Editors' view

In defence of polypharmacy

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The Greek word *πολύς* (*polus*) had several meanings, such as many, mighty, and wide. The English prefix *poly-* usually takes the first of these meanings; *polymyalgia* means pain in many muscles, *polyneuropathy* disease of many nerves. However, *πολύς* could also mean too much or too many. We all have many red blood cells, so *polycythaemia* means having too many; and *polydactyly* means too many fingers or toes. So *polypharmacy* can mean the prescribing of either many drugs (appropriately) or too many drugs (inappropriately). The term is usually used in the second of these senses, and pejoratively. However, when talking about *polypharmacy* it would be wise to qualify it as appropriate or inappropriate.

Polypharmacy has a long tradition, which can be traced back at least to Mithridates, King of Pontus (120–63 BC), who tried to prepare a universal antidote for poisoning (hence called a *mithridate*) by combining many substances in a single formulation, which he then took in increasing doses, in an attempt to achieve immunity to their toxic effects. This approach left a deep footprint in the therapeutic sands (one seventeenth century recipe listed 48 different ingredients), until William Heberden started to wash it away in his *Essay on Mithridatium and Theriaca* of 1745. A *mithridate*, he wrote, is 'made up of a dissonant crowd collected from different countries, mighty in appearance, but in reality an ineffective multitude, that only hinder one another.' [1]. Even so, in 1775, for example, when William Withering was shown a Shropshire woman's recipe for the treatment of dropsy, he noted that it 'was composed of 20 or more different herbs', all but one of which (foxglove) he rejected as the active ingredient [2]. Of course, when most or all of your ingredients are inactive it doesn't matter how many you have.

But the real rejection of *polypharmacy* is a twentieth

century notion, starting with Ehrlich's idea of a *Zauberkugel* or magic bullet, since when we have become increasingly obsessed by the idea that a single compound should be used to treat a single condition. Nevertheless, we know well that there are many conditions in which the combined use of three or more drugs is beneficial. Following Waksman's discovery of streptomycin in 1943, it rapidly became clear that using it alone led to the emergence of resistant mycobacteria, and it soon became commonplace to combine three or four different antituberculosis drugs, as we do today. Other infections are treated similarly: we use three drugs to eradicate *Helicobacter pylori* from the stomach and three or four in the HAART regimen used to treat AIDS. Indeed, it is surprising, given the continuing emergence of resistant malaria parasites, that *polypharmacological* treatment of malaria has only been introduced recently.

Polypharmacy has also become useful in other areas, such as diabetes mellitus [3]. A striking recent example of proposed beneficial *polypharmacy* is the *Polypill*, which contains six ingredients – aspirin, a statin, and folic acid, plus three antihypertensive drugs [4]. The antihypertensive drugs are recommended in half the usual doses, reducing the risks of adverse effects, which are distinct for the different types of drugs, while multiplying the therapeutic benefit, since all lower the blood pressure. In some patients this strategy will be ineffective, since the doses may be too low to produce any beneficial action at all, and several times nothing is still nothing; I have occasionally seen patients who failed to respond to low doses of three or more antihypertensive drugs but responded well to a large dose of just one. But for many patients the strategy will work well. And if everybody over the age of 55 years took the *Polypill*, it would, according to predictions based on a

large amount of published evidence, reduce the burden of heart attacks and strokes in the population by over 80% [4].

But the other side of the coin is that polypharmacy is associated with an increased risk of adverse drug reactions and interactions, particularly when several drugs are used to treat different conditions. The extent to which the risk of an adverse drug reaction is increased by any combination of drugs cannot be predicted, unless the exact risks of each medicine are known and the risks of adverse reactions to each medicine are independent of each other. For example, if a patient takes eight drugs, each of which carries an independent 5% chance of an adverse drug reaction, the overall risk of an adverse reaction is 34% (not, it should be noted, 40 per cent – what would the risk be if a patient took 11 drugs, each with a risk of 10 per cent?). However, sometimes there are unpredictable interactions. For example, in one study [5] the risk of hyponatraemia in patients taking an SSRI compared with other antidepressants had an odds ratio of 3.9, larger than the effect of diuretics (odds ratio 2.0); however, the combination of an SSRI with a diuretic had an odds ratio of 14, a striking interaction.

On the other hand, for some therapies the risks are well known from large randomized controlled trials. For example, the risk of any adverse effect from the Polypill is an estimated 17% and of an adverse effect serious enough to warrant withdrawal 1–2%; aspirin is the major contributor to these figures, and those unable to tolerate aspirin could beneficially take the other five ingredients of the Polypill with little risk.

Polypharmacy looms large in three papers in this month's *Journal*. In their review of adverse drug reactions in elderly people, Routledge, O'Mahoney, and Woodhouse (pp. 121–5) cite polypharmacy as an important contributor, in addition to frailty. But they do concede that rational polypharmacy is legitimate in the appropriate circumstances.

Elsewhere, Wilson, Thabane, and Holbrook (pp. 126–33) discuss the application of data-mining techniques in pharmacovigilance. Terminology is confusing in this area. Data mining of large databases can identify adverse events. If an adverse event is linked with a medicament it can be described as a suspected adverse drug reaction, and if the link is proven or largely substantiated it can be described as an attributed adverse reaction. The term 'adverse drug event', as used by some workers in the field, is illogical; once an adverse event has been linked to a drug it is either a suspected or an

attributed adverse reaction. In forging such links polypharmacy can be an important confounder. For example, in one study the fact that tolterodine can cause hallucinations was at first missed, because the patients in whom it occurred were taking other drugs that can do the same [6].

Another type of polypharmacy is the administration of probes for different cytochrome P450 isozymes in cocktails that trade under different names, such as the Pittsburgh, Karolinska, and Cooperstown cocktails. Blakey *et al.* (pp. 167–73) describe a version that seems to be free of metabolic interactions of the probe drugs and has no important pharmacodynamic or adverse effects, albeit in a small study. Such cocktails may be useful in predicting drug–drug interactions in drug development. And with many different inhibitors of the several isozymes to choose from, this technique, in its numerous avatars, looks set to run and run.

What should the clinician do about polypharmacy? The short answer is to adopt it when appropriate and avoid it when not. And a knowledge of the pharmacology and clinical pharmacology of the component drugs and their interactions is essential, whether espousing polypharmacy or treating its consequences. Taking his lead from one of Homer's epithets for the sea, William Makepeace Thackeray, in his *Irish Sketchbook* of 1834, invented the word *poluphloisboiotatotic*, meaning very loud-roaring. The extent to which we make a loud roar about polypharmacy will depend on whether it is justifiable or not. The distinction is important.

References

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