PERSPECTIVE

Medical treatment of glaucoma – a reappraisal of the risks

Paul Diggory, Wendy Franks

There has been an accumulation of evidence in recent years to demonstrate that surgical treatment is more effective than eyedrops at lowering intraocular pressure and preserving the visual field in primary open angle glaucoma.^{1 2} The argument against primary surgery for glaucoma has been the risk to the eye of performing an intraocular operation. The risks of topical medical therapy to general health, particularly that of elderly people, have been underestimated and surgery is likely to be both a safer and a more effective option for patients requiring treatment for glaucoma.

The only therapeutic approach to have proved effective in glaucoma is lowering intraocular pressure. Eyedrops are the mainstay of glaucoma treatment and, because they are excellent ocular hypotensives with few local side effects, topical β antagonists are the class of drug most often prescribed.³ Therapy is life long and many people of extreme old age receive treatment.

Ophthalmologists and geriatricians have many patients in common. Open angle glaucoma is predominantly a disease of old age, affecting up to 5% of the population by 65 years and becoming even more common in older age.^{4 5} Respiratory and cardiovascular disease are also common in this age group and both may be affected by eyedrops prescribed for glaucoma.

Topical β antagonists

There are two main classes of β adrenergic antagonists; non-selective, which affect both β_1 receptors, found predominantly in the heart, and β_2 receptors, found in the lungs. Timolol, carteolol, and levobunolol are non-selective preparations. Cardioselective β antagonists bind to β_1 receptors preferentially and have relatively less effect on β_2 receptors. Respiratory side effects are less common with cardioselective preparations but they may still occur and they should be avoided in patients with airways obstruction.

Side effects of treatment with oral β antagonists include heart failure, hypotension, and bronchospasm. The same side effects occur with topical therapy.^{6 7} Drugs administered topically to the eye gain access to the systemic circulation via the nasolacrimal duct and the nasal mucosa. This avoids first pass metabolism by the liver and significant amounts of topically administered drugs may be absorbed into the systemic circulation. For example, two drops of a 0.5% timolol solution, one to each eye, can approximate to the 10 mg oral dose given to treat systemic hypertension or angina.^{8 9}

When treating elderly patients physicians avoid using β antagonists because they are poorly tolerated. If there are no suitable alternatives cardioselective preparations are usually chosen. Ophthalmologists are the only specialists using non-selective β antagonists as first line therapy for elderly patients.

Airways disease and the elderly

Few studies of systemic side effects with topical β antagonists have focused specifically on the elderly population, who form the majority of glaucomatous patients. Respiratory disease is very common in the elderly and can develop insidiously over many years.^{10 11} One population survey¹² found that as many as 41% of elderly people have airways disease, much of it undiagnosed and unsuspected. Other medical conditions frequently prevent breathlessness being noticed. In addition, elderly people have a reduced awareness of bronchoconstriction and may not notice symptoms with a decrease of 20% in spirometry.¹³ This, together with a stoical attitude that accepts reduced exercise tolerance and breathlessness as part of old age, results in elderly patients reporting fewer respiratory symptoms than the young. In the absence of a history of chest problems β antagonist therapy has been regarded as safe. Recent work challenges this assumption.

The number and density of β adrenergic receptors fall with age.¹⁴ In addition changes in receptor sensitivity (uncoupling of the receptors from the intracellular second messengers) and gradual down regulation occur with age and exposure to agonist and antagonist drugs.^{15–17} This may make elderly people especially vulnerable to β antagonist therapy and implies that continued exposure to β antagonists increases the likelihood of deteriorating respiratory function over time.

Two studies of respiratory function of elderly people taking topical timolol have identified a high proportion of unrecognised, asymptomatic respiratory impairment.

The first study, recently published in the *Lancet*, recorded changes in spirometry, an exercise walk tolerance test and measurement of blood pressure, and resting and exercise pulse.¹⁸ Eighty patients, aged over 60 years, without history of airways disease, using timolol for at least 1 year, were recruited into a randomised, double masked, crossover study changing therapy to betaxolol or dipivefrine. The study comprised two phases and all patients who completed both phases underwent a change in therapy. Third party randomisation produced four groups: TTB (timolol-timolol-betaxolol); TTD (timolol-timolol-dipivefrine); TBT (timolol-betaxolol-timolol); and TDT (timolol-dipivefrine-timolol). During phase I, group TBT was allocated to receive one drop to both eyes of 0.5% betaxolol and group TDT one drop of 0.1% dipivefrine twice daily for four weeks. Groups TTB and TTD continued to receive topical timolol for four weeks. In the second phase, groups TBT and TDT returned to timolol while group TTB was allocated to receive one drop to both eyes of 0.5% betaxolol and group TTD one drop of 0.1% dipivefrine twice daily for 4 weeks. Outcome measures were recorded on enrolment and at the end of each phase. The study design allowed comparisons between treatment change and controls as well as treatment change and return to original therapy (Table 1).

Table 1 Mean values (SD) of spirometry, walk distance, and intraocular pressure (IOP) on enrolment and at end of each phase

Outcome measures	Treatment group			
	TTB	TTD	TBT	TDT
Peak flow (litre/min)				
Enrolment	316 (91)	300 (95)	295 (91)	328 (121)
Phase I	322 (87)	301 (91)	337 (104)	372 (112)
Phase II	361 (98)	344 (76)	297 (84)	322 (117)
FEV ₁ (litres)				
Enrolment	1.88 (0.51)	1.72 (0.46)	1.84 (0.60)	1.99 (0.66)
Phase I	1.92 (0.51)	1.71 (0.45)	1.98 (0.61)	2.22 (0.65)
Phase II	2.09 (0.49)	1.86 (0.41)	1.83 (0.57)	1.92 (0.74)
FEV ₁ /FVC (% age)				
Enrolment	79 (6)	75 (11)	75 (8)	75 (8)
Phase I	76 (5)	74 (7)	78 (7)	82 (16)
Phase II	77 (7)	75 (8)	75 (8)	75 (8)
Walk distance (metres)				
Enrolment	176 (51)	170 (59)	181 (36)	188 (53)
Phase I	189 (45)	176 (60)	195 (40)	202 (56)
Phase II	220 (48)	193 (56)	186 (33)	184 (58)
IOP (mm Hg)				
Enrolment	19.0 (2.5)	20.0 (2.5)	18.1 (3.2)	19.1 (2.7)
Phase I	17.4 (3.8)	19.2 (3.0)	18.9 (3.1)	19.5 (2.7)
Phase II	19.6 (3.6)	21.9 (4.8)	17.0 (2.4)	17.8 (2.3)

TTB=timolol-timolol-betaxolol; TTD=timolol-timolol=dipivefrine; TBT=timolol-betaxolol-timolol; TDT=timolol-dipivefrine-timolol; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity.

Analyses of variance, adjusting for period and group effects, demonstrated a statistically significant effect of changing treatment to betaxolol or dipivefrine ($p<0.001$) for peak flow (PF) and forced expiratory volume in 1 second (FEV₁). There was a significant ($p<0.01$) improvement in the changes in FEV₁/FVC ratio. In patients with airways obstruction the amount of air that can be expelled in the first second (FEV₁) decreases, but the total volume that can be expelled, the forced vital capacity (FVC) is relatively preserved and a low FEV₁/FVC ratio results. An increased FEV₁/FVC ratio is, therefore, consistent with improvement in mean spirometry to values demonstrating less airways obstruction. Compared with timolol, mean PF (95% confidence interval) using betaxolol and dipivefrine were greater by 39 l/min (27,51) and 42 l/min (30,54) respectively. In addition, mean FEV₁ (95% CI) using betaxolol and dipivefrine were greater by 0.14 litres (0.10,0.18) and 0.20 litres (0.16,0.25).

Of the 80 patients enrolled, 21 (26%) demonstrated clinically significant reversible airflow tract obstruction^{19 20} by improving both FEV₁ and PF by more than 15%. Symptomatic improvement was noticed in nine of these patients when timolol was stopped.

The exercise tolerance test²¹ consisted of a 2 minute timed walk up and down a 40 metre corridor. To minimise learning and target setting effects the starting point along the corridor was varied between enrolment and review. The test showed that, at the end of the first phase, those changing to betaxolol had improved walk distance (95% CI) by 8% or 13.8 metres (8.9,17.7) and those changing to dipivefrine by 7% or 13.3 metres (8.6,17.9). Those continuing timolol improved by 3% or 5.2 metres (1.9,8.6). The differences in the changes between timolol and betaxolol, as well as timolol and dipivefrine groups, were statistically significant, $p=0.004$ and $p=0.001$ respectively. Analysis of the exercise tolerance test (Table 1) suggested significant carryover effects between phases, probably as a result of learning effects. Other measures of exercise tolerance, such as treadmill walking tests are often difficult for elderly people to perform, are also likely to show learning effects, and may not reflect exercise capacity²² in daily life. The corridor walk test still represents one of the most reproducible measures of respiratory function for elderly people.

Changing from timolol to dipivefrine or betaxolol was associated with significant increase in mean resting and exercise pulse (Table 2). The reduced exercise tachycardia

with timolol may contribute to the shorter mean distance walked by patients with timolol (Table 1). Topical timolol was acting as a systemic hypotensive agent. Mean systolic and diastolic blood pressures were also lower with timolol than with dipivefrine or betaxolol (Table 2). Though no patient was found to have a blood pressure less than 100/60, many of the 80 patients were receiving other agents likely to cause a reduction in blood pressure. Ten used a diuretic, three an angiotensin converting enzyme (ACE) inhibitor, three calcium antagonists, and nine nitrates.

The second paper reported an open study of changes in lung function tests.²³ Fifty two patients taking timolol had treatment changed to pilocarpine or betaxolol and 20 controls continued to take timolol. Spirometry was recorded at enrolment and repeated after 4 weeks. Changing from timolol (0.5% twice daily) to either pilocarpine (2% four times daily) or the cardioselective betaxolol (0.5% twice daily) produced improvement in lung function tests. In the treatment change group mean PF increased from 278 l/min to 328 l/min ($p<0.001$) and mean FEV₁ from 1.66 litres to 1.85 litres ($p<0.001$). Spirometry in a control group of 20 subjects was unchanged. Nineteen out of 47 patients completing the trial demonstrated clinically significant reversible airflow tract obstruction, defined as 15%, or more, increase in both PF and FEV₁.^{19 20} Eight of these 19 reported symptomatic improvement in breathing.

Of particular concern is the high (26% in the first and 40% in the second) proportion of patients demonstrating clinically significant reversible airflow tract obstruction. It is important that such people be identified because they are liable to develop severe bronchospasm, especially if they contract a respiratory tract infection. Because of this risk, therapy with β antagonists is contraindicated in such patients, even if they are asymptomatic.

Both studies attempted, by using a standard symptom inquiry and the spirometric response to nebulised salbutamol, to identify patients who would show reversible airflow tract obstruction, in advance of change in therapy. Unfortunately, even using such predictors, some asymptomatic patients experiencing clinically significant airflow obstruction would be missed. The studies suggest more than a quarter of those receiving timolol, apparently without complication, should not be and there is no method of identifying them. In clinical practice the proportion is likely to be higher because of the strict entry criteria that were used in these studies.

Table 2 Mean values of outcome measures at end of each 4 week treatment period

Outcome measures	Study period	Treatment received (SD)			Significance of treatment effect*
		Timolol	Betaxolol	Dipivefrine	
Resting pulse	One	74 (13)	84 (14)	84 (12)	p<0.001
	Two	72 (12)	76 (15)	89 (13)	
Post exercise pulse (litres)	One	110 (24)	125 (21)	131 (21)	p<0.001
	Two	107 (18)	114 (22)	132 (26)	
Systolic blood pressure (mm Hg)	One	133 (18)	142 (18)	141 (19)	p<0.001
	Two	125 (18)	140 (18)	143 (19)	
Diastolic blood pressure (mm Hg)	One	81 (10)	89 (11)	90 (10)	p<0.001
	Two	81 (10)	89 (11)	96 (9)	

*p Value from analysis of variance adjusting for period and ordering effects.

A survey²⁴ of drugs given to a population of 125 000 elderly people, receiving Medicaid, commencing topical β antagonists, found 21 096 first prescriptions for bronchodilators were subsequently issued. Prior therapy for airways disease was increased in a further 3386 without discontinuing eyedrops. The message about airways disease and topical β antagonists is not being passed between ophthalmologist and physicians.

Ophthalmologists should question patients about changes in their breathing and their use of bronchodilators at each review. We recommend spirometry, or at least a peak flow recording, be performed before commencing β antagonist therapy and that it be repeated at each outpatient visit. This could be performed by nursing staff and a decrease of 15% should prompt a change in management.

Falls in the elderly

The risk of falls increases with age, so that by the age of 80 years, there is a 40% chance per year of falling.²⁵ The consequences of a fall are more serious for elderly people and 10% to 15% of falls result in serious injury, half of which are fractures.^{25 26} To remain upright requires the integration of visual, vestibular, and proprioceptive input with a coordinated motor response. Rapid, accurate central processing is needed and stable blood pressure in the face of changes in posture is required. Vasomotor tone and changes in heart rate are essential if blood pressure is to remain constant on standing and the impaired autoregulation of cerebral blood vessels means that elderly people are more vulnerable than the young if cerebral perfusion pressure is not maintained. Any fall is likely to be due to a combination of factors and successful intervention to prevent recurrence must address all potentially modifiable risk factors.²⁷ Impaired cardiovascular responses by drugs are common contributing factors to falls.²⁸

Topical β antagonist drugs have been implicated as a major risk factor for falls in elderly glaucoma patients. Glynn *et al*²⁹ reviewed the determinants of serious falls among 489 ambulant glaucomatous patients aged 65 to 93 (mean 73) years recruited consecutively from glaucoma clinics. The greatest risk factor (95% CI) for falling was the use of non-miotic eyedrops, odds ratio (OR) 5.4 (1.8, 8.4). This was by far the largest risk, others identified included >40% loss of visual fields (OR 3.0), use of sedatives (OR 2.5), cardiac medication (OR 2.2), and female sex (OR 2.0). The bradycardia, hypotension, and impaired heart

rate response found with β antagonists may cause an already unsteady elderly person to fall.

Effectiveness of punctal occlusion

It has been suggested that occlusion of the tear punctum for 5 minutes reduces by 67% the amount of topically applied timolol reaching the systemic circulation.³⁰ Occlusion of the tear duct, especially for such a long time, is a difficult manoeuvre for elderly people to perform and few are likely to comply. In the study by Diggory *et al*,^{18 19} out of 80 patients enrolled claimed to occlude their tear punctum, but no statistically significant (Mann-Whitney) differences between enrolment and review values of spirometry, blood pressure, resting or exercise pulse were found between those who claimed to occlude their punctum after instillation and those who did not (Table 3). Systemic delivery of topically applied drugs must be assumed to occur.

Alternative medication

Using cardioselective β antagonists reduces the risk of respiratory impairment, but the risks of cardiovascular problems associated with other β antagonists, such as falls, still exist. Betaxolol is a less effective ocular hypotensive agent than timolol (Table 1) and combination rather than single therapy may be required. Other β antagonists are non-selective and likely to have the same respiratory and cardiovascular side effects as timolol.

The cholinergic agonist pilocarpine, administered topically, lowers intraocular pressure but has unpleasant local side effects. Systemic absorption can cause gastrointestinal side effects and confusion.³¹ The local side effects and four times daily dosage, make it unpopular therapy with patients and many comply poorly.³² Pilocarpine is an excellent ocular hypotensive agent; long acting and slow release formulations are available and their more widespread use should be considered.

Topical adrenaline and dipivefrine are commonly used second line drugs. They are less effective than β antagonists at lowering intraocular pressure and have more ocular side effects, particularly red eye and follicular conjunctivitis. Their long term use has been shown to make subsequent drainage surgery more likely to fail from fibrosis.³³ This has led some eye departments to remove sympathomimetics from their formulary. As with the withdrawal of the β antagonist metipranolol, for causing uveitis in a small

Table 3 Influence of punctal occlusion on mean values of enrolment outcome measures

	FEV ₁ (litres)	FEV ₁ / FVC (%)	Resting pulse	Exercise pulse	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	IOP (mm Hg)
Punctum occluded (n=19)	1.90	73.8	73.8	111	135.7	88.8	18.5
Punctum not occluded (n=61)	1.86	76.1	73.0	115	135.8	84.3	19.1

percentage of cases, ophthalmologists are quick to abandon drugs when ocular side effects are found. When severe and potentially life threatening systemic complications occur they present to other physicians and the contribution of the eyedrops is commonly overlooked or underestimated.

Laser trabeculoplasty

Laser trabeculoplasty has not fulfilled its early promise of producing a reliable and sustained fall in intraocular pressure. It is a low risk strategy for elderly patients, who are unable to use, or have poor compliance, with topical therapy. Of most concern is the tendency for the effect to wear off, sometimes quite suddenly. Nevertheless, about 50% of elderly patients will have a satisfactory response to treatment for up to 5 years.³⁴ It is less effective in younger patients and in those with secondary glaucomas. The fall of intraocular pressure achieved may not be adequate in patients presenting with very high pressures and advanced field loss. Intraocular pressures in patients of African origin also respond poorly to laser trabeculoplasty. It is of limited use in secondary glaucomas although pseudoexfoliative and pigmentary glaucoma may respond well. It is not useful in the treatment of pseudophakic or aphakic eyes.³⁵

Trabeculectomy

Two studies, by Jay *et al* from Glasgow, and the Moorfields primary treatment trial by Migdal *et al* have shown primary trabeculectomy to be the most effective method of reducing intraocular pressure.^{1,2} Both studies suggested that visual field deterioration was also less in the surgery group but, because of the methods of visual field analysis used and the lack of universally accepted criteria for assessing visual field change, the results were not as convincing in showing a beneficial effect on visual field survival for patients undergoing trabeculectomy as might be hoped.

Ideas as to the desired level of intraocular pressure reduction are changing. No longer is an intraocular pressure of 21 mm Hg or less considered satisfactory for all glaucoma patients, but a 'target pressure' for each patient should be set; for example, for eyes with severe field loss, an intraocular pressure of 15 mm Hg or less is more appropriate.³⁶ Surgery may be the only way to achieve this and this has led some North American glaucoma specialists, traditionally resistant to early surgical treatment of glaucoma, to undertake a prospective study of primary trabeculectomy. The Moorfields primary treatment trial patients were white, predominantly elderly, and had had no previous intraocular surgery, and could be expected to have a high success rate with surgery – only one failure was reported. Prior medical therapy prejudices the outcome of subsequent drainage surgery by promoting fibroblast activity and subsequent scarring of the drainage bleb.³⁷ Young patients and Africans patients also have a poor success rate and antiproliferative agents such as 5-fluorouracil and mitomycin C are commonly used for these cases.

Whether the use of antiproliferative agents at the time of trabeculectomy does lower intraocular pressure and enhance visual field survival in all patients undergoing trabeculectomy, will be addressed by the Moorfields 5-fluorouracil trial.

Trabeculectomy can be performed as a day-case procedure under local anaesthesia, either with local infiltration, retrobulbar, or peribulbar anaesthetic³⁸ avoiding the risks of general anaesthesia.

Risks of surgery include failure, a flat anterior chamber with hypotony, choroidal detachment and haemorrhage,

malignant glaucoma, and endophthalmitis. These complications are rare and trabeculectomy is a successful surgical procedure with little risk to the patient's general health. Cataract is the commonest complication of glaucoma surgery, particularly in cases complicated by shallowing or flat anterior chamber, but the outcome of subsequent cataract surgery is generally excellent. By contrast, complications of topical β antagonist therapy are falls, asthma, worsening of heart failure and peripheral vascular disease, hypotensive strokes, and impotence. Which risks would you choose to take?

PAUL DIGGORY

Department of Elderly Care Medicine,
Mayday Hospital,
Croydon CR4 7YE

WENDY FRANKS

Glaucoma Unit,
Moorfields Eye Hospital,
City Road,
London EC1V 2PD

- Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. *Ophthalmology* 1994; 101: 1651-7.
- Jay JL, Murray SB. Early trabeculectomy versus conventional management in primary open angle glaucoma. *Br J Ophthalmol* 1988; 72: 881-9.
- Bene DJ, Zimmerman TJ. Perspectives in the drug treatment of glaucoma. *Curr Opin Ophthalmol* 1994; 5: 99-104.
- Klein BEK, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, *et al*. Prevalence of glaucoma: the Beaver dam eye study. *Ophthalmology* 1992; 99: 1499-504.
- Coffey M, Reidy A, Wormald R, Xian WX, Wright L, Courtney P. Prevalence of glaucoma in the west of Ireland. *Br J Ophthalmol* 1993; 77: 17-21.
- McMahon CD, Shaffer RN, Hoskins HD, Bachorik PS, Quigley HA. Adverse effects experienced by patients taking timolol. *Am J Ophthalmol* 1979; 88: 736-8.
- Jones FL, Ekberg NG. Exacerbation of asthma by timolol. *N Engl J Med* 1979; 301: 270.
- Passo MS, Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. *Ophthalmology* 1984; 91: 1361-3.
- Alvan G, Caissendorff B, Seideman P, Widmark K, Widmark G. Absorption of ocular timolol. *Clin Pharmacokinet* 1980; 5: 95-100.
- Burr ML, Charles TJ, Roy K, Seaton A. Asthma in an elderly population: an epidemiological survey. *Br Med J* 1979; i: 1041-3.
- Caird FI, Akhtar AJ. Chronic respiratory disease in the elderly. A population survey. *Thorax* 1972; 27: 764-8.
- Banerjee DK, Lee GS, Malik SK, Daly S. Underdiagnosis of asthma in the elderly. *Br J Dis Chest* 1987; 81: 23-9.
- Connolly MJ, Crowley JJ, Neilson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992; 47: 410-3.
- Schocken DD, Roth GS. Reduced beta-adrenergic receptor concentrations in ageing man. *Nature* 1977; 267: 856-8.
- Nijkamp FP, Engels F, Hendricks PAJ, Van Oosterhout AJM. Mechanisms of beta-adrenergic receptor regulation in lungs and its implications for physiological responses. *Physiol Rev* 1992; 72: 323-6.
- Vestal RE, Alastair JJ, Wood MB, Shand MB. Reduced beta-adrenoceptor sensitivity in the elderly. *Clin Pharmacol Ther* 1979; 26: 181-6.
- Cheung DC, Timmers MC, Zwiderman AH, Bel EH, Dijkman JH, Sterk PJ. Long term effects of a long-acting beta 2-adrenoceptor agonist, Salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; 327: 1198-203.
- Diggory P, Cassels-Brown A, Vail A, Abbey LA, Hillman JS. Avoiding unsuspected respiratory side-effects of topical timolol by using cardio-selective or sympathomimetic agents. *Lancet* 1995; 345: 1604-6.
- Quanjer PH, Tammeling GH, Cotes JE, Peterson OF, Peslin R, Yernaut JC. Lung volumes and forced ventilatory flows. Report of the working party standardisation of lung function tests European Community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993; 6 (suppl 16): 5-40.
- Becklake M, Crapo RO, Buist AS, Burrows B, Clausen JL, Coates AL, *et al*. Lung function testing: selection of reference values and interpretative strategies. An official statement of the American Thoracic Society. *Am Rev Respir Dis* 1991; 144: 1202-18.
- Butland RJA, Pang J, Gross ER, Woodcock AA, Geddes DM. Two, six and twelve minute walking tests in respiratory disease. *BMJ* 1982; 284: 1607-8.
- Greig C, Butler F, Skelton D, Mahmud S, Young A. Treadmill walking in old age may not reproduce the real life situation. *J Am Geriatr Soc* 1993; 41: 15-8.
- Diggory P, Heyworth P, Chau G, Mckenzie S, Sharma A. Unsuspected bronchospasm in association with topical timolol: a common problem in the elderly. Can we easily identify those affected? Do cardioselective agents lead to improvement? *Age Ageing* 1994; 23: 17-21.
- Avorn J, Glynn R, Gurwitz JH, Bohn RL, Monane M, Everitt DE, *et al*. Pulmonary effects of beta blockers. *J Glaucoma* 1993; 2: 158-65.
- Prudham D, Evans JG. Factors associated with falls in the elderly: a community study. *Age Ageing* 1981; 10: 141-6.
- Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; 319: 1701-7.
- Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, *et al*. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 1994; 331: 821-7.

- 28 Gurwitz JH, Soumerai SB, Avorn J. Improving medication prescribing and utilisation in the nursing home. *J Am Geriatr Soc* 1990; **38**: 541–52.
- 29 Glynn R, Seddon J, Sahagian C, Chiavelli M, Campion E. Falls in elderly patients with glaucoma. *Arch Ophthalmol* 1991; **109**: 205–10.
- 30 Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP. Improving the therapeutic index of topically applied drugs. *Arch Ophthalmol* 1984; **102**: 551–3.
- 31 Reyes PF, Dwyer BA, Schwartzman RJ, Sacchetti T. Mental status changes induced by eye drops in dementia of Alzheimer's type. *J Neurol Neurosurg Psychiatry* 1989; **50**: 113–5.
- 32 Kass MA, Meltzer DW, Gordon M, Cooper D, Goldberg J. Compliance with topical pilocarpine treatment. *Am J Ophthalmol* 1986; **101**: 515–23.
- 33 Broadway D, Greierson I, Hitchings R. Adverse effects of antiglaucomatous medications on the conjunctiva. *Br J Ophthalmol* 1993; **77**: 590–6.
- 34 Schwarz AL, Love DC, Schwartz MA. Long term follow up of argon laser trabeculoplasty for uncontrolled open angle glaucoma. *Arch Ophthalmol* 1985; **103**: 1482–4.
- 35 Reiss GR, Wilensky JT, Higginbotham EJ. Laser trabeculoplasty. *Surv Ophthalmol* 1991; **35**: 407–28.
- 36 Hitchings R. Primary surgery for primary open angle glaucoma – justified or not? *Br J Ophthalmol* 1992; **77**: 445–8.
- 37 Lavin MJ, Wormald RPL, Migdal CS, Hitchings RA. The influence of prior therapy on the success of trabeculectomy. *Arch Ophthalmol* 1990; **108**: 1543–8.
- 38 Nouredin B, Jeffrey M, Hitchings R, Franks WA. Conjunctival changes after subconjunctival lignocaine. *Eye* 1993; **7**: 457–60.