The 'polypill', friend or foe?

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In June 2003 the British Medical Journal (BMJ) published a paper which claimed that taking a daily pill containing six active ingredients would prevent more than 80% of cardiovascular events.[1] The proposed 'polypill' contains aspirin, a 'statin', three blood pressure lowering agents (a thiazide, a beta blocker and an ACE inhibitor) and folic acid. Few papers have provoked such debate and raised tempers so high. One correspondent wrote: 'I have read some rubbish in medical journals in my time, but none as appallingly bad as this'. On the other hand, the Editor of the BMJ said the paper made that issue of the journal possibly the most important in 50 years.

It is generally accepted that patients with previous cardiovascular disease require treatment with antiplatelet, blood pressure lowering and cholesterol lowering therapies.[2,3] Where the controversy lies is the concept of a fixed dose, and widespread use of the polypill in primary prevention. (The paper suggested that as death from cardiovascular disease increases with age everyone over 55 years old should take the polypill.) Mass medication can be justified from a population perspective when the burden of disease is high, but it is difficult to defend at an individual level in those at low risk.

Another big question is whether benefits of the individual components really would accumulate as suggested. Clinical trials show that adding one more class of medication does confer additional reduction in risk, but no-one has carried out a study with as many components as in the proposed polypill. Estimates of benefit range from a **relative** reduction in risk around 55% to over 80%, according to the composition of a polypill, with those at highest risk achieving the greatest benefit in **absolute** terms.[1,3]

Would a one-size-fits-all approach be safe and effective? We don't know if a combination approach would magnify the adverse effects of individual components, although there seems no *a priori* reason to believe it would. It is estimated that the polypill would cause symptoms in 8–15% of people.[1] Some have argued that it would be difficult to tease out which component of the polypill is causing an adverse effect. However, the same is true in any patient who is taking separate drugs at the same time. The components of the polypill and their adverse effects are well known so it should be possible to attribute the cause of an adverse effect.

Critics claim that for many individuals, risk factors would not be adequately controlled by a fixed dose combination. It would however still be possible to tailor treatment with 'top-up' single ingredient tablets where the clinician considered this necessary and different versions of the polypill might be available. Nevertheless, fine-tuning the components of the polypill actually makes little difference to the magnitude of the risk reduction in the whole population. The authors of the BMJ paper argue against intensive monitoring of risk factor levels and subsequent adjustment of treatment, as individual measures of cardiovascular risk discriminate poorly between people who subsequently experience disease events and those who do not.[1]

Some people are concerned that a polypill could be too effective, a 'magic bullet' that removes any incentive to adopt healthier lifestyles. This is a weak reason to reject a potentially effective therapy, as is the concern that the polypill would medicalise prevention (iodine in salt and fluoride in the water are perhaps two respectable antecedents). However, it is true that medical interventions can have serious unintended consequences, and the polypill would be to the detriment of personal and population health if it diverted funds and energy from 'upstream' health promotion measures such as smoking cessation, healthy food choices and active environments.

Would people take a polypill? Everyone has a relative or friend who complains of 'rattling' with all their tablets.

In this issue…

Common problems can sometimes be difficult to treat. It is therefore important that the diagnosis is correct. The importance of a thorough history and examination is therefore emphasised in the articles by Gayle Fischer on childhood vulval disease, and by Mark Paine on dealing with dizziness.

While history and examination are essential for diagnosis, laboratory tests are indicated in some cases. Huy Tran tells us about the role of biochemical testing during pregnancy.

The use of antidepressants is increasing. One reason for this rise is the use of the drugs for other indications such as those discussed by Lisa Lampe.

Intuitively the greatest benefit of a polypill is the simplicity of the regimen, resulting in improved adherence and better clinical outcomes, but surprisingly, few clinical trial data are available.[4] Nevertheless, fixed-dose combinations of four or more medications are being developed for tuberculosis and HIV. For people with cardiovascular disease, in whom the separate ingredients are recommended, only a small minority receive the full combination.[5] This may result from confusion due to complicated regimens, the sheer inconvenience of managing large numbers of pills, a reluctance to take (or prescribe) multiple medicines, and cost.

A polypill could be very inexpensive because its ideal components are now off-patent. World Health Organization (WHO) analyses show that combination therapy given to people at high absolute risk of cardiovascular disease is more cost-effective than current treatment patterns based on single risk factors (for example treating 'hypertension'). Population approaches like salt reduction in foods are the most cost-effective of all, according to the WHO report.[6]

So why don't we have a polypill already? Innovator companies are reluctant to invest, because profit margins are likely to be thin. Generic manufacturers do not have large research and development budgets. This leaves a gap that government agencies are not ready to fill. What is more, the regulatory hurdles for combinations of three or more ingredients are poorly defined. Despite all this, there are now 'mini' versions of the polypill. For example, last year the United States Food and Drug Administration approved a combination of amlodipine and atorvastatin. The authors of the BMJ paper have a patent on their version of the polypill, though it is difficult to know how defensible this would be, given the components are all generics and the concept is based on published evidence.

At present there seems more heat than light in the polypill debate. It is time to move on and seek direct evidence from trials. Relatively small studies could investigate whether adherence is improved in patients with established indications for the component medications. An even bigger question is what works best for primary prevention; long-term trials with several thousand participants will be needed to show a reduced event rate. Before casting the polypill as 'friend' or 'foe', we need better information on acceptability, safety and effectiveness.

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Dr Rafter is applying for funding for a randomised controlled trial of combination cardiovascular medication.

Transparency – in the eye of the beholder?

Editorial Executive Committee, Australian Prescriber

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The Editorial Executive Committee of *Australian Prescriber* is concerned about the increasing difficulty of obtaining good information about new drugs. It is not unusual for a drug to be marketed in Australia despite a lack of published peer-reviewed information to support its manufacturer's claims. This is particularly the case for adverse effects and for 'head-to-head' comparisons with older drugs used to treat the same conditions as the new drug. The data (both published and unpublished) may have been evaluated by drug regulatory authorities so there is a strong argument that their evaluations should be available to health professionals and consumers.

A lot of prominence has recently been given to the need for 'transparency' in the drug regulatory system. For example, there have been calls for an international register of clinical trials so that unfavourable results are not hidden.[1,2] Greater transparency in the process for subsidising drugs was also an important part of the free trade agreement between Australia and the USA. However, transparency means different things to different people.