Polypill holds Promise for People with Chronic Disease

Efforts are under way to make medicines for chronic diseases more accessible to people in developing countries.

Bulletin of the World Health Organization Volume 83, Number 12, December 2005, 881-968

Editor's Comments

Polypill is an upcoming concept in conventional medicine where a fixed dose combination of various active compounds is prepared in the form of a single pill. This is very useful in certain conditions where a group of medicine are prescribed on a regular basis to almost every patient. This prevents the missing doses and also reduces the cost and hence eventually increases the compliance and eventually a better prevention and control of the targeted disease. Surprisingly in Ayurveda, a polypill concept is practiced since ages. In every pill of Ayurveda, eventually, there are multiple active ingredients addressing differently to a single set of problem.This is how some time just a single pill of Ayurveda is able to care for a complex set of associated problems.

A "polypill" containing a fixed-dose of aspirin, a statin and one or two bloodpressure-lowering drugs, has enormous potential in developing countries, where the rate of cardiovascular disease is rising rapidly, according to an expert working party.

No fixed-dose combination pill of this kind has been widely marketed anywhere in the world to date, and the full benefits of such a pill remain unclear until it can be put to the test in upcoming large-scale clinical trials in India and New Zealand.

"Combination pharmacotherapy offers the potential to decrease the incidence of cardiovascular disease worldwide, perhaps especially in people who have never had a cardiovascular event," concluded the Combination Pharmacotherapy and Public Health Research Working Group, convened by the Centers for Disease Control and Prevention in the United States.

The report, which was published in the Annals of Internal Medicine in October 2005 (Vol. 143, pp. 593–599), came up with the dramatic finding that combining several anti-hypertensive drugs at low doses is likely to be more effective and have fewer side-effects than high-dose therapy with a single drug.

However, more research is needed on the side-effects and bioavailability as well as tolerability and adherence to combination pills. "Combination pharmacotherapy may prove especially effective in the developing world, where studies may precede those done in wealthier countries," the report concluded.

The study's findings provide a timely boost to efforts to improve access to treatment for chronic diseases in developing countries. Chronic diseases are often associated with developed countries, but their prevalence is increasing in many low-and-middle-income countries, according to the recent WHO report, *Preventing chronic diseases: a vital investment*. Only 20% of chronic disease deaths occur in high-income countries — while 80% occur in low-and-middle-income countries and these deaths occur in equal numbers among men and women, the report said.

Deaths from infectious diseases, maternal and perinatal conditions, and nutritional deficiencies combined are projected to decline by 3% over the next 10 years globally. However, over the same period deaths due to chronic diseases are projected to increase by 17%.

A recent study carried out in Andhra Pradesh found that

noncommunicable and chronic diseases are the leading causes of death in this rural state of India. One of the authors of the study, Dr Bruce Neal, Director of the Cardiac and Renal Division at the George Institute for International Health, in Sydney, said that the health delivery system was in urgent need of "reorientation" to enable the implementation of evidence-based strategies to address the challenge of noncommunicable diseases.

Neal told the Bulletin: "While many lower-income countries have made very substantial advances in the treatment and prevention of acute communicable conditions and in the management of maternal and child health, services for chronic disease care are relatively undeveloped."

Dr Robert Beaglehole, Director of WHO's Department of Chronic Diseases and Health Promotion, said: "The epidemic of chronic disease is rapidly evolving, the threat is growing, but the response is not keeping pace. More and more people are dying too early and suffering too long from chronic diseases. We know what to do to prevent most of this and so we must act now."

"There are important gaps that could readily be filled if health systems use measures that are already available relatively cheaply, such as aspirin," said Beaglehole. This was illustrated by the WHO-PREMISE study published in the Bulletin last month.

The study, conducted by a team led by Dr Shanthi Mendis, WHO's Coordinator for Cardiovascular Diseases, sampled 10 000 patients in 10 low-and-middle-income countries and found about one-fifth of patients with coronary heart disease were not receiving any aspirin and about half the patients were not on beta-blockers, which are low cost and widely available.

Two of the main barriers to providing adequate care for chronic conditions are the limited financial and infrastructure resources available for health care in most lower-income countries. "High-cost, physician-based models of care for chronic diseases developed mainly in higher-income countries are usually completely unsuited to lower-income settings," said Neal.

The use of fixed-dose combination therapy in the form of a single pill for cardiovascular disease prevention was first proposed in a WHO publication on secondary prevention of noncommunicable diseases in 2001.

Two years later, Dr Nicholas Wald and Dr Malcolm Law provided evidence for the potential efficacy of a polypill as a public health approach to cardiovascular prevention in their paper in the BMJ. The BMJ's editor at the time, Richard Smith described the article as the journal's most important for 50 years. They suggested giving a combination pill containing a statin, a diuretic, a beta-blocker, an ACE inhibitor, aspirin and folic acid to all adults over 55 and to adults of any age with diabetes or cardiovascular disease, regardless of risk factors.

This approach contrasts with that of the Working Group study, which recommended such treatment for patients who are at risk of and those who have had a heart attack or stroke. The Working Group said it may be necessary to target such a combination pill at patients who are at greatest risk of having a heart attack or stroke for maximum cost-effectiveness.

This approach could mean targeting urban areas rather than rural ones. In urban Delhi, India, 22% of people older than 55 years of age have more than a 20% risk of developing cardiovascular disease over 10 years, whereas in the rural state of Haryana only 8% have more than a 20% risk.

WHO has also explored the benefits of fixed-dose combination drugs for high-risk patients. Last year, a WHO report, Priority Medicines for Europe and the World: A Public Health Approach to Innovation, provided compelling evidence that high-risk patients would enjoy clear benefits from such fixed-dose combinations.

Neal said: "The chief advantages of the polypill will be that it will be much cheaper to manufacture and distribute

and much simpler to prescribe."

Because the components of a polypill are no longer covered by patent restrictions it could be produced at a cost of little more than US$ 1 per patient per month, according to the WHO chronic diseases report. Combination drug therapy — using aspirin, beta-blocker, diuretic and a statin for people with an overall risk of a cardiovascular event above 5% over the next 10 years — was shown to be highly cost-effective in all regions by the WHOCHOICE project, the WHO chronic diseases report said.

Neal said: "Because the risks of side-effects from the components are very low and the potential benefits are very high, the polypill will be very safe. The goal will be to use non-physician health workers to identify and treat high-risk individuals which should decrease costs and increase access in resource-poor settings."

Polypills are also expected to increase patient adherence. This has been shown with combination drugs for diabetes, hypertension and HIV/AIDS, according to a study published in the Bulletin in December 2004.

A study to find out if this is also the case in patients with established cardiovascular disease is to start recruiting from January to March 2006. The GAP, or Guidelines Adherence to Polypill study, set up by the George Institute for International Health, will randomize 1000 patients with established cardiovascular disease to a polypill-based approach or to standard care. The patients will be followed for two years.

A similar study of 600 patients is to start in New Zealand next year, led by Anthony Rodgers of the University of Auckland. Patients with a definite indication for all medicines, such as following a heart attack or stroke, will be randomized to polypill or conventional care. The main outcome measures will include compliance, blood-pressure and cholesterol levels.

Fixed-dose combinations are now a core component of care for people with HIV/AIDS, tuberculosis and malaria. As well as improving clinical outcomes, they simplify distribution of multiple medications, which can be an important advantage in resource-limited health-care settings.

Some public health experts say another way of improving access to medicines and treatment for chronic disease would be through public-private partnerships (PPPs). A report by a team from the London School of Economics and Political Science, led by Dr Mary Moran, found that PPPs have driven the recent considerable increase in research activity into so-called neglected diseases, such as malaria and tuberculosis.

After a time when few new therapies were introduced, there are now over 60 drug research projects under way. Three-quarters of these are conducted under the auspices of PPPs and should result in six or seven new drugs being developed by 2010.

There are no PPPs working in the area of chronic disease, a situation Rodgers, who is director of the Clinical Trials Research Unit at the University of Auckland, in New Zealand, wants to change. Rodgers is involved in early consultations to set up a PPP to make treatment for chronic diseases more accessible to people in need.