

DRUG UPDATE

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FIXED-DOSE COMBINATIONS (Part 2)

-Use in specific medical conditions-

Despite their potential to reduce the pill burden in patients with chronic diseases, the evidence demonstrating improvements in concordance and outcomes in diabetes, hypertension and other cardiovascular disease is inconsistent. More good quality studies and an assurance that new formulations will be at least cost-neutral are required before fixed dose combinations (FDCs) should be widely accepted. In resource-limited countries, FDCs are recommended by the international agencies for first-line treatment of tuberculosis and HIV infection. In most other clinical situations, regimens comprising single-component generic drugs are more cost-effective in the long term and should remain the treatment of choice.

Overview

Combinations of drugs are necessary to treat some chronic diseases successfully and there is renewed interest in fixed-dose combination products (FDCs) as a means of improving patient concordance and clinical outcomes.

In this second review, the evidence to support the use of FDCs in selected chronic diseases is presented.

Diabetes

An observational study of a database of pharmacy prescription refills for 6,502 patients taking metformin and glibenclamide over six months showed no significant differences in concordance among newly treated patients receiving monotherapy, a combination of the two drugs or a FDC.¹ However, patients switching to the FDC had improved concordance compared with those previously taking the two drugs separately (87% vs. 71%; $p < 0.001$) but the number of patients was small ($n = 59$). Another retrospective study with a FDC of metformin and glibenclamide did show better concordance compared with taking the two drugs separately (84% vs 76%; $p < 0.0001$, $n = 1,421$).² In the latter study, improved HbA_{1c} levels were also observed with the FDC, although these may have been due to different pharmacokinetic and pharmacodynamic properties of the FDC formulation observed by the authors, compared to the drugs administered separately.² Patients who were at least 80% concordant with either therapy did not achieve significantly better glycaemic control than those who were less concordant with the same treatment.² Elsewhere, only small increases in HbA_{1c} were seen in patients who were non-concordant with metformin (a 10% reduction in concordance produced an increase of 0.14% in HbA_{1c}, $p < 0.01$).³

Another retrospective study of 11,532 patients with diabetes, found that non-concordant patients had higher rates of hospitalisation (odds ratio (OR) 1.58; 95% confidence interval (CI) 1.38 to 1.81; $p < 0.001$) and higher all-cause mortality (OR 1.81; 95% CI 1.46 to 2.23; $p < 0.001$) than adherent patients.⁴

Inhaler therapy

The treatment of reversible airways disease often requires the use of two inhalers, such as the combination of a steroid with a long acting beta-2 agonist (LABA). It has been shown that the combination of budesonide and formoterol in one inhaler can provide both maintenance and reliever therapy.^{5, 6} This approach potentially eliminates the need for a separate short-acting beta-2 agonist for patients at step 3 of the BTS/SIGN guidelines. Although no concordance studies have been done, it is likely that inhalers containing combinations of corticosteroid and LABAs will have a favourable impact on patient convenience. They also ensure that patients continue to use an inhaled steroid with their LABA therapy.

However, the reduced flexibility of dose adjustment may affect the feasibility of both stepping up and stepping patients down from their treatment. NICE guidance currently states that in adults and children over 12 years with chronic asthma, the use of a combination corticosteroid and LABA device is recommended as an option.⁷

HIV

Poor concordance with HIV drugs leads to drug resistance and the need for more expensive second line combinations. The WHO has endorsed the use of FDCs of antiretroviral drugs for poorer countries.⁸ It is widely acknowledged that poor concordance is the most frequent cause of treatment failure,⁹ but there are few studies which show that FDCs are a solution. FDCs containing two drugs have been shown to improve concordance in some studies,^{10, 11} but others have shown insignificant improvement over separate components and no change in outcomes such as viral load.^{12, 13}

Hypertension

Many clinical trials have shown that multiple antihypertensive drugs are required to control blood pressure in the majority of patients and current guidance endorses multi-drug regimens.¹⁴ This may create problems with concordance because of the increased tablet burden on the patients, particularly on asymptomatic patients.

The British Hypertension Society recommends FDCs, provided that there are no cost disadvantages.¹⁵ Despite many methodological problems and confounding factors, it is generally accepted that good concordance with antihypertensive drugs is associated with better blood pressure control.^{16, 17} However, there is a paucity of direct evidence to show that outcomes such as mortality are affected. Commentaries which support the treatment of hypertension with FDCs have not provided evidence of improvements in clinical outcomes.^{18, 19}

Other cardiovascular disease

Non-concordance to medication has been associated with poor outcome in various cardiovascular conditions.²⁰⁻²³

It has been suggested that good adherers to medication may represent those who also adhere to other health interventions.²⁴ A claim in the British Medical Journal that a single daily 'polypill' containing six drugs might lower cardiovascular risk factors in a large proportion of patients has made an interesting, albeit sensational, case in support of FDCs.²⁵

Tuberculosis

The treatment of tuberculosis requires several months of multiple drug therapy and the erratic use of anti-tubercular drugs contributes to the emergence of drug-resistant strains.²⁶

The International Standards for Tuberculosis Care recommend the use of FDCs²⁷ and the WHO includes two, three and four-drug FDCs in its Model List of Essential Drugs.²⁶ However, currently there is no direct evidence to show that FDCs limit the emergence of drug-resistant tuberculosis.²⁸ A Chinese

study showed similar rates of adverse effects and concordance in patients taking a FDC containing three drugs compared with separate administration.²⁹

How safe are they?

There is no evidence to suggest that the incidence of adverse effects to drugs used in FDCs is different from the same doses administered separately.^{11, 29, 30} Possible exceptions exist when the pharmacokinetic and/or pharmacodynamic profile of single-component and FDC regimens differ.

When should they be used?

Despite the widely held view that FDCs improve concordance, there are few good quality studies which show this and even fewer which demonstrate improved outcomes. The WHO recommend FDCs for the first-line treatment of tuberculosis and HIV infection in developing countries. The rationale lacks a sound supporting clinical evidence base but the practice is widely accepted and plausible. The evidence to support the use of FDCs compared with separate administration of the drugs in the treatment of asthma, hypertension and diabetes is sparse and conflicting, although such formulations already exist. More good quality studies are needed. New FDCs may have potential benefits in some therapeutic areas and patient demand could be high, but ultimately they will be judged on their comparative cost-effectiveness.

For a review of the evidence for the use of FDCs, please see the first update in this series – "Fixed dose combinations (Part 1) – What is the evidence for their use?"³⁰

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KEY RCT – CT - controlled trial, G – Guidelines, O – open label, MA – meta-analysis, R – review, RCT – randomised controlled trial

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