ORIGINAL COMMUNICATION

Prospects and possible pitfalls of a preventive Polypill: confessions of a health promotion convert

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A proposal by Wald and Law (2003) for a single pill containing a statin, three half-dose antihypertensives, aspirin, and folic acid, met with a storm of controversy and seemed to have been relegated as much to the fanciful as to the accolades it might have deserved. The benefits such a Polypill could confer on people age 55 + y were to reduce both cardiovascular and stroke events by 80% or more. Considering the daunting and, at best, slow process of changing the same risk factors through health promotion interventions on food policy, dietary and physical activity behaviors, and urban planning to make less prevalent the sedentary lifestyles developed over decades, the argument here is to view the Polypill as a harm reduction strategy that would complement health promotion, as Nicotine Replacement Therapy did for tobacco control, seat belts did for traffic injuries, and needle exchange programs did for secondary complications of injection drug use.

European Journal of Clinical Nutrition (2005) 59, Suppl 1, S4–S9. doi:10.1038/sj.ejcn.1602167

A case has been made, convincingly for many, that the combination of six active ingredients in a single daily-dose pill could be made available without prescription to everyone of age 55y or over with the prospect of reducing heart attacks by 88% and strokes by 80% compared with age peers not on any CVD-risk-reducing pharmacotherapy (Wald & Law, 2003). One-third of the people taking this 'Polypill' from age 55y would benefit with a gain, on average, of 11 y of life free from CVD events. The ingredients recommended for this Polypill cocktail would include a statin to reduce low-density lipoprotein (Law *et al*, 2003), three half-dose blood-pressure lowering drugs (Law *et al*, 2003), aspirin (75 mg) to improve platelet function, and folic acid (0.8 mg) to lower serum homocysteine. The *British Medical Journal* editor declared that this and the accompanying articles made it arguably the most important issue published by the journal in the past 50y (Smith, 2003).

Scientific responses to the Polypill proposal

The prodigious outpouring of letters to the *BMJ* Editor and other reactions indicate strong sentiments in both directions, pro and con, optimistic and dubious. The major scientific opposition and doubts center on the strength of evidence cited by Wald and Law, the magnitude of combinatorial effects and minimal estimates of side effects produced by their meta-analyses, the wisdom of allowing such ingredients to be made available without medical screening, prescription, or monitoring to everyone over 55y, the prospect of manufacturing such a pill in the patent-protection environment of Western countries, and the concerns that people would not use it consistently, and even if they did, they might do so as a substitute for lifestyle reforms that could confer the same and other benefits.

Despite the elegant presentation of evidence that such a cocktail in a daily pill could eliminate over 80% of the coronary and stroke events in a population of 55 + adults, and the *BMJ* Editor's paeon, the proposal has continued to generate a barrage of critical letters to the editor, skeptical editorials in other journals (Mulrow & Kussmaul, 2005), and derision in some biomedical circles. Edward Jenner's smallpox vaccine proposal met just such opposition from the Royal Society of London in 1797 and so did his first paper on it in 1798, but that was followed by rapid international adoption in the years immediately following (Rosen, 1993).

The scientific support converging on the evidence cited by Wald and Law for the plausibility of the Polypill approach

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Commentary article for *European Journal of Clinical Nutrition* as part of special issue from the conference of Heelsum IV, the Netherlands, December 2004.

includes growing consensus that '...a comprehensive evaluation of risk profile, and accurate stratification of global (absolute) risk in individual patients...should be used as the main determinant of whom to treat, how to treat, and how much to treat' (Volpe *et al*, 2004). This approach acknowledges that the individual risk-factor approach has produced inconsistent definitions of elevated and borderline levels for treatment, and that some combination of risk factors, including age, should guide the treatment of blood pressure, lipids, diabetes or prediabetes, overweight, etc, rather than the level of each individual risk factor.

Scientific consensus also brings to the debate a recognition that over 95% of IHD and stroke deaths occur in people of age 55 y and over, regardless of their risk factors, and a large proportion of those are in people never diagnosed with a particular risk factor. This aligns with the proposal to make the Polypill available to everyone aged 55 y and above, but the debate will continue on whether that should be with or without screening for contraindications. The growing consensus that there may not be a threshold level for at least blood pressure and LDL below which the risk of IHD and stroke events disappear will also align with the suggestion of treating everyone from age 55 y to lower these risk factors. As Wald and Law show with a series of dose-response relationships, a given reduction in these risk factors reduces the risk of disease by a constant proportion of the existing risk regardless of the baseline level of the risk factor. Recent analysis of data from the Framingham Study and the Third National Health and Nutrition Examination Survey in the US indicate, however, that only 8% of CHD events will occur in individuals with only 'borderline', as opposed to some 'elevated' risk factors (Vasan *et al*, 2005).

'What if there were a magic pill...?' Anticipated professional and public response

Apart from the scientific debates, even assuming they can be quieted with mounting evidence and new clinical trials, what will be the reaction of the health professions and the public if the proposed Polypill can be brewed from this combination of ingredients known individually to confer life-extending benefits to people over 55 y of age, but uncertain as to their combined, long-term effects?

An ethic of primitivism pervades the understanding many people have of nutritional and other lifestyle advice to the public, and possibly the tacit beliefs of many professional nutritionists, physicians, and other health educators. It holds that people are best guided by imagining what prehistoric diets were as our species evolved, and adhering to an approximation of that dietary regimen. Nativism and primitivism are variations of a 'belief that it is best to live simply and in a natural environment' (INSO Corporation, 1996). Various values have produced various nutritional ethics that have found their way into popular notions and fad diets, and even into government nutritional guidelines. As Kunkel (1996) has found for the Recom-

mended Daily Allowances and other US nutritional guidelines, 'Ethical vegetarianism, a belief system that would limit RDAs and guidelines to those that can be translated to vegan and other vegetarian diets, has been a more recent entry into the discussions. Such human value issues suggest that a set of RDAs or of nutrition guidelines is analogous to and may be considered to be an ethic.' Such Nativism also resists the use of pills, except in the face of illness or pain.

At the other extreme is a technological ethic, a belief system surrounding the growing faith that science and technology will solve our most difficult problems and simplify our most tedious tasks. Much has transpired in a short span of recent centuries to fuel this belief, giving some people an excuse to abuse their health today in anticipation of a technological fix that will be there to save them when they need it later. The energy and investments driven by the technological ethic have contributed to some of the successes of our health-care and public health systems, but some aspects of technological advancement have been at the peril of our health and the systems that support it. Technologically designed convenience foods and motorized lives, for example, produce obese and overweight populations that now threaten to overwhelm our health-care systems.

The technological ethic has been the target of much posturing in the field of health promotion. As health promotion has sought social and behavioral change solutions for which technology or the promise of technological solution often seems an excuse for inaction and lack of political will, technology often becomes the enemy. We have spent so much of our professional and scientific energy proclaiming 'there is no such thing as a magic pill', that we are resistant and even incredulous at the thought that a pill could be a solution to some of the damage that food and motorized technologies have done to contemporary lives over a lifetime. Health promotion has its own ethics that range from nativistic dietary inclinations to technological fitness fixes on the individual behavior side of health promotion, and from abolitionist absolutism to social engineering solutions on the policy side. We have moralistic tendencies to dismiss technological solutions, including medical solutions that seem either to detract from the behavioral changes individuals must still make to maintain their health or from the policy changes that would make healthful lifestyle behaviors easier to adopt and maintain. We are susceptible, in short, to the belief that one only takes a pill when one is sick (David, 1992).

What these tendencies of mind suggest for a prediction of the response of professionals to a CVD Polypill is that many will have difficulty advocating for, or even supporting, its adoption in public policy, much less promoting it to the public. In addition to our nativistic or antitechnology ethics, we bring our experience with commercial interests in tobacco, 'health foods,' and fast foods where we have learned to be guarded about any industry that stands to

profit by exploiting people's health or interest in health and fitness, including the pharmaceutical industry. Buchanan worries less about the pill industry's morals than about those who follow them: 'the means become corrupted...Just so, losing weight through diet pills does not enable us to realize the internal goods of self-knowledge, self-discipline, dignity, and integrity' (Buchanan, 2000, p 109).

Last but not the least, we will need to be convinced that a Polypill would not become a substitute for those behavioral commitments that people have made, or need to make, to maintain lifestyles that protect not only against the same risk factors and chronic conditions or deaths but also against other risk factors and causes of death such as cancer, diabetes, and lung diseases.

The Polypill as a harm reduction strategy

Our experience in getting health promotion from a more or less rigid stance on behalf of primary prevention to a more productive strategy of saving lives and minimizing the damage of bad habits, bad circumstances, or bad luck falls largely in the realm of 'harm reduction' strategies. The most dramatic of these in terms of lives saved and injury prevented or minimized would be the harm reduction strategies of seat belts, automobile design, and highway crash barriers, none of which prevented crashes, but all of which prevented much of the harm brought on by crashes (Robertson, 1998).

What convinced others in health promotion of the desirability of harm reduction was the intractable HIV transmission among injecting drug users and a growing recognition of their amenability to a needle exchange program. This was not primary prevention of drug abuse, but it was harm reduction in relation to the more lethal problem of HIV transmission and subsequent AIDS (Platt *et al*, 2004).

The association of the Polypill with a harm reduction approach to cardiovascular events could come with the recognition that such events are the cumulative effect of a lifetime of health habits and conditions over which most of today's older adults had little control, or little knowledge and understanding. In this light, we could accept a certain poetic justice in a pill that rights some of the irreversible wrongs done to people during an era of changing food and tobacco supplies, inconsistent nutritional advice, and technological substitutes for physical activity. With this, poetic justice must follow an acceptance of letting some sinners off the hook for the conscious abuse of their health.

The alternatives to harm reduction—early primary and secondary prevention—would not be precluded by the Polypill strategy. Indeed, new generations of children will be no less the object of future health education and health promotion efforts than they are today. They must be persuaded and supported in their efforts to control weight,

resist smoking, and maintain physically active lifestyles, not just to prevent CVD, but all the other diseases and conditions that are consequent to these lifestyle behaviors and the conditions that produce them. Similarly, secondary prevention in the form of screening for high blood pressure, hypercholesterolemia, and high blood glucose at earlier adult ages will continue to be needed regardless of the harm reduction fallback of a universally available Polypill at age 55 y, because earlier development of CVD or diabetes will be an indicator of the need to prescribe the Polypill and specific risk-factor medications earlier than age 55 y for them. Primary prevention and secondary prevention, as complementary to a Polypill harm reduction strategy, must be seen as part of a comprehensive strategy for chronic disease control.

One of the ethics of health promotion that has tended to forestall its potential partnership with medicine has been the fear of 'medicalizing' what could be under the greater control of people themselves. The Ottawa Charter for Health Promotion defined health promotion in such a way as to make 'enabling people to have greater control' over their health the centerpiece of the field (First International Conference on Health Promotion, 1986), one that created a tendency to view professional, especially medical, control with suspicion.

The demography of primary prevention vs harm reduction

Among the relevant, and possibly most compelling, experiences from the tobacco control policies and programs in which this author was immersed before being drawn into the Polypill debate was the tilting of the balance of interest from primary prevention to harm reduction. The progress in tobacco control seemed to make its greatest leap forward when the field backed away from its prior preoccupation with relatively ineffective strategies of primary prevention—trying to get youth not to start smoking—and redirected its priorities toward the harm reduction of separating smokers from others who were exposed to their second-hand smoke. This accomplished a denormalizing of smoking and a consequent strengthening of the motivation of smokers to quit smoking (Green *et al*, 2000b). In setting long-range (10-y) national goals for reduction of tobacco consumption, we had to face the demographic reality in the United States that the number of youth susceptible to starting smoking was far less than the number of smokers susceptible to stopping smoking (Green *et al*, 2000a). This was partly because the population pyramid has a bulge of middle-aged adults approaching their later years, referred to in the US and some other countries as the 'baby boomers' (those born in 1946 and in the years following World War II). That same population bulge is now passing age 55, and bringing with them unprecedented rates of obesity and overweight, diabetes, and other CVD risk factors.

Table 1 For each of five smoking cessation methods, estimated efficacy (6-month cessation maintenance rate), reach (number of people using the method in the United States) and impact (efficacy $\times$ reach = total number of smokers in the United States who successfully quit while using that method)

Intervention	Ef* (%)	Reach: no. using US	Impact US
None (unaided)	3	22 800 000	684 000
R $\times$ NRT	14	2 500 000	350 000
OTC NRT	14	6 300 000	882 000
Behavioral	24	395 000	94 800
Inpatient Rx	32	500	160

*Efficacy = 6-month cessation maintenance rates.

Source: Adapted from Shiffman S, Mason KM, Henningfield JE. Tobacco dependence treatments: review and prospectus. *Annu Rev Public Health*. 1998; 19: 335–358.

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Generalizing from harm reduction experiences pre-Polypill

The most hopeful harm reduction strategy at hand when the tobacco control field recognized the need to make a renewed push on smoking cessation was nicotine replacement therapy (NRT). The use of NRT in the form of chewing gum, skin patches, lozenges, and other delivery mechanisms was, at first, available only by prescription. Then, with new rulings by the federal Food and Drug Administration, the NRTs were made available as over-the-counter nonprescription drugs. The parallel with the Polypill strategy offers a source of evidence on the potential effect of making the Polypill, consisting of drugs mostly available heretofore only by prescription, available without prescription.

The experience with tobacco cessation in the late 1990s, as shown in Table 1, revealed that most people who tried to quit smoking did so 'cold turkey', without the aid of any professional or medicinal aid. This produced a 6-month successful cessation rate of only 3%, but when multiplied by the large numbers (over 22 million smokers), this unaided method of quitting yielded some 684 thousand *former* smokers. When NRT became available by prescription from medical doctors, the uptake in its use was some 2.5 million users, and with a success rate of 14%, produced 350 thousand successful quitters. With the release of the prescription requirement, however, NRT reached far more people who could buy it over the counter without a physician consultation. The efficacy rate did not change, but the reach jumped by more than 150%, producing the largest impact in number quitting. The other more intensive professional support methods shown (behavioral counseling and inpatient care) are more effective for smokers reached by these methods, but far fewer people avail themselves of such methods, so their impact is much less.

Generalizing this harm reduction strategy to a Polypill's impact is a stretch, but the main inference is that a much larger impact on the population is possible, assuming

roughly equal efficacy rates for the drugs as when prescribed by physicians. This impact differential might be less in Europe, with universal coverage of health care, than in the United States, where physician access is more restrained by the economics of medical care.

The extrapolation of risk-factor harm reduction strategies to CVD prevention in populations 55 y and older might be made more directly from the fledgling experience with low-dose aspirin taken prophylactically by middle-aged adults first for secondary heart attacks, and more recently for prevention of primary heart attacks (Jeffreys, 2004), and the more recent exploration of making statins available without prescription (Pearson, 2004). These provide more direct evidence insofar as they are ingredients that would be part of the proposed Polypill.

The aspirin experience is informative for its long-standing availability over the counter, and the growing public knowledge that it can be protective against coronary heart disease through its reduction of blood platelet activity. In a survey of over 23 158 persons aged 40 y or over with no prior CVD and 3818 who reported prior CVD, 19% of all respondents reported regular use of any analgesic for primary prevention and 8% specifically reported using aspirin. Among those reporting prior CVD, only 43% used aspirin for secondary prevention. What might be more encouraging for the Polypill is that most of the 1.3 million people nationally who appear to be 'erroneously taking non-aspirin products for CVD prevention' (Cook *et al*, 1999) could be taking the right analgesic (aspirin) and at the right dose (75 mg) if they were taking the Polypill.

Consumer use of statins has been studied in a controlled trial of making them available over the counter in the US (Brass, 2004) and in their introduction OTC in the UK in 2004 (Nash & Nash, 2004). Both of these studies offer encouraging evidence of the potential for greatly expanding the reach and for the appropriate use of the drug OTC. Potential drug-drug interactions remain a concern, but appeared infrequently in the studies so far.

The need to prepare for the advent of polypharmacy

Whether in the form of a Polypill containing just two of the ingredients proposed by Wald and Law, or a larger number of ingredients, the need to prepare for the arrival of combinations of pharmacotherapies is incumbent on those professionals who work with patients on chronic disease prevention and management, and those who educate the public on the prevention of disease. The Polypill is almost certainly coming soon in some developing countries, notably India, where the patent issues have been resolved to their satisfaction and where the impact in numbers could be even greater than in the high-income countries. Their experience is likely to fuel a greater demand for something similar in Europe, North America, and other countries. Those of us struggling with the issues of patient adherence and

other social and behavioral aspects of nutritional and other CVD risk reduction, represented in this issue of the *EJCN*, should be especially prepared to integrate the Polypill into our practice. We should prepare ourselves to contribute to research and intervention design to make this potentially great public health innovation an integral part of the lives of people 55 y of age and older, as well as other adults at high risk of CVD. Nothing else we have designed as an intervention could make such a large difference in so many lives.

Acknowledgements

I am indebted to the Planning Committee (co-chaired with William Weintraub and staffed by Andrew Friede and Kristen Copes, the Constella Group, LLD) and the Expert Panel members sponsored by the US Centers for Disease Control and Prevention (especially Venkat Narayan, Michael Engelgau, George Mensah, Frank Vinicor, and David Williamson) to identify issues and to recommend strategies for the testing and development of the Polypill approach in the United States. This paper represents the personal views of the author and not necessarily those of the Committee, the Expert Panel, or the CDC.

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Abbreviated discussion after Green

Kok: The title of this session is 'Creating a supportive environment for family doctors and patients'. What is your opinion: could the use of the Polypill contribute to a supportive environment?

Green: Yes. This is an environmental intervention.... Let me put it this way. I think that attention for environmental support to reduce risk factors is worthy of consideration. With tobacco control, it was not until we started addressing environmental factors seriously that we began to have an impact on behavior.... This is only a harm reduction strategy for people aged 55y and over, so there still is much to be done in other respects. For example, lifestyle education to prevent obesity early in childhood.

Brug: I do not think that this is only an environmental intervention. It is behavior. People need to take those pills. And in the way they are supposed to take it; not take two when they have had a big meal.

Helman: I am worried that studies (on which the Polypill is designed) were not conducted with non-selected over 55-y-old people.

Green: Yes. That is why we have to have an RCT in people over 55 y.

Truswell: I have three additional concerns. First, the pharmaceutical question: Are all these ingredients compatible in one pill? The acid nature of some components might damage some of the other components. Secondly, are we going to see people living 3–6 months longer, and more of them coming to some kind of cancer or Alzheimer's; a lot of older people would prefer to have a brisk stroke or coronary

than most cancers or certainly Alzheimer's. And thirdly, this may not save money on health services. People are not going to live forever. They will still have diseases when they are somewhat older.

Becker: I have concerns about the anticipated magnitude of effect. Epidemiological evidence about risks and risk reductions may lead to wrong answers. For instance, from the plasma cholesterol reduction, a 60% reduction in coronary heart disease is expected, but the statin trials only came up with 30%. I do not believe the effects will be additive. If there are multifactorial causes of coronary events, and we interfere at different spots, it may not be at all appropriate to add the effects. For example, if the statins are reducing the circulating LDL levels, folic acid is decreasing the incorporation of the LDL in the plaque, and aspirin is stopping the thrombotic events, then stopping all three will not necessarily have three times the effect of stopping one of them.

Green: You are right. In the following issues of the BMJ, dozens of critical letters have been published concerning this problem. But nobody has yet to my knowledge come up with a way to correct for this.

Laws: The Polypill is not going to address obesity *per se*, and also obesity works to increase cardiovascular risk and the metabolic syndrome.... and diabetes.

Green: That is true. It does nothing about smoking either, and seat belts. And a list of other things. We will still be fully employed. This a major argument for treating this as a complementary medicine, not as a substitute for lifestyle changes.