

because multiple other drugs have been detected at autopsy in the majority of opioid-related deaths (Darke & Zador, 1996) and because such combination drug use may have additive respiratory depressant effects.

All these authors suggested that continued employment of the term "overdose" in initiatives to reduce such fatalities was counterproductive because it ignored the contribution of other drugs to the cause of death and implied that users had control over the 'safe' or 'right' dose of heroin. Other explanations for heroin-related deaths in the past have included anaphylactic or hypersensitivity reactions and contaminant theories, which presently enjoy little currency.

White & Irvine's (1999) impressive and long-needed review of the mechanisms of opioid overdose does not buy into the various theories surrounding the cause of an opioid death. Indeed they do not define 'fatal opioid overdose' at all except to state that opioid drug-induced respiratory depression is the underlying mechanism of death. The aim of their paper is to examine in detail the pharmacological basis of this respiratory depression.

Ambulance officers, witnesses and drug and alcohol workers have noted on occasion that a batch of heroin which resulted in a fatal outcome for one person did not do so for another who shared the same deal. Here, White & Irvine meticulously investigate the contribution of other factors which may account for some of the intra- and inter-personal variation in susceptibility to overdose. Heroin metabolites, rate of methadone metabolism, concomitant use of other drugs as well as variable development of tolerance to the different effects of opioids (about which we know too little) are examined and their implications for better prevention of overdose discussed.

The review also briefly draws attention to the contribution of non-pharmacological factors to risk of overdose such as physical environment which has been reported previously in the literature (Gutierrez-Cebollada *et al.*, 1994). However, ingesting heroin in an unusual or unfamiliar setting is not currently publicized as a risk, probably because the role of environmental factors in opioid overdose prevention has not been fully explored or understood.

Clearly, further research into the pharmacology of opioid overdose is needed to better prevent and manage this event. The review in

this issue of *Addiction* defines the key directions this rapidly developing field of research should take.

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More on opioid overdose

Rafael de la Torre & Jordi Cami

Fatal opioid overdose is still one of the major contributors to mortality among heroin users. According to recent data, about a thousand deaths in Britain¹ and several hundreds in Australia² are due to heroin overdose. In this context the comprehensive review³ on the mechanisms involved in fatal opioid overdose published in this journal is of great interest. We particularly enjoyed the sections focused on "anatomy and physiology of respiration" and "opioid actions and effects".

However, several comments concerning metabolic factors contributing to opioid overdose seem pertinent. While the inability of subjects to hydrolyse heroin because of a silent cholinesterase could contribute to opioid toxicity, especially in first users, in our opinion it is unlikely that after months or years of opioid

consumption this very rare genetic trait could be the main cause of an overdose episode in most drug addicts. Genetic variations in the expression of uridine diphosphate glucuronyl transferase or drug interactions with the rate of morphine glucuronidation (its major metabolic pathway) are probably of academic interest, but of low clinical impact as the authors recognize that morphine and morphine glucuronide conjugates have similar pharmacological activities. Nevertheless, we fully agree that morphine glucuronides play a major role in the overall opioid activity in cases of non-fatal overdose.^{4,5}

In relation to methadone, a general comment on its clearance from a clinical perspective is that there are very few patients under treatment with this compound who are drug free from concomitant medications (psychotropic drugs, antivirals, antimicrobials, etc.). Methadone disposition in this very small subset of drug-free patients is quite foreseeable and there is a good correlation between dose and steady state concentration. Most patients enrolled in methadone maintenance programmes are treated with a myriad of drugs acting either as inducers or inhibitors of its metabolism.⁶ Potential contributors to interindividual variations in methadone disposition not considered by the authors but ranking first among the most common prescribed and/or abused drugs by these patients are benzodiazepines. Most benzodiazepines popular among these patients, such as flunitrazepam and alprazolam, are cleared hepatically by CYP3A4, which is the same isoenzyme of cytochrome P450 involved in methadone metabolism. Future studies on methadone should include a much larger series of patients that will allow researchers to stratify the population according to concurrent pharmacological treatments to gain insight on the relevance of methadone itself against drugs interactions.

We have no more comments regarding the rest of this excellent review. With regard to future research directions, we would like to add a further comment not strictly related to the mechanisms of fatal opioid overdoses but with its prevention. Up to the present there are several well-known factors contributing to opioid overdose, including the concomitant consumption of depressant drugs such as alcohol and benzodiazepines, changes in tolerance after a period of abstinence or differences in the environment in which drug is administered. As has been sug-

gested recently, overdoses among opioid users are preventable either by educating patients on risk factors² or by facilitating the supply of resuscitation drugs such as naloxone, which is available today as a nasal spray.¹ Most of our efforts in the future should be focused on those directions.

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The answer lies within selective ligands and pharmacogenomics

Robert Kerwin

This is an excellent review¹ both of opioid receptor pharmacology, metabolizing enzyme pharmacology of opiates and the physiology and pharmacology of the brain stem control of respiration.

Although not an expert on addictions myself I