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Fixed dose combination diabetes medicines

Usage in the Australian veteran population

Objective
To examine initiation and prescribing patterns of metformin-glibenclamide and metformin-rosiglitazone fixed dose combination products within the Australian veteran population.

Method
A retrospective observational study using Department of Veterans' Affairs pharmacy claims data. We examined overall trends in the utilisation and proportion of patients who had been previously dispensed both, one, or none of the individual ingredient products before initiating combination products.

Results
Of metformin-glibenclamide initiations, 9% involved a switch from metformin and glibenclamide as separate products, while 22% had used neither metformin nor a sulfonylurea. Thirty percent of metformin-rosiglitazone initiations involved a switch from both individual products, while in 10% neither metformin nor thiazolidinedione had been dispensed.

Discussion
A minority of veterans started taking the combination products after being stabilised on the individual products; many had no prior history of oral hypoglycaemic use. This prescribing may lead to wastage if combination medications are poorly tolerated or, more importantly, may cause adverse events.

Keywords: diabetes mellitus, type 2; drug utilisation; quality of health care

The number of Australians with type 2 diabetes mellitus has more than doubled in the past 2 decades and continues to increase.[1] When oral antidiabetic monotherapy does not control blood glucose sufficiently, guidelines recommend intensifying therapy with a combination treatment regimen.[2] However, polypharmacy may reduce adherence and increase the risk of medication errors.[3] Fixed dose combination (FDC) products increase the simplicity of prescribing, decrease the number of required tablets (which may improve adherence), and under certain circumstances, decrease costs for the patient.[4] However, there are potential disadvantages of FDC use, including lack of flexibility of dosing, difficulty ceasing only one component, and potential for patient confusion because of switching.[4]

Metformin-glibenclamide and metformin-rosiglitazone are two combination products listed for subsidy under the Pharmaceutical Benefits Scheme (PBS) in Australia for type 2 diabetes mellitus. At the time of PBS listing, educational material on the use of these products was provided by the National Prescribing Service (NPS), an independent, not-for-profit organisation which supports evidence based prescribing. The NPS published NPS RADAR (Rational Assessment of Drugs and Research) articles on each of these diabetes combination products.[5,6]

The NPS recommendations relating to initiation and prescribing of the FDC products included the following key points:

- fixed dose combination therapy is preferred for patients who are already stabilised on co-administered individual standard tablets to improve treatment compliance[5,6]
- combination tablets should not be used to initiate therapy for diabetes in patients who have not previously used an oral antidiabetic,[5,6] and
- patients switching to (initiating) the combination tablets need to stop their individual standard tablets.[6]

While the metformin-glibenclamide combination product is listed on the PBS as an unrestricted benefit, the metformin-rosiglitazone combination product requires a special authorisation (ie. a 'PBS authority listing') restricted to people already stabilised on either of the PBS subsidised single ingredient thiazolidinediones (glitazones) products plus metformin, with or without a sulfonylurea.[7]

This study examines initiation and prescribing patterns of fixed dose combination diabetes medicines in the Australian veteran population, and whether prescribers were concordant with PBS subsidy restrictions and NPS recommendations regarding initiation of therapy.

Method

This was a retrospective study of pharmacy claims data from the Department of Veterans' Affairs, Australia. This dataset includes spouses and dependents and provides de-identified patient level information on all medicines subsidised under the Repatriation Pharmaceutical Benefits Scheme (RPBS), including the drug dispensed, date of dispensing, quantity supplied, dosage form

and strength, and patient information (age, gender, date of birth, and residential status). Medicines were coded according to the World Health Organization (WHO) Anatomical and Therapeutic Chemical (ATC) classification[8] and the Schedule of PBS item codes.[9]

Overall drug utilisation trends from January 2001 to June 2009 were investigated for diabetes combination therapies to establish existing trends. Monthly utilisation was calculated as the proportion of veterans using a specific combination of medicines (either as single agents concurrently or as fixed dose combination products) in each month among the overall diabetes population in that month. The diabetes population was defined as veterans who were dispensed any oral diabetes medicine (ATC code: A10B) or insulin (ATC code: A10A). To calculate the population using specific combinations of medicines each month, prescription durations were applied. The prescription duration was calculated from the data and reflected the time period within which 75% of prescriptions were refilled. For example, 75% of prescriptions for the metformin-rosiglitazone combination product were dispensed every 34 days, thus for the purposes of these analyses it was assumed that the person was using the medicine from the date of dispensing until 34 days later. To account for the aging population, monthly prevalence rates were age standardised, using the veteran population in January 2001. Poisson regression models were used to test for a linear trend over time in yearly prescription rates.

To investigate the prescribing history of patients initiating the fixed dose combination products, a cohort study was undertaken. Time periods (each of 12 months) were defined to allow comparison of initiation patterns. The first period covered the first 12 months after FDC product listing, the second period covered the subsequent year, continuing until the end of available data. The cohort in each period included veterans who received their first (index) prescription for the FDC in that time. The prescribing patterns in the 12 months before the index prescription were investigated to identify what proportion of patients initiated the combination product after previously being dispensed either:

- both individual products (one after another or concurrently)
- metformin with another product from the same group (ie. a sulfonylurea other than glibenclamide or pioglitazone)
- one of the individual products only, or
- none of the individual products (in the past 12 months).

Prescribing patterns of FDC products (alone or co-administered with the individual ingredient products) were investigated for each 12 month period after listing of the FDC. In order to reduce the likelihood that switching was misclassified as codispensing, we excluded the first dispensing episode after the index script and only included subsequent dispensing as coprescribing.

Data extraction and analysis were performed using SAS software (version 9.2, SAS Institute Inc, Cary, North Carolina).

Ethics approval was obtained from the University of South Australia Human Research Ethics Committee and the Department of Veterans' Affairs Human Research Ethics Committee.

Results

Overall utilisation

There were 20 016 veterans dispensed oral diabetes medicines or insulin in January 2001, increasing to 21 413 by June 2009. The majority of patients were aged 70–89 years (median age 79 years, SD: 6.2) in January 2001 and 69% were male. Overall trends in use of combinations of diabetes medicines (either as single agents concurrently or as fixed dose combination products) are presented in *Figure 1*. Use of oral metformin and sulfonylurea combinations decreased from 28% to 21% over the study period (trend slope = 0.959, 95% confidence interval [CI]: 0.952–0.967, $p<0.0001$), while use of insulin in combination with oral hypoglycaemics increased from 7.0–11.2% (trend slope = 1.064, CI: 1.058–1.070, $p<0.0001$). Triple therapy has been only a small percentage of the overall population; 2.4% in 2009. A shift has occurred away from rosiglitazone to pioglitazone with either metformin or sulphonylureas.

FDC Initiation and use

Utilisation of the two fixed dose combination products comprised a small proportion of antidiabetic therapy, with an average of 0.43% and 0.60% of the veteran diabetes population receiving metformin-glibenclamide and metformin-rosiglitazone combination product respectively in a given month (ie. prevalent use) in the first 12 months after each product listing.

Metformin-glibenclamide combination product initiations most commonly involved a switch from metformin and a sulfonylurea other than glibenclamide (*Table 1*). The proportion of veterans receiving the FDC after being dispensed both metformin and glibenclamide varied across the cohorts. One in five of metformin-glibenclamide combination product initiations observed in the first 12 months after listing occurred after a step-up from metformin

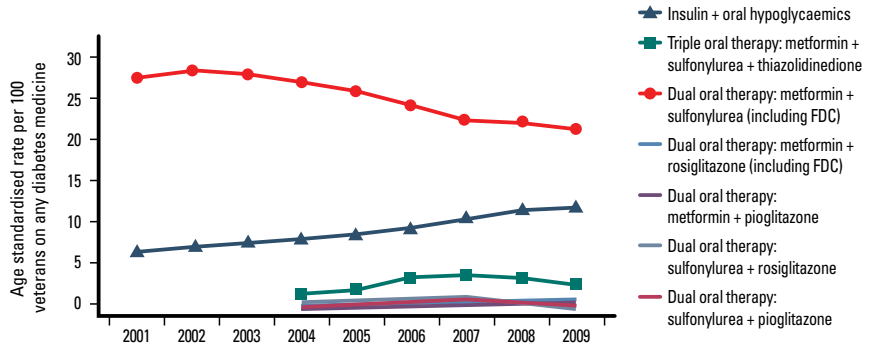

Figure 1. Age standardised prevalence rates of diabetes combination therapies in veterans who were dispensed medicines indicative of diabetes

alone. The proportion of those who initiated metformin-glibenclamide combination product after sulfonylurea alone varied across the cohorts. An increasing proportion of patients initiated metformin-glibenclamide combination product without previously being dispensed either of the individual ingredients over time (13% for cohort one up to 34% for the last cohort, χ^2, $p<0.001$).

Most of the metformin-rosiglitazone combination product initiations involved a step-up from metformin alone (*Table 2*). An increasing proportion had initiated the FDC without receiving the individual products in cohort two compared to cohort one (7% for cohort one; 17% for cohort two, χ^2, $p=0.002$).

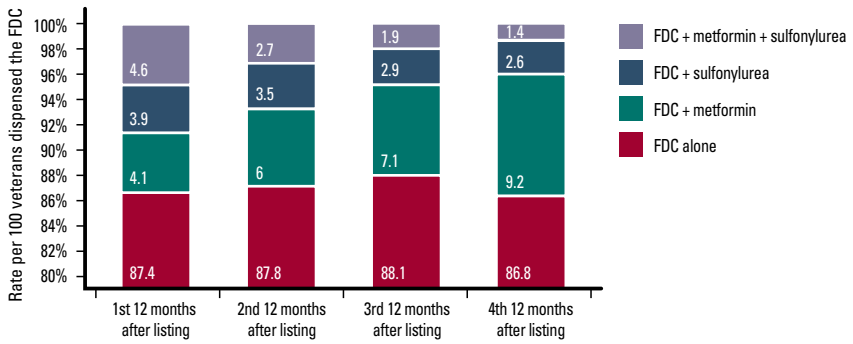

Figure 2. Prescribing rates in veterans dispensed metformin-glibenclamide combination product

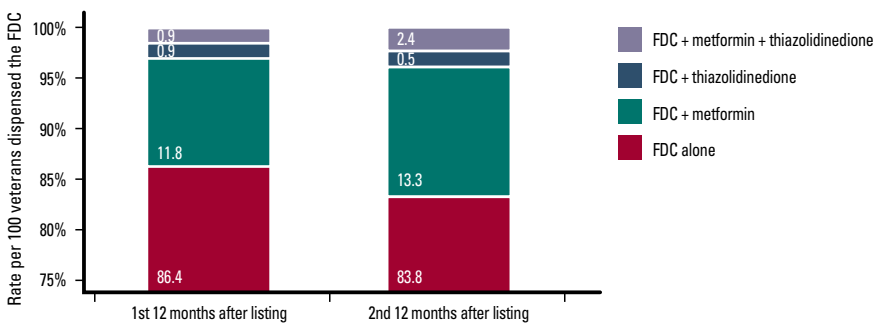

Figure 3. Prescribing rates in veterans dispensed metformin-rosiglitazone combination product

Once initiated, FDC was used as sole treatment in about 80% of the FDC treatment population (*Figure 2, 3*). An increasing proportion of veterans were dispensed metformin-glibenclamide combination product together with metformin tablets (from 4.1% in the first period up to 9.2% in the last period, χ^2, $p<0.001$) (*Figure 2*). A decreasing proportion was dispensed metformin-glibenclamide combination product with both individual ingredient products (from 4.6% in the first period down to 1.4% in the last, χ^2, $p<0.001$); 11.8% (year 1) and 13.3% (year 2) of veterans who were dispensed the metformin-rosiglitazone combination product were also dispensed metformin tablets (*Figure 3*).

Discussion

From 2001–2009, dual therapy with metformin and a sulfonylurea remained the most widely used combination therapy for type 2 diabetes among the veteran population. However, use of the combination decreased significantly over the period, with corresponding increases in combinations involving insulin, and to a lesser extent, triple oral therapy involving a thiazolidinedione. These trends may reflect a shift by prescribers away from the sulfonylureas, but may also represent diabetes progression within the cohort. The prevalence of thiazolidinedione dual therapy was low, and use of either metformin-glibenclamide or metformin-rosiglitazone fixed dose combination tablets remained small relative to overall combination prescribing.

Table 1. Prescribing history in the 12 months prior to the index script for metformin-glibenclamide combination product

	Cohort one Index script April 2005 to March 2006 n=242 (%)	Cohort two Index script April 2006 to March 2007 n=216 (%)	Cohort three Index script April 2007 to March 2008 n=101 (%)	Cohort four Index script April 2008 to March 2009 n=79 (%)
Metformin and glibenclamide (one after another or concurrently)	33 (13.6)	14 (6.5)	4 (4.0)	5 (6.3)
Metformin and sulfonylurea other than glibenclamide (one after another or concurrently)	101 (41.7)	70 (32.4)	33 (32.7)	26 (32.9)
Metformin alone	48 (19.8)	52 (24.1)	33 (32.7)	14 (17.7)
Any sulfonylurea alone	30 (12.4)	28 (13.0)	2 (2.0)	7 (8.9)
None of the individual products in the past 12 months	30 (12.4)	52 (24.1)	29 (28.7)	27 (34.2)

Metformin-glibenclamide combination product uptake most commonly (36%) represented a switch from prevalent use of metformin and a sulfonylurea other than glibenclamide. Glibenclamide is not generally recommended in the elderly due to its long half-life and associated risk of hypoglycaemia.[5] A small minority of veterans (9%) received their index script for metformin-glibenclamide combination product after treatment with metformin and glibenclamide, in keeping with NPS recommendations. Initiating the metformin-glibenclamide combination product without any prior use of metformin or sulfonylurea was a common occurrence (22%), despite advice to the contrary in the regulator approved prescribing information.[10]

The majority of metformin-rosiglitazone combination product initiations (57%) occurred after a step-up from metformin alone. The PBS listing for metformin-rosiglitazone combination product permits it to be used to intensify therapy when metformin monotherapy fails and a sulfonylurea is contraindicated.[7,11] Thirty percent of the initiations followed the NPS recommendation and initiated the metformin-rosiglitazone combination product after treatment with metformin and rosiglitazone as separate products. As with metformin-glibenclamide, many metformin-rosiglitazone combination product initiations were for veterans who had used neither ingredient (10%). Prescriptions for this group were contrary to NPS recommendations and also conflicted with the restrictions of the PBS authority listing.

A significant proportion of veterans received repeated prescriptions for metformin tablets concurrently with a fixed dose combination tablet that contained metformin. Around 10% of those who initiated metformin-glibenclamide combination product or metformin-rosiglitazone combination product maintained continuous metformin dispensing concurrently, suggesting that additional metformin was needed to achieve the required treatment dose. A small percentage of combination product users continued to receive both individual ingredients in addition to the combination product. These findings suggest that the rationale for using a FDC preparation was not met (ie. reduced pill count, reduced patient cost) or in other cases may indicate unintended duplication of therapy. The NPS recommendation that patients be stable on individual tablets before initiating the corresponding FDC product is in part to ensure that the relatively inflexible metformin dosing of FDCs is compatible with the patient's requirements.

Prescribers may diverge from recommended practice when they are unfamiliar with a new medicine. A retrospective study of Taiwanese outpatient claim data found that up to 12% of thiazolidinedione prescriptions were potentially inappropriate, ie. apparently in conflict with contradictions, and that the proportion of new inappropriate prescriptions was greatest when the drugs were new.[12] However, in the present study, the increasing proportion over time of combination product prescriptions in individuals with no previous prescriptions for diabetes medicines suggests that unfamiliarity was not the cause in these cases.

A limitation of our study is that the results were based on prescription claim data which did not provide direct diagnostic information to confirm diabetes diagnoses. However, diabetes medicines are unlikely to be prescribed in the older population for indications other than diabetes.

The veteran population have slightly more general practice visits (rate ratio: 1.17; $p<0.05$) and hospitalisations (rate ratio: 1.21; $p<0.05$) per year than other Australians aged 40 years and over.[13] Veterans with no service related disability have similar levels of use to other Australians.[13] Similar numbers of prescriptions per general practitioner visit are observed between the veteran population and the Australian populatio. However, because of the higher rate of GP visits, veterans receive slightly more prescriptions annually than other Australians (rate ratio: 1.13, $p<0.05$).[13] In the absence of specific comparative information regarding diabetes prevalence in the DVA and general Australian populations, this suggests our study results are likely to reflect the general Australian population for diabetes, but may slightly overestimate the utilisation rates.

Table 2. Prescribing history in the 12 months prior to the index script for metformin-rosiglitazone combination product

	Cohort one Index script December 2006 to November 2007 n=313 (%)	Cohort two Index script December 2007 to November 2008 n=126 (%)
Metformin and rosiglitazone (one after another or concurrently)	100 (31.9)	31 (24.6)
Metformin and pioglitazone (one after another or concurrently)	6 (1.9)	4 (3.2)
Metformin alone	181 (57.8)	68 (54.0)
Rosiglitazone-pioglitazone alone	4 (1.3)	2 (1.6)
None of the individual products in the past 12 months	22 (7.0)	21 (16.7)

Implications for general practice

General practitioners need to consider the risks of initiating fixed dose combination products without first stabilising patients on individual products. For example, the fixed dose combination product of metformin with glibenclamide may cause hypoglycaemia in elderly patients who have not previously been stabilised on a longer acting sulfonylurea. This study shows some patients cannot be managed on the FDCs alone and require additional metformin or possibly both single ingredients, suggesting the fixed dose combinations may not always provide a simplified dosing regimen. General practitioners should be alert to unintended double dosing at the time of

switching and should discuss this carefully with their patients.

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