

Interestingly, freedom from seizures was almost identical, whether patients were treated first with a standard drug or a new drug.

The recent guidelines from the National Institute for Health and Clinical Excellence (NICE) on newer drugs for epilepsy in adults is therefore vague on the management of refractory epilepsy because of a lack of data comparing the new drugs with each other or with standard drugs, either as monotherapy or combination therapy.<sup>8</sup> NICE recommends that combination therapy should be considered only when attempts at monotherapy have not resulted in freedom from seizures but gives no guidance on the number of attempts at monotherapy or which combination to try. I estimate that the bewildered general neurologist or physician can choose from up to 13 options for monotherapy and 91 options for combination therapy. This is clearly an unsatisfactory situation for patients and physicians alike.

Doctors tend to opt for their own favourite combinations, influenced by marketing pressures or based on speculative concepts of different mechanisms of drug action or synergy—concepts that originally led to the subsequently discredited combined capsules of phenobarbital and phenytoin.<sup>9</sup> Switching to alternative monotherapy is more time consuming and requires careful clinical monitoring. It is easier to add a second drug, and if there is some clinical improvement, as occurs in up to one third of patients, it is tempting but possibly erroneous to assume that improvement is due to the combination rather than to the second drug. Such thinking perpetuates the phenomenon and scale of polytherapy.<sup>2</sup> Furthermore, combination therapy increases the risk of side effects, including teratogenicity,<sup>10</sup> especially if the drugs are similar (for example, carbamazepine and oxcarbazepine) or if they interact (for example, lamotrigine and valproate or carbamazepine).

In treating epilepsy in childhood, similar problems arise. Compared with adults, however, children have a much higher incidence of idiopathic generalised epilepsy syndromes, for which some standard or new drugs, such as carbamazepine or vigabatrin, may be

inappropriate. In addition, fewer of the new drugs have been licensed for use in children, and comparative data on different drug treatments are even scarcer.<sup>11</sup>

The pharmaceutical industry finances 90% of all clinical trials in the UK.<sup>12</sup> But industry has no interest in supporting large scale, long term pragmatic trials that might provide evidence to reduce much unnecessary polytherapy and therefore restrict the market for many of the newer drugs. Academics specialising in epilepsy will therefore have to clarify, through research, how much real progress has been made in managing resistant epilepsy since the era of phenobarbital and phenytoin.

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Competing interests: None declared.

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## The burden of chronic kidney disease

*Is rising rapidly worldwide*

The number of patients with chronic kidney disease worldwide is rising markedly.<sup>1</sup> In the United Kingdom, the annual incidence of end stage renal disease is around 100 per 1 000 000 population.<sup>2</sup> This incidence has doubled over the past decade and is expected to continue to rise by 5-8% annually, but it remains well below the European average (around 135/1 000 000) and that of the United States (336/1 000 000).<sup>3</sup>

Disparities in the incidence of end stage renal disease within and between developed countries reflect racial and ethnic diversity. In the US, the annual incidence is 256/1 000 000 in white people compared

with 982/1 000 000 in African-Americans.<sup>3</sup> In Australia, the incidence in white people is comparable to that in the UK (94/1 000 000), but the incidence in aboriginals is 420/1 000 000.

The rise in end stage renal disease worldwide most probably reflects the global epidemic of type 2 diabetes and the ageing of the populations in developed countries, with a higher incidence in elderly people (the annual incidence in people over 65 in the UK is greater than 350/1 000 000,<sup>2</sup> and in the US it is greater than 1200/1 000 000).<sup>3</sup> The number of people with diabetes worldwide, currently around 154 million, is set to double within the next 20 years, and the increase will be

most notable in the developing world, where the number of patients with diabetes is due to reach 286 million by 2025.<sup>4</sup>

The cost of treating patients with end stage renal disease is substantial and poses a great challenge to provision of care. In Europe, less than 0.1% of the population needs renal replacement therapy, which accounts for 2% of the healthcare budget. In the US, the annual cost of treatment for end stage renal disease is expected to reach \$29bn (£17bn; €25bn) by 2010.<sup>1</sup> Few countries will be able to meet these growing medical and financial demands; five countries—the US, Germany, Italy, Japan, and Brazil—with 12% of the world's population—already treat more than half of the world's people with end stage renal disease.<sup>5</sup>

More than 100 developing countries, together with a population in excess of 600 million, do not have any provision for renal replacement therapy.<sup>5</sup> Consequently, more than a million people die every year worldwide from end stage renal disease. The huge disparity in the prevalence of this disease between the industrialised world and emerging nations reflects different priorities for health care and the inadequacy of resources allocated to renal replacement therapy.

Programmes to detect chronic kidney disease, linked to comprehensive primary and secondary prevention strategies, are needed urgently. Successful examples of such programmes have been shown in developed and developing countries; in the Netherlands, the prevention of renal and vascular end stage disease (PREVEND) screening programme detected albuminuria in around 6-7% of the population of the city of Groningen.<sup>6</sup> In India's Chennai province<sup>7</sup> and in the aboriginals of the northern Australian territories,<sup>8</sup> the detection of chronic kidney disease and predisposing conditions such as diabetes and hypertension led to effective interventions. In Singapore, the national kidney foundation has launched a nationwide comprehensive screening and detection programme for chronic kidney disease.<sup>9</sup>

Patients with end stage renal disease comprise only a small percentage of people with chronic kidney disease.<sup>10</sup> The total prevalence of chronic kidney disease may be 50 times that of treated end stage renal disease. In the US, up to 11% of the population (19 million) may have chronic kidney disease.<sup>10</sup> Surveys in Australia, Europe, and Japan show that the prevalence of at least some degree of this chronic disease is 6-16%.<sup>11</sup> Population based studies show that 6-7% of the population has albuminuria (or microalbuminuria) and around 0.6-0.7% proteinuria.<sup>11</sup> The prevalence of chronic kidney disease is even higher (16%) when those at risk, including relatives of patients with the disease, are screened.<sup>12</sup>

Mass population screening for chronic kidney disease with tests such as urinalysis is neither practical nor likely to be successful or cost effective. Yet most clinical practice guidelines now recommend identifying those at risk—people with hypertension, diabetes, obesity, and other predisposing conditions or medicines as well as older people and relatives of patients with chronic kidney disease.<sup>13</sup>

Screening of urine samples with dipsticks for albuminuria and proteinuria is useful as long as it is confirmed by quantitative spot urine analysis for albumin:creatinine ratio or protein:creatinine ratio.<sup>13</sup> These

tests are more accurate than those based on the analysis of 24 hour urine collections in view of the inaccuracies of the latter. Serum creatinine is a readily available and reliable indicator of chronic kidney disease but it may be altered by a variety of factors, and renal function may be compromised considerably before serum creatinine concentrations rise. Reporting of serum creatinine is nowadays often linked to that of a calculated glomerular filtration rate.

Structured and well resourced primary prevention programmes based on reducing the risk factors for chronic kidney disease could make a big difference.<sup>11</sup> Patients should be encouraged to give up smoking and to lose weight. Secondary prevention depends on tight control of blood pressure (to less than 130/80 mm Hg)<sup>9 14</sup> and the use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers concomitantly to reduce proteinuria (to less than 1g/24 hours). Guidelines also recommend strict control of diabetes with an HbA1c level of around 7%.<sup>13</sup> Statins may benefit patients with chronic kidney disease through preventing arteriosclerosis. Such a multifactorial approach to risk reduction may slow or even reverse declining renal function.<sup>15</sup>

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Competing interests: None declared.

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