Strong medication overdose data, but we need to consider both toxicity and therapeutic need when prescribing

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Suicide and self-harm rates in Australia are increasing, especially among young people.[1] Poisoning leads to 80% of hospitalisations following self-harm,[2] and substantially contributes to the number of premature years of life lost.[3] The focuses of pharmacovigilance and medication safety research have been adverse drug reactions, unintentional toxicity (daily dosing of methotrexate; digoxin toxicity in acute kidney injury), and drug–drug interactions. While these are important considerations, self-poisoning deaths have been largely ignored in prescribing decisions, despite their considerable role in medication-related fatalities. Awareness of frequently implicated agents leading to death is essential for considering restrictions and ensuring safer prescribing practices for reducing harm. However, knowing which medications are most frequently involved in suicide deaths is not sufficient. Critical questions include whether the person was prescribed the medication, the lethality of the medication, and whether the prescribed medication is more harmful in overdose than alternatives.

The importance of the article by Lim and colleagues in this issue of the *MJA*[4] is that the authors examined the lethality of 2132 poisoning suicides, involving 140 medicines, during 2013–19 relative to their dispensing patterns (dispensed to the individual), population use, and lethality in overdose. By linking coronial toxicology findings with Pharmaceutical Benefits Scheme records and New South Wales Poisons Information Centre (NSWPIC) data, they paint a clearer picture for clinicians seeking to identify medications that pose a greater hazard for people at risk of suicide.

Lim and colleagues found that highly toxic substances implicated in suicide deaths include opioids, hypnosedatives (such as benzodiazepines), tricyclic antidepressants, and propranolol.[4] For each of these drugs, we need to examine the evidence for efficacy, therapeutic toxicity, and fatality. For example, most clinicians are aware of the high rates of adverse effects and the risk of misuse of opioids and hypnosedatives. Numerous coronial and clinical studies attest to the severe toxicity of opioids.[5]

In contrast, many physicians are unaware of the potential lethality of propranolol, often prescribed for people with anxiety symptoms (tremors and palpitations). Propranolol overdoses (as low as 2 g) can be severely toxic, causing seizures, cardiac arrhythmias, and death.[6] In Australia, propranolol is usually dispensed as 10 mg and 40 mg tablets in pack sizes of 100 or 200 tablets. Alarmingly, the United Kingdom National Poisons Information Service reported a 41% increase in the number of propranolol prescriptions from 2007 to 2017, followed by a 205% rise in propranolol-related deaths between 2017 and 2021.[7] In 2024, a British coroner commented on the unrecognised risk of propranolol among general practitioners and their prescribing of large quantities of the drug.[8] Further, a recent systematic review found that beta blockers, including propranolol, are ineffective for treating anxiety.[9] Neither the United Kingdom National Institute for Health and Care Excellence guidelines[10] nor the Royal Australian and New Zealand College of Psychiatrists[11] recommend propranolol for treating anxiety.

Lim and colleagues found that antidepressants such as doxepin, dothiepin, and nortriptyline had the highest estimated case fatality rates among antidepressants.[4] This finding is consistent with other overdose reports, according to which dothiepin was associated with a greater risk of seizures and arrhythmias than other tricyclic antidepressants.[12] Further, therapeutic use of tricyclic antidepressants in clinical trials is associated with greater likelihood of adverse effects (compared with placebo).[13] These findings illustrate the importance of using less toxic agents, such as selective serotonin reuptake inhibitors, as first-line treatments for depression. For people with major depression, the risk of toxicity must be carefully weighed against drug efficacy.[13] In these circumstances, it is important to consider harm reduction by prescribing the lowest efficacious dose and limiting the amount dispensed.

One limitation to basing drug recommendations on suicide fatalities alone is that it does not take into account toxicity related to therapeutic use or unintentional toxicity. Lim and colleagues found lithium to be less toxic than other psychotropic medications,[4] consistent with acute lithium overdose rarely causing severe effects. Nevertheless, therapeutic lithium use has many adverse effects, and there is a risk of chronic lithium toxicity, which can lead to significant injury and the need for dialysis, especially in older people.[14] Although it is relatively safe in overdose, clinicians must be mindful of the long term side effects of lithium.

Lim and colleagues present valuable information,[4] but prescribing decisions must balance efficacy and toxicity, and all forms of drug toxicity. Avoiding drugs solely because of their relative toxicity does not always benefit the patient, as many are essential for treating mental health disorders that, if untreated, can lead to suicide or diminished quality of life. The findings of the study by Lim and colleagues should be considered alongside other toxicity and efficacy data. Given the rising suicide and self-harm rates in Australia, harm reduction and the linkage of various data sources, including coroners' findings, are essential for safer prescribing and improving outcomes for patients. To reduce harm, physicians must be aware of medications that they should prescribe in limited quantities and only after less toxic alternatives have been tried.

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