Long-Acting Opioid-Agonists in the Treatment of Heroin Addiction: Why Should We Call Them “Substitution”?  

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Research Note

Long-Acting Opioid-Agonists in the Treatment of Heroin Addiction: Why Should We Call Them “Substitution”?

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Many studies have documented the safety, efficacy, and effectiveness of long-acting opioids (L-AOs), such as methadone and buprenorphine, in the treatment of heroin addiction. This article reviews the pharmacological differences between L-AO medications and short-acting opioids (heroin) in terms of reinforcing properties, pharmacokinetics, effects on the endocrine and immune systems. Given their specific pharmacological profile, L-AOs contribute to control addictive behavior, reduce craving, and restore the balance of disrupted endocrine function. The use of the term “substitution,” referring to the fact that methadone or buprenorphine replace heroin in binding to brain opioid receptors, has been generalized to consider L-AOs as simple replacement of street drugs, thus contributing to the widespread misunderstanding of this treatment approach.

Keywords long-acting opioids; substitution; street drugs; stigma; heroin; methadone; buprenorphine; drug treatment

Introduction

During the last 40 years many studies have documented the safety, efficacy, and effectiveness of long-acting opioids (L-AOs), such as methadone, in the treatment of heroin addiction.

“The views expressed herein are those of the author(s) and do not necessarily reflect the views of the United Nations.”

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and demonstrated their mechanisms of action, including normalization of those functions disrupted by chronic heroin use (Kreek, 2000). L-AO agonists have been shown to also be effective in reducing the incidence of HIV and Hepatitis infections and the rate of crime among substance abusers, while improving their quality of life.

In spite of this evidence, stigmatization of addiction in general and misleading concepts of the role of medications prevented the implementation of such treatment in many countries and delayed the systematic use of L-AO agonists for years. The word “substitution” itself, utilized to define methadone or buprenorphine maintenance treatment and referring to their substitution of heroin (actually morphine) on opioid receptors in the brain, contributed to widespread misunderstanding. Public opinion, policy makers, and even health professionals often considered L-AOs, rather than being effective medications prescribed to reduce or stop addictive behavior, as simply being substitutive agents, and being equivalent to illicit drugs, to be administered in place of street heroin. This misleading interpretation of treatment was spread by the media that at times referred to opioid medications for addiction treatment as “state drugs” instead of “street drugs.”

To understand the role of methadone and buprenorphine in addiction treatment, recent evidence from behavioral pharmacology concerning addiction has to be considered. The abnormal associative learning underlying addictive behavior (Di Chiara et al., 2004) seems to be related to the reinforcing effects of drugs and their ability to change monoamines’ threshold activation in the motivational system responses to salient stimuli. The compulsive symptoms characterizing heroin addiction, with drug seeking exceeding any other interest in life and behavioral under-control, appear to be associated with stable neurobiological changes (Koob and Kreek, 2007), including persistent alterations of opioid peptides, CRH, dopamine, and GABA.

Because of their specific pharmacokinetic and pharmacodynamic properties, long-acting opiates could be effective in interrupting the compulsive circuit and facilitating the extinction of the conditioned behavior induced by the prolonged exposure to heroin in addicted individuals. Particularly at higher doses oral methadone may be able to produce greater cross-tolerance to the reinforcing effects of heroin (Donny, Brasser, Bigelow, Stitzer, and Walsh, 2005), without producing immediate and intense rewarding effects expected from heroin injection. Thus, while a substitution has been done in relationship to opioid receptor binding, this does not mean that the treatment medication would substitute for the reinforcing effects of heroin. The prolonged absence of an intensive rewarding experience may contribute to the extinction of conditioned behavior (abnormal learning) and the reduction of compulsive drug seeking.

**Differences in Reinforcing Properties**

Protocols of oral self-administration in experimental animals demonstrated that oral methadone did not serve as a reinforcer, suggesting reduced effects of the long-acting opiate on the reward system (Vivian, Liang, Higley, Linnoila, and Woods, 1999). Although methadone was found to produce a profile of effects, including measures of euphoria, indistinguishable from that of morphine and heroin when administered intravenously in humans, methadone itself cannot be considered to be a selective euphoriant (Jasinski and Preston, 1986). The rewarding effect of the drug was reduced in the oral formulation, in comparison with intravenous administration. When tested in humans, orally administered methadone showed a significantly lower level of “drug liking” than slow-release oral morphine (Mitchell, White, Somogyi, and Bochner, 2004).
Similarly, despite the high affinity of buprenorphine for the mu opioid receptor, this long-acting opiate appears to be a remarkably safe drug, with a benign overall side effect profile via the sublingual route (Tzschentke, 2002). The limited rewarding effects of buprenorphine, compared to full mu agonists such as heroin or oxycodone, was recently reported in morphine-maintained heroin-dependent individuals. The study found I.V. buprenorphine produced significant increases in ratings of “I feel a bad drug effect” and was not self-administered above placebo levels at any dose tested, most likely because of precipitated withdrawal. Thus, the abuse liability of buprenorphine in opiate-dependent individuals seems to be low, despite the fact that it produces increases in positive subjective ratings. In contrast, the abuse potential of fentanyl, morphine, oxycodone, and heroin was found to be high under the same experimental conditions (Comer, Sullivan, Whittington, Vosburg, and Kowalczyk, 2007).

**Differences in Pharmacokinetics**

Pharmacokinetic evidence also suggests that the L-AO agonists utilized in heroin-addiction treatment should not be considered as being simple substitutions for heroin. The pharmacokinetics of methadone significantly differs from that of morphine and morphine-like drugs: methadone has a higher oral bioavailability, a much longer half-life, and is hepatically metabolized by cytochrome P450 enzymes (Lugo, Satterfield, and Kern, 2005). Estimates of the long terminal elimination half-life of methadone are of 33–46 hr in healthy subjects and, possibly, longer in opiate users (Wolff et al., 1997).

In contrast with heroin, and similar to methadone, buprenorphine has a long half-life and has been reported to be effective in the treatment of opioid dependence even when given on alternating days, probably as a result of long-lasting occupation of opioid receptors (Greenwald et al., 2007). These pharmacokinetic properties favor the therapeutic use of this opiate, permitting its administration once a day and avoiding withdrawal intervals.

**Differences in Endocrine and Immune Responses**

A variety of evidence has demonstrated that neuroendocrine function is significantly changed in humans receiving any narcotic on a short-term basis or short-acting narcotics on a chronic basis (Garland and Zis, 1989). A consistent disruption of the endogenous opioid system and stress responsiveness has been found in heroin addicts and may possibly contribute to the perpetuation of self-administration of opiates (Gerra et al., 2004; Kakko et al., 2007; Kosten, Morgan, and Kreek, 1992).

In contrast, long-term steady state methadone treatment of former heroin addicts has been reported to induce a normalization of the opioid system and hypothalamic-pituitary-adrenal axis function, as reflected by normal levels and normal circadian rhythm of levels of beta-endorphin, ACTH, and cortisol (Kreek et al., 1983). Atypical hypo-responsivity to stressors during cycles of heroin addiction and sustained hyper-responsivity to stressors in the medication-free state appear to be normalized in long-term, methadone-maintained (Stimmel and Kreek, 2000) and buprenorphine-maintained patients (Nava, Caldiroli, and Lucchini, 2006).

Furthermore, recent studies comparing untreated heroin addicts, heroin-addicted patients who were prescribed methadone and buprenorphine maintenance for at least 6 months and healthy controls, showed that lymphoproliferation, interleukin IL-4, and
TNF-alpha production were significantly lower in untreated heroin addicts, in comparison with methadone- and buprenorphine-treated patients (Sacerdote et al., in press).

**Conclusion**

Taking into account all of this evidence, L-AOs such as methadone and buprenorphine should not be considered as being replacements (substitution) for the rewarding effects of heroin but instead as medications for heroin addiction, particularly because of their ability to reduce craving and control addictive behavior. There are sufficient examples of the differential effects of short and L-AOs to justify calling the latter “maintenance agents” or simply “long-acting opioid agonists” rather than “substitute agents” with its pejorative overtones.

**RÉSUMÉ**

Opioides de acción prolongada en el tratamiento de la adicción a heroína: ¿Por qué llamarlos sustitución?

Muchos estudios han documentado la seguridad, eficacia y eficiencia de los opioides de acción prolongada tales como la metadona y la buprenorfina en el tratamiento de la adicción a heroína. Este artículo revisa las diferencias farmacológicas entre los medicamentos opioides de efecto prolongado y los opioides de acción rápida (tales como la heroína) en términos de sus propiedades reforzadoras, farmacocinéticas y efectos sobre los sistemas endocrino e inmunológico. Dado su perfil farmacológico específico, los opioides de acción prolongada contribuyen a regular el comportamiento adictivo, reducen el deseo por la droga y restituyen el equilibrio de la función endocrina. El uso del término “sustitución,” referiéndose al hecho de que la metadona o la buprenorfina remplazan a la heroína al ocupar los receptores-opiáceos µ cerebrales, se ha generalizado hasta el punto de considerar a los opioides de acción prolongado como un simple reemplazo de las drogas de la calle, contribuyendo, de esta manera a la creación de un concepto equivocado de esta modalidad de tratamiento.

**RESUMEN**

Les agonistes des opiacés à longue durée d’action dans le traitement des dépendances à l’heroïne: Pourquoi devrait-on les appeler “substitution”?

De nombreuses études ont documenté l’efficacité, la sureté et l’efficience des opiacés à longue durée d’action, tels que la méthadone ou la buprénorphine, dans le traitement des dépendances aux opiacés. Cet article passe en revue les différences entre les médicaments à longue durée d’action (L-AOs) et les opiacés à courte durée d’action, tel que l’heroïne, en termes de renforcements, de pharmacocinétique, effets sur les systèmes endocriniens et immunitaires. Vu leur profil pharmacologique particulier, les L-AOs contribuent au contrôle des comportements de dépendance, réduisent les syndromes de sevrage, et reconstituent l’équilibre des fonctions endocriniennes déréglées. L’utilisation du terme “substitution,” en référence au fait que la méthadone ou la buprénorphine occupant la même place que l’heroïne en se liant aux récepteurs morphiniques du cerveau, a généralisé l’idée que les
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opus à longue durée d’action simplement remplacent les drogues de rue, et donc a contribué au malentendu très répandu autour des ces approche thérapeutique.

Опиоиды-агонисты длительного действия в лечении героиновой зависимости:
Почему мы называем их “заместительными”?

АННОТАЦИЯ

Краткий обзор: Ряд исследований завидствовал безопасность, действенность и результативность применения опиоидов длительного действия, таких как метадон и бупренорфин, при лечении героиновой зависимости. Эта статья включает обзор фармакологических различий между препаратами ряда опиоидов длительного действия (ОДД) и кратко действующими опиоидами (героин) с точки зрения усиливающих свойств, фармакокинетики, воздействия на эндокринную и иммунную системы. В силу специфики их фармакологического профиля ОДД способствуют контролю зависимого поведения, уменьшают тягу и восстанавливают баланс нарушенной эндокринной функции. Использование термина “замещение”, относящееся к тому факту, что метадон и бупренорфин замещают героин в святилии и связывания опиоидных рецепторов мозга, стало применяться в более широком смысле при рассмотрении ОДД в качестве простой улучшённых наркотиков, вяно, таким образом, свой вклад в широко распространенное неправильное понимание этого метода лечения.

"Lang wirksame Opioiden Agonisten in der Behandlung gegen Heroinabhängigkeit:
Warum sollten wir diese als “Substitution” bezeichnen?"


长效阿片受体激动剂在海洛因依赖治疗中的作用：为什么叫替代治疗？

摘要

许多研究已证实长效阿片类药物如美沙酮与丁丙诺啡对治疗海洛因依赖具有安全性和有效性，本文总结了长效阿片类药物与短效阿片类药物的不同药理特点，包括强效作用、药物动力学特征、对内分泌及免疫系统的作用等。由于其独特的药理特征，长效阿片类药物具有控制成瘾行为、减少渴求与调节内分泌功能失调的作用，使用“替代”这一词是指美沙酮或丁丙诺啡具有替代海洛因与脑内阿片受体结合的作用，但是“替代”这一词却被推广使用到长效阿片类药物是街头毒品的简单替代，因此导致人们对这种治疗方法的广泛误解。
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