Fall and Rise of Polypharmacy?

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Early in the 20th century, in an era before the wide availability of effective drugs with established dose ranges and proven outcomes, the use of multiple drug combinations in individual tablets and capsules, described as polypharmacy, was common. Although there may have been a rational selection of agents sometimes, on more occasions a mixture was developed of dubious efficacy and rationale. With the introduction of specific drug entities with established efficacy and dose ranges in the 1950s and 1960s, there was an academic reaction against these combination products. In many cases, multiple drugs were combined without clear evidence that each contributed to the efficacy of the preparation at least in the dose used. There were justifiable fears that multiple drugs would increase the risk of adverse drug reactions, particularly idiosyncratic or allergic ones. This academic reaction in undergraduate medical schools discouraged combination products and encouraged the use of effective doses of drugs with established actions and mechanisms.

Generations of medical graduates from the 1960s, 1970s, and 1980s were presented with a view that polypharmacy was dangerous therapeutics and indefensible practice. Most fixed-dose combination tablets were viewed with suspicion. Most attitudes were consolidated by the new policies of drug registration and licensing introduced in many countries in the 1960s. Older multiple drug combinations rarely justified the expensive evaluation required for approval and registration. Existing multidrug formulations were largely withdrawn from the therapeutic arena, and few new combinations followed. The 1960s and early 1970s were an era of heroic monotherapy in hypertension. Grams of methyldopa, propranolol, or thiazides were used, pushing doses to the limit from the therapeutic arena, and few new combinations. Followed. The 1960s and early 1970s were an era of heroic monotherapy in hypertension. Grams of methyldopa, propranolol, or thiazides were used, pushing doses to the limit (and beyond) of patient acceptability in attempts to achieve blood pressure control. The introduction of step care therapy was a major improvement with its rational pragmatic basis to dual and triple therapy. However, to the therapeutic purists, this required individual dose titration of each of the 3 or more drug classes and their administration as separate preparations! Although there was widespread recognition that the majority of hypertensive patients required 2 or more drugs and acknowledgement that compliance or concordance with drug treatment regimens fell off after 2 or more doses a day, in many countries there was reluctance to embrace fixed-dose combination tablets. The development of fixed-dose combinations of effective established drugs with complementary actions was an obvious step but not widely accepted by doctors or regulators. Registration of these combinations was made difficult by a requirement to limit the indication to patients who had already shown that they needed both drugs in the dose used in the combination formulation and by the need for extensive and expensive clinical trials exploring the dose range of the 2 agents alone and in combination, often in a factorial design. Not surprisingly, combination products, although likely to improve patient compliance and convenience and often less expensive than 2 preparations alone, were slow to take off in many countries around the world. The undergraduate students exposed to the antipolypharmacy views of teachers in the 1960s and 1970s were now in active clinical practice, and they also made up a high proportion of those involved in drug regulation at the government and regulatory agency level!

It would seem that the early years of the 21st century are seeing a resurgence of interest in combination products, particularly low-dose products of drugs with established efficacy used in relatively low doses. The aim is to improve the adverse effect profile, as well as convenience, to patients. In some cases, a combination of relatively low doses has resulted in superior efficacy not only to the constituents given alone but to higher doses of the individual constituents (perindopril plus indapamide). Systematic review and meta-analysis has confirmed that there is evidence that low-dose combination products could provide equal or enhanced efficacy with potentially reduced adverse effect burden. This group has also proposed combination products with multiple constituents acting on a range of different cardiovascular targets. These include, in addition to multiple anti hypertensive drugs, aspirin and lipid-lowering statins. It has been estimated that such a “polypill” could, if given to a relatively unselected older population, have a dramatic effect on the incidence of new cardiovascular events. It is important to recognize, however, that these reports do not describe randomized prospective trials confirming the effects of low-dose combinations but are based on retrospective review of literature and sophisticated data analysis. In contrast, in this issue of Hypertension, Mahmud and Feely report a prospective study using a capsule containing 4 different anti hypertensive drug classes, each given in a dose one quarter of the usual dose of the preparation. This randomized trial indicates that the capsule containing 4 widely use agents of different classes at a quarter of the usual dose was more effective at lowering blood pressure than any of the individual drugs alone in the usual dose. This is a relatively short-term study lasting a few weeks but otherwise provides intriguing prospects for enhanced efficacy of multiple drug combinations in low doses compared with standard therapy. It has been increasingly
recognized from prospective outcome trials with more recent blood pressure targets, as well as clinical experience in routine practice, that to achieve target blood pressures, most patients require 2 or more drugs. This study suggests that we may be able to achieve the same or greater blood pressure responses with much lower doses than we are currently using. As is acknowledged by the authors, the choice of drugs included in their 4-drug combination was pragmatic as was the decision to use one quarter of the standard dose. It will be important to determine that not only were all 4 of the constituents contributing to the overall effect but that the doses selected of the active components were optimal.

There is clearly a lot of work to be done before any product could be registered for use in hypertension, but this preliminary report confirms the theoretical basis of the polypill concept and suggests that other multiple drug therapy approaches using low doses may be able to realize benefits at least as great as those predicted from the controlled trials. It is unlikely that polypharmacy in the form prevalent in the earlier 20th century will return to hypertension therapy. However, rational multiple dose combination therapy could have attractions not only to patients but also to those responsible for delivery of cardiovascular prevention to populations.

Disclosures

None.

References
