International Journal of Drug Policy 26 (2015) 1177–1182

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Commentary

Addressing the stimulant treatment gap: A call to investigate the therapeutic benefits potential of cannabinoids for crack-cocaine use

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 8 September 2015
Accepted 15 September 2015

Keywords:
Crack-cocaine
Treatment
Pharmacotherapy
Cannabinoids
Cannabidiol
Americas

ABSTRACT

Crack-cocaine use is prevalent in numerous countries, yet concentrated primarily – largely within urban contexts – in the Northern and Southern regions of the Americas. It is associated with a variety of behavioral, physical and mental health and social problems which gravely affect users and their environments. Few evidence-based treatments for crack-cocaine use exist and are available to users in the reality of street drug use. Numerous pharmacological treatments have been investigated but with largely disappointing results. An important therapeutic potential for crack-cocaine use may rest in cannabinoids, which have recently seen a general resurgence for varied possible therapeutic usages for different neurological diseases. Distinct potential therapeutic benefits for crack-cocaine use and common related adverse symptoms may come specifically from cannabidiol (CBD) – one of the numerous cannabinoid components found in cannabis – with its demonstrated anxiolytic, anti-psychotic, anti-convulsant effects and potential benefits for sleep and appetite problems. The possible therapeutic prospects of cannabinoids are corroborated by observational studies from different contexts documenting crack-cocaine users' 'self-medication' efforts towards coping with crack-cocaine-related problems, including withdrawal and craving, impulsivity and paranoia. Cannabinoid therapeutics offer further benefits of being available in multiple formulations, are low in adverse risk potential, and may easily be offered in community-based settings which may add to their feasibility as interventions for – predominantly marginalized – crack-cocaine user populations. Supported by the dearth of current therapeutic options for crack-cocaine use, we are advocating for the implementation of a rigorous research program investigating the potential therapeutic benefits of cannabinoids for crack-cocaine use. Given the high prevalence of this grave substance use problem in the Americas, opportunities for such research should urgently be created and facilitated there.

Globally, up to 0.5% – or 21 million individuals – of adults are estimated to be cocaine users; while the precise extent is unknown, a substantive proportion of cocaine use consists of crack-cocaine use, i.e. a (typically smoked) freebase form of cocaine (Degenhardt & Hall, 2012; United Nations Office on Drugs and Crime (UNODC), 2015). Crack-cocaine use is most common in (both hemispheres) of the Americas, typically concentrated in

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http://dx.doi.org/10.1016/j.drugpo.2015.09.005
0955-3959/

urban and highly marginalized drug user populations, as documented in studies from multiple jurisdictions from North to South (Fischer & Coghlan, 2007; Fischer, Cruz, Bastos, & Tyndall, 2013; Werb et al., 2010). Brazil alone is reported to have one of the world's largest crack markets, with an estimated 370,000 in its 27 capitals yet comprising possibly as many as 1 million – predominantly young – users in total: in many North American cities crack-cocaine has been a highly prevalent street drug for many years (Bastos & Bertoni, 2014; Fischer et al., 2013; Santos Cruz, Andrade, Bastos, Leal, Bertoni, Villar, et al., 2013).

Crack-cocaine use is associated with extensive health and social burdens. Crack-cocaine use commonly occurs by way of intensive use ('binge') patterns, and is documented to result in both acute and long-term physical (e.g., cardiac, pulmonary, neuro-vascular, gastro-intestinal, nutrition and sleep) (Afonso, Mohammad, & Thatai, 2007; Cornish & O'Brien, 1996; Falck, Wang, Siegal, & Carlson, 2003; Fischer et al., 2006; Haim, Lippmann, Goldberg, & Walkenstein, 1995; Lange & Hillis, 2001; Vogenthaler et al., 2010), as well as cognitive-behavioral and psychiatric problems (e.g., impulsivity, depression, psychosis/anxiety disorders) (Coffey, Dansky, Carrigan, & Brady, 2000; Falck, Wang, Siegal, & Carlson, 2004; Ford et al., 2009; Hoffman et al., 1996; McDermott, Tull, Gratz, Daughters, & Lejuez, 2009), although the causal relations are not always clear. Crack-cocaine users – typically facilitated through both intensive drug use and/or sexual risk (e.g., survival sex work or sex-for-drug exchanges) pathways – also feature elevated risks for HIV, Hepatitis C Virus (HCV), tuberculosis and other chronic infectious diseases, as well as high rates of mortality, even when compared to other drug users (Booth, Kwiatkowski, & Chitwood, 2000; Cook et al., 2008; Degenhardt et al., 2011; Khan et al., 2013; Scheinmann et al., 2007; Story, Bothamley, & Hayward, 2008). Many crack-cocaine users are poor and homeless, commonly engage in drug or acquisition crimes and are subject to violence in the context of volatile crack markets (Bennett, Holloway, & Farrington, 2008; Bungay, Johnson, Varcoe, & Boyd, 2010; Carvalho & Seibel, 2009; Grogger & Willis, 2000; Milby, Schumacher, Wallace, Freedman, & Vuchinich, 2005; Robertson et al., 2004). In Brazil, 'cracolandias' have become iconic phenomena of entire communities ravished by the destructive impacts of crack-cocaine use, trade and violence (often involving drug gangs and police) (Alves & Alves, 2015; Raupp & Adorno, 2011).

Contrary to its prevalence and extensive health and social harms, few effective interventions exist for crack-cocaine use (Fischer et al., 2015; Richard, Montoya, Nelson, & Spence, 1995; Santos Cruz, Andrade, Bastos, Leal, Bertoni, Lipman, et al., 2013; Santos Cruz, Andrade, Bastos, Leal, Bertoni, Villar, et al., 2013; Strathdee & Stockman, 2010; Van den Brink, 2005; Wallace, 2014). A variety of secondary prevention-type interventions to reduce crack-cocaine use and related sexual risk behaviors – e.g., through community-based behavioral or material ('safer crack use kit' distribution) interventions – have been implemented, yet only demonstrated limited, and rarely sustained, uptake and impacts (Ivsins, Roth, Nakamura, Krajden, & Fischer, 2011; Malchy, Bungay, Johnson, & Buxton, 2011; Ti et al., 2012). Equally limited is the situation regarding evidence-based treatments for crack-cocaine use. Various psycho-social treatment options have been examined. While some have shown (mainly short-term) effects aided by contingency management, such treatments are resource-intensive and politically controversial, and therefore rare in availability (Corsi, Rinehart, Kwiatkowski, & Booth, 2010; Farronato, Dürsteler-Macfarland, Wiesbeck, & Petitjean, 2013; Grella, Hser, & Hsieh, 2003; Henskens, Garretsen, Bongers, Van Dijk, & Sturmans, 2008; Maude-Griffin et al., 1998; Prendergast, Podus, Finney, Greenwell, & Roll, 2006; Schottenfeld, Moore, & Pantalon, 2011). A large number of studies have examined diverse pharmacotherapeutic agents (e.g., including various GABA agents, topiramate, modafinil, disulfiram, varenicline) as candidates for crack-cocaine use disorder treatment, ideally to identify a 'gold-standard' treatment option (for example, similar to the use of methadone/buprenorphine for opioid dependence) (Amato et al., 2011; Mattick, Breen, Kimber, & Davoli, 2009). However, outcomes of pharmacological treatment studies for crack-cocaine disorders overall have been summarized as mostly "disappointing" (Nuijten, Blanken, van den Brink, & Hendriks, 2011), and even concluded that "no pharmacological treatment [to date] has proven to be effective" (Karila et al., 2011); see furthermore (Ciccarone, 2011; Fischer et al., 2015; Kampman, 2010; Shorter & Kosten, 2011). Very recent clinical trials with two promising pharmacological compounds – modafinil and topiramate – have produced more disappointing results regarding clinical acceptance, adherence and efficacy (Nuijten, Blanken, van den Brink, & Hendriks, 2014; Nuijten, Blanken, van den Brink, & Hendriks, 2015). Relatively promising prospects for pharmacotherapeutic interventions for cocaine dependence may exist with a 'maintenance treatment' approach with high-dose dexamphetamine; however, these remain to be systematically examined, yet would be both politically controversial and pose major practical challenges for implementation in ordinary treatment settings (Nuijten et al., 2011; Shearer, Wodak, van Beek, Mattick, & Lewis, 2003). On this basis, evidence-based options for effective therapeutic interventions towards reducing health and social harms related to crack-cocaine use that are feasible in clinical practice are rather limited, if non-existent in real-world settings.

There have been numerous recent examples of 're-purposing' of existent pharmaceutical compounds for possible treatment of psycho-behavioral disorders (including substance use disorders) (Nutt, Lingford-Hughes, & Chick, 2012). Given the acute treatment gap for crack-cocaine, it therefore appears timely and expedient to examine the potential therapeutic benefits of a pharmacological compound group that has long existed, yet is receiving increasing attention (again) only recently: Cannabinoids, or cannabis-based therapeutics (Ben Amar, 2006; Borgelt, Franson, Nussbaum, & Wang, 2013; Devinsky et al., 2014; Robson, 2014). Cannabinoid-based therapeutics were widely used in Western medicine by the late 19th century, yet subsequently became subject to cannabis prohibition emerging in the early 20th century, and largely eliminated in therapeutic availability (Borgelt et al., 2013; Zuardi, 2008). In recent years – also in the context of the expansive proliferation of 'medical cannabis' programs in several countries, including the region of the Americas – there has been accelerating interest in the potential therapeutic benefits and applications of cannabinioids. Although the quality of investigations and evidence remains heterogeneous, a considerable number and variety of animal and human studies exist which examine the effects of cannabis-based products on various diseases or symptoms (Ben Amar, 2006; Fischer et al., 2015; Hoffmann & Weber, 2010; Koppel et al., 2014; Robson, 2014; Whiting et al., 2015; Zuardi, 2008). Conceptually, potential for therapeutic effects for crack-cocaine use may exist since cannabinoid formulations have shown benefit potentials directly acting on substance use processes and outcomes, as well as on problem symptoms or co-morbidities many crack-cocaine users suffer from, including: dependence/withdrawal, impulsivity/aggression, anxiety/psychosis, sleep and nutritional problems. Based on available data, cannabinoid-based therapeutic interventions – which have been implemented involving a variety of compounds or formulations that include smoked cannabis, synthetic or synthetic analogue (oral) formulations of key cannabis components (e.g., THC; dronabinol, marinol, nabilone) or cannabis extracts (e.g., cannador), or oramucoscal spray administration (e.g., nabiximol) (Grant, Atkinson, Gouaux, & Wilsey, 2012; Koppel et al., 2014) – in terms of main effects have shown potential to: reduce (primarily neuropathic) pain symptoms; reduce nausea–emesis and stimulate appetite; and facilitate muscle/spasticity-relaxation

(e.g., in the context of multiple sclerosis), as well as exert other desirable neurological effects (see key reviews: Ben Amar, 2006; Grant et al., 2012; Koppel et al., 2014; Robson, 2014). In addition, there is some evidence of attenuation of withdrawal effects for purposes of cannabis dependence treatment (Allsop et al., 2014).

Notably, cannabis pharmacologically consists of some 100 cannabinoids (with THC as a main psychoactive component) and therapeutic effects greatly depend on the specific composition of the compound (e.g., cannabis strain) used. Most recently, the specific cannabinoid cannabidiol (CBD) has gained increasing attention for possible and distinct (isolated) therapeutic effects (Mechoulam, Parker, & Gallily, 2002; Pertwee, 2006; Russo, 2011; Zuardi, 2008). CBD can make up as much as 40% of the cannabis extract; its multiple action pathways are not yet fully understood, although have been described to modulate some of THC's – and probably those of other cannabinoid elements – effects (Devinsky et al., 2014; Fernandez-Ruiz, 2012; Scuderi et al., 2009; Zuardi, 2008). Potential therapeutic benefits of CBD have been established in several relevant domains for crack-cocaine use related symptoms and problems, including: Anti-psychotic effects: CBD has shown to be safe and effective compared to standard antipsychotic medication in both animal models and psychiatric patients and seems to improve cognitive functioning, which is often compromised in schizophrenic patients; it has resulted in reduction of positive psychotic symptoms among ketamine users and furthermore, psychotic effects of cannabis are lower in strands where THC:CBD ratios are slanted towards the latter (Iseger & Bossong, 2015; Leweke et al., 2012; Morgan et al., 2012; Schubart et al., 2014; Zuardi, 2008; Zuardi, Rodrigues, & Cunha, 1991). Anxiolytic effects: CBD has demonstrated anxiolytic effects in animal models relying on various methods and outcomes (Almeida et al., 2013; ElBatsh, Assareh, Marsden, & Kendall, 2012); it has shown to reduce general and social anxiety disorder symptoms, as well as the anxiogenic effects of THC (Bergamaschi et al., 2011; Crippa et al., 2011; Fusar-Poli et al., 2009). Anti-convulsant effects: In animal studies, CBD featured powerful anti-convulsant activity; similarly, anecdotal human patient reports and (limited) clinical trial data suggested CBD's protective effects for generalized seizures in epileptics (Cortesi & Fusar-Poli, 2007; Cunha et al., 1980; Karler & Turkanis, 1981). Furthermore, there is initial evidence that CBD may therapeutically aid in sleep disorder-related behaviors (Chagas et al., 2014). In addition, CBD has been shown to exert potential (e.g., anti-inflammatory, neuro-/cardio-protective, anti-emetic, anti-oxidant) effects that, however, do not seem to be primarily pertinent to crack-cocaine use and related problem symptoms (Ben Amar, 2006; Fernandez-Ruiz, 2012; Mechoulam et al., 2002; Scuderi et al., 2009; Zuardi, 2008).

Beyond CBD's aforementioned benefits for various CNS-related symptoms, there is growing recent evidence – albeit based on a small number of studies – for CBD's potential more specifically for the treatment of addictive disorders (Prud'homme, Cata, & Jutras-Aswad, 2015). For example, CBD appears to reduce the intoxication and reward effects of opioids (e.g., morphine), and may – in combination with THC – blunt opioid-related withdrawal effects (Bhargava, 1976; Katsidoni, Anagnostou, & Panagis, 2013; Ren, Whittard, Higuera-Matas, Morris, & Hurd, 2009). CBD may also have beneficial effects on cannabis-related intoxication or withdrawal symptoms (Crippa et al., 2013; Morgan, Pace-Schott, Pittman, Stickgold, & Malison, 2010). Specifically for psycho-stimulants, Parker, Burton, Sorge, Yakiwchuk, and Mechoulam (2004) demonstrated the extinction effect of CBD on cocaine-and amphetamine-induced place preference learning, which may aid in preventing stimulant-related relapse effects (Parker et al., 2004). A randomized controlled trial with tobacco (nicotine) smokers found reductions in both the number of cigarettes smoked and tobacco-related craving associated with the CBD-treatment intervention (Morgan, Das, Joye, Curran, & Kamboj, 2013). Commentators have recently suggested – also in reference to psycho-stimulants – that CBD presents "an interesting pharmacological candidate to treat substance-use disorders" (Prud'homme et al., 2015) and "should be evaluated ... as a potential agent to treat human addictive behaviors" (Devinsky et al., 2014). Importantly for potential therapeutic usages, CBD allows for multiple routes of administration (e.g., nasal, oral, etc.); in addition to the absence of psychotropic effects, no evidence exists for CBD-induced teratogenic or mutagenic effects, and it exhibits markedly little (if any) toxicity in humans (Bergamaschi et al., 2011; Scuderi et al., 2009).

Notably, while laboratory or clinical human studies on cannabinoids' possible therapeutic benefits for psychostimulant use disorders are limited to date, data from several observational human studies have provided evidence for possible benefits among crack-cocaine users. Among $n = 25$ young/male crack-cocaine addicts in Sao Paulo, Brazil, the majority (68%) stopped crack-cocaine use and reported that cannabis use had reduced their craving symptoms for crack-cocaine, and helped them to overcome crack addiction (Labigalini, Rodrigues, & Da Silveira, 1999). An ethnographic study of 33 inner-city female crack-cocaine users in Kingston, Jamaica, found cannabis to be used in conjunction with crack-cocaine to minimize the undesirable effects of crack-cocaine smoking, specifically paranoia and weight loss; cannabis cigarettes ("spliffs") were found to constitute the most effective and readily available therapy for discontinuing crack-cocaine consumption (Dreher, 2002). Andrade, Santiago, Amari, and Fischer (2011), based on qualitative data, documented the combined smoked use of crack-cocaine and cannabis ('pitilho') as a way to reduce the undesired effects of crack-cocaine use (e.g., aggression, anxiety, appetite deficits) among users in Salvador, Brazil. Similarly, multiple Sao Paulo-based studies demonstrated how past and active crack-cocaine users used cannabis as a 'survival strategy' to reduce adverse crack-cocaine related experiences, including, craving, paranoia and aggression (Chaves, Sanchez, Ribeiro, & Nappo, 2011; Goncalves & Nappo, 2015; Ribeiro, Sanchez, & Nappo, 2010). These observational data – from diverse socio-cultural settings – suggest potential therapeutic benefits from cannabinoids experienced by crack-cocaine users in natural life settings.

Feasible and effective therapeutic options for crack-cocaine use are urgently needed. Based on the emerging evidence for the multifold therapeutic potentials of, as well as the observational data on crack-cocaine users' 'self-medication' efforts with cannabinoids, it is reasonable to assume that there may indeed be varied valuable therapeutic benefits for crack-cocaine use. There are several advantages to cannabinoid agents that render experimental therapeutic interventions relatively easy and feasible. None of the cannabinoid products – i.e. whether THC- or CBD-based formulations – pose high risks for abuse or adverse effects (e.g., overdose or diversion); they likely offer options for various non-invasive routes of administration (e.g., oral or nasal) and thus could easily be provided in community-based/low-threshold treatment settings (Bergamaschi et al., 2011; Borgelt et al., 2013; Devinsky et al., 2014; Grant et al., 2012; Scuderi et al., 2009). These provisions may be important simply for attracting and retaining crack-cocaine users – many of whom are marginalized and disconnected from conventional or institutional treatment systems – into possible CBD-based treatment studies (Fischer et al., 2006; Malta et al., 2011; Santos Cruz, Andrade, Bastos, Leal, Bertoni, Lipman, et al., 2013; van der Poel, Barendregt, & van de Mheen, 2006). While it may be unrealistic to assume that cannabinoid agents will offer an actual 'cure' for crack-cocaine use, select formulations may entail valuable and substantive 'therapeutic relief' effects, both towards possible crack-cocaine use reductions but specifically for the powerful adverse physical, behavioural and psychological problem symptoms distinct for

crack-cocaine use which gravely affect both many users and their social environments (Andrade et al., 2011; Nuijten et al., 2011; Ribeiro et al., 2010). Based on the evidence available, and given the widespread prevalence and harm impacts of crack-cocaine use in the context of a categorical lack of effective treatment options, we are calling for the urgent development and implementation of a research program to examine the therapeutic potential of cannabinoids for crack-cocaine use. The Director of the NIH's National Institute on Drug Abuse (NIDA), Dr. Nora Volkow, in a recent testimony to the US Senate (24 June 2015), suggested that "CBD may have therapeutic value as a treatment of substance use disorders" and emphasized the "need for rigorous clinical research in this area" (Volkow, 2015). Such a research program with a specific focus on crack-cocaine use would need to first answer multiple basic questions – e.g., including the feasibility of therapeutic cannabinoid provision for the target population, preferred compounds and delivery modalities, etc. – but should be particularly opportune and desirable in jurisdictions of the Americas where crack-cocaine use related problems and their negative individual and social impacts are widespread, and therapeutic options are direly needed.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors. We confirm that we have given due consideration to the protection of intellectual property associated with this work.

Acknowledgements

Dr. Fischer acknowledges research support from CIHR for the Ontario CRISM Node Team (grant# SMN-139150) and a CIHR/PHAC Applied Public Health Research Chair award. Dr. Wood acknowledges funding support from a Canada Research Chair (CRC) in Inner City Medicine.

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