Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Combination products

Editor, – We refer to the article 'Combination products – love them or loathe them?' (Aust Prescr 2001;24:127-9) and comment on the unrealised potential of this type of agent in treating medical syndromes. Polypharmacy is a chief cause of poor compliance.[1] The recent trend for evidence-based medicine supports the use of multi-drug regimens. This is exemplified by heart failure, in which angiotensin-converting enzyme inhibitors[2], beta blockers[3] and spironolactone[4] have all been shown to improve mortality. In addition, diuretics ameliorate symptoms[5], and digoxin reduces hospital admissions.[6] Heart failure thus demands a pharmaceutical quintet, even before addressing the cause of the cardiac dysfunction. We believe that the true niche for combination products is in the management of medical syndromes, such as heart failure or the metabolic syndrome, rather than in specific risk factor control. In this context the arguments against combination therapies, as outlined in the article, are less persuasive. The doses may still need to be initially adjusted, but the stable dose will depend upon the evidence from the trials. A starter pack with graded dosages may ease initial concerns and allow manipulation of certain dose sensitive components. There would not be 'unnecessary risk' as all the components would be of proven benefit. The differing pharmacokinetics of the components would, however, still need consideration. Validation would require randomised trials comparing the combination product to the individual drugs, on an intention-to-treat basis. These combinations, rather than promoting 'lazy prescribing' would help doctors to ensure the best, evidence-based care for patients with complex problems.

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Associate Professor Robert Moulds, author of 'Combination products – love them or loathe them?', comments:

Editor, – Dr Phillips and Dr Worthley have raised an interesting point. However, it is not necessarily correct to assume that because ACE inhibitors, beta blockers and spironolactone have each individually been shown to improve mortality in heart failure, then all, or even most, patients should be treated with all three drugs. Similarly, trials which show digoxin reduces hospital admissions do not mean all patients should be treated with digoxin. Each of the sets of trials studying those drugs had significant (and different) inclusion and exclusion criteria, and the results cannot necessarily be extrapolated to all patients with heart failure. Indeed it would be an interesting exercise to look at a series of patients with heart failure and see how many would have met the entry criteria, and would have had no exclusion criteria, for each of the trials showing the benefits of ACE inhibitors, beta blockers, spironolactone and digoxin. My guess is relatively few patients would qualify.

There would also be difficulty in finding kinetically suitable combinations, and difficulty with the initial dose titration required with some of the drugs, not to mention finding a pharmaceutical company with deep enough pockets to sponsor the clinical trials necessary to establish that a combined heart failure tablet is equally as efficacious as the individual components.

Despite the seeming attraction, I doubt we will see a combination treatment for heart failure in the near future.

Managing warfarin therapy in the community

Editor, – In the article 'Managing warfarin therapy in the community' (Aust Prescr 2001;24:86–9) the authors state that there is good evidence that warfarin therapy is indicated for patients more than 50 years old who have non-valvular atrial fibrillation. This implies that almost all patients with non-valvular atrial fibrillation – including those with and without risk factors for stroke such as previous cerebrovascular events, structural heart disease, significant left ventricular systolic dysfunction, hypertension, left ventricular hypertrophy and diabetes – warrant anticoagulation with warfarin. The Framingham experience[1] would suggest that only about 5% of all patients with non-valvular atrial fibrillation are less than 50 years old.

The American College of Chest Physicians Consensus Conference on anti-thrombotic therapy[2] suggests that there is no need to consider warfarin in patients under the age of 65 years in the absence of risk factors for stroke. There is uncertainty about the risk faced by those with non-valvular atrial fibrillation including women up to the age of 75 years and men of any age. The 65–75 year age range includes a substantial proportion (approximately 20%) of the patients with non-valvular atrial fibrillation.

More recent data from a study[3] of more than 1700 American Medicare beneficiaries (aged 65–95 years and clearly a sicker population than patients in previous anticoagulant trials) supported the view that in the absence of risk factors anticoagulant therapy could not be strongly recommended before the age of 75 years in either males or females.

It is therefore important for the clinician to try and assess the benefits of anticoagulation based on the risk of ischaemic and especially disabling stroke in the patient with non-valvular atrial fibrillation. Unfortunately debate on the age factor is undermined by the difficulties of managing warfarin in practice and by the lack of prospective trial data on patients randomly anticoagulated according to age cohorts.

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Professor Alex Gallus, one of the authors of 'Managing warfarin therapy in the community', comments:

Dr Hale's comments are correct and we cannot better his reading of the literature. The decision to start preventive treatment with warfarin in atrial fibrillation is a serious one. Apart from the immediate inconvenience it commits a patient who may be otherwise well to a lifelong increase in bleeding risk. Therefore, before starting warfarin in any individual with atrial fibrillation, the risks of systemic embolism without therapy and of bleeding due to therapy must be formally assessed, recorded and balanced. We had not intended our Table 1 to suggest that all patients with atrial fibrillation need warfarin if they are more than 50 years old. The American College of Chest Physicians Consensus Conference provides useful information. There were detailed discussions on the indications for warfarin in atrial fibrillation[1], and about patient related risk factors for bleeding during therapy.[2]

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Top 10 drugs

These tables show the top 10 subsidised drugs in 2000-01. The tables do not include private prescriptions.

Table 1

Top 10 drugs by defined daily dose/thousand population/day*

Drug	*PBS/RPBS †*
1. atorvastatin	52.814
2. simvastatin	38.596
3. celecoxib	34.527
4. salbutamol	26.452
5. frusemide	23.797
6. ranitidine hydrochloride	19.891
7. ipratropium bromide	18.479
8. omeprazole	18.229
9. amlodipine besylate	17.992
10. irbesartan	17.366

Table 2

Top 10 drugs by prescription counts

Drug	*PBS/RPBS †*
1. simvastatin	4,785,785
2. paracetamol	4,752,399
3. atorvastatin	4,745,607
4. celecoxib	3,850,569
5. ranitidine hydrochloride	3,790,947
6. salbutamol	3,588,326
7. codeine with paracetamol	3,015,979
8. temazepam	2,837,752
9. omeprazole	2,761,884
10. atenolol	2,646,123

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

Table 3

Top 10 drugs by cost to government

Drug	*PBS/RPBS † DDD/1000/day*	*PBS/RPBS scripts*	*Cost to government ($A)*
1. simvastatin	38.596	4,785,785	284,848,016
2. atorvastatin	52.814	4,745,607	279,681,834
3. celecoxib	34.527	3,850,569	210,259,889
4. omeprazole	18.229	2,761,884	198,064,392
5. olanzapine	2.557	507,167	112,921,245
6. pravastatin	10.202	1,473,711	87,904,278
7. sertraline	16.989	2,256,615	87,259,122
8. ranitidine hydrochloride	19.891	3,790,947	85,803,001
9. insulin (human)	11.426	421,974	78,922,474
10. bupropion	3.005	297,662	74,852,706

† PBS Pharmaceutical Benefits Scheme RPBS Repatriation Pharmaceutical Benefits Scheme