



Polypills-A Systematic review

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Abstract

Polypills can contain multiple pharmaceutical agents targeting the cardiovascular system. The use of polypills in the secondary prevention of cardiovascular disease (CVD) has received broad support; however, the use of polypills in the primary prevention of CVD is more controversial. This controversy stems from an inherent resistance to the medicalization of primary prevention, and the lower CVD event rate in this population means that smaller absolute benefits are derived. Indeed, drug-related adverse effects, such as from aspirin, might even outweigh the benefits. The role of fixed-dose combination (FDC) therapy for blood pressure (BP) lowering in combatting the widespread under treatment of high BP — the leading modifiable risk factor contributing to the global burden of CVD — has gained momentum. Increasing evidence suggests that FDC pills containing multiple low doses of BP-lowering drugs produce more effective BP lowering than the use of fewer separate BP-lowering drugs at higher doses, without an increase in adverse effects.



Trials of FDC pills comprising three half-dose or four quarter-dose BP-lowering drugs have shown substantial efficacy. In this Review, we summarize the current evidence on low-dose BP-lowering FDC pills and the justification for this approach in the context of polypills in the primary prevention of CVD.

Keywords: Fixed-dose combination, blood pressure, Cardiovascular disease, Polypills.

Introduction

A **polypill** is a type of drug combination consisting of a single drug product in pill form (i.e., tablet or capsule) and thus combines multiple medications (that is, more than one active pharmaceutical ingredient). The prefix "poly" means "multiple", referring to the multiplicity of distinct drugs in a given "pill". In precise usage, a pill is a polypill if it contains at least 4 drugs (meaning that fixed-dose combinations of 2 or 3 drugs are not polypills). An occasional synonym is combopill. A polypill is commonly targets treatment or prevention of chronic conditions.¹



Polypills may be aimed to be consumed by healthy people as a means of preventive medicine, and/or treating actual pathophysiological condition(s), the former typically involving lower dosages than the latter. Polypills can reduce the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of pharmaceuticals as well as alleviate patient pill-burden. Sometimes the multiple drugs in a given polypill might all be aimed at a single underlying condition (or, group of related conditions), partly because this expands the pool of potential patients for whom a given combination of drugs/dosages might be appropriate (particularly in the case of mass-produced polypills, i.e. FDCs). The term



polypill was first coined in the context of cardiovascular disease prevention,^{[2][3]} but has since gained broader acceptance, including now for combinatorial drug products that existed before the term was actually coined (as the bare term without any modifiers is now quite generic).

In addition to the noted fixed-dose types of polypills, polypills can also be custom-made for specific patients through a process called pharmacy compounding. Physicians in most jurisdictions have wide discretion to prescribe customized drug products containing unique drug-dosage combinations (and/or formulations thereof) specifically for individual patients, which certain pharmacies can then sometimes produce for such patients^{2,3}

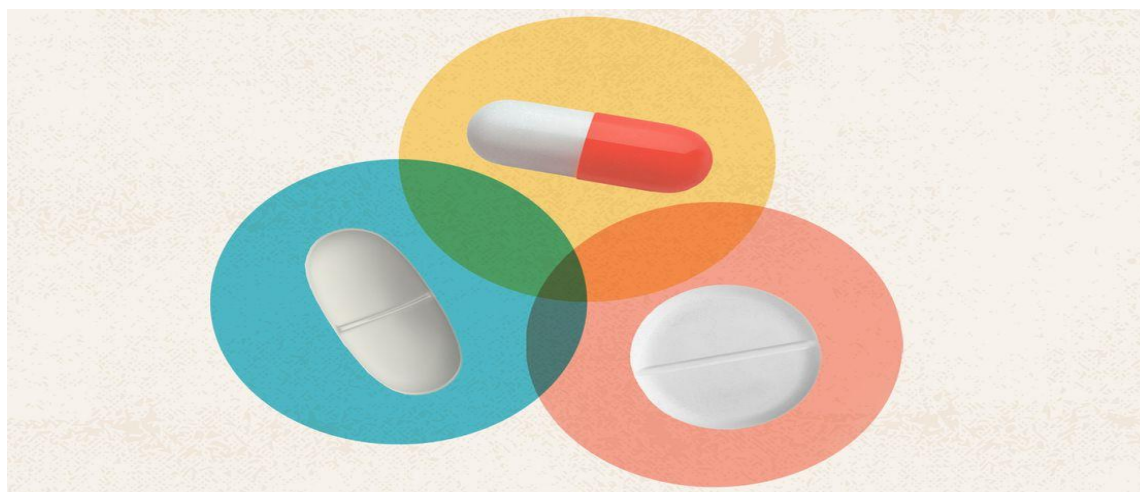
Developments in polypill usage for disease therapy[Treating cardiovascular disease



One of the first recommended roles of a polypill was as a means of providing recommended medications to people with heart disease, stroke and other forms of cardiovascular disease. Most cardiovascular disease patients do not receive recommended medications long-term: the proportion of cardiovascular disease patients *not* receiving a statin, aspirin and blood pressure



lowering medication long-term ranges from about 50% in high income countries to over 90% in low income countries.⁴ In 2001, a World Health Organisation and The Wellcome Trust meeting of experts to discuss interventions for non-communicable diseases noted “the use of a single pill could well encourage patients to adhere to treatment as well as seriously reduce the cost of the drugs” A programme of research was outlined, including stability and bio-availability testing followed by assessment of short-term effects on blood pressure, cholesterol, platelet aggregation, safety and side effects. In 2002, the World Health Organisation Annual Report outlined the substantial potential public health impact and cost-effectiveness of scaling up access to combination cardiovascular treatment⁵ and an editorial in The Lancet noted that a four component combination pill would reduce cardiovascular risk by about 75% among people with vascular disease.⁶



Polypill' Reduces Risk of Repeat Heart Attacks | Everyday Health

Cardiovascular disease (CVD), such as heart attack and stroke, is a leading cause of death and disability in the US. [High blood pressure](#) and high cholesterol are major risk factors for CVD, and even though they are quite common and highly treatable, they tend to be undertreated. This is especially true among those who are poor or members of a minority. It's estimated that



thousands of lives could be saved each year if more people with high blood pressure and high cholesterol received treatment for these conditions⁷.

The appeal of the Polypill:

One reason that high blood pressure and high cholesterol are poorly treated is that medications prescribed to treat them aren't reliably taken as prescribed (the common medical expression for this is poor medication adherence). Among the most important reasons for this are that these conditions usually cause no symptoms, it's hard to remember to take multiple medications or multiple doses of medications each day, medications may cause side effects, and they may be expensive⁸.

One potential way to improve medication adherence is to combine one or more medications into a single pill, or polypill. Advantages to this approach include:

- Lower doses of each medication may be needed, possibly reducing the incidence of trouble some side effects.
- Multiple medications (in low doses) may be more effective than higher doses of a single Medication.
- Fewer doses are easier to remember
- Depending on the specific medications and doses, a polypill could be less expensive than taking several individual medications.
- Fewer pills and lower doses of medications may require fewer office visits, blood tests, and other monitoring.

Treating diabetes and metabolic syndrome.

Polypills have been proposed for managing diabetes (and potentially for pre-diabetes)



Diabetes - particularly Type II diabetes - is a major cause of morbidity and mortality. Diabetes also contributes substantially to cardiovascular risk, yet some ingredients appropriate for a cardiovascular polypill may not be advisable for patients with diabetes (such as beta-blockers and thiazide diuretics). A polypill for diabetes could include a statin (to reduce LDL cholesterol and for their anti-inflammatory properties), an ACE inhibitor (for blood pressure control and to protect the kidneys), aspirin (for antiplatelet and anti-inflammatory properties), and metformin (a medication for diabetes that is also associated with weight loss).

Role of compounding pharmacy

As noted, not all polypills are mass-produced fixed-dose (FDC) drug products. Physicians in many countries have wide discretion to prescribe customized drug products containing unique drug-dosage combinations and/or formulations thereof specifically for individual patients, which can then be custom-produced in a compounding pharmacy. Some kinds or compositions of polypills or similar drug products are more amenable to custom-compounding than others, and most retail pharmacies no longer offer compounding services at all (although hospital pharmacies still commonly compound intravenous medications). While fewer pharmacists are trained and experienced in the relevant skills anymore, especially regarding oral dosage forms, such compounding pharmacies nevertheless can be found and utilized via mail-order (if not available locally) with sufficient notice and planning. Generally, if a customized drug product is produced for a specific patient in response to a prescription specifying said patient's drug(s)/dosage(s), it is *not* subject to regulatory approval⁹ (e.g., FDA in the US) but is instead regulated under the practice of pharmacy (governed at the state-level in the US).

Technologies are under development to facilitate production of customized polypills, such as for example by the use of ink-jet printing mechanisms to precisely deposit selected drug substance(s) onto sheets which can then be inserted into capsules (enabling "individualized dosing and automated fabrication of medicines containing multiple drugs," in addition to custom single-drug products). Similar technology can also be used to print tablets, more directly. Ink-jet or fluid-jet



approaches require each drug substance to be dissolved in a liquid solvent, but they can be particularly conducive to custom formulation with various possible excipients^{10,11}(in addition to custom drug/dose selections).

Poltential downsides of the Polypill

While the potential advantages of a polypill are clear, they could be outweighed by their downsides, including:.

- **Side effects:**Taking multiple medications, even at low doses, may lead to higher rates of side effects. If a side effect does occur, it may be impossible to know which of the medicines in the polypill is responsible
- **Drug interactions:**When combined, medications can interact, causing serious problems such as too much or too little potency,allergic reactions,or combined side effects.
- **Overtreatment:** Some people need only one or two medications to treat a condition; polypills may provide more medication than is needed
- **Cost:**A polypill may be more expansive than the individual medications they contain.
- **Less dosing flexibility:** Polypills have fixed doses of several medications. so it may not be possible to adjust the dose of one medication without adjusting them all.

List of currently available polypills for research and clinical use



Brand name	Constituents	Manufacturer
Red Heart Pill™ 1	Aspirin (75 mg), atenolol (50 mg), lisinopril (10 mg), simvastatin (40 mg)	Dr. Reddy's Laboratories, India
Red Heart Pill™ 2	Aspirin (75 mg), hydrochlorothiazide (12.5 mg), Lisinopril (10 mg), simvastatin (40 mg)	Dr. Reddy's Laboratories, India
Trinomia®/Sincronium® ^a	Aspirin (100 mg), ramipril (2.5, 5 or 10 mg), atorvastatin (20 mg)	Ferrer Internacional, Spain
Trinomia®	Aspirin (100 mg), ramipril (2.5, 5 or 10 mg), simvastatin (40 mg)	Ferrer Internacional, Spain
Polycap®	Atenolol (50 mg), hydrochlorothiazide (12.5 mg), ramipril (5 mg), simvastatin (20 mg), optional aspirin (100 mg)	Cadila Pharmaceuticals Ltd., India
Starpill®	Aspirin (75 mg), losartan potassium (50 mg), atenolol (50 mg), atorvastatin (10 mg)	Cipla, India
Polypill ^b	Amlodipine (2.5 mg), losartan (25 mg), hydrochlorothiazide (12.5 mg), simvastatin (40 mg)	Cipla, India
PolyIran	Aspirin (81 mg), enalapril (5 mg); or valsartan (40 mg), hydrochlorothiazide (12.5 mg), atorvastatin (20 mg)	Alborz Darou Pharmaceutical Company, Iran
Ramitorva®	Aspirin (75 mg), ramipril (5 mg), atorvastatin (10 mg)	Zydus Cadila, India



Conclusion: In its journey of the past decade, the polypill has travelled from a hyped concept to attaining acceptability in the competitive world of pharmacotherapeutics. The available studies do seem to favour the polypill in terms of improving adherence and reducing the cardiovascular risk burden of high blood pressure and dyslipidemia. The extent of its impact on major cardiovascular events would become evident in the near future through large trials with outcome endpoints. If positive, this would probably increase its acceptability among physicians and health administrators to unreservedly accept it in their armamentarium to fight the mounting burden of CVD. In the meanwhile, strategies to prevent CVD through improved behaviours and judicious use of available drugs must be implemented effectively through an efficient health system. The polypill can fit well in to such a system but cannot substitute for it. A polypill regimen decreases the incidence of fatal and non-fatal CV events in patients with intermediate- and high- cardiovascular risk, and therefore may be an effective treatment for these patients.

Conflicts of Interest:

The authors declare no conflicts of interest

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