

Commentaries on Hickman *et al.* (this issue)

UNDERSTANDING THE HEALTH OF POPULATIONS AND OF INDIVIDUALS

Hickman and colleagues [1] suggest that we need a translational approach in addiction science whereby basic or bench science combine with neuroscience and social science to provide us with a better understanding of how alcohol and opiate use combine to produce a risk of overdose. The central argument of Hickman and colleagues' paper is inarguable. There is little question that scientific knowledge needs to advance through a combination of approaches and that epidemiology and molecular biology, to take just two examples, both have something different, and in many cases complementary, to contribute to our understanding of the production of disease. There is, however, an important distinction to be made between the goals of epidemiological and molecular studies that is blurred in Hickman and colleagues' paper. I will elaborate here on this distinction and why it is central to how we tackle important research questions in addiction science.

The goals of epidemiological studies (or population-based studies in general) and molecular studies (or laboratory-based studies in general) are fundamentally different. Epidemiology uses methods that concern population averages and is best suited to provide us with estimates of the occurrence of disease, or of the determinants of disease at the population level [2]. Hence, when a particular factor is identified as a determinant or a cause of disease through a series of epidemiological studies, this shows us that at a population level, factor A is a determinant of outcome B. Unfortunately, this tells us very little about the likelihood that a particular individual who is exposed to factor A will indeed develop outcome B. It can be shown quite readily that most of the typical measures of association documented in epidemiological studies (e.g. relative risks in the ranges of 2–4) are practically useless in determining an individual's likelihood of disease or, put technically, what the positive predictive value of factor A for outcome B is for any given individual [3]. This is, of course, quite different from the methods and intent of molecular studies, be they basic science or animal simulation models. These studies attempt to understand the precise molecular interactions that result in pathophysiological changes that we then recognize as disease. This understanding of molecular processes is, in a perfect world, applicable to an individual whose molecular structure we can map and completely understand.

Therefore, epidemiological and molecular studies are fundamentally asking different questions. The former are

best suited to ask: 'what are the factors that predict population rates of health and disease?', while the latter are best suited to ask: 'how do specific factors interact within individuals to initiate, or influence, pathophysiological processes?'. This distinction is critical and adds nuance to the essential argument being made by Hickman and colleagues [1]. It is important to adopt a translational approach in addiction science not because epidemiological studies cannot provide an answer conclusively to the alcohol-opiate problem raised by Hickman and colleagues but, rather, because epidemiological methods can only tackle one aspect of this problem—that concerned with the production of overdose rates in the population. We need molecular studies to help us understand pathophysiology within individuals, another equally important aspect of the same problem that is simply not addressed by epidemiological methods.

This reasoning suggests, then, that Hickman and colleagues' [1] criticism of observational studies in epidemiology is somewhat misplaced. The issue is not whether observational studies are 'good methods', but rather whether they are applied appropriately to provide valuable results to the questions of interest. While there is no doubt that there have been findings from epidemiological studies that have been shown by experimental studies to have been incorrect, there have also been many observations drawn from molecular and bench studies that have also been shown later to be incorrect through other studies. I note this distinction not simply to quibble about the relative merits of one method versus another, but rather to note that different methods, be they molecular or epidemiological, may well have merit in pursuit of specific questions and that there is little scientific reason to argue that some methods are 'good' and others 'bad'.

Recognizing this difference is of more than academic importance. Hickman and colleagues [1] suggest that a better understanding of the alcohol-opiate interaction would suggest different health education campaigns. Perhaps. But more fundamentally, educational campaigns are but one type of intervention and I suggest that there might be different types of interventions that are suggested by different research approaches. The epidemiological demonstration that the coincident presence of alcohol and opiates is associated with greater population rates of drug overdose suggests population-level educational interventions to highlight the dangers of the concomitant use of alcohol and opiates, regardless of the precise molecular mechanism underlying this relation. Conversely, molecular evidence that alcohol

and opiates act synergistically as respiratory depressants might suggest a pharmacological intervention that reverses the respiratory suppressant effect of either or of both drugs together that can be made available to individuals who may use both drugs concurrently.

In sum, I commend Hickman and colleagues [1] on raising the importance of a multi-disciplinary approach to addiction science. I could not agree more. It is one of the most appealing aspects of this area of research that there are so many fascinating scientific questions, ranging from molecular to population-level questions. However, we need different methods to address these different questions. Greater precision in understanding the questions we are asking will help us to use the tools at our disposal more efficiently [4].

Keywords Addiction, drug use, epidemiology, methods, public health.

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ALCOHOL AND THE RISK OF OVERDOSE DEATH FROM HEROIN

Fatal intoxications are by far the most common reason for the excess mortality in drug users, followed by various somatic disorders, suicide, trauma and homicide [1]. Research in this area may help to reduce mortality in drug dependence. One of the apparent risk factors in fatal overdose are polyintoxications, and especially the role of alcohol. We read with interest the article from Hickman *et al.* [2], which suggests that animal models could provide evidence for pharmacodynamic or pharmacokinetic interactions between alcohol and opioids which should be corroborated within clinical challenge and epidemiological studies.

While some issues on this subject are clear, many are open for debate. In their recent publication, Darke *et al.* [1] have discussed most of the issues concerning mortality among illicit drug users and this paper is an outstanding and highly informative research monograph. Hickman *et al.* [2] state with reason that many studies have reported that alcohol is present in half or more cases and that there is an inverse relationship between blood alcohol and blood morphine concentrations [3]. The fact that central nervous system depressants such as alcohol increase the risk for fatal overdose by respiratory depression is not surprising. One of the more interesting questions is the chronological relationship between alcohol and heroin intake. There is some evidence [3,4] that the risk is highest when using heroin following the consumption of alcohol, and not the other way around, but this has to be studied in more detail. There is also evidence for a much faster than usual respiratory depression after heroin consumption in alcohol-intoxicated individuals [5]. A possible explanation might be a decreased metabolism of monoacetylmorphin to morphin in the presence of high blood alcohol levels [5]. This question can be answered only through a translational research approach.

Both from epidemiological and clinical perspectives, it seems noteworthy to point out that the number of individuals with alcohol intoxications in methadone maintenance is lower than in heroin users. Two studies published in *Addiction* emphasize this: Bryant *et al.* [6] examined 7451 overdose deaths in New York City between 1990 and 1998; 1024 were methadone-induced overdose deaths and 4267 heroin-induced deaths. Alcohol was detected in 10.9% of methadone-induced overdose deaths but in 72% of heroin-induced deaths. Similarly, Shah *et al.* [7] studied 1120 drug overdose deaths in New Mexico. Alcohol was present in 20.3% of the methadone-related and 30.6% of the non-methadone-related deaths. These studies do not provide information about level of blood alcohol and heroin concentration or the chronological inter-relationship. These issues can be studied only in a translational research approach, not by only analysing toxicological data.

Keywords Alcohol, drug dependence, intoxication, mortality, opioids, overdose risk.

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