocaine addiction in individuals on methadone maintenance programmes [10,11] with some success, but despite reducing reported cocaine use, open [12] and controlled studies showed that bupropion did not significantly affect cocaine-related behaviour [13], partly cooling the enthusiasm about its usefulness in cocaine addiction. However, this occurred at therapeutic doses, not exceeding 300 mg/day. In a non-therapeutic human experiment, cocaine users provided higher ratings for the positive subjective effects of cocaine while taking 100 or 200 mg bupropion than when they were not taking bupropion, reducing simultaneously their cocaine preference with respect to placebo [14]. Combined, these findings do not yield a definitive response as to whether bupropion affects cocaine cues in the human. We report two cases showing that in fact, in line with previous animal literature, bupropion elicits a cocaine-like cue without increasing craving for cocaine.

Case Reports

Case 1. A 28-year-old man with past history of drug misuse (including cocaine, alcohol, tetrahydrocannabinol, and lysergic acid diethylamide, but not amphetamine (or its derivatives)) developed chronic depression with anhedonia, interrupted by brief periods of euphoria. The patient was a socially withdrawn university student with poor academic performance, the reason for which he sought psychotherapy. His psychotherapist referred him to us for pharmacotherapy, considering psychotherapy alone to be insufficient to treat his patient's condition.

When he came to our attention he was 26. The patient was considerably anergic, with motor retardation, decreased expressiveness, poverty of speech, reduced ideation, blunted affect, anxiety, difficulties with concentration, intrusive thoughts, and somaesthetic disturbances. His depression had developed subtly from the age of 19, reaching a peak when he was 25. About that time he had started his polydrug misuse, including cocaine, until he reached the age of 23. He was poorly motivated, anhedonic, with suicidal ideation, and suffering from sleep disturbances, scoring 30 on the Hamilton Rating Scale for Depression (Ham-D) [15]. We diagnosed him with DSM-IV-TR bipolar disorder, type II, moderate depressive episode, based on a SCID-I interview, comorbid with borderline personality disorder, based on a SCID-II interview.

Treatment with both oral, slow-release bupropion, 150 mg/day, and immediate-release quetiapine, 25 mg at bedtime, was started. At the two-week follow-up, he reported thought acceleration and restlessness when going to bed, which he described as similar to those post-cocaine binges he had experienced in the past. This was paralleled by an increase in self-esteem and increased self-confidence, as when he was abusing cocaine. He characteristically stated "This treatment reminds me of when I was taking cocaine". This sensation lasted for about two weeks, and by the third week these sensations disappeared. At the same time, his depressive and sleep symptoms had improved considerably, with his Ham-D scores dropping to 24, and then to 20 after three months of treatment, progressively reaching a score of 16 one year later (cut-off, 7).

Case2. A 56-year-old man reached our attention after a serious suicide attempt. He owned a successful bookshop, but faced economic difficulties due to his pathological gambling and cocaine addiction. He started developing cocaine abuse at the age of 52, increasing it with time to about 1 g on three occasions per week in a short time, thereafter maintaining this weekly dose. His mood rapidly deteriorated following his father's death four years ago, and then gradually worsened over time. Following a serious suicide attempt, he was referred to our unit. On admittance, he had scored 26 on the Ham-D scale and was started on 150 mg/day slow-release bupropion, 1000 mg/day controlled-release valproate, 10 mg oral olanzapine at bedtime, and diazepam *p.r.n.*. Based on SCID-I and -II interviews we made diagnosis of bipolar disorder, type I, comorbid with pathological gambling and cocaine use disorder; we diagnosed comorbid gambling because it occurred also independently from manic episodes. One month later he had already stopped both cocaine misuse and gambling activities; this was paralleled by mood improvement. Bupropion dosage was then increased to 150 mg *b.i.d.* Two months later he had reached a score of 16 on the Ham-D. However, marital conflicts did not improve. In coincidence with intense conflicts, his depression worsened, prompting him to increase bupropion intake to 150 mg *t.i.d.* and olanzapine to 10 mg *b.i.d.* In particular, bupropion reportedly made him feeling overstimulated and active, as when he was taking cocaine. Although his family and economic problems persisted eight months later, his Ham-D scores had dropped to 10, which is mild depression. Both patients gave free, informed consent for all treatment received as well as for the publication of their cases.

Discussion. In line with the existence of overlap between the mechanisms of bupropion and cocaine [5-8], our two cases seem to suggest that bupropion intake elicits cocaine-like cues in cocaine-experienced humans. Bupropion acts by inhibiting dopamine and noradrenaline transporters, hence increasing the intra-synaptic concentrations of these neurotransmitters [16]. Cocaine blocks both these transporters and the serotonin transporter as well [17], while amphetamine is a dopamine releaser and dopamine transporter blocker [18,19]. Hence, the theoretical basis for cross-elicitation of their cues is sufficient to let us hypothesise that our cocaine-exposed patients were able to identify a cocaine-like cue with bupropion intake. Hence, cocaine-exposed subjects are able to identify bupropion intake as having a cue similar to cocaine. This is further backed by animal studies showing generalisation of the bupropion cue to amphetamine, cocaine, and caffeine [5-8,20] and substitution of both bupropion and cocaine for methamphetamine [21]. However, it is in contrast with the results of another study, which found nicotine and methamphetamine, but not cocaine substitution for bupropion in the rat [9].

Differently from previous reports [22,23] we observed no psychotic symptoms in these two patients. Both our patients were on antipsychotic medication, and this might have prevented psychotic symptoms. It should be stressed that antipsychotic drugs behave differently from one another as regards co-administered bupropion, at least in facilitating smoking cessation, but the two atypical antipsychotics used in our patients did not interact with bupropion at this respect [24].

Our second patient used bupropion not according to prescription; clinicians must inform their patients about possible dangers arising from such practice, since five fatalities with bupropion intake have been recorded by the National Programme on Substance Abuse Deaths in the UK (Corkery, personal communication).

Conclusions. Despite the neurochemical background of addictions and the mechanism of action of bupropion, we did not observe negative effects of bupropion on cocaine craving in former cocaine users, even in the case of inappropriate dose self-adjustment. However, a generalisation of the bupropion cue to cocaine, which has not been previously reported in medical literature, was found in two patients, leading us to question the universal validity of animal studies showing bupropion to generalise to amphetamine, but not cocaine. Clinicians should be aware of the possibility that

bupropion may elicit cocaine-like cues in cocaine-experienced individuals and ask about it to their patients, cautioning them for the dangers of non-prescription use of bupropion.

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