

# DRUG UPDATE

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## FIXED-DOSE COMBINATIONS (Part 1) -What is the evidence for their use?-

With the increasing use of multi-drug treatments, fixed-dose combination products (FDCs) offer a potential means of reducing the pill burden for patients. The evidence to support the assumption that they improve concordance and outcome, compared with combinations of separate component drugs, is sparse. There is a need for well designed clinical studies to prove their value, otherwise single-component generic drugs remain an equally efficacious and often more cost-effective alternative. In most situations, regimens containing single-component drugs should remain the treatment of choice.

### What are they?

Fixed-dose combination products (FDCs) are medicines which contain two or more drugs in fixed proportions in the same formulation.

FDC products are often claimed to make medicine-taking more convenient for patients taking multiple medication with the potential of improving concordance. They are also a means of prolonging the patent life of a product.

FDCs can be classified into several categories:

- Some of the earliest FDCs have been widely accepted as rational combinations of drugs which are suitable for all of their target groups of patients, on the basis of their pharmacology or patient acceptability. Examples are the combination of oestrogen with progestogen in combined oral contraceptives and levodopa with carbidopa to treat Parkinson's disease. Many topical preparations, such as eye and ear drops and skin formulations, contain combinations which increase patient acceptability by reducing the number of products to be used.
- Inappropriate drug combinations, where pharmacological claims for synergy are supported by little clinical evidence, e.g. the combination of caffeine with analgesics.
- Mixtures of drugs which are of benefit to only a few patients. Examples are combinations of potassium-sparing diuretics with thiazides and multi-component antacid mixtures.
- Those endorsed for use in resource-limited countries, specifically in the treatment of HIV/AIDS and tuberculosis.
- Combinations of drugs for chronic conditions in which multiple drug regimens are recommended (e.g. HIV/AIDS). Such regimens place a significant pill burden on patients, particularly those with co-morbidities, and FDCs in these patients may improve adherence.
- Some formulations (e.g. asthma inhalers) contain two drugs but only one prescription charge is payable, which benefits patients who pay for their prescriptions.

### Do concordance and clinical outcomes correlate?

Patient concordance with medication can be estimated in several ways, all of which are imperfect.<sup>1</sup> These include observation of prescription refills via pharmacy records and monitored electronic measurement devices. The majority of methods used in studies give an indirect measure of the actual use of medication by patients.<sup>1,2</sup> Direct methods such as measurement of drugs in body fluids or direct observation of medicine-taking by a healthcare professional/worker are expensive in terms of time and resources, especially in routine clinical practice, and are not practical in a 'real-life' situation.<sup>1,2</sup>

When collected in selected clinical trial populations they are also potentially non-representative of 'real-life' patients.

Despite this, there is some evidence that good concordance is associated with better clinical outcomes in clinical trials<sup>2-4</sup> and in some observational studies using patient registries in 'real-life' clinical practice.

For example non-concordant diabetic patients prescribed oral hypoglycaemics, antihypertensives and statin medications, had higher rates of hospitalisation and higher all-cause mortality than concordant patients.<sup>5</sup> In a retrospective analysis of the prescription records for statins in survivors of acute myocardial infarction, the relative risk of mortality was 25% higher ( $p = 0.001$ ) in patients with low (< 40%) compared with good ( $\geq 80\%$ ) concordance over a median period of 2.4 years.<sup>6</sup> Most studies define concordance in absolute terms as good or bad by setting the compliance rate at a pre-defined level (e.g.  $\geq 80\%$  and < 80% respectively).<sup>5</sup> This level varies among studies and few studies exist which have graded compliance on a sliding scale to indicate the threshold at which outcome is affected.

A meta-analysis of 21 studies in patients with various diseases showed that good concordance with drug therapy as well as with placebo was associated with positive health outcomes and lower mortality.<sup>7</sup> Thus concordance with drug therapy may be a surrogate marker for individuals who also follow other healthy behavioural and lifestyle interventions

e.g. stopping smoking and increasing exercise. Findings in other studies also serve as a reminder that factors other than medication adherence can explain how patients respond to treatment.<sup>8, 9</sup> These confounders may not always be accounted for in study analyses.

### Do FDCs improve drug concordance?

There is little evidence to support this. A systematic review of the literature between 1966 and 2003<sup>10</sup> found three trials, of which only one (a non-inferiority study designed to establish clinical equivalence) showed a significant but small improvement in concordance with a FDC, in patients with HIV infection at 16 weeks compared with the same drugs taken separately.<sup>11</sup> A meta-analysis of nine studies which included over 20,000 patients with hypertension, diabetes, HIV and tuberculosis, demonstrated that FDCs reduced the relative risk of non-concordance by 26% compared with single-component regimens (35% vs. 38%,  $p < 0.0001$ ).<sup>12</sup> Follow up was between 6 months and 2 years. This equates to an absolute risk reduction of 3%, i.e. 34 patients would need to be treated with an FDC to avoid one case of non-concordance.

In contrast, a retrospective study of newly treated patients with Type 2 diabetes ( $n = 6,502$ ) taking metformin and glibenclamide over six months showed no significant difference in concordance rates between patients receiving either monotherapy, a combination of the two separate drugs or a FDC.<sup>13</sup>

### How safe are they?

There is little evidence to suggest that the incidence or nature of adverse effects to drugs used in FDCs is different from combinations of the same drugs administered separately at the same doses.<sup>14</sup> In HIV patients ADR adverse effects were the same in each treatment group.<sup>11</sup>

### When should they be used?

For patients who have to take many different drugs, FDCs offer a strategy to reduce the pill burden and a simple, more convenient way of managing their medicines. Despite the widely held view that FDCs improve concordance, there are

few good quality studies which demonstrate this. Similarly, there is a paucity of evidence to suggest that the use of FDCs yields better clinical outcomes compared with combinations of the same drugs given separately.

In specific diseases, such as tuberculosis and HIV/AIDS where omitting one component of a multi-drug regimen may be particularly detrimental to outcome, FDCs have become accepted.

Disadvantages of FDCs include;

(a) Reduced dosage flexibility. While this could be overcome if manufacturers were to produce a range of doses of components, this could lead to patient confusion with a corresponding increase in prescribing, dispensing and patient errors. Furthermore, potential for wastage might be increased.

(b) There is sometimes a lack of knowledge amongst prescribers about the actual components of FDCs

(c) FDCs may prolong patents, increasing long term costs. While FDCs often cost the same as or less than the separate components at launch, they often become more expensive once generic version(s) of the original drug(s) become available.

When evaluating the need for FDCs, judgements need to be made as to whether there is evidence that use will improve concordance, clinical outcomes or convenience to patients and if they do, whether these benefits justify possible longer term costs. There is also a need for discussion on the use of monitored dosage systems and the appropriateness of using FDCs in them if this increases prescribing costs. Better designed clinical studies are needed and the impact of FDCs on drug costs must be assessed.

For a review of the evidence on FDCs in patients with specific chronic diseases, please see the second update in this series – “Fixed dose combinations (Part 2) – Use in specific medical conditions”.<sup>15</sup>

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

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