Published in final edited form as:
Am J Addict. 2010 January 1; 19(1): 96. doi:10.1111/j.1521-0391.2009.00010.x.

Drug Interactions between Antiretroviral Medications and Medications Used in the Treatment of Drug Addiction: Research Needs

Jag H. Khalsa, PhD and **Ahmed Elkashef, MD**
Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, Bethesda, Maryland

Abstract

Today substance dependence is one of the major public health problems in the world with millions of people abusing legal and illegal drugs. In addition, almost one-third of the world's population suffers with one or more infections. Both drugs of abuse and infections are associated with serious medical and health consequences, some of which may be exacerbated by the occurrence of pharmacokinetic and/or pharmacodynamic interactions between medications used in the treatment of these conditions when they co-occur. This review briefly discusses issues surrounding clinical management related to drug interactions experienced by substance abusing patients. The emphasis of this paper is on the research needed to further study the extent, nature, and underlying molecular/genetic mechanism(s) of interactions between drugs of abuse, medications used in the treatment of drug addiction, and co-occurring infections.

Drug abuse and associated addiction/dependence and infections are two major health problems in the world with an estimated 200 million people who abuse illegal drugs regularly,1 and an estimated one-third of the global population of 6.7 billion living with one or more infections. 2 In the United States (US) alone, according to the 2007 National Survey on Drug Use and Health,3 an estimated 19.9 million people over the age of 12 years are current users of an illicit drug. An estimated 30–36 million people in the world are living with human immunodeficiency virus (HIV) infection,2 about 200 million are infected with Hepatitis C virus (HCV), 1.2 billion people are infected with tuberculosis (TB), and many more millions are infected with various other bacterial and viral infections. An estimated 1 million people infected with HIV, and 4 million people infected with HCV live in the US alone.4 Both HIV and HCV are prevalent among substance abusers. Injection drug use (IDU) directly and indirectly accounts for more than one-third (36%) of acquired immunodeficiency syndrome (AIDS) cases.5 In 2008, CDC reported that an estimated 23,364 AIDS diagnoses were made for IDUs during 1993; while an estimated 7,153 AIDS diagnoses were made among IDUs in 2006.6 Further, an estimated 80–90% of HIV positive injection drug users may also be infected with HCV.7 Other viral and bacterial infections also have been reported in drug abusers including TB, sexually transmitted infections (STIs), and streptococcal and staphylococcal infections (eg, often associated with serious infections in this population including cellulitis and endocarditis).8 Social, economic, and health costs to the society from substance abuse and infections are enormous. Legal and

Address correspondence to Dr. Khalsa, Medical Consequences Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, 6001 Executive Blvd. Room 4137, Bethesda, MD 20892. jk98p@nih.gov.

Declaration of Interest
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

illegal substance abuse alone costs American society an estimated $534 billion dollars annually,9 dwarfing costs of diabetes and cancer at an estimated $174 billion10 and $263 billion,11 respectively. The global cost of drug abuse would be even more staggering. Both drugs of abuse and infections, such as HIV and HCV, affect almost every physiological/biochemical system in the body. Therefore, adverse health effects related to drug interactions either from the use of abused substances, interactions between therapeutic agents used to treat these disorders, or adverse effects related to continued substance abuse and medications prescribed to treat these conditions are possible. In this paper, we will touch briefly on examples of the adverse effects related to such interactions. We will also suggest areas of research investigation needed to better understand these adverse effects, how to predict and/or avoid such events, and how to enhance the clinical care of patients who suffer with these diseases and are, of necessity, exposed to multiple medications simultaneously.

DRUG INTERACTIONS

In 2008, the US Food and Drug Administration received 526,527 reports of adverse drug reactions from pharmaceutical drug companies, pharmacists, treating/practicing individual clinicians, and patients. Of these reports, 319,741 were classified as serious and 58,000 deaths were reported.[12] The Institute of Medicine reported in January 2000 that from 44,000 to 98,000 deaths occur from medical errors; of this total, an estimated 7,000 deaths occur due to adverse drug reactions.[13] But Lazarou et al.[14] estimated that there were 2.2 million adverse drug reactions causing 106,000 deaths in hospitalized patients annually, making it the fourth leading cause of death in the US. Drug–drug interactions represent 3–5% of all in-hospital medical errors.[15]

Such findings underscore the need to evaluate, pharmacokinetic (PK)/pharmacodynamic (PD) interactions and, of particular importance, are interactions between medications used in the treatment of drug addiction/dependence (eg, methadone, buprenorphine), infections (eg, antiinfective or antiretroviral [ARV] medications), and mental disorders (eg, benzodiazepines). Understanding the potential for such interactions is important to providing effective clinical care to patients who suffer with these conditions. Failure to recognize the potential for drug interactions or the interactions themselves as they occur in patients may lead to failure of the intended pharmacological action of the drug(s) administered. Further, the individual may experience adverse effects (several examples follow) that may cause harm or may result in nonadherence to prescribed regimens resulting in poor clinical outcomes for the illnesses that these medications were meant to treat. For example, in the case of HIV disease in opioid-dependent individuals, opioids (methadone and buprenorphine) are known to be substrate of cytochrome P450 3A4 metabolic enzymes; enzymes whose function can be significantly affected by administration of some ARV medications. When this occurs, altered therapeutic profiles, toxicities, and side effects have been observed.[16] These interactions then may decrease adherence to prescribed clinical regimens in patients with HIV/AIDS,17 leading to lack of efficacy of HIV treatment, development of viral resistance to ARV therapies, and possibly to an increase in drug and alcohol abuse.18

Examples of adverse interactions between the opioid therapy, methadone, and ARV have accumulated in the literature over the past 12 years. A complete review of these interactions is beyond the scope of this paper (and is provided in a review article in this issue of the American Journal on Addictions; see McCance-Katz et al.). However, it is worth noting that awareness of the importance of drug interactions between opioids and ARV was heightened when zidovudine (ZDV), the first medication available to treat HIV/AIDS, was found to be associated with adverse effects in patients receiving methadone maintenance therapy for opioid addiction. Observations of symptoms that appeared to be those of opiate withdrawal including myalgias, anxiety and depression, and insomnia were reported. However, methadone serum

concentrations in these individuals were found to be therapeutic. A drug interaction study between methadone and ZDV revealed that methadone decreased metabolism of ZDV through inhibition of glucuronidation.[19] Further drug interaction studies examining whether similar interactions occurred with other opioids and opioid medications used to treat opioid dependence showed that neither buprenorphine, l-acetylmethadol, or naltrexone were associated with adverse interactions with ZDV.20 This was the first indication that it might be possible to "match" treatments to patients requiring treatment with several drugs for multiple diseases with the goals of enhancing their clinical outcomes and reducing the likelihood of adverse drug interactions. These findings underlined the need to conduct drug-interaction studies in humans, particularly since in vitro findings are often not predictive of clinical realities in humans receiving multiple medications. An example of this can be demonstrated in findings from the drug interaction study that examined methadone and lopinavir/ritonavir given concomitantly. Although protease inhibitors have been reported to inhibit the function of CYP 450 3A4 in vitro, methadone-maintained individuals were shown to have significant decreases in methadone serum concentrations when given therapeutic doses of this protease inhibitor combination.21 Similarly, nelfinavir is a protease inhibitor used in treatment of HIV/AIDS and reported to inhibit CYP 450 3A4, but which has been associated with reduced methadone concentrations in humans and rarely, opiate withdrawal.22

An example of the potential for treatment-patient matching can be demonstrated in the adverse drug interaction identified between methadone and efavirenz, a nonnucleoside reverse transcriptase inhibitor frequently used in the treatment of HIV/AIDS. Efavirenz has been associated with severe opiate withdrawal when given at therapeutic doses to methadone-maintained individuals,23 but buprenorphine-treated, opioid-dependent patients did not experience withdrawal when they were administered efavirenz over 15 days, despite a significant decline in buprenorphine plasma concentrations.[24] These findings point to the need for additional research to identify mechanisms for drug interactions (or lack thereof). Whether such differences in responses are related to potency of opioids, affinity of or dissociation from opioid receptors, the presence (or lack of, as for methadone) of active opioid metabolites, the metabolic pathways for these medications which are still being elucidated for opioids, or genetic differences in hepatic metabolic enzyme activity is unknown at this time. Studies to clarify the contributions of such factors to clinically observed effects are important to improved patient care for these diseases.

Another area of concern in drug–drug interactions is with pharmacodynamic interactions that can occur when several drugs having similar pharmacological effects, but acting by different mechanisms (for example sedation that is associated with mu-opioid receptor occupancy and that occurs through agonism of GABA-ergic receptors that increase chloride ion flux). A significant concern arises with the coconsumption of opioids and benzodiazepines. Diazepam has been shown to time-dependently increase sedation and decrease psychological performance in both methadone and buprenorphine-treated patients independent of the opioid dose.[25]

In vitro data can help to illuminate potential toxicities between medications not yet studied in combination in humans. Amitriptyline, buprenorphine, methylene-dioxymethamphetamine (MDMA), and zolpidem inhibit the N-demethylation of methadone.[26] Amitriptyline is a strong reversible inhibitor of CYP 3A4, while amitriptyline and MDMA are also inhibitors of CYP 2D6, and zolpidem is an inhibitor of CYP 3A4. Amitriptyline, MDMA, and zolpidem are likely to inhibit metabolism of methadone and thereby increase its serum concentrations. Indeed, in the article in this issue of the American Journal on Addictions, Maxwell and McCance-Katz show epidemiological data linking toxicities and deaths to concomitant use of methadone or buprenorphine and several of these drugs. Thus, the in vitro evidence of drug–drug interactions will also help to improve patient care during opioid maintenance treatment.26

Pharmacogenomics plays an important role in drug–drug interactions. Research investigations in recent years have revealed the presence of a large number of single nucleotide polymorphisms, many of which are responsible for changes in drug metabolizing enzyme activity. Of the major cytochrome P450 enzymes involved in drug metabolism (CYP 450 1, 2, and 3 families of enzymes), mutations in CYP 2D6 are the best studied.[27] Genotype and enzyme activity for CYP 2D6 have been linked to ethnicity ranging from no gene/no enzyme activity in 6% of Caucasians to two copies of a fully active gene. Genotyping for CYP 2D6 enzyme function can be undertaken with classification as poor, intermediate, extensive, and ultrarapid metabolizers.28 Likewise for CYP 2B6, varying levels of enzyme activity have been identified and are genetically mediated. Although a variety of SNPs have been identified in the CYP 3A4 family of enzymes, none have yet been associated with altered enzyme function.29 There are clinical examples that make the point of the importance of pharmacogenomics in drug metabolism and in drug–drug interactions. For example, certain genotypes of CYP 2D6 are associated with low activity which has been found to predict poor analgesia with codeine administration since CYP 2D6 must metabolize codeine to morphine, the analgesic in codeine tablets.30 CYP 2B6 has been shown to have a higher activity enzyme form that more rapidly metabolizes substrates of this enzyme. This was shown to be the case in a series of patients who experienced toxicities associated with bupropion when it was rapidly converted to its active and longer-acting metabolite hydroxybupropion.[31] Conversely, a low activity form of CYP2B6 has been associated with increased concentrations of efavirenz given at therapeutic doses and resulting in efavirenz-associated neurotoxicity.[32] Considering the complexities of studying drug interactions while accounting for the genetic composition of individual patients is important and is an area of much needed research in this field.

RESEARCH NEEDS

Table 1 shows identified areas of needed research. Understandings gained from these lines of scientific investigation will help to provide the tools necessary for clinicians to render the best possible care to patients with multiple, chronic, and sometimes life-threatening illnesses. Knowing of the likelihood and expected responses to drugs administered simultaneously are important to direct clinical care. However, understanding mechanisms of drug interactions as well as genetics of drug interactions will help clinicians to predict who may be more susceptible to adverse drug interactions and can provide guidance to medication selection in vulnerable populations. Developing standards for determining when the risks of or adverse effects associated with a drug interaction outweigh the benefits of treatment with the medications is important to minimize the extent, severity, and consequences of these interactions.

In summary, the value of clinical awareness of the likelihood of and presence of drug interactions cannot be underestimated. As has been demonstrated for several infectious diseases that co-occur frequently with substance use disorders, drug interactions can lead to multiple, severe consequences. These consequences include poor clinical outcomes for affected individuals as well as increased risk of transmission of infectious diseases. Ongoing research supported by the National Institutes of Health (NIH)[33] and new NIH initiatives will, over time, address important questions related to pharmacokinetic and pharmacodynamic interactions between drugs leading to improved clinical care of those who suffer with these chronic diseases.

Acknowledgments

This work was carried out as part of the authors' official duties at the U.S. National Institute on Drug Abuse, a part of the National Institutes of Health, Department of Health and Human Services.

REFERENCES

1. United Nations Office on Drugs and Crime: World Drug Report 2007. United Nations Office on Drugs and Crime, ISBN 92-1-148214-7. 2007. Available at: http://www.unodc.org/pdf/research/wdr07/WDR_2007.pdf.
2. United Nations AIDS Accessed November 8, 2009. (UNAIDS). 2008 Report on the Global AIDS Epidemic; UNAIDS/08-25E/JC1510E, ISBN 978 92 9 173711 6; Joint United Nations Programme on HIV/AIDS/WHO. 2008 [Accessed November 8, 2009]. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/.
3. Substance Abuse and Mental Health Services Administration (SAMHSA). Overview of Findings from the 2007 National Survey on Drug Abuse and Health, Office of Applied Studies, NSDUH Series H-24. Rockville, MD: DHHS Publications; 2007 [Accessed November 8, 2009]. Available at: http://www.oas.samhsa.gov/nsduh/2k7nsduh/2k7Results.pdf.
4. National AIDS Control Organization (NACO) report on cases of HIV in India. 2007 [Accessed November 8, 2009]. Available at: http://www.nacoonline.org/Quick_Links/HIV_Data/.
5. Gayle H. An overview of the global HIV/AIDS epidemic, with a focus on the United States. AIDS 2000;14:S8–S17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11061637. [PubMed: 11061637]
6. Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services, HIV/AIDS Surveillance in Injection Drug Users (through 2006). Available at: http://www.cdc.gov/hiv/idu/resources/slides/slides/idu.pdf.
7. Thomas D. Hepatitis C and Human Immunodeficiency Virus infection. Hepatology 2002;36:S201–S209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12407595. [PubMed: 12407595]
8. Contoreggi C, Rexroad VE, Lange WR. Current management of infectious complications in the injecting drug user. J Subst Abuse Treat 1998;15:95–106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9561947. [PubMed: 9561947]
9. Office of National Drug Policy. The Economic Costs of Drug Abuse in the United States: 1992–2002. Washington, DC: Executive Office of the President; 2004 [Accessed November 8, 2009]. Available at: http://www.ncjrs.gov/ondcppubs/publications/pdf/economic_costs.pdf.
10. American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care 2003;26:917–932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12610059. [PubMed: 12610059]
11. American Cancer Society. Cancer Facts & Figures 2008. Atlanta, GA: 2008 [Accessed November 8, 2009]. Available at: http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf.
12. The US Food and Drug Administration. 2009 [Accessed November 8, 2009]. Available at: http://www.fda.gov/cder/aers/statistics/aers_received.htm.
13. Kohn, LT.; Corrigan, JM.; Donaldson, MS. To err is human: Building a safer health system. Institute of Medicine 2000. Washington, DC: National Academy Press; 2000. Available at: http://www.nap.edu/openbook.php?isbn=0309068371.
14. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 1998;279(15):1200–1205. PMID: 9555760. Available at: http://www.ncbi.nlm.nih.gov/sites/entrez. [PubMed: 9555760]
15. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE prevention study group. JAMA 1995;274(1):35–43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7791256. [PubMed: 7791256]
16. McCance-Katz EF. Treatment of opioid dependence and HIV/HCV co-infection in opioid dependent patients: The importance of drug interactions between opioids and antiretroviral medications. Clin Infect Dis 2005;41:S89–S95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16265622. [PubMed: 16265622]
17. Arnsten JH, Dumas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV infected drug users. J Gen Intern Med 2002;17:377–381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12047736. [PubMed: 12047736]

18. Bruce RD, McCance-Katz E, Kharasch ED, et al. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. Clin Infect Dis 2006;43:S216–S223. PMID: 17109308. [PubMed: 17109308]
19. McCance-Katz EF, Jatlow P, Rainey P, et al. Methadone effects on zidovudine (AZT) disposition (ACTG 262). J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:435–443. [PubMed: 9715839]
20. McCance-Katz EF, Rainey PM, Friedland G, et al. Effect of opioid dependence pharmacotherapies on zidovudine disposition. Am J Addict 2001;10:296–307. [PubMed: 11783744]
21. McCance-Katz EF, Rainey P, Friedland G, et al. The protease inhibitor lopinavir/ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin Infect Dis 2003;37:476–482. [PubMed: 12905130]
22. McCance-Katz EF, Rainey P, Smith P, et al. Drug interactions between opioid and antiretroviral medications: Interaction between methadone, LAAM and nelfinavir. Am J Addict 2004;13:163–180. [PubMed: 15204667]
23. McCance-Katz EF. Treatment of opioid dependence and HIV/HCV co-infection in opioid dependent patients: The importance of drug interactions between opioids and antiretroviral medications. Clin Infec Dis 2005;41:S89–S95. [PubMed: 16265622]
24. McCance-Katz EF, Moody DE, Morse G, et al. Interactions between buprenorphine and antiretrovirals I: Non-nucleoside reverse transcriptase inhibitors: Efavirenz and delavirdine. Clin Infect Dis 2006;43:S224–S234. [PubMed: 17109309]
25. Lintzeris N, Mitchell TB, Bond AJ, et al. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. Drug Alcohol Depend 2007;91:187–194. PMID: 17624687. [PubMed: 17624687]
26. Bomsien S, Skopp G. An in vitro approach to potential methadone metabolic-inhibition interactions. Eur J Clin Pharmacol 2007;63(9):821–827. PMID: 17598095. [PubMed: 17598095]
27. Flockhart, DA.; Bertilsson, L. Clinical pharmacogenetics. In: Atkinson, AJ.; Abernathy, DR.; Daniels, CE.; Dedrick, RL.; Markey, SP., editors. Principles of Clinical Pharmacology. New York, NY: Academic Press; 2007. p. 179-195.
28. Daly AR, Brockmoller J, Broly F, et al. Nomenclature for human CYP2D6 alleles. Pharmacogenomics 1996;6:193–201.
29. He P, Court MH, Greenblatt DJ, et al. Genotype-phenotype associations of cytochrome P450 3A4 and 3A5 polymorphism with midazolam clearance in vivo. Clin Pharmacol Ther 2005;77:373–387. [PubMed: 15900284]
30. Armstrong SC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: Theory and clinical reality, Part II. Psychosomatics 2003;44:515–520. [PubMed: 14597688]
31. Zanger UM, Klein K, Saussele T, et al. Polymorphic CYP2B6: Molecular mechanisms and emerging clinical significance. Pharmacogenomics 2007;8:743–759. [PubMed: 17638512]
32. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV infected patients: Swiss cohort study. Pharmacogenet Genomics 2005;15:1–5. [PubMed: 15864119]
33. Khalsa JH, Treisman G, McCance-Katz EF, et al. Medical consequences of drug abuse and co-occurring infections: Research at the National Institute on Drug Abuse. Subst Abuse 2008;29:5–12.

TABLE 1

Identified areas of needed research related to drug interactions

Drug interaction studies opioid therapies (methadone, buprenorphine) and new ARV (eg, maraviroc, etravirine) and medications currently in development	Studies designed to illuminate the role of hepatic enzymes and/or P-glycoprotein in observed interactions
Neuroimaging studies to determine the mechanism for lack of opiate withdrawal in buprenorphine-maintained individuals versus methadone-maintained individuals receiving medications that lower serum concentrations of these opioids	Develop new or validate current in vitro/in vivo models to study drug–drug interactions
Study of mechanisms of induction of drug-metabolizing enzymes	Expand drug interaction studies to include other illicit (cocaine, methamphetamine, cannabis, heroin) and licit drugs (alcohol, nicotine products) with medications frequently utilized by substance-abusing populations (ARV, HCV medications, TB medications, psychotropics)
Studies of methodological issues in drug interactions studies	Development of protocols for the management of drug interactions
Study of genetic factors associated with drug interactions	Design of simplified protocols for special populations that may have difficulty with standard drug interaction paradigms
Utilization of clinical trial networks to undertake greater numbers of drug interaction studies	Study the impact of pharmacokinetic and pharmacodynamic interactions on the therapeutic efficacy of drugs; develop guidelines for cutoffs that would trigger discontinuation of a drug and substitution of another