

Understanding polydrug use: review of heroin and cocaine co-use

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ABSTRACT

The use of cocaine by heroin-dependent individuals, or by patients in methadone or buprenorphine maintenance treatment, is substantial and has negative consequences on health, social adjustment and outcome of opioid-addiction treatment. The pharmacological reasons for cocaine use in opioid-dependent individuals, however, are poorly understood and little is known about the patterns of heroin and cocaine co-use. We reviewed anecdotal evidence suggesting that cocaine is co-used with opioid drugs in a variety of different patterns, to achieve different goals. Clinical and preclinical experimental evidence indicates that the simultaneous administration of cocaine and heroin (i.e. 'speedball') does not induce a novel set of subjective effects, nor is it more reinforcing than either drug alone, especially when the doses of heroin and cocaine are high. There is mixed evidence that the subjective effects of cocaine are enhanced in individuals dependent on opioids, although it is clear that cocaine can alleviate the severity of symptoms of withdrawal from opioids. We also reviewed preclinical studies investigating possible neurobiological interactions between opioids and cocaine, but the results of these studies have been difficult to interpret mainly because the neurochemical mechanisms mediating the motivational effects of cocaine are modified by dependence on, and withdrawal from, opioid drugs. Our analysis encourages further systematic investigation of cocaine use patterns among opioid-dependent individuals and in laboratory animals. Once clearly identified, pharmacological and neuroanatomical methods can be employed in self-administering laboratory animals to uncover the neurobiological correlates of specific patterns of co-use.

KEYWORDS Cocaine, heroin, opioid-dependence, speedball, withdrawal.

INTRODUCTION

'Street pharmacology' provides information about the manufacture of drugs, combinations of different substances, dosages, tests for quality and home remedies for the ill effects of drugs of abuse (Hunt *et al.* 1984). Although not always scientifically validated, such information can nevertheless identify important issues in the study of the psychopharmacology of drug abuse.

The abuse of cocaine by opioid-dependent individuals is a 'street phenomenon' that has received clinical and experimental attention. The opioid-dependent individual,

as referred to here, is either physically dependent on opioids through the regular use of heroin or, as in the case of former heroin users, through maintenance on synthetic opioid agents such as methadone or buprenorphine (DSM-IV: APA 1994). This review does not include studies of individuals that become dependent by the regular use of opioid analgesics such as Vicodin and OxyContin (Kalb 2001).

Cocaine administration by opioid-dependent individuals can occur simultaneously and/or separately. Among drug users, the simultaneous injection of heroin and cocaine is often referred to as 'dynamite', 'whizbang' or,

more commonly, as 'speedball' (Ellinwood, Eibergen & Kilbey 1976; Cox *et al.* 1983). In a speedball, the cocaine is either injected in a mixture with heroin or it is 'piggy-backed', that is, injected immediately before or after the heroin, sometimes without removal of the syringe (Hunt *et al.* 1984), the drug being 'back-loaded' directly in the same syringe. Heroin users, as well as individuals on methadone maintenance treatment, also report cocaine use separate from opioid administration. In this paper, we will review both the clinical and preclinical evidence concerning the simultaneous and separate co-use of opioid drugs and cocaine. Following a discussion of the prevalence, consequences of co-use and a brief review of the neurobiological effects of opioid drugs and cocaine administration (acute and chronic), we will discuss various patterns of co-use and possible reasons for them.

PREVALENCE AND CONSEQUENCES OF OPIOID AND COCAINE CO-USE

The concomitant use of opioids and stimulants has been documented in diverse subgroups of the drug-using population. Interestingly, such co-use does not appear to be confined to specific regions; stimulant use in opioid-dependent individuals has been reported in a number of countries including the United States (Ellinwood *et al.* 1976; Kosten, Rounsaville & Kleber 1987; Hasin *et al.* 1988; Kosten, Rounsaville & Kleber 1988; Schottenfeld *et al.* 1993b; Hartel *et al.* 1995), Canada (Lauzon *et al.* 1994), Switzerland (Hausser, Kubler & Dubois-Arber 1999) Spain (Torrens *et al.* 1991; Perez *et al.* 1997), Italy (Guadagnino *et al.* 1995) and Australia (Kaye & Darke 2000).

The prevalence of cocaine use in opioid-dependent individuals not in treatment is high. Hasin *et al.* (1988) reported that 92% of heroin-using subjects were also using cocaine. Schutz *et al.* (1994) found that, in drug users who had injected at least once in the last 30 days, 66% used heroin, 76% used cocaine and 58% used both heroin and cocaine. In a study on patterns on drug use in Montreal, Lauzon *et al.* (1994) found that 50% of intravenous cocaine users reported using heroin regularly. Over time, cocaine use in opioid-dependent individuals has been increasing. For example, Kosten *et al.* (1986) indicated that in the early 1970s, cocaine abuse was observed in about 17% of opioid addicts seeking treatment whereas, by the 1980s, 74% of opioid addicts applying for treatment used cocaine. Overall, the prevalence of cocaine use among heroin addicts not in treatment ranges from 30% to 80% (Hasin *et al.* 1988; Schottenfeld *et al.* 1993a; Schutz *et al.* 1994; Grella, Anglin & Wugalter 1995; Frank & Galea 1996; Grella, Anglin & Wugalter 1997).

Similarly, high rates of cocaine use have also been observed in individuals in methadone maintenance treatments, at entry as well as during follow-up (Kosten *et al.* 1987; Kosten *et al.* 1988; Condelli *et al.* 1991; Kidorf & Stitzer 1993; Bux, Lamb & Iguchi 1995; Hartel *et al.* 1995; Hudgins, McCusker & Stoddard 1995; Joe & Simpson 1995; Levin, Foltin & Fischman 1996; Grella *et al.* 1997; Perez *et al.* 1997; Magura *et al.* 1998). In a study by Magura *et al.* (1998), of the 1038 patients newly admitted to 15 methadone clinics in New York City, 73% had cocaine-positive urine. Grella *et al.* (1997) reported that 50% of heroin users used cocaine before and during methadone treatment, and Black *et al.* (1987) found that cocaine was present in 63% of urine samples collected from a group of methadone-maintained patients over a 6-year period.

It is important to note that use of cocaine by opioid-dependent individuals is by no means the only type of polydrug consumption observed in this population. In fact, the use of alcohol, marijuana, benzodiazepines, tobacco and caffeine is also prevalent and equally concerning (Fairbank, Duntzman & Condelli 1993; Darke, Ross & Hall 1995; Budney, Bickel & Amass 1998; Pomerleau 1998; Gelkopf *et al.* 1999; Rooney *et al.* 1999; Ross & Darke 2000; Hser *et al.* 2001; Zinkernagel *et al.* 2001; Gossop, Marsden & Stewart 2002; Staines *et al.* 2002). It appears, however, that the negative health and social consequences of cocaine use by opioid-dependent individuals are particularly severe. Because cocaine is used intravenously most often by this population (Schottenfeld *et al.* 1993a; Schutz *et al.* 1994; Bux *et al.* 1995; Hudgins *et al.* 1995; Grella *et al.* 1997; Perez *et al.* 1997; Hausser *et al.* 1999), and because of its short half-life, the frequency of injection is high (Bux *et al.* 1995; Hudgins *et al.* 1995; Joe & Simpson 1995). Frequent injections coupled with widespread sharing of syringes (Dolan *et al.* 1987; Grella *et al.* 1995; Hudgins *et al.* 1995; Joe & Simpson 1995) increase the risk of contracting HIV or other blood-borne infectious diseases (Bickel & Kelly 1988; Torrens *et al.* 1991; Hudgins *et al.* 1995; Joe & Simpson 1995; Rowlett *et al.* 1997). Furthermore, cocaine use inevitably makes the drug habit of the opioid-dependent individual more expensive (Hunt *et al.* 1984; Strug *et al.* 1985), leading individuals to engage in income-generating strategies that often include crime (Strug *et al.* 1985; Bickel & Kelly 1988; Grella *et al.* 1997) and sex trade (Grella *et al.* 1995; Joe & Simpson 1995).

A high level of cocaine use at intake has been shown to be an independent predictor of poor treatment outcome of heroin-dependent polydrug abusers (Downey, Helmus & Schuster 2000). Methadone maintenance treatment reduces illicit opiate use, reduces patients' involvement in illicit activities, stabilizes their physical and mental health and increases socio-economic integration and function-

ing (Kreek 1997; Joseph, Stancliff & Langrod 2000; von Krambeer *et al.* 2001; Raisch *et al.* 2002). However, no pharmacological intervention has yet been demonstrated to be effective in the treatment of cocaine abuse (Dackis & O'Brien 2001; Soares *et al.* 2001). Hartel *et al.* (1995) reported that of 652 individuals in methadone maintenance treatment, 52% continued to use cocaine regardless of the dose of methadone. In the study of Magura *et al.* (1998) mentioned above, it was found that about 80% of the patients admitted to various methadone clinics significantly reduced heroin intake whereas only about 50% reduced cocaine intake. The remaining patients displayed consistently high, continually fluctuating, or increased cocaine use over time in treatment. Finally, it has been reported in a number of studies that cocaine-using opioid addicts suffer more severe co-morbid psychopathology (Dolan *et al.* 1987; Torrens *et al.* 1991; Malow *et al.* 1992; Grella *et al.* 1995; Walsh *et al.* 1996; Rowlett *et al.* 1997), are more likely to drop out of drug-abuse treatment, to have their treatment terminated and to relapse (Perez *et al.* 1997; Downey *et al.* 2000; Dolan *et al.* 2001) than pure heroin users.

In summary, it is clear that the use of cocaine by opioid-dependent individuals is not a trivial phenomenon and that this practice has several negative outcomes for the user and for society. It is therefore important to better identify the most common patterns of opioid–cocaine use and to understand the neurobiological mechanisms fostering this co-administration.

NEUROBIOLOGY OF OPIOIDS AND COCAINE

Opioids and cocaine have different pharmacological modes of action. The term opioid is generally used to designate drugs that act with varying degrees of selectivity at one or more identified opioid receptors throughout the body and brain. The different classes of opioid receptors, mu, delta and kappa, are naturally activated by three families of endogenous neuropeptides: the enkephalins, the endorphins and the dynorphins (Akil *et al.* 1984; Cooper, Bloom & Roth 1987). Opioid drugs are classified according to the receptors that they agonize or antagonize (Gustein & Akil 2001). Those most likely to be self-administered by humans are morphine-like in their effects, acting as agonists primarily at mu, but also at delta and kappa receptors (Herz 1998). Methadone, a common treatment for heroin addiction, is a long-lasting mu-receptor agonist with pharmacological properties qualitatively similar to those of morphine, but with a much longer half-life (Gustein & Akil 2001). Other substances currently used in treatment of opioid

dependence are long-acting agonists such as levo-alpha-acetylmethadol (LAAM), partial agonists such as buprenorphine, and full antagonists, such as naloxone and naltrexone, all of which act primarily at the mu opioid receptor (Mello *et al.* 1993; Ling, Rawson & Compton 1994; Strain *et al.* 1994a; Strain *et al.* 1994b; Ling *et al.* 1996; Comer, Collins & Fischman 2001; Gustein & Akil 2001; Petitjean *et al.* 2001).

Heroin, or diacetylmorphine, is a semisynthetic drug produced through chemical modification of the natural alkaloid morphine (Cox *et al.* 1983). The addition of the acetyl group allows heroin to penetrate the blood–brain barrier more quickly than morphine (Oldendorf *et al.* 1972) but once in the brain, heroin is rapidly de-acetylated into the active metabolite 6-monoacetylmorphine which is then de-acetylated again to form morphine (Umans & Inturrisi 1981). Like morphine, therefore, heroin has a greater affinity for mu receptors, the activation of which is associated with the induction of analgesia, respiration depression, miosis, reduced gastrointestinal motility and euphoria (Gustein & Akil 2001).

Cocaine is a powerful stimulant drug obtained from the plant *Erythroxylum coca* and has two main modes of action. Cocaine blocks the re-uptake of serotonin (5-HT), dopamine (DA) and noradrenaline (NA) (Ritz, Cone & Kuhar 1990), thus enhancing the duration and magnitude of their postsynaptic actions. Cocaine also blocks voltage-dependent sodium channels, an action that is responsible for the topical anaesthetic effects of this drug.

Although pharmacologically different, heroin and cocaine share an important characteristic: they serve as powerful motivators of appetitive behaviour. Humans, non-human primates and rodents will learn and perform a variety of different behaviours in order to obtain these drugs (Henningfield, Luckas & Bigelow 1986). In animals, both heroin and cocaine have been shown to control behaviour in much the same way as conventional reinforcers such as food and water (Spealman & Goldberg 1978; Young & Herling 1986).

There is considerable evidence that the common reinforcing and incentive effects of these drugs are mediated, at least in part, by increasing extracellular dopamine within the mesocorticolimbic dopaminergic system of the brain (Wise 1987; Koob 1992; Di Chiara 1995). The integrity of the nucleus accumbens (NAcc), a terminal region of the mesolimbic DA cells originating in the ventral tegmental area (VTA), is required for both cocaine and heroin self-administration (Zito, Vickers & Roberts 1985). Furthermore, self-administration of both heroin and cocaine has been shown to increase DA levels in the NAcc (Di Chiara & Imperato 1988; Pontieri, Tanda & Di Chiara 1995; Wise *et al.* 1995a; Wise *et al.* 1995b; Gratton 1996).

There are different cellular mechanisms, however, mediating the acute effects of heroin and cocaine on the mesolimbic DA system (North 1992). In the VTA, opioid-induced activation of dopamine cells is indirect. Morphine acts at mu opioid receptors located on GABAergic cells which normally inhibit DA neurones. Activation of mu receptors inhibits these inhibitory GABA interneurons, releasing DA cells from inhibition, thereby increasing DA release from terminals in NAcc (Joyce & Iversen 1979; Johnson & North 1992). Cocaine, on the other hand, increases DA activity in the NAcc mainly by prolonging the extrasynaptic life of whatever DA is released in the NAcc (White 1990; Gratton 1996; White 1996).

Although both of these drugs increase DA levels in the brain, each has multiple effects which may also play a role in their reinforcing effects. Furthermore, some of the effects of these drugs are opposite in direction; for example, acute opioids reduce activity in the NA systems of the brain (Maldonado 1997), whereas acute cocaine increases extracellular NA by blocking re-uptake (Pitts & Marwah 1987b; Ritz *et al.* 1990). Additionally, it is important to note that some of these acute actions are enhanced by repeated use whereas others show tolerance (for a review, see Stewart & Badiani 1993). Thus, when considering the effects of cocaine in opioid-dependent individuals, one must take into account a number of factors such as: duration of drug exposure, whether the addict is currently using heroin or is maintained on opioid-like medications, whether the addict is in acute withdrawal from heroin or in a period of chronic, prolonged abstinence. As an example of this complexity, let us consider the neurobiological effects of chronic exposure to heroin and cocaine.

The concept of within-systems adaptation (Koob & Bloom 1988) suggests that whereas heroin and cocaine lead to increased activity within the mesolimbic DA system, acute withdrawal from these drugs may result in decreased functional activity of the system (Koob *et al.* 1989; Koob *et al.* 1997). Indeed, it has been demonstrated that chronic exposure to opioids or cocaine is followed by a rebound inhibition of basal DA levels in the NAcc (Pothos *et al.* 1991; Rossetti, Hmaidan & Gessa 1992; Weiss *et al.* 1992; Maisonneuve, Ho & Kreek 1995). These decreases in DA activity in the NAcc after acute withdrawal from chronic heroin or cocaine are accompanied by a variety of intracellular, extracellular and receptor changes (Beitner-Johnson, Guitart & Nestler 1992; Volkow *et al.* 1993; Kreek 1997; Nestler & Aghajanian 1997; Volkow *et al.* 1997; Druhan, Walters & Aston-Jones 2000). Interestingly, this reduced activity may, in turn, be followed by long-lasting enhancement of DA activity that leads, at later time points, to enhanced responsiveness to these drugs and to other motivational

events (Robinson & Berridge 1993; Tjon *et al.* 1994; Nestby *et al.* 1997; Vanderschuren *et al.* 1999; Robinson & Berridge 2000). As a result, the acute effects of cocaine in opioid users at different times during the addiction cycle (Koob & le Moal 1997) cannot be predicted simply on the basis of acute cocaine pharmacology; the neural substrates on which cocaine is acting will be changed over time by opioid exposure.

Additionally, as mentioned above, heroin and cocaine can have effects on multiple neurochemical systems. Although indirect, cocaine, like heroin, has significant acute and chronic effects on the endogenous opioid system (Forman & Estilow 1988; Sivam 1989; Sweep *et al.* 1989; Unterwald 2001). Also, after withdrawal from chronic exposure to opioid drugs, there is hyperactivity within the NA neurones in the locus coeruleus (LC) (Childers 1991; Beitner-Johnson *et al.* 1992), an effect thought to underlie some of the symptoms of opioid withdrawal (Rasmussen *et al.* 1990; Aghajanian *et al.* 1992; Nestler, Alreja & Aghajanian 1994; Maldonado 1997; Nestler & Aghajanian 1997; Aston-Jones *et al.* 1999). Because cocaine acts to block NA re-uptake (Pitts & Marwah 1987b), its acute effects will vary as a function of heroin exposure and withdrawal.

Both opioids and stimulants also have multiple effects on glutamatergic transmission within the mesocorticolimbic DA system. Acute injections of opioid drugs suppress glutamate release in nucleus accumbens (Enrico *et al.* 1998; Sepulveda *et al.* 1998) and cortex (Nicol *et al.* 1996), whereas acute injections of cocaine lead to increased levels of glutamate in the VTA, nucleus accumbens, striatum and prefrontal cortex (Kalivas & Duffy 1995; Smith *et al.* 1995; Reid & Berger 1996; Reid *et al.* 1997). There are also profound changes in glutamatergic activity in the nucleus accumbens during exposure, withdrawal and after withdrawal from opioids (Sepulveda *et al.* 1998; Martin *et al.* 1999a, 1999b). Interestingly, the development of sensitization to the behavioural activating effects induced by chronic exposure to morphine or cocaine (Stewart & Badiani 1993) is dependent on glutamatergic activity within the mesocorticolimbic systems (Wolf 1998; Vanderschuren & Kalivas 2000). This suggests that chronic exposure to heroin and cocaine, through the alteration of neural plasticity at glutamatergic synapses (Ungless *et al.* 2001; Nestler 2001), can induce permanent alterations in the neural circuitry upon which these substances act to induce drug-taking and drug-seeking behaviours (see also Flores & Stewart 2000).

Given the complexity of all of these possible interactions, there could be multiple pharmacological explanations for cocaine use in opioid-dependent individuals. A study of patterns of heroin and cocaine co-use may provide some insights into which of these is more likely.

PATTERNS OF CO-USE

In general, two different, but not mutually exclusive, patterns of drug co-use have been identified (Ellinwood *et al.* 1976). The first involves the simultaneous administration of the two substances, as in the case of heroin and cocaine, a speedball, or in the case of heroin and amphetamine, a 'bombitas' (Ellinwood *et al.* 1976; Cox *et al.* 1983). Presumably, this method would occur if: (1) the combination of the two substances produced a unique set of subjective effects that was preferable to that produced by either drug alone, (2) the combination induced greater positive affect than either drug alone, or (3) the combination of the two substances served a particular purpose, such as self-medication.

The other pattern of co-use is the sequential administration of two drugs at different points in time during a typical day or even over longer periods (Ellinwood *et al.* 1976). Possible reasons for this pattern of co-use could be: (1) that one drug potentiates a desired effect of the other or (2) that one drug reduces an undesired effect of the other, such as withdrawal sickness during periods of abstinence. Below, we review the evidence bearing upon these different possible reasons for simultaneous and sequential co-use.

SIMULTANEOUS USE OF COCAINE AND HEROIN

The combination 'feels different'

The hypothesis that users inject a mixture of heroin and cocaine to induce a unique set of subjective effects has been investigated both in humans and in laboratory animals. Foltin & Fischman (1992) compared the subjective effects of intravenous cocaine and morphine taken alone or in combination in humans. Cocaine alone increased ratings of 'stimulated', whereas morphine alone increased ratings of 'sedated'. When administered together in a single bolus, subjects reported feeling the typical subjective effects of both morphine and cocaine. The authors concluded that the simultaneous self-administration of cocaine and morphine does not produce subjective effects that are qualitatively different from those produced by either drug alone. In a similar study, Walsh *et al.* (1996) evaluated the physiological and subjective effects of intravenous cocaine, hydromorphone, and their combination, in volunteers with a history of cocaine and heroin abuse. Similar to what was found by Foltin & Fischman (1992), cocaine and hydromorphone produced different profiles of physiological and subjective effects, and the combination of the two produced a profile that was characterized by effects typical of both cocaine and hydromorphone.

From these studies it can be concluded that the simultaneous administration of cocaine and opioids does not induce a novel set of subjective effects; rather, it induces, simultaneously, effects that are typical to both drugs. This, in itself, might be what attracts users to co-administer these two substances concurrently.

Studies of the similarities and differences between the subjective effects of heroin, cocaine and their combination have also been carried out in animals using the drug discrimination paradigm. In a typical drug discrimination experiment, monkeys or rodents are trained, using food reward, to perform one response following the injection of a drug, and to perform a second response following the injection of the drug vehicle. At the time of testing, the subjects receive other doses of the training drug or a different 'test' drug. The similarity between the discriminative properties of the training drug and the test drug is assessed by the degree to which the animal makes the response associated previously with the training drug (Colpaert 1986). Interestingly, the results of speedball discrimination studies in animals confirm the results from human studies. In both rhesus monkeys (Mello *et al.* 1995) and rats (Lamas *et al.* 1998), the discriminative stimulus properties of the speedball resemble those of either heroin or cocaine. In rats it has been found that morphine does not generalize to the discriminative stimulus properties of cocaine, but pre-treatment with morphine can potentiate the discriminative stimulus properties of cocaine (Suzuki *et al.* 1997). In monkeys, however, there is little evidence to suggest that heroin potentiates the effect of cocaine or that the effects of the two drugs are additive (Negus, Gatch & Mello 1998). These data suggest that, when tested with a heroin/cocaine combination, animals trained on either heroin or cocaine make their discrimination choice using the subjective cues of the training drug even when it is in combination, or in spite of the fact that it is in combination.

Given the nature of this evidence, it is concluded that heroin and cocaine are not likely to be administered simultaneously because the combination induces a unique set of subjective effects. It could be, however, that the mixture of heroin and cocaine mixture feels 'better' than heroin or cocaine alone.

The combination 'feels better'

Several studies carried out in both humans and laboratory animals investigated whether a mixture of heroin and cocaine is more rewarding than either drug alone.

In humans, there are anecdotal reports suggesting that opioid-dependent individuals self-administer cocaine and heroin simultaneously because the combination feels better (Kosten *et al.* 1988; Stine *et al.* 1993), but experimental evidence supporting these claims is weak. In the

study mentioned above by Foltin & Fischman (1992), it was found that subjects' ratings of 'high' and 'liking' were not greater for the combination of morphine and cocaine than for each drug alone, nor did the subjects estimate the value of the combination to be greater than that of each drug alone, when asked how much they would pay for the drug infusions. Similar findings were obtained by Walsh and associates (1996), using a hydromorphone/cocaine mixture.

Although a number of studies in laboratory animals have investigated the relative reinforcing effects of opioid/cocaine combinations compared to those of either drug alone, the data from such experiments are not easy to interpret. It has been found, for example, that monkeys, rats and mice will self-administer a combination of heroin and cocaine (Mello *et al.* 1995; Hemby, Smith & Dworkin 1996; Mattox, Thompson & Carroll 1997; Roberts, Polis & Gold 1997; Rowlett & Woolverton 1997; Duvauchelle, Sapoznik & Kornetsky 1998; Negus *et al.* 1998; Ranaldi & Munn 1998; Rowlett, Wilcox & Woolverton 1998) or a combination of methadone and cocaine (Wang *et al.* 2001), but because of difficulties that arise when trying to assess reinforcement magnitude, there is little direct evidence that the combination is more reinforcing than either drug alone. This issue has been studied by comparing the dose-response functions for each drug under different schedules of reinforcement with those generated by the addition of various doses of the second drug. Under these conditions, using a progressive-ratio schedule (PR) (Rowlett & Woolverton 1997) or a second-order fixed-ratio schedule (Mello *et al.* 1995), it has been found that monkeys will work harder for, or take more of, the low doses of one drug when it is in combination with the other. Such findings lead to the conclusion that cocaine and heroin enhance each other's reinforcing effects under certain limited conditions (Negus *et al.* 1998). Mattox *et al.* (1997) examined self-administration of heroin, cocaine and their combination by inhalation in monkeys. Using a behavioural economics analysis, they found greater demand for the combination than for heroin alone, but not for cocaine alone. In a recent study in monkeys by Wang *et al.* (2001), a solution of methadone and cocaine was preferred to either methadone or cocaine alone, but the preference for the combination was present when low doses of cocaine were used. There are two studies in rats (Duvauchelle *et al.* 1998; Ranaldi & Munn 1998) comparing the final ratios achieved under a PR schedule when animals were given heroin/cocaine combinations or either drug alone. The dose ranges used in the two studies varied considerably but, somewhat consistently, no synergistic effects were seen at middle doses. Interestingly, when the dose of cocaine was very high, the addition of heroin increased the breakpoint (Ranaldi & Munn 1998), but this finding could be explained by fac-

tors other than reinforcement magnitude. It is possible, for example, that the addition of heroin to a high dose of cocaine could reduce the aversive effects of cocaine or reduce the intensity of cocaine-induced stereotypy. In general, it appears that heroin and cocaine have synergistic effects on reinforcement only when low doses of both drugs are combined (Rowlett & Woolverton 1997; Duvauchelle *et al.* 1998; Rowlett *et al.* 1998).

Some researchers have investigated whether the administration of a mixture of heroin and cocaine would have synergistic or additive effects on levels of dopamine in the nucleus accumbens using *in vivo* microdialysis in rats (Zernig, O'Laughlin & Fibiger 1997; Gerasimov & Dewey 1999; Hemby, Dworkin & Smith 1999). Although pointing in the same direction, the results of these studies vary considerably. Gerasimov & Dewey (1999) reported that acute injections of heroin (0.5 mg/kg) and cocaine (20 mg/kg) that increased extracellular dopamine by 70% and 380%, respectively, when combined, produced a synergistic elevation of 1000%. The elevation in dopamine concentration induced by the mixture was slower to peak and lasted significantly longer than the increases caused by either drug alone. Similarly, Zernig *et al.* (1997) found that acute injections of heroin (0.15 mg/kg) and cocaine (3 mg/kg) that increased extracellular dopamine by 130% and 150%, respectively, when combined, produced a synergistic elevation of 220%, but no differences in time course were observed. Finally, Hemby *et al.* (1999) monitored dopamine levels in the nucleus accumbens in animals actively self-administering heroin, cocaine or a heroin-cocaine mixture. Similarly to Gerasimov & Dewey (1999), they observed that the combination of cocaine and heroin produced a synergistic elevation in dopamine of 1000%; however, this elevation was not accompanied by significant changes in locomotion, stereotypy or operant behaviour during self-administration (Hemby *et al.* 1999).

Taken together, the evidence presented in this section suggests that simultaneous use of heroin and cocaine can be more reinforcing than either drug alone, but only when low doses of heroin and cocaine are mixed. Thus, if the user has only a little heroin or cocaine, mixing the two in a speedball might induce effects that each drug alone would not produce.

The combination is used for self-medication

There is evidence that certain personality styles and profiles of psychopathology are associated selectively with the abuse of particular drugs (Milkman & Frosch 1973; Dolan *et al.* 1987; Brehm & Khantzian 1992; Hutchison, Wood & Swift 1999; Oswald, Roache & Rhoades 1999). Therefore, it might be thought that certain drugs or combinations of drugs might be used by individuals as medi-

cation for personality characteristics or moods. Malow *et al.* (1992) found some support for this idea when they compared speedball and pure cocaine users on measures of depression, anxiety and modal profile of personality characteristics measured by the Minnesota Multiple Personality Inventory (MMPI). Compulsive speedball users scored higher on depression, trait anxiety and related symptomatology, and were characterized more uniformly by more severe psychopathology and maladjustment than cocaine users. The argument that these psychological profiles motivate the use of specific combinations of drugs, however, is difficult to make because it might very well be that the intake of these drugs contributes to the development of these psychopathologies. There is a problem of circularity.

Self-medication can take other forms. There is evidence that some opioid-dependent individuals use the speedball to reduce their intake of opioids, and thus eliminate physical dependence. In a study of methadone maintenance programmes in New York, New Jersey and Connecticut, Hunt *et al.* (1984) interviewed addicts not in treatment, methadone patients and clinical staff. A self-medication regimen was described in which a combination of heroin and cocaine was used to reduce dependence on opioids. Users reported injecting heroin and cocaine simultaneously, increasing or keeping constant the amount of cocaine, but gradually decreasing the amount of heroin. This procedure would take 2–3 weeks to complete and it was said to allow for the elimination of heroin without withdrawal symptoms. Several respondents also suggested that a similar regimen is followed by methadone patients whereby methadone is taken orally, followed by injections of cocaine. The amount of methadone is gradually reduced over time in the same way that the heroin content of the speedball is reduced (Hunt *et al.* 1984). The same pharmacological procedure is also used in order to delay the onset of opioid dependence (Hunt *et al.* 1984). The effectiveness of this technique is, again, attributed to the fact that less heroin is taken when used in a speedball. Furthermore, there is the additional 'street belief' that cocaine reduces the effects of heroin and methadone (Hunt *et al.* 1984; Strug *et al.* 1985). As a result, cocaine is the drug of choice to be mixed with heroin because cocaine 'uses up' opioid drugs while still providing the rush, high or pleasure associated with the injection (Hunt *et al.* 1984). There is evidence that cocaine use in methadone-maintained patients is indeed associated with low serum methadone concentrations because cocaine accelerates methadone elimination (Tennant & Shannon 1995). On the other hand, cocaine can also enhance some of the effects of opioids. For example, as reviewed above, cocaine can increase the reinforcing properties of heroin or of methadone. Cocaine has been found to potentiate the analgesic efficacy of mor-

phine in rats, mice and monkeys (Nott 1968; Misra, Pontani & Vadlamani 1987; Shimada, Tsuda & Yanagita 1988; Sierra *et al.* 1992; Gatch *et al.* 1995). It appears, therefore, that there are several pharmacological reasons for using cocaine simultaneously with opioids, and different pharmacological interactions are exploited differentially by users in an attempt to achieve specific goals.

SEQUENTIAL USE OF COCAINE AND HEROIN

The sequential administration of opioids and cocaine may be more common than simultaneous administration, but this issue has not been addressed directly. As discussed above, a sequential pattern of self-administration would presumably be implemented if one drug was effective in potentiating the desired, or in reducing the undesired, effects of the other drug.

Cocaine 'feels better' to opioid-dependent individuals

Sequential use of cocaine by opioid-dependent individuals might be expected if the subjective effects of cocaine were enhanced by the regular use of opioids. Indeed, it has been suggested that the positive subjective effects of cocaine might be enhanced in patients maintained on methadone or buprenorphine (Rowlett *et al.* 1997). However, the experimental evidence for this idea is mixed.

Foltin *et al.* (1995) evaluated the effects of single and repeated doses of intravenous cocaine given to patients maintained on different doses of methadone. Patients maintained on the highest dose of methadone showed the largest increase in subjective measures of 'liking' and 'stimulated' following an acute injection of cocaine. Similar results were obtained by Preston *et al.* (1996), who compared the effects of cocaine in patients maintained on methadone to its effects in those who were neither dependent on opioids nor receiving opioids at the time of the study. Methadone-maintained patients displayed larger increases in heart rate and rated the positive subjective effects of cocaine more highly. Finally, Foltin & Fischman (1994) found that buprenorphine reduced ratings of 'bad drug effect' and increased ratings of 'high' associated with the administration of cocaine.

In contrast to these findings, there are several reports of no effects of opioid pre-treatment on the response to cocaine. In a subsequent study, Foltin & Fischman (1996) reported that the subjective effects of cocaine, including ratings of 'high', 'stimulated' and 'good drug effects' were not affected by methadone or by buprenorphine pre-treatment. Teoh *et al.* (1994) reported no change in response to cocaine on measures of detection, euphoria and plasma cocaine levels when cocaine was adminis-

tered before and during maintenance on buprenorphine. Similarly, Schottenfeld *et al.* (1993b) found no effect of the maintenance dose of buprenorphine on cocaine-induced euphoria. In monkeys, Winger & Woods (2001) studied the intake of intravenously delivered cocaine before, during and after daily administration of morphine. No changes in the reinforcing effects of cocaine were detectable during the period of chronic morphine administration. Rodefer *et al.* (1997) reported that buprenorphine pre-treatment had no effect on the number of cocaine deliveries obtained in monkeys trained on a progressive ratio schedule, suggesting that buprenorphine did not modify the reinforcing properties of cocaine. Similarly, Wang *et al.* (2001) reported that the intake of cocaine in monkeys simultaneously self-administering methadone was within the range of cocaine intake found in self-administration studies of cocaine alone (Meisch & Stewart 1995). Along the same lines, Leri & Stewart (2001) have found that rats readily self-administered heroin and cocaine sequentially, and the intake of each drug displayed by these animals did not differ from the intake of heroin and cocaine observed in animals trained to self-administer either drug alone. Finally, Downs (1979) found that the effects of cocaine on food-reinforced operant responding were not different in monkeys chronically treated with methadone and monkeys treated with vehicle; nor were there differences in blood level of cocaine between the two groups.

There is also some evidence that pre-treatment with opioid drugs, specifically with buprenorphine, suppresses cocaine self-administration, suggesting that this partial opioid agonist might reduce the reinforcing effects of cocaine. For example, Foltin & Fischman (1994, 1996) found that humans maintained on buprenorphine showed a decreased preference for high doses of cocaine and lower levels of self-administration of low doses. However, in an out-patient, double-blind study comparing cocaine use by buprenorphine and methadone maintenance, neither compound reduced cocaine-positive urine samples (Schottenfeld *et al.* 1993b). In monkeys, Mello & Negus (1998) found that buprenorphine reduced self-administration of speedball combinations of low, but not high, heroin and cocaine doses. In the case of low doses, buprenorphine shifted the dose-effect curve for speedball downward and to the right. In monkeys self-administering cocaine alone, Winger *et al.* (1992) found that buprenorphine suppressed responding maintained by cocaine, but the dose-effect curve was only shifted downward. Even in rats, it has been found that buprenorphine reduces cocaine self-administration (Comer *et al.* 1996), but as suggested by the type of dose-response shift (i.e. downward), this effect might not be selective to the reinforcing effects of cocaine. Supporting this conclusion, it has been shown that buprenorphine also suppresses the

self-administration of other drugs such as PCP, ethanol (Carroll *et al.* 1992) and, most importantly, of non-drug reinforcers such as saccharin solutions (Carroll & Lac 1992; Carroll *et al.* 1992).

Clearly, although there is some evidence that the subjective effects of cocaine are enhanced in individuals maintained on opioids, there is considerable evidence suggesting that they are not. Most probably, the dosage of opioid maintenance is a critical factor modulating the response to cocaine in these patients (Borg *et al.* 1999). None the less, because cocaine continues to induce euphoria in patients treated with methadone or buprenorphine, these individuals may keep using it to replace the euphoria formerly obtained from heroin (Strug *et al.* 1985; Kosten *et al.* 1987).

Reduction of side-effects

There are several examples in the literature describing the use of one drug to reduce the side-effects of the other (Kipperman & Fine 1974). This is exemplified by the pattern of oral stimulant use that was prevalent during the 1970s in middle-class businessmen, professionals and housewives (Ellinwood *et al.* 1976). It involved the use of amphetamines to stimulate mood and activity during the day, and alcohol or sedatives at night to calm the 'jitters' and to induce sleep. Not infrequently, individuals acquired dual dependence (Ellinwood 1973). Similarly, street users may inject doses of cocaine at short intervals, taking large quantities over a period of a few days, without sleeping or eating. Gradually, during such a 'binge', the user becomes more tense, irritable and exhausted and finally 'crashes', usually after the ingestion of large doses of alcohol and/or sedatives (Kramer, Fischman & Littlefield 1967; Gawin & Kleber 1986). Interestingly, the pattern of intake developed during this type of co-use varies with the drug preferences of the individual. Kipperman & Fine (1974), for example, identified two groups of alcohol and amphetamine co-users. One alcohol-preferring group used small quantities of amphetamine to maintain a wakeful state that enabled them to drink more alcohol. The other group used amphetamines primarily and took small doses of alcohol to 'level off during a trip' and large quantities to induce sleep. Particular patterns of use can develop out of personal circumstances; opioid addicts use amphetamines to sustain the activity level needed to 'hustle' the necessary funds for their opioid habit (Ellinwood *et al.* 1976).

Two distinct groups of heroin and cocaine co-users can also be identified. The first group, although of minimal relevance to the present discussion, is represented by heavy cocaine users who seek the depressant effect of heroin to deal with the state of over-excitability produced by frequent cocaine abuse (Hunt *et al.* 1984; Foltin &

Fischman 1992; Frank & Galea 1996); heroin is reported to 'mellow out' and ease the 'crash' experienced when the cocaine effect wears off (Strug *et al.* 1985; Kosten *et al.* 1987; Kreek 1997). This type of user may not be physically dependent on opioids, although increasing the frequency of the combination might increase the likelihood of physical reliance on heroin (Levin *et al.* 1996). The second group of individuals that use both cocaine and heroin, and of primary importance for this review, is made up of those who use heroin regularly and cocaine periodically to alleviate the most unpleasant side-effects of heroin dependence: that is, symptoms of opioid withdrawal (Burroughs 1977; Wikler 1980). Interestingly, cocaine was proposed as a treatment for withdrawal sickness in morphine-dependent individuals in the early 1900s (Grinspoon & Bakalar 1976). Most notably, Freud treated a patient who was morphine-dependent with cocaine (Freud 1887). In the same era, one of the founding fathers of the Johns Hopkins School of Medicine attempted to gradually reduce his morphine intake by self-administering cocaine, but found the effects of cocaine to be more debilitating than morphine dependence (Penfield 1969).

Several recent studies have provided evidence that cocaine can decrease the intensity of opioid withdrawal. In opioid-dependent individuals not in treatment, cocaine has been used to postpone withdrawal symptoms (Rosen *et al.* 1992) and to modulate the severity of opioid withdrawal (Kosten *et al.* 1989a). In humans and in rats physically dependent on heroin, morphine or methadone, withdrawal signs precipitated by naloxone are attenuated by acute cocaine administration (Kosten 1989; Kosten 1990). Curiously, it has also been reported that in heroin dependent individuals, a history of chronic use of high doses of cocaine reduces the symptoms of withdrawal induced by naloxone (Kosten & Kosten 1989).

These observations might be explained by known pharmacological actions of opioids and cocaine at the level of the noradrenergic (NA) system. For example, although opioid drugs suppress activity in NA neurones, chronic opioid treatments lead to tolerance of this effect and, after withdrawal, to increased activity in these systems (Maldonado 1997). In withdrawal, there is increased adenylate cyclase activity in the NA neurones in the LC (Beitner-Johnson *et al.* 1992), increased rate of cell firing and consequent increases in NA release in target regions (Maldonado 1997; Nestler & Aghajanian 1997). Furthermore, blockade of this NA hyperactivity reduces the severity and aversive nature of opioid withdrawal (Aston-Jones *et al.* 1999). Interestingly, although cocaine acts to block the NA transporter leading to greater availability of NA at postsynaptic sites (Williams & Lacey 1988; Thomas, Post & Pert 1994), it also reduces

NA cell firing because of greater activation of the NA alpha-2 autoreceptors (Pitts & Marwah 1986a, 1986b, 1987a, 1987b, 1987c). With chronic exposure to cocaine, these receptors become desensitized (Pitts & Marwah 1989), but there is evidence that after a period of withdrawal from cocaine, the NA-mediated inhibition of NA neurones caused by acute exposure to cocaine is enhanced (Harris & Williams 1992). Thus, paradoxically, cocaine could be an effective way to medicate the symptoms of opioid-withdrawal that are associated with NA hyperactivity.

The relationship between cocaine and opioid withdrawal is complicated further by the fact that the acute effects of cocaine are modulated by the severity of opioid dependence and by the severity of withdrawal the user is experiencing at the time of cocaine administration. In a series of interviews carried out with regular opioid users by Stine *et al.* (1993), over 70% reported opioid-like withdrawal symptoms immediately after cocaine use when they were under the influence of opioids. When in mild withdrawal, however, most subjects reported that cocaine relieved the symptoms for a short period of time.

Stine & Kosten (1994) attempted to assess the validity of these subjective reports by studying levels of withdrawal symptoms associated with cocaine use in opioid-maintained patients (buprenorphine, 2 or 6 mg, or methadone, 35 or 65 mg), monitored for cocaine use via urine tests. They hypothesized that cocaine use might have reduced the intensity of symptoms of withdrawal whereas, when no opioid withdrawal symptoms were present and the subjects were dependent on high opioid doses, cocaine use might have precipitated withdrawal. In support of this hypothesis, they found that in patients maintained on low doses of either drug (neither of which eliminated withdrawal symptoms), cocaine use was associated with a reduction of withdrawal symptoms. In contrast, in patients maintained on high doses of buprenorphine (i.e. 6 mg), opioid-like withdrawal symptoms were experienced after cocaine use. They argued that this was not found after the highest dose of methadone because this dose was, in fact, quite low. The finding that cocaine can precipitate withdrawal in patients maintained on high doses of opioids could explain why cocaine use is decreased dramatically in patients maintained on high buprenorphine doses (i.e. 8 mg) or in subjects maintained on high doses of methadone (100–120 mg) (Stine *et al.* 1992; Borg *et al.* 1999). In fact, subjects maintained on high doses do report that they decrease cocaine use because cocaine becomes 'unpleasant' (Kosten *et al.* 1989b).

In summary, there is evidence that cocaine can be used to decrease the intensity of opioid withdrawal symptoms in individuals maintained on low doses of opioids. As reviewed above, heroin and cocaine can interact in a

number of different ways through different neuronal systems. Cocaine could alleviate the dysphoria associated with opioid withdrawal by virtue of its agonistic activities within the mesolimbic dopamine system or the endogenous opioid system. In addition, it remains possible that cocaine could alleviate opioid withdrawal by decreasing the hyperactivity of the NA system.

CONCLUSIONS

A significant number of heroin users and of methadone- or buprenorphine-maintained individuals use cocaine. Co-use of cocaine in these populations has serious detrimental effects on physical health, mental health and social integration. Abundant anecdotal and clinical evidence documents the existence and relevance of this drug practice, but the patterns and the reasons for cocaine use are poorly understood.

There is evidence that cocaine is co-used with opioid drugs in different ways for different reasons. Some users inject the two substances simultaneously in the form of a speedball to experience the effects of both drugs at the same time. Some use the speedball to achieve a greater level of euphoria, especially when they have insufficient quantities of either drug. Other users mix cocaine with heroin with the goal of gradually reducing heroin and, consequently, eliminating their physical reliance upon opioids. Heroin users often report co-use of cocaine in a sequential manner either to enhance euphoria or to reduce the withdrawal symptoms commonly experienced during their typical day (Kreek 1997) or when they decide to detoxify from opioid drugs (Hunt *et al.* 1984).

Many of the questions raised in this review can be approached through pre-clinical behavioural pharmacological studies of co-use in self-administering laboratory animals. The fact remains, however, that little is known about the importance of pharmacological factors and their interplay with social factors, such as the so-called 'drug culture' or 'street fashion', in the induction and maintenance of heroin-cocaine co-use.

Our review of the literature suggests the need for systematic studies of the patterns of co-use in both humans and animals. In humans, it would be particularly important to determine the temporal relationship between heroin and cocaine self-administration. The method of Ecological Momentary Assessment (EMA) might be useful to the investigation of this issue. As implied by the term, EMA involves assessing the occurrence of target behaviours at the moment they occur in the natural setting, thus maximizing ecological validity while avoiding retrospective recall (Stone & Shiffman 1994). EMA has been used extensively to analyse smoking behaviour

(Shiffman *et al.* 1996; Shiffman *et al.* 1997; Catley *et al.* 2000; Shiffman *et al.* 2000). This method has been used to examine the covariation between smoking and drinking in clinical samples (Shiffman *et al.* 1994). We suggest that a EMA analysis of heroin-cocaine co-use, coupled with questionnaires specifically designed to determine reasons for co-use, might help identify common patterns and reasons for heroin-cocaine co-use. Furthermore, because patterns of co-use are likely to be affected by non-pharmacological variables, we suggest that such descriptive information should be gathered into different groups of heroin-dependent individuals. For example, we are currently collecting information about patterns and reasons of heroin-cocaine co-use, using the same survey instrument, in a number of different cities across Canada. It is predicted that some patterns will be observed in all cities, thus indicating a major pharmacological determinant.

Studies in laboratory animals will also be very useful in investigating the pharmacology of heroin-cocaine co-use. Obviously, there is the need to explore further the behaviour of animals that are allowed to self-administer both opioid and stimulant drugs (e.g. Leri & Stewart 2001; Wang *et al.* 2001). In animals so trained, it would then be possible to explore a number of issues raised in this review such as the effect of opioid dependence, opioid withdrawal and methadone/buprenorphine pre-treatments, on concurrent self-administration of heroin and cocaine.

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