

## Editorial

# Reassessing the Future of the Experimental Treatments for Cocaine Addiction: Conventional Pharmacotherapies?

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Addiction disorders have been largely documented as chronic and relapsing with irrepressible drug consumption behavior and compulsiveness [1]. Cocaine addiction is a comprehensive social and health-impairing issue that carries significant burden to many countries worldwide, especially to the developed societies [2]. It is causing heightened load of diseases, criminality, domestic violence, disability and death, among others [3,4]. Given the severity and potential threat that all these social maladies embody to human kind, it is imperative to develop effective treatments for cocaine addiction and dependence. However, despite all scientific studies on pharmacological substances, an effective treatment for this terrible condition does not exist, and currently there are no definite approved medicines for cocaine addiction disorders [5].

Cocaine is a powerful psychostimulant of the central nervous system (CNS) that increases alertness, energy and motor activity [6]. It also induces feelings of euphoria and happiness and amplifies personal sensations including sexuality [7]. In humans, the physiological mechanisms by which cocaine exerts its stimulatory effects relay in the increased levels of the neurotransmitter dopamine within the brain [8]. For decades, drug addiction problems have been regarded to men [9]. And, although cocaine dependency in men continues to be higher than in women, the later initiates its use sooner [10], show higher exploit [11], progresses more avidly from informal use to dependence [12] [13] exhibit increased behavioral issues associated to drugs [14], have less clean periods [11] and even respond to stress and depression differently because these increase their relapse episodes more than in men [15-17]. The evidence suggests that the dynamic interactions of fluctuating sex steroids (e.g., estrogen, progesterone) regulating women's reproductive cycles may be physiologically relevant to the subjective response to cocaine in addicted females [18]. Furthermore, gonadal hormones seem to have important mediating effects on addictive behaviors, particularly in females; while estradiol increases the motivation to take cocaine, progesterone counteracts its facilitatory effects [18-20]. It is clear that drug abuse and dependency exhibit different and perhaps more intricate patterns in women compared to men [9,10]. Furthermore, according to SAMHSA 2008 report, young girls initiate into drugs between the ages of 12 and 17 years old [21].

*What is the current status on cocaine addiction research? What are the treatment options?*

Addiction research had progressed enormously during the last decades, and certainly the understanding of addictive behaviors continues to improve [22]. However, the final mechanisms by which cocaine induces CNS dependency and adaptation are not well understood and much still yet to be determined [7].

To date, there is no FDA approval for the use of a definite pharmacological therapy for cocaine abuse and dependency [5,7,23,24]. Although there are several treatment options, the cost for such therapies is exorbitant, their effectiveness is limited and some have considerable side effects [5,25]. Hence, the National Institute on Drug Abuse (NIDA) had focused most research efforts for the development of effective medications to treat addictive behaviors [6]. After decades of investigations on varied experimental therapies there are several pharmacological contenders. Among them are drug agonists (e.g. nicotine, methadone), drug antagonists and metabolic modulators such as naltrexone and disulfiram, respectively [26]. The use of antidepressants, antipsychotics and anticonvulsants therapeutic agents has also been explored [27-29]. In addition, compounds such as anticocaine antibodies [30], passive [31,32] and active immunization [33] have been proposed. However, drug interceptors-Butyrylcholinesterase (BChE) or enzymatic destruction (cocaine hydrolase), bacterial cocaine esterase (CocE) and newer hydrolases ("CocH", "CocH2") [34-38] have acquired a great deal of attention more recently [22]. Furthermore, some researchers suggest that the combination of anticocaine vaccines and enzyme destruction therapies may hold the key for the treatment of cocaine addiction disorders [22,36,38,39]. However, while these outcomes seem promising there are significant concerns (e.g., safety, pharmacoeconomics, bioethics) and clinical barriers to consider, especially because none of these pharmacotherapies have proven to treat cocaine dependency in a complete, safe and practical manner [40,41]. In addition, many of these treatments cause potentially catastrophic side effects and carry major clinical challenges that may prevent a suitable transition to the bedside [5, 41-43].

*Addiction: the relationship between therapy and disease?*

The clinical and neurobiological views on addiction have differing perspectives [44]. Clinically, addiction has been regarded to a continuous lack of control in the use of drug despite its deleterious consequences [45]. Neurobiologically, addiction has been defined as "a chronic, relapsing disease of the brain" [46]. Based on the latest, one main goal for the research in neurosciences is to elaborate effective therapeutic treatments [44].

The ideal cocaine addiction treatment agent must be practical and long-term effective; that includes preventing the onset of cravings and subsequent unpredictable relapse that at times occur even after

extended periods of abstinence [47]. It should not adversely affect the immunogenicity of cocaine addicted patients, and should effectively thwart their upsurge of drug consumption. Which may transpire inevitably not necessarily to defy the treatment efficacy (clinical challenge), but coerced by their brain disease and impaired mental state (neurobiological challenge) [43,44]. In addition, the therapy should have minimal side effects; that is, no risk for cardiac conditions (i.e., arrhythmias), vascular complications (e.g., cerebral, coronary, systemic), ischemic conditions, seizures, brain chemistry imbalances, systemic toxicity and hyperthermia [43]. Also, given the important role of sex steroids on addictive behaviors of women [18-20], the ideal treatment should also consider these fluctuating hormones, since drug abuse and dependency manifest differently among sexes [9,10]. Moreover, the ideal treatment should act in the best interest of human bioethical and neuroethical principles, public health and socioeconomics [43,48].

However, despite all years of research trying to understand the complex mechanisms underlying cocaine addiction, none of the proposed pharmacological options seems genuinely practical. On one hand, agonists and antagonists pharmacological formulations have proven ineffective [22]. On the other hand, current vaccination therapies have shown strong limitations because they only produce the desirable high titers of anticocaine antibodies in a small number of inoculated addicts [22,49]. That is, because human vaccination responses are subjective to varied uncontrollable variables such as the individual's wellbeing status, the use of comorbid medications (e.g., immunosuppressive agents) and genetic polymorphisms, among others [22,50]. The study of genetic polymorphisms is particularly important because of the different genetic regulatory forces on the patient's humoral responses upon antigenic induction [51]. In view of these limitations, new research approaches are necessary; perhaps supporting alternatives treatments such as natural agent therapies may be not only reasonable but opportune.

On this regard, some addiction researchers are shifting gears by investigating alternative and natural medicine treatments such as acupuncture and herbal therapies [25]. Other alternative therapies include meditation [52-55] and aerobic exercise [56-60]. Among these treatments the use of natural herbal medicines seems most appealing primarily because they have been used for hundreds of years in traditional and oriental medicine [25]. Several investigations on natural herbal agents have reported benefits such as anxiolytic, adaptogenic, anti-stress and antidepressants [61-64]. Some studies have specifically supported the use of herbal extracts for the treatment of cocaine addiction [65-67]. Preliminary results reported a reduction in cocaine self-administration and cocaine-induced reinstatement [68,69]. Others showed an inhibition in cocaine-induced behavioral sensitization through central modulatory mechanisms in the dopaminergic system [70], and the suppression of cocaine effects in a dose- dependent manner through the attenuation of its enhancing effects on evoked dopamine release [71]. Altogether, these studies suggest that natural formulation therapies may be potentially beneficial for the treatment of cocaine addiction. However, a major obstacle is that all these alternative areas of treatment are vastly unexplored. Therefore, the evidence is inconclusive and inadequate to support the viability of any of these natural agents as a primary or adjunctive therapy [72].

Although there have been significant advances in the study of the neuroscience of addiction, the proposed new pharmacotherapies appear to lack overall pragmatism, clinical suitability and carry robust bioethical and pharmacoeconomic concerns. Consequently, it is imperative to promote more and improved investigations to increase the scientific understanding of natural, alternative and complementary medicines. For many years, these therapies have been used to treat effectively many chronic mental conditions such as anxiety and depression. Needless to say, natural agent formulations merit attention because they may potentially support the development of more innocuous, financially conscious and clinically sustainable therapies to treat cocaine addiction disorders. Despite all developmental hurdles and experimental obstacles, we all hope and eagerly wait for the discovery of the idyllic therapy to treat cocaine addiction.

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