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Drug Interactions of Clinical Importance with Methadone and Buprenorphine

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Drug interactions are a significant source of morbidity and mortality in the United States. The Institute of Medicine reported in 2000 that as many as 44,000 to 98,000 deaths are estimated to occur annually as a result of medical errors.[1] Included in these numbers are deaths related to adverse drug interactions that may contribute to up to 7,000 deaths yearly. Others have reported that 6.7% of hospitalized patients have a serious adverse drug reaction with a fatality rate of 0.32%.[2] Taken together, these estimates indicate that adverse drug interactions are an important contributor to patient morbidity and mortality. However, these statistics do not reflect adverse drug interactions that occur in out-patient and ambulatory settings. While difficult to calculate because of limitations on data collection and methodological issues, it appears that adverse drug interactions are a significant but preventable public health problem.

In recent years, it has become apparent that drug interactions that occur in the context of treatment of opioid dependence with current US Food and Drug Administration (FDA) approved medications (methadone or buprenorphine), or when methadone is used in the treatment of pain, have become an important factor in adverse events associated with these therapies. These adverse events have significant impact on the patient and on the treatment of their disease.

For example, heroin-addicted injection drug users with HIV/AIDS require pharmacotherapy for both diseases. However, there are a number of adverse drug interactions that may occur when medications such as methadone, and to a lesser extent thus far, buprenorphine, are administered concomitantly with certain antiretroviral therapies or antibiotic medications (which are discussed in detail in the review paper on drug interactions with opioids). An

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Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Expert Panel on Drug Interactions

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important consequence of such interactions is the potential for self-medication with illicit drugs and non- or sporadic-adherence to prescribed regimens. This may precipitate a further array of problems including poor clinical outcomes, development of HIV resistance to current therapeutic agents, and risk for transmission of these viruses.

Our knowledge of drug interactions that occur in the treatment of those who suffer with addiction and other co-occurring medical or psychiatric illnesses is limited. One problem is that in vitro studies may not be predictive of what occurs in humans. Another issue is that studies that methodically examine drug interactions between opioids, other addiction pharmacotherapies, other frequently prescribed medications, and other illicit drugs, to a large extent, have not been undertaken. This is contributed to by a lack of understanding of the importance of such interactions and is also impacted by funding limitations.

The growing problem of adverse events and drug interactions principally involving methadone, but increasingly buprenorphine, have been recognized by leadership at the Center for Substance Abuse Treatment for some time. In May 2008, an Expert Panel on Drug-Interactions was convened by Dr. H. Westley Clark, Robert Lubran, MS, MPA, and Anthony Campbell, RPh, DO. This panel was composed of clinicians, toxicologists, pharmacists, epidemiologists, and clinical pharmacologists who were charged with compiling current literature and available data to produce a document that could be used in educating physicians and clinicians about this issue. As a result of the proceedings of these meetings, panel members contributed to articles in their various areas of expertise that are included in this Special Issue of The American Journal on Addictions.

This Special Issue of The American Journal on Addictions includes a series of 10 papers that underscore the clinical consequences of drug interactions between opioid therapies and other medications as well as with other abused substances. The issue includes a review article that summarizes the current knowledge of drug interactions between methadone or buprenorphine and other medications with a focus on studies that have been conducted in humans rather than in vitro data. This issue also includes two new original research papers on drug interactions between buprenorphine and HIV medications as well as two original research articles indicating that chronic cocaine use can decrease serum concentrations of buprenorphine or methadone. Another article speaks about clinical consequences of cocaine use in buprenorphine/ naloxone treated individuals.

Benzodiazepines are frequently used in combination with methadone or buprenorphine, either as prescribed medications or they may be abused along with opioids and can be associated with serious adverse events or, in some cases, death. A review article in this journal reviews opioid-benzodiazepine drug interactions, the potential adverse effects of these drugs in combination, and clinical recommendations for the use of these medications concomitantly.

There have been surprisingly few articles on toxicological issues involving methadone and buprenorphine—articles that would be of significant assistance to physicians seeking to understand the risks and benefits of prescribing these opioids alone or in combination with other medications. Two articles in this Special Issue address these questions including one article focusing on the indicators of misuse and abuse of methadone and buprenorphine, and an article focusing on toxicities that occur in children who may ingest these drugs. Finally, this Special Issue is rounded out with an article by officials at the National Institute on Drug Abuse who discuss research priorities in this area.

This Special Issue of The American Journal on Addictions is intended as an educational approach to improving identification and management of drug interactions in the clinical setting. Funding sources for initiatives such as this include the Center for Substance Abuse

Treatment, the National Institutes of Health, and the Office of National Drug Control Policy. Pharma should include educational initiatives in their required Risk Evaluation and Mitigation Strategies (REMS) for opioid medications that they are now required to submit to the FDA.

Educational initiatives such as this should be followed with practical strategies for the integration of information on adverse drug interactions into continuing medical-education of physicians and healthcare professionals as well as education of the lay public.

Patients should be matched to treatments when possible based on knowledge of drug interactions. When this is not possible, clinicians need to be prepared to address the occurrence of drug interactions rapidly and provide the necessary clinical intervention to assure the patient's stability.

The problem of adverse drug interactions will be ongoing. Continuing to focus on this concern through undertakings such as this Special Issue will help to keep the problem in the minds of clinicians leading to improved clinical care and outcomes for our patients with complex medical conditions.

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