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Toxicity: exploring and expanding the concept

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Drug use is much more than just a pharmacological phenomenon. The same is true for toxicity. Harms may often be mediated by intermediary drug-triggered behaviours through which the harm occurs, or even by behaviours resulting from distorted reputation of the drug. We need to broaden our consideration of toxicity.

The purpose of this editorial is to provoke wider consideration of unintended harms of medications given/taken with the intention of benefitting the recipient. We propose that the concept of toxicity be expanded beyond simple drug-induced adverse events. We consider two additional forms of 'toxicity'. Each is a 'mediated toxicity' in which the harm (toxicity) occurs via intermediate behaviour or reputational damage that are triggered by a medication. Both scenarios lead to the altered use of a medication to the detriment of the intended recipient.

We are all familiar with the notion of toxicity in terms of the potential of a particular medication to cause harm to the recipient [1], which may occur in a dose-related or idiosyncratic fashion. We understand this easily when we can identify a simple cause-and-effect relationship (drug>harm). Liver damage in paracetamol overdose or allergic reactions to penicillin are examples where toxicity is directly attributable to the medication. But sometimes there is an intermediate step (drug->behaviour->harm) or even a series of steps (drug->reputation->behaviour->harm).

Behaviourally-mediated toxicity: In some circumstances and some patients, a medication may provoke atypical behaviour which then causes harm (toxicity). While the harm is not a direct effect of the medication, it results from the behaviour that is nevertheless triggered by the medication - hence 'behaviourally-mediated'.

We give three examples:

- (i) A patient receives disulfiram (Antabuse) treatment with limited knowledge and with ambivalence and engages in binge drinking in an effort to 'drink through' the unpleasant and potentially dangerous disulfiram-ethanol reaction [2].
- (ii) An excessive naloxone dose is used to reverse overdose and triggers acute opioid withdrawal ('over-antagonism'). The overdose victim consequently engages in further active drug-seeking to end withdrawal, with risk of rebound toxicity and potentially fatal outcome when the effect of the short-acting naloxone wears off [3].
- (iii) A patient in a trial of cocaine vaccine reports escalation in quantity of cocaine used in those with higher antibody titres, who attempt to over-ride vaccines or blockade [4].

Technologically remarkable anti-drug vaccines and ultra-long-acting blocking drugs are currently in development, but we must be mindful of possible unanticipated adverse consequences. Could these new medications trigger use of other drugs not blocked by the antagonist or the vaccine, thereby provoking a potential new substance use disorder, or even switching to a more rapid route of administration (e.g. from snorting to injecting) to circumvent the blockade? We should contemplate the possibility.

Reputationally-mediated toxicity: It may seem strange to include, in a consideration of toxicity, a medication's reputation. However, shaped by scientific and clinical reports, promotion from manufacturers, media and political assertions, and street folklore, the reputation of a medication (good or bad) can greatly influence whether clinicians offer it to patients and whether patients accept, use, and adhere to a particular medication (separate from its actual appropriateness or otherwise). We propose the term "reputationally-mediated toxicity" to describe when a medication acquires a reputation that alters the medication usage behaviour which then causes toxicity.

Examples from general medicine illustrate how the harm (toxicity) results from the behaviour that is triggered by the reputation of the drug - hence 'reputationally-mediated'. The positive reputation attached to antibiotics led to overprescribing over a half-century, creating penicillin-related allergic reactions and the evolution of medication-resistant bacteria. In the opposite direction, the negative reputation of childhood vaccinations leads to 'vaccine hesitancy' and fewer vaccinations for fear of relatively rare adverse reactions, causing a resurgence of measles outbreaks and associated fatalities [5,6].

For the addictions field, reputationally-mediated toxicity is an overlooked major influence on the extent to which valuable medicines are considered and the competence with which they are used. Yet we pay it no real attention.

i) The reputation of naloxone among drug users in Glasgow in the late 1990s was that of a punishment for drug users, to be avoided at all costs [7], likely deterring help-seeking as well as hostility to emergency care. For widespread take-home naloxone distribution, a reputational turn-around of naloxone was essential for service user acceptance and for public preparedness to assist lay-observer administration.

ii) Medications to clear chronic hepatitis C infection (thereby preventing cirrhosis or primary liver cancer) have produced only limited benefit, because first-generation antiviral treatments were unpleasant to take, required long-term treatment and were only partially effective,

leading to frequent avoidance of treatment. New-generation Hep C treatments have much milder side-effects and shorter duration of treatment and produce near-universal clearance of the virus; but a reputation turnaround is needed if real benefit is to be achieved.

iii) Methadone is one of the most extensively researched medications in medicine, but the influence (sometimes supporting, sometimes opposing) of public and professional reputation has been profound. Concerns about dependence liability sometimes deter consideration of Opiate Substitution Treatment [8] despite consistent evidence of reduced deaths and improved social functioning [9,10], and accounts that 'methadone gets into your bones' (perhaps true, who knows?) imply that, for personal safety, it should be avoided. The paper by Uebelacker [11] illustrates how profound the influence of beliefs (their term) can be.

iv) Naltrexone powerfully blocks the effects of virtually all opiates, and may protect former heroin users at times of vulnerability. However some practitioners and agencies communicate that any pharmacological assistance is antithetical to what they consider to be recovery. This reputational issue can close off a potentially valuable therapeutic option before it is even considered.

In conclusion, we want to draw attention to the fact that drug toxicity is much more than a pharmacological event. A drug does not act in a vacuum – patterns of use depend on user characteristics and social context. We understand it as having bio-psycho-social dimensions. We argue that the same is true for toxicity. There are pathways to adverse consequences that need examining if we are to understand and prevent them; behaviour and reputation are two examples of mediators but there are likely to be more.

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