Reducing the "pill burden"

Simplify, simplify, simplify! So instructed the philosopher Henry David Thoreau, who believed a life lived simply was a life better lived, in his 157-year-old classic book *Walden*. These words also seem apropos in the increasingly complex world of health care, where making care simpler for patients has been shown to reap benefits.

"One way to get around the complexity issue is to make a drug regimen less complicated," says Dr. Mark Fendrick, professor of health management and policy at the University of Michigan in Ann Arbor. "How do you do that? You take two pills you take every day and make them into one."

As the burden of chronic diseases, which often require multiple medications, increases around the world, the appeal of fixed-dose combination drugs may also increase. These products, which combine two or more drugs into a single tablet, have been shown time and again to increase adherence to drug regimens.

In one study, to which Fendrick contributed, 9170 people with diabetes were treated either with two medications or with a fixed-dose combination product (*J Gen Intern Med* 2008; 23:611-4). Adherence to the drug regimen was 12.8% higher in the group that took a single-component pill.

A meta-analysis of research in this area found an even greater positive effect (*Am J Med* 2007;120:713-9). Noncompliance to medication decreased by 26% when people took fixed-dose combinations for conditions such as hypertension, HIV and tuberculosis, states the paper, which concludes with a recommendation for increased use of combination drugs for chronic illnesses.

"The pill burden becomes an issue for a patient," says Dr. Franz Messerli, one of the paper's authors and the director of the hypertension program at the St. Luke's–Roosevelt Hospital Center in New York City, New York.

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Some patients find their pill regimen confusing.

Fixed-dose combination products also hold great appeal for the pharmaceutical industry, suggests Messerli. It can sometimes cost in the neighbourhood of US$1 billion to bring a new drug to market, he notes, but it may cost only a quarter of that to release a combination of existing drugs.

"It's hard to come up with new drugs," says Messerli. "It's easier to combine drugs and make money that way."

Of course, drug manufacturers that produce combination products must still go through the regular approval process, even if the individual components have already been approved for sale. In Canada, manufacturers must submit the same level of evidence of efficacy, safety and quality as for single -component drugs.

"All drug submissions must undergo rigorous scrutiny and satisfy scientific requirements under the Food and Drugs Regulations, including those for fixed-dose drugs, before the drug can be marketed," Olivia Caron, media relations officer for Health Canada, writes in an email. "The choice of a primary efficacy endpoint in a randomized clinical trial for fixed-dose drugs is based on the same standards established for single component products."

In the United States, manufacturers must present efficacy and safety data to the Food and Drug Administration (FDA). If sufficient data exists for each individual component, however, drug makers may or may not have to conduct additional studies, depending on several factors.

For example, new research may be required if there is potential for the active agents to interact in a way that could prove harmful, or if there is the possibility that one component could chemically modify another component and compromise its effectiveness. But if there are no apparent safety issues, the manufacturer may not have to conduct any additional research.

"If existing clinical and nonclinical safety data for each separate drug or biologic are sufficient to support the safety or the proposed new indication, including the dose, dosing schedule, duration, and new patient population, then addition nonclinical studies may

not be needed," the FDA states in a guidance document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079243.pdf).

In some situations, FDA may even accelerate the approval process if sufficient data exists for the component drugs. This appears to be the case, for instance, for fixed-dose combinations or copackaged drug products made from previously approved antiretrovirals to treat HIV.

"FDA believes that when adequate evidence of safety and efficacy exists for the use of combination therapy with individually approved HIV drugs, the path to regulatory approval of an FDC [fixed-dose combination] or copackaged configuration of those drugs is straightforward," the agency states in another guidance document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf). "FDA is prepared to move swiftly to evaluate such products when applications are submitted for approval."

This is good news for people with certain conditions, such as glaucoma, who have been shown to not only better comply with fixed-dose combination drug regimens but also to save money while reducing their pill burden, according to the American Academy of Ophthalmology (www.oculist.net/Soft/ShowSoftDown.asp?UrlID=1&SoftID=377#page=162).

Those benefits, though, may come at a cost.

"In an era of many drug choices and the ability to individualize patient care as never before, the fixed combinations limit clinicians' ability to customize dosing regimens," the document states. "Unless prescribed with caution, fixed-combination drugs may result in overtreatment for patients who may be controlled with a single agent or fewer doses of combined medications if dosed concomitantly."

Still, the primary benefit of combination drugs — a substantial increase adherence to treatment — may outweigh the potential problems as aging populations require more medications to control chronic illnesses, says Fendrick. "As we realize that many chronic diseases will require more than one agent to appropriately manage conditions such as hypertension and diabetes and asthma and emphysema, it wouldn't surprise me at all to see additional and perhaps more sophisticated combination therapies to help patients comply with increasingly complex drug regimens." — Roger Collier, *CMAJ*

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