

Could the polypill improve adherence?

The patient perspective

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ABSTRACT

INTRODUCTION: Multiple medications are recommended for the management of ischaemic heart disease. Unfortunately, increasing the number of medicines reduces adherence to medicines therapy. The concept of a polypill with a fixed dose combination of the common cardiovascular medicines (aspirin, statin, two blood pressure-lowering medicines) has been promoted. Patient perceptions about this concept have not been explored.

METHODS: People taking at least three cardiovascular medicines were interviewed using a semi-structured interview about their views on a polypill that could reduce the number of tablets they would need to take.

FINDINGS: The participants considered that the polypill would be very convenient, especially when travelling and would reduce the pill burden. If the polypill was subsidised by the government, they would have reduced dispensing fee costs. There were concerns around the inflexibility of dosing of individual components of the polypill, and some concerns about safety and efficacy. Medical practitioners were identified as having an important role in influencing participants about the acceptability of the polypill.

CONCLUSION: Generally the concept of the polypill was acceptable to participants, primarily because of the convenience and reduced number of tablets required daily. There were concerns about whether the polypill would be as effective and safe as the individual medicines.

KEYWORDS: Cardiovascular diseases; medication adherence; prevention

Introduction

Cardiovascular disease (CVD) is the leading cause of hospitalisation and premature death in New Zealand (NZ), resulting in significant years of life lost to disability.¹ Ischaemic heart disease (IHD) is the most common cause of CVD. Since the peak of the IHD epidemic in the late 1960s, rates of IHD have fallen, but this trend is not applicable to the Maori population where the burden is projected to increase over the next decade.^{1,2}

Strong evidence supports the use of a statin, an antiplatelet agent and blood pressure-lowering medicines to reduce IHD morbidity and mortality.³ The absolute risk of having a cardiovascular event can be halved by taking this 'triple thera-

py'.⁴ Efficacy of medicines therapy is hampered by poor medication adherence, unaffordable costs of treatment and inadequate prescribing of medication.⁵ Many people find it difficult to take their medications⁶ and the number of medicines may seem overwhelming. Multiple medications and complexity of treatment regimens are major determinants of poor medication adherence⁷⁻¹⁰ which threatens health outcomes.¹¹ O'Brien et al.¹² found that when patients were prescribed a single medication, it was taken 85% of the time. When five or more medications were prescribed, this reduced to 65%, highlighting that an increase in the number of prescribed medications reduces the likelihood of adherence. Reducing the pill burden by reducing the number of medicines taken has been shown to improve medication adherence.¹³⁻¹⁶

J PRIM HEALTH CARE
2013;5(1):28-35.

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Strategies for simplifying complex medication regimens to reduce the patient's pill burden¹⁰ include decreasing the frequency of dosing intervals and using fixed-dose combination medications.¹⁷ Historically, fixed-dose combinations were not widely accepted due to dosing inflexibility,¹⁸ but there are an increasing number of fixed-dose blood pressure-lowering medicine combinations available, such as a thiazide plus an ACE inhibitor.

Fixed-dose combination medications are a combination of two active ingredients combined into a single tablet to reduce the complexity of the drug treatment.¹⁰ Fixed-dose combination medications, as opposed to multiple individual drug component regimens, have been shown to improve adherence by 19% after 12 months in people with high blood pressure.¹⁰ Using once-daily dosing as opposed to multiple-dosing strategies may improve patient adherence by up to 42%.^{10,19}

A controversial 2002 paper suggested that over 80% of cardiovascular disease could be prevented if patients over 55 years old took a polypill that contained cardiovascular preventative medications.²⁰ It was argued this would increase convenience and reduce pill burden. This would be expected to lead to improved adherence, although it is uncertain whether this would be more for unintentional non-adherence (forgetting to take, running out of medicines, misunderstanding of which tablets to take) or intentional non-adherence (overwhelmed by the number of tablets and so selectively being non-adherent). It could be an integral part of the solution to the pharmacological management of IHD.⁴

Currently, two different polypill formulations combining four different medications are being trialled in NZ: simvastatin 20 mg or 40 mg, aspirin 75 mg, lisinopril 10 mg and either hydrochlorothiazide 12.5 mg or atenolol 50mg.⁴

The aim of this research was to explore patient perceptions of the polypill, focusing on people already taking multiple cardiovascular medicines.

Methods

Pharmacies within the Auckland region were selected randomly using a computer-generated

WHAT GAP THIS FILLS

What we already know: Adherence to medication regimens is less than satisfactory and this impinges on optimal medication-related health outcomes. People with cardiovascular disease have multiple medicines, and multiple medicines are recognised as reducing medication adherence. The concept of a polypill, with one capsule containing four cardiovascular medicines, has been promoted as a method to improve compliance.

What this study adds: People on cardiovascular medicines think that a polypill would be convenient and likely to improve adherence, with possible cost reductions. They are concerned about the lack of flexibility of the combination formulation, and issues around safety and efficacy.

system. The pharmacy manager was invited to assist with the study. A researcher attended each pharmacy for one day, with the pharmacist identifying potential participants and inviting them to participate in the interview. If the participant agreed to be interviewed, the pharmacist referred him/her to the researcher, who obtained informed consent.

Inclusion criteria were that the person was on three or more cardiovascular medicines and could communicate in English. Participants were recruited until thematic saturation was reached.

A semi-structured interview was conducted in a private consultation room at the pharmacy (See appendix in the web version of this paper). Interviews were audiotaped and transcribed into the qualitative data software NVivo (QSR International Pty Ltd, Doncaster, Australia). Student researchers collectively explored trends and identified common themes.

Ethics approval was granted by the University of Auckland Human Participants Ethics Committee on 10 June 2010 (Reference 2010/178).

Results

Forty-nine semi-structured interviews were undertaken from seven pharmacies (see Table 1 for details of participant demographics). Slightly more female participants (53%) were interviewed, with the majority of participants aged 61–80 years. Most participants were taking between four and nine medicines daily. Approximately

Table 1. Participant demographics

Characteristics	n (%)
Gender	
Male	23 (47)
Female	26 (53)
Age group (years)	
41–50	4 (8)
51–60	8 (16)
61–70	16 (33)
71–80	16 (33)
>80	5 (10)
Ethnicity	
New Zealand European	30 (61)
Maori	3 (6)
Asian	6 (12)
Other	10 (21)

Table 2. Participant medication-related factors

Medication-related issues	n (%)
Blister packing use	
Yes	17 (35)
No	32 (65)
Number of medications	
<4	5 (10)
4–6	24 (49)
7–9	16 (33)
>9	4 (8)
Duration of taking cardiovascular medications	
0–5 years	18 (37)
6–10 years	17 (35)
>10 years	14 (28)
Participant views on which medications were most important	
All medications are equally important	25 (51)
Cardiac medications	19 (39)
Diabetic medications	5 (10)
Perceived importance of medication adherence	
Very important	33 (67)
Important	12 (25)
Neutral	3 (6)
Not important	0 (0)
I don't know	1 (2)
Knowledge of what their medications were for	
Yes	20 (41)
No	4 (8)
Some knowledge	25 (51)

90% were taking more than four medications each day. The majority did not use any form of adherence packaging, such as pharmacy-prepared blister packs or self-prepared pill boxes (Table 2).

About half the participants believed that all their medications were equally important. Others regarded either their cardiac or diabetic medications to be the most important. Most had some knowledge of their medications such as why they were taking them and how they worked, although four were unaware of the reasons for taking them. Nevertheless, they claimed to adhere to their doctor's instructions.

Reasons for non-adherence

Forgetting to take medications on an occasional basis was reported to be an issue by 32 of the 49 participants.

I forget to take my medicines quite often, especially the lunchtime ones. I get far too busy and forget. (B11)

Being out of routine was the other most common reason for missed medication doses. Many expressed the importance of having a routine to assist in adhering to complicated dosing schedules. It was common that participants missed their doses as a result of missing meals. Changes in sleeping patterns or shift work also had an effect on adherence. When participants were away from home, the likelihood of missing doses was increased.

The other day we had to go out... we planned to come home at 12 o'clock, but we actually came home at four in the afternoon, so I missed my tablets. If I knew I was going to go out for so long, I would take my tablets with me. This only really happens once every four months or so. The other time I had to take my daughter to the hospital, so I had a period where I didn't have my tablets. If I was to go out for dinner, I would take my tablets with me. (J6)

Five participants made a conscious choice to deliberately miss doses, considering them unnecessary. Other reasons given for not taking medicines included lack of organisation, such as not picking up repeat prescriptions on time and forgetting

which medications had not been taken due to complex regimens. Participants also mentioned that they would avoid taking their medications if they knew alcohol was to be consumed, so as to prevent any potential interactions.

Seven participants stated they had never missed a dose and that taking medications regularly had become part of their routine. The fear of the consequences that may occur if doses were missed was one of the main reasons for this.

I have never missed a dose. I'm too scared to in case my heart stops. This is what I've been told. You get so used to taking them. It was initially a big deal. It isn't anymore. (A3)

Perceptions of the polypill concept

The polypill concept was conveyed to participants as a tablet that combined all their cardiac medications. Benefits and concerns were raised by participants, and the main themes identified were convenience, efficacy, inflexibility, safety, pill burden, and cost (Table 3).

Convenience

Convenience was the most popular benefit to emerge from the interviews; 35 participants believed that taking their medication would be made easier with the polypill, particularly those with complex regimens. Participants envisaged that the polypill would save them time and, when travelling, save them space.

Simplified regimens

Multiple medications with doses at varying times throughout the day were described as 'difficult' and 'inconvenient'. Therefore, the idea of a single tablet taken once a day was appealing to ease the burden associated with complex medication regimens.

The thing is people today have got attention spans like a lightning flash, so anything that saves people taking that many medicines has got to be a good thing. It would make it a lot easier; you won't need to take so many pills. One would be much easier than four or five. (J8)

Travelling

Participants who travelled frequently or those who were not at home often found taking multiple medications a burden. This appeared to hinder adherence. Travelling for prolonged periods created further problems.

[The polypill] would be ideal for someone like myself, who travels regularly and takes regular medication. I end up taking, literally, plastic bags filled with boxes and boxes away with me. Imagine when I go away for three months on business and have five lots of medicines that I must take on a daily basis. That's 450 tablets to take. It's a wonder I don't get arrested for drug pushing. It would certainly be much simpler if all I had to take was 90 tablets. (A2)

Time saving

Of the 17 participants who had their medications incorporated into a blister pack or other type of container, seven had been organising their medications themselves. A common concern was the amount of time spent coordinating blister packs and pill containers to ensure they were accurate.

If there was a polypill that fit your doses, then definitely. It would save me the trouble of making my monthly package in my pill box. Also, occasionally one pill will pop out of the pill box and I have great trouble finding it. Taking one pill will save me the hassle of all of this. (L4)

Table 3. Themes identified about use of a polypill cardiovascular medication

Benefits		Concerns	
Convenience	Simple regimen	Efficacy	Published evidence
	Ease of use when travelling		That polypill is equivalent to current medications
	Time-saving		Practitioner recommended Reputable manufacturer
Safety	Reduced confusion	Inflexibility	Set formulation Dose titration
		Safety	Adverse effects Compatibility
			Inability to adjust dosages
Pill burden	Reduced number of tablets	Pill burden	Size of tablet

Efficacy

The efficacy of the polypill was one of the most important issues raised by the participants. There were many questions surrounding its efficacy compared to their current individual medications. These participants wanted assurance that combining the four individual medications in the polypill was appropriate. Participants mentioned that if a study had been conducted with significant results displaying the efficacy of the polypill, they would feel more comfortable and be more likely to accept it.

Dose differences between their current medications and the polypill were a concern raised by four participants.

Will it be effective? I think it's too generic for my condition. As my cholesterol is sky high, I need a maximum dosage for my simvastatin, whereas my other three tablets are on the lowest possible dosage. Taking more tablets on top of my statin dose will just defeat the purpose of taking the polypill. (L4)

Participants valued their medical practitioner's recommendations and trusted their advice. If their medical practitioner recommended the polypill, participants were more willing to accept the concept.

Participants commented on the importance of the polypill being developed by a reputable manufacturer. In order to be considered, the manufacturer must be renowned within the pharmaceutical industry for producing medication of a high standard. Several participants were aware of the strict guidelines associated with manufacturing medication and believed well-known pharmaceutical companies were more likely to adhere to these.

Inflexibility of the polypill

Eleven participants were concerned about having their medications included in a single-dose form due to the inability to alter doses or remove medication from the combination if required. The timing of doses was mentioned frequently, particularly for simvastatin, which participants had been advised to take at night. Four participants reported that there had been trial and

error involved to find a suitable dose for certain medications. From this, it appeared that a 'one-size-fits-all' approach may not be viable.

Safety

Safety of the polypill was a major concern for 39 participants. This included side effects, compatibility, stability of the combined medication, and dose adjustments. Many were worried about the consequences of missing a dose of polypill, as they would not be protected by any of the four medications. Similarly, some participants raised concerns about overdosing if they took additional tablets by mistake. Either of these situations was perceived as relatively dangerous.

Conversely, some participants said that there were some times when they were confused about whether or not they had taken their medications and, without an established routine, they could forget or miss tablets accidentally. Condensing medications into one tablet would not only reduce the problems of taking multiple medications, but also would remove the need to develop strategies to ensure that they were all taken as directed.

It would be so much easier. Sometimes in the past, I got confused about whether or not I have taken one specific tablet. I would be too worried to double up and experience bad side effects so I would just not take it. With one pill only, I would know that I would have covered all the medications by just swallowing the one pill. (M10)

Eight participants were worried that they would experience additional adverse effects if their current medications were combined into a single pill. For those who had experienced adverse effects from their medication in the past, the concern was much greater. Some participants queried the formulation of the polypill, and whether it was possible to combine all their medication into a single tablet. Four participants were unsure of the chemical stability when combining all medications into a single formulation.

Pill burden

Thirteen participants thought the number of tablets they took each day was a burden. The complexity of their medication regimens also brought

with it a psychological burden. Two participants reported issues of embarrassment and the perception of increased illness according to the number of medications they took. Although they still adhered to their prescribers' instructions, their sense of wellbeing and integrity were adversely affected.

[The polypill] would be great! It cuts down on my medication, so it's good. Well, sitting in a restaurant taking out every pill, I feel I'm a showcase for other people. (J3)

The polypill would address these problems, although eight participants were apprehensive about the possible size of the polypill, questioning whether the formulation was likely to 'block the throat'. However, the majority of participants had no trouble swallowing, and often took all their tablets in one single gulp.

[The polypill] is only one tablet. One of the problems is I can't swallow the tablet if it is a little bigger. I need to swallow a big glass of water just to swallow it. Instead of taking 10 tablets a day, I could take 4 or 5 tablets a day. (J6)

Cost

Cost influenced the willingness of participants to accept the polypill. Two participants mentioned that if the polypill was subsidised, it would reduce the cost burden associated with their medication, as they would only be required to pay a single dispensing fee instead of four. Participants would be reluctant to consider the polypill if it was not subsidised by the government. Although they were appreciative of the concept behind the polypill, the cost burden related to financing it was far greater than the convenience of using it.

Thirty-three participants on multiple drug therapies strongly favoured the polypill concept for other medical conditions. Many perceived the number of tablets they took each day to be a burden which made the idea of a polypill very appealing.

Yes, for my diabetes tablets definitely. I take metformin and gliclazide. That is 10 tablets a day just for my diabetes. It would be much easier to take just one dose rather than multiple doses. (L1)

Discussion

Of the six themes identified, convenience was the most important benefit participants associated with the polypill. Inflexibility and efficacy were the concerns participants would like to see addressed before considering the concept appealing. Cost and safety were seen as providing benefits but also raising some concerns.

Perceived benefits of the polypill

The polypill concept was perceived to assist participants in taking their medications regularly, improving adherence and optimising health outcomes. Participants placed an emphasis on the benefits associated with the increased convenience, making the polypill an appealing alternative to their current regimens. Many participants expressed concerns about multiple dosing of their medications disrupting their daily routine, especially frequent travellers who reported greater difficulties adhering to their medication. The polypill would cause minimal interference in daily activities and improve convenience.

Participants valued their medical practitioner's recommendations and trusted their advice. If their medical practitioner recommended the polypill, participants were more willing to accept the concept.

Independent blister packing of their medications was seen as time-consuming and tedious, and so the polypill was seen as a time-saving approach. Other studies have reported that fixed-dose combinations offer advantages of convenience.^{7,18} The literature correlates well with the findings in this research and it appears to be generally accepted that the use of a combination pill will improve the convenience of taking regular medication, leading to greater adherence to regimens and improved health outcomes.

Since the majority of participants were taking four or more tablets on a daily basis, a reduction

in pill burden was appealing. Decreasing the total number of daily doses can aid drug adherence.^{13–16} A meta-analysis demonstrated that fixed-dose combination regimens reduced the risk of non-adherence by 24 to 26% compared to free-drug combination regimens.⁸

The cost burden when taking regular medications was seen as a further barrier to adherence. The majority of participants were paying at least four dispensing fees each time they collected their prescriptions, and based on the presumption that the polypill would be subsidised, participants perceived it would reduce the cost of their medication.

Concerns about the polypill

The size of the polypill was a concern to participants. Tablet-related factors, such as the size and shape, negatively influenced patient preference and acceptance, which may lead to non-adherence. One study found that participants preferred smaller, soft-gel capsules as opposed to tablets because they were easier to swallow, despite a twice-daily dosing.²¹ Such findings demonstrate an important limitation that has been associated with fixed-dose combination medication. This may be an issue if the polypill tablet size is not considered when being manufactured.

Participants emphasised the importance of adhering to their medications to manage their condition effectively. This meant that they were reluctant to accept the concept behind the polypill unless it was equally, if not more, effective than the individual medications. They were aware that valid trials and studies were required to demonstrate efficacy for their current medications, and therefore required similar evidence that the polypill was comparable. Research has demonstrated that, from a patient perspective, there is a need for an effective, highly tolerable and convenient medication regimen that would not interfere with their daily lives.²³

Compatibility and stability issues with combination preparations were raised by participants. Medical practitioners played an important role in influencing participants' decisions around medication. Participants strongly believed in the importance of medications being developed by a reputable manufacturer. Therefore, provided that participants were convinced that the polypill was proven to be effective, they would find the concept more appealing. A study reported that many participants did not find combination therapy appealing and would not be keen to change, as a fixed combination may not adequately mirror their personalised medication regimen. However, they also mentioned that they would consider switching if their medical practitioner recommended it.²⁴

Research has demonstrated that, from a patient perspective, there is a need for an effective, highly tolerable and convenient medication regimen that would not interfere with their daily lives.

The majority of participants were concerned with possible adverse effects of the polypill and restrictions associated with dose titration, particularly with blood pressure-lowering medications. It is unlikely that combining medications into one formulation would increase adverse effects, but using lower doses of different medications would reduce the incidence.²² Some participants felt it would be safer to continue with their current regimen as it provided them with the option of adjusting doses to maintain therapeutic benefits.

Limitations of the study

This study involved a small, non-randomised sample of people attending a community pharmacy who were willing to engage with the pharmacy student researchers, and so were perhaps inclined to answer in a socially desirable way. Despite the questions being hypothetical, there did appear to be consideration to the potential negative aspects of the polypill concept. Unfortunately, being a sampling of convenience, only three Maori participants and no Pacific people were included in the sample. Considering the CVD risk is significantly higher in these populations, perceptions of these patients would be much valued as they are likely to be potential users of a polypill. There is a need for further research involving Maori and Pacific people, and

also of the concepts concerning how the number of tablets taken by a person may influence illness or health behaviours.

Conclusion

The majority of participants found the concept of the polypill appealing. The benefits of convenience, reduced pill burden, improved safety associated with reduced confusion about dosing, and reduced cost, were all key factors that made the polypill favourable. Conversely, participants had concerns with the inflexibility and efficacy of the polypill. Many enquired about dose changes and various formulations of the polypill that would be required for those who needed dose titration. Other concerns were the manufacturer reliability, subsidy issues and tablet size. Willingness of participants to switch to a combination therapy may be hampered if a polypill formulation that mirrored their current regimen was unavailable.

Participants discussed having greater confidence in the polypill following medical practitioner recommendation. Initiation of the polypill immediately on diagnosis of IHD may reduce some concerns about dosing. There is a need to explore whether the proposed improved adherence using a polypill will produce improved outcomes that are greater than the individualisation of dosages for some medicines, that is, whether compliance with one polypill may improve adherence and outcomes compared to requiring four or five tablets that have dosing 'fine tuned'. A further area of research is whether the prescribing of all classes of medicine recommended for IHD would be improved through having one medicine to prescribe rather than three or four medicines.

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ACKNOWLEDGEMENTS

We wish to thank the community pharmacists who identified patients and allowed students to interview them in the pharmacy; and also to thank the patients who took time to discuss the polypill concept with the student interviewers.

FUNDING

This study was undertaken as a fourth-year student project through the School of Pharmacy, University of Auckland, and funding was met through standard student project funds.

COMPETING INTERESTS

None declared.

APPENDIX INTERVIEW SCHEDULE

Age: Patient code:
 Ethnicity: Pharmacy location:
 Gender: Pharmacy name:
 Occupation:

Questions:

- How many different medications do you take each day and how often do you take them?
- How long have you been taking them for?
- Do you take your medications regularly?
- On the occasions when you have missed a dose, what was the reason for it?
- What makes it harder for you to take your medications?
 - Number of medications
 - Timing of doses
 - Side effects
 - Don't feel ill
 - Other (please specify)
- What adjustments did you have to make to your daily routine when you first started taking these medications?
- Do you currently use blister packing? Do you find it easier with blister packing? Please explain why this is?

Researcher to explain the idea of polypill e.g. 'A scientist came up with an idea of combining all your heart medication into one single pill and you only need to take them once a day. This polypill is made up of a medication to lower cholesterol (like Lipex/Lipitor), two medications to lower your blood pressure and aspirin.'

- How would you feel about taking the polypill and why?
- What would you like to know before you felt comfortable taking the medication? For example, side effects, efficacy, safety, or the size of the tablet.
- What would your concerns be with taking a polypill?
- Do you think the polypill concept could be used for other medications that you take? (That is, for combining other medications?)
- Scenario: You have two different medications and both are equally effective but Medication 1 requires you to take 2 tablets 3 times a day. This tablet has very few unwanted side effects. Medication 2 has a 1 in 10 chance of causing bad side effects, like minor stomach bleeding and mild kidney problems, but you only need to take 1 tablet once a day. Which one would you prefer to take and why?
- You mentioned that you took '#' amount of medications. Can you tell me why you are taking them? Do you know what each of these medications are used for?
- Do you think any of your medications are more important than any other? If yes, which one is more important? Please explain why you think this is so?
- From the following, how important do you think it is to take all your medications?
 - Very important, Important, Neutral, or Not important.