Review Article

Opiate addiction - current trends and treatment options

Achal Bhatt*, Aminder Gill

Windsor University School of Medicine, Brightons Estates, Cayon, St kitts, West Indies

ABSTRACT

Opioids are widely used drugs for treatment of pain and related disorders. Opiate addiction is a major public health concern in the United States causing significant increase in healthcare expenditure. They produce euphoria and sense of well-being which makes them addictive to some people. Used in higher doses they can lead to cardiac or respiratory compromise. They also impair cognition leading to impaired decision making. Opioids exert their effects by acting on three different types of receptors mu, delta, and kappa located on neuronal cell membranes causing inhibition of neurotransmitter release. Prolonged use of these drugs can lead to physical dependence causing withdrawal symptoms if a person stops using them. Commonly used medications to treat opiate addiction are methadone, LAAM (longer acting derivative of methadone), buprenorphine, and naltrexone.

Keywords: Opiates, Prescription, Addiction, Methadone, Naltrexone

INTRODUCTION

Opiate Addiction is a fast growing major public health problem in the United States and around the world. It causes significant morbidity and mortality related to overdose, HIV, and hepatitis C leading to higher healthcare costs. In 2009, the global opiate market was valued at a whooping $68 billion. Of that heroin users alone contributed to $61 billion. About 12-14 million heroin users consumed about 375 mt of heroin globally in the same year. Apart from heroin, non-medical use of different prescription opioids has been increasing in prevalence in some areas of the world especially in North America. About 1.2 million ER visits in 2009 were related to abuse of prescription opioids. This represents an increase of 98.4% since the year 2004.

In 2010, approximately 35 million people between the age 15-64 used an illicit opiate.[1] The rates of abuse have been climbing up in the recent past with almost three millions Americans having abused heroin.[2] In the US, mortality related to opioid overdose exceeds those caused by both heroin and cocaine combined.[3] Access to, adherence to, and outcome for the treatment of general medical illness and infectious diseases such as HIV, viral hepatitis, and tuberculosis are reduced in opiate addicts. Addictions are also comorbid with major infectious diseases like HIV. Opioid addiction requires long term treatment and also is associated with poor outcomes with more than eighty percent of patients relapse into drug use. Despite stable levels in heroin use, prevalence of illicit opioid use in the United States has increased due to the illicit use of prescription opioids.[1,4] In 2009, opiates caused second highest treatment admissions only next to alcohol abuse.[5] Annual admissions increased from 280,000 to 421,000 between the years 1999 and 2009.[5] The addiction potential of opioids is related to its effect on reward center in the brain producing pleasure and sense of well-being. People usually crush the opioid pills to snort or inject them to get as sense of euphoria but doing so they are putting themselves at serious complications like respiratory arrest, coma, and death in some instances. Opiate addiction causes impairment of cognitive functions by acting on the prefrontal cortex promoting compulsive drug use and relapse.[6,7] It also causes memory deficits, cognitive disability and impaired

decision making. The degree of neuropsychological impairment has been related to the dose and duration of opiate abuse. These effects are long lasting and require rehabilitation for cognitive deficits that impair day to day activities thus adding significant treatment burden.[8,9]

Mechanism of opiate addiction

Genetic factors, environmental factors, and pharmacological effects of opiates all play a role in developing opiate addiction.[2] Multiple studies have found an increased genetic risk for addiction in first degree relatives of addicts.[2] Traumatic experiences early in life can also increase the risk of opioid addiction. In a study among rodents, maternal separation early in life increased vulnerability to opiate addiction in both the pup and the dum.[10,11] Among humans, there is an association between PTSD and opiate addiction with more prevalence in people exposed to significant mental trauma in their life.[12,13] Studies also show that selective breeding can produce rodent strains prone to opiate self-administration. There are some genetic factors that contribute to developing addictions and there seems to be a inter-individual variability in terms of treatment efficacy for drug addiction.[14] Polymorphisms have been found in several genes encoding opiate receptors and ligands that are indicated in association with addiction.[14-16] One particular gene is the MOP-r gene (OPRM1). These gene variants may function synergistically with genetic polymorphisms involved in common comorbid conditions, such as anxiety or depression, and stress responsivity. Multiple genetic loci associated with opiate self-administration have been identified; and selective disruption of the gene encoding the mu opioid receptor, the principal target of opiates, can eliminate opiate self-administration and conditioned place preference. The primary site of action for heroin and other prescription opioids like oxycodone are MOP-r receptors. These drugs act as MOP-r agonists with short duration of action. This is in contrast to cocaine and other psychostimulants like amphetamines, which increases synaptic dopamine by inhibiting dopamine reuptake or an increase in release. Activating dopaminergic mesocortico/mesolimbic and nigrostriatal systems indirectly appears to be a common biological consequence of exposure to heroin and prescription opioids.[17-19] Once the dopaminergic systems are activated there are regulatory changes at the mRNA level in neurotransmitter and neuropeptide systems.[20-24] Chronic use of heroin or prescription opioids also causes upregulation of KOP-r/dynorphin system, which causes dysphoria, anhedonia, depression like or anxiety like states caused by opiates abuse. Such a counter-regulatory action by the KOP-r/dynorphin system may therefore mediate, in part, the negatively reinforcing aspects of withdrawal from drugs of abuse and may exacerbate the chronic relapsing nature of addictive diseases.[25] The euphoria and abuse liability caused by opiates is related to its rewarding and reinforcing effects on brain because of its rapid entry. This is apparent in the transition from oral or intranasal to smoked or I.V routes in order to achieve immediate absorption. The brain has mu opioid receptors throughout with higher concentration in areas related to pain and reward such as thalamus, striatum, anterior cingulate cortex and amygdala). Opiates primarily target these mu receptors and activate them. This causes inhibition of GABA-mediated inhibition of dopaminergic neurons initiating a cascade of effects in the above mentioned areas of the brain.[26] This results in release of dopamine into the projection fields, where it interacts with pre- and postsynaptic dopaminergic receptors.[27] A substantial portion of MOP-r agonists' rewarding effects and addiction potential may thus be related to this downstream activation in dopaminergic fields.

Treatment of opioid addiction

Commonly used medications to treat opiate abuse are the ones that acts similar to opiates themselves by attaching to the mu receptors in the brain. Methadone and LAAM (longer acting derivative of methadone) stimulate the cells like the illicit opioids but have different durations of action. Drugs like buprenorphine and naltrexone stimulate the cells in ways distinct from the illicit opioids. All these drugs are effective in treatment of opioid addiction but there is no randomized double-blind controlled trials available comparing all three medications (methadone, buprenorphine, and naltrexone). In a randomized trial comparing each of these medication found that 6 months retention rates of 84 percent, 59 percent and 21 percent for methadone 50 mg, buprenorphine 5 mg and naltrexone 50 mg respectively.[28]

Role of methadone in reducing heroin use has been long established. Methadone is a long-acting opiate used in treatment of opiate addiction. Compared to drugs like heroin, morphine, oxycodone and other opiates, methadone remains in the brain and body for a long time making its effects last for many days making it an ideal medication for treatment of opiate addiction. Methadone produce minimal tolerance and alleviates craving and compulsive drug use.[29] Compared to buprenorphine, methadone when used at high doses exhibit longer periods of abstinence and drug-free urine screenings.[30] Treatment with methadone reduces relapse rates as well thus enabling patients to concentrate on their day-to-day tasks, maintain relationships and holding jobs.[31] Methadone is usually well tolerated but like other opiate agonists it can cause lethal respiratory suppression when given at high doses that exceed an individual's tolerance. However for addiction treatment, higher levels of dosing supervision causes reduced mortality rates.[32] LAAM, a longer acting derivative of methadone, can also be used for opiate addiction. It can be given three times a week but its side effect profile related to cardiac rhythm problems, especially prolonged QT interval, has limited its widespread use.

Buprenorphine acts as a partial agonist on mu opioid receptors with weak partial agonist effects on delta and

kappa receptors. It is usually taken sublingually in tablet form or film formulations.[33] A subdermal implant that can deliver the drug for a period of six months is in development.[34] The bioavailability of buprenorphine after taken sublingually is approximately 50%.[34] Peak plasma levels are reached within 1-3 hours and the elimination half-life at steady state is approximately 37 hours, allowing for once daily, and in some instances every other day, dosing. It is bound to globulin fragments and is distributed to various tissues with an apparent volume of distribution during steady state of 3.7 L/kg. Buprenorphine is hepatically metabolized mainly by CP450 3A4 enzyme and is eliminated renally and through fecal routes. Buprenorphine elicits two different responses acting on the mu opioid receptors in the brain cells depending on the dose. At low dose it acts like methadone and at high dose it acts similar to naltrexone by blocking the receptors strongly and can precipitate withdrawal in highly dependent patients. Because of its safety and convenient dosing, it may be useful for treating opioid addiction in primary care settings, which is especially helpful since most opioid addicts have significant medical problems (for example, hepatitis B or C and HIV infection). Buprenorphine can be given three times per week compared to methadone which needs to be taken every day; this would be a safer choice than methadone and also increases compliance and decrease office or methadone clinic visits. Also, it has less overdose potential than methadone since it blocks other opioids and even itself as the dosage increases.[31]

Naltrexone is another opiate that helps patients avoid relapse after detoxification. It is a semi-synthetic mu and kappa opioid receptor antagonist used in the treatment of opiate addiction. It can be administered either orally or intramuscularly. Naltrexone attaches to the mu receptors hundred times more strongly than other opioids do but it does not promote the brain processes responsible to produce feelings of pleasure.[35] This is the reason the compliance rates are lower for naltrexone compared to other opiates. The mechanism of action for naltrexone in treating opiate addiction is different than that of buprenorphine and methadone. Naltrexone can achieve 95% mu receptor occupancy following steady state after oral administration.[36] Its safety is well established. In some patients it can cause hepatotoxicity in high doses thus it is used with caution in patients with acute hepatitis and end stage hepatic disease.[37] Naltrexone may precipitate withdrawal in patients with physical dependence on opioids since it is an opiate antagonist. The other characteristic that differentiates naltrexone from methadone and buprenorphine is that it has no intrinsic opiate activity, and thus posing a minimal risk abuse.

CONCLUSION

Opiate addiction is a growing public health problem in the United States and around the world. Understanding the disease process and clinical awareness of the neurohormonal basis of opioid dependence is quite essential in treatment of patients with opiate addiction. Though the data shows that pharmacological treatment with methadone, buprenorphine, and naltrexone have superior treatment outcomes to non-medication based therapies, medications alone are not effective in treatment of opiate addiction. Understanding the psychosocial aspects of addiction accompanied by appropriate psychosocial treatments combined with pharmacological therapy will be an effective strategy to combat opiate addiction.

REFERENCES

1. UNODC. World drug report 2011. 2011. United Nations Publication (Sales No. E.11.XI.10).
2. Blum K, Thomas JH Chen, John Bailey, Abdulla Bowirrat, John Femino, Amanda LC Chen. Can the chronic administration of the combination of buprenorphine and naloxone block dopaminergic activity causing anti-reward and relapse potential? Mol Neurobiol. 2011;44(3):250-68.
3. Centers for disease control and prevention. Vital signs: Overdoses of prescription opioid pain relievers - United States, 1998-2008. MMRW. 2011;60:1487-92.
4. Substance abuse and mental health services administration. Rockville, MD: Office of Applied Studies; 2011. Results from the 2010 National Survey on Drug Use and Health: summary of national findings. DHHS Publication; SMA 11-4658. NSDUH Series H-41.
5. Substance Abuse and Mental Health Services Administration. Treatment episode data set. 2011.
6. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behaviour by reward-related stimuli. Psychopharmacology. 1999;146:373-90.
7. Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb. Cortex. 2000;10:318-25.
8. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nature Neurosci. 2005;8:1458-63.
9. Ornstein TJ. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology. 2000;23:113-26.
10. Kalinichev M, Easterling KW, Holtzman SG. Long-lasting changes in morphine-induced locomotor sensitization and tolerance in long-evans mother rats as a result of periodic postpartum separation from the litter: a novel model of increased vulnerability to drug abuse? Neuropsychopharmacology. 2003;28:317-28.

11. Brook JS, Brook DW, Zhang C, Cohen P. Pathways from adolescent parent-child conflict to substance use disorders in the fourth decade of life. Am J Addict. 2009;18:235-42.

12. Tsuang MT, Lyons MJ, Meyer JM. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry. 1998;55:967-72.

13. Mills KL, Teesson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being. Am J Psychiatry. 2006;163:652-8.

14. Kreek MJ, Bart G, Lilly C, LaForge KS, Nielsen DA. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. Pharmacol Rev. 2005;57(1):1-26.

15. Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. Ann N Y Acad Sci. 2010;1187:184-207.

16. 16. Levran O, Yuferov V, Kreek MJ. The genetics of the opioid system and specific drug addictions. Hum Genet. 2012;131(6):823-42.

17. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci. USA. 1988;85(14):5274-8.

18. Maisonneuve IM, Kreek MJ. Acute tolerance to the dopamine response induced by a binge pattern of cocaine administration in male rats: an in vivo microdialysis study. J Pharmacol Exp Ther. 1994;268(2):916-21.

19. Pettit HO, Ettenberg A, Bloom FE, Koob GF. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berl). 1984;84(2):167-73.

20. Tsukada H, et al. Effects of binge pattern cocaine administration on dopamine D1 and D2 receptors in the rat brain: an in vivo study using positron emission tomography. J Neurosci. 1996;16(23):7670-7.

21. Spangler R, Zhou Y, Maggos CE, Zlobin A, Ho A, Kreek MJ. Dopamine antagonist and binge cocaine effects on rat opioid and dopamine transporter mRNAs. Neuroreport. 1996;7(13):2196-200.

22. Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R,. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psychiatry. 1990;147(6):719-24.

23. Zhou Y, Leri F, Cummins E, Hoeschele M, Kreek MJ. Involvement of arginine vasopressin and V1b receptor in heroin withdrawal and heroin seeking precipitated by stress and by heroin. Neuropsycho-pharmacology. 2008;33(2):226-36.

24. Zhou Y, Bendor J, Hofmann L, Randesi M, Ho A, Kreek MJ. Mu opioid receptor and orexin/hypocre-tin mRNA levels in the lateral hypothalamus and striatum are enhanced by morphine withdrawal. J Endocrinol. 2006;191(1):137-45.

25. Kreek MJ, Levran O, Reed B, Schlussman SD, Zhou Y, Butelman ER. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. Clin Invest. 2012;122(10):3387-93

26. Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci. 1992;12:483-88.

27. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. Proceedings of the National Academy of Sciences. 2011;108:15037-42.

28. Ahmadi J, Ahmadi K, Ohaeri J. Controlled, randomized trial in maintenance treatment of intravenous buprenorphine dependence with naltrexone, methadone or buprenorphine: a novel study. Eur J Clin Chem Clin. 2003;33:824-9.

29. Bonhomme J, Shim RS, Gooden R, Tyus D, Rust G. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. J Natl Med Assoc. 2012;104(0):342-50.

30. Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. Am J Psychiatr. 2005;162(2):340.

31. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. science & practice perspectives. 2002;1(1):13-20.

32. Strang J, Hall W, Hickman M, Bird SM. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland. BMJ. 2010;341:c4851.

33. Bentley KW, Hardy DG. Novel analgesics and molecular rearrangements in the morphine-thebaine group 3. Alcohols of the 6,14-endoethenotetrahydrooripavine series and derived analogs of N- allylnormorphine and norcodeine. J Am Chem Soc. 1967;89:3281-92.

34. Ling W, Casadonte P, Bigelow G. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010;304:1576-83.

35. Kosten TR, Morgan C, Kreek MJ. Beta endorphin levels during heroin, methadone, buprenorphine, and naloxone challenges: preliminary findings. Biol Psychiatry. 1992;32:523-8.

36. Weerts EM, Kim YK, Wand GS. Differences in delta- and mu-opioid receptor blockade measured by positron emission tomography in naltrexone-treated recently abstinent alcohol- dependent subjects. Neuropsychopharmacology. 2008;33:653-65.

37. Pfohl DN, Allen JI, Atkinson RL, Knopman DS, Malcolm RJ, Mitchell JE. Naltrexone hydrochloride

(Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr. 1986; 67:66-72.