Drug and Alcohol Dependence 133 (2013) 795–804

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Review

A systematic review of evidence on the association between cocaine use and seizures

L. Sordo[a,b,c,*], B.I. Indave[d], L. Degenhardt[e,f,g], G. Barrio[h], S. Kaye[e], I. Ruíz-Pérez[c,i], M.J. Bravo[a,c]

[a] National Centre of Epidemiology, Carlos III Health Institute, Madrid, Spain
[b] Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University, Madrid, Spain
[c] Network Biomedical Research Centers, Epidemiology and Public Health (CIBERESP in Spanish), Spain
[d] Service of Preventive Medicine, Mostoles Hospital, Madrid, Spain
[e] National Drug and Alcohol Research Centre, University of New South Wales, NSW 2052, Australia
[f] Burnet Institute, VIC 3004, Melbourne, Australia
[g] Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, VIC 3010, Australia
[h] National School of Public Health, Carlos III Health Institute, Madrid, Spain
[i] Andalusian School of Public Health, Granada, Spain

ARTICLE INFO

Article history:
Received 3 April 2013
Received in revised form 25 July 2013
Accepted 22 August 2013
Available online 2 September 2013

Keywords:
Neurologic disorder
Seizures
Cocaine use
Systematic review

ABSTRACT

Background: Institutional monographs/medical textbooks mention seizures as a neurological complication of cocaine, but no systematic reviews (SRs) have been published on this issue. We aimed to conduct a SR of the literature on the relationship between cocaine use and seizures and to summarize the biological plausibility of that relationship.
Methods: The pathophysiological mechanisms that may underlie an association between cocaine and seizures were summarized; a SR was then performed using three databases (EMBASE, Medline, PsycINFO) and the Cochrane-library to search for published papers (1980–2012) aimed at quantifying the associations between cocaine use and seizures. The inclusion criteria for selection were: articles based on clinical trials, cohort, case-control (CC) or cross-sectional (CS) studies, participants ≥14 years old and not pregnant, and use of cocaine in the last 72 h. Information was extracted, evaluated and cross-checked independently by two researchers.
Results: Of the 1243 potentially relevant articles initially identified; one CC and 22 CS studies were finally selected. The CC study did not find cocaine use to be a risk-factor for seizures. In addition to the limitations of the CS design, these studies had important methodological weaknesses and biases.
Conclusions: Despite its biological plausibility, no rigorous scientific evidence supports a causal relationship between cocaine use and seizures. The misinterpretation of the role of cocaine may have important implications in medical services. Well-conducted studies are urgently needed.

Contents

* Corresponding author at: National Centre of Epidemiology, Carlos III Health Institute, Avda Monforte de Lemos 5, 28029 Madrid, Spain. Tel.: +34 918222678.
E-mail address: lsordo@isciii.es (L. Sordo).

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http://dx.doi.org/10.1016/j.drugalcdep.2013.08.019

1. Introduction

Globally, cocaine use is a significant public health problem. The United Nations Office on Drugs and Crime World Drug Report (UNODC, 2013) estimated the past-year prevalence of cocaine use in 2011 as between 0.3% and 0.5% of the world population aged 15–64 (13.9–20.7 million people), with regions of North America (1.5%), West/Central Europe (1.2%) and Oceania (1.5%) having the highest levels of use. Cocaine use has been associated with a range of adverse consequences that potentially increase mortality (Degenhardt et al., 2011). These include: cocaine dependence; psychiatric morbidity; blood-borne viral infections among users who inject the drug; and cardiovascular and neurological complications (Devlin and Henry, 2008; Farooq et al., 2009; Roussotte et al., 2010; Trask and Kosofsky, 2000; van Holst and Schilt, 2011; Yeung et al., 2011). Seizures have also been a frequently reported complication since the early 1970s.

Preclinical evidence supports the contention that cocaine can produce seizures. Seizures have been observed in animal experiments (Karler et al., 1989), both at high-toxic doses of cocaine and after the repeated administration of subconvulsant doses of this drug (Karler et al., 1989; Post and Weiss, 1988). The two most important mechanisms thought to be involved in seizure occurrence that have been observed in preclinical studies are cocaine's inhibitory effect on GABAergic neurons and its effect of increasing serotonin levels (O'Dell et al., 2000b). Both mechanisms may produce seizures through the excitation of certain sets of neurons (Witkin et al., 2007).

In humans, seizures have also been observed at high-toxic doses (Hoffman et al., 1990). However, studies at the lower doses usually self-administered by addicts or abusers, while fairly numerous, are highly heterogeneous and have not yet been systematically reviewed. Furthermore, cocaine consumption is frequently accompanied by use of alcohol or other psychoactive substances that may influence the epileptogenic capacity of cocaine (Macedo et al., 2004). Thus, concomitant alcohol consumption must necessarily be taken into account in studying the relation between cocaine and seizures, given its effect of reducing the epileptogenic threshold (Leach et al., 2012).

Cocaine is mentioned as a factor related to seizures in multiple references in textbooks of internal medicine (Lowenstein, 2011), neurology (Roper and Samuels, 2009), institutional reports (Daras, 1996; EMCDDA, 2007), and journal articles (Cregler and Mark, 1986; Devlin and Henry, 2008; Meehan et al., 2010). In most cases, however, this relationship is treated in vague terms, either by merely mentioning its existence or simply including seizures in the list of neurological alterations that may follow cocaine use.

Even assuming the existence of a relationship between cocaine use and seizures, no published papers have addressed evidence on the specific role played by cocaine in inducing seizures systematically. This article aims to summarize the pathophysiological mechanisms underlying the aforementioned relationship as well as to provide a systematic review of available scientific evidence on the role of cocaine use in human seizures.

2. Summary of the biological plausibility of the relationship between cocaine use and seizures

Seizures include a variety of paroxysmal events and have been defined as clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or seizure disorder. A seizure or a series of seizures may be the manifestation of an ongoing neurological disease that demands the implementation of special diagnostic and therapeutic measures (Roper and Samuels, 2009).

Viewed from an overall physiological perspective, seizures require three conditions: a set of pathologically excitable neurons; an increase in excitatory glutaminergic activity through recurrent connections in order to spread the discharge, and a reduction in the activity of the normally inhibitory GABAergic projections (Roper and Samuels, 2009).

Cocaine stimulates the central nervous system, and at high-toxic doses, seizures have been observed in humans (Hoffman et al., 1990). It has been generally accepted that seizures induced by cocaine are related to the repression of central inhibitory nervous systems such as GABAergic and other inhibitory neurons due to their blockade of sodium ion (Na^+) current, thereby stimulating excitatory neuronal activity (Dohi et al., 2005).

In addition, there is evidence of a relationship between cocaine use and a special mechanism that ostensibly creates a secondary seizure focus called "kindling," a progressive sensitization to the seizurogenic effects of cocaine (Meehan and Schechter, 1996). This cocaine-induced sensitization is produced when a constant dose of cocaine is intermittently and repeatedly administered over time; "kindling" is the mechanism that could explain the possible increase in convulsions associated with chronic cocaine consumption, as has been described in human cases (Rolland et al., 2011).

A growing body of evidence also suggests that serotonergic mechanisms play a major role in the seizurogenic effects of cocaine (Morita et al., 2005; O'Dell et al., 2000b). Cocaine augments the effects of serotonin (5-HT) by blocking reuptake, which leads to increased serotoninergic stimulation (Morita et al., 2005). Pharmacological animal studies have supported the role of 5-HT in mediating this toxic effect of cocaine: the occurrence and severity of cocaine-induced convulsions are increased by the selective serotonin reuptake inhibitors (SSRI) fluoxetine, citalopram, paroxetine and the tricyclic antidepressant imipramine (O'Dell et al., 2000a). On the contrary, both 5-HT_2 receptor antagonists (cinanserin, ketanserin, and pirenperone; Ritz and George, 1997), and deletion of the 5-TH receptor gene (Witkin et al., 2007) antagonize cocaine-induced convulsions. Thus, concomitant use of cocaine and SSRI may lower the seizure threshold.

Accordingly, multiple theories could explain the neurobiology of the relationship between cocaine use and seizures. The GABAergic system, kindling and inhibition of serotonin reuptake are all mechanisms that may plausibly underlie this relationship.