

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

Alessandro E. Vento^(a, b), Fabrizio Schifano^(c, d), Federica Gentili^(e), Francesco Pompei^(e), John M. Corkery^(c, d), Georgios D. Kotzalidis^(a) and Paolo Girardi^(a, f)

^(a) Dipartimento NESMOS, Sapienza Università di Roma, Ospedale Sant'Andrea, Rome, Italy

^(b) Facoltà di Scienze di Formazione, Università degli Studi "Guglielmo Marconi", Rome, Italy

^(c) School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK

^(d) National Programme on Substance Abuse Deaths, International Centre for Drug Policy, St George's University of London, London, UK

^(e) Clinica Neuropsichiatrica Villa von Siebenthal, Genzano, Rome, Italy

^(f) Villa Rosa, Suore Ospedaliere del Sacro Cuore di Gesù, Viterbo, Italy

Abstract

Background and objective. Despite animal studies having 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.

Key words

- bupropion
- cocaine abuse
- depression
- internal stimulant cue
- monoamine transporter inhibitors

INTRODUCTION

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dopamine transporter inhibitor, amineptine, which has been used for some time as an antidepressant, and which has been withdrawn due to its abuse/dependence potential, was shown to generalise its cue to other weakly dopaminergic antidepressants, like fluoxetine [3] and venlafaxine [4],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 somesthetic 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).

Case 2

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 six 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.

Acknowledgments

The authors wish to thank the late Tiziana Mattei, and Mimma Ariano, Ales Casciaro, Teresa Prioesci, and Susanna Rospo, Librarians of the Sant'Andrea Hospital, School of Medicine and Psychology, Sapienza University, Rome, for rendering precious bibliographical material accessible, as well as their Secretary Lucilla Martinelli for her assistance during the writing of the manuscript.

Conflict of interest statement

PG in the past three years has received research support from Lilly and Janssen, has participated in

Advisory Boards for Lilly, Organon, Pfizer, and Schering and received honoraria from Lilly and Organon. Please further note that GDK is the recipient of an Italian Ministry of Education Ph.D. Grant for Early Intervention in the Psychoses. FS is a full member of the Advisory Council on the Misuse of Drugs/ACMD in the UK and that JC is a member of the ACMD New Psychoactive Drugs working group in the UK. None of these authors has any relevant affiliation or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. All other authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Received on 19 March 2013.

Accepted on 11 September 2013.

REFERENCES

- Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 2006;26:6583-8. DOI: 10.1523/JNEUROSCI.1544-06.2006
- Rohsenow DJ, Martin RA, Eaton CA, Monti PM. Cocaine craving as a predictor of treatment attrition and outcomes after residential treatment for cocaine dependence. *J Stud Alcohol Drugs* 2007;68:641-8.
- Taïeb O, Larroche C, Dutray B, Baubet T, Moro MR. Fluoxetine dependence in a former amineptine abuser. *Am J Addict* 2004;13:498-500.
- Quaglio G, Schifano F, Lugoboni F. Venlafaxine dependence in a patient with a history of alcohol and amineptine misuse. *Addiction* 2008;103:1572-4. DOI: 10.1111/j.1360-0443.2008.02266.x
- Johanson CE, Barrett JE. The discriminative stimulus effects of cocaine in pigeons. *J Pharmacol Exp Ther* 1993;267:1-8.
- Jones CN, Howard JL, McBennett ST. Stimulus properties of antidepressants in the rat. *Psychopharmacology (Berl)* 1980;67:111-8. DOI: 10.1007/BF00431964
- Lamb RJ, Griffiths RR. Self-administration in baboons and the discriminative stimulus effects in rats of bupropion, nomifensine, diclofensine and imipramine. *Psychopharmacology (Berl)* 1990;102:183-90. DOI: 10.1007/BF02245920
- Kleven MS, Anthony EW, Woolverton WL. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther* 1990;254:312-7.
- Wilkinson JL, Li C, Bevins RA. Pavlovian drug discrimination with bupropion as a feature positive occasion setter: substitution by methamphetamine and nicotine, but not cocaine. *Addict Biol* 2009;14:165-73. DOI: 10.1111/j.1369-1600.2008.00141.x
- Margolin A, Kosten T, Petrakis I, Avants SK, Kosten T. Bupropion reduces cocaine abuse in methadone-maintained patients. *Arch Gen Psychiatry* 1991;48:87. DOI: 10.1001/archpsyc.1991.01810250089015
- Margolin A., Kosten T. R., Avants S. K., Wilkins J., Ling W., Beckson M., et al. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 1995;40:125-31. DOI: 10.1016/0376-8716(95)01198-6
- Montoya ID, Preston KL, Rothman R, Gorelick DA. Open-label pilot study of bupropion plus bromocriptine for treatment of cocaine dependence. *Am J Drug Alcohol Abuse* 2002;28:189-96.
- Shoptaw S, Heinzerling KG, Rotheram-Fuller E, Kao UH, Wang PC, Bholat MA, Ling W. Bupropion hydrochloride versus placebo, in combination with cognitive behavioral therapy, for the treatment of cocaine abuse/dependence. *J Addict Dis* 2008;27:13-23. DOI: 10.1300/J069v27n01_02
- Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Influence of acute bupropion pretreatment on the effects of intranasal cocaine. *Addiction* 2012;107:1140-7. DOI: 10.1111/j.1360-0443.2011.03766.x
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62. DOI: 10.1136/jnnp.23.1.56
- Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry* 2004;6:159-66. DOI: 10.4088/PCC.v06n0403
- Ritz MC, Cone EJ, Kuhar MJ. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: a structure-activity study. *Life Sci*

- 1990;46:635-45. DOI: 10.1016/0024-3205(90)90132-B
18. Schwarz RD, Uretsky NJ, Bianchine JR. The relationship between the stimulation of dopamine synthesis and release produced by amphetamine and high potassium in striatal slices. *J Neurochem* 1980;35:1120-7. DOI: 10.1111/j.1471-4159.1980.tb07867.x
 19. Wei Y, Williams JM, Dipace C, Sung U, Javitch JA, Galli A, Saunders C. Dopamine transporter activity mediates amphetamine-induced inhibition of Akt through a Ca²⁺/calmodulin-dependent kinase II-dependent mechanism. *Mol Pharmacol* 2007;71:835-42. DOI: 10.1124/mol.106.026351
 20. Blitzer RD, Becker RE. Characterization of the bupropion cue in the rat: lack of evidence for a dopaminergic mechanism. *Psychopharmacology (Berl)* 1985;85:173-7. DOI: 10.1007/BF00428409
 21. Reichel CM, Wilkinson JL, Bevins RA. Methamphetamine functions as a positive and negative drug feature in a Pavlovian appetitive discrimination task. *Behav Pharmacol* 2007;18:755-65. DOI: 10.1097/FBP.0b013e3282f14efc
 22. Hahn M, Hajek T, Alda M, Gorman JM. Psychosis induced by low-dose bupropion: sensitization of dopaminergic system by past cocaine abuse? *J Psychiatr Pract* 2007;13:336-8. DOI: 10.1097/01.pra.0000290673.32978.e8
 23. Farooque M, Elliott J. Delayed psychosis induced by bupropion in a former cocaine abuser: a case report. *Prim Care Companion J Clin Psychiatry* 2010;12(5) pii:PCC.09100943. DOI: 10.4088/PCC.09l00943gry
 24. Wu BJ, Chen HK, Lee SM. Do atypical antipsychotics really enhance smoking reduction more than typical ones?: the effects of antipsychotics on smoking reduction in patients with schizophrenia. *J Clin Psychopharmacol* 2013;33:319-28. DOI: 10.1097/JCP.0b013e31828b2575