Primary Care in the NHS

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Published for the APCGT by: Scorpio Publishing Limited, 5-8 Brigstock Parade, London Road, Thornton Heath, Surrey CR7 7HW.

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FOREWORD

The NHS Trusts Association (formerly the Association of Primary Care Groups and Trusts) is delighted to present the 2004 edition of Primary Care in the New NHS, the latest edition published by the APCGT.

In line with the National Service Framework on Diabetes it is delighted to include several important articles on this subject. Diabetes costs the NHS the largest single financial item. Estimates place it in the region of £10 billion per annum. Approximately 500,000 sufferers, diagnosed or not yet diagnosed, require constant supervision, management and treatment, not just for the condition but its complications. Eye conditions such as cataract and retinopathy, vascular disease, involving the coronary and renal arteries and neurological conditions producing impotence.

The increasing incidence of type 2 diabetes, partly originating from obesity and lack of exercise, provides a challenge for all of us involved in primary care in terms of prevention. Primary care is taking increasing responsibility for the diagnosis and management of stable diabetes. To this end the increasing involvement of diabetic nurses is to be welcomed.

The Association is delighted to announce the publication of the NHS Directory of Complementary and Alternative Practitioners in response to demands from general practitioners and the interest of the public in complementary and alternative medicine. As a result of this initiative, the Association is discussing with the Prince of Wales Foundation for Integrated Health future development within the NHS of the use of complementary and alternative medicine.

As a member of the Department of Health screening group on the development of Codes of Conduct for the employment of overseas doctors in the NHS, the Association hopes that a similar code can be developed for CAM practitioners. The Association is suggesting this proposition to the Department of Health because the Association is fortunate in already having had discussions with the various statutory and non-statutory bodies involved, as well as various politicians of political parties.

The Association welcomes the proposed increased use of pharmacists in not just advising but also prescribing drugs previously prescribed by doctors. This is particularly of value for repeat prescriptions. Those who have travelled abroad know value of the local pharmacist in diagnoses of treatment of medical condition. As a former examiner in medicine for the Society of Apothecaries, I would be delighted to see a return of the "Apothecary".

All these developments will increasingly reduce the workload of the individual GP. With increasing use of nurse specialists, counsellors and nurse practitioners, there is no reason why the GP list of patients should not rise above 2,000. This will help alleviate the problems created by the manpower shortage in general practise.

Other developments are taking place such as the increased development of part time general practise. One practice with over 20,000 patients has 20 partners, another the appointment of a principal partner operating 2 sessions per week. Do these partners/principals have lucrative sources of income outside the NHS? These various types of practise offer our future GPs various options and not just self-employed or salaried, full time or part time. The Association welcomes the opening of the new undergraduate medical schools in those areas where teaching and research have not been a feature.

These will increasingly play a major role in providing improved postgraduate facilities for GPs and primary care teams. To this end the postgraduate medical school at the University of Surrey in Guildford is to be welcomed.

All these medical schools face the problem of medical student selection. Perhaps the answer is to demand not 'A' levels but the Baccalaureate examination with its broad curriculum demands. Medical schools must provide facilities not just for teaching, but also for research, the funding for which is becoming an increasing problem. It is alarming therefore to read that of £600,000 reserved monies for the NHS directed to clinical care, two thirds go to London teaching hospitals. Should this be correct, why should the London medical schools have the icing on the cake? As an Edinburgh graduate who practiced for some 40 years in London, I hope this state of affairs will not continue indefinitely.

The recent proposed transfer of responsibility for GP clinical tutors to the local primary care trusts does not seem encouraging either for teaching or research in general practise. Increasingly the NHS sees doctors as service providers provided by medical schools, hospitals and general practise. Research and teaching no longer seems to have the value they require if quality is to be maintained. This is because the Department of Health and Education seem unable to deal with the problem of funding research and teaching in our medical schools and universities.

Finally, the new GP contract, far from solving problems, seems to be creating new ones. Watch this space. I recently met the new opposition team on health headed by Tim Yeo, well meaning, intelligent and committed to the NHS but at the same time hoping for more money for healthcare to be available from the private sector. Is this a solution? I don't see the political parties proposing any solutions to those problems and solutions suggested by Professor Dyson (see Review).

Finally, I would like to thank all our contributors, the editorial staff and my secretaries Pamela and Maggie for their hard work in making this edition possible.

Dr E D Macrae Tod OBE FRCGP
Editor & Chief Executive, NHSTA.

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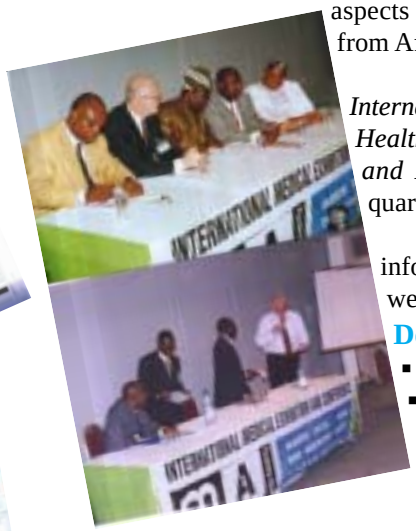

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The Importance of being Earnest & Creative

GPs, Nurses & Allied Health Professionals with Special Interests: an opportunity for PCTs

Ram Dhillon

Primary Care Trusts (PCTs), Workforce Development Confederations (WDCs) and a raft of other organisations are charged with assessing local healthcare needs and allocating resources, within the framework of national NHS policies. One particular aim is to examine the present workforce resources and see if improved healthcare can be delivered by introducing new ways of working.

Upwards of 75% of NHS financial resource will be distributed via PCTs. Mechanisms to both assess and deliver needs will be paramount but the one element that cannot be lifted off a shelf are individuals with requisite skills. Enhanced knowledge, but particularly acquisition of clinical expertise needs time and additional resources.

GPs with a Special Interest (GPwSI) and likewise Nurses (Nurse Consultants/Practitioners) and Allied Health Professionals (AHPs) are seen as vital components that will deliver the agenda. An agenda which rains from the DOH, from demand management, improving patient access, shortening care pathways to National Service Frameworks (NSFs). The healthcare model will have to alter substantially to include the above groups. However, the risk is that simply inappropriate re-labelling of the workforce, without supporting activity to gain required skill levels, will undermine this unique opportunity to do things differently. An individual deemed worthy of carrying such titles and the consequent responsibilities will have considerable influence on development of healthcare and will be important Key Opinion Leaders (KOLs) for the New NHS.

Central Policy

The current administration has made success in fulfilling its promises to the electorate on the NHS an essential plank for re-election. A tropical rainfall of such promises, include, more consultants and nurses, national service frameworks, new GP and consultant contracts, reducing waiting lists, revalidation and the creation of GP specialists.

In the NHS Plan 2000,[1] a short paragraph indicated the development of "GP Specialists" to practise at an Intermediate Tier level of Care. There was, as with most policy statements, a strategic vision, with little indication of details for implementation. Who precisely would be GP specialists? How would they be trained and accredited? Where would they practise? What would be the line of clinical accountability? There was no specific mention of Nurses or AHPs, groups that could assist in delivering the Healthcare envisaged.

Serendipity appears to have made this policy statement one that is both achievable, but more importantly, as having potentially huge benefits for delivering huge swathes of the " New NHS ".

Reaction to GPwSI

Reactions to GPwSIs were predictable. These ranged from "GPs are specialists in Family Medicine" through "This is secondary care work being pushed into an under resourced primary care sector", to "An increase in Secondary care specialists is what is required."

A significant minority of GPs were already practicing as " GP Specialists, " as were some nurses with the status of Nurse Consultant/Practitioner. These individuals had acquired and could demonstrate an enhanced level of services and skills in areas such as asthma, diabetes and ophthalmology. Innovative individuals and PCTs had developed frameworks for intra and inter practice referrals.

Some GPs were employed as clinical assistants in local specialist hospital departments. However, the pool of professionals with established enhanced skill levels was clearly finite and too small to have a major long term impact to the degree demanded by central and local policy. The future lay in investment in supporting up-skilling across the 3 main groups initiating and providing the majority of care in the NHS i.e. GPs, Nurses and AHPs.

The Royal College of Practitioners (RCGP) and the Royal College of Nursing (RCN)has recognised that this concept will continue to develop and are now actively involved in producing some generic frameworks for training and accreditation, and this is also being duplicated by various sections of the NHS Modernisation Agency.

Who is the one with a Special Skill in Primary Care?

The generally accepted definition is "*Someone who has developed enhanced skills so as to provide a variety of extended services in a primary or intermediate tier level care setting*". The RCGP have produced a more comprehensive definition although it is intended only to apply to GPs. However, it can be modified to define the individual who is a Nurse or AHP.

Definition of GPs with Special Interests (GPwSIs)

"General Practitioners with Special Interests supplement their important generalist role by delivering high quality improved access services to meet the needs of a single PCT or group of PCTs. They may deliver a clinical service beyond the normal scope of general practice, undertake advanced procedures or develop services. They will work as partners in a managed service not under direct supervision, but keeping within their competencies. They do not offer a consultant service and will not replace local consultants or interfere with access to consultants by local general practitioners."

The special interest could be defined as a procedure e.g. cystoscopy, excision of simple skin lesions, or the delivery of a range of healthcare services across a particular specialty e.g. cardiology, ENT, diabetes, urology, ophthalmology.

How are Special Skills to be acquired?

There is already a pool of Special Skills, and the individuals will be relatively easily identified and already utilising them for patient services. However, this pool is small and for the de novo professional the relevant clinical expertise must be acquired through structured experience or by following appropriately accredited training courses. This process will of necessity be a combination of core knowledge (anatomy, pathophysiology)and clinical skills (history taking, examination and diagnostics/procedural skills). A variety of such Postgraduate Diploma courses are now offered across a range of clinical areas (see appendix).

Training de novo will be time and resource hungry. The investment will however, ensure that the skills will enable new ways of working to be implemented and have an impact on delivering the various agendas.

It is absolutely essential that there is involvement of the local hospital specialty team in the training and in any accreditation panels convened to look at individuals with existing enhanced skills. Such involvement will facilitate the vital axis of trust, expertise and communication across primary and secondary care sectors. All these are aspects that are essential in providing the integrated patient services essential for the success of the NHS Plan.

What are the benefits of Special Skills?

The raising of standards of clinical expertise will allow numerous stakeholders to share benefits. For the NHS, generally, these professionals will be a pool of medical resource, equipped to deliver an extended range of clinical services. In effect these skilled personnel will be delivering care at an " Intermediate Tier Level, " in a facility that is considered suitable at a local level e.g. specially resourced practice, community hospital, a diagnosis & treatment centre, polyclinic.

Primary Care Trusts (PCTs) will have an appropriately trained clinical workforce which can help deliver the numerous targets set by central policy and respond appropriately to local healthcare needs e.g. implementing NSFs, improving patient access, managing demand, increasing throughput and clinical activity. *By encouraging and supporting training to develop special interests and skills, the PCTs will be better placed to retain and recruit not only GPs but also nurses and AHPs.*

Practitioners will see their extended skills enhance professional status and allow self-development. It will provide opportunities for greater involvement in service development as the PCT will be able to consult with the local specialty practitioner(s) and local hospital specialists in decisions affecting local healthcare delivery.

The ultimate benefactors – the patient

The patient will derive the major benefit with the introduction of these specialty practitioners. Experience shows an impact on numerous measurement parameters e.g. improvement in waiting times, more streamlined care pathways, increase in one stop consultations in primary care. Extended skills will reduce the numbers needing hospital services and as a consequence assist in hospital waiting times. Patients will be seen in locations with which they are familiar, find less threatening and near to home. The secondary care sector will be dealing with patients, in the main, who require specialist expertise.

The general view of the politicians and many health care commentators is that the PCTs are ideally placed to deliver more cost effective healthcare in local settings. GPwSIs, Nurse Consultants/Practitioners are a vital piece within the mosaic of components that will bring this to successful fruition.

A real integration of primary & secondary care

The skills required for this Intermediate Tier Level Care work needs to be acquired from local hospital specialists. The relationships engendered during skills training will evolve into an important primary/secondary care axis. This axis will be in a position to provide the PCT with advice on the format and delivery of healthcare, in formulating guidelines and referral criteria. Structures related to clinical governance, continuing professional development and audit will be more easily devised. **With these specialty practitioners there will be, for the first time, an opportunity to effectively integrate across primary and secondary sectors** with individuals on both sides having a true understanding of the patients' and their own professional needs.

The politics

Major resources appear to be available for projects and schemes that enable delivery of targets set in the NHS Plan. There are a myriad of agencies e.g. WDCs, Care Group Working Teams etc, who have funds to support projects. Reformatting of the delivery of care by blurring the boundaries between primary and

secondary care, with the creation of an intermediate tier level of care, would seem to be logical and sensible, and in reality can have positive benefit across a range of objectives.

Such a tier MUST be adequately staffed with properly trained and accredited practitioners and would assist in achieving many of the national goals with specific local modification to reflect the locality health economy. Details around exact work patterns, location of facilities and remuneration can be agreed between the local stakeholders.

Practitioners with special skills and hospital specialists

The hospital clinical fraternity is in constant turmoil with its relationship to NHS policy, due to the frequent government determined structural changes. Many millions of pounds can be expended in an attempt to realign, restructure, audit, govern, facilitate, appraise, revalidate etc. This cycle of change has been a regular feature for over 25 years and there is no sign of it abating.

The present government's policies are a myriad of initiatives and directives. The sensible approach would be to identify what, amongst all the rhetoric, ideas, pronouncements, documents and spin, is reasonable, generally backed by the professional groups and likely to be supported by the public. At this time the development of GPs, Nurses and AHPs with Special Interests is a winner in most respects.

It is therefore vital that clinicians, in primary and secondary care, recognise this major reformatting of healthcare delivery. **The axis of the primary care practitioner with special skills and the local hospital specialist team will be fundamental to the success of many government, PCT and clinical ideals. It would be a negation of responsibility to ignore this extraordinary opportunity.**

Summary

- Providing Intermediate Tier Level Care through Practitioners with Special Interests is a workable model.
- Such Practitioners will be needed if PCTs are to deliver national and local healthcare agenda targets.
- Developing Special Skills is a win-win for all parties, the individual, the healthcare economy and the patient.
- PCTs will need to take a lead role in the support and development of such a programme of skills enhancement.

References

1. The NHS Plan – a plan for investment, a plan for reform. DOH, London 2000
2. Implementing a scheme for general practitioners with a special interest. DOH and the Royal College of General Practitioners; London 2002.

Appendix

Further information on a range of Postgraduate Diplomas, specifically devised to develop Special Interests/Skills in GPs, Nurses and AHPs, is available at www.pgdip.com and click on the relevant discipline in the general info box on the home page. All diplomas offered are validated and quality assured by Middlesex University, London and accredited and endorsed by the Royal college of General Practitioners and the National Association for Primary Care (NAPC). The courses are offered through Rila, a collaborative organisation of Middlesex University.

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A Book Review by Dr David Tod

Why the NHS Will Fail and What Should Replace it?

Author: Professor Roger Dyson

In this fascinating book, he examines the present state of the NHS, in particular the problems created by encouraging public and professional dissatisfaction with the services provided. He points out that league tables, performance management and clinical targets expose the inequality and variation throughout the NHS.

He points out the problem of equity caused by the diversity and the failure to publicise the imbalance between public demand and the professional services.

He points out that many of these problems are created by the shortage of consultants, General Practitioners, medical scientists, radiographers and nurses. He points out that the use of 'rationing' is a process political parties dare not use. PCTs may end up by informing the public "you either pay for this – or go without".

He points out that the lack of social service support for hospitals is dependant on the presence or absence of local nursing or residential homes. He is highly sceptical of much of the extra funding of hospitals and points out that the long standing recommendations of the Royal Colleges of Physicians and Surgeons for their rationalisation have been largely ignored for political reasons.

His analysis of the 'demographic time bomb', i.e. falling numbers due to poor recruitment, increasing demand and impending massive numbers of retiring doctors, medical scientists, midwives, nurses and others, makes frightening reading. He further envisages the problems created by the August 2004 EEC Directive reducing the hours worked by trainee registrars.

Professor Dyson suggests some solutions – increasing the number of sub-specialists, whether in surgery, medicine, general practice or nursing. He is sceptical about the ability of PCTs and patient forums to achieve a balance in determining its expenditure. He is even more sceptical about foundation hospitals and their increasing uptake of NHS revenue.

He berates our educational system, which encourages university training for over 50% of the population, discouraging plumbers, electricians and nursing. He suggests that if young people want to take 'a year off' to do good overseas by voluntary work, why not do such work in the UK?

Finally, he points out that due to their impending retirement during the next five years nearly a quarter of GPs will not be replaced by existing trainees, even if half of these GPs are persuaded to continue. He points out to solving this shortage by using more nurses will merely aggravate the nursing shortage in hospitals!

Professor Dyson rightly describes the problems within the NHS which affect us all. Whilst many of his recommendations have merit, regretfully I see little use being made of them, mainly because firstly they involve more hospital closures. Even if quality of service is the result, distance will remain a problem (political as well as geographic). Secondly, increasing use of overnight consultants in hospitals. Thirdly, the increasing use of self-employment contracts for all grades of staff – from consultants to porters.

One conclusion from reading this most interesting and informative book is that the practice of medicine will become increasingly interesting, but not an easy option to media studies or hairdressing.

I can recommend it to any practitioner interested in knowing more about the present state and future of the NHS.

Dr E David Macrae Tod OBE FRCGP
Editor & Chief Executive, NHSTA (Formerly APCGT)

Why the NHS Will Fail and What Should Replace it?

Author Roger Dyson

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If you, or someone in your practice, can't work through illness, the right financial protection can make sure your income stays healthy.

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If someone in your practice becomes incapacitated, the kind of replacement cover you can expect depends on the kind of financial protection your practice has in place. Likewise, the level of income each staff member can expect over the long term depends on the cover they've arranged for themselves.

Protection for your practice

Practice Protection is the most effective way to make sure your practice continues to run smoothly in the event that you or one of your staff is absent due to sickness. It covers the cost of employing a replacement for you or anyone in your practice, from a receptionist or nurse to a manager or GP, for the period of the absentee's illness (up to a maximum of 52 weeks). However, choosing the right cover can make for a tough decision, particularly when definitions of disability and the amount and length of cover vary from policy to policy. For example, while you may not be fit to return to your practice, your insurer may feel that you are well enough to take a different kind of job elsewhere. In that case, how would your practice cope with the inconvenience and expense of hiring a new member of staff?

One company with an excellent reputation is Medical Sickness. They have years of experience in working with medical professionals, combined with a clear understanding of a practice's needs; which helps them to offer tailored policies that provide the right level of cover.

Whether you need a locum or a temporary receptionist, a protection policy can help you pay for a fully qualified replacement, allowing you to meet your patients' needs with minimum disruption. In one practice, for instance, £587 a week was paid in locum expenses to cover a GP's absence due to receiving treatment for depression (52 weeks* in total).

Personal income protection

Practice Protection is essential if you want to keep staffing levels at your practice constant, but what about your own income in the event of illness? Depending on your practice agreement, you could receive sick pay for a set period of time. However, any long term illness or serious accident that leads to a prolonged absence could mean that one day the money runs out. If you work in private medicine, you may even have nothing more than your own resources to rely on.

That's why Medical Sickness offers a personal Income Protection plan tailored to medical professionals. The payments can cover up to 50% of gross income for as long as you are off work. Plus, the benefit is tax free and index linked to beat inflation.

Even if you can only return to work part time, a policy through Medical Sickness may still be able to help you meet your financial responsibilities. If ill health means you have to work fewer hours, with a lower salary, you might still be able to claim some benefits to make up the shortfall.

One GP, who was paid full benefit as he underwent a hip replacement, still receives 66% of his Income Protection after going back to work for just 10 hours a week.*

Helping doctors back to work

Naturally, if someone falls ill, all they really want to do is recover quickly and carry on with the career they've chosen. The Income Protection cover available through Medical Sickness takes this into account as the policy is an 'own occupation' plan. Benefit will not stop until the claimant is fully able to work in his or her own job. Which means they'll receive payments until they can resume work once again.

Specialist financial solutions

It's probably because the company was founded by doctors for doctors that Medical Sickness can offer such support for practices and individual medical professionals. Doctors still sit on the advisory committee today; while over 70,000 medics hold policies and receive financial advice.

Results that speak for themselves

In 2002, 95% of new claims were paid out through Medical Sickness with over 1,600 claimants still being paid after six months*. The total benefit paid amounted to £34.32m worth of payouts compared to £32.83m in 2001†.

In short, these figures suggest that, for a monthly premium, policies through Medical Sickness can provide stability and peace of mind for you and your practice. Long term illness or a serious accident can be as unexpected as they are unwanted. But at least here you might be able to find a protection plan without any nasty surprises.

For more information on Practice Protector and Income Protection plans through Medical Sickness, call 0870 411 9212 or visit www.medical-sickness.co.uk

*Wesleyan actual claims history 24.03.03. †Up to a maximum benefit of £93,600 each year. This information is based upon our understanding of current taxation legislation, which could change in the future. This information is intended to assist you with making your choice about your financial arrangement. It does not give you financial or professional advice, if you are in any doubt please contact us for advice.

Medical Sickness

Don't let illness affect your income.

If you or a member of your practice are incapacitated through an accident or illness, Medical Sickness can help make sure your finances are taken care of.
We offer practice protection plans that can help pay for temporary cover if you're unexpectedly short-staffed.
And personal income protection plans that can help make sure you can afford to take time out and still meet your financial responsibilities and commitments.

To find out more, make an appointment with a Medical Sickness consultant by calling 0870 411 9212 or visit www.medical-sickness.co.uk

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When you are looking for a business partner, you instinctively make your decision based on some fundamental requirements. Who can you trust? Who understands your needs? Who is a specialist in their business and will be fair with you? Who can you rely on to help you day to day and who will stand by you in a crisis too?

Business Partner, a specialist finance division of Ford Credit, is proud to have been providing a solution to these requirements for our customers in the NHS for over a decade. As Ford Credit is wholly owned by Ford Motor Company we operate exclusively using the Ford family of brands, Ford, Mazda, Land Rover, Jaguar and Volvo. By focusing solely on these brands, we have been able to build an enviable reputation in our ability to assist customers. This starts with the initial product decision-making process, and continues with our flexible approach during the contract period right through to the end of that contract.

In addition to the Ford Motor Company's dealer network, Business Partner also offers you access to Rapid-fit and Kwik-fit and ancillary services such as RAC roadside services. Just as our NHS partners choose us with care, similarly we have taken time to choose the partners that are part of our proposition to you. We believe this proposition has developed and matured, offering our customers class-leading value for money.

Value for money is as important in today's fast moving environment as it ever has been. We daily need to evaluate cost vs benefits in a whole range of products and services – whether in our home life or in the office. Business Partner's loyal customers have made that cost vs benefits equation and have subsequently been rewarded by choosing Business Partner as their finance provider.

As a long-standing supplier to the NHS, Business Partner is pleased to continue to offer our services to their members and associates. Our association began in 1988 and since that time, we have developed a very close working relationship and a detailed understanding of what is required by the members of the NHS. This ensures that you are able to feel completely confident that our finance products relate to your specific needs

Ford Motor Company has a long history of manufacturing cars, this is our 100th year, and of providing finance for our customers too. Our founder Henry Ford, who brought motoring to the mass market with the famous Model T, launched the "Universal Credit Company" in 1928 to provide finance for his customers. In 1959 the Ford Motor Credit Company was formed and it is now the largest automotive finance company in the world. We operate in 36 countries around the globe and have provided finance to more than 11 million customers for over 50 million vehicles.

Ford knows that their customer's satisfaction with the vehicles and finance package they offer is fundamental to their success. This is why Ford has always kept the customer uppermost in their mind and indeed their current product line up bears testament to this. So what do our customers think of Business Partner? A recent independent Leasing company survey revealed some interesting data when compared to 17 other Leasing companies:

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Achieved delivery promise	**1st**
Alternative transport arrangements	**1st**
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Dealer repair relations	**1st**
Communication regarding contract termination dates	**1st**
Attitude regarding "fair wear and tear"	**1st**
Attitude regarding over/under mileage	**1st**
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Attitude to early terminations	**1st**
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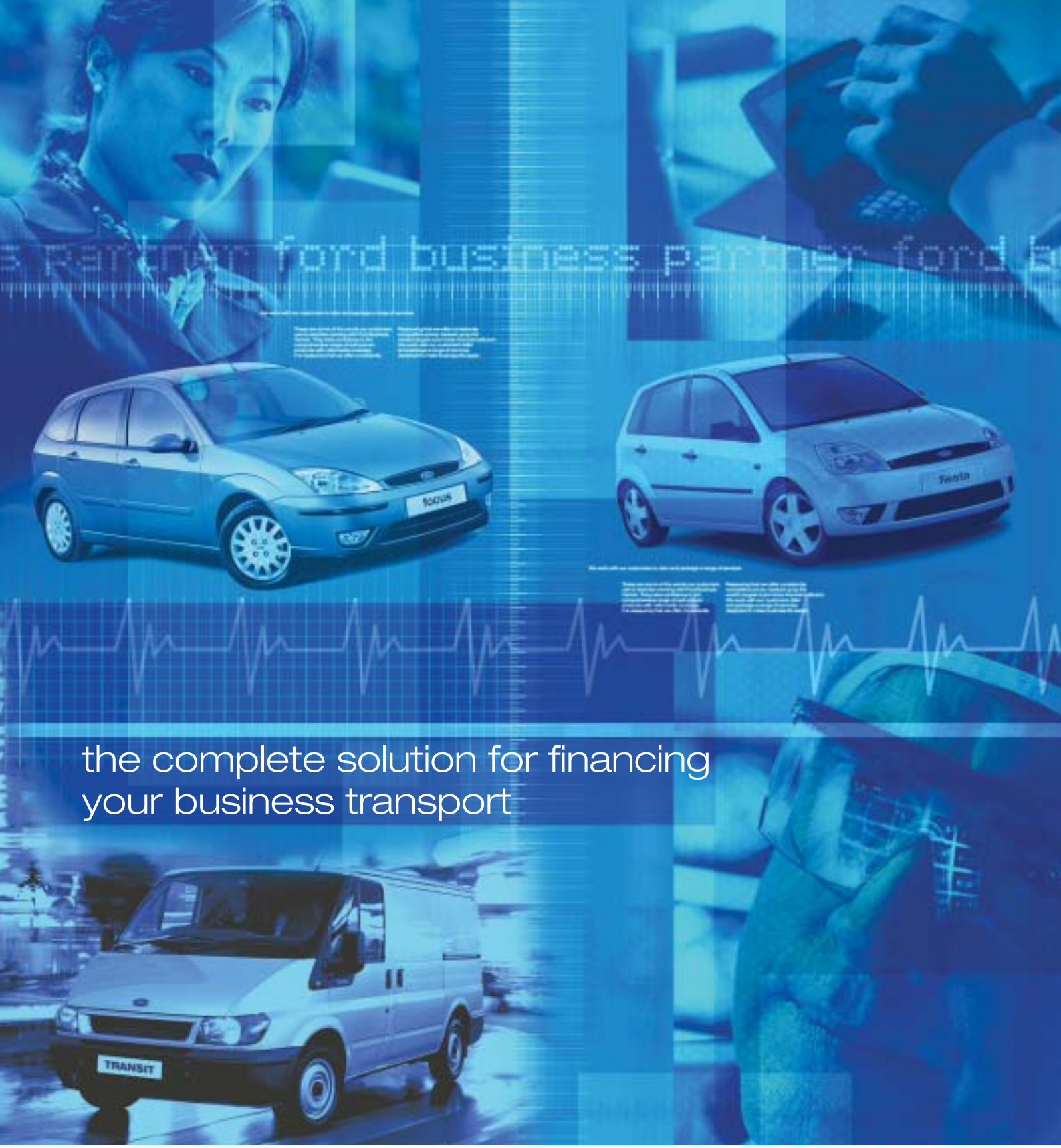
As Ford enters its second century we are proud of our achievements and aware of the need to continue providing the best service we can – especially to our customers within the NHS. If we are not already working with you we hope we will soon have the chance to show you that the real value of a partner is someone you can trust and someone you can rely on.



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Inheritance Tax

Yet Another Tax on Middle England

Chris Marney

Inheritance Tax used to be a tax on the so-called "Rich and Famous". In the past it has been called a voluntary tax as many people took appropriate measures to mitigate it. The increasing wealth of Middle England, particularly the huge house price increases and the fact that IHT allowances have not kept pace with the increases, means that more and more people have estates that will be subject to IHT. Also, as a percentage, fewer people are doing anything about it as there is a misconception that costs of expensive city solicitors means Estate Planning is just not worth it. This is incorrect. Whilst not cheap, Estate Planning is readily available and can save your loved ones hundreds of thousands of pounds.

The Nil Rate Band, up to which IHT is taxed at zero per cent, has increased very slowly over the years and currently stands at £255,000. Every year there are demands that it is substantially increased, to perhaps £400,000, although these demands have fallen on deaf ears. The fact is that, for a married couple, the Nil Rate Band is effectively £510,000 already! This is as long as some simple steps are taken to ensure tax allowances are fully utilised. It is at this point we will look at how an estate of £610,000 need pay little or no IHT and we will then move on to look at what can be done for the estates far above that figure, particularly where the house value is substantial.

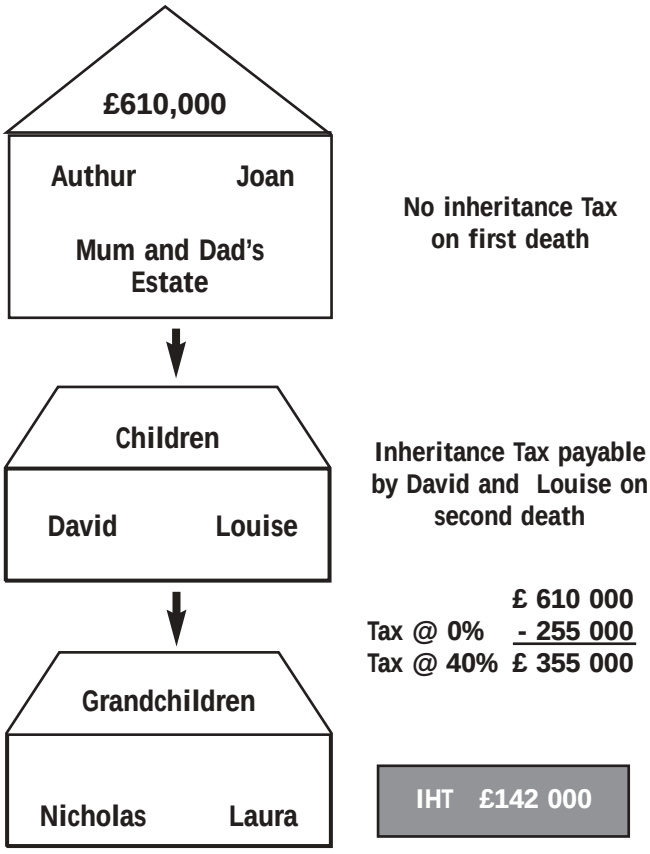
An excellent method of ensuring tax allowances are fully utilised is the use of Discretionary Trust Arrangements.

A Married Couples Discretionary Trust Arrangement is designed to achieve the following objectives:

- Reduce the amount of inheritance tax your beneficiaries will have to pay;
- Ensure this is achieved whilst, at the same time, retaining total control in your own hands;
- Ensure your estate passes to those for whom it is intended;

Figure 1. A typical example

- Mr & Mrs Jones' house is valued at £300,000 and other investments bring the total estate to £610, 000.
- Mr & Mrs Jones have made Wills, leaving everything to each other and then to the children.
- They have two children and two grandchildren



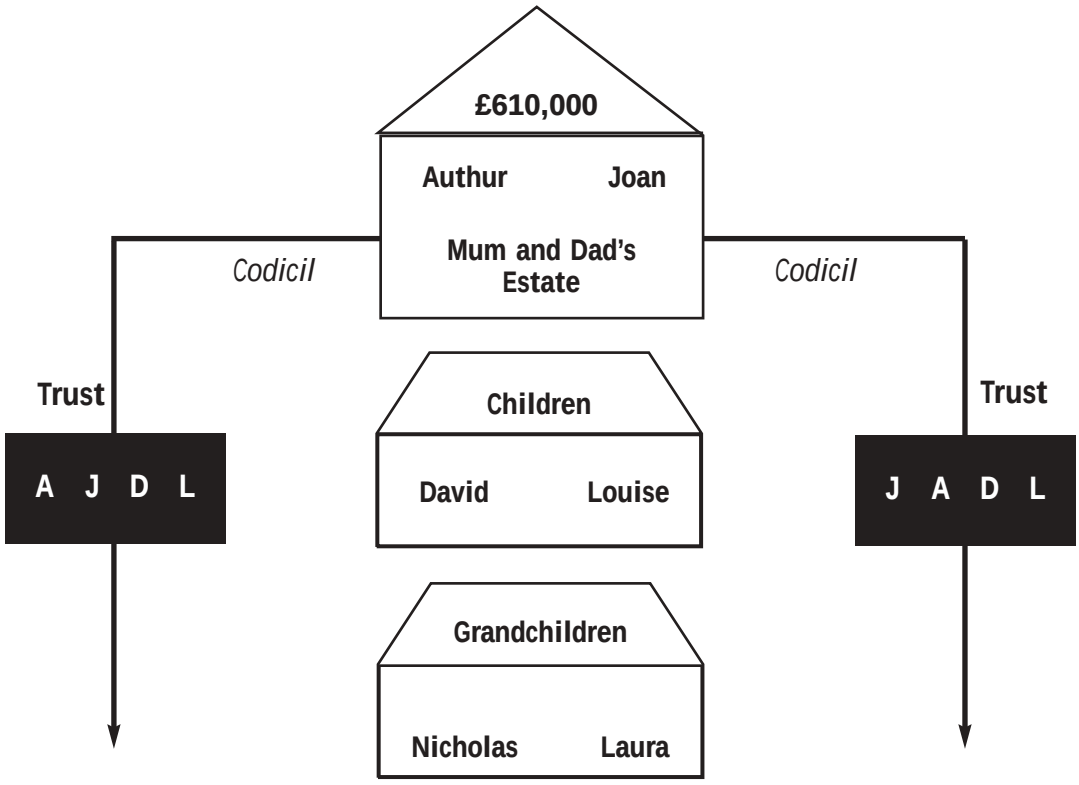


Figure 2a. A Discretionary Trust Arrangement

- Ensure the estate is not taxed again and again as it passes down the generations;
- Protect as much as possible from means testing in respect of later life care costs.

As can be seen in figure 1, Arthur and Joan's children are faced with an inheritance tax bill of £142,000. In addition, the whole of the estate will be subject to means testing in respect of the survivors later life care costs. The solution is a Discretionary Trust Arrangement.

As can be seen in figure 2, we have set up two trusts. These are designed to take a Nil Rate Band of inheritance tax (currently £255,000) on death, via a Codicil to the Wills into Trust to ensure both partners take advantage of their IHT allowance. Without this arrangement the first person to die has thrown away their Nil Rate Band entitlement. It is a Family Trust Arrangement, with Arthur and Joan and their children being the Trustees.

When Arthur dies, instead of everything going to Joan's estate, a Nil Rate Band is transferred/conveyed into his Trust (figure 2b). Joan and her children/grandchildren have total access to the Trust although Joan has overall control. This is achieved by making Arthur and Joan the appointors of their own Trusts during their lifetime and then the deceased partner's Trust after first death. In effect they have the power to hire and fire Trustees. The assets in Arthur's Trust are not included in Joan's estate for means testing for later life care costs.

After Joan's death the inheritance tax payable by David and Louise has been reduced to £40,000 as the £255,000 in Arthur's Trust is not included in her estate. This results in a saving of £102,000. In addition the assets transferred into the Trusts are:

- Not included in David and Louise's estates in the event of a divorce claim or attack from their creditors;
- Not included in David and Louise's estates for inheritance tax calculation when they in turn pass it to their children.

The initial objective has been achieved and we can now look at saving the rest of the £40,000 IHT bill that David and Louise still have to find.

During their lifetime, Arthur and Joan can make gifts or loans to their Trusts to further reduce their IHT liability. In this example the IHT liability is £40,000. It may of course be far more although the principles are the same.

You can make annual gifts of £3,000 that are immediately free from IHT. Any gift above £3,000 and you need to live for seven years before it is free from IHT. You can of course give money directly to your children. This is fine if your children need the money. If they do not, giving them money to reduce your IHT liability is only dumping the problem on them and you certainly lose control. It is better to gift to the Lifetime Discretionary Trusts that have been set up. Whilst you cannot benefit from capital or income from any gift you make, you retain control and can distribute capital

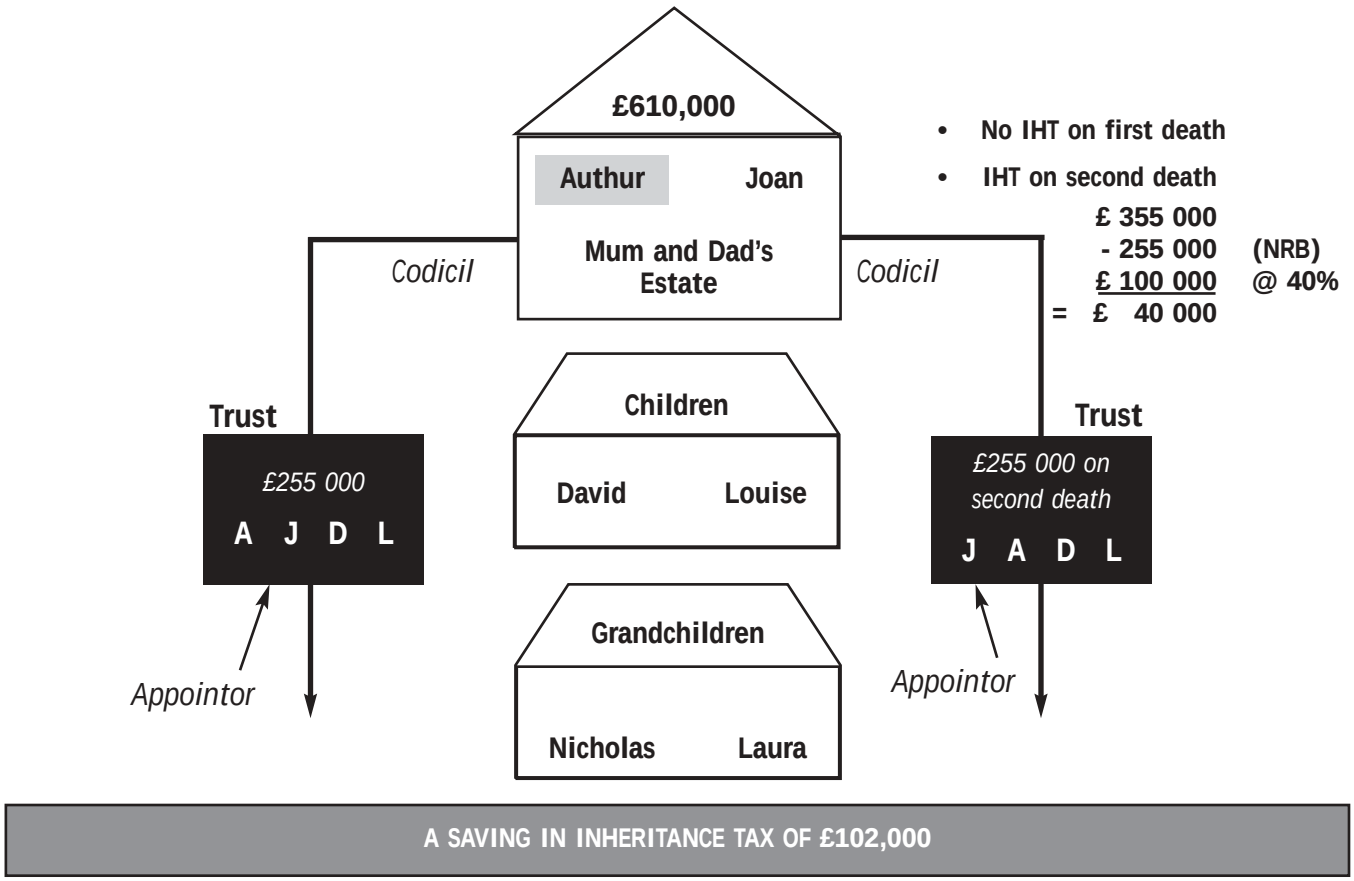


Figure 2b.

or income to the beneficiaries at any time. It may be that you are thinking of paying for your grandchildren's education. If you gift £10,000 to them in ten years' time, it will be outside of your estate in seventeen years' time. If you gift the money to a Trust now, in effect park it there until it is required, it will be outside of your estate in seven years' time.

It may be that you do not wish to give up access to capital but still wish to create trust funds. In that case you can loan money to your Trust. The growth on any investment the trustees make with the loan proceeds are immediately free from inheritance tax. You have access to capital on demand. Whilst any outstanding loan balance remains in your estate for IHT purposes, many people gradually reduce the loan over, say, 20 years, through regular loan repayments.

For many estates, setting up Discretionary Trust Arrangements and utilising them for gifting and/or loaning will totally negate the IHT liability. For the larger estates this is much more difficult, especially if the main residence forms a significant part of the estate. You cannot simply give your house away, even to a Trust, and continue to live in it unless you pay a market rent, which can be very expensive. There are schemes that remove the value of your family home from your IHT liability. After losing in the courts recently, the Inland Revenue passed a law that effectively put paid to one of these schemes known as a defeasible interest trust arrangement. At the time of writing, whilst new schemes are not possible, existing schemes were not affected. Estate Planning companies such as Trust Matters Ltd are constantly looking at new arrangements for the family home and it is always worth checking with us.

In conclusion, Estate Planning can help all estates reduce or eliminate their IHT liabilities, no matter what the size. All estates and family situations are different and it is best to ask the experts for tailor made solutions. It should be noted that, whilst our example relates to a married couple, we do have solutions for single people as well.

Chris Marney, ACIB is General Manager, Trust Matters Ltd.

THE TRUST MATTERS GROUP

Estate Planning Specialists

Trust Matters Ltd have many arrangements to eliminate or drastically reduce the inheritance tax liability on your estate, no matter how large it is.

Our objectives are:

- **To reduce or eliminate the amount of inheritance tax your beneficiaries will have to pay.**
- **Ensure this is achieved whilst, at the same time, retaining total control in your hands.**
- **Ensure your estate passes to those to whom it is intended.**
- **Ensure the estate is not taxed again and again as it passes down the generations.**

NO MATTER HOW LARGE YOUR ESTATE IS

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Allergies In Children

Dr Stuart F Wood

It is perhaps worth noting that it was in fact a paediatrician who first used the word "allergy". Clemens von Pirquet, an Austrian, was working at the time at John Hopkin's Hospital in Baltimore about 1906. The limited range of disease seen in children when compared with adults certainly includes allergies along with infections and accidents. Children may present with conditions which are clearly allergic eg seasonal rhinitis secondary to pollen allergy but may also suffer from symptoms which are more commonly attributed to infection eg catarrh but which may have more of an allergic aetiology than is sometimes thought. This relationship between allergy and infection in children is an interesting and important one. The concept of "allergic inflammation" is a relatively recent development and has implications for our understanding of the pathophysiology of allergies and for our thoughts on therapeutic intervention. **The increase in prevalence in allergies and asthma in children** has been the focus of much attention in recent years.

Although asthma in adults does not always have a clear relationship with allergy, children with **asthma** are usually allergic to the common house dust mite, dermatophagoides pteronyssinus and often to a range of other allergens such as cats and grass pollen. On the basis of its frequency and potential severity, therefore, asthma must be considered the major allergic disease of children. **Allergic rhinitis and allergic conjunctivitis** are also common in children. They frequently co-exist as part of the syndrome described as "hay fever" The "**ARIA guidelines"** have proposed a different classification for rhinitis.

Although eczema is often present in atopic children who also suffer from asthma and hay fever, it is really **urticaria** which is the truly allergic skin condition, certainly in terms of it's mediation through the Type I immune reaction. **Atopic eczema** is even more complex to understand and in terms of management, for example, the use of antihistamines in eczema has a very limited role when compared to their place in the management of urticaria.

Bite and sting reactions are important mainly because of their ability to cause an **acute anaphylactic reaction**. Peanut ingestion may provoke a similar serious reaction via the oral route although the topic of **food allergies** in general is a difficult one and confused by misunderstandings and misconceptions. **Drug allergy** also has the potential for causing acute anaphylaxis but once again this diagnostic label is often applied inappropriately. Many children who have simply had a minor adverse event to penicillin, in particular, have subsequently been denied the benefits of the drug at a later date. It takes a brave doctor who chooses to challenge such a label subsequently, however, for fear of the risk of provoking anaphylaxis having been "pre-warned"

Some conditions of childhood are often considered more as infections than as having an allergic component to a greater or lesser extent. These include **rhinorrhoea, catarrh and sinusitis as well as otitis media.**

The increase in prevalence in allergies and asthma

The possible protective role of childhood infections ("the hygiene hypothesis")has aroused much interest. It is proposed that increased hygiene combined with a reduction in the infections of childhood resulting from immunisation and the use of antibiotics in early life has led to an increase in the prevalence of hay fever (and other atopic diseases including asthma) This effect of childhood infections is thought to relate to their role in favouring a type 1 helper T (Th1) cell response rather than the Th2 response associated with hay fever (and asthma). Children exposed to a range of infections, bacterial or viral, including, for example, measles or hepatitis A, may be less likely to develop hay fever.

The size of families and sibling order are also relevant with children who have more older brothers or sisters being less likely to be hay fever sufferers and vice versa. This is presumed to be the result of the increased likelihood of exposure to a range of childhood infections. Children who are born during the hay fever season are more likely to be sufferers themselves as a result of stimulating a Th2 rather than a Th1 response. Birth month (May-June) has been shown to be a significant risk factor for rhinitis in subjects whose age at onset was under 20 years.

The populations of the former East Germany and West Germany have attracted interest. These populations are considered to be of similar genetic background and there has been an in increase in prevalence of hay fever in those living in the east of Germany after re-unification.

The role of atmospheric pollution has also been considered, and, in particular, the role of diesel particulates. Studies of 12-15 year olds, carried out in Bochum and in Munster, in Germany, have shown a positive correlation between traffic density and allergic rhinitis.

These epidemiological findings are not only of interest in explaining the increasing prevalence of hay

fever; prevention of hay fever rather than treatment might become a real possibility. if the protective effect of poorer hygiene and childhood viral and bacterial infections can be reproduced in some safe and acceptable way

The increase in prevalence does however remain largely unexplained.

Asthma

The diagnosis of asthma in childhood is, of course, a clinical diagnosis. This means that there is a balance to be struck between having a healthy index of suspicion in order not to miss cases while trying to be careful to avoid overdiagnosis. The recently published British Guideline on the Management of Asthma (from the Scottish Intercollegiate Guidelines Network and the British Thoracic Society) has sections which deal separately with children aged 5-12 years and with children under 5 years.

The Guideline suggests, for both of these age groups, that "Asthma should be suspected in any child with wheezing, ideally heard by a health professional on auscultation, and distinguished from upper airway noises." It further is suggested that the diagnosis of asthma in children is based on:

- "the presence of key features and careful consideration of alternative diagnoses
- assessing the response to trials of treatment, and ongoing assessment
- repeated reassessment of the child, questioning the diagnosis if management is ineffective"

The "stepwise management" of asthma is also revised in this new Guideline with children aged 5-12 years and children under 5 years dealt with separately.

Step 1 (mild intermittent asthma) is the same for both age groups – inhaled short-acting beta-2 agonist as required.

Step 2 (regular preventer therapy) is very similar for both age groups – Add inhaled steroid 200-400mcg/day (BDP or equivalent) Start at dose of inhaled steroid appropriate to severity of disease. For children aged 5-12 years it is suggested that 200mcg is an appropriate starting dose for many patients

Another preventer drug is advised if inhaled steroid cannot be used. In children under 5 years it is suggested that a leukotriene receptor antagonist is added if inhaled steroid cannot be used.

Step 3 (add-on therapy) for children aged 5-12years, suggests adding a long-acting beta-2 agonist (LABA). If the response to LABA is good, continue, if control is still inadequate, continue LABA and increase inhaled steroid dose to 400mcg/day (if not already on this dose). If there is no reponse to LABA and increased inhaled steroid dose institute trial of other therapies, eg leukotriene receptor antagonist or SR theophylline. In children aged 2-5 years the guideline suggests considering a trial of leukotriene receptor antagonist but in children under 2 years consideration should be given to proceeding directly to step 4.

Step 4(persistent poor control), for children under age 5 years means referral to a respiratory paediatrician. Step 4 for children aged 5-12 years is – increase inhaled steroid up to 800mcg/day.

Step 5 (continuous or frequent use of oral steroids) is relevant only to children aged 5-12 years – Use daily steroid tablet in lowest dose providing adequate control. Maintain high dose inhaled steroid at 800mcg/day. Refer to respiratory paediatrician.

Allergic rhinitis and allergic conjunctivitis

The main therapeutic options in allergic rhinitis and allergic conjunctivitis are antihistamines, oral and topical, and nasal steroids. Cromones have a part to play in allergic conjunctivitis but are disappointing in allergic rhinitis.

The oral antihistamines used are increasingly from the "newer generations". Cetirizine, desloratadine, loratadine, are available in syrup as well as tablet form. Levocetirizine is only available in tablet form. Cetirizine, desloratadine and loratadine are licensed for use from age two years, levocetirizine from age six years.

The topical antihistamines available are azelastine and levocabastine (nose and eye), and antazoline (with xylometazoline) (eyes only)

Eye drops containing the cromones sodium cromoglycate or nedocromil sodium may be helpful in allergic conjunctivitis as may drops containing emedastine or lodoxamide.

Nasal sprays of beclomethasone, mometasone and triamcinolone are licensed for use from age six years, fluticasone from age four years and flunisolide and dexamethasone(with tramazoline) from age five years.

The "ARIA guidelines"

The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines have suggested a new classification for allergic rhinitis. A new subdivision of allergic rhinitis has been proposed: Intermittent andPersistent.

"Intermittent" means that the symptoms are present less than 4 days a week or for less than 4 weeks.
"Persistent" means that the symptoms are present more than 4 days a week and for more than 4 weeks.

The severity of allergic rhinitis has been classified as "mild" and "moderate/severe" depending on the severity of symptoms and quality of life outcomes.

"Mild" means that none of the following items are present:

- Sleep disturbance;
- Impairment of daily activities, leisure and/or sport;
- Impairment of school or work;
- Troublesome symptoms.

Table 1

Age	Dose	Volume of adrenaline 1 in 1000 (1mg/ml)
Under 6 months	50 micrograms	0.05ml
6 months – 6 years	120 micrograms	0.12ml
6-12 years	250 micrograms	0.25ml

"Moderate-severe" means that one or more of the following items are present:

- Sleep disturbance;
- Impairment of daily activities, leisure and/or sport;
- Impairment of school or work;
- Troublesome symptoms .

Urticaria and Atopic eczema

Although sometimes grouped together under the heading of "allergic skin diseases" urticaria and atopic eczema are really very different problems. In brief, urticaria usually responds to oral antihistamines and sometimes necessitates long term treatment. The search for the responsible allergen is usually fruitless. Atopic eczema in a child may prompt a parent to pursue complex searches for avoidance or therapeutic interventions. These too are usually fruitless. the liberal use of emollients can not be overstressed. Fortunately, exacerbations usually respond well to the use of topical and systemic antibiotics aimed at reducing bacterial colonisation of the skin.

Acute anaphylactic reaction

Acute anaphylaxis may result from **bites and stings** (especially bee and wasp stings), from **food allergy** (especially peanut allergy) and from **drug allergy** (especially penicillin antibiotics). Attention to the airway and maintenance of blood pressure and the administration of intramuscular adrenaline form the cornerstone of treating the acute anaphylactic reaction. The doses of adrenaline for children are given in table 1.

These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse and respiratory function.

The antihistamine chlorpheniramine may also be given by slow intravenous injection over 1 minute. (unlicensed indication) The doses are:

Under 1 year	**250 micrograms/kg**
1-5 years	**2.5-5mg**
6-12 years	**5-10mg**

Rhinorrhoea, catarrh, sinusitis and otitis media

It is often assumed that these conditions, associated with the upper respiratory tract, are infections of a viral or bacterial nature only. It is wise to keep an open mind about the possible role of allergy in their aetiology. In some children, an anti-allergic approach ie with antihistamines and/or intranasal steroids may result in a gratifying improvement in the child's symptoms and well-being.

Stuart Wood MD FRCGP is a General Practitioner in Glasgow and Senior Lecturer in General Practice at the University of Glasgow. He is Senior Partner in a practice of 4,800 patients in West Glasgow where he has been since 1977. He has a long-standing interest in asthma, allergic rhinitis, antihistamines, inhaled and nasal corticosteroids, and in therapeutics in general. His research interests are currently focused on inhaled steroids in asthma and on the effect of improving house ventilation in maintaining reduced house dust mite populations in the homes of asthmatics.

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A Guide to Diagnosing and Treating Allergy

Jane Lucas & John Warner

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The prevalence of allergic disorders has increased in children and adults over the past three decades. The allergens associated with these diseases are everywhere – in the air we breathe, the food we eat and even the beds in which we sleep. Symptoms range from rhinitis, asthma and skin rashes to life-threatening anaphylaxis. Allergies cause severe impairment to the quality of life of individuals, and add to the socio-economic burden of the whole community. Recent advances are refining our approach to diagnosis and treatment and may lead to prevention strategies. Greater public awareness is required to improve current disease management.

The role of the physician is to determine the importance of allergy in the symptoms of their patient. In some patients this may be a simple decision on the basis of a good clinical history, but many patients require specialist allergy testing to aid accurate diagnosis. For the purposes of this review and indeed the medical profession as large, the medical term 'allergy' is confined to an inappropriate reaction of the immune system to an otherwise harmless substance. The mechanism is commonly IgE mediated although sometimes cell mediated mechanisms are responsible. However, some apparently allergic diseases may have no underlying allergic cause. Seasonal rhinitis (hayfever) is entirely IgE mediated, however, only 50%

Therapy	Specific Allergy	Comments
Allergen Avoidance	Single food Animal dander	Complete avoidance usually possible
	House dust mite Multiple foods	Complete avoidance difficult Allergen reduction possible
	Pollens Moulds	Almost impossible
Immunotherapy	Pollens Wasp and bee venom	Only for severe disease unresponsive to other treatments.
Drug prophylaxis	Asthma	Corticosteroids, sodium cromoglycate, leukotriene antagonists
	Rhinitis	Non-sedating anti-histamine, topical antihistamine/ sodium cromoglycate/ corticosteroid
		Topical anti-histamine/ sodium cromoglycate/ corticosteroid.
	Conjunctivitis	Non-sedating anti-histamine, emollients, topical corticosteroids.
	Atopic dermatitis Multiple food allergies	Oral anti-histamine. Oral sodium cromoglycate.
Drugs for acute reactions	Depends on severity of reaction	Adrenaline Sedating anti-histamine Systemic corticosteroids Bronchodilators

Table 1 Management of allergic disorders

of perennial (chronic) rhinitis is allergic in origin. It is unusual to identify a causative factor in chronic urticaria, and many patients with food related symptoms have 'intolerance' rather than a true IgE mediated, or even cell mediated, allergy.

Diagnosis

The clinical history is central to the diagnosis of allergic patients, with additional diagnostic tests as adjuncts. The patient may easily identify the responsible allergen if the reaction is acute and rapid in onset (e.g. peanut allergy). Similarly, patients allergic to environmental allergens such as cat, if there is not constant domestic exposure, may identify acute reactions within minutes of exposure.

Seasonal variation in symptoms may aid diagnosis. Rhinoconjunctivitis in early spring suggests tree pollen allergy, but in autumn fungal spores may be responsible. For many allergy sufferers the relationship between exposure and response is not so clear. This is particularly the case where chronic exposure occurs, for example to house dust mite. The history identifies potential exposures such as domestic pets, as a guide to subsequent allergen testing.

The principle components of allergen testing are skin prick tests (SPT), specific IgE antibody measurements, usually by radioallergosorbant technique (RAST), and finally the gold standard of a double-blind, placebo-controlled challenge. Occasionally allergens produce symptoms in a non-IgE mediated response. In such circumstances SPTs and IgE antibody measurements will be unhelpful. Avoidance and subsequent challenging can diagnose such allergy or intolerance.

Most European allergists and physicians initially use SPTs to identify the allergens suspected on the basis of the clinical history. The quality of the allergen extract and the expertise of the physician in the performance and interpretation of the SPTs are paramount. The test relies upon the presence of sensitising antibodies on subcutaneous mast cells. When the allergen is introduces into the skin, the antigen cross-links IgE antibodies if they are present, releasing mediators including histamine from the mast cell. A wheal-and-flare reaction appears which can be measured after 15 minutes. Since the wheal is dependant on histamine release, drugs that affect histamine will invalidate the test. Patients should not be on anti-histamine treatment at the time of testing and a positive control (usually 1% histamine) should be used. A positive control wheal diameter of less than 5mm in a child over 4 years usually invalidates the test. If the negative control produces a wheal, the patient has dermatographism and the results cannot be interpreted. The value of the skin test depends on the experience of the interpreter. The results must be related to the clinical history and physical examination.

The issue of false positives is pertinent. Many patients show sensitisation on SPT without having clinical disease and decisions about treatment should therefore never be based on SPTs alone. For some acute food allergies, a skin wheal greater than or equal to the histamine control indicates approximately 85% certainty that an allergen will produce a response if the patient is challenge. However, patients with a grass pollen allergy have an increased chance of having a false positive skin test to wheat. Adults who had egg allergy as infants may continue to produce a skin wheal to egg white protein despite no ongoing disease.

A negative SPT response, with a wheal less than or equal to 3 mm diameter is associated with a negative challenge in 95% of cases. The size of the wheal does not predict the severity of allergic reactions. Although SPTs are extremely safe when performed correctly, adrenaline should always be available in case of anaphylaxis. In a patient with a history of severe allergy the allergen in the test solution should be diluted, or RAST should be used for investigation of the allergy.

Specific IgE antibody measurements can be made if specialist SPT facilities are not available, or if skin testing is not possible because of extensive skin disease or recent use of anti-histamine. It can also be used as an adjunct to SPT results if interpretation is difficult. For many allergens the negative predictive value of specific IgE is lower than for SPT. The blood test is expensive and there is inevitably a delay in obtaining a result. For these reactions SPTs are generally preferable to diagnose specific allergies.

A double-blind placebo-controlled challenge is the gold standard in the diagnosis of allergy. In some situations open challenges provide satisfactory results and are easier to perform. Challenge tests are indicated where there is some doubt about the diagnosis. For

- **Confirm allergic origin of disease** e.g. recurrent urticaria, perennial rhinitis.
- **Identify responsible allergen.** This is essential in patients with anaphylaxis.
- **Complex allergic disease** e.g. multiple food allergies.
- **To monitor changes in allergic status.** e.g. milk and egg allergy in childhood usually resolve.
- **Patients on self-imposed restricted diets** to liberalise diet if appropriate.
- **Immunotherapy**

Table 3 - When to refer to an allergist

example, where there is a suggestive history, but the SPT is negative. Challenge should only be conducted in a clinical setting where full resuscitation can be given, including intubation and ventilation, in the event of anaphylaxis. To perform an open challenge, initially a very tiny dose of the allergen is given. After observing for a reaction, doubling incremental doses are given until a reaction occurs or a reasonable threshold dose is reached. For food allergies an oral challenge[1] is performed, but for asthma or rhinitis inhaled routes are used. For the latter, late reactions, 3-4 hours after the exposure, are quite common. Therefore, prolonged observation is necessary.

Allergy Management

Avoidance of the allergen is central to the management of allergy (table 1). This is not always easy because of emotional attachment (e.g. pets) or sometimes even possible (e.g. avoiding airborne pollen). However is should always be possible to reduce exposure.

Patients with a risk of anaphylaxis always need strict avoidance measures to prevent exposure. For patients with symptoms from chronic exposure resolution of symptoms may take weeks after instigation of avoidance measures. Animal allergens remain in clothes and carpets sometimes for months after the domestic pet has been removed, and vigorous efforts are needed to remove this reservoir of allergen if confidence in the treatment is to be sustained. To be effective, avoidance measures should be applied at home, in school or in the workplace i.e. other children in the classroom who have pets should not sit next to the allergic individual.

Avoiding exposure to house dust mite (HDM) can partially relieve symptoms in patients with mite-related asthma, although complete avoidance is not possible in temperate climates. Measures to reduce HDM concentrations, particularly in bedrooms should be made. These include frequent cleaning using a vacuum cleaner with a good filter, hot-washing bed linen and use of specific covers for the mattress, quilt and pillow. Ideally carpets should be removed and soft furnishings kept to a minimum.

Patients with pollen allergy should keep windows and doors closed during the day when the pollen count is high. Pollen levels are usually lower near the sea than in the country, when choosing holiday destinations. Washed bed linen should not be hung outside to dry when pollen counts are high.

Significant advances have been made in the last 20 years in the drug treatment of allergic diseases. Non-sedating anti-histamines (e.g. cetirizine, loratadine) do not cross the blood-brain barrier and, unlike older anti-histamines, do not cause drowsiness. Their use is well established in treating seasonal and perennial rhinitis, chronic urticaria and atopic dermatitis. They may be of use in the treatment of atopic asthma,[2] and evidence is accumulating that they may even prevent asthma developing in some children with existing atopic dermatitis.[3] Sedating antihistamines (e.g. chlorpheniramine) confer benefits in acute reactions where mild sedation is therapeutic.

Key Points

- The prevalence of allergy is increasing
- Allergic diseases include food allergy, atopic asthma, atopic dermatitis and seasonal rhinitis.
- The diagnosis is usually made on the basis of the clinical history and examination, with skin prick tests or specific IgE measurements as adjuncts.
- The gold standard investigation is a double-blind placebo-controlled challenge.
- Avoidance of the allergen is central to the management of allergy.
- Intra-muscular adrenaline must be used in the treatment of anaphylaxis.

Topical antihistamines, sodium cromoglycate and corticosteroids are prescribed for allergic rhinitis and allergic conjunctivitis. Nasal spray treatment is preferably started 2-3 weeks before the hayfever season commences and may have to be continued for months or even years in some patients.

Atopic asthma is a chronic inflammatory disease of the airway, involving complex and interdependent immunological events. The airway inflammation is present even in the absence of severe symptoms, and requires treatment with anti-inflammatory drugs such as inhaled corticosteroids, sodium cromoglycate and theophyllines. Leukotriene modifiers (e.g. montelukast, zafirlukast) are an entirely new class of anti-inflammatory drug, which entered clinical practice in 1996-97. They block inflammatory pathways that are not effected by corticosteroids and are valuable as supplements to corticosteroids in symptomatic patients. Patients with atopic dermatitis and rhinitis also benefit from treatment with a leukotriene antagonist. Immunotherapy has been used in the treatment of allergy for 90 years.[4] Progressively

Age	Volume of 1 in 1000 adrenaline
Under 1 year	0.05 ml
1 year	0.1 ml
2 years	0.2 ml
3-4 years	0.3 ml
5 years	0.4 ml
6-12 years	0.5 ml
Adult	0.5-1 ml

Table 2. Volume of adrenaline injection 1 in 1000 for intramuscular injection in anaphylactic shock. These doses may be repeated every 10 minutes until improvement occurs.

increasing doses of the allergen to which the patient is sensitive are administered, usually by subcutaneous injection. Once the maximum dose is tolerated, treatment is continued, often for 3 or more years. Subcutaneous immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma and allergy to wasp and been venom.[5] Further studies are needed to evaluate oral, inhaled and sublingual routes. Immunotherapy has been associated with adverse events including death. Its use should therefore be reserved for patients with severe disease (but not asthma) where avoidance is impossible and pharmacological treatment has failed. Such circumstances include anaphylaxis to bee or wasp venom, and severe rhinoconjunctivitis resistant to other treatments.

Most allergy is managed by primary care providers. Many patients will benefit from assessment by a specialist allergist, to clearly identify responsible allergens before undertaking often expensive and difficult avoidance measures. This can usually be achieved with one or two visits. Occasionally patients with more complex problems require on-going specialist advice. (Table 3) All patients on nutritionally restricted diets, particularly children, require assessment by a dietician.

Acute allergic reactions

All medical practitioners should be competent in the treatment of acute allergic reactions. It is the responsibility of the physician prescribing rescue medication for severe acute reactions, to ensure that the patient and their carers understand the principles of avoidance and the practical treatment of an acute reaction, including intra-muscular adrenaline and cardiorespiratory resuscitation.

In the case of an acute reaction a rapid assessment should be made of whether it is severe, remembering that mild and moderate reactions can progress to become life threatening. Urticaria and angioedema (not involving the throat or airway) are not life threatening but if the symptoms are troublesome should be treated with anti-histamine.

Laryngeal oedema is a medical emergency and requires the urgent administration of intra-muscular adrenaline and oxygen if available, followed by a transfer to hospital. If available inhaled adrenaline is also effective for this manifestation. Anti-histamines are given secondarily to minimise the development of later symptoms.

Anaphylaxis is a life-threatening systemic reaction. Patients become flushed and may have urticaria, angioedema and purities. They may develop stridor or a hoarse voice, and severe bronchospasm. Severe abdominal pain is also common. As they develop hypotension they feel faint and may collapse. They will be tachycardic with a weak pulse. Untreated anaphylaxis causes death, but rapid treatment is nearly always effective. Rarely reactions will be fatal even when treatment is given; avoidance of known allergens by sufferers is therefore paramount.[6]

Where possible the provoking cause of the anaphylactic reaction should be removed. They key to successful resuscitation is the early administration of intra-muscular adrenaline. People known to be at risk of anaphylaxis should always have two pre-assembled auto-injectors of adrenaline available (e.g. Epi-pen). A second injector is necessary because adrenaline is rapidly metabolised and improvement may not be sustained. Also, a second dose is needed if there is no clinical improvement after 5-10 minutes. If a pre-assembled pen is not available, a 1:1000 solution of adrenaline should be given by IM injection (Table 2). If available, oxygen should be administered, and the patient must be transferred to hospital by ambulance. Anti-histamines and corticosteroids are not beneficial in acute anaphylaxis, but are given for at least 24 hours after a reaction to prevent late symptoms. Anti-histamines and corticosteroids must never be used as a substitute for adrenaline in laryngeal oedema or anaphylaxis.

Conclusions

The increasing prevalence of allergic disease would appear to be a genuine phenomenon. We now understand some of the allergic mechanisms involved in diseases such as asthma, and this has aided diagnostic and therapeutic procedures. Current research may also explain the increase of allergic diseases in the Western world and help us establish preventative measures.

With the high prevalence of allergic disease all practitioners must be competent in the initial evaluation and treatment of these disorders, managing the underlying allergy as well as prescribed symptomatic relief. In addition, some patients will need referral to a specialist allergist for further evaluation and management.

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Hypertension Guidelines – A Survival Guide

Dr Sarah Jarvis

Some of us have been waiting for years for the New GMS Contract.[1] For those of us committed to providing high quality care, the lack of remuneration for quality has been incredibly frustrating. In challenging areas with high consultation rates, practices have effectively been forced to decide between providing a high quality service to a small (but demanding) practice population, and providing a minimal service to a large list. With remuneration so heavily skewed towards list size, GPs have effectively been financially penalised for providing high quality care.

Thus, the fiasco that resulted from the global sum allocation was worrying indeed. Inevitably, with GPs across the country likely to earn less for more work, the GPC negotiators and the NHS Confederation were forced to rethink. A compromise, in the shape of MPIG (minimum practice income guarantee), was finally agreed, and this allowed negotiations to proceed. In the event, the endlessly delayed ballot produced an 80% "yes" vote. But for many of us, the loss of confidence these financial miscalculations brought was just as disastrous as the flawed formula itself. Many GPs admit to having voted in favour of the contract not out of pure enthusiasm, or even the optimism with which many of us greeted the announcement of financial rewards for quality work. Instead, their primary motivator was the prospect of the government refusing, as it did after the consultants rejected their new deal, to negotiate any more.

In the confusion and alarm, many GPs, then, have lost sight of the principles that lie at the heart of the New GMS Contract. If their disillusionment with the process of negotiation had resulted in the contract being turned down, it would have been nothing short of a tragedy. As it is, many GPs will suspend judgement on the New Contract until they see it in operation.

Apart from the inevitable teething troubles, there is a good chance that in the medium term, GPs offering a high quality service will be convinced. For the fundamental concepts of the contract are sound, and offer, for the first time, the chance for GPs to satisfy both their vocations and their bank managers.

The commitment to high quality care that lies at the heart of the New GMS Contract is, for many, its most innovative aspect. Quality indicators are laid out in the smallest detail, and have been carefully thought through. Of course, the consequence of local variations in morbidity should have been factored in at the outset, and not negotiated as an afterthought. Of course, GPs with exceptionally high proportions of diabetics, hypertensives or other groups should not have to work harder for the same reward. But these problems look as if they may be soluble, now that formulae for calculating workload are based on practice figures and not some formula plucked out of the air by a bureaucrat in Leeds or Yorkshire.

It would have been a tragedy if primary care "threw the baby out with the bathwater". Quality indicators are the prime example, but other innovative aspects include increased freedom to implement skillmix and flexibility in service provision. For if we examine the quality indicators in details, we see that far from offering yet another set of targets to strive for, they could actually offer a framework to streamline our work.

The last decade has seen an ever-rising tide of clinical guidelines, protocols and National Service Frameworks (NSFs). Their aim has been to improve quality and consistency of care. When added to all the other changes heaped upon primary care, however, they are seen by many as simply adding to confusion.

Yet these guidelines, while addressing different clinical areas, have many overlapping themes. The sound evidence base for their conclusions can be inferred from the consistency of their targets. This consistency ensures that by striving towards one set of guidelines, we are effectively meeting another set without any extra effort.

Better still, the quality indicators in the New Contract bear a comforting resemblance to most of the existing guidelines. In fact, they appear to be based on existing guidelines for good practice, with a little leeway built in to allow for human factors (like poorly complying patients!) GPs who have been striving towards existing targets and guidelines can relax,safe in the knowledge that by meeting NSFs, we will qualify for quality indicators, too. And while the former may offer vocational satisfaction of a job well done, the latter will translate directly into remuneration.

Let us take, as an example, hypertension in the elderly. With 20-30% of the adult population[2] and more than 50% of over 65s[3] affected, it is the commonest medical condition in the UK. It is also one of the most rapidly changing. Less than twenty years ago, hypertension in the elderly was virtually never treated, with minimum figures for treatment of 200/100-120mm Hg.[4] Within a decade, it had become

clear that far from doing more harm than good, controlling hypertension in the elderly saved more lives than in younger counterparts.[5] Treatment when blood pressure consistently exceeds 160/100mm Hg, regardless of age, has become the norm.[6]

The NSF for Older people, then, recommends that older patients should not receive less stringent or less favourable treatment on account of their age.[7] The widely accepted Joint British recommendations for treatment of hypertension set a target figure of 140/85 mmHg.[6] The NSF for Coronary Heart Disease (CHD)[3] also recommends a target of 140/85mm Hg, or 130/85mm Hg for diabetics.

Management of hypertension also features prominently in guidelines for diabetes – not surprising, with CHD the leading cause of mortality in type 2 diabetics.[8] Thus the Scottish Intercollegiate Guidelines Network (SIGN) guidelines on Management of Diabetic Cardiovascular Disease support blood pressure control to 140/90mm Hg or below in diabetic hypertensives.[9] The National Institute of Clinical Excellence (NICE) guidance on blood pressure in type 2 diabetics sets a figure of 140/80mm Hg (or 135/75 in patients with microalbuminuria or proteinuria).[10] The NICE guidances on diabetic retinopathy and renal disease concur.[11, 12]

In fact, the quality indicators in the New GMS Contract are slightly less stringent. For hypertension in non-diabetics, a maximum figure of 150/90, achieved in 70% of diagnosed patients, will attract payment. For diabetics, the figure is 145/85mm Hg, met in 55% of patients.[1]

While the figures above show that there is still some discrepancy, it can be seen that by aiming for the most stringent criterion, all the others will be met. Thus the upper limit to aim for in non diabetics is 140/85, and for diabetics 140/80 (or 135/75 in those with diabetic renal disease).

Of course, conflict of opinion extends far beyond targets for elderly hypertensives. The best medication to achieve those targets is a matter of equally vociferous debate. Current guidelines favour thiazide diuretics or beta-blockers as first line therapy, if no contraindication exists.[7] The ALLHAT study backed this up.[13] Yet within months, a study comparing ACE inhibitors with diuretics in the elderly hypertensives found the former led to better outcomes, despite similar reductions in blood pressure.[14] The ACE inhibitors, like the Angiotensin II receptor antagonists (AIIRAs), act on the renin-angiotensin system of the kidneys. Studies comparing the two reveal additive benefits together and similar levels of efficacy apart, with AIIRAs better tolerated than ACE inhibitors.[15] There is also robust evidence that both groups have "added benefits" over and above their blood pressure reducing properties. These include slowed progression of diabetic nephropathy[15-17] and improved outcomes in heart failure.[18]

The largest study of elderly hypertensives in recent years, the SCOPE study, compared the AIIRA candesartan with other treatments. It, too, found the AIIRA to improve outcomes (a 28% reduction in non fatal stroke compared to controls) despite similar levels of blood pressure control.[19]

In fact, however, the debate about whether to use thiazides, beta-blockers, AIIRAs or ACE inhibitors as first line treatment for elderly hypertensives is largely academic. With blood pressure targets so much more stringent than a few years ago, the vast majority of these patients will need more than one therapy anyway. Even the ALLHAT study admitted that most patients needed more than one therapy to control their blood pressure adequately.[13]

Polytherapy, as well as increasing costs, reduces compliance.[20] The increasing trend towards integrated budgets for primary care means that these costs can be offset by savings from improved morbidity figures. To improve compliance, however, it is essential that side effects are kept to a minimum and that complementary combinations are used.

In this respect, potassium losing diuretics and AIIRAs or ACE inhibitors are well matched. The potassium sparing effects of the last two will offset the first. As we have seen, AIIRAs (and to a lesser extent ACE inhibitors[15]) have a very favourable side effect profile. Not only does a low incidence of side effects improve compliance, it also fits in well with the aspirations of the elderly. A recent survey of elderly hypertensives[21] reveals them as an active group, deeply concerned about losing their independence as a result of illness.

With elderly patients so motivated to protect themselves against major morbidity such as stroke, improved patient education on the rationale for blood pressure control must surely help to secure their support in our efforts to keep them healthy. If we can ensure their co-operation, the battle is almost won.

Providing our elderly patients with the quality, as well as the quantity, of life they deserve will always be hard work. But the combination of consistent targets, remuneration for quality, motivated patients and well tolerated and effective drugs mean that it can be done.

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Homocysteine: An Important Breakthrough in Assessing Coronary Heart Disease Risk and Other Diseases

Most people are aware of the dangers of high cholesterol but who has heard about the dangers of elevated levels of homocysteine?

Heart disease is the biggest single killer in the western world and accounts for more than 125,000 deaths per year in the UK, yet approximately 70% of people who die from heart disease have normal levels of cholesterol.

Despite being one of the strongest predictors of CHD,[1] with more and more research showing homocysteine as a greater risk factor for heart disease than cholesterol, it is still relatively unknown in the UK.

What is homocysteine?

Homocysteine is a harmful, sulphur-containing amino acid that, when levels are raised, injures and thickens artery walls, increasing the risk of abnormal blood clotting.

However, homocysteine does not just cause arterial damage. A high accumulation reduces the body's ability to produce vital bio-chemicals that reduce your risk of developing a variety of conditions and diseases including Alzheimer's Disease, thyroid disease, Parkinson's Disease, problem pregnancies and even some cancers.

Homocysteine is measured in µmol/l and until the last few years it was believed a 'high' level was above 15 units. But now levels as low as 10 units are associated with a two-fold increase in heart disease risk while for each increase in the homocysteine level of 5 µmol/l, the Alzheimer's Disease risk is increased by 40%.[2]

Are your patients at risk?

- Family history of heart disease, strokes, cancer, Alzheimer's, diabetes;
- Male gender;
- Smoking;
- Excessive tea, coffee or alcohol intake;
- Oestrogen deficiency;
- Lack of exercise;
- Diabetes;
- Strict vegetarian or vegan diet;
- Poor diet.

Patients rely on medical professionals to recognise their risk factors and advise what tests and treatments are suitable. The American Heart Association recommends doctors to screen all high-risk patients with a personal or family history of heart disease for elevated homocysteine levels.[3]

Testing homocysteine levels

A simple homocysteine test will let you know what your patients risk is, allowing you to take the necessary preventative action to help reduce that risk.

Until recently, the only way to test homocysteine levels was to take a full venous blood sample (fasting) from which the plasma would need to be extracted within an hour and sent to a lab for analysis. This method requires speed and accuracy due to the volatility of the sample – and can also be expensive. A breakthrough by YORKTEST, a bioscience laboratory in York, now means that a stable sample of plasma can be taken from a simple pinprick blood test and returned to the lab for analyse at your convenience.

The British Cardiac Patients Association has welcomed this new testing method. A spokesperson has said, "*It is vitally important that people are informed about all of the possible risk factors of heart disease. The evidence emerging around the world about the risk of high homocysteine levels is overwhelming. However, information must go hand in hand with the availability of testing, and we welcome the YORKTEST initiative.*"

Lowering homocysteine levels

The good news is high homocysteine levels can be reduced to normal within two to three months simply and inexpensively using the correct combination of diet and vitamin supplementation. Clinical studies have shown that the most effective way of reducing levels is through supplementation of folic acid and vitamins B6 and B12 which are essential to the biochemical pathways that break down homocysteine.[4]

For a fact sheet on homocysteine, together with a research bibliography, contact **YORKTEST on freephone 0800 074 6185.**

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Improving Blood Cholesterol Levels

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- **The landmark Heart Protection Study [1] reported that prescribing statins to patients at increased risk of cardiovascular disease could reduce rates of heart attack and stroke by at least one third.**
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- **The Benecol range of foods can be a useful option for patients on cholesterol lowering medication to help lower cholesterol levels further without necessarily increasing their dosage. [2,3]**

Background

- 70% of UK adults have elevated cholesterol levels (above 5.2mmol/l).[4]
- Benecol's cholesterol-lowering ability is supported by over twenty studies, published in peer reviewed journals.[5]
- A 1% reduction in cholesterol may lead to a 2% reduction in coronary heart disease.[6]

Benecol®

Landmark Heart Protection Study calls for new guidelines

The widely reported, five year Heart Protection Study followed more than 20,000 adults aged between 40 and 80 with coronary disease and other types of arterial disease or diabetes. It showed that statins may have substantial benefits for people with "normal" or "low" blood cholesterol concentrations who may be at risk of heart disease for other health reasons, rather than only those with established heart disease. The Heart Protection Study concluded that by tripling the number of patients on statins, heart attacks and strokes in Britain could be cut by at least one third.

Benecol & Statins - A complementary action

The role of plant stanol ester, Benecol's cholesterol lowering ingredient, in reducing cholesterol as part of a healthy diet is already well proven.

Importantly, a number of studies also demonstrate that the addition of plant stanol ester to the diet of patients on statins can produce a reduction of 10% in LDL cholesterol levels over and above the cholesterol lowering effects of statins used alone. [2,3]

Whilst statins work by slowing down the production of cholesterol in the liver, plant stanol ester can have a complementary effect - reducing blood cholesterol levels by decreasing cholesterol absorption from both dietary and biliary sources in the small intestine.

The additional 10% reduction is clinically significant and may exceed the expected 6% reduction in LDL cholesterol achieved when doubling the dose of statins.[2]

This is encouraging news for healthcare professionals, as the Benecol range of foods could help patients on statins to achieve the recommended cholesterol levels, by easy dietary steps, without necessarily requiring an increase in dosage of their medication.

If you wish to receive further information about the Benecol range of foods please call on 0800 0184010 and quote AC06A, or visit our website at **www.benecol.co.uk**.

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The Benecol range is designed to encourage patient compliance to a cholesterol lowering diet through taste and variety, and comprises delicious low fat yogurts, spreads including Buttery Taste, Light and Olive varieties, light cream cheese style spreads and snack bars.

The Importance of High Density Lipoprotein Cholesterol

Dr Elizabeth Hughes

Cardiovascular Disease (CVD) remains the most common cause of deathamongst men and women in the United Kingdom. Current statistics from the British Heart Foundation estimate that 120,000 deaths from Coronary Heart Disease (CHD) in the UK occur every year.[1]

The death rate from CHD in the UK is one of the highest in the world and within the UK there are also regional variations in mortality from CHD, being highest in Scotland and lowest in the South of England.[1] Ethnic differences also prevail with South Asians living in Britain having a higher premature death rate from CHD than the national average - a disparity which is increasing.[1]

The role of Low Density Lipoprotein Cholesterol (LDL- C) in atherogenesis is well supported by a number of pathological experiments, epidemiological observations and clinical studies. The long term benefits of reducing elevated serum low-density lipoprotein (LDL) cholesterol levels in reducing coronary heart disease (CHD) morbidity and mortality have been demonstrated conclusively over the last decade by a series of clinical trials encompassing both those with and without coronary disease.[2-6]

Supported by this wealth of data, current guidelines such those of the Joint British Societies,[7] focus on LDL reduction as a strategy for reducing CHD. However although treatment with 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors (statins) has been shown to result in a reduction of approximately 30% in coronary events, 70% of patients at risk of myocardial infarction (MI) who received treatment in these 'statin' trials nevertheless still experienced coronary events (Figure 1). Thus to improve the reduction of coronary events with lipid lowering therapy, additional or alternative targets of the lipoprotein profile must be identified.

There is a strong relation between baseline HDL cholesterol and subsequent event rates present in statin treated patients in many of the trials. For example, the Cholesterol and Recurrent Events (CARE) trial[4] shows that coronary event rates decreased as baseline HDL cholesterol increased with a slope that was almost identical in both the statin-treated and placebo-treated patients.

In this trial whether they were actively treated or not, patients with low HDL-C continued to be at greater risk of CHD than their counterparts with higher levels of HDL-C (Figure 2).

The cardio protective effect of HDL cholesterol was first recognised in 1950,[8] since when population studies from many parts of the world have consistently reported that a low plasma level of High Density Lipoprotein (HDL) cholesterol is a strong predictor of CHD.[9, 10] The relation between HDL cholesterol and the incidence of CHD is curvilinear and mirrors that of the corresponding curve cholesterol as seen in the Framingham Heart Study. Low HDL cholesterol predicts CHD in both sexes (Figure 3) but the strength of the relation may be greater in women than in men.[9]

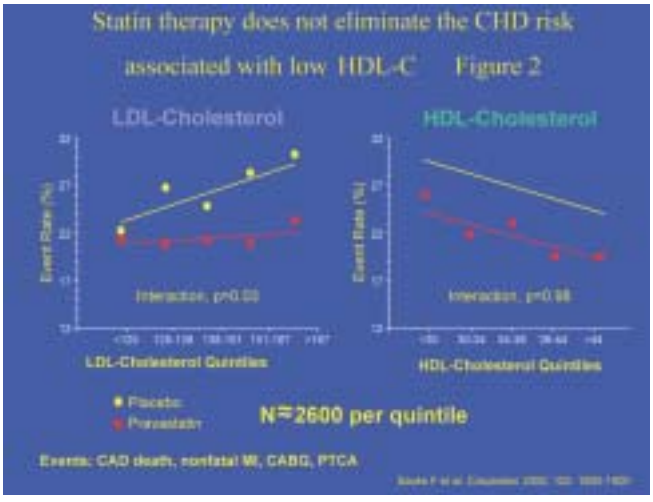
A meta-analysis of 4 large prospective epidemiological studies has demonstrated that an increase in HDL cholesterol of 0.026mmol/L (1 mg/dl) is equated with an independent risk reduction in the incidence of coronary events by 2 % in men and 3% in women.[9]

In the 4S trial[4] with simvastatin each 1% increase in HDL-C predicted a 1% reduction in coronary events (Figure 4). Thus low levels of HDL herald increased risk for CHD at all levels of LDL cholesterol and triglycerides across a wide spectrum of patients.

The beneficial effect of HDL cholesterol is believed to be derived primarily from its involvement in the

Events in the Major Prevention Trials (Figure 1)

Trial	N	# Events Control	# Events Statin	% Risk Reduction	% Events Not Avoide
4S/CARE/WOS/ AFCAPS/LIPID	30,817	2,074	1,537	26	74
HPS	20,536	1,212	898	26	74
PROSPER	5,804	356	292	18	82
ALLHAT	10,355	421	380	9	91
ASCOT	10,305	154	100	36	64
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]



He's drop dead gorgeous

(if you look closely enough)

"HDL may be the most consistent predictor of CHD in type 2 diabetes"[1]

The improved formulation of fenofibrate[2]

SUPRALIP® 160

fenofibrate 160mg film-coated tablet

Indications include dyslipidaemia in type 2 diabetes

SUPRALIP®160 ABRIDGED PRODUCT INFORMATION: fenofibrate 160mg film-coated tablets
Prescribing Information : Refer to Summary of Product Characteristics before prescribing.
Presentation: White, oblong, film-coated tablets engraved "160" on one side and "Fournier logo" on the other side. Each tablet contains 160mg fenofibrate (micronised, modified release).
Indications : Hypercholesterolaemia and hypertriglyceridaemia alone or combined in patients who fail to respond to diet and other non-therapeutic measures. Treatment of secondary hyperlipoproteinaemias (e.g. dyslipidaemia in diabetes mellitus).
Dosage and administration : **Adults** : One tablet of Supralip 160mg taken once daily with food. Patients taking one Lipantil® Micro 200mg capsule can be changed to one Supralip 160mg tablet without further dose adjustment. **Elderly** : In patients without renal impairment, the normal adult dose should be used. **Renal Impairment** : The dosage may need to be reduced (use Lipantil® Micro 67mg).
Contra-indications : Hypersensitivity to fenofibrate or any excipient in Supralip, hepatic insufficiency (including biliary cirrhosis), renal insufficiency, children, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen, gallbladder disease, pregnancy and lactation.
Precautions and warnings : In patients who develop increases in transaminase levels, therapy should be discontinued if ASAT and ALAT levels increase to more than 3 times the upper limit of the normal range or 100 IU. Pancreatitis has been reported in patients taking fenofibrate. Combination therapy with HMG-CoA reductase inhibitors or other fibrates should be used with caution.
Interactions : Reduce concurrent oral anti-coagulants by one third initially, and then adjust. Closely monitor renal function in patients during concomitant administration of fenofibrate and cyclosporin.
Side-effects : *Most commonly reported* : Gastrointestinal disorders : abdominal pain, nausea, vomiting, diarrhoea and flatulence. Skin : rashes, pruritus, urticaria or photosensitivity reactions. *Less frequently reported* : Liver : Moderate elevation of serum transaminases, hepatitis, gallstones. Muscle : Muscle toxicity (diffuse myalgia, myositis, muscular cramps and weakness), rhabdomyolysis. *Rarely reported* : Sexual asthenia, alopecia, slight increases in serum creatinine, urea and slight decreases in haemoglobin and leukocytes, very rare cases of interstitial pneumopathies.
Basic NHS Cost : Supralip 160mg film-coated tablets: £14.75 for 28 day calendar pack.
Legal category: POM
Marketing Authorisation Number : PL 12509/0017
Marketing Authorisation Holder : Fournier Pharmaceuticals Ltd UK
Date of Preparation : July 2002
Lipantil and Supralip are registered trademarks. Supralip and Lipantil Micro product range are distributed for Fournier Pharmaceuticals Ltd by Pharmacare Logistics Ltd, Walton Manor, Walton, Milton Keynes, Bucks, MK7 7AJ. Further information is available on request from the address below.

References: 1. American Diabetes Association Diabetes Care 2001; 24(Suppl.1): S58-S61. 2. Guichard JP. Curr Med Res and Opinion 2000; 16(2): 134-138.

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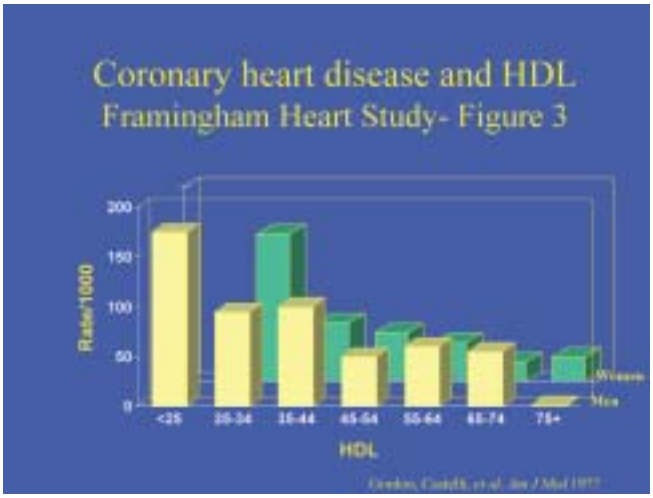
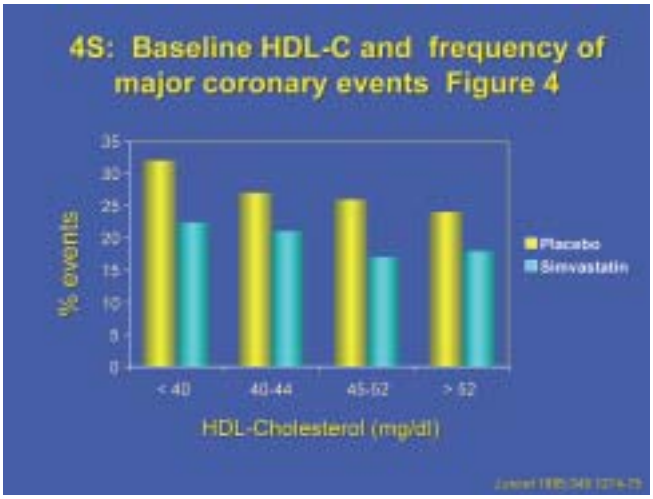
Date of preparation of item: August 2002 2116/2001





reverse cholesterol process by which potentially atherogenic lipid particles are cleared from the circulation including from atherosclerotic plaques. Such cholesterol efflux from cells is mediated via Apolipoprotein A-1, the major protein in HDL.[11]

Different lines of evidence indicates that HDL has a direct beneficial effect on the arterial wall -intravenous infusion of HDL in rabbits prevents atherosclerosis[12] and the introduction and expression of the human apo A-1 gene in mice stimulates the regression of pre-existing atherosclerosis.[13]

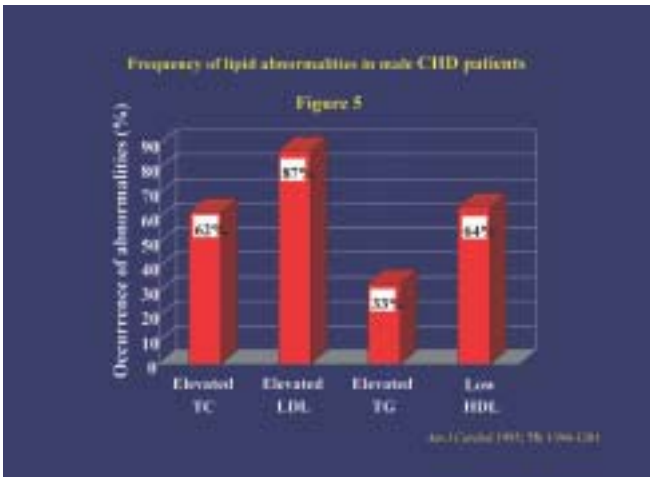
HDL also has other functions which may contribute to its protective ability against CHD such as anti-inflammatory and anti-oxidant properties.[14] Low HDL is found very frequently in survivors of MI (Figure 5) and in those lipoprotein phenotypes associated with increased risk of CHD (Figure 6). Framingham demonstrated that low HDL levels confer increased risk of CHD even with normal LDL (Figure 7) Other causes of low HDL are shown in Figure 8.

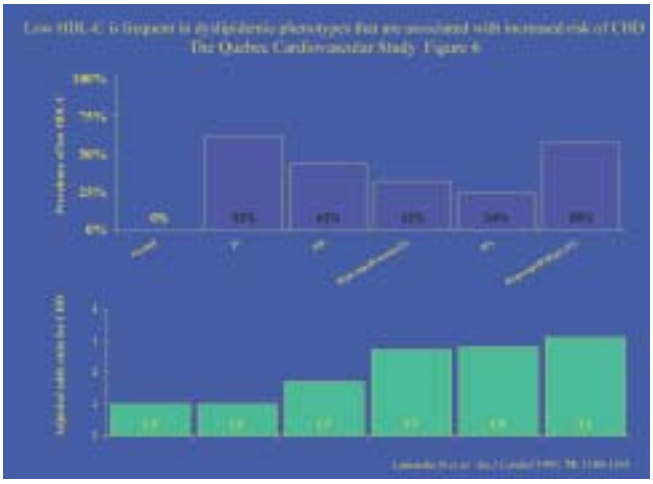
Many patients with low level of HDL cholesterol also have high triglyceride levels and elevated concentrations of highly atherogenic triglyceride-rich lipoprotein remnant particles. The PROCAM study demonstrated the high risk associated with this type of lipoprotein profile (Figure 9). Often such patients may have also abdominal obesity, insulin resistance and glucose intolerance in addition to hypertension. Insulin resistance causes increased VLDL production and this combined with impaired VLDL lipolysis results in high triglycerides and low concentrations of HDL cholesterol. This constellation of risk factors is known as the metabolic syndrome and has recently been identified as a separate target for treatment in the ATP III Guidelines.

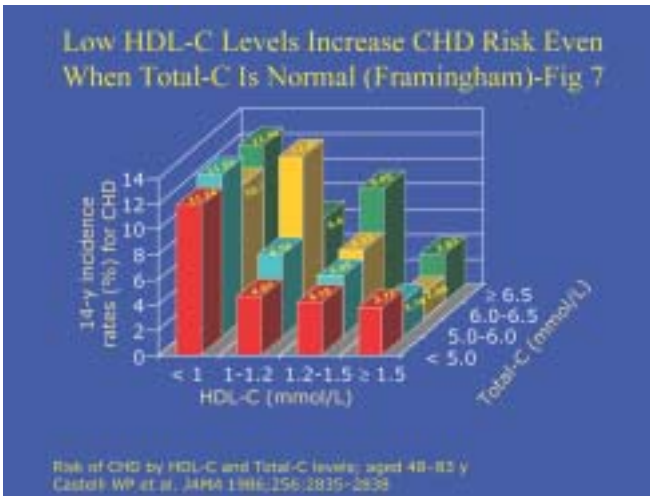
Such dyslipidaemia is seen very commonly in Type 2 diabetes where the characteristic picture is of low levels of HDL-C, increased triglycerides and abnormally composed LDL-C particles which are smaller and more dense. Such particles have an increased susceptibility to oxidation, glycation and retention by the vascular matrix contributing to the significantly increased cardiovascular disease risk seen in this group despite overall LDL-C levels being very similar to an age and sex matched population without diabetes. A similar lipoprotein profile is seen in people originating from the South Asian continent and may start to explain the excess of coronary disease seen in this group.[1]

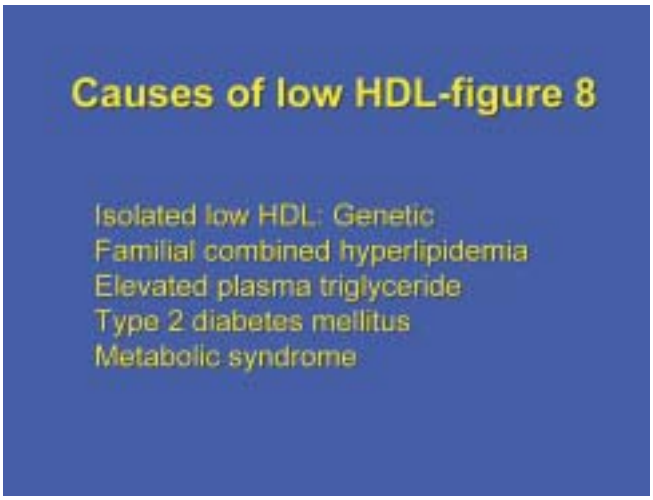
Interventions to Increase HDL

Smoking causes depressed HDL and smoking cessation is an important lifestyle modification in the prevention of CHD. Regular physical exercise of an aerobic nature increases HDL cholesterol. Weight loss in an overweight person increases HDL cholesterol. Although low fat high carbohydrate diets does lower









cholesterol, they also lower HDL -C and increase triglycerides. This may be a particularly important in patients with Type 2 Diabetes and metabolic syndrome. For this reason it is often suggested that mono or polyunsaturated fats replace saturated fats in the diet. Regular moderate intake of alcohol will also increase HDL but this must be set against the potential disadvantages of alcohol excess. Whilst statins do increase HDL levels their effect is much less marked than fibrates or nicotinic acid.

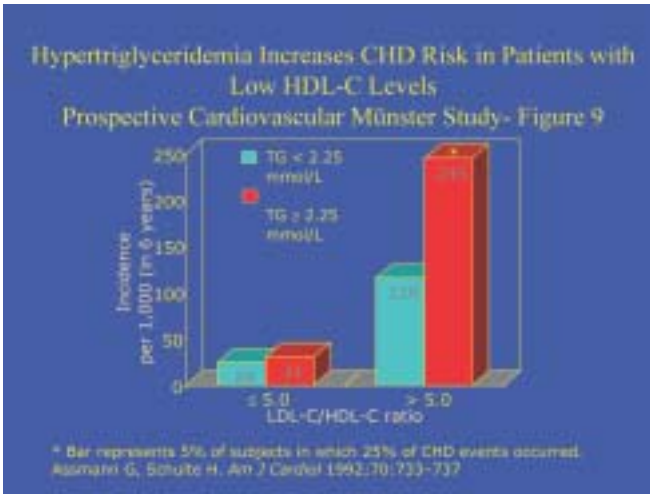
Fibrates activate peroxisome proliferator activated receptor alpha, a nuclear transcription protein that mediates several metabolic actions which stimulate reverse cholesterol transport. These actions include increased production of HDL by the liver, increased synthesis of apo AI and apo AII also by the liver and acceleration of lipolysis of triglyceride-rich lipoproteins. This may explain the increased efficacy of the HDL rise in reducing coronary events by a fibrate, gemfibrozil, in the Helsinki Heart Study as compared to that seen in the statin trials.[15]

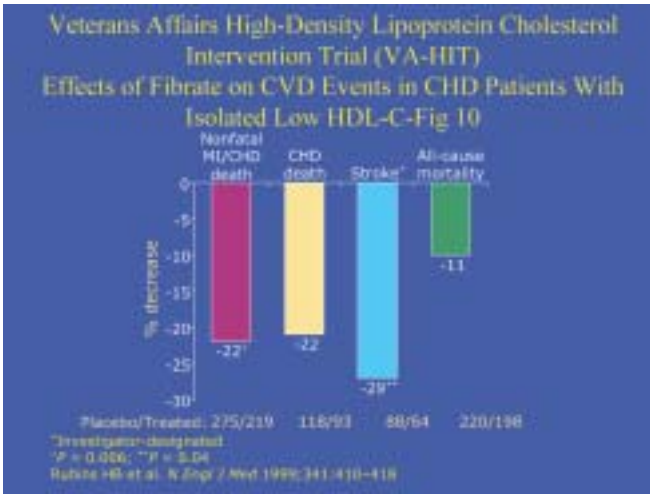
In another study, the Veterans Administration HDL Intervention Trail (VA-HIT), gemfibrozil was used in patients with known CHD, low HDL and low LCL-C . Significant reductions in clinical events of both coronary and cerebrovascular nature were seen by increasing HDL (6%) and reducing triglycerides (35%) without affecting the LCL-C concentrations[16] (Figure 10).

Multivariate regression analysis showed that HDL cholesterol concentration during gemfibrozil treatment was highly inversely predictive of coronary events.

The patients who appeared to benefit most in the Helsinki Heart Study and the VA-HIT study were those who were overweight, or had high fasting serum insulin concentrations suggesting that fibrates may be beneficial in patients with the metabolic syndrome which is often associated with obesity. This was supported by the finding that the Helsinki Heart Study found that the greatest risk reduction in coronary events with gemfibrozil occurred in patients who were obese (BMI >30).[15] Niacin (Nicotinic acid) is also effective in increasing HDL cholesterol in a dose dependent manner. The Coronary Drug project published in 1975[17] was one of the first trials to show lipid-modifying therapy could prevent new events in patients with established CHD. It also demonstrated that such therapy had clear benefits in improving mortality in such patients.

The beneficial effects of niacin therapy are thought to be due to a reduction in the rate of hepatic holoparticle uptake of HDL particles. This hypothesis is supported by the finding that niacin raises HDL by decreasing catabolism of Apo AI without increasing cholesterol transport from HDL to the liver. It does not increase HDL synthesis.[18] However, HDL levels achieved during combination therapy with simvastatin and niacin were related to improvement in coronary





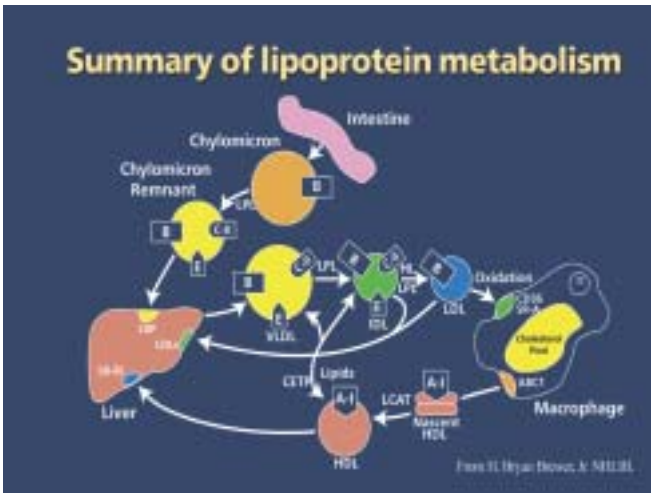
stenosis and reduction in CHD in the HDL Atherosclerosis Treatment Study (HATS).[19]

Conclusion

There is significant evidence to support the importance of HDL cholesterol in CHD risk. Epidemiological and trial data indicate that raising HDL is beneficial in reducing coronary events and that this is independent of LDL cholesterol lowering.

A recent Expert Group[20] has recommended that an HDL of >1.0mmol/L be recommended as a goal for patients with cardiovascular disease and those free of CHD but at high risk especially those with Type 2 diabetes or features of the metabolic syndrome including patients from the South Asian continent.

Lifestyle changes such as smooth cessation, weight loss and exercise should be encouraged. Whilst LDL-C reduction remains the cornerstone of lipid lowering therapy, it is clear that there is considerable benefit to be gained in treating the low HDL and high triglyceride levels seen in many patients particularly those with Type 2 diabetes mellitus, metabolic syndrome and in those from the South Asian subcontinent in whom cardiovascular risk is very high. Consideration should be given to fibrate or niacin therapy for such patients to improve their cardiovascular risk and reduce coronary events.



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Plant Sterols and Stanols:

Spreading the Cost of Managing Heart Disease

The importance of lowering cholesterol

Serum total cholesterol is a major risk factor for coronary heart disease (CHD),[1] with no threshold levels below which there is no added risk of CHD death.[2] The majority of preventable CHD deaths occur in people with raised serum cholesterol,[3] which includes over 60% of the UK adult population.[4]

A reduction in serum total cholesterol of 10% is associated with a decrease in incidence of CHD of around 25% over 5 years, with most of the benefit seen within 2 years.[5] The younger the patient the greater the gain: a 40 year old male can expect a risk reduction in excess of 50%, while in the over 70s CHD risk is reduced by just 20%.[5] While statins can achieve LDL-cholesterol reductions of up to 60%,[6] such treatment is only currently recommended in the UK for the minority of patients with established CHD. The tremendous potential burden that wider prescribing would place on prescribing budgets, with corresponding knock-on effect on other NHS service provision, means that the majority of individuals with elevated coronary risk will not be considered for active drug treatment. The need to look at effective, non-pharmacological ways of lowering cholesterol has therefore never been greater.

It has been estimated that if LDL cholesterol could be reduced by 10% by dietary means, then 75% of at-risk adults would reach target cholesterol without drug treatments.[3] Unfortunately, simple dietary advice carried out in primary care has been shown to reduce cholesterol by only around 2-4%.[7,8] Clearly, additional measures are required.

Plant sterols/stanols as cholesterol-lowering agents

Plant sterols and stanols are chemically related to cholesterol[9] and their capacity to lower cholesterol *in vivo* has been extensively evaluated over five decades.[10] They appear to reduce serum cholesterol mainly by reducing its incorporation into mixed micelles and so reducing its absorption from the intestine.[10] In healthy adults, less than 5% of ingested phytosterols are absorbed and none is synthesised endogenously.[10, 11]

As fats are needed to stabilise sterols and stanols, margarines are ideal vehicles for them.[12] Regular use of sterol/ stanol-enriched spreads can be expected to reduce total cholesterol by approximately 10% and LDL by up to 14%.[4] These benefits are seen in both normocholesterolaemic[13] and hypercholesterolaemic[14-16] individuals. The effect is additive to that of a low fat diet[17, 18] and that of statins,[15, 19] thereby reducing the need for, or the required dose of, statins in reaching target cholesterol levels. The effect is also additive to that of fibrates.[20]

The use of stanol/sterol enriched spreads combined with a Step I or II fat-restricted diet has been shown to reduce LDL cholesterol by 20-25%, which will bring most patients to target levels, and should be tried as first-line therapy for six months.[21]

There is an associated dose-dependent decrease in levels of some fat-soluble vitamins, in particular carotenes, but this can be avoided when the spread is consumed as part of a healthy diet including the recommended five serves of fruit and vegetables per day.[23] These reductions are well within the variation observed in dietary intake of carotenoids between winter and summer.

Achieving a balance – empowering patients and reducing costs

The widespread use of sterol and stanol enriched spreads in primary prevention, sustained for 5 years, could save the NHS almost £90m each year in prevented CHD events.[4] These savings could be significantly increased, were these spreads also used in a statin-sparing role for secondary prevention. As the patient pays for the spread, the cost is not drawn from NHS funds. At around 16p a day, enriched spreads are more expensive than standard margarines, but compare favourably with other lifestyle choices and are equivalent to a single NHS prescription charge over a month.

Case study: Blackwell Medical Centre, Somercoates, Derbyshire

Dr. David Holland has been encouraging patients to use sterol/stanol enriched spreads as part of his rigorous strategies to implement the CHD National Service Framework, since the products appeared on the market. As patients with high lipids are identified, they are given dietary advice and a patient information leaflet which recommends the use of the enriched spreads. About half the targeted patients have managed to lower their cholesterol levels adequately by these measures alone.

Dr. Holland and his team have used visual aids to motivate his patients, including personalised graphical representations of how their CHD risk is falling as their cholesterol levels drop, and empty spread cartons

visible around the consulting room! Since the scheme began, the practice's admission rates for MIs have fallen from one of the highest in the area to the third lowest, despite operating in an area of high deprivation.

Dr. Holland would like to see a greater emphasis on the benefits of dietary intervention in the country as a whole. He says, "If diet alone can bring about a 70% reduction in coronary mortality in patients with CHD, it's got to be worth promoting!"

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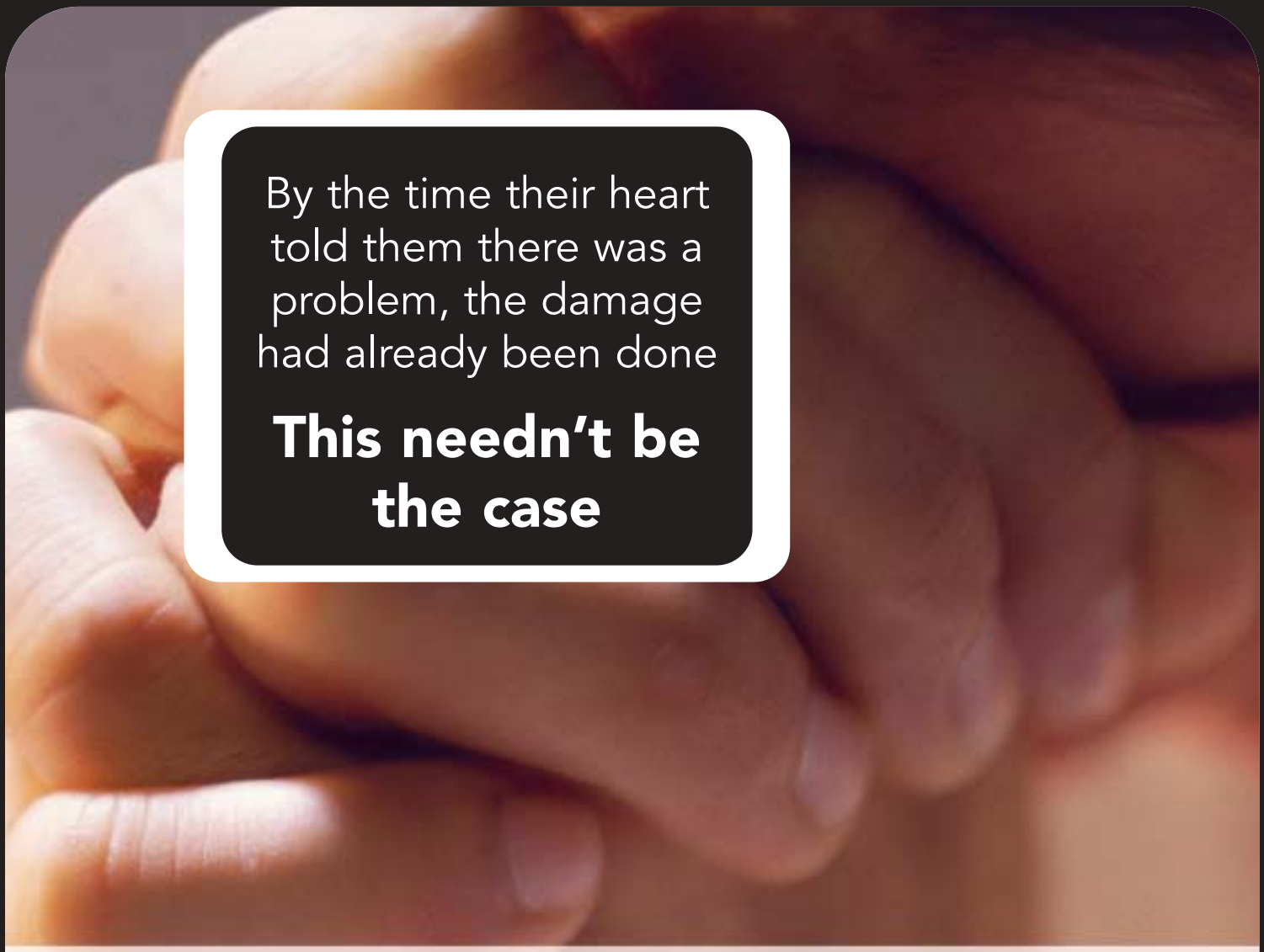

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The Elderly and Hypertension

What Patients Really Think

Dr Sarah Jarvis

Hypertension is the single most common medical condition among the elderly. The condition affects 20-30% of the adult population in the UK, and more than 50% of people over 65.[1] The number of patients affected, then, has risen with the increasing age of the UK population. Between 1995 and 2025, it is estimated that the number of people over the age of 80 will have increased by 50%, and the number over 90 will have doubled.[2]

In the last 15 years, meta-analysis of clinical trials has proved that the risk of stroke can be reduced over 5 years by 35%, and the risk of coronary events by 20%– simply by treating elderly hypertensives with the same vigour as their younger counterparts.[3]

The recommendations in the National Service Frameworks for CHD and the elderly, then, are that all patients – regardless of age - should be treated with medication effective enough to reduce their blood pressure to a maximum of 140/85mmHg, or 130/80mmHg if they are also diabetic.[2,4]

This means that a huge swathe of the population should be taking medication for a condition which, until it precipitates a cardiovascular event, is assymptomatic. If the medication gives rise to side effects, their quantity of life may be extended at the expense of their quality of life. That this eventuality is undesirable is self-evident.

The second potential consequence, however, is more easily overlooked. If patients feel unwell as a result of their medication, they are more likely to default than if the medication is side effect free. If their blood pressure rises as a result, they are more likely to suffer a non-fatal, as well as a fatal, cardiovascular event.[3] The residual effects of a CVA on quality of life can be catastrophic. If patients are to make an informed decision about their medication, they must be fully aware of both the short and the long term consequences of compliance and non compliance.

Persistence rates for antihypertensive medication are notoriously low. In one study of over 21,000 hypertensives on medication, persistence with thiazide diuretics was only 38%, with beta-blockers 43%, with calcium channel blockers 50% and with ACE inhibitors 58%. Even with AIIRAs, which had the highest compliance rates, 36% of patients were no long persisting with medication after one year.[5]

How then, can we improve compliance in this enormously important area? A recent lifestyle survey may well provide some clues.

Attitudes of elderly hypertensives

In June 2002, the results of the SCOPE study on hypertension in the elderly were announced. These revealed a 28% reduction in non fatal stroke among elderly patients with mild hypertension treated with candesartan compared to control. They also highlighted the excellent tolerability of candesartan, with side effect rates not significantly different from placebo.[6]

It is against this background that a survey was conducted to explore the attitudes of elderly hypertensives, both to their medication and to all aspects of their lives.[7] The survey was sponsored by the manufacturers of candesartan, and the questions might thus be open to accusations of bias towards tolerability and quality of life. These are, undeniably, the "strong points" of AIIRA therapy, accounting as they do for the high compliance rates compared with other antihypertensives.[5] Nonetheless, other nationally accepted guidelines might equally be accused of bias towards reducing cost, at the expense of quality of life. How else can one explain the recommendation by the National Institute of Clinical Excellence (NICE), that beta interferon should not be prescribed for patients with multiple sclerosis, despite admitting that "patients currently receiving beta interferon for MS…could suffer loss of wellbeing if their treatment is discontinued at a time they did not anticipate"?[8]

Even with the caveat that quality of life is top of the survey's agenda, it still provides valuable lessons about our elderly patients' priorities. The survey was divided into three parts. The first was qualitative, looking at the attitudes of elderly hypertensives to life and ageing. The second was quantitative, and was conducted among patients attending the pharmacy to collect any antihypertensive medication. The final group included elderly hypertensives, who were asked for their views on the quantitative findings.

Qualitative findings

The key findings from the qualitative findings included:

- Respondents described over 70 year olds as being "old" but did not include themselves
- Positive experiences of retirement outweighed negative ones (2/3 of respondents in the qualitative group were "enjoying" retirement overall)

- Patients are extremely active in their older years, with walking, gardening, family activities among the most popular pastimes
- Tiredness, lack of stamina and dizziness were perceived as the most debilitating activity-limiting factors
- The most pressing concerns are loss of memory, loss of mobility and inability to continue driving.

Quantitative findings

For me personally, the most enlightening findings came from the quantitative elements of the survey. They revealed a widespread lack of education among patients about the risks of their condition, and the reasons for changes in medication. 23% of respondents cited "the doctor told me to" as their only reason for taking antihypertensive medication. Even more surprisingly, in this age of perceived patient empowerment, 40% of patients who had changed medication had only done so "because my doctor told me to".

It is worth reminding ourselves at this point that the patients questioned were all compliers. While no comparable quantitative survey was taken of non-compliers, many studies have suggested that patient education, as well as side effects and dosage frequency of medication, affect compliance.[5,9] It follows, therefore, that non- compliant patients are likely to be even less well educated about the consequences of stopping their medication. And with side effects playing such a major role in compliance,[5] it is also likely that had non-compliers been questioned, the cited incidence of side effects would have been higher.

The most commonly prescribed drug group was beta-blockers, which may account for the extremely high incidence of tiredness, as well as sleeping problems and cold extremities, among respondents.[10] Dry cough is a recognised complication of ACE inhibitors,[11] and swollen ankles and headache are frequently seen with calcium antagonist therapy.[12]

Conclusions from the survey

The qualitative findings confirm that elderly people often lead active and fulfilling lives, and that maintaining their independent existence is of major concern. While such conclusions may appear self-evident, the quantitative findings suggest that doctors and nurses are not taking advantage of the opportunity to educate elderly patients about the importance of controlling hypertension in maintaining quality of life.

One of the major hurdles faced by health professionals in tackling compliance in hypertension is the lack of short-term symptoms. If patients gain no short-term benefit, and are unaware of longer term protection offered by their medication, their tolerance to side effects and being "labelled" with a medical condition is likely to be low.

It follows from these quantitative findings that patients are likely to be very receptive to education on the benefits of antihypertensive medication (in terms of stroke and myocardial infarct reduction). By teasing out the issues of key concern to the elderly, elderly patients can come to informed conclusions about the risk:benefit profile of their medication.

The highly active lifestyles of these elderly patients also highlight the benefits of well tolerated antihypertensive medication on quality of life. The average elderly hypertensive, it seems, is not sitting at home knitting, but out enjoying life. For those with high activity levels, side effects such as diuresis, lethargy, swollen ankles and dry cough are simply unacceptable.

If primary care is to rise to the challenge of tackling hypertension in our ever-rising elderly population, it is essential that our patients work with us. For them to do so, we must be aware of their concerns, so that we can tie them in to treatment rationale. Patient education may require short term input in terms of time, but it is likely to pay dividends in terms of quality of care.

Quantitative findings

Reasons for taking antihypertensive medication

To prevent a heart attack	57%
To prevent a stroke	53%
To keep healthy	46%
My doctor tells me to	23%
Other	1%
Don't know	2%

Reasons for changing medication in the last year

Doctor told me to	40%
Medication did not work	20%
Medication side effects	17%
Don't know	7%
Other/not stated	23%

Proportions of patients on different drug groups

Beta blockers	39%
ACE Inhibitors	28%
Calcium antagonists	27%
Thiazide diuretics	16%
AIIRAs	9%
Other antihypertensives	4%

(respondents were taking an average of 2.91 medications)

Perceived side effects of hypertension/antihypertensives

Tiredness	39%
Headaches	26%
Swollen ankles	25%
Cough	20%
Sleeping difficulties	20%
Cold extremities	17%
Sexual problems	16%

Key concerns about ageing among elderly hypertensives

Loss of mobility/paralysis	76%
Loss of memory	72%
Going into a home	71%
Loss of dignity	69%
Loss of independence	69%
Reliance on others for help	65%
Losing their home	63%
Conditions associated with wear and tear	50%
Side effects from taking medication	44%

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Dr Sarah Jarvis is a GP trainer and Fellow of the Royal College of GPs. She writes extensively for the medical and lay press, and her particular interest is patient information and education.

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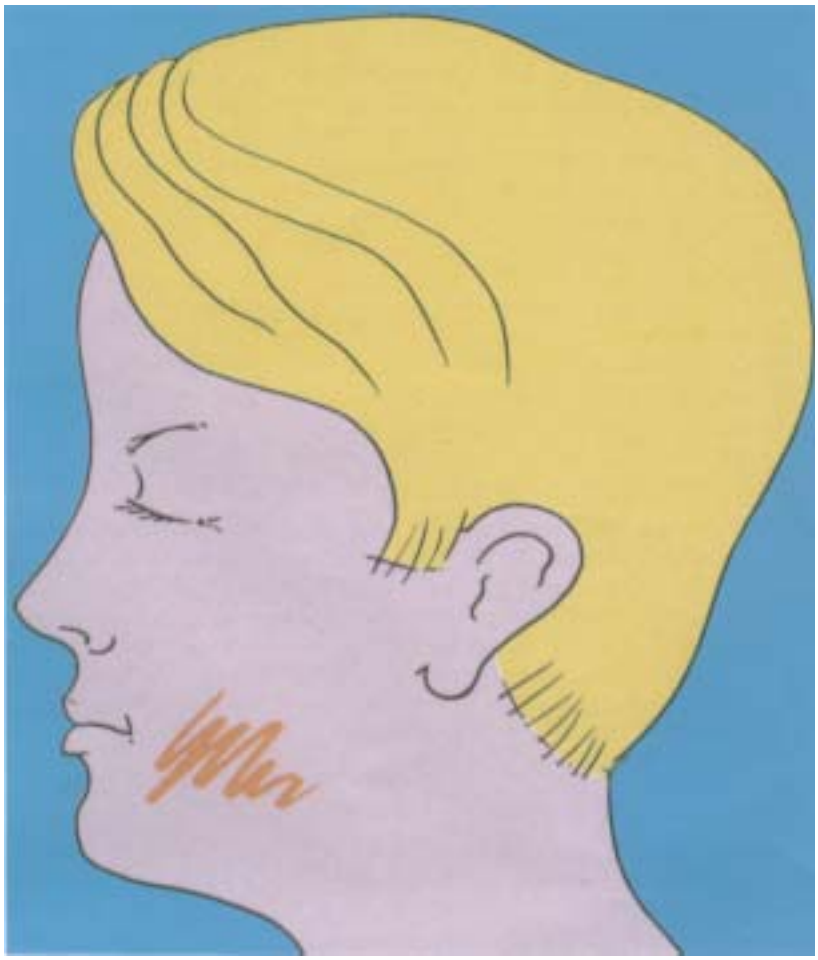

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References: 1. Shalita A R. Clin Ther 11 No 2 1989 **2.** Gloor et al. Z Hautz 54. [19] 856 86. **3.** Shalita A R. Derm Times. Sept 1990.

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Acne Vulgaris: A Rational Approach to Treatment

Dr Tony Chu

Acne Vulgaris is the commonest skin condition to affect man. Although the peak incidence occurs in adolescence, the disease can persist throughout adult life. 70% of patients will spontaneously remit within the first 4-5 years, but that leaves 30% of patients who will continue for a variable period into adult life. My eldest patient suffering from acne is now 82 and has had acne since she was 15 years of age. Even those patients in whom the disease remits spontaneously at an early age, the disease can leave permanent physical and mental scars.

There are a vast number of different treatments available for acne, which the patient can either purchase over the counter or receive on prescription from their general practitioner. Most physicians will treat acne primarily with antibiotics, however, without an understanding of the pathophysiology of acne it is difficult to develop a rational approach to treating the disease, antibiotics are not necessarily the major agent that is required in treating certain forms of acne.

Pathophysiology

A number of abnormalities develop in the skin, which eventually lead to the development of clinical acne. Acne should be regarded as a hypersensitivity syndrome to circulating androgens. Androgen levels are never abnormal in men and in the majority of women are within normal range. It is not that too much male hormone is present , but the fact that the skin overreacts to it. Increased sensitivity to androgens leads to increased sebum secretion. This is almost universal in the acne patient, but the skin is a mosaic and therefore, areas of skin will be very greasy while other areas of skin will be quite dry. The second and probably most important event that occurs in the development of acne is the formation of the micro-comedone. This is due to a growth change in keratinocytes of the follicular osteum causing a partial blockage or follicular hyper-cornification. The micro-comedone is the primary lesion that leads to the development of all inflammatory and non-inflammatory lesions. The development of this partial blockage restricts oil flow to the surface, which leads to a build up of sebum within the follicle and resulting solidification results in blackheads and whiteheads. Finally, occlusion of the follicle leads to a build up of oil in the follicle and proliferation of anaerobic bacterium Propionibacterium acnes (p. acnes). Inflammation then develops with pus formation.

Treatment rationale

When developing a treatment rationale for patients the pathophysiology must be carefully considered. The primary lesion is the micro-comedone and the only totally effective regimens must address this lesion as well as the inflammatory lesions. It is of course the inflammatory lesions that cause the most concern to the patient; red and purulent spots are both disfiguring and very embarrassing. If the microscopic blockage that is the precursor of these inflammatory lesions is not addressed, they will continue to come.

Treating the micro-comedone

The micro-comedone and microscopic open and closed comedones (blackheads and whiteheads) do not respond to antibiotics. The micro-comedone is caused by growth change in keratinocytes, which lead to a build up of dead keratinocytes within the follicular osteum. Agents that normalize the keratinocyte growth and agents that will dissolve the keratin blockage are, therefore, both very useful in treating the micro-comedone.

Topical preparation	Mode of action
Isotretinoin 0.05% gel	Normalises keratinocyte growth
Isotretinoin 0.05% with erythromycin 2% gel	Normalises keratinocytes and treats inflammatory lesions
Tretinoin 0.025% with erythromycin 4% lotion	Normalises keratinocytes and treats inflammatory lesions
Tretinoin 0.01% and 0.025% gel and 0.035% cream	Normalises keratinocyte growth
Adapalene 0.01% gel or cream	Retinoid-like aith an anti-inflammatory action

Table 1: Topical agents for use against microcomedones and non-inflammatory lesions

Table 2: Topical antibiotics used in acne

Preparation	Characteristics
Clindamycin 1%	Alcoholic solution or lotion for more sensitive skin
Erythromycin 2% and 4%	Alcohol-based gels
Erythromycin 2%	Alcoholic solution
Tetracycline 0.22%	Alcoholic solution
Erythromycin 4% with zinc acetate 1.2%	Alcoholic solution - addresses drug resistance
Erythromycin 3% with benzoyl peroxide 5%	Gel - addresses drug resistance

Topical retinoids

Topical retinoids are the major agents in treating the micro-comedone. Vitamin A will normalize keratinocyte growth and will, therefore, prevent the formation of the micro-comedone. They will have little or no effect on the on the inflammatory lesions of acne. A major drawback in the treatment with topical retinoids is that they tend to be an irritant to the skin and many patients do not tolerate them well. Patients must be carefully instructed to use the agents very sparingly (a quantity the size of a small pea is enough to cover the entire face) and the preparation should only be used on totally dry skin. Because topical retinoids can photosensitise the skin these agents should only be used at night and then washed off in the morning. In patients who have very sensitive skin the agents can be used in a short contact regimen. Patients should be instructed to apply the preparation in the evening for one hour and then to wash it off and apply a non-comedogenic moisturiser. After the first week as long as there is no irritation the time of application can be extended until hopefully the patient will be able to tolerate the preparation overnight. Table 1 lists the available topical retinoids for the treatment of acne. In patients who cannot tolerate topical retinoids azelaic acid 20% cream can be tried. This agent is comedolytic and also has some antibacterial action.

An extremely useful agent in dermatology is salicylic acid; this agent is keratolytic, which means that it dissolves dead keratin. It is used in a number of preparations to reduce thick keratin and allow better penetration of active ingredients. In acne salicylic acid can help reduce the micro-comedone by dissolving the follicular hyper cornification. This allows a free flow of oil to the surface and, therefore, reduces the risk of follicular occlusion and inflammatory spots developing. Currently a 2% salicylic acid wash is available for the treatment of acne.

Topical retinoids and azelaic acid are not recommended during pregnancy. Retinoids are teratogenic but the levels of retinoids that are absorbed through the skin is extremely low and, therefore, this risk is only theoretical with their topical use. It is however, advisable to warn patients of the potential risk and to avoid it in patients who are trying to conceive or who are pregnant.

Treating inflammatory lesions

Inflammatory lesions of acne respond to topical or oral antibiotics or anti microbial agents. These agents are assumed to work by killing P. acnes but topical and systemic antibiotics do have a secondary effect of reducing inflammation. A general rule is that patients who have mild to moderate acne should be started on topical agents first and only if they fail to respond to topical agents should systemic agents be used. Topical antibiotics have the advantage of achieving high levels of antibiotics at the skin where they are needed with low systemic absorption and therefore, low toxicity. The majority of topical antibiotics used in acne are in alcoholic solutions and these preparations may be irritant to patients, who will, therefore, have poor compliance and poor response rates to them. Newer gel preparations may be preferable to the patient. A list of topical antibiotics used in acne is given in table 2.

Oral antibiotics are the mainstay of treatment for moderate to severe acne and these are particularly useful if more than one site of the body is involved. It can be extremely time consuming for patients to treat both the face, back and chest with a topical preparation and if patients do not have family or friends who can help apply preparations to their backs topical agents may not be appropriate. Side effects can occur with any systemic treatment . In the case of antibiotics used in acne these are generally mild and of very low incidence. Gastrointestinal upsets occur in 5% of patients and vaginal thrush in 4% of women patients using long term antibiotics. Prescribing doctors must be aware of the potentially serious side effects of oral antibiotics. Hepatotoxicity is a relatively common event with erythromycin. Benign intracranial hypertension may occur with any of the tetracyclines, and these should not be used in patients under the age of 12 because of the risk of permanent staining of the final dentition.

Minocycline has been associated with a lupus-like syndrome and can also cause bluish discolouration of scarred areas due to deposition of the drug complexed with melanin within the skin. The physician must be aware of the bio availability of oral antibiotics and must give full instructions to patients on how to use them properly. The older tetracyclines such as oxytetracycline are inhibited by fat and iron in the stomach, and therefore should be taken on an empty

stomach without eating for an hour afterwards. The half life of the drug is also relatively short at eight hours and, therefore, patients should really take the drug four times daily to achieve good levels of the drug within the blood. Erythromycin is inhibited by carbohydrate in the stomach so should not be taken with carbohydrates. Cost is a major issue in the treatment of acne and that is why many prescribing physicians will tend to go for the cheaper option such as oxytetracycline. However if patient compliance is poor then a better option would be to go for a longer acting tetracycline that is not inhibited by food so that the patient can take the drug once daily.

Antibiotic drug resistance in acne

Antibiotic drug resistance in acne has been documented for the last decade and is increasing in all parts of the world where it has been looked for. In Leeds the antibiotic drug resistance rose from 38% in 1992 to 68% in 1997. The antibiotic resistance was highest to erythromycin cross-reacting with clindamycin; this was also seen in tetracycline. The importance of drug resistance is however very difficult to evaluate. There is no doubt that patients continue to respond to antibiotics despite the fact that they carry resistant bacteria. It is possible that the use of topical or systemic antibiotics will achieve levels within the skin that can kill off even resistant bacteria. The problem however, will not go away and may become an important feature in our future management of the disease. The search for non-antibiotic alternatives is still very important.

How to use antibiotics in acne

Topical antibiotics should be used on the whole affected area and not just individual spots. They should be alternated with a topical retinoid, using the retinoids in the evening and the antibiotic during the day. Newer preparations that combine a retinoid with an antibiotic are extremely useful when using topical antibiotics as these agents can be used in the evening with the antibiotic during the day. There is no such thing as a course of topical antibiotics and patients will need to continue the treatment for as long as they have active disease. As a rule of thumb patients should achieve a 50% improvement in the first two months of therapy if they are going to respond. Patients should always be regularly assessed and if the disease is not responding adequately treatment should be changed. Systemic antibiotics should be used at high dose until control of the disease is achieved and then the dose can be reduced. Optimal doses for initial therapy are given in table 3.

Once again there is no such thing as a course of oral antibiotics for acne, the drugs need to be continued for as long as the patient needs them. The dose, however, should be progressively reduced as the patient improves. Always use a topical retinoid with an oral antibiotic. As the dose of the antibiotic is withdrawn a topical antibiotic can be introduced to take over from the oral antibiotic.

Hormonal treatment

As stated before, acne should be regarded as a hypersensitivity syndrome to androgens. In women we have the facility to block androgens and this is a viable form of therapy in some patients who have particularly severe disease. Ethinyloestradiol 35 micrograms and cyproterone acetate 2 mgs can be taken for twenty one days with a seven day pill-free period. Although this preparation is not licensed as a contraceptive it is an effective contraceptive. This drug works in 2 ways: firstly the Ethinyloestradiol will increase sex hormone binding globulin which will inactivate circulating testosterone; secondly cyproterone acetate is an anti-androgen reducing the conversion of testosterone to its more active dihydroxy-testosterone within the skin. A major problem with the drug is that when it is withdrawn the enzymes that have been blocked will tend to have a rebound increase in activity, which will often lead to a particularly active rebound of acne. This drug is licensed for the treatment of severe acne in women that are not responding to conventional antibiotic therapy. It should not be used in a woman who has mild acne and wants the contraceptive pill. Women with acne who want to be on the oral contraceptive should be given a third generation combined oral contraceptive as these are acne friendly. If women are already on long-term antibiotics for acne no precautions need to be taken when introducing the oral contraceptive pill. If women are on the oral contraceptive pill and a long term systemic antibiotic is started, the patient should be warned that the pill will be less effective for the first 21 days and barrier precautions should be taken as well.

Drug	Initial Dose	Serum half life	Regime	Precautions
oxytetracycline	1g	8 hours	250mg QDS	Inhibited by fat and iron in the stomach
erythromycin	1g	2.5 hours	250mg QDS	Inhibited by carbohydrate in the stomach
Lymecycline	408 to 816mg	7 to 14 hours	408mg od or bd	None
Minocycline	100mg	12 to 16 hours	100mg od	None
Doxycycline	100mg	22 hours	100mg od	None
Trimethoprim	400mg	10 hours	200mg od	None

Table 3: Oral antibiotics used in acne

Severe acne: when to refer to the dermatologist

- Severe nodulocystic acne;
- Moderate acne not responding to at least two different antibiotics with topical retinoids;
- Patients suffering severe psychological sequelae.

Referral guidelines have been identified by the National Institute for Clinical Excellence. The guidelines reflect the range of potential treatments the dermatologists have for the above groups of patients. The most significant treatment for acne remains oral isotretinion, but oral isotretinion is not without its side effects, which can be severe. The risks and benefits of treating patients with oral isotretinion must be weighed up before a decision is made to prescribe the drug.

What's new in acne treatment

New preparations continue to be launched for the treatment of acne. Most are new formulations of topical antibiotics or retinoids, which may suit some patients improving patient compliance. Antibiotics, such as clarithromycin are now being used as second line antibiotics and may be useful in patients who fail on conventional antibiotics.

Considerable interest has been shown in the treatment of acne using both light and laser therapy. Generally, these treatments are only available either in hospital settings or in private clinics, and these treatments can be expensive. Light treatments tend to be based on blue light at about 440 nanometres. Light at this wavelength has been shown to activate protoporphyrins present within P. acnes, which results in killing of the bacteria. Light at this wavelength, therefore, acts as an antibiotic. As you would expect, long term treatment with this form of light is necessary to achieve resolution of the acne. Recent studies at Hammersmith hospital have shown the efficacy of a low intensity pulse dye laser with a wavelength of 385 nanometres. This laser has been shown to be effective in reducing inflammatory acne and the studies also showed a trend towards resolution of non-inflammatory lesions. A single treatment would give improvement of acne over a three month period, which gives this form of laser major advantages over forms of light therapy currently available.

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New Treatments for Atopic Eczema

Sue Ward

Atopic eczema is a common skin condition, affecting all age groups, but more prevalent in children. It has increased threefold over the last thirty years[1] and today 14-20 per cent of school children in the UK suffer to some degree from eczema.[2] In addition, 1 to 2 per cent of adults have atopic eczema, which is often severe. Eczema in general accounts for about 30 per cent of dermatological consultations in general practice.[3]

The main stay of treatment continues to be emollients and topical corticosteroids but recently two new treatments have been developed. Tacrolimus (Protopic) and Pimecrolimus (Elidel) are topical immunomodulatory therapies and both are non-steroidal anti-inflammatory agents that have proved helpful in the treatment of atopic eczema.

Tacrolimus

The skin's immune system is normally responsible for protection against things such as infection, but in atopic eczema it is overactive to some degree. Tacrolimus helps to suppress this over-activity. Tacrolimus was initially used in systemic form as an immunosuppressive drug in transplant patients. In it topical form it comes as an ointment and in the UK it is available in 0.1 per cent and 0.03 per cent strengths. At present Dermatologists and General Practitioners who have experience in the treatment of atopic eczema can prescribe it. However, it likely to become available for all GP's to prescribe.

There have now been a number of trials using tacrolimus ointment to treat atopic eczema; it has been compared to placebo and to 1 per cent hydrocortisone and the results look very good when compared against these. It has also been

compared to hydrocortisone butyrate and the results of this study suggest that the 0.1 is as effective at treating eczema as hydrocortisone-butyrate. Hydrocortisone butyrate was more effective that the 0.03 per cent tacrolimus in that study.

The skin begins to improve in about the first week of using the ointment, with an improvement in itching and redness, and this continues whilst the treatment carries on.

How is it used?

Tacrolimus ointment is applied thinly to the affected parts of the skin, twice a day. It can be used on the skin on any part of the body, including the face except mucosa (inside the nose, mouth and internal genital area). It is important that patients continue to use their emollients alongside the tacrolimus ointment.

Tacrolimus can be used to treat moderate to severe atopic eczema in adults who are not adequately responsive to, or are intolerant of, conventional therapy. The lower strength may be used in children aged two years and over who fail to respond to conventional therapy.

Pimecrolimus

Pimecrolimus (an ascomycin derivative) is also an immunomodulatory drug, which has been developed specifically as a topical anti-inflammatory agent. It comes in the form of a cream and is available in 30g, 60g and 100g tubes, which contain 1 per cent pimecrolimus. It has been available to secondary care since September 2002 and to a few General Practitioners with experience of treating atopic eczema. It is now being launched into the whole of primary care. Pimecrolimus is intended for use at the first signs of redness and itch, when emollients alone have proved inadequate but prior to the use of topical corticosteroids.

To date clinical studies are very encouraging in both children and adults.

How to use?

The cream should be applied thinly to the affected skin twice daily and can be continued until the signs and symptoms clear. For long-term treatment, it can be applied at the first signs and symptoms to prevent progression to flare. Pimecrolimus can be used for mild to moderate atopic eczema in adults and children aged two and over. It can safely be used on delicate skin areas such as the face, flexures and neck. Emollients can be applied immediately after using Pimecrolimus.

Side effects

The main short- term effect from both agents, reported by some patients, is a burning feeling on the skin for a day or two but this sensation seems to disappear within the first few days of using the ointment or cream.

Precautions/Contraindications

Tacrolimus & Pimecrolimus should not be used in patients with a history of hypersensitivity to the drugs or any of their formulation excipients. Trials of tacrolimus ointment have only been in children aged two years or older. Therefore, it should not be used in children under two years.

Both Tacrolimus and Pimecrolimus should be used with caution in patients with pre-existing viral skin

infection such as eczema herpeticum , chicken pox or shingles and herpes simplex infection and during pregnancy and lactation. Neither agent should be used under occlusion.

Questions yet to be answered

We don't as yet know what, if any, the long-term effects of using immunomodulatory drugs may be. Thus far, data indicates that absorption is minimal, but more data is needed. It is important to emphasize that comparative studies with systemic agents are required to assess their role in patients with recalcitrant and severe disease. Because both agents suppress the inflammatory response, the issue of photocarcinogenesis has been raised and, although there is no evidence of this happening with tacrolimus ointment or pimecrolimus cream, patients using either of these agents long-term on sun-exposed areas should avoid excessively strong sun exposure until such time as the safety of sun exposure with these agents has been established.

Impact

There is no doubt that the prescribing costs for these new topical immunomodulatory agents will be considerably more than the cost of prescribing a topical steroid, possible 10 times as much. However, there is no doubt that once atopic eczema patients learn about these new treatments, health professionals will start to receive requests for them to prescribe it. It should be remembered that many patients are desperate, especially where topical steroids have failed, and we know that topical steroids are under used by many mothers because of fears of skin thinning in their child. It may be that the cost of prescribing one of these new treatments can be offset by savings from fewer specialist consultations and from fewer days of ill health if these new treatments deliver a favourable benefit: risk ratio in clinical practice.

What next?

Long-term clinical trials are continuing for both tacrolimus and pimecrolimus. Tacrolimus is also being tested to determine if there are benefits for other skin conditions. Clinical trials that are being carried out on pimecrolimus in children under two, and as young as 3 months, look promising.

In summary

- Tacrolimus and Pimecrolimus are non-steroidal immunomodulatory agents.
- They are licensed for use in atopic eczema only.
- Both are licensed for use in adults and children two years of age and over
- A burning sensation commonly occurs after applying these agents to the skin. This normally settles after a few days.
- Neither agent appears to cause skin thinning, which can sometimes occur with potent topical steroids when used incorrectly.
- Short-term studies suggest that both Tacrolimus and Pimecrolimus are safe drugs, but far less is known about their long-term effects on the immune system.

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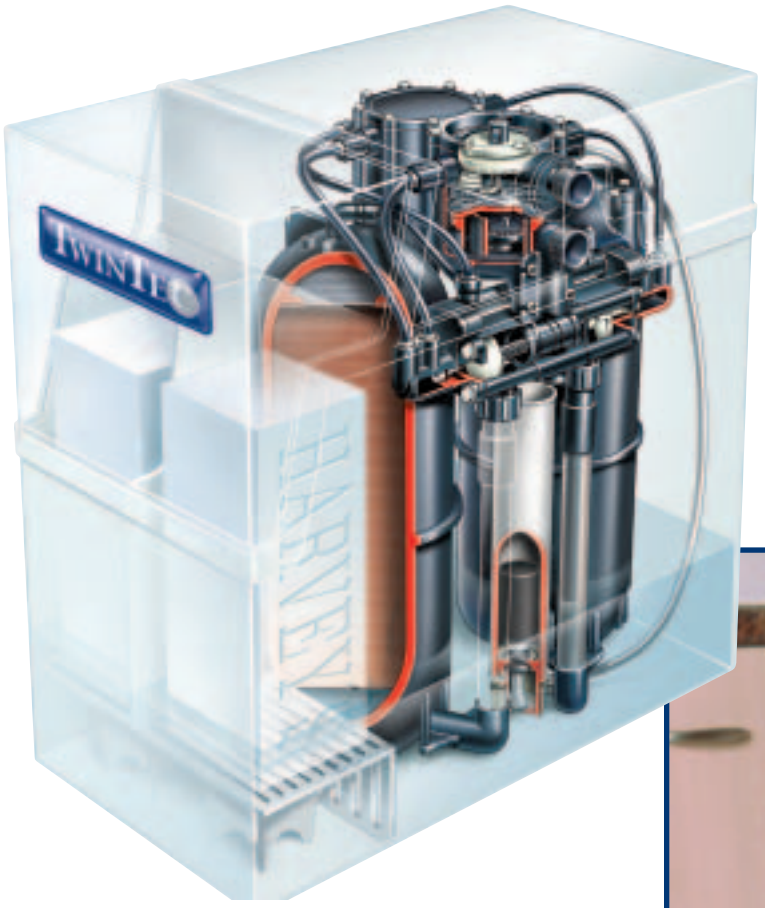
- ✔ Lower usage of soap, detergent, washing-up liquid, shampoo, etc
- ✔ More luxurious bathing experience



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Softened water benefits

The benefits of softened water have been appreciated for many years. In the early 1900's, the first industrial water softening units used naturally-occurring, regenerable zeolites for softening steam-engine, boiler-feed water. Use of softeners in the home started in 1918 and by the 1930's were very popular. Many people still remember the name Permutit. Although the control systems are now very sophisticated compared to the manually regenerable ones that were sold up to the 1960's, the principle is unchanged.

Hard water causes excessive use of soaps and detergents. It causes scale in the pipework of hot water systems, in shower-heads and around taps, and scum marks around the bath and sinks. Bathing in softened water is also a more pleasurable experience. Hard water problems have an even greater impact on industry, causing scaling in boilers and cooling systems. It has been estimated that the cost due to hard water to industry alone is about £1bn per year.

The cause of hard water is calcium and magnesium salts that dissolve into the water as it permeates through the substrata. Therefore water hardness is prevalent in areas of the country where the substrata is primarily limestone and, since this includes the south-east, central and north-east England, some 60% of the population are provided with hard water. In these areas, the hardness varies from 250 to 450 ppm (this is total calcium and magnesium salts expressed as calcium carbonate). Soft water is generally regarded to be less than 50ppm.

As already mentioned, water can be softened in the home by installation of an ion exchange softener. This device treats the water at "point of entry" of the premises and it is usually installed under the kitchen sink. It employs a synthetic resin that contains sodium ions. As the water passes over the resin, the calcium ions in the water are exchanged for the sodium ions in the resin. It is a very efficient process and modern softeners will consistently produce water with close to zero hardness. In fact, the resin removes all multi-valent cations, so magnesium, iron, etc are also removed.

The softener is regenerated periodically by passing brine (sodium chloride) through the resin. The sodium and calcium ions switch places again and the regenerated system is put back into service. There are several ways of detecting when the softener needs regenerating, but the most common system used today measures the water usage and, dependant upon consumption, regenerates, on average, every 3 or 4 days – usually at 2.00 am when water demand is unlikely.

Modern softeners are highly efficient in terms of both salt and regenerant-water consumption.

Health Implications

Eczema

The possibility that atopic eczema can be aggravated by bathing in hard water has emerged over recent years – initially due to care reports of people with eczema reporting that their skin condition improved when they moved from a hard to soft water area . A study[1] conducted in the Nottingham area showed that variation of water hardness between approximately 125mg/l and 275 mg/l was associated with an increased prevalence in children with atopic eczema in the harder water area by about one third.

This, of course, could be due to something else in the hard water – rather than the hardness itself – or, perhaps, to a beneficial ingredient of the naturally soft water. However, domestic water softener manufacturers regularly receive reports from their distributors of anecdotal evidence that installation of a softener has improved the symptoms of an occupant eczema sufferer.

As a consequence of the Nottingham study, an application was made in May 2003 to the Medical Research Council for a randomised, double blind clinical trial, involving the installation of some 300 softener units (50% placebo) into homes of confirmed eczema patients. Unfortunately the application for funding was declined in September 2003 on the grounds of priority, but it is intended to resubmit the application later in 2004 or in 2005.

Potability

Softened water has been criticised in the past with regard to its suitability for drinking purposes – largely due to three concerns: minimum hardness, microbial regrowth and sodium level.

Minimum hardness

As early as 1961, epidemiologists were aware of a slightly higher (10 –15%) incidence of cardiovascular disease among the population living in very soft water (25mg/l as $CaCO_3$) regions compared to those living in moderately hard water (>170 mg/l as $CaCO_3$) areas.[2] The precise cause of the relationship has not been established: it is not known whether it is a positive benefit of drinking hard water or a negative (toxic) attribute of the soft water. Attempts to correlate the

incidence of heart disease with specific minerals, such as calcium or magnesium, have proved inconclusive – perhaps not surprisingly, in view of the fact that the major portion of the daily diet for these minerals is satisfied by food intake. However, in the instances where "artificially softened" water impacted on the studies, there was no evidence that it contributed to the adverse effect attributed to the naturally soft water. The British Heart Foundation[3] concludes that "There is no evidence that softening the water has any effect on the incidence of heart disease".

Microbial regrowth

The primary objective of municipal water treatment is to ensure that the treated supply "is free from any micro-organisms and parasites and any substances which, in numbers or concentrations, constitute a potential danger to public health." At the water treatment works, therefore, pathogens are effectively removed and a residual chorine level is dosed as a protection against possible contamination (in-leakage) en-route to the consumer, but also to reduce microbial growth which could otherwise present a nuisance problem in terms of odour and/or taste. Heterotrophic bacteria will grow in the distribution system particularly in areas of stagnation. Growth of heterotrophic bacteria in domestic softeners has been assessed[4, 5] and is typically less than 1 log (factor of 10), which, in microbiological terms, is not significant. It complies with the European Drinking Water Directive[9] and the national Water Regulations.[7] Indeed, when raised at a World Health Organisation conference in April 2002, the conclusion of the subsequent expert consultation[8] was: "Increases of HPC (due to growth) in these devices therefore do not indicate the existence of a health risk, so long as the entry water meets acceptable water microbial quality norms (e.g. WHO Guidelines for Drinking-water Quality[9])."

Sodium

The sodium levels of softened water will depend upon the hardness level of the water supply. A typical 300 mg/l hard supply will increase the sodium level in the softened water by 137 mg/l. The European Drinking Water Directive includes sodium as an indicator (i.e. non-mandatory) parameter only – at 200 mg/l based on taste. The UK has translated the EU Directive into a mandatory level of 200 mg/l for the England and Wales Regulations – no other European country has applied this restriction. This tightening of the sodium parameter by DEFRA was based on Department of Health advice "that the primary aim is to help prevent infantile hypernatraemia and a secondary aim is to assist recommendations to reduce sodium intake in the general population." Notwithstanding the controversy that surrounds the ultimate benefit of universal dietary salt restriction,[10] softened water contribution is minimal comprising, in the worst case, only 10% of the normal dietary salt intake. The installation of a water softener in the majority of the hard water areas does not increase the sodium level above the recommended 200ppm.

Separate drinking water tap

Most would argue that the justification for an unsoftened drinking water supply at the kitchen sink, emanated from the above historical concerns. Water supply companies, on the other hand are charged with verifying water quality "at the point where it is available for consumption" and they require an unsoftened sample for this purpose. The Water Supply Industry recommendations[11] to the Water Fittings Regulations include provision of a separate drinking water tap on the grounds of potential "improper operation and maintenance". Perhaps the basic requirements here, are that the softener should be professionally installed and in regular use.

The pragmatic view of the industry is that, wherever possible, a separate tap should be offered in order, at the very least, to give the consumer the option to choose.

Conclusion

Water softeners have been used in domestic applications for many years and show benefits in economy of soap and detergent usage, reduced scaling of hot water systems with consequent saving in operating and maintenance costs, and convenience in terms of domestic cleaning chores. There is anecdotal evidence that softening the hard water supply can have a beneficial effect for atopic eczema patients and, to verify this observation, double-blind, intervention trails are being proposed to obtain clinical support.

Latest data and regulations support the contention that softened water meets recognised drinking water quality standards, but recommendation that a separate "hard" drinking water tap should be provided, where possible, are supported by industry and regulators alike.

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Empowering and Educating People with Diabetes in the Light of the NSF

Gwen Hall

Background

The National Service Framework for Diabetes: Standards[1] and Delivery Strategy[2] focus on key areas in the modern management of diabetes and confirm that;

- The onset of Type 2 diabetes can be delayed, or even prevented;
- Effective management of the condition increases life expectancy and reduces the risk of complications;
- Self-management is the cornerstone of effective diabetes care.

People with diabetes will surely welcome this news. After all, many at risk of type 2 diabetes, who have not yet got this serious condition, are going to be educated to help them avoid it and, if they do develop diabetes, they are going to be empowered to make decisions about their own care. Welcome too will be the expected improved communication between all health care professionals - and the people for whom they care. NSF Standard 3 is highly relevant here (Figure 1).

How is Standard 3 going to be achieved?

The Oxford Dictionary definition:

Educate: *give intellectual and moral training to; provide schooling.*

Empower: *Authorise; license; give power to; make able.*

It will be achieved through teamwork, involving the person with diabetes at the centre of that team, and through education and empowerment. New and innovative ways of working are emerging and will continue to develop throughout the ten years planned to reach the NSF targets. See www.doh.gov.uk/nsf/diabetes for examples of good practice.

This is in keeping with the DOH principles of The NHS Plan, The Expert Patient and Shifting the Balance of Power (Figure 2).

What are people's concerns?

An Audit Commission[4] survey (Figure 3) informed the NSF and highlighted gaps in patients' understanding of diabetes and variations in their care. It considered the high cost of diabetes, not just in terms of hospital admissions and community care but patient suffering too, could be alleviated through better standards of education and systematic care.

Four key stages were identified which will be discussed here.

Prevention of diabetes

Up to half of all new cases could, in theory, be prevented by reducing rates of obesity.

Early diagnosis

Up to half of all people with diabetes already have serious complications when diagnosed.

Long Term Care

Good blood glucose control can reduce kidney damage by one third, and good blood pressure control can reduce strokes by one third.

Intervention for complications

Eye screening and treatment can reduce blindness by half and footcare can reduce complications by two-thirds

Prevention of Diabetes

The implications for those planning the service requires a review of local strategies for improving diet and nutrition, increasing physical activity, reducing overweight and obesity, and helping people to maintain weight loss. Not only do these need to be developed but people at risk need to be involved in the

Figure 1 National Service Framework for Diabetes: Standards[1]

Standard 3: Empowering people with diabetes	All children, young people and adults with diabetes will receive a service which encourages partnership in decision-,aking, supports them in managing their diabetes and helps them to adopt and maintain a healthy lifestyle. This will be reflected in an agreed and shared care plan in an appropriate format and language. Where appropriate, parents and carers should be fully engaged in this process.

Figure 2 Shifting the Balance of Power: The Next Steps[3]

Patient Experience

These reforms will and must be driven by giving patients a greater voice in the running of the NHS. Patients will become active partners in their care, receiving more information so they can make more informed choices, both about the health services they receive and about their own treatment. Communities will also be involved in the strategic planning and decision making to ensure the NHS is responsive both clinically and to patient experience overall.

Figure 3

"I did not realise how serious diabetes was at first. Perhaps I might have taken it more seriously if I knew then what I know now"

Audit commission survey of people with diabetes

planning and the message needs to reach those who would most benefit. This is, of course, most relevant for Type 2 diabetes – research is underway to detect measures for Type 1.

This prevention strategy bridges many NSFs, particularly Older People, Coronary Heart Disease (CHD) and Diabetes. Diabetes prevention cannot be seen in isolation. 75-80% of people with Type 2 diabetes will die of macrovascular disease,[5] mainly CHD.

People who have risk factors for developing diabetes (Fig 4) should be screened at an early stage and offered education and support to empower them to make the necessary lifestyle changes to increase their chances of preventing, or delaying, its onset.

National health promotion programmes, such as the Five-a-day scheme (www.doh.gov.uk/fiveaday) will be expanded but other local initiatives will be valuable too and can be tailored to local need.

Early Diagnosis

People with Type 1 diabetes normally become ill rapidly and seek medical attention. There is failure of the Beta cells to produce sufficient insulin and referral to specialists a matter of urgency. Awareness of the symptoms might enable people to seek that advice earlier but it is in Type 2 again where early diagnosis makes all the difference.

An agreed, and shared, care plan (Fig 5) involves the person with diabetes in their own care and aids communication between the many members of the team, both primary and secondary, specialist or non specialist.

Empowerment requires education and experience shows this is best handled by a known and respected figure. The NSF proposes a named local contact for people with diabetes. This person acts as an initial point of contact, helping the person with diabetes navigate the service and access other members of the multidisciplinary team as appropriate. They may also be the team member who takes the lead in reviewing the diabetes management.

The role of the named contact is particularly important at those times when diabetes care is most difficult – for example, at diagnosis, when changing treatment, or during adolescence and the transition to adult services. Good practice shows that they should be identified in discussion with the person with diabetes (figure 6).

Screening for diabetes should be offered to those who:

- **Have a strong family history of diabetes**
- **Are in an ethnic group at increased risk**
- **Are obese**
- **Have hypertension**
- **Have heart disease**
- **Have slow to heal infections or repeated infections**
- **Have had gestational diabetes**
- **Have had impaired glucose tolerance or impaired fasting glucose in the past**
- **Are elderly; especially if confused**

Figure 4.

Figure 5. NSF Delivery Strategy; Care Plan

A personal diabetes record:

- **Includes an agreed care plan, including education and the personal goals of the person with diabetes;**
- **Sets out how their diabetes is to be managed until their next review to foster greater understanding and ownership of the goals of diabetes care;**
- **Identifies health, social care and education needs, how they will be met and who will be responsible;**
- **Identifies the named contact.**

"I have nobody to contact after hours and sometimes feel very alone with this"

Audit commission survey of people with diabetes

Figure 6

There is emerging evidence that group education enables learning through shared experiences and pooled knowledge. Where this is practical service providers need to consider how best to organise scant resources and involve people with diabetes in their plans. Has Diabetes UK got a local group running? If not, is there a way to facilitate it? Is there an Expert Patient group? This self management scheme for people with long term medical conditions is developed and run by patients for patients. More information can be found at www.ohn.gov.uk/ohn/people/expert.htm . Pilots are currently being run in primary care.

The most important thing about education is that it is available to ALL and a variety of methods may need to be deployed.

Long Term Care

Figure 7 provides a particularly sad statement, especially when you consider that spending on testing strips in some areas outweighs that of medication. One study[6] concluded that testing with Type 1 diabetes was effective but that there was less evidence for Type 2.

The National Institute of Clinical Excellence (NICE),[7] whilst advocating HbA1c 2 – 6 monthly to assess long term control, acknowledges the usefulness of self monitoring when combined with an education plan and care package:

- Self-monitoring should not be considered as a stand-alone intervention;
- Self-monitoring should be taught if the need/purpose is clear and agreed with the patient;
- Self-monitoring can be used in conjunction with appropriate therapy as part of integrated self-care.

Combine that with the knowledge gained from the DARTS[8] study, that approximately half of our patients do not take all of their medication as we might think they do, and education and empowerment emerge as the backbone of care. Only 7 per cent of adults with diabetes manage to follow all the steps healthcare professionals prescribe for optimal management and good glycaemic control.[9] Care plans will enable patients to be involved in the decision making process – but only if the plans are tailored to their needs.

A key element of the NSF Delivery Strategy emphasised the need for regular review. This would enable the person with diabetes and the lead health professional to bring together all the relevant information and agree a care plan for the future. It also provides the opportunity to discuss:

"I have no idea whatsoever why I do daily blood checks.... I have not the remotest idea what I am keeping the record for"

Audit commission survey of people with diabetes

Figure 7

- The successes of and barriers to self-care;
- The key elements of diabetes care including glycaemia, blood pressure and cardiovascular risk reduction;
- The results and implications of the surveillance programmes for eyes, feet and kidney damage;
- Ensuring speedy access to appropriate services should problems occur.

A checklist for the review discussion is available at www.doh.gov.uk/nsf/diabetes

Intervention for complications

It is now clearly understood that early detection and treatment can prevent, or halt the progression of, complications,[10, 11] It is important that people with diabetes, and their carers, understand this too.

Diabetes UK publishes a plethora of patient education materials. One, *What diabetes care to expect*, is particularly relevant in the context of empowerment and education.

If people with diabetes are to be fully involved they should know what to expect. Health professionals should not see this as a threat.... It is not there to be used as a stick with which to beat us. It is there to enable, yes, and empower, us to work with patients and carers to achieve high standards. Testing Times highlighted inequalities in care. Surely it is advisable for one person with diabetes to understand what care they should be receiving and work with health professionals to see that it is available to all? Read this booklet – your patients should!

"The most important thing is education in all aspects of the disease... I have been insulin-dependent for 43 years and can still do 10 press-ups.... It is not all gloom and doom!"

Audit commission survey of people with diabetes

Figure 8

The future

That self management is pertinent to diabetes is ably demonstrated in Type 1 by DAFNE.[12] Few patients alter their insulin from day to day or achieve the degree of glycaemic control known to be ideal but this study has achieved considerable success by educating and empowering people with Type 1 diabetes to make appropriate adjustments to their insulin regime in order to improve their overall control.

Empowerment cannot be achieved without education and Diabetes UK has published a report and recommendations, including examples of good practice, on its website.[13] People with diabetes will be involved in planning issues too – through Networks and, where they exist, Local Diabetes Services Advisory Groups (LDSAGs), or other local initiatives. The NSF Delivery Strategy provides an example of the suggested setup of a Network (Figure 9).

So, it is accepted that people with diabetes are going to be involved in service development and individual care plans at all levels. How will health professionals obtain feedback from these individuals?. Patient Satisfaction Questionnaires are becoming more widely used and will give an unbiased opinion on service development. One leader in this field reported back as early as 1999.[14] It's not just patients who need empowerment and education. Seek the views of those who use the service and prepare to change your practice to suit.

Useful websites

Changing Workforce Programme pilots:
www.modernnhs.nhs.uk

Department of Health
www.doh.gov.uk

Diabetes UK
www.diabetes.org.uk

Expert Patient programme
www.ohn.gov.uk/ohn/people/expert.htm

National Electronic Library for Health (NeLH)
www.nelh.nhs.uk

NHS Modernisation Agency
www.modernhs.nhs.uk

NICE
www.nice.org.uk

NSF for diabetes
www.doh.gov.uk/nsf/diabetes

Quality Indicators in Diabetes Services (QUIDS) system
www.quids.org.uk

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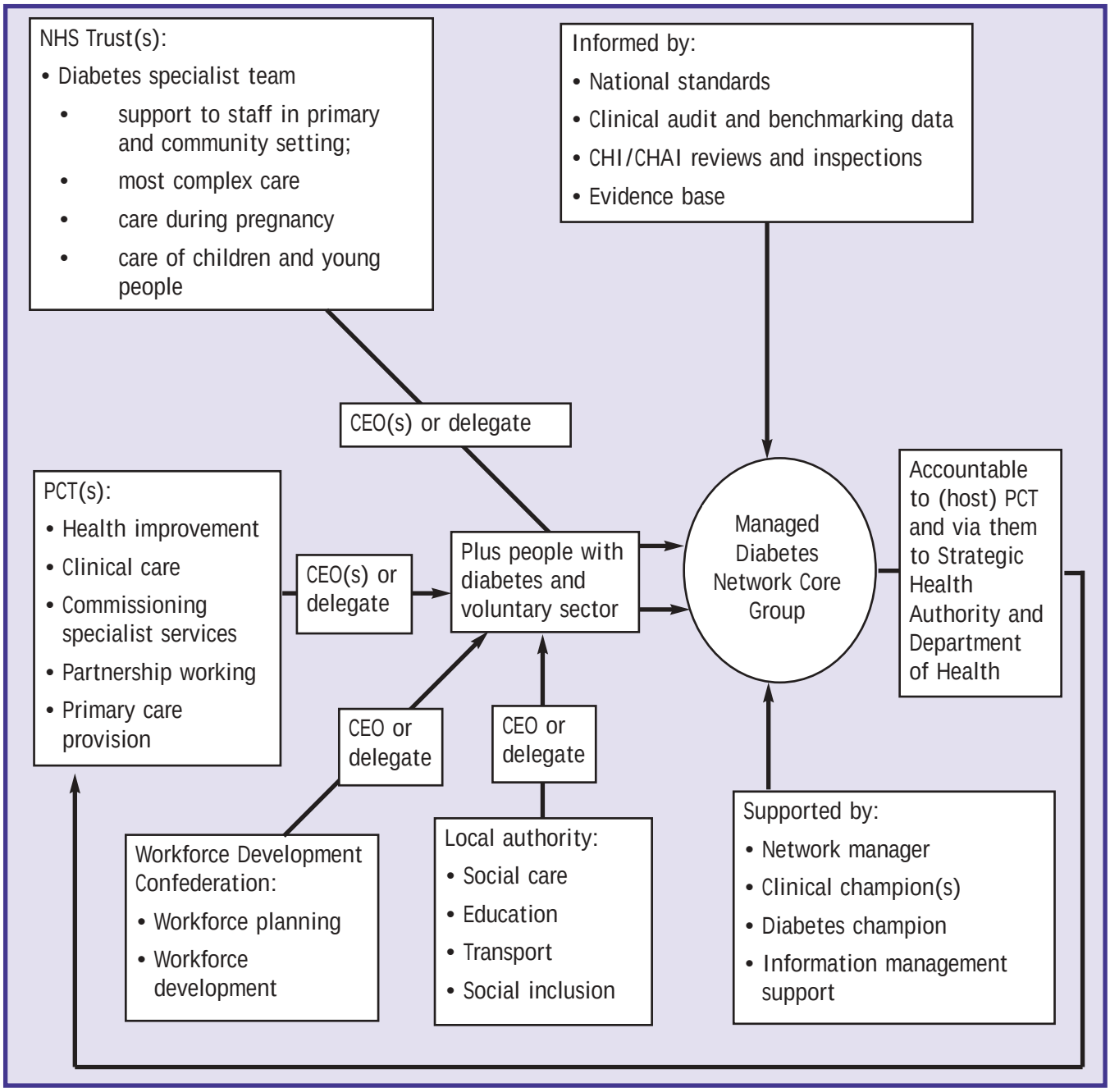
Figure 9. NSF for Diabetes delivery strategy local network



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Gwen Hall RMN RGN BSc (Hons) is a Diabetes Specialist Nurse for Guildford and Waverley PCT and a Practice Nurse for Haslemere Health Centre which is featured as a case study on the Audit Commission and NSF websites as an area of good practice.

She is an Advanced Leader for the University of Warwick Certificate in Diabetes Care involving GPs and primary care nurses. In addition, Gwen is a leader for Making It Happen training for the British Heart Foundation.

She is associate editor of Diabetes and Primary Care Journal and on the editorial board of Practice Nurse. Gwen was a founder member of Primary Care Diabetes UK.

Insulin Prescribing & Delivery Systems in Primary Care

Dr Roger Gadsby

The vast majority of people with type 1 diabetes in the UK will have been started on insulin under the auspices of a hospital consultant, and continue to receive supervision and follow up in secondary care. They will get their insulin prescriptions from general practice, but may not have much other contact with primary care. Many health care professionals in primary care have therefore had little practical experience or understanding of insulin therapy. When they open MIMS and see the huge variety of insulins, delivery systems and insulin regimes that are available, many feel overwhelmed. Insulin prescribing may then get viewed as a very abstruse art that only diabetologists and diabetes specialist nurses understand.

People with Type 2 diabetes who do not achieve good glycaemic control despite maximal doses of oral hypoglycaemic agents may benefit from insulin. In the UK we are in the midst of an explosion in the numbers of people diagnosed with type 2 diabetes.[1] Many secondary care services are already feeling overwhelmed. In some parts of the country, people with type 2 diabetes can wait for 6 months to be assessed for, and initiated on, insulin in secondary care[2] The ability to decide whether or not to start insulin treatment, and the practical initiation of that therapy will therefore be skills that need to be developed in primary care. Insulin prescribing can be simplified, and I hope that by the time you have finished reading this article you will agree!

Insulin delivery systems

Most insulins are available in 10ml vials, pen cartridges and disposable pens. A good analogy is that of pen and writing. Vials are like dipping a quill into ink, insulin cartridges are like cartridge pens, and disposable pens are biros! Pen technology enables insulin to be carried about easily and enables injections to be given where and when required. Insulin doses can be dialled up more accurately using the pen devices, and it is easier to teach people to use pen devices than it is to draw up insulin into a syringe from a vial. Most people moving onto insulin when offered a choice prefer pen devices and they are now commonly being prescribed for initiation of insulin in both Type 1 and Type 2 insulin. Some health care professionals prefer cartridges and others the disposable pens. Patient choice should inform the decision as to which to use.

A few people with Type 1 diabetes use continuous infusion pumps, which give a slow steady infusion of short acting insulin. Pump technology has developed significantly in the past few years. However it is expensive and there are limited NHS funds for it.

Insulin regimes

Basal Bolus therapy is the insulin regime in which an injection of short acting insulin is given just before each meal with one injection of long acting insulin at night. People using this regime usually have 4 injections a day. It gives flexibility to cope with different meal times, size of meals and exercise.

Another regime is to have two daily injections of premixed insulin one before breakfast and the other before the evening meal.

People with Type 2 diabetes who come to need insulin may be best controlled on one injection of long acting insulin per day, with the continuation of some or all of their oral agents.[3]

Types of insulin

Pork and Beef insulin is still available for those who need it. However the large majority of people use recombinant human insulins. There are basically short and longer acting insulins.

Short acting insulin - These are known as clear or soluble insulins. They have a peak action 2 to 6 hours after injection. They should be given 20 to 30mins before meals. One of the best known examples is Human Actrapid

Longer acting insulins - These are cloudy insulins. They are made by precipitating insulin or protamine-insulin in the presence of zinc. This forms insoluble crystals that are injected as a suspension and absorbed slowly. These insulins have a peak action at around 8hours after injection, but their effect may last for up to 18hours in some people.

Pre-mixed insulins - These contain combinations of soluble, short acting and crystalline long acting insulin. A combination of 30% short acting and 70% long acting is one that is often used, but 10:90, 15:85, 20:80, 25:75, 40:60,and 50:50 combinations are produced by different companies.

Short acting insulin analogues - These have been developed by minor alterations to the amino acid sequences of human insulin to produce insulins that have a quicker onset of action, and shorter duration of action than normal soluble insulin. Two are available, Insulin lispro, which is identical to human insulin apart from inversion of lysine and praline residues at positions B28 and B29, and Insulin aspart which is identical to human insulin apart from the substitution of praline at B28 with aspartic acid.

Both analogues have similar pharmacokinetic profiles, peak action is around 1 hour after injection

and their effect wanes after 4 hours. This means that they can be injected just before a meal, and they reduce the risk of postprandial hypoglycaemia.

They are now available pre mixed with longer acting cloudy insulins in varying combinations for those using a twice daily premix regime.

Long acting insulin analogue - Insulin glargine is the first long acting analogue to be developed and marketed. It is the same as human insulin apart from a substitution of glycine for asparagines at A21 and the addition of two arginine molecules at the C terminal end of the B chain. This results in a change in properties of insulin glargine. It is soluble at acidic pH and so is the first clear long acting insulin. When it is injected it forms a microprecipitate within the more neutral ph of the subcutaneous tissues. This results in slow absorption from the injection site. It has a flat profile of action with no pronounced peaks, a duration of action of around 24hours and is subject to less inter and intraperson variability than previous cloudy long acting insulins.[3] As a result there is often a reduction in hypoglycaemic episodes in people using insulin glargine.

Repeat prescription monitoring

1. Ensure that they are receiving a full annual review. If this is being done in secondary care make sure that the results are documented on the general practice computer system, and that results from eye screening and footcare screening are tabulated. If there are not receiving an annual review in secondary care, ensure that it is carried out in primary care, and that the results are documented.

2. Ask about any problems or difficulties they may be having, and how they feel.

3. Review self monitoring results and discuss self adjustment of insulin doses.

4. Inspect injection sites.

5. Review any educational issues.

Initiating insulin therapy in type 2 diabetes in primary care

Deciding that this person would benefit from insulin. There is no strong evidence base to determine exactly when insulin therapy should introduced, but that it should be considered in patients who meet the following criteria:

1. Very poor glycaemic control as evidenced by persistently elevated HbA1c (no consensus as to exactly what level!)

2. Symptoms of polyuria, polydipsia, nocturia and/or recurrent infections such as balanitis and thrush

3. Currently receiving maximal dosage of oral agents

4. Already have optimised lifestyle changes

A key factor that will need to be addressed is the individuals views, attitudes and fears. These usually involve worries about the fear and pain of injections, and the risks of hypoglycaemia. The needles used for insulin injections today are very short and thin, and as a result injections are almost painfree. The risks of hypoglycaemia may be minimised by using simple insulin regimes, continuing oral agent therapy with metformin, and considering using once daily insulin glargine with its lower hypoglycaemic risk profile.

Initiating insulin. Individuals starting on insulin need to be monitoring their glycaemic control by measuring blood glucose using a meter.

The techniques of how to dial up the correct dose of insulin from a pen device, giving the injection and adjustment of insulin dosage all need to be demonstrated, and taught.

The person newly starting on insulin needs to be observed giving an injection. They then may need close support and supervision over the first few days and weeks. Diabetes specialist nurses (DSN's) are the heath care professionals that usually do this work. Practice nurses in some areas are beginning to initiate therapy with the support of GP's, local DSN's and consultant diabetologists. There are now short courses available on insulin initiation in primary care to teach these skills.

In some areas, groups of individuals are being initiated on insulin in so called "group start" programmes often supervising by a DSN working in the community.

Courses on insulin initiation

For details contact: Warwick Diabetes Care
Tel 02476 572958, Fax 02476 572959,
Emai:l diabetes@warwick.ac.uk
Website: www.diabetescare.warwick.ac.uk

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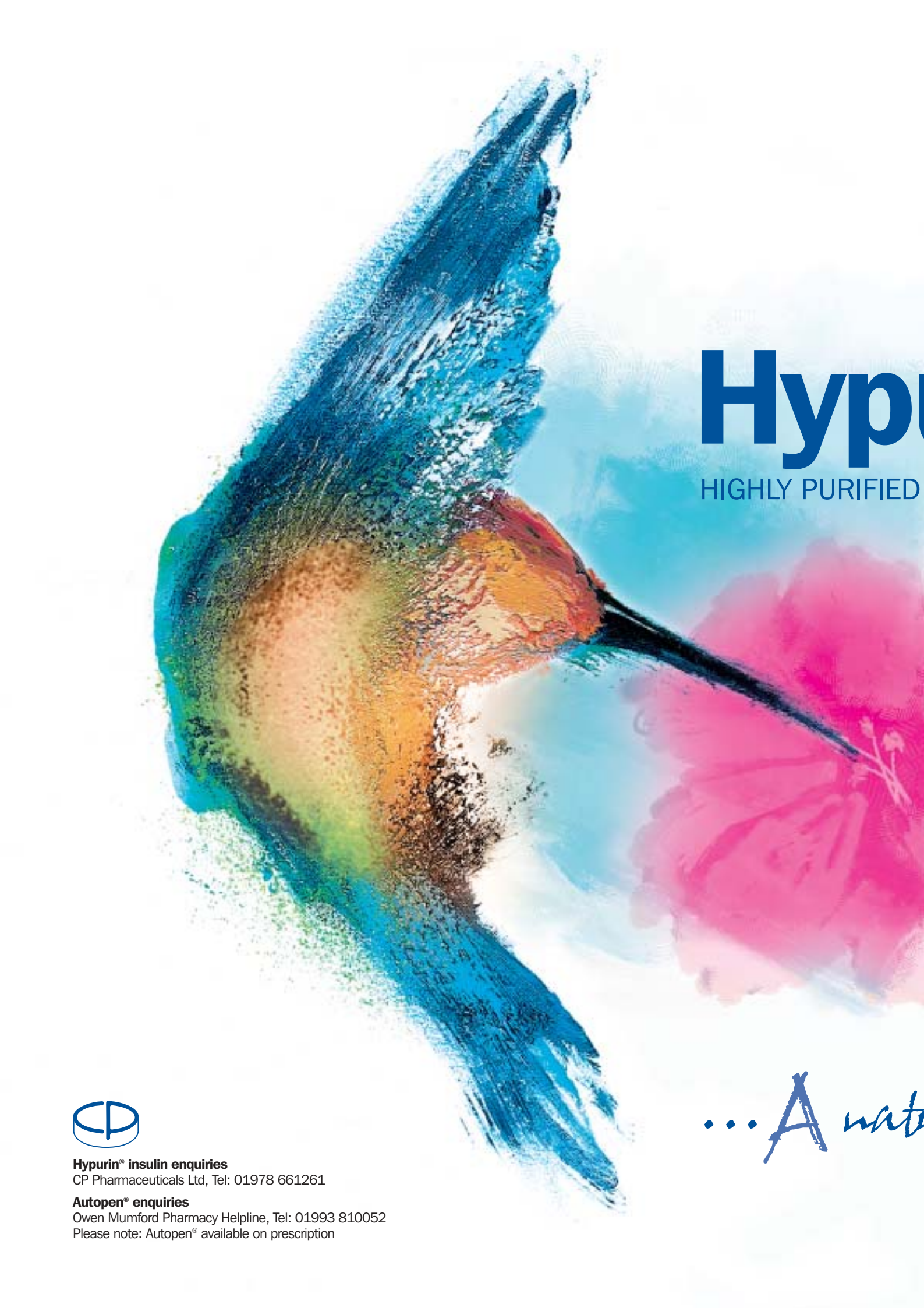

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HP11/03 March 2003

Type 2 Diabetes
Management in a Primary Care Setting

Dr Louise Newson

Why is type 2 diabetes important?

It is a very common disease

Diabetes is one of the most common chronic diseases in the Western world; 1.4 million people in England have diabetes and it has been estimated that there are one million people with undiagnosed diabetes.[1] The numbers are expected to more than double, reaching 3 million by 2010.[2] This increased incidence is mainly due to:

- Increasing ageing population (10% of people over 65 years have diabetes)
- Increasing obesity (approximately 1 in 5 of the UK population is now obese; predicted to rise to 50% of the population by 2030)
- Increasingly sedentary lifestyles

Diabetic patients have a higher risk of other important diseases

A diagnosis of diabetes is associated with high levels of morbidity and mortality; there is overwhelming evidence that the complications of diabetes cause numerous problems for people with the disease, their carers and also the NHS. Diabetes is the leading cause of blindness, kidney failure and limb amputation. Patients also have a higher incidence of heart disease (4/5 of deaths of diabetics are due to coronary heart disease) and strokes. Early treatment for diabetes reduces the risk of complications.[3] Life expectancy is reduced by up to 10 years in type 2 diabetics.

Diabetes is expensive to treat

Treatment of type 2 diabetes accounts for 5% of total NHS resources and 10% of hospital in-patient resources; the average cost for an in-patient stay is six times more for a diabetic compared with a non-diabetic for the same condition. In addition, people with type 2 diabetes are five times more likely to be admitted to hospital than the general population; once admitted they are likely to stay there twice as long as average. Surprisingly, expenditure on oral therapy for type 2 diabetes is relatively low – accounting for only 2% of the total disease expenditure.[4] It has been estimated that treating diabetes costs £1500 - £1700 per patient annually; equating to £4.33 million for an average Primary Care Trust per year.

Complications of diabetes

There is increasing evidence to confirm that meticulous glycaemic control can prevent or delay the onset of the complications of diabetes. The impact of these complications can also be greatly reduced if they are detected early and appropriately managed. Thus, regular surveillance for and early diagnosis of the complications of diabetes are also important.

There most important study to date regarding this is the UKPDS (UK Prospective Diabetes Study). This was a massive study involving over 5000 type 2 diabetic patients over a 20 year period, which studied whether intensive control of blood glucose after diagnosis of diabetes was beneficial.[3] It demonstrated that better glycaemic control reduced microvascular complications and intense management of cardiovascular risk factors reduced macrovascular complications. Essentially, the lower the levels of blood glucose, HbA_{1c} , and blood pressure; the lower the risk of complications.

Hypertension in diabetic patients

A study using the UKPDS data showed that any reduction in blood pressure for type 2 diabetic patients reduces the risk of complications.[5] Intensive blood pressure control is at least as (probably even more) important than intensive treatment of glucose levels in the reduction of complications in diabetic patients. However, it has been estimated that the number of diabetics taking antihypertensive medication would need to **double** in order to meet the target set from the UKPDS of 140/80!

Results from the HOPE (Heart Outcomes Prevention Evaluation) study also showed that adding ramipril to the drug regimen of high-risk diabetic patients provides vascular-protective and reno-protective effects independent of its effect on hypertension.[6]

Importance of diabetes in primary care

GPs have a pivotal role to play in ensuring that people with diabetes receive effective diabetes care. Diabetes care has been shown to be as good in primary care as secondary care; 75% of diabetic patients are currently routinely managed in primary care. However, most GPs still feel they need more education about diabetes[7] and many do not feel confident about treating diabetic patients. In addition, many health care professionals consider diabetes harder to treat than other chronic conditions and also feel they have less time and resources to treat their diabetic patients effectively.[8]

Secondary care diabetes services are stretched and many patients still complain of long clinic waits and insufficient time with clinical staff.[9] It is therefore very unlikely that secondary care will be able to cope with the expanding numbers of diabetic patients.

Patients with type 2 diabetes often present to their GP late, with many people having established complications at the time of their diagnosis.

Management of type 2 diabetes

The key elements of effective diabetes care can be summarised as having:

- A planned programme of care for all patients with diabetes
- Clear management plans agreed with each patient, tailored to meet the needs of the individual and their carers
- Practice-based diabetes registers to facilitate regular call and recall of patients.

The management of diabetes is not just about managing the patients' glucose levels. In view of the high risk of cardiovascular disease in people with diabetes, particularly those with type 2 diabetes, the careful management of other cardiovascular risk factors, including smoking, physical inactivity, obesity and especially hypertension, in their annual diabetes review is essential. The goals of treatment are to prevent complications, improve quality of life and to avoid excess mortality.

NICE have produced guidelines on the management of blood glucose for type 2 diabetes.[10] It is recommended that patients have their HbA_{1c} reviewed every 2-6 months. The targets given in these guidelines are the ones used in practice (Table 1), although they are not always easy to reach. The guidelines address various important aspects of diabetes care, including blood pressure, early retinopathy, renal care and lipids management.

Patient education

Patient education is the cornerstone for effective management of diabetes. Healthcare professionals have a responsibility to provide appropriate education to equip people with diabetes with the knowledge, skills, attitudes and motivation to effectively manage their diabetes care and modify their lifestyle in such a way as to maximise their well-being.

The value of patient education is evident from research demonstrating that patients who never received diabetes education showed a striking four-fold increased risk of a major complication.[11] Diabetes education has been shown to be effective in promoting self-regulation behaviours such as self-monitoring of blood glucose and insulin adjustment but not lifestyle change such as dietary modification and increasing physical activity.[12] One study showed that people followed recommendations on average 50% of the time for diet, 35% for physical activity and 47% for foot care advice.[13]

Smoking cessation advice is also given, if appropriate. Stopping smoking is actually the most effective action a diabetic patient can take to improve their health.

HbA_{1c}	6.5 – 7.5%
BP	< 140/80
Total cholesterol	< 5 mmol/l
LDL-cholesterol	< 3 mmol/l
Triglycerides	< 2.3 mmol/l

Table 1 Treatment Targets for Type 2 Diabetics (based on NICE recommendations)

Control of blood glucose

First line treatment of type 2 diabetes is a three month trial of weight reduction and exercise, which improves metabolic control by reducing hyperglycaemia and body weight.[14] However, this is rarely sufficient in the long term, as diabetes is a progressive disease, almost all patients will eventually require drug treatment to control their glucose levels.[15]

Drug treatment

There are different effective medications available to treat type 2 diabetes. Many patients will need more than one drug to control their blood glucose levels. In the UKPDS after four years the mean HbA_{1c} levels had returned to pre-treatment levels in those patients given monotherapy.[15] Around 50% of patients will need more than one medication three years after diagnosis and after nine years from diagnosis 75% of patients will require combination therapy to maintain glucose and HbA_{1c} levels at acceptable levels.[14]

Metformin

Metformin suppresses hepatic glucose production and also enhances glucose uptake into muscle. It is the current preferred first-line treatment of type 2 diabetes as it is not associated with weight gain. In addition, it is the only agent which has been shown to reduce cardiovascular mortality.[14] It has been shown to reduce HbA_{1c} levels by 1.4% after 29 weeks in patients not well controlled by diet alone.[16] The most common side-effects are gastrointestinal in nature, these can be reduced by gradually increasing the dose from 500mg daily. The maximal efficacy is demonstrated at 2g daily; increasing the dose further is not associated with any additional benefit.[17] It should not be used in patients with renal impairment (creatinine > 130mmol/l), hepatic or cardiac failure.

Sulphonylureas

These drugs work by stimulating the production of insulin from ß-cells. Their mode of action leads to hyperinsulinaemia resulting in weight gain and hypoglycaemia. Although they have proved to be effective in reducing HbA_{1c} and fasting glucose levels, they have been shown to have a high secondary failure rate, with nearly 50% of patients failing to maintain good glycaemic control after six years of treatment.[18] They are still commonly used as either monotherapy or in combination with metformin.

Thiazolidinediones

These are a new class of drugs (also known as "glitazones") for type 2 diabetics which have fairly recently been introduced; rosiglitazone and pioglitazone were launched in 2000. They are highly selective and potent agonists of PPAR-gamma receptors (peroxisome proliferators-activated receptor), which are involved in the regulation of lipid synthesis and carbohydrate metabolism. They act to enhance insulin sensitivity within the body so are most effective in patients who still secrete insulin. As they resensitise the body to its own insulin, they can also be considered as insulin sensitisers.[19] As insulin resistance is an independent risk factor for cardiovascular disease,[20] the glitazones can often be a rational choice in therapy for type 2 diabetic patients.

They are licensed for combination use with a sulphonylurea or metformin (they are contraindicated for use with insulin). Although some clinical trials have demonstrated the benefits of using the glitazones as monotherapy, they are not licensed in the UK for this purpose. In addition they are not licensed to be used with insulin.

The addition of a glitazone to metformin or a sulphonylurea results in significant improvements to both HbA_{1c} and fasting plasma glucose concentrations. Combined therapy with metformin can achieve average reductions of HbA_{1c} of 0.8% and fasting plasma glucose of 2.1mmol/l.[21]

These new agents offer a real alternative in the treatment of obese patients who do not achieve sufficient blood glucose control with metformin. They are expected to postpone the need for insulin therapy in type 2 diabetics for some years. They also hold out the possibility that through treatment of insulin resistance, the macrovascular complications of type 2 diabetes may be reduced.

The glitazones can produce a modest increase in weight, typically 2-3kg during the first six months of treatment. They are contraindicated in patients with cardiac failure or hepatic impairment.

Other oral medications

Alpha-glucosidase inhibitors

This medication is a digestive enzyme inhibitor and works by delaying the digestion and absorption of carbohydrates leading to a small but significant effect in lowering blood glucose. Its use is limited by the marked gastrointestinal side effects, including flatulence, abdominal bloating and diarrhoea.

Meglitinides

These act in a similar way to sulphonylureas. They stimulate the rapid secretion of insulin from ß-cells when taken and therefore need to be taken before meals. They can be either used as monotherapy or in combination with metformin.

Insulin

Insulin is used for patients whose blood glucose control is poor, despite receiving optimal oral therapy.

What does all this mean for patients?

It is well known that in practice it is very difficult to maintain any reductions in glucose concentrations and blood pressure, even when multiple drugs are used in combination.

It has been estimated that to reach targets for HbA_{1c} and blood pressure, it could mean up to 10% of patients needing nine different medications.[22]

The compliance of diabetic patients is poorer than expected – one study[23] collected anonymous information on prescriptions from diabetic patients in Dundee and it showed that only one third of patients comply with single medications and about 10% comply with two medications!

The future of diabetes care in the UK will be challenging to primary care. Although clear therapeutic goals have been defined, doctors may need to negotiate realistic goals with individual patients regarding their optimal treatment.

Useful Websites:

www.diabetes.org.uk - Diabetes UK (formally the British Diabetic Association)
www.audit-commission.gov.uk - Audit Commission report
www.doh.gov.uk/nsf/diabetes/research - NSF for diabetes
www.nice.org.uk - NICE guidelines about diabetes

Summary points for diabetes

- Incidence of diabetes is rising
- 75% diabetic patients are routinely managed in primary care
- Meticulous glycaemic control can reduce complications
- Careful management of other cardiovascular risk factors is essential
- Targets are not always realistic

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In addition to treating patients, Louise also enjoys writing about medical conditions. She has a weekly column in GP Magazine called Pass Notes and authored the books 'Hot Topics for the MRCGP and General Practitioners' and 'MRCGP: Approaching the Modular Examination'. She also writes regularly for the medical website Onmedica.net on various topical clinical subjects.

Within your reach?

" In childhood...major differences in appearance may lead to enduring and profound personality difficulties" [1]

" Any child whose growth is causing serious concern to his or her parents should be assessed with care and considered for specialist referral" [2]

In short, children should be seen and referred

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References:
1. Skuse D. *J Child Psychol Psychiat* 1987; 28: 641–650.
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GEN019

Growth Hormones

matching patients to products – who decides?

Pauline Musson

There are currently four licensed indications for the use of Biosynthetic Growth Hormone (GH) in children. The NICE guidance whilst approving the use of GH in these patient groups draws attention to the high costs of the treatment and the importance of addressing concordance issues. Involvement of the family in choosing the device to administer the child's growth hormone has been shown to increase concordance. The features of the devices currently available and ways in which this information is shared with the family are outlined. The apparent inconsistencies in the usage of the different devices across the UK, and possible reasons for this are then discussed.

Biosynthetic Growth Hormone (GH) is currently licensed for use for promoting growth in children with growth hormone deficiency, chronic renal insufficiency and Turner syndrome. In children with Prader Willi syndrome the license is for use to improve growth and also for the metabolic effects of improved muscle tone and body composition. The daily dosage is dependent on diagnosis and body size. As highlighted by the National Institute for Clinical Excellence (NICE May 2002) it is a very expensive treatment (£23-24 per mg, see table 1) with £12,000,000 spent annually.

The NICE guidelines give clear advice that treatment with growth hormone should be withdrawn if there is not a 50% increase in growth rate or there are 'persistent and uncorrectable problems with adherence to treatment.'

In the management of any chronic condition there are potential difficulties ensuring concordance with treatment. That growth hormone can at the present time only be given by injection or transjection is likely to increase these difficulties. It is well recognised that some children with diabetes deliberately omit their insulin, even though they are aware that this is likely to result in re-admission to hospital with keto-acidosis (Morris et al 1997). However, as there are generally no ill effects from missing growth hormone (except in infants), apart from a decrease in rate of growth, and a final height shorter than that predicted (Hunter 2000) the importance of good concordance can be can be difficult for the families to appreciate.

Diagnosis	Mean annual costs in £
Growth hormone deficiency	6,103
Turner syndrome	10,126
Chronic renal insufficiency	11,132
Prader Willi syndrome	9,840

Table1: Mean annual costs for treating a child weighing 30 kg taken from NICE (2002).

Issues of compliance and concordance must therefore be taken into account when planning treatment with children and their families. Kirk (2001) and Burke (2001) discuss these issues and suggest strategies to promote concordance. Further work by Burke (2001) demonstrates a positive correlation between patients who were involved in choosing their own injection device and improved concordance.

So what are the choices?

Biosynthetic GH is currently available as 5 preparations in the UK.

Genotropin (Pfizer), Humatrope (Lilly), Norditropin (Novo Nordisk), Saizen (Serono) and Zomacton (Ferring). Each is produced by recombinant DNA technology and has a gene sequence identical to human GH.

All 5 pharmaceutical companies who manufacture growth hormone supply their own delivery device(s) and needles/consumables free of charge. The devices are not interchangeable. They also provide good support services to patients comprising of the following:

- Home training by a Registered Nurse to demonstrate and train family in use of chosen device.
- Follow up visits for concordance or difficulties with the device/injection as needed.
- Home delivery / dispensing service.
- Feedback to GP / Secondary care re concordance issues.
- Delivery of consumables and collection of clinical waste.

The features of all devices currently available are outlined in tables 2 & 3. The needle free transjection devices can be very useful for truly needle phobic children (or parents!) but care must be taken to stress that needle free does not mean pain free. Children report a sensation similar to being flicked firmly with thumb and middle finger. It is however instantaneous, whereas the injection pens may take 15 -20 seconds to deliver the required dose. For parents needing to restrain their unco-operative child this can be a major factor in their choice.

Figure 1. Some of the injection/transjection devices available.

As the services provided by all the companies appear equitable and they all claim to have reliable and user friendly devices, It would perhaps be a reasonable assumption that the choices outlined above are offered to all children requiring treatment with GH. This is however quickly dispelled by the variations in prescribing patterns across the UK.

So how much choice is there?

This is variable across the UK. A few centres offer the family free choice; some offer the choice between 2 or more products and a small number of centres do not offer any element of choice.

However even those that offer choice do not all fully demonstrate the device. Some centres demonstrate injection technique with each pen – others give the family videos / CD-ROM's to take home and ask the family to make their choice after watching them all. It is important to remember that the pharmaceutical companies provide the videos and they have been designed to highlight only the advantages of their particular devices.

Neither of these approaches gives the family all the information they need to make an informed choice. Ideally when offering options to the family all devices should be demonstrated in full, including reconstitution of the GH, assembly of the device, and administration of the daily injection. Time should be allowed for the family to handle each device and ask questions. This avoids them choosing the device that they feel offer the easiest daily injection and finding, too late, that they have great difficulty putting it together.

In reality it is usually part of the role of the Paediatric Endocrine Nurse Specialist to assist the family in making their choice. If the nurse specialist is unavailable or the centre does not have a nurse, then the consultant will need to give them the information. Unfortunately it is not often possible during busy clinics to give the family the time they need to make this decision. A further appointment may be offered, however some families, for a variety of reasons such as socio-economic or difficulties with transport, will not be able to attend.

Who Makes the Choice?

At the present time the Paediatric Endocrinologist who initiates treatment has ultimate control over the extent of the choice given to the families. Examples of ways in which choices are currently managed include:

- Using only one product: This may be historic – they have traditionally used this company and can see no benefits in change, or because they feel there is less likelihood of confusion/errors in dosages.
- Offering a limited choice: The products will be demonstrated as above. This may be historic or based on current preference of the consultant or other members of the multi disciplinary team (MDT).
- Selection by members of the MDT: For a child with complex needs, within a family with educational or social difficulties the team may feel that it is not appropriate to give the family the choice. This is a decision taken in conjunction with nurses from other specialty teams and the community nurses who will be involved in ongoing care and assisting in administering the GH.
- Based on diagnosis: The child is allocated a product according to the reason for treatment. E.g. A child with GH deficiency will be started on Genotropin, Turner syndrome will have Norditropin etc.
- In rotation: The first five patients each year will receive Saizen, the next five Zomacton etc.

Company /device	Features of device and *possible disadvantages*
Ferring ***Zomajet***	Dose delivered by pressing single button *Only available in 4mg vials.* *Requires loading daily.Frequent reconstitution needed.*
Serono ***cool click***	Available in 8mg vials. Multi dose. Dose delivered by pressing single button. *Fairly complex process to reconstitute GH prior to loading cartridge into device.*
Pfizer ***Zip Tip***	Dose delivered by pressing single button. Simple reconstitution of GH. *Fairly complex process to load device.Needs daily loading.*

Table 2. Features of currently available transjection devices.

Table 3. Features of injection devices currently available

Company / device	Features of device & *possible disadvantages*
All ***Autoinjector***	Needle is hidden. Quick. Pressing one button inserts needle and delivers dose. *Needs daily drawing up into syringe and loading device.Noisy.*
Serono ***One click***	8 mg vials. Multi dose. Needle is hidden.One button inserts needle and administers dose. *Fairly complex process to reconstitute GH prior to loading cartridge into device.*
Lilly ***Pen***	6, 12 & 24mg vials. Multi dose. Optional needle cover.Child/carer inserts needle. GH delivery by pressing button. *Not very child friendly Device needs updating (due within next 12 months)* *Support services not so well established in all areas.*
Novo Nordisk ***Pen***	Liquid GH. No reconstitution required.Multi dose.5/10/15 mg cartridges available. Refrigeration not required for 5 & 10mg. *More difficult to correct 'overdialling' of dose.*
Novo Nordisk ***Pen Mate***	As above.Needle covered. Automatic needle insertion. *Two buttons to press - one to insert needle other to administer dose.*
Pfizer ***Pen***	Available in 5.3 & 12 mg. Multi dose. Digital display in mg. Child/carer inserts needle. Optional needle cover. GH delivery by pressing button. *Button needs fair amount of pressure - can be difficult for younger children.*
Pfizer ***MiniQuick***	Single use device. No refrigeration needed.10 dosages available in increments of 0.2mg. *Larger volume 0.25ml.* *Dose increments mean optimum dosing not always achievable. Looks like needle & syringe.*

Free Choice?

Taken at face value these variations in prescribing patterns could be merely the result of consultant idiosyncrasy. However scratch beneath the surface and you may find another explanation.

As in many areas within the NHS there is insufficient funding to support the changes required to meet the challenges of the New NHS (1997) and reduction in junior doctors hours. Yet there has been a marked increase in the number of nurse specialists who have developed new skills and are an invaluable part of the MDT.

Look closely and it becomes apparent that in many centres the service would collapse if the pharmaceutical companies withdrew their financial support. As well as providing funding for education and training they also directly fund healthcare professional posts. At the present time for example, Pfizer part or fully funds 35 nurses within endocrinology.

The potential problems of dependence on pharmaceutical companies are clearly identified by Lexchin (2003) and Watkins (2003). Certainly within paediatric endocrinology, unless the practical and ethical issues related to funding are addressed, free choice will remain a concept, not an automatic right for the child and family.

Until then it could be argued that *'He who pays the piper calls the tune.'*

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Pauline Musson. RGN/ RSCN. Prior to joining the endocrine team at Southampton General Hospital in 1994 I had worked in neonatal surgery, medicine and outpatients.

In my role as Paediatric Endocrine Nurse Specialist I have learnt a great deal and developed many new skills, some of which were previously in the medical domain. In the future my role will continue to evolve, as I am fortunate to be part of an expert team more concerned with improving the service offered to families than preserving the boundaries between disciplines.

Obesity: Body Fat Analysis in a Clinical Setting

Professor Andrew Prentice

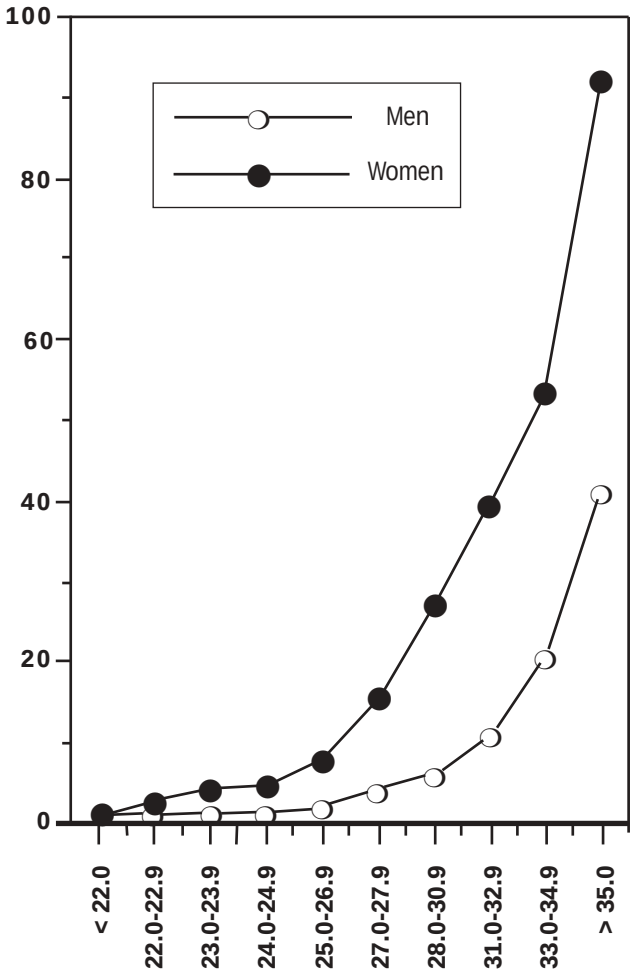
The escalating epidemic of obesity

The people of Britain are getting fatter – and fast. Figures from the Health Surveys of England have shown that obesity rates in England have almost trebled in less than two decades. Around one fifth of all adults are now classified as clinically obese (body mass index (BMI) > 30 kg/m^2) and well over half the population are overweight (BMI > 25 kg/m^2). The situation in middle-aged people is much worse than this.[1]

All clinicians are aware of the fact that obesity is an important risk factor for a range of serious co-morbid conditions, but many are unaware of the full strength of this relationship. Calculations show that obesity contributes about 20% to the attributable risk of heart disease and stroke. The figures for Type II diabetes are considerably greater since there is a particularly strong association between obesity and insulin resistance. This takes the form of a gradual, but usually inexorable, progression through impaired glucose tolerance (IGT) to non-insulin dependent diabetes mellitus (NIDDM). The strength of the obesity/NIDDM relationship is shown in Figure 1 from which two key messages can be drawn.[2,3] First that the association between obesity and NIDDM is stronger than for almost any other risk factor/disease relationship. Second, that the increased risk is almost continuous and starts at low levels of BMI. Note that in women the odds ratio for developing NIDDM rises to over 10-fold even in those who are simply classified as overweight. This has led to a call for NIDDM to be reclassified as 'obesity-related diabetes' .[4]

The National Audit Office has recently highlighted the need for the NHS to face up to the obesity epidemic and has estimated its current costs to the health service as £500 million.[5] The NAO report estimated that obesity accounted for 18 million days of sickness absence and 30,000 premature deaths in 1998. On average, each person whose death could be attributed to obesity lost 9 years of life. The wider costs to the economy in lower productivity and lost output were put at £2 billion each year.

Figure 1. Obesity as a risk factor for NIDDM in middle age



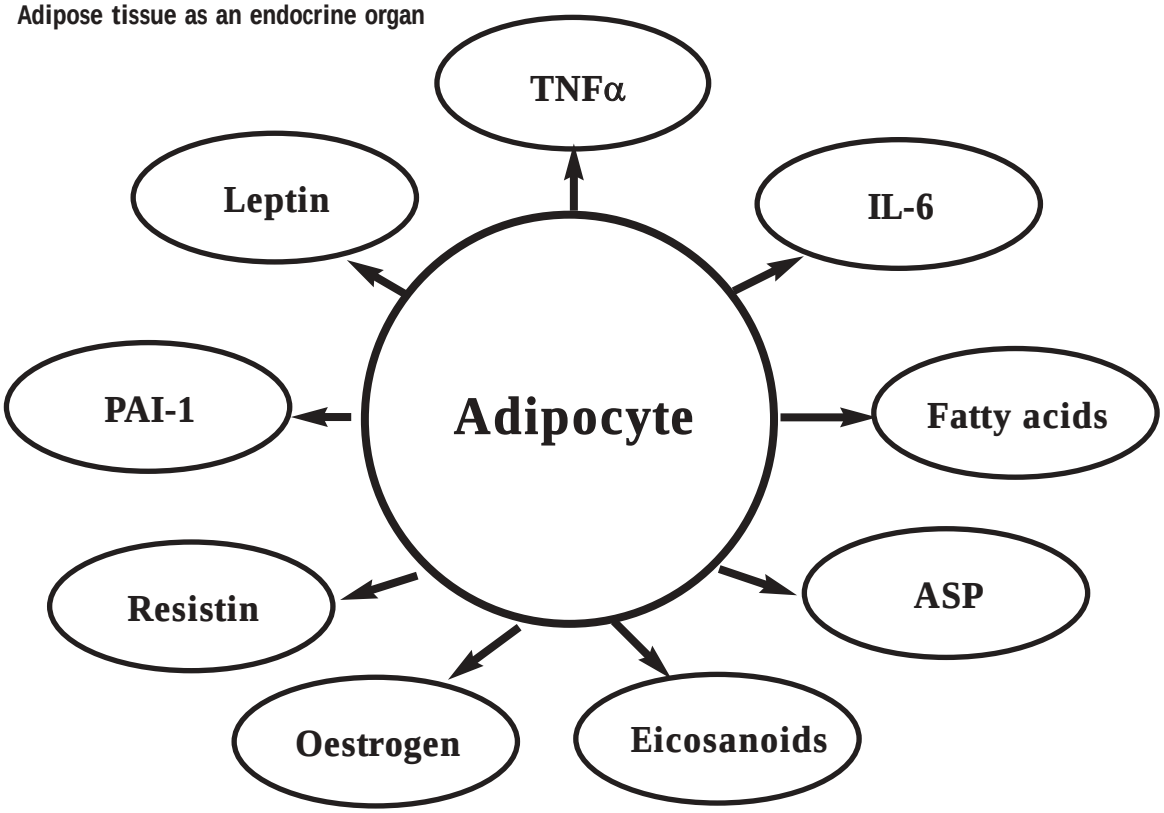
Adipose tissue: a new endocrine organ

Our understanding of fat cell metabolism has been revolutionised by new insights from molecular medicine. Adipose tissue has graduated from being viewed as a minimally active storage depot for unwanted fat (deserving less than a single page in Gray's Anatomy) to a fascinating metabolic tissue with multiple endocrine actions. Adipose tissue acts as a processor for a range of important metabolites and hormones such as oestrogen, and as the primary source for many others (see Figure 2). The circulating concentration of many of these highly-bioactive molecules is proportional to the size of the excess adipose tissue mass. Hence people whose fat mass expands can be thought of as growing a new endocrine organ.

Year of Survey	Prevalence of Clinical Obesity (%)*	
	Men	Women
1980	6.0	8.0
1986	8.2	12.1
1992	13.2	16.4
1998	17.3	21.2

**Percent of 16-64 year olds with BMI > 30kg/m^2. Data from Health Surveys of England.[1]*

Figure 2. Adipose tissue as an endocrine organ



Although the full details of the metabolic pathways have not been worked out yet, there is overwhelming evidence that the endocrine, exocrine and paracrine actions of several of these molecules are responsible for much of the comorbidity of obesity. Prime candidates among these are plasminogen-activator inhibitor (PAI1), interleukin-6 (IL-6), tumour necrosis factor (TNFa), leptin and resistin.[6] Resistin is a new adipocyte-derived hormone whose discovery was announced in Nature in January 2001.[7] As the name implies it is being heralded as possibly the key mediator of the link between obesity and diabetes, but only time will tell whether it lives up to the initial excitement.

Significance for clinical practice

Judging from the experience of running specialist training workshops for the Association for the Study of Obesity there are high levels of pessimism about obesity at all levels of the health service. There is a feeling that little can be done within a clinical setting. The National Audit Office report confirmed that NHS investment in the prevention and treatment of obesity falls far short of the level that would be justified on the basis of its health burden.

One of the key problems in this respect is the degree of ignorance about the true medical consequences of carrying excess fat. Most patients still consider it to be largely a cosmetic issue, and their own investment of time and effort in tackling the problem is rarely motivated by health concerns. Both preventive and treatment strategies could be improved if we can get across the message that maintenance of a healthy weight is one of the most powerful means that patients can use to avoid the chronic diseases of middle age.

To this end there has been much use of the body mass index as an educational and monitoring tool. Most GPs and primary health workers will be familiar with BMI charts marked with colour coding to indicate the different levels of health risk. Even within the general public there is quite a widespread (if somewhat vague) appreciation of BMI, and it is certainly well appreciated among the weight conscious. This much is progress, but surely we could do better - especially within the primary care setting?

Although BMI is an extremely useful index it has limitations in terms of its ability to assess actual body fat (and hence health risk) at the level of an individual patient. An often-quoted example highlights the problem of people with a well-developed musculature. For instance, many elite American football player has a BMI close to 40 kg/m^2 which would classify them as 'morbidly obese'. It would be a brave and foolish physician who would pass on this diagnosis. In fact, the average defensive linesman has a body fat percent at the bottom end of the normal range for men. This is an extreme example of a more general problem, particularly with black people who tend to have a higher lean-to-fat ratio. In the reverse direction BMI seriously underestimates body fat and health risk in most Asians, to such an extent that it is being proposed that the BMI cut-offs for overweight and obesity should be radically reduced for Asians.[8] A further example of the possible mismatch between BMI and body fat is shown in Figure 3 which illustrates the gradual conversion of lean to fat tissue which occurs with ageing.[9] A simple measure of BMI fails to detect this since BMI might remain constant even though there has been very significant fat gain. Direct monitoring of body fat would be far preferable.

Monitoring body weight and fat in a clinical setting

In the depths of rural Africa I have frequently been impressed by a mother's ability to show me her child's 'Road to Health' card with its weight plotted on the growth chart at each visit to the health centre. This graphical representation, against a set of accepted norms, is a powerful way of summarising the child's current nutritional status and the recent trends. A quick glance at the chart is all that is needed to aid clinical assessment. Similar charts could be used for adults in the UK. Yet extremely few general practices plot the weight of their patients over time so that they can monitor weight gain and give appropriate advice. This would be an important first step in raising the awareness of both patients and medical personnel to the dangers of weight gain.

The microchip and computer revolutions have provided us with a myriad of electronic devices for monitoring risk factors, and most GP practices are now moving over to computerised patient records. The possibility therefore exists for developing simple systems whereby patients are weighed (or even weigh themselves) as they enter the surgery, and for this data to be downloaded onto their patient record and plotted on an appropriate chart. Since height remains essentially constant in adulthood it would not be necessary to re-measure height each time in order for the computer to calculate BMI.

An advance on this system would be to actually monitor body fat. The state-of-the-art methods for doing this require impossibly expensive and time-consuming equipment such as dual X-ray absorptiometry, underwater weighing, or plethysmography. However, several manufacturers produce ranges of cheap body-fat monitors based on the principle of bio-impedance. This passes a minute electric current through the body (from foot-to-foot or wrist-to-ankle) and can assess body fat due to the differential electrical impedance of lean tissue (a good conductor) and fat tissue (a good resistor). Like all methods for measuring body fat (apart from cadaver analysis) bio-impedance relies on a number of assumptions and it uses in-built prediction equations derived against more complex techniques. Nonetheless it validates surprisingly well,[10] and could certainly be a useful clinical tool. The foot-to-foot methods have the great advantage of simplicity since patients simply need to remove their shoes and any heavy outdoor clothing before standing on a set of scales with electrodes on the footplate. Information on weight, BMI, body fat percent and lean body mass can be read off, printed or downloaded instantaneously.

Beyond BMI

It is important not to undermine the progress made through using BMI as an index of obesity. However, there may be real advantages in now trying to move one step further by focussing on the actual mass of excess body fat, since it is this that is causing the metabolic disturbances leading to disease. Regular monitoring of body fat and charting it in the patients' notes would provide primary health professionals with a valuable education tool. Its particular merit may be as a preventative tool whereby patients can be provided with real data as to how much fat they are gaining and lean tissue they are losing as they age. Since regular exercise, which is the most appropriate prescription to combat such trends, is not available at the pharmacist, motivational factors assume great importance.

Each year the HSE statistics show that the obesity epidemic moves on with a relentless predictability. The

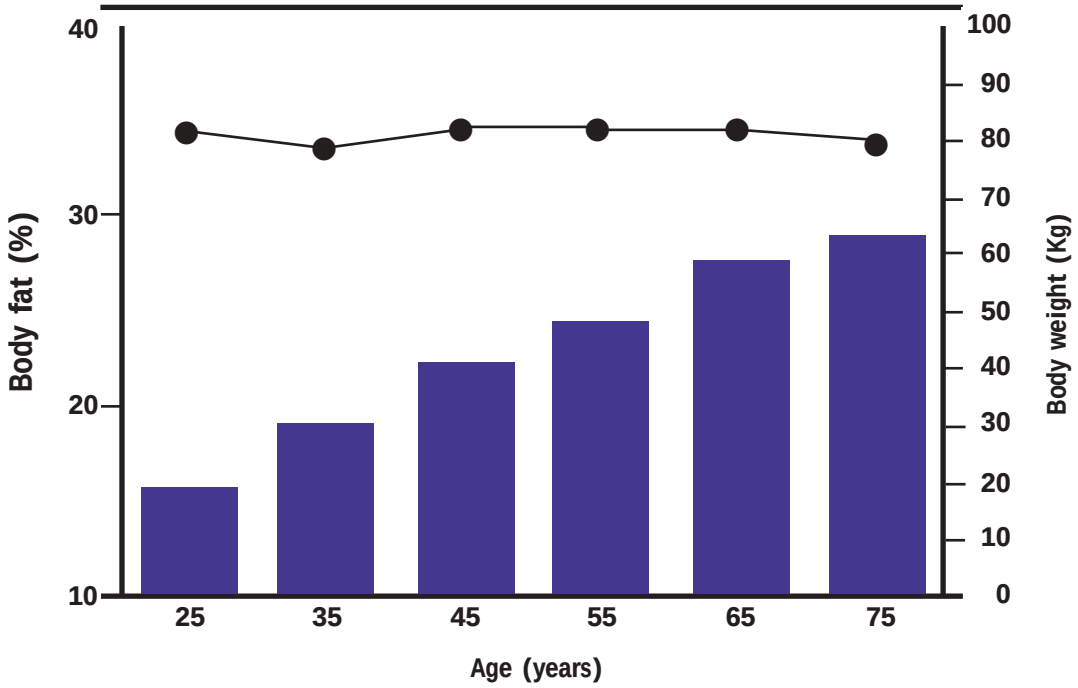


Figure 3. Changes with body composition with ageing (circles = body weight, columns = bodyfat)

Note that this data was collected several decades ago when body mass tended to stay quite constant in adulthood. Even under these conditions there are major changes in body composition with ageing. Current trends are even more pronounced.

National Audit Office projections indicate an annual cost to the economy of £3.5 billion in the year 2010 if nothing is done to stop it. The time has surely come for body fat analysis to join blood pressure as a common means of monitoring health risk in primary health care.

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Multiple Modes of Action of Antiepileptic Drugs

Dr Graeme J Sills

The number of drugs available for the treatment of epilepsy has doubled in the last ten years. With increasing choice has come inevitable uncertainty about the most appropriate treatment for the individual patient. Advances in our understanding of how antiepileptic drugs exert their effects at the cellular level may prove useful in the drug selection process. This article reviews the current status of antiepileptic drug pharmacology, highlighting those agents with multiple primary modes of action that may offer significant clinical advantages over their single mechanism counterparts.

The serendipitous discovery of the anticonvulsant properties of phenobarbital in 1912 marked the foundation of the modern pharmacotherapy of epilepsy. The subsequent 70 years saw the introduction of phenytoin, carbamazepine, ethosuximide, sodium valproate and a range of benzodiazepines. Collectively, these agents have come to be regarded as the "established" antiepileptic drugs.

The last decade of the 20th Century witnessed an explosion in the number of drugs available for the treatment of seizure disorders. In the UK alone, eight new drugs were licensed as add-on treatment for difficult-to-control adult epilepsy with some becoming available as monotherapy in newly diagnosed epilepsy. These agents have become known as the "new" or "modern" antiepileptic drugs.

This welcome expansion of the pharmacological armamentarium for the treatment of epilepsy does, however, complicate selection of the most suitable antiepileptic drug (or combination of drugs) for individual patients. Indeed, with more than 30% of epilepsy patients continuing to experience seizures on maximum tolerated doses of theoretically appropriate drugs, a rational basis for the use of all available antiepileptic agents in the management of seizure disorders is required. Twenty years ago, the successful selection of drugs for individual patients relied upon a combination of clinical experience, personal preference, and a healthy slice of good fortune. Since then, however, our understanding of how antiepileptic

Table 1: Proposed pharmacological targets of antiepileptic drugs

	Sodium channels	Calcium channels	GABA receptors	GABA synapse	Glutamate receptors
Phenobarbital			+ + +		
Phenytoin	+ + +				
Ethosuximide		+ + +			
Carbamazepine	+ + +				
Sodium valproate	+	+		++	
Benzodiazepines			+ + +		
Vigabatrin				+ + +	
Lamotrigine	+ + +	+			
Felbamate	+ +	+ +	+ +		+ +
Gabapentin	+	+		+ +	
Topiramate	+ +	+ +	+ +	+	+ +
Tiagabine				+ + +	
Oxcarbazepine	+ + +	+			
Levetiracetam	?	?	?	?	?

Key: + + + = primary target; + + = probable target; + = possible target; ? = unknown

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***In a double-blind trial in newly diagnosed epilepsy, 49% overall and 63% of children on topiramate were seizure free for the last 6 months of the study[1,2] ‡Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures**

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. Uses: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. Dosage and Administration: Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 – 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 – 3 mg/kg. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. Contra-indications: Hypersensitivity to any component. Precautions and Warnings: May cause sedation; so caution if driving or operating machinery. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use. Requires discontinuation of Topamax and treatment of symptoms. Side Effects: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diplopia, headache, hypoaesthesia, fatigue, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma reported rarely. Pharmaceutical Precautions: Tablets: Do not store above 25°C. Keep container tightly closed. Sprinkle Capsules: Do not store above 25°C. Legal Category: POM Package Quantities and Prices: Bottles of 60 tablets.25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ.
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drugs exert their effects at the cellular level has advanced remarkably, to the stage where mechanism of action may prove to be an important scientific criterion in the rational drug selection process.

Whether by either accident or design, the drug treatment of epilepsy has traditionally relied upon the control of symptoms, i.e. suppression of seizures. Recurrent seizure activity is the physiological manifestation of an intermittent and excessive hyperexcitability of the nervous system and, while the pharmacological minutiae of currently marketed antiepileptic drugs remains to be completely unravelled, these agents essentially redress the balance between neuronal excitation and inhibition. At the cellular level, three major mechanisms of action are recognised; modulation of voltage-gated ion channels, enhancement of γ-aminobutyric acid (GABA) mediated inhibitory neurotransmission and attenuation of glutamate mediated excitatory neurotransmission. The principal pharmacological targets of each currently available antiepileptic drug are highlighted in table 1.

Voltage-gated ion channels

Ion channels regulate the flow of positively and negatively charged ions across neuronal cell membranes and ultimately control the intrinsic excitability of the nervous system (figure 1). Sodium channels are responsible for depolarisation of the nerve cell membrane and conduction of impulses throughout the nervous system. At nerve terminals, calcium channels are recruited by sodium channel dependent depolarisation, leading to calcium entry, neurotransmitter release and cell signalling across the synapse. Sodium channels are ubiquitously expressed on the neuronal cell membrane, whereas calcium channels are distributed according to channel type. The N-, P- and Q-type calcium channels are found on pre-synaptic nerve terminals and are believed to regulate neurotransmitter release. In contrast, the L- and T-type calcium channels are expressed on the dendrites and cell bodies of post-synaptic cells where they are involved in cell-to-cell signalling in response to neurotransmitter release.

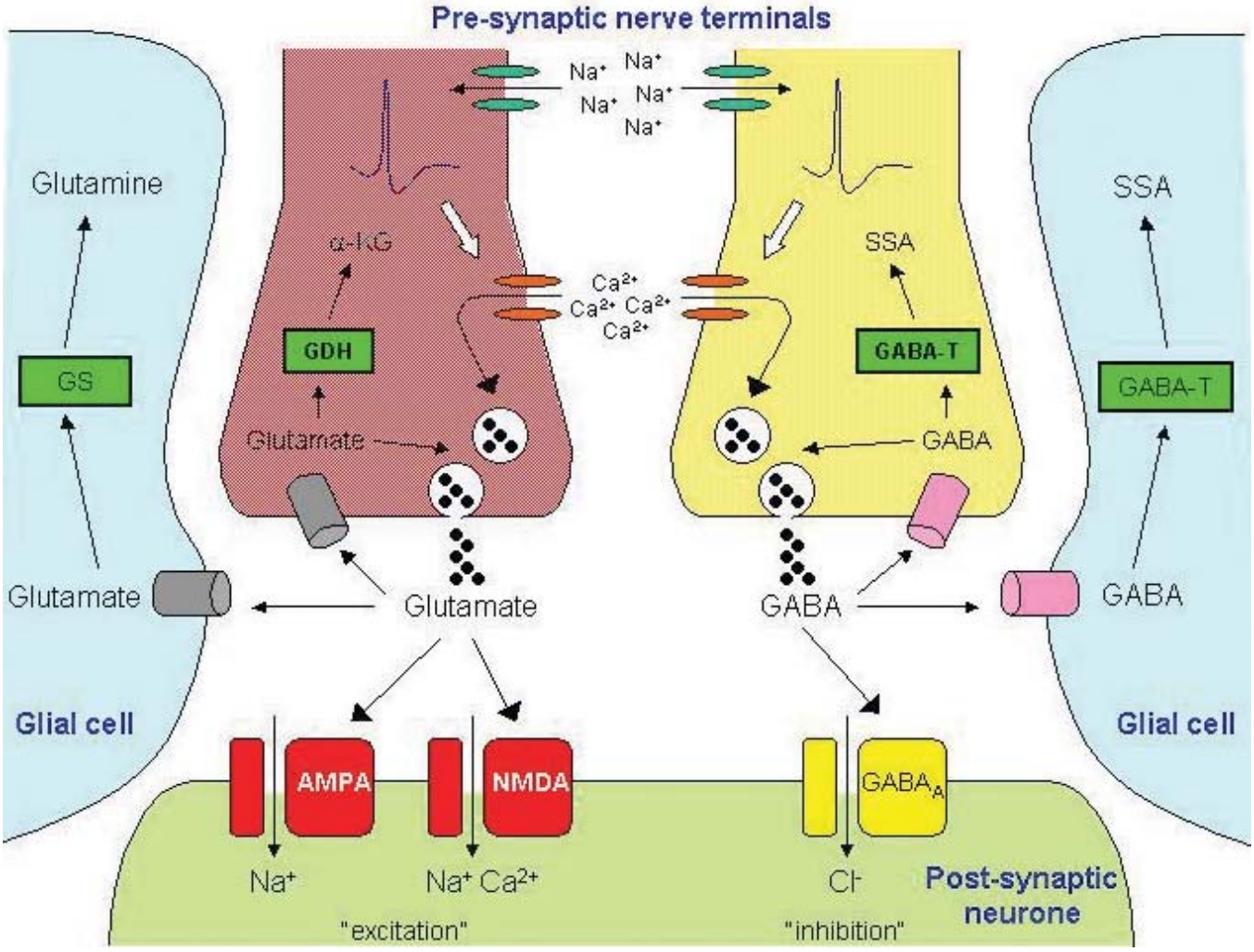

Figure 1: Schematic representation of glutamatergic and GABAergic neurotransmission. Sodium dependent action potentials invade nerve terminals leading to voltage-dependent calcium influx and neurotransmitter release. Glutamate (excitatory) and GABA (inhibitory) act on specific receptors before active removal into both glial cells and nerve terminals, where they undergo inactivation by selective enzymatic metabolism. Abbreviations: α-KG, α-ketoglutaric acid; AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; GABA, γ-aminobuytric acid; GABA-T, GABA-transaminase; GDH, glutamate dehydrogenase; GS, glutamine synthetase; NMDA, N-methyl-D-asparate; SSA, succinic semialdehyde.

Inhibitory neurotransmission

GABA is the predominant inhibitory neurotransmitter in the mammalian central nervous system (figure 1). GABA is synthesised from glutamate by the action of the enzyme glutamic acid decarboxylase. Following release from GABAergic nerve terminals, it acts on the post-synaptic $GABA_A$ receptor which responds to GABA binding by increasing chloride ion conductance, resulting in neuronal hyperpolarisation or inhibition. GABA is removed from the synaptic cleft into localised nerve terminals and glial cells by a specific transport system and is either recycled to the readily releasable neurotransmitter pool or metabolised by the action of the mitochondrial enzyme GABA-transaminase.

Excitatory neurotransmission

Glutamate is the principal excitatory neurotransmitter in the mammalian brain (figure 1). Following release from glutamatergic nerve terminals, it exerts its effects on three specific subtypes of receptor, AMPA, kainate and NMDA, which respond to glutamate binding by increasing sodium ion and calcium ion (NMDA only) conductance, resulting in neuronal depolarisation or excitation. The AMPA and kainate subtypes are involved in normal excitatory synaptic transmission, while the NMDA receptor is recruited only during periods of prolonged depolarisation, as might be expected in epileptic discharges. Glutamate is removed from the synapse into nerve terminals and glial cells by specific transport molecules and is inactivated by the enzymes glutamine synthetase and glutamate dehydrogenase.

Antiepileptic drug pharmacology

Blockade of voltage-gated sodium channels is the most common mechanism of action amongst currently available antiepileptic drugs (table 1). The established agents phenytoin and carbamazepine are archetypal sodium channel blockers, a mechanism shared with the newer drugs, lamotrigine, felbamate, topiramate and oxcarbazepine. There is also anecdotal evidence to suggest that sodium valproate and gabapentin have inhibitory effects on neuronal sodium channels. These drugs bind to the inactivated state of the sodium channel and produce a voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing with little or no effect on the generation of single action potentials.

It is now apparent that voltage-gated calcium channels also represent an important target for antiepileptic agents (table 1). The efficacy of ethosuximide in generalised absence epilepsy is believed to be mediated by blockade of the T-type calcium channel in thalamocortical relay neurones. There is some evidence to suggest that sodium valproate may have similar effects. Lamotrigine has been reported to limit neurotransmitter release by blockade of the N- and P-subtypes of voltage-gated calcium channel and gabapentin appears to bind to the $\alpha 2\delta$-subunit of the L-type channel. Felbamate and topiramate also influence calcium channel conductance, although these effects are less well characterised in terms of channel subtypes.

Several antiepileptic drugs exert their pharmacological effects on the GABAergic system (table 1). The established agents phenobarbital and the benzodiazepines bind to distinct sites on the $GABA_A$ receptor complex and differentially influence the opening of the chloride ion channel in response to the binding of GABA. Phenobarbital increases the duration of channel opening, while the benzodiazepines increase the frequency of opening. Felbamate and topiramate also activate the $GABA_A$ receptor and current evidence suggests that they also have distinct binding sites and different effects on chloride channel kinetics.

Vigabatrin and tiagabine are modern antiepileptic agents that exert their actions by selective neurochemical effects at the GABA synapse (table 1). Vigabatrin is an irreversible inhibitor of the enzyme GABA-transaminase, while tiagabine prevents the removal of GABA from the synaptic cleft by selective blockade of GABA transport. These distinct mechanisms result in the global elevation of brain GABA concentrations and the temporarily prolonged presence of neuronally released GABA in the synapse, respectively. Other antiepileptic agents, including sodium valproate, gabapentin and topiramate have also been reported to influence GABAergic neurotransmission by increasing the synthesis and/or release of GABA.

None of the currently available agents exert their effects solely by an action on the glutamate neurotransmitter system (table 1). Nevertheless, blockade of the NMDA subtype of glutamate receptor is believed to contribute to the antiepileptic effects of felbamate and topiramate is similarly distinguished by an inhibitory action on the AMPA and kainate receptors. Although several antiepileptic drugs have been reported to selectively reduce glutamate release, this effect is more likely related to an inhibitory action on pre-synaptic calcium channels than a direct effect on the glutamate system.

Multiple mechanisms of action

While many antiepileptic drugs can be categorised according to a single, principal mechanism of action (table 1), it is increasingly recognised that several agents may have multiple primary effects and most have additional anecdotal actions which remain to be definitively clarified. Sodium valproate and gabapentin are "assumed" to have multiple mechanisms of action on the basis that extensive laboratory investigations have failed to find a single foremost mechanism that would explain their spectra of clinical activity. In the case of felbamate and topiramate, the evidence for multi-factorial pharmacology is considerably more convincing.

Sodium valproate is an established antiepileptic drug with a broad spectrum of efficacy in both partial

and primary generalised epilepsies. It is a branched-chain fatty acid (figure 2) that most likely exerts its antiepileptic effects by blockade of voltage-gated sodium channels, enhanced GABA synthesis and decreased GABA metabolism. Other proposed cellular effects include reduced γ-hydroxybutyric acid release, blockade of T-type calcium channels, blockade of the NMDA subtype of glutamate receptor and non-specific effects on the dopamine and serotonin neurotransmitter systems.

Gabapentin is a modern antiepileptic agent with particularly utility in the treatment of partial and secondarily generalised seizure disorders. It is a cyclohexyl analogue of the inhibitory neurotransmitter GABA (figure 2) and is believed to exert its pharmacological effects by blockade of voltage-gated sodium and calcium channels and enhanced GABA synthesis. Other possible antiepileptic mechanisms include interaction with the system L-amino acid transporter, inhibition of branched-chain amino acid aminotransferase and reduced release of monoamine neurotransmitters. Like sodium valproate, there is currently little or no evidence to support the specific contribution of any of these proposed mechanisms to the clinical activity of the drug.

Felbamate is a dicarbamate compound (figure 2) that was approved for use as an antiepileptic drug in the USA in 1993. It has since been largely withdrawn as a result of its association with aplastic anaemia and hepatotoxicity in a small percentage of patients. Limited post-marketing experience revealed efficacy in a broad range of seizure disorders, including the often problematic Lennox-Gastaut syndrome in children. Felbamate exerts its antiepileptic effects by several, clearly defined mechanisms of action. It blocks voltage-gated sodium and calcium channels, potentiates the actions of GABA at the $GABA_A$ receptor and inhibits binding of the co-agonist glycine to the NMDA subtype of glutamate receptor.

Topiramate is a sulphamate-substituted monosaccharide (figure 2) which is active as both monotherapy and add-on treatment for partial seizures (with or without secondary generalisation) and with emerging evidence of efficacy in some primary generalised epilepsies. It has multiple mechanisms of action, which include blockade of voltage-gated sodium and calcium channels, potentiation of GABA effects at the $GABA_A$ receptor and inhibition of the AMPA and kainate subtypes of glutamate receptor. In addition, topiramate inhibits carbonic anhydrase

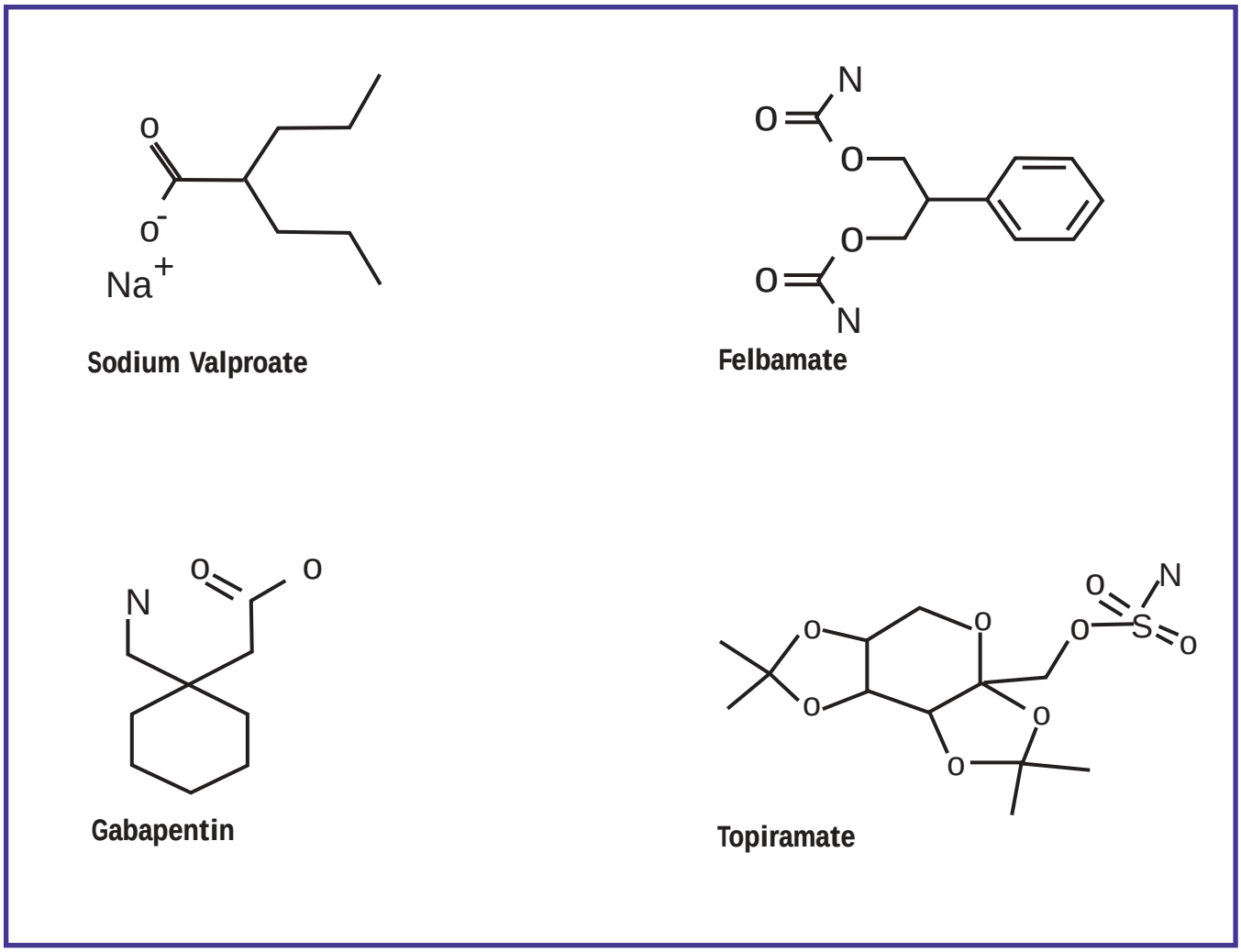

Figure 2: Structures of antiepileptic drugs with multiple mechanisms of action.

isozymes II and IV resulting in altered bicarbonate equilibrium in the brain, an effect that may also contribute to its antiepileptic activity.

Implications of multiple mechanisms

There is little or no consistent evidence to support the use of specific drugs in specific seizure types on the basis of pharmacology alone. Nevertheless, it has been suggested that the use of antiepileptic drugs with multiple mechanisms of action may be more effective in patients with multiple seizure types and under conditions, such as refractory epilepsy, where polypharmacy may have previously been advocated. Indeed, the use of a single drug with multiple but modest cellular effects may be an attractive proposition for all patients with epilepsy.

Such drugs cover all the pharmacological bases but have limited potential for overload on any given system. This may reduce the likelihood of both pharmacodynamic tolerance and adverse effects and increase the possibility of synergism between pharmacologically distinct mechanisms. In addition, prescribing single drugs with multiple mechanisms of action can eliminate the difficulties associated with pharmacokinetic interaction between antiepileptic agents, simplify titration schedules and promote ease of use amongst non-specialists.

Conclusions

The last decade has witnessed an explosion in the number of drugs available for the treatment of epilepsy. With increasing choice has come increasing uncertainty about the selection of the most appropriate antiepileptic drug for the individual patient. A rational basis for the treatment of seizure disorders is required in which pharmacology may prove to be an important criterion. At the cellular level, three basic mechanisms of antiepileptic drug action are recognised; modulation of voltage-gated ion channels, enhancement of GABA mediated inhibitory neurotransmission and attenuation of glutamate mediated excitatory neurotransmission. Although many antiepileptic drugs can be categorised according to one of these principal mechanisms of action, it is increasingly recognised that several agents have multiple primary effects. The use of a single drug with multiple but modest cellular effects may offer a significant advantage in terms of spectrum of activity, likelihood of severe adverse effects and ease of use amongst epilepsy specialists and non-specialists alike.

Acknowledgement

The author would like to thank Kimberley Butler for expert assistance in image preparation.

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Dr Sills has a particular interest in antiepileptic drug pharmacology, identification of synergism between antiepileptic drugs and the molecular basis of refractory epilepsy. Dr Sills is a member of several UK, European and US societies for both neuroscience and epilepsy and has published widely on many aspects of laboratory and clinical epilepsy research.

Challenges of Treating Epilepsy in Children

Dr KB Das and Dr JH Cross

Epilepsy affects up to 1% children; in the majority seizures will be controlled on anticonvulsant medication or children will enter spontaneous remission. However, a significant minority go on to be resistant to medication, and have associated learning and/or behavioural difficulties. Challenges present throughout the management of children with epilepsy - from diagnosis, decision making in treatment to ongoing review. These can be minimised by appropriate specialist review, and integrated multiagency working.

Epilepsy by definition is a condition where an individual is prone to recurrent epileptic seizures, and is diagnosed after two or more. It is not a single condition but a manifestation of various underlying causes. Epilepsy is the commonest neurological problem affecting children, affecting up to 1% of children. A diagnosis of epilepsy has a great impact on the child and his/her parents affecting all aspects of life – schooling, social life, hobbies and career choices. Thus it is essential that the diagnosis be established with accuracy and appropriate management instituted for the child to fulfil his/her potential. The challenges facing the clinician in managing a child with epilepsy are manifold.

Challenges in establishing the diagnosis

Diagnosis is the most important step and probably the one most prone to errors .Even now up to 25% of patients have been reported as having been misdiagnosed as epilepsy on referral to tertiary epilepsy clinics resulting in treatment with unnecessary medications. These risks can be minimised by following a logical and pragmatic approach to diagnosis. This is not only in diagnosing whether an individual has epilepsy, but also what type of epilepsy. A useful schema to follow is set out in the new proposed ILAE classification (*Engel 2001*). This follows a five axes system which formulates the basis of the diagnostic process. This looks at the problems the child with epilepsy faces in a more comprehensive manner:

Axis 1: Is it a seizure? (Ictal phenomenology) - This is the description of the ictal events .

Axis 2: If a seizure – what type ? The attacks are characterised into generalised and partial/focal seizures following the ILAE classification of seizure types.(*1981*).

Axis 3: Is it an epilepsy syndrome? An attempt is made to identify an epileptic syndrome (*ILAE 1989*) after taking into consideration the electro-clinical findings. It will help in guiding drug therapy, prognosticating the outcome and counselling. Sometimes this may not always be possible, although recent studies suggest broad syndromic diagnosis is possible in all but 12%.(*Berg et al*)

Axis 4: Is there an underlying aetiology? An underlying cause when detected - whether genetic, structural, metabolic etc. is mentioned

Axis 5: Is there an impairment? This is a useful addition which describes the impairments the child has because of his epilepsy , especially learning disabilities and behavioural problems.

History and Examination

The history of the events is the most important part of the assessment. A good history taken from a reliable eyewitness is still the most important feature necessary for diagnosing epilepsy, usually readily available in children from a parent or carer (not forgetting the child who may be able to relay some information). The majority of children will be diagnosed on the basis of history alone. The exact description of the seizure will aid in making a decision, especially if backed up by a home video recording. It can however, especially in young children be difficult to distinguish epileptic from nonepileptic seizures, and ultimately the type of seizure, e.g. focal vs generalised in onset. Misdiagnosis rate is high .The most common reasons for this are inadequate history and lack of awareness of alternative diagnoses, particularly wide in childhood (*see Table 1*). The key feature when determining whether an event is epileptic or nonepileptic is what is the primary event – in epileptic seizures this is the change in the electrical activity of the brain causing the changes in behaviour or movement. The latter can still occur in nonepileptic seizures e.g. reflex anoxic seizures or vasovagal events as a secondary phenomenon, and may lead to confusion. A point of caution is that an unreliable witness may give a misleading account leading to inappropriate investigations and therapy, particularly if the beginning of the episode is not seen.

Examination may be helpful but not with the actual diagnosis of epilepsy. This is targeted to pick up features of any neurocutaneous or dysmorphic syndrome, subtle focal neurological deficits (growth asymmetry, reflex changes, visual field defects, fine motor and sensory deficits), fundal examination ,and any other systemic clues which might explain an underlying aetiology. Abnormal neurological findings do not imply a diagnosis of epilepsy.

Investigations

The electroencephalogram (EEG) remains a key investigation in epilepsy, but often too much may be expected from it. A popular misconception is that it is required to diagnose epilepsy , whereas it is most useful in diagnosing the seizure syndrome A routine interictal EEG is helpful in only 50% of patients in demonstrating epileptiform discharges .This value may rise to ~ 80% with activation procedures like sleep, hyperventilation and photic stimulation . If an ictal event is captured during the recording (as is attempted in Video telemetry), then the diagnostic value of this investigation rises considerably.

Children without clinical seizures, may also have abnormalities seen on EEG, especially if they have a pre-existing neurological disability. There can also be a risk of misinterpretation of normal developmental patterns if one is not used to reporting paediatric EEGs. An EEG should however be performed in all children who present with a probable diagnosis of epilepsy. There is ongoing debate as to whether the EEG should be performed after a first or second seizure but on balance, management is unlikely to be affected until after a second seizure. The EEG is of limited predictive value as to whether a second seizure will occur. However, in certain circumstances e.g. a teenager presenting with a single generalised tonic clonic seizure, it may be helpful (as in the teenager if unrecognised absences were occurring).

All children who present with a focal seizure and certainly all with epilepsy who are resistant to two anticonvulsant medications should undergo neuroimaging. However, again it will not contribute to the diagnosis of epilepsy, only to the underlying cause. Over the last 10 years the technique has enhanced our understanding of many symptomatic epilepsies with the detection of brain malformations (*Figure 1*). Choice of type of scan may be limited to availability and sedation issues but undoubtedly MRI scan is the modality of choice for investigating a child with epilepsy but there is considerable shortage of availability of paediatric MRI in view of the need for safe sedation or general anaesthesia .CT scan requires less time, and therefore need for sedation is less. It may give immediate answers and will detail calcification, but detail with regard to developmental lesions may be missed.

The role of other investigations is limited. Some children may need detailed metabolic investigations especially if the clinical picture suggests a progressive course. This may be helpful in detecting an inherited disorder of metabolism or a neurodegenerative

Aetiology	Disorders
Behavioural/psychiatric	Daydreams Self gratification behaviour Hyperventilation Panic/anxiety Non epileptic attack disorder Fabricated attacks Pseudosyncope Stereotypies/ritualistic behaviour
Neurological	Tics Myoclonus Paroxysmal dystonia Sandifers syndrome Paroxysmal dyskinesias Cataplexy Benign paroysmal vertigo/torticollis Migraine Alternating hemiplegia Eye movement disorders Overflow movements
Syncopal	Cardiac (e.g. long QT, hypertrophic obstructive cardiomyopathy) Vasovagal Reflex & expiratory apnoeic syncope ('fainting lark') Upper airway obstruction
Sleep phenomena	Sleep myoclonus Headbanging Confusional arousal REM sleep disorder/night terrors

Table 1: Differential diagnosis of epilepsy in children

condition, however very few metabolic or neurodegenerative conditions present with seizures. Seizures may be an added manifestation, but not usually the primary problem. Routine monitoring by blood tests and drug levels is not recommended unless clinically indicated (suspected toxicity especially with phenytoin, checking compliance, serious drug interactions) . A baseline ECG should be done to rule out prolonged QT syndrome and other cardiac causes.

Sometimes children with epilepsy may appear to regress in skills, and the assessment may be required to determine whether there is an underlying progressive course, or whether this may be due to the epilepsy itself. Possibilities to be considered then are recurrent sub clinical seizures, or frequent electrical activity in sleep, particularly a specific syndrome of CSWS (continuous spike wave of slow sleep), side effects of medication, or systemic illness. More often there is a widening of the cognitive gap between children with existent learning difficulty and their peers rather than a true loss of skills. However, in children with difficult symptomatic epilepsies the possibility of nonconvulsive status must be considered as clinical signs may be subtle.

Challenges in treatment

Seventy five percent of children with epilepsy are controlled on medication or enter into spontaneous remission.. At diagnosis, the child and parents should be given practical advice regarding safety issues such as not swimming alone, and not climbing. Thereafter the first line treatment is with anticonvulsant medication. This is always a highly anxious and difficult time for the family and time should be taken to fully explain the condition, prognosis and treatment implications. Although alternatives such as dietary and surgical management are available they are considered in children resistant to drugs, and may only be suitable for selected cases. What differentiates the management issues in children from adults is the involvement of the whole family in the decision making process.

Drug therapy

The decision to start medication should be taken by the parents and child after all the facts have been clearly explained to them and have to be individualised. It is likely that treatment decisions will be made in the majority at a secondary care level, although liaison and communication with primary care is imperative. Although medication is usually started after the occurrence of two or more seizures, sometimes it can be deferred. The challenge remains in choosing a medication that will work for the individual child without side effects. Advice regarding emergency medications should be given and parents/carers should be trained to administer them as appropriate as well as Information leaflets about epilepsy and details of epilepsy support groups and organizations.

An appropriate drug for the child's seizure type or syndrome is chosen and gradually the dose is increased until efficacy is achieved, or a maximal dose (or toxicity) is seen. Choosing an appropriate agent gives us a further challenge. Although important to take note of the seizure type, and preferably syndrome in the decision, medication will still be on a trial basis, the first medication not always being the most suitable. Care should also be taken as some medications aggravate certain seizure types. If there is good response then this medication is continued, but if there is no or partial response, another suitable medication will be required. Few patients may need two drugs for adequate seizure control .Use of more

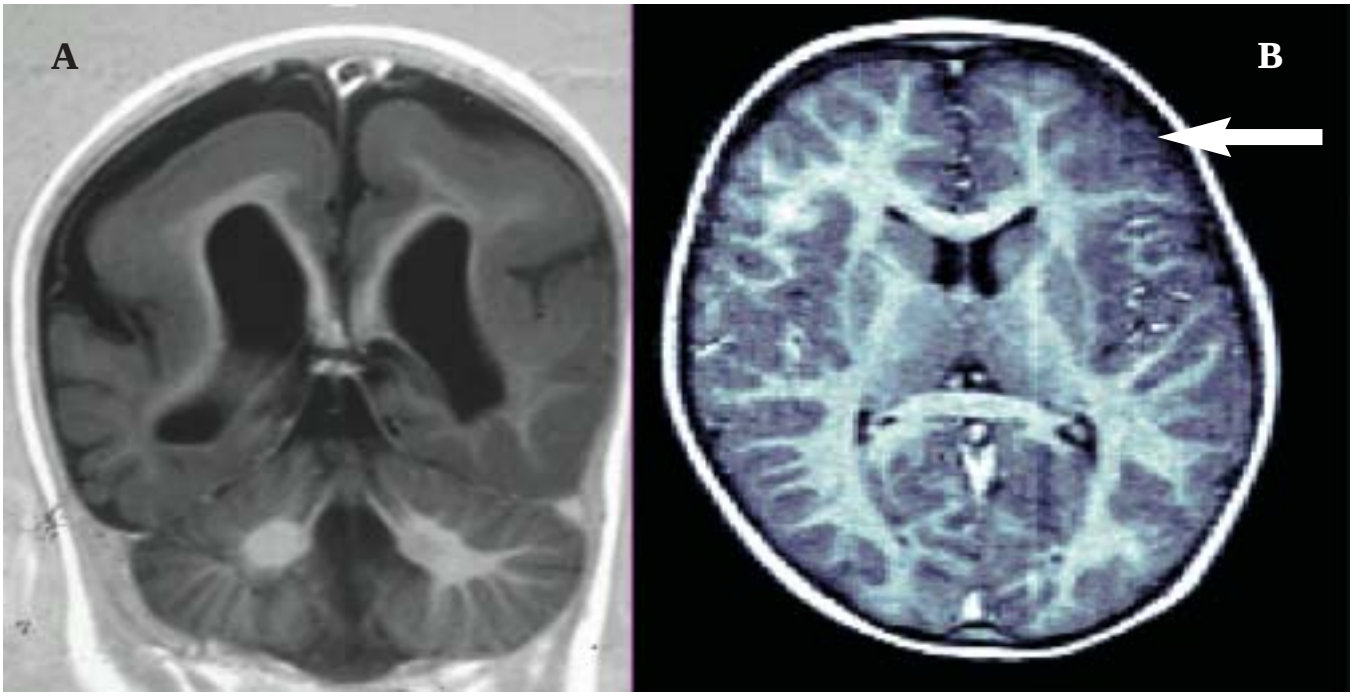

Figure 1: Examples of developmental brain lesions as a cause of epilepsy seen on MRI: ranging from the widespread as in lissencephaly (A, smooth cerebral hemisphere with no sulcation), to the subtle focal cortical dysplasia (B, arrowed)

than three drugs adds significantly to toxicity without much evidence of therapeutic benefit. The age of the child usually determines the formulation used - syrups /suspensions/sprinkled powders/dispersible tablets for babies and younger children, although the type of formulation available for each respective medication may influence in part those used. The palatability of the preparation also improves compliance. If the response is not adequate, the diagnosis should be reviewed, drug selection and dose verified remembering compliance may be an issue particularly in older children. Some epilepsies have a favourable self limited outcome and may not need treatment on occasion. There is no empiric fixed duration of therapy. The decisions have to be taken on an individual basis after considering the clinical and EEG findings, investigation results and syndromic diagnosis. Sensible advice regarding precautions, travel and recreational activities should be given. An outline of drug therapy in some selected conditions is shown in Table 2.

Nowadays there is a tendency for the newer drugs to be increasingly used as first line agents and as monotherapy in view of their favourable profile and tolerability. This may be problematic in that some drugs may therefore be prescribed off licence, an issue of continuing debate in children. A factor to be considered is that there are few drug trials exclusively conducted in children. Children may be considered only at the end stage of clinical trials, thus delaying a drug's licensing requirements for children. Currently a NICE HTA is taking place due to be published in November 2003 on the role of the newer antiepileptic drugs, as well as NICE guidelines on diagnosis and management of epilepsy due in 2004.

Alternative therapies

Ketogenic diet

This is an adjunctive therapy which can be tried in drug resistant epilepsies . The exact mode of action is not known. It is a high fat, low carbohydrate diet designed to mimic starvation by production of ketones. The classical diet uses long chain fats, whereas the MCT diet uses medium chain triglycerides as the main fat source. It requires intense dietetic support for dietary calculation. It has been shown to be efficacious in ~50% children achieving 50% reduction of seizure frequency without significant side effects, although it is not possible to predict which children are likely to respond.

Vagal nerve stimulation

This is a pacemaker implanted within the chest wall which delivers repeated impulses to the left vagus nerve through electrodes. This has been effective in 30-60% of children with intractable seizures as in the Lennox Gastaut Syndrome in reducing seizures although there is limited long term data available in children. The main side effects are hoarseness of voice. The exact mode of action is unknown, although few become seizure free. Selection is required through tertiary/quaternary centres.

Epilepsy Surgery

About 20-30% of children may be intractable to medical management. Possibly 30% of these children may be surgical candidates. There are predominantly two types of surgery – resective and functional. The challenge is determining suitable candidates early in the natural history of the epilepsy. Children should be considered early for resective surgery should this be an option to minimise the long term cognitive and psychosocial morbidity associated with recurrent uncontrolled seizures. Children are suitable should they have seizures arising from one area of the brain, and would functionally be no worse should that area be removed. This may range from a lesionectomy in the case of a tumour, to a localised resection of an area of dysplasia, to ultimately hemispherectomy in children with abnormality of the whole of one hemisphere with a pre-existing contra lateral hemiparesis. In adult practice a pre-requisite is also given as resistance shown to at least two anticonvulsant drugs over at least a two year period. In many children many more drugs are tried over a shorter duration of time and a more suitable definition would be that given as 'inadequate seizure control despite adequate anticonvulsant therapy'.

Where possible presurgical evaluation is non-invasive, but there remain a small number of children where the exact extent of the seizure focus cannot be determined, or it may lie within functional tissue and such children may require invasive EEG recording that involves the placement of an electrode grid on the surface of the brain for a short time.

The child and parents are fully supported and counselled at every step in the decision making process and the risk vs benefits from the procedures are clearly explained. Sometime when definitive resective surgery is not an option, functional surgery such as division of the corpus callosum may lead to improvement in children with drop attacks .

Challenges in management

Management issues in difficult epilepsy may be complex. These may be due to epilepsy directly or may be secondary to some underlying neurological problem.

Most children with epilepsy do not have significant associated problems. Some children, especially those with intractable epilepsy may have additional learning difficulties, behavioural problems, psychiatric co-morbidity, motor handicaps and speech and language disorders. Such children have high rates of emotional and behavioural difficulty, when compared with healthy controls and children with other chronic disorders. For example, in the Isle of Wight study, *Rutter, Graham and Yule (1970*) reported that 29% of the 63 children with uncomplicated epilepsy had a psychiatric disorder relative to 12% of the 138 children with chronic but non-neurological disorders.

Table 2: Likely medications used in certain seizure types/syndromes

Epilepsy / Syndrome	Usual first line drug	Alternative therapy
IGE with GTCS	VPA	LTG,LEV,TOP
IGE with absences	LTG, VPA	ESM, LEV,BDZ
IGE with Myoclonus	VPA	BDZ,ESM,LEV,PB,TOP
Focal/Partial seizures	CBZ,VPA	LTG,OXC,TOP,LEV,PHT
Infantile Spasms	VGB	Steroids,VPA,BDZ
Lennox Gastaut Syndrome	VPA,LTG	TOP,BDZ,VGB
SMEI	VPA,TOP	BDZ, Stiripentol

IGE-Idiopathic Generalised Epilepsy, **GTCS**-Generalised Tonic Clonic Seizures, **SMEI**-Severe Myoclonic Epilepsy of Infancy,**VPA**-Valproic Acid, **LTG**- Lamotrigine, **ESM**- Ethosuximide,**CBZ**-Carbamazepine,**VGB**-Vigabatrin,**LEV**-Levetiracetam,**TOP**-Topiramate, **BDZ**-Benzodiazepines, **PB**-Phenobarbitone,**OXC**-Oxcarbamazepine,**PHT**-Phenytoin

Management of these issues may need the involvement of other professionals such as specialist liaison nurses, psychologists, psychiatrists, physiotherapists, speech & language therapists, occupational therapists. All professionals involved will require close liaison to achieve maximal support for the family; the provision of an integrated service across all agencies provides us with a further challenge to which we have to rise.

Extreme vigilance has to be entertained to detect any cognitive/behavioural deterioration .It may be difficult to decide whether this is primarily due to seizures, the underlying aetiological cause or as a result of medication. More often there is a multifactorial cause. Multiagency working is imperative. Plans and services should also cater for the adolescent where many issues need to readdressed and revisited – does the child require medication, are they aware of the underlying issues, career choices, conception and contraception as well as driving. Being aware of appropriate timing to address such issues can improve compliance with health care.

Outcome

As already indicated, most children with epilepsy do well with seizures controlled in 70-80% of cases. The majority of these patients can come off medication after 2-3 years of seizure freedom. The prognosis can be predicted to some extent from the epilepsy syndrome and the underlying aetiology. For example in the case of Juvenile Myoclonic Epilepsy, the seizures are easily controlled ,but withdrawal of medication leads to relapse, necessitating life long therapy. Similarly children with structural lesions have a high risk of relapse, so may need long term treatment. In surgical candidates, outcome is in part related to the procedure, extent of removal and underlying pathology but up to ~ 60-70% patients may become seizure free or have significant reduction of seizures, and in a proportion medication may be discontinued. This leads to significant saving in cost of healthcare despite the initial heavy investment.

Thus overall the outlook for children with epilepsy is improving with development of more efficacious and less toxic drugs, better supportive services and early consideration of a surgical option when indicated. The future development of epilepsy clinical networks should help in improving delivery of services to children.

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Epilepsy and the Importance of Seizure Freedom in the Light of the National Audit Report

Professor Stephen Brown, Cornwall Partnership NHS Trust

Introduction – Epilepsy and mortality

Epileptic seizures can be fatal. The number of deaths attributed to epilepsy in the UK suggests it is at least ten times as risky as having asthma (Hanna 1997). The causes of this excess mortality include underlying disease such as stroke or brain tumour (especially in the newly diagnosed), suicide, seizure-related accidents especially including drowning, status epilepticus, and sudden unexpected death in epilepsy (SUDEP). Among people with chronic epilepsy, SUDEP accounts for more than half of all deaths. SUDEP is defined as 'sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomic cause for death.' (Nashef *et al*, 1995). There was a previous, erroneous belief that many deaths that we now know to be SUDEP were caused by suffocation on the pillow, and this held back recognition of and research into the condition. The actual mechanism may be a consequence of either central apnoea (the respiratory centre being shut down by seizure activity) or lengthening of the QT interval of the ECG as a consequence of EEG epileptic activity known as the lockstep phenomenon (Lather & Schraeder 1990)

The risk factors for SUDEP have been described by Shorvon (1997) and are mainly related to a continuing predilection for tonic-clonic seizures, especially those which may be unobserved. The risk of SUDEP appears to be directly related to the frequency of seizures, indeed most of the overall excess mortality of epilepsy seems to be related to seizure frequency. Nilsson *et al.* (1999), found the risk of early death among people with epilepsy to be 23 times greater if they were not seizure-free, and Tomson (2000) in a review suggested a 40 times higher risk in people who continue to have seizures. Sperling *et al.* (1999) showed that elimination of seizures after surgery reduced the mortality rate in people with epilepsy to same level as the general population. This is because most, if not all, SUDEPs are seizure-related (Shorvon, 1997; Nashef *et al*, 1998; Nilsson *et al*, 1999; Langan, 2000).

Optimising the management of epilepsy should therefore reduce the mortality associated with epilepsy, but management of epilepsy in the UK is less than optimal (Jacoby *et al*, 1996, CSAG 2000). Despite attempts to put epilepsy on the NHS Commissioning Agenda ((Brown *et al*, 1993, 1998, England and Wales NHS Executive Letter EL95(120)), service planners still have not focused attention on this area (Brown & Lee, 1998; Brown *et al*, 1999). The situation has been compounded by inconsistencies in reporting the causes of death in people with epilepsy, a lack of awareness of SUDEP among coroners, pathologists and clinicians (Lip and Brodie, 1992; Coyle *et al*, 1994, Timmings, 1998), and a myth that individual seizures are benign (Nashef and Sander 1996). Anecdotal evidence from the charity Epilepsy Bereaved & others attested to the poor quality of support given to bereaved relatives, and suggested that deficiencies in care may play a part such that at least some deaths might be potentially avoidable. Nilsson (1999) showed that poor medical note keeping is a risk factor, perhaps representing an inadequate standard of clinical care.

Standards exist for epilepsy care in the arenas of primary care, specialist secondary services, the overall structure of services and how to commission them (e.g. Brown *et al*, 1993, 1998; Hall *et al*, 1997; SIGN 1997; Wallace *et al*, 1997; Epilepsy Task Force 1999; Taylor 2000) and the Royal College of Pathologists has issued guidelines with standards for post-mortem examinations (RCPath, 1993). In an attempt to take things forward, an international symposium on epilepsy and sudden death was held in London in 1996 (Nashef and Brown, 1997). At this, there was a call for a National Confidential Enquiry into epilepsy mortality along the lines of those already in existence for maternal and infant deaths. Subsequent lobbying from clinicians, researchers and the voluntary sector, led by Epilepsy Bereaved, resulted in the National Sentinel Clinical Audit (Hanna *et al*, 2002). The steering group for this included representation from the voluntary organisations as well as the Royal Colleges and other professional organisations, and was supported by government in all four UK legislations.

The National Sentinel Clinical Audit

This investigated the standard of epilepsy care received by people with epilepsy-related death to identify examples where deficiencies in health service or clinical management may have contributed to death, and included a study of post-mortem investigation of cause of death, and management of the situation including contact with the bereaved family. Prior to the completion of the audit, the annual report of the

Chief Medical Officer for England in 2001 highlighted its importance and recommended that an action plan aimed at cutting level of preventable epilepsy deaths should be in place within 3 months of completion of the audit report (CMO 2001).

The Audit looked at a sample of deaths in England, Wales, Northern Ireland, Scotland from 1 September 1999 to 31 August 2000 where epilepsy was mentioned somewhere on the death certificate. Investigation included study of post-mortem examination reports, coroners' officers and police reports and available case notes both in primary and secondary care. The final audit sample included 285 GP practices and 94 hospital Trusts across the UK.

There was also a survey of service provision via questionnaire to NHS Trusts and GP practices. Separately, a survey of bereaved relatives who contacted Epilepsy Bereaved during the audit period was commissioned by Epilepsy Bereaved from the College of Health, and was published separately.

Findings

The findings gave great cause for concern. Regarding investigation of cause of death where there had been a post-mortem examination, many of the deaths were considered to have been inadequately investigated. Not all post-mortems included appropriate further investigations and these investigations were non standardised. In a small number of deaths the post mortem examination was itself considered inadequate. The cause of death was certified inconsistently and sometimes inappropriately. The majority of pathologists indicated that they were not aware of a mechanism for discussing the findings with relatives. If the post mortem investigation is inadequate and/or the certification of death inappropriate then it is difficult to establish the true number of epilepsy related deaths. If we cannot establish who has died from epilepsy it is more difficult to determine why such deaths occur and how to prevent them.

The findings from the study of pre-mortem care were hardly more encouraging. There was evidence of breakdown in communication between professionals in both primary and secondary care and between specialist departments. Where people had missed outpatient appointments there was frequently no documentation to suggest that proper effort had been made to establish why. There were problems with access and waiting times for specialist advice. Clinical assessment and investigations were sometimes inadequate and there was little evidence of management plans or structured review. In a proportion there was inappropriate use of anti-epileptic drugs. There was little documentation of adequate information given to people with epilepsy and their carers. Panel opinion suggested that in some cases better care could reduce mortality, such that more than half of the adults, and more than three-quarters of the children were regarded as having received inadequate care, or had major errors in their care.

It seems that about 1000 people per year in UK die of epilepsy. A substantial number, up to half of these, may be avoidable. The audit found serious problems with investigation of deaths, and with co-ordination of care in the health system. Problems were identified in the investigation of deaths such that 87% were considered inadequately investigated. It seems that the coronial/procurator fiscal system is failing people, being unreliable and lacking quality assurance. The care of the subjects when alive was such that many deaths were considered potentially avoidable, due to various factors involving a systems failure in their health care. There was lack of access to services with inappropriately long waiting times, lack of handover between services, lack of follow-up and lack of information provision as well as some major errors in clinical management. Of those only receiving GP care, 67% had no structured review in previous year, and 47% none in the previous 2 years. Of those receiving specialist care, seizure frequency was not recorded in the recent clinical notes for 41% of children and 47% adults. 32% had not had an EEG. Adults with learning disabilities were less likely to have seen a consultant. Secondary care was considered inadequate in 54% adults and 77% children. Deaths were regarded as potentially avoidable in at least 39% adults & 59% children.

The College of Health study (Kennelly & Riesel, 2002)

The parallel College of Health study investigating the views and experiences of bereaved relatives and carers supported the findings from the main audit. Access was mixed. Most did not know of the expertise of the professionals involved in the care of their loved ones. A parent said, "we would have wanted to know that the paediatrician that L was seeing was not an epilepsy specialist and had advice to go somewhere else". Monitoring and review varied greatly. Concern was expressed about lack of systematic review, with comments that included "They never called him up. I thought this is what GPs are for... they deal with smear tests and with diabetic people, why are epileptic people so different", and "I didn't know x had stopped his medication until after he died... the last medication they'd given him was over a year before he died... and I think they should have kept a check on him and made sure he was on medication". Only a few had been offered information about their medical condition, lifestyle & trigger factors and the vast majority had not heard of SUDEP, " If you've got anything (else) life threatening you are told and epilepsy you're not". Suggestions included providing information verbally or in writing, "If anyone said to me what was the one thing I'd like to change in our family, it would be that my Dad had more information... to come to terms with it because he would have had the choice to talk to people, to see people, or just to read up on it and learn a bit more about the ways of avoiding it". Although some carers said they were actively included, others reported that

their role was ignored, " I did (keep records of seizures) for quite some time, but then nobody seemed interested so I stopped writing them down".

Relatives' feelings after death included shock, guilt, devastation, difficulty coming to terms with the death and a desire to know why. Relatives often felt alone and isolated, "There's an awful lots of guilt involved, terrible guilt, because we all thought we could do something, we could have done something, you know, to help him." Some relatives reported being contacted after the death, and some felt supported & informed. There were some positive experiences, "The doctor who was on call was also my doctor ... she came out and chatted to me about what happened, the subsequent days, even weeks she was in constant contact with me ... if everyone could have the same care I had it would be much easier." However, some thought that professionals were insensitive & unsympathetic. Negative experiences followed where there was no or delayed contact with medical professionals, or where there was lack of information & follow up, "I went up to see my GP and she didn't know that X had died, so I had to tell her...", and "I actually wrote to him, it must have been a good 6 or 7 weeks after ... and I just wanted an appointment to see him for 5 or 10 minutes to just try and explain to me ... and he just wrote me a letter back saying he was very sorry and did I know that sudden death could occur ... and I was very unsatisfied that I just got a letter back." Most were not provided with information on how sudden deaths were investigated, what investigations would be carried out or how long it would take, and more than half faced difficulties in receiving information. There was a general consensus that information on risks of sudden death should be provided to patients, carers & relatives before death. There were differences over whether information should be provided on diagnosis or once treatment begins. It was felt that information on risks should be written as well as verbal but as part of discussion with the clinician. In conclusion it was suggested that better individual packages of care could be created by taking into account the variety of patients and carers' circumstances, experiences of epilepsy and desires for information and involvement. Guidelines governing investigations into sudden death and treatment of bereaved relatives should be drawn up in consultation with relatives and carers. Such change would require additional resources, but these recommendations are supported by recent Government legislation such as the NHS Plan, which encourages improvements in the quality of public services through greater user, patient and carer involvement.

Aftermath

As stated earlier, the Chief Medical Officer (CMO) for England indicated there would be an action plan to reduce epilepsy-related mortality. The current modernisation of the NHS is an opportunity to set up and to monitor such a plan. There are aready many guidelines for epilepsy management and service development that remain to be implemented. When the audit was published in May 2002, the authors wrote to all 4 UK CMOs suggesting that components of an action plan should include a more serious approach to epilepsy service governance. Our proposals were subsequently extended by our colleagues in the voluntary sector into a cohesive framework that the CMOs could have used to produce a realistic action plan. It was suggested that a target could be set for reduction in epilepsy related deaths. We thought it a reasonable aim to reduce deaths by 40% by providing access by all patients with epilepsy and their families to an epilepsy service. The strategy for achieving this would involve primary care organisations and secondary care providers developing epilepsy service implementation plans together with the voluntary sector, with named people taking responsibility for taking the work forward. In doing this, commissioning bodies must recognise the important role of learning disability, mental health and community paediatric services in the delivery of epilepsy care as well as neurology services. Primary care services should be encouraged to develop registration, recall, review and appropriate referral for people with epilepsy as happens in other chronic conditions, and secondary and primary care providers need to ensure that arrangements are made for epilepsy risk management and provision of information about the condition. To achieve this government needs to provide leadership, direction and resources, including acceleration of specialist clinical posts for doctors and nurses, national investment of resources to support specialist training and funding for clinical leadership and administrative support. There should be formal monitoring through Strategic Health Authorities or equivalent bodies. We also called for more quality assurance and accountability in the coronial system. The English Action Plan was eventually published early in 2003 (Department of Health 2003). In this, no target was set for reduction of deaths, and much reference was made to existing developments in the health service that could or should have an impact on epilepsy services. Thus there is mention of forthcoming NICE Health Technology Appraisal of new anti-epileptic drugs (due autumn 2003), the NICE epilepsy treatment guidelines due in 2004, and the forthcoming National Service Frameworks on long-term health conditions and for children. There is reference to various ways of working with the voluntary sector, and an unfortunate emphasis on neurology services with little mention of paediatric or learning disability services. Hope is also pinned on the activities of the Royal Colleges in improving standards. Not surpisingly perhaps, the voluntary sector was less than overwhelming in its reaction to the Action Plan ("Epilepsy Charities Dismiss Government's Action Plan For Epilepsy" was a headline on Epilepsy Action's website on 19th February 2003).

However, there were two glimmers of hope. Firstly, the Department of Health has contributed to the current government (Home Office) review of the

coronial system, and has highlighted concerns around the investigation and certification of epilepsy deaths. The Review reported in June 2003 (Death Certification and Investigation in England, Wales and Northern Ireland, 2003) and is currently being considered by Ministers. It does recommend that there should be a small inspectorate to monitor coroner service standards, and makes various proposals regarding certifying and investigating deaths and support for the bereaved, with explicit service standards for the provision of information, advice on bereavement counselling, and the involvement of families in key aspects of any post mortem examination decisions.

Secondly, the CMO for England wrote to all English NHS Trust and Strategic Health Authority Chief Executives in May 2003 pointing out the audit findings and suggesting that local NHS organisations and clinicians review their policies and practices for the management of epilepsy and epilepsy-related death in the light of the audit findings and the action plan and address any shortfalls as part of local planning arrangements and priorities. The letter commends the development of appropriately managed shared care protocols between GPs and hospital specialists with support from Trust clinical governance teams, and ensuring that patients with ongoing seizures are aware of the risks of epilepsy, including SUDEP. This is an opportunity for practitioners and service users to take matters further by pressing their local commissioners and providers on their response to the CMO's letter. As always, improvement in services will only happen if there are strong local advocates. The proposed GP contract gives some incentive for better primary care by structured registration, recall and referral. The stakes are worth playing for; the residual life expectancy at age 15 in the UK is a further 63.1 years for the general population. For people with epilepsy as a whole this reduces to 48.9 years, but there is a marked effect of seizure frequency. Those with 2 or less seizures per year have a residual life expectancy similar to the general population (61.5 years), while in those with 3 or more seizures per year this is about 41 years (Remak *et al*, 2003). Getting better seizure control, by taking epilepsy seriously, could add nearly 20 years to someone's life.

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Female : 16
Partial Epilepsy with Secondarily Generalised Tonic-Clonic seizures
If she was your daughter how would you treat her?
Lamictal
lamotrigine
PEACE OF MIND

Progress in Epilepsy Management: An Overview of the Revised 2003 SIGN Guideline

Rod Duncan, Margaret Jackson, Hilary Mounfield

This article has been supported by an educational grant from GlaxoSmithKline

During the Annual Meeting of the International League Against Epilepsy (ILAE, UK branch), held in Manchester on 26-28 June 2003, GlaxoSmithKline sponsored a Satellite Symposium entitled, The First Revision of the SIGN Guideline on Epilepsy – Implications for Patients and Services. *Three members of the Scottish Intercollegiate Guidelines Network (SIGN) scientific committee, Dr Margaret Jackson, Dr Rod Duncan and Ms Hilary Mounfield, presented the recommendations of the revised SIGN guideline to an audience that included epileptologists, neurologists, GPs with a special interest in epilepsy, epilepsy specialist nurses, and other specialists with an interest in epilepsy.*

Chairperson's introduction Progress in epilepsy care and management

Dr Margaret Jackson, Consultant Neurologist, Royal Victoria Infirmary, Newcastle

In the past couple of years, a number of initiatives have helped to raise the profile of epilepsy care and management throughout the UK. Dr Margaret Jackson highlighted the major events that have taken place recently in the UK, stimulated by the publication of the *National Clinical Audit of Epilepsy-Related Death* in May 2002.[1] This report revealed that major deficiencies in epilepsy care contributed to premature death in about half of the approximately 1000 epilepsy-related deaths observed per year. In response to this report, the Chief Medical Officer, Sir Liam Donaldson, released a letter promising an Action Plan to reduce the numbers of epilepsy-related deaths; the Action Plan, *'Improving services for people with epilepsy'* was published in February 2003.[2] Furthermore, the General Medical Services contract has included epilepsy as a quality marker; a welcome recognition of the importance of epilepsy in primary care. A significant and recent initiative is the publication of an updated version of the 1997 SIGN clinical guideline, *'Diagnosis and management of epilepsy in adults'*, which was published in April 2003.

SIGN guideline

SIGN was established in 1993 by the Academy of Medical Royal Colleges in Scotland (funded by the Scottish Executive) as a collaborative network of clinicians, other healthcare professionals and patient organisations. It was set up to fulfil the need for evidence-based and workable guidelines in clinical practice, to provide clinical guidance to physicians and, importantly, to incorporate the views of patients in the process. Dr Jackson noted that once a topic such as epilepsy is selected, a 'Herculean task' of conducting a systematic literature review (Figure 1) is undertaken before evidence-based recommendations can be formed and graded according to the strength of supporting evidence. The guidelines are targeted at a wide audience, including GPs, practice nurses, hospital-based specialists and patient organisations. This approach aims to establish evidence-based and widely accepted standards of care for patients with epilepsy. Although the guidelines are produced for, and focus on Scotland, it is likely that their impact will extend to the whole of the UK, as the previous 1997 SIGN guideline did.

SIGN guideline: Grades of recommendation

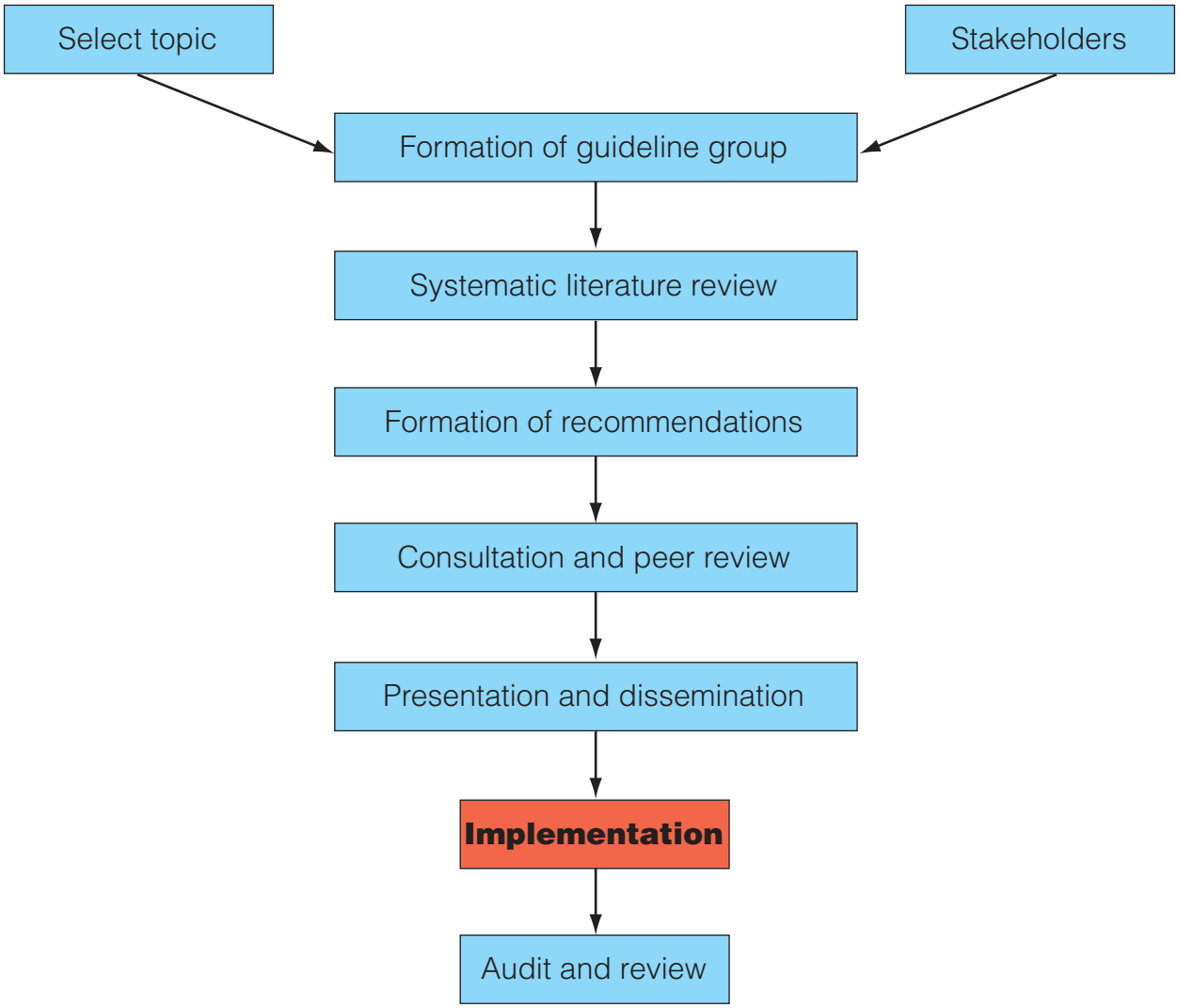
Each recommendation in the SIGN guideline is awarded a grade (A to D) which relates to the strength of evidence on which the recommendation is based. The level of evidence ranges from high quality meta-analyses and systemic reviews of randomised controlled trials to expert opinion. However, the grade does not reflect the clinical importance of the recommendation. In addition, good practice points (denoted by a tick) are highlighted throughout the SIGN guideline recommending best practice, based on the clinical experience of the guideline development group.

The revised SIGN epilepsy guideline: An overview

Dr Rod Duncan, Lead Clinician, West of Scotland Regional Epilepsy Service

A summary of the revised SIGN guideline, *'Diagnosis and management of epilepsy in adults'*, was presented by Dr Rod Duncan, who highlighted the major points from each section. Significant developments in the diagnosis and management of epilepsy have been made since the publication of the previous guidelines. Dr Duncan commented that the revised content reflected a shift from the 1997 guidelines, which represented the epilepsy practices at that time, towards an aspirational view of recommending current best practices. Indeed, the concept behind the epilepsy

Figure 1. SIGN guideline development[3]



SIGN guideline is to provide a template for the development of local services and local guidelines which aim to establish good working practices for epilepsy care and management.

Diagnosis

An important factor, addressed by the *Diagnosis* section, was 'who should make the diagnosis of epilepsy?' Epilepsy is often difficult to diagnose, with a misdiagnosis rate of up to 20%.[4] Recognising these points, SIGN highlights the need for expertise in diagnosing patients by recommending the early involvement of a neurologist or other epilepsy specialist. An epilepsy specialist has been defined as a consultant with expertise in epilepsy as demonstrated by training and continuing education in epilepsy, peer review of practice and regular audit of diagnosis. Epilepsy must be a significant part of their clinical workload (equivalent to at least one session per week).[5]

Once a diagnosis of epilepsy is made, an accurate classification of the seizure type (e.g. partial or generalised) is required to help guide the most appropriate choice of treatment.

Treatment

Dr Duncan continued by stating that the emphasis within the *Treatment* section was upon individual patient needs. SIGN recommends that the type of epilepsy should be taken into consideration together with the efficacy, side effects and drug interactions of antiepileptic drugs (AEDs), before selecting the most appropriate treatment for the individual. Clinical studies have shown that the efficacy of carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and sodium valproate in adults is similar for the treatment of patients with newly-diagnosed partial and generalised tonic-clonic seizures.[6-14] The SIGN guideline acknowledges that carbamazepine, lamotrigine, oxcarbazepine and sodium valproate can all be regarded as first-line treatment for partial and secondary generalised seizures in this population[3] (Table 1). In addition, lamotrigine and sodium valproate are singled out as AEDs that treat a wide range of seizure types;[15, 16] both are named as drugs of choice for idiopathic-generalised seizures or whenever there is uncertainty over the seizure type[3] (Table 1).

The guidelines give recommendations for the

commencement of AED therapy taking into account the risk of recurrence after a single seizure, the type of seizure(s), the result of investigations, potential side effects from AEDs and the view of the patient regarding treatment. If there is no response to AEDs the diagnosis of epilepsy should be revisited and confirmed.

When determining the appropriate treatment for each individual, the comparative tolerability of AEDs must also be taken into consideration. AEDs may induce side effects and although most are mild, some may lead to drug withdrawal. Therefore, SIGN recommends that AED side-effect and interaction profiles should be considered in the choice of drug for the individual patient. Some newer AEDs, such as lamotrigine and oxcarbazepine, appear to produce fewer side effects and adverse drug interactions.[9-11, 13, 17]

In general, 60-70% of patients become seizure free on treatment with a single AED.[6,17] Patients who fail to respond to monotherapy with two sequential first-line AEDs or with one monotherapy and one combination regimen, are considered to have drug-resistant epilepsy. If this occurs, the chance of further monotherapy working is low.[18] A combination of AEDs that have different, and perhaps complementary, mechanisms of action may enhance effectiveness of pharmacological treatments.[19,20] In addition, resective neurosurgical procedures should be considered early in patients who are drug-resistant.

The SIGN guideline addresses the issue of AED withdrawal after epilepsy has entered a period of remission and emphasises the importance of the need for accurate risk assessment and the need to involve patients in the decision-making process.

Contraception, pregnancy and hormone replacement therapy (HRT)

One of the major changes to the 1997 SIGN guideline is the addition of a section that is devoted entirely to women with epilepsy. Approximately 40% of patients with epilepsy are women of childbearing age, therefore it is crucial that women's issues are taken into account.[21] This revision recognises the importance of providing women with epilepsy who are of childbearing age with advice about issues such as contraception and pregnancy. The choice of epilepsy medication for women may be influenced by factors that include interactions with combined oral contraceptives (COC), cosmetic side effects and potential risks to the fetus.

AEDs that induce hepatic enzymes accelerate oestrogen metabolism and increase the risk of COC failure, even with COCs that contain a higher strength (≥50 mg) of oestrogen (Table 2). Similarly, women with epilepsy receiving HRT may have a reduction in the efficacy of their hormonal treatment if they are receiving enzyme-inducing AEDs (Table 2). Other factors that may influence the choice of AEDs are cosmetic side effects, such as weight gain, which are associated with sodium valproate.[22, 23]

Currently, no AEDs are licensed for use during pregnancy unless the clinician feels that the benefits of treatment to the mother outweigh the potential risks to the fetus. All older AEDs are known to be associated with an increased risk of major fetal malformations, but current data suggest that the risk with sodium valproate may be higher than with carbamazepine or lamotrigine.[24] In addition, there is evidence to suggest that in utero exposure to sodium valproate has an adverse effect on cognitive development.[25]

Lamotrigine may have potential advantages for young women because it is well tolerated,[9, 13, 17] does not interact with oral contraceptives[17, 26] and does not lead to weight gain;[27] these are all issues that are important to women of childbearing potential.

Outcome measures

Although seizure frequency is a sensible, primary outcome measure for AED studies, Dr Duncan commented that it should not be overemphasised as a quality marker in GP contracts. Seizure frequency should be one of a number of indicators taken into account, in addition to seizure severity, side effects, the impact of epilepsy on the patient's quality of life and others.

Seizure type	Recommended AED
Partial and secondary generalised seizures	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate
Idiopathic-generalised seizures	Lamotrigine Sodium valproate
Uncertain seizures types	Lamotrigine Sodium valproate

Table 1. Choice of AED monotherapy[3]

Table 2. Action of AEDs on hepatic enzymes can influence the effectiveness of COCs and HRT[3]

Non-enzyme-inducing AEDs *Do not alter the effectiveness of the COC and HRT*	Hepatic enzyme-inducing AEDs *Increased risk of COC failure and reduced efficacy of HRT*
Acetazolamide	Carbamazepine
Benzodiazepine	Oxcarbazepine
Ethosuximide	Phenobarbital
Gabapentin	Phenytoin
Lamotrigine	Primidone
Levetiracetam	Topiramate
Tiagabine	
Sodium valproate	
Vigabatrin	

COC = combined oral contraceptive

Models of care

A structured management system for epilepsy should be established, linking primary care with secondary care. In addition, an annual review in primary care, as applied to other chronic diseases, is recommended. The goals of the shared care management system include:

- identifying all patients with epilepsy and recording basic demographic data
- making the provisional diagnosis in new patients
- monitoring seizure frequency and date of last seizure (aiming to improve control by adjustment of medication or re-referral to hospital services)
- minimising side effects of medications and drug interactions
- addressing specific women's issues and the needs of patients with learning disabilities.

Information for discussion with patients and carers

This section of the guideline is intended to highlight the main issues that healthcare professionals should discuss with patients and carers by providing examples of information checklists (Table 3). A wide range of topics are covered including:

- information on epilepsy (e.g. what seizures are, types of epilepsy)
- antiepileptic drugs
- seizure triggers
- first aid
- issues for women (Table 3)
- lifestyle
- possible psychosocial consequences
- support organisations.

Checklist points	Issues for women *Topics for discussion*
Contraception	Enzyme-inducing AEDs reduce the efficacy of the COC
Preconception	Effect of seizures on fetus Effect of AEDs on fetus development
Pregnancy and breastfeeding	Effect of AEDs on fetus development Dose of AEDs
Menopause	Enzyme-inducing AEDs reduce the efficacy of HRT Effect of menopause on epilepsy

Table 3. Checklist for women with epilepsy

People with epilepsy need clear, accurate and appropriate information and advice. If healthcare professionals adopt the use of checklists regularly, the chances of major issues being overlooked may be reduced significantly.

What does this mean for patients and healthcare professionals?

Ms Hilary Mounfield, Chief Executive, Epilepsy Scotland

The revised SIGN guideline has been welcomed by patients as recognising their concerns and needs. However, there are only six epilepsy specialists for adults in Scotland, with only a few specialist epilepsy clinics established. Indeed throughout the UK, the number of specialists with an interest in epilepsy does not match patient requirements. As a consequence, the waiting lists for an appointment with a neurologist are very long in some areas, and currently epilepsy care from most GPs is minimal. These factors contribute to the misdiagnosis rate of 20%[4] and the sub-optimal management of epilepsy[28,29] meaning that patients with epilepsy are often not receiving the information and treatment they require.

If this is the current situation six years after the first SIGN guideline for epilepsy, how will the revised guidelines make a difference? SIGN is a partnership model that involves patients with epilepsy, their families, epilepsy specialists, epilepsy specialist nurses, GPs, practice nurses, social workers and voluntary organisations. An important initiative by the Scottish Executive Health Department that reflects this partnership and will aid the implementation of the SIGN guideline, is the establishment of Managed Clinical Networks. This is a pioneering approach in Scotland that is currently underway, with the approval of two pilot Managed Clinical Networks for epilepsy while others are in development. The aim is to build services that link together all the points at which patient care is delivered (primary, secondary and tertiary care). The evidence base for the Managed Clinical Networks will be the SIGN guideline. Furthermore, reviews and audits of the Managed Clinical Networks will be conducted on a regular basis to ensure that the goals of high quality, clinically effective services for epilepsy care are being reached.

Other activities, such as conferences to help primary care implement the SIGN guideline, are being organised. The targets of each initiative are to improve epilepsy care and management, and to try to achieve the vision of best practice documented in the SIGN guideline. Some of these aspirations include access to first seizure clinics within two weeks of experiencing a seizure; diagnosis made by a specialist; and all women with epilepsy to receive preconceptual counselling (Table 4). Ms Mounfield concluded by stating her wish that in five years' time, epilepsy will be discussed as easily with GPs as asthma and diabetes are today.

Conclusion

The revised SIGN guideline reflects the significant progress that has been made in improving the diagnosis, treatment and management of epilepsy in Scotland. Addressing the needs of both healthcare professionals and patients has been a great step forward in improving epilepsy care. Other initiatives are expected within the UK, e.g. the National Institute for Clinical Excellence (NICE) Health Technology Appraisal and Guidance documents for newer drugs for epilepsy in adults and children is expected later in 2003. In addition to this, the National Service Framework (NSF) will be releasing a report on long-term neurological conditions, including epilepsy in 2004. These initiatives, in addition to the SIGN guideline, are a significant move in the right direction. However, the momentum needs to be maintained to continue improving services and raising awareness to ensure that patients with epilepsy receive the treatment they deserve.

For a free copy of the SIGN guideline on the 'Diagnosis and management of epilepsy in adults', visit:

http://www.sign.ac.uk/pdf/sign70.pdf

- **Access to first seizure clinics within two weeks**
- **Diagnosis made by a specialist**
- **Local support available from primary care clinics**
- **Surgery considered early if seizures are not controlled by two first-line AEDs**
- **All women with epilepsy receive preconceptual counselling**
- **Appropriate information always available for patients**

Table 4. Targets for improving epilepsy care and management

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LAM/MTR/03/09032/1

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Presentation Epilim 200 Enteric Coated and Epilim 500 Enteric Coated: Enteric coated tablets containing 200 mg, and 500 mg Sodium Valproate Ph.Eur. respectively. Epilim Crushable Tablets containing 100 mg Sodium Valproate Ph.Eur. Epilim Syrup and Epilim Liquid (sugar free) both containing 200 mg Sodium Valproate Ph.Eur. per 5 ml. Epilim Chrono 200, Epilim Chrono 300, and Epilim Chrono 500: Controlled release tablets containing a mixture of Sodium Valproate Ph. Eur. and Valproic Acid Fr.P. equivalent to 200 mg, 300 mg, and 500 mg Sodium Valproate respectively. **Indications** All types of epilepsy. **Dosage and Administration** *Adults:* titrate at three day intervals until seizure control is achieved. Initially 600 mg/day increasing in steps of 200 mg to a maximum dose of 2500 mg/day. *Children over 20 kg:* initially 400 mg/day increasing in steps to a maximum dose of 35 mg/kg/day. *Children under 20 kg:* initially 20 mg/kg/day – the dose may be increased in severe cases provided that plasma levels are monitored; above 40mg/kg/day chemistry and haematology should be monitored. Epilim Chrono should not be used in this group of patients, due to the tablet size and need for dose titration. Epilim Chrono may be given once or twice daily. All other formulations should be given twice daily. *Combination therapy:* levels of Epilim and co-administered anticonvulsants may be affected and optimum dosage is determined by seizure control. Adjust dose in renal impairment. **Contraindications, Warnings, etc.** *Contraindications* Active liver disease, family history of severe liver disease, porphyria, hypersensitivity to valproate. *Warnings* Hepatic dysfunction: liver function tests are advised before therapy and periodically during the first six months and in those most at risk. Haematological: blood cell count, bleeding time and coagulation tests are advised before therapy to avoid bleeding complications. Pancreatitis: measurement of serum amylase is required in patients presenting with symptoms of pancreatitis. Hyperammonaemia: metabolic tests are advised before therapy in those at risk. In women of child-bearing age, Epilim is anti-epileptic of choice in certain types of epilepsy, such as generalised + myoclonus/photosensitivity. For partial epilepsy, Epilim should only be used in patients resistant to other treatment. Caution should be used in patients with systemic lupus erythematosus. Risk of weight gain. *Side effects* Impaired hepatic function, particularly in children. Hyperammonaemia with or without hepatic dysfunction, and associated with neurological symptoms. Blood dyscrasia – impaired platelet function, prolonged bleeding time, thrombocytopenia, occasional leucopenia, pancytopenia and red cell hypoplasia. Rare reports of severe pancreatitis, sometimes fatal. Increased appetite, weight gain, transient hair loss, behavioural disturbances, hearing loss, vasculitis, hirsutism, acne, allergic reactions and alterations to the menstrual cycle and pancreatitis. Symptoms of intoxication include ataxia, tremor, and stupor. A reversible Fanconi's syndrome, reversible dementia/ parkinsonism and cutaneous reactions. *Drug interactions* Phenytoin, lamotrigine and other anticonvulsants. Caution advised when using Epilim with newer drugs and clinical monitoring is recommended at the beginning of combined therapy. Epilim may potentiate the effects of neuroleptics, MAOIs and other antidepressants, benzodiazepines, anticoagulants and salicylates. Patients may suffer transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines. The serum plasma concentration of zidovudine may be raised by Epilim. Cimetidine and erythromycin may inhibit the metabolism of Epilim. Mefloquine and chloroquine may lower seizure threshold and mefloquine may increase Epilim metabolism. Carbapenem antibiotics may reduce valproic acid levels. No effect on efficacy of oral contraceptives. *Pregnancy and Lactation:* Rate of malformations in offspring born to mothers with epilepsy receiving any anti-epileptic medication has been shown to be 2-3 times higher than that in the general population. Malformations most frequently described are cleft lip and cardio-vascular malformations. Studies have suggested an association between in-utero exposure to sodium valproate and developmental delay. Increased incidence of congenital abnormalities has been demonstrated in offspring born to mothers with epilepsy on sodium valproate therapy. Use with sodium valproate is associated with neural tube defects at a frequency of 1-2%. Women of childbearing age should be informed of the risks and benefits of continuing anti-epileptic medication throughout pregnancy. Folate supplementation prior to pregnancy can reduce the incidence of neural tube defects in the offspring of high-risk women. Anticonvulsant monotherapy is preferable, at lowest effective dose, in divided doses. Sodium valproate treatment should not be discontinued during pregnancy if it has been effective. However, prenatal monitoring initiated in order to detect the possible occurrence of any malformation. Pregnancies should also be screened by ultrasound and other techniques. Rare reports of haemorrhagic syndrome (related to hypofibrinaemia) in neonates whose mothers received sodium valproate during their pregnancy. Afibrinaemia has also been reported and may be fatal. Haemorrhagic syndrome may also be induced a decrease of vitamin K factors by phenobarbital and other anti-epileptic enzyme-inducers. Neonatal platelet counts, fibrinogen plasma levels and coagulation status should be fully investigated. **Legal category** POM. **Further information** Epilim is hygroscopic – keep tablets in blister pack until use and avoid cutting blister strips. 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Health Economics of Epilepsy

Mr Christopher L.I. Morgan and Dr Michael P. Kerr

Epilepsy is the most common, serious neurological condition affecting approximately 440,000 people in the United Kingdom. The average general practitioner list will include fourteen patients with epilepsy. Whilst onset can occur at any age, it is more commonly diagnosed amongst children and adolescents (where it is usually of unknown or genetic origin) and the elderly (where it is most commonly associated with an underlying condition such as cerebrovascular disease.)

Compared with other neurological conditions such as multiple sclerosis, epilepsy is relatively inexpensive in terms of the mean cost of treatment per patient. However due to the high prevalence of the disease, the total cost of epilepsy within the United Kingdom has been estimated to be in excess of £2,000 million per annum. The large cost of epilepsy treatment inevitably focuses close attention to issues of cost effectiveness. All health systems need to ration health care. Finite resources determine that the decision to use one treatment must also be seen as a decision to forego the next best alternative available, that is the opportunity cost. Whilst rationing has always been an imperative of the National Health Service, recent years have seen, at least in theory, a more focused evidence based approach to how resource allocation decisions are taken.

What are the costs of epilepsy?

Costs to the National Health Service for the treatment of epilepsy will typically include:

- Anti-epileptic drugs (AEDs);
- General practice and outpatient appointments;
- Inpatient and accident and emergency admissions relating to seizures;
- Diagnostic investigations;
- Surgical admissions;
- Biochemical monitoring.

As such the costs per patient will not be uniform but will vary depending on the severity and complexity of the condition and also the stage of onset. The first year from diagnosis is predictably costly due to investigations, likelihood of specialist involvement and potential uncontrolled seizures. Almost half of patients will be controlled on their first AED,[1] and a further 20% will be controlled either by switching to an alternative monotherapy or the addition of another AED as polytherapy.[2] Approximately 30% patients will therefore have refractory epilepsy. The cost implications of successful treatment are highlighted by an Italian study.[3] This found that cost of treatment ranged from €412 for those cases in remission to €2,198 for those which were drug resistant. Those with newly diagnosed epilepsy cost €1,002.

Seizure control can therefore be considered an economic imperative in addition to the obvious benefits of health status and quality of life for the individual. Poor seizure control is associated with increased inpatient admissions, specialist contacts and admissions to accident and emergency.

Novel anti-convulsants

In addition to the cost consequences of poor seizure control, the health economics of epilepsy has become increasingly important due to the development of new AEDs. Over the last decade these novel anti-convulsants have offered a greater choice of treatment to patients. Crudely however, in terms of a dose-to-dose comparison, these newer medications are more expensive than their traditional counterparts. This is a concern as drug costs are second only to hospital admissions as the major component of the cost of epilepsy.[3, 4]

Counting the cost of epilepsy

Current literature highlights the problem of non-standard methodologies for costing epilepsy treatment. There are huge variations in estimated cost with different methodological approaches possibly a significant cause. International comparisons of epilepsy have demonstrated nearly a tenfold difference in costs. Kotsopoulos[5] found that direct costs per patient ranged from $680 (Sweden) to $5,278 (Switzerland). However the major course of this discrepancy is that the former only included direct health care costs where as Gessners Swiss study included indirect costs. The definition of direct and indirect cost may also vary. Typically direct costs will include those incurred in the diagnosis and treatment of epilepsy such as drug prescription, inpatient and outpatient costs whereas indirect costs will include those from a wider societal viewpoint such as the costs associated with restricted employment opportunities.

Levy[6] has discussed several factors which will affect comparison of cost of illness studies and those considering the economic evaluation of AEDs. These

include the nature of the population selected for study based on criteria of age, seizure type or severity, whether the study includes direct or indirect costs and the time span under review. In addition some cases will consider incident cases and others prevalent cases. It is clear that each of these cohorts will have differing costs. Implicitly, those with refractory epilepsy will have greater costs than those controlled and newly diagnosed (incident) cases will have greater costs than prevalent cases.

There will often be a bias as cases identified for prevalent analyses will tend to be those with active epilepsy whereas new onset cases may be excluded. The effect of this therefore will be to underestimate the cost of epilepsy treatment.

When assessing the cost effectiveness of different treatment regimens it is important to consider how direct costs such as inpatient and outpatient contacts will have different fixed costs in different setting. This is also true of drug costs which vary significantly within the European community. An average weekly dose of carbamazepine and lamotrogine for example cost €5.45 and €52.34 respectively in Belgium but €2.71 and €34.13 in the United Kingdom.[7]

The most common type of study to be conducted for the economic evaluation of epilepsy is the cost effectiveness study. This produces a ratio of the cost of treatment against the resulting health benefit. This health benefit is usually defined in terms of improvement in seizures. However this is not standardised over every study. Some may choose seizure freedom, others a defined reduction rate. However other factors will be important such as adverse events which may negatively outweigh any benefit the patient receives in terms of seizure reduction. A weighted indicator may be created but this is often disputable and adverse effects may not become immediately apparent.

Other types of study are also possible for example the cost benefit analysis which defines outcomes in cash terms. The cost-utility analysis defines outcomes using a global scale such as the quality adjusted life year (QALY).

Conclusion

Ambiguity still surrounds the cost assessment of epilepsy treatment and care. Whilst differences in methodology and study criteria may be inevitable it is necessary to be aware that such differences exist. Whilst physicians and planners may express increasing awareness and acceptance of cost-effectiveness issues, complexities and subtleties remain which need to be understood.

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Salvage Chemotherapy and Stem Cell Mobilisation in Relapsed Lymphoma

Dr Andy Haynes

To understand a review of the titled topic it is first necessary to introduce the principle of stem cell transplantation and the natural history of relapsed lymphoma.

Stem cell transplantation

Dose Escalation

When malignant cells are resistant to killing by conventional doses of chemotherapy it has demonstrated in vitro, in a limited number of tumour types, that dose escalation can result in cell killing. In vivo the application of this principle is restricted by dose limiting toxicity to cells in normal tissue since chemotherapy is given systemically and cannot be targeted only to the malignant cells. It is possible to deliver effective escalated chemotherapy doses which do not irreversibly damage lung, liver, heart, gut, brain and kidney. The bone marrow, because it is highly proliferative, will always be severely affected by even small dose escalations. As a consequence, effective dose escalation is clinically limited by myelosuppression; it would take the blood count 6 -9 weeks to recover after such treatment when high mortality and morbidity would be seen from infection and bleeding.

Stem Cells

Bone marrow is a mixture of fat and haemopoietic cells present in the upper femora, humeri, sternum, pelvis, ribs and vertebrae of adults. Trillions of cells are made each day and the marrow is essentially a factory producing 3 lines; red cells, white cells and platelets. At the start of each line is a pool of lineage specific stem cells but these are renewed from a very small pool of special stem cells, termed pleuripotent because they can give rise to any type of lineage specific stem cell. These are the key to long term marrow function; when they are destroyed by chemicals, drugs or lethal doses of irradiation blood production stops and patients die from aplastic anaemia within 6 - 9 weeks.

Autologous Transplantation

It follows that to deliver effective dose escalated chemotherapy a source of pleuripotent and lineage committed stem cells protected from the drugs must be used to repopulate the bone marrow. Initially marrow was harvested in 20ml aliquots under general anaesthetic by multiple needle puncture, anticoagulated and frozen. This was then thawed and returned to the patient like a blood transfusion 24 hours after the last dose of escalated chemotherapy. The lineage committed stem cells resulted in normal blood developing by 3 weeks and the pleuripotent stem cells produced long term marrow function. This was termed autologous transplantation but is actually autologous rescue from the inevitable side effect that dose escalation has upon the marrow. When bone marrow was used as the source, effective dose escalated chemotherapy could be delivered but still had a related mortality of 10-15% due to infection or bleeding. This was partly due to the length of time required for counts to recover and also the fact that in some cases the dose of stem cells was inadequate and the recovery of blood counts suboptimal. The discovery that stem cells appear in the blood as the white cell count recovers from chemotherapy, particularly if primed by the administration of granulocyte colony stimulating factor (G-CSF) was the next major breakthrough in the early 90's. The stem cell dose which can be harvested and stored under these circumstances is greater than that collected from unstimulated bone marrow. As a result when these are used for autologous rescue, blood counts return within 2 weeks and the procedure related mortality is reduced to less than 5% and in many cases less than 1%. This procedure is termed an autologous peripheral blood stem cell transplant (PBSCT). This can now be safely performed in patients up to the age of 65yrs if they have adequate renal, liver, cardiac and lung function.

Relapsed lymphoma

Lymphoma is the commonest indication for an autologous PBSCT. There are 3 main types of lymphoma which are transplanted; Hodgkin's disease (HD), low grade follicular lymphoma (FNHL) and aggressive B cell diffuse large cell lymphoma (DLCL).

Hodgkin's Disease

In HD we expect to cure 70% of patients with conventional therapy hence about 30% of cases have relapsed disease and given the median age of 30yrs for this tumour most will be eligible for PBSCT. All cases relapsing within a year of initial chemotherapy and in practice most of those doing so within 3 years will be offered PBSCT. The best outcomes are when the PBSCT is done at first relapse when 5 year event free survival of 60-70% is obtained.

Diffuse Large Cell Lymphoma

In DLCL a much more heterogeneous cure rate is seen with 15-70% of cases being cured by initial chemotherapy. Given that the median age at diagnosis is 70years, less than half of those not cured are eligible for PBSCT. All cases under 65years who achieve a durable response to salvage chemotherapy would be considered for PBSCT in second response. For these cases 5 year event free survival of 50% is achieved.

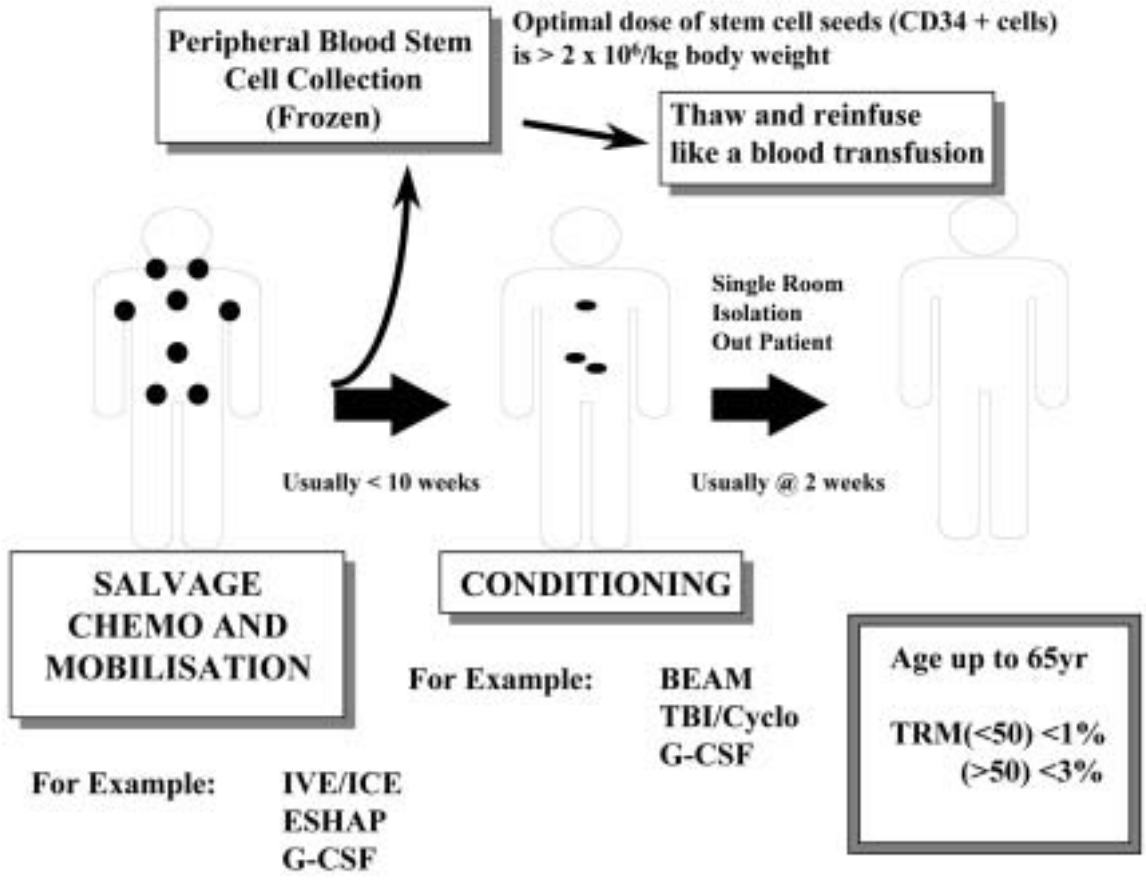
Low Grade Follicular Lymphoma

The role of PBSCT in this disease is much less well defined. The median survival for cases is 10 years and the median age at diagnosis 70 years hence many patients do not need or will be too old to receive PBSCT. Prognostic scores are inadequate to pick out cases for more aggressive therapy. Currently patients with evidence of transformation to a DLCL, those with relapse within a year of anthracycline based therapy and those with multiple sites of extranodal disease are more likely to be considered for PBSCT. The results for PBSCT performed at first relapse are better than those done at later time points in the course of the disease; in this setting 5 year event free survival of 50% is seen. Only cases responding to salvage treatment would usually proceed to PBSCT. It is not clear if PBSCT is curative in this disease. An additional problem in these patients is stem cell contamination by lymphoma cells which occurs even in patients in very good remission. The clinical significance of this remains unclear.

What is the purpose of salvage chemotherapy in the context of PBSCT ?

It follows that we can define a number of criteria for outcomes of salvage chemotherapy in relapsed lymphoma.

- Bring the relapsed disease under durable control
- In the case of non Hodgkin's lymphoma induce the best possible response prior to transplant and ideally achieve a complete remission
- Mobilise an adequate dose of stem cells. A surface protein, CD34, can be used as an indirect marker of the dose of stem cells collected. A dose above 2 x 106/Kg body weight will permit PBSCT but a dose of 6 x 106/Kg or more will ensure rapid engraftment within 2 weeks hence the lowest risk of mortality. A peripheral blood CD34 positive cell count of > 30/uL on the day of collection predicts a satisfactory harvest. It is better for the patient if the target dose of stem cells can be collected in a single leucapheresis
- In the process of achieving the above aims, it is vital that the salvage chemotherapy does not have an impact upon major organ function and performance status which will exclude transplantation
- Where a risk of CNS disease is present, the salvage regime should contain drugs which will deal with this.



- In FNHL it is emotionally desirable but not scientifically proven that stem cell contamination with lymphoma cells should be minimised.
- It may be desirable but not necessary for a salvage regime to be administered on an outpatient basis
- It is possible to collect stem cells simply after G-CSF monotherapy and it is also possible to mobilise stem cells using single agent cyclophosphamide after salvage chemotherapy. These could be used to collect stem cells before a very active lymphoma regime which would damage subsequent stem cell yield or to collect after a very active lymphoma salvage regime with poor mobilisation qualities.

In general, salvage will contain drugs which the patient has not been previously exposed to and the same combination will be active in all relapsed lymphoma. There is currently no evidence that one regime is better than another because no statistically adequate randomised trials have been reported. Care must be taken if anthracyclines are used in salvage not to exceed the maximum recommended cumulative dose; past treatment history is therefore important. The initial salvage regimen used in Europe was DHAP which contains an anthyracycline, ara C and cis platinum. This gives response rates of 50-70% with myelosuppression as the major toxicity but also renal impairment from the platinum. Stem cells can be mobilised from DHAP. The Americans developed ESHAP from DHAP; it contains etoposide and has similar response rates with less myelosuppression. Further regimes developed in Europe were based around BEAM (mini BEAM and dexa BEAM) which contains BCNU, etoposide, ara C and melphalan. These regimen have response rates of 50% but the BCNU and melphalan can cause stem cell damage leading to difficulty in mobilisation. Regimen have developed around the use of infusional ifosphamide and high dose etoposide (IVE) or carboplatin (ICE). These regimen have high response rates 70-80%, mobilise stem cells well and often collect an adequate stem cell dose in a single leucapheresis. Fludarabine containing regimen are less commonly used but in combination with ara C (FluDAP) considerable activity is seen in relapsed lymphoma. Fludarabine can make it difficult to mobilise stem cells. Regimen containing high dose ara C or ifosphamide provide CNS directed therapy; the latter can be associated with a reversible acute encephalopathy if dose reductions are not applied in the presence of renal/liver impairment or a low serum albumin.

Whilst response rates are important in choosing the optimal salvage therapy other factors should be considered:

- Mobilisation failure rate
- Serious toxicity, such as renal, which prevents subsequent transplantation.
- The durability of responses; in the paper reporting the use of DHAP in DLCL, a third of patients did not get to the autologous transplant because of disease progression before the transplant could be scheduled

It is very important when comparing schedules that these factors are considered and standard definitions of response are applied. A discounted score should be considered where the mobilisation failures and patients not proceeding to transplant due to toxicity or progression are subtracted from the overall response rate to give a comparable indicator of salvage regimen. There is no evidence that any of these regimen are superior in terms of reducing stem cell contamination by low grade lymphoma cells.

New developments

In general, the complete remission rates (CR) for salvage regimen in DLCL are low; perhaps the ifosphamide regimen (ICE or IVE) giving the highest rates in the region of 20%. Evidence suggests that DLCL patients achieving a CR on salvage do better after high dose therapy. Preliminary data show that combining the anti CD20 monoclonal antibody Rituximab with chemotherapy gives rise to higher response rates, better CR rates and in untreated DLCL better survival. When Rituximab is added to ICE salvage in DLCL, early data suggest a CR rate of 50%. If confirmed this suggests that Rituximab immunochemotherapy will get more patients to transplant but it remains to be confirmed whether these responses will translate into a higher cure rate after PBSCT. This question is about to be addressed in the international CORAL study which will include patients from North America and Europe. It is clear from the limited evidence available that Rituximab immunochemotherapy can induce responses in patients failing a first line salvage regime and allow some patients to reach transplant. More experience is needed in this area.

In follicular lymphoma, there is also evidence that Rituximab treatment before stem cell mobilisation either with or before mobilising chemotherapy results in stem cell collections with reduced contamination by lymphoma cells. It remains to be seen whether this translated into better outcome after PBSCT. This is also the subject of a current European study.

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He is Lead Clinician for Cancer at the Trust and Chairs the Mid Trent Cancer Network Drugs and Therapeutics Committee. He has published over 50 peer reviewed articles and 6 book chapters. He is a national co-ordinator for an NCRN approved trial in follicular lymphoma and a member of the medical panel advising the Lymphoma Association. He was educated at Cambridge and Kings College and appointed in Nottingham in 1996.

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The Management of Small Cell Lung Cancer

Fergus Macbeth

What is it?

Small cell lung cancer (SCLC) is a variant of lung cancer with characteristic histological appearance and clinical course, and a generally poor prognosis. Biopsy typically shows infiltration with small blue cells with multiple atypical mitoses and immunological markers of neuro-endocrine cells, implying their origin in neural cells in the bronchial mucosa. It is appears to be at the malignant end of a spectrum of tumours ranging from carcinoid (generally regarded as a benign tumour) through atypical carcinoid to SCLC.

Small cell carcinoma, although almost always a lung tumour, can occasionally occur at other sites such as oesophagus, small bowel and cervix.

How common is it?

In the UK small cell tumours constitute around 15% of lung cancers. This means that there are around 5,000 new cases each year.

How does it present?

As with other kinds of lung cancer SCLC is typically a tumour of middle-aged and older people, with a median age at presentation of around 70 years. It occurs almost exclusively in current or ex-smokers and, although commoner in men, is being seen increasingly often in women.

SCLC tends to grow quickly and the patients often have large, central chest tumours and mediastinal and/or distant metastases at presentation. The presenting symptoms are usually no different from other types of lung cancer with cough, breathlessness, haemoptysis, chest pain and symptoms of metastases all being quite common. Patients are also often anorexic and losing weight.

Non-metastatic syndromes occur more often with SCLC than with other lung cancers. The most frequent is inappropriate ADH secretion and an older smoker found to have a low serum sodium (less than 130 mmol/l), with or without chest symptoms, should have a chest X-ray. Less common are non-metastatic hypercalcemia and ACTH secretion and the neurological syndromes such as cerebellar ataxia, peripheral neuropathy and the myasthenia-like Lambert-Eaton syndrome.

How is it diagnosed?

SCLC cannot be reliably distinguished from other forms of lung cancer on clinical grounds alone but its management is significantly different. So it is important to try to get a histological diagnosis. This is most often done by bronchoscopy but some patients have a CT guided biopsy or needle biopsy of sites of metastasis (such as lymph nodes, skin, liver or bone).

How is it staged?

Staging is the assessment of the extent of tumour spread. For patients with SCLC complex staging investigation is not usually undertaken. It is only necessary to establish whether they have 'limited' disease, confined to one hemi-thorax or 'extensive' disease with evidence of metastases following basic investigation with CT thorax and upper abdomen and serum biochemistry. More complex investigations such as CT brain and bone scan need only be done if there are suspicious symptoms.

However it is also important to make a formal assessment of prognosis which can be done quite simply on the basis of performance status (what the patient can actually do in their daily life), extent of disease and serum biochemistry. This is useful not only for discussion with the patient and his/her relatives but may also determine the treatment.

What is the best treatment for patients with 'good prognosis'?

'Good prognosis' patients are those with limited disease, good performance status and few biochemical abnormalities. There is no doubt that these patients should be treated with chemotherapy. There is a very good chance of a significant response to chemotherapy and a small but realistic chance of complete response and eventual long term survival.

A wide variety of regimens are used and are effective. Despite many years of clinical research no particular regimen has been shown to be the most effective. However, in the UK the drugs cisplatin, carboplatin, doxorubicin and etoposide are most frequently used, generally in combinations of at least two drugs. Usually four to six course of chemotherapy are given depending on the response and level of toxicity.

Toxicity with these drugs is variable but sometimes severe with a significant risk of neutropenia and thrombocytopenia which is potentially fatal if associated with untreated infection. The patients need to be carefully monitored during treatment and given rapid access to appropriate inpatient care if neutropenic sepsis is suspected.

Those patients who achieve a complete response to initial chemotherapy should then receive radiotherapy to the site of original disease and also prophylactic cranial irradiation (PCI). Both of these additional

treatments have been shown by meta-analysis of randomised trials to significantly improve local recurrence and survival. PCI is given because of the very high risk of subsequent brain metastases.

Despite the very high response rate (up to 80 or 90%) to initial chemotherapy, the majority of patients relapse, usually within 18 months. Median survival is less than two years and only 15% or so reach 3 years without relapse and are potential long term survivors.

Is surgery ever appropriate?

There is no strong evidence to suggest that patients with truly early disease should be operated on. Most patients have mediastinal nodes or distant metastases at presentation and so surgery is rarely considered. However occasional patients with SCLC do have surgery, either because there was no definite histology pre-operatively or because careful investigation confirmed localised disease. It is generally recommended that these patients go on to have chemotherapy because of the high rate of occult metastases.

What is the best treatment for patients with 'poor prognosis'?

The majority of patients with SCLC in the UK fall into the poor prognostic category. Unless they are very unwell at presentation (see below) these patients should also be offered chemotherapy. There is little or no chance of long term cure but there is good evidence that they benefit in terms of symptom control and survival. Untreated, median survival is around 6 to 8 weeks but with chemotherapy it is 6 to 9 months. During this time most patients have significant palliation and improvement in quality of life.

Because these are iller patients often with obvious metastatic disease, they are at significant risk of serious toxicity from chemotherapy. So a careful balance has to be kept between the risks and benefits and the doses of drugs or the number of courses may be reduced in order to achieve good palliation.

Radiotherapy is not usually given as part of first line treatment but can be very useful for palliation of patients at relapse. Second line chemotherapy at relapse can also be effective, especially for patients who had a good response to initial treatment that has lasted several months. However the response rate is less good and so the trade off against the risks of toxicity less favourable.

How should patients over 70 be managed?

The median age at presentation is around 70 years and so we are often presented with the dilemma of how intensively to treat older patients. Although in general older patients tolerate chemotherapy less well and experience more toxicity, especially with the bone marrow, chronological age should not necessarily be a contra-indication to chemotherapy, even with quite intensive regimens. More important is the presence or absence of significant co-morbidity and the patient's overall performance status.

How should very ill patients be managed?

It is not unusual for patients to be very unwell by the time a diagnosis is made, either because of very extensive mediastinal tumour compressing major airways or from the effects of widespread metastatic disease. The decision about whether or not to give chemotherapy can be very difficult. Without treatment the patient is likely to die within a few days or weeks, but treatment may cause fatal neutropenic sepsis and death within a week to ten days.

Our policy is whenever possible (and it may not always be appropriate) to discuss this openly with the patient and the relatives. Some may accept the situation and not want treatment while others may be prepared to take the risk. In that case we generally reduce the dose of chemotherapy for the first course with the intention of increasing it if they have a good response and tolerate it well.

What research is being carried out?

Research into the treatment of SCLC has been somewhat stagnant over the past five years. Although new chemotherapy agents and combinations have been tested, none have shown significant advantages over well established regimens. At the moment there is interest in the use of thalidomide which seems to have an anti-angiogenic effect on tumours and a small preliminary study suggests that it may have an effect on survival in patients with SCLC. A large randomised trial of its use in combination with standard chemotherapy has just started in the UK.

Fergus Macbeth has been a Consultant Oncologist with a special interest in lung cancer at Velindre Hospital, Cardiff since 1998. After training in Oncology in Glasgow, Southampton and Cambridge, he returned to Glasgow as a consultant at the Beatson Oncology Centre, where he worked for 8 years. He has been involved in lung cancer clinical research for 15 years. In addition he was Director of the Clinical Effectiveness Support Unit for Wales between 1996 and 2000 and since January 2003 has been Director of the NICE National Collaborating Centre for Cancer.

Exemestane: a potent irreversible aromatase inactivator and a promising advance in breast cancer treatment

J Michael Dixon

With the introduction of orally-active, potent and selective third-generation aromatase inhibitors and inactivators – anastrozole, letrozole, and exemestane – approaches to the treatment of advanced breast cancer are undergoing re-evaluation. In advanced breast cancer, aromatase inhibitors and inactivators are likely to become established as the primary choice over tamoxifen in postmenopausal female breast cancer patients when hormonal therapy is indicated in the first-line setting. The current evaluation of exemestane, an oral steroidal irreversible aromatase inactivator, for primary and adjuvant therapy and the potential role of potent estrogen-deprivation therapy in prevention of postmenopausal breast cancer may extend the use of antiaromatase therapy as an increasingly valuable palliative treatment option, conferring survival benefit and possible preventative outcomes across several treatment settings in the management of breast cancer.

Expert Rev Anticancer Ther 2(3): 267-275 (2002)

Hormonal therapy is an effective treatment for patients with estrogen or progesterone receptor-positive (ER, PgR) breast cancer. There has been a reappraisal of what is optimal endocrine treatment for advanced breast cancer. For many years, the antiestrogen tamoxifen has been considered the standard first-line hormonal treatment for postmenopausal patients with hormone-responsive metastatic breast cancer. Following tamoxifen failure, sequential hormonal therapy may be effective. Since the major goal of treating metastatic breast cancer is palliative, minimally toxic alternatives to tamoxifen are required that produce improved clinical benefit by ameliorating clinical symptoms, maintaining acceptable performance status and quality of life, and possibly delaying the need for chemotherapy.

Orally-active, potent selective third-generation aromatase inhibitors and inactivators- anastrozole (Armidex™, AstraZeneca), letrozole (Femara™, Novartis) and exemestane (Aromasin™, Pharmacia) – fulfil these criteria and this has led to a re-evaluation of the treatment approaches to the management of advanced breast cancer in postmenopausal women. Initial randomized clinical trials established these antiaromatase agents as the treatment of choice following tamoxifen failure, providing significant gains in clinical efficacy together with improved tolerability over the progestins.[1-3]

Results from subsequent studies of these aromatase inhibitors and inactivators are now challenging the conventional position of tamoxifen as standard therapy for advanced breast cancer. Importantly, recent data demonstrate that antiaromatase agents are more effective and better tolerated than tamoxifen in the treatment of postmenopausal women with hormone-sensitive advanced breast cancer. Data from a randomized Phase III study demonstrate that letrozole, an oral reversible nonsteroidal aromatase inhibitor, may improve short-term survival of postmenopausal women with locally advanced or metastatic breast cancer who are appropriate candidates for first-line hormone therapy, when compared with tamoxifen.[4] Preliminary data also suggest that the oral aromatase inactivator exemestane can cause significant regression of breast cancer tumors, allowing more patients to receive conservative surgery. The first results from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study showed a 17% reduction in risk of breast cancer recurring with anastrozole treatment compared with tamoxifen.[5] Furthermore, the use of exemestane in the adjuvant treatment of postmenopausal women with early breast cancer is being assessed and other studies in the setting of hormonal chemoprevention are ongoing.[6] Antiaromatase agents are therefore likely to gain increasing prominence in the treatment of breast cancer.

Introduction to the compound

Pharmacological approaches to hormonal therapy of breast cancer are based on blocking estrogen effects. Two general strategies have been developed: blockade of estrogen receptor action with antiestrogens, or inhibition of estradiol biosynthesis with competitive enzyme inhibitors or enzyme inactivators. Tamoxifen remains the standard first-line hormonal therapy in an adjuvant breast cancer setting. However, since tamoxifen possesses partial estrogenic activity, tamoxifen-treated patients may be exposed to a modest increased risk of endometrial cancer. Likewise, its partial agonist activity can in some patients result in the development of acquired resistance, whereby tamoxifen may stimulate tumor regrowth following prolonged therapy.[7]

The first aromatase inhibitors were discovered nearly 30 years ago and included aminoglutethimide and testololactone. Aminoglutethimide was already in clinical use as an inhibitor of steroid biosynthesis and was associated with a similar antitumor effect to that

of tamoxifen. However, the lack of specificity of aminoglutethimide for aromatase and inhibition of other enzymes, such as 11-hydroxylase, as well as troublesome side effects limited its use. More potent and specific inhibitors were subsequently developed for clinical application. The introduction of the third-generation aromatase inhibitors anastrozole and letrozole and the inactivator exemestane represents a major advance in hormonal therapy. Inhibiting estrogen synthesis by 97-99%, these agents act exclusively on the aromatase enzyme and inhibit aromatase nearly completely without causing significant side effects.[8-11] Aromatase inhibitors and inactivators, such as anastrozole, letrozole and exemestane are highly selective inhibitors or aromatase and suppress estrogen production in postmenopausal women effectively. While estrogen synthesis in the ovary ceases at the menopause, estrogens are still produced in different peripheral tissues, including benign and malignant breast tissue.

There are two different classes of aromatase inhibitors, steroidal (or irreversible, substrate-site binding Type I) and nonsteroidal (heme-binding, Type II reversible) inhibitors. Exemestane is an orally-active steroidal aromatase inactivator with a distinct mechanism of action, binding irreversibly to the substrate binding site of the enzyme to inhibit its activity and thereby reduce plasma estrogen levels. Reversible nonsteroidal aromatase inhibitors, such as anastrozole and letrozole, compete for the substrate on the enzyme's active site, bind reversibly for the substrate on the enzyme's active site, bind reversibly to the heme site of the enzyme and prevent product formation only as long as the inhibitor occupies this site.

All three selective antiaromatase agents are now widely accepted as the preferred second-line therapy over megestrol acetate, representing a new standard of care in hormonal treatment of postmenopausal women with hormone-sensitive advanced breast cancer. While these three compounds have comparable activity in terms of *in vivo* aromatase inhibition, it remains unclear whether there are clinically significant differences in activity in the tumor level. While exemestane is approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy, anastrozole and letrozole are both licensed for use in the first - and second-line treatment of advanced breast cancer in postmenopausal women.

Pharmacodynamic & pharmacokinetic profile

Inhibition of estrogen biosynthesis is an attractive form of endocrine deprivation therapy for postmenopausal women with breast cancer. Aromatase inhibitors and inactivators are drugs that suppress estrogen production through inhibition of the final step in their synthesis, conversion of androgens to estrogens.

Type I inhibitors, such as exemestane and formestane (Lentaron™) and androgen analogs which bind irreversibly to and inactivate the enzyme. Exemestane, unlike formestane, can be administered orally and is a more potent enzyme inactivator *in vivo*. In contrast, Type II agents, such as the aromatase inhibitors aminoglutethimide, letrozole and anastrozole are nonsteroidal compounds that cause reversible enzyme inhibition. While all inhibit aromatase activity *in vitro*, the more recent third-generation agents are substantially more potent and selective than aminoglutethimide.

Differences in the mechanisms of action of Type I inactivators and Type II inhibitors can be elicited *in vitro*. Preincubation of cultured fibroblasts with Type II inhibitors often results in an increase in subsequent aromatase activity, whereas preincubation with Type I inactivators produces marked inhibition. Enhanced aromatase activity observed with nonsteroidal Type II inhibitors may result from enhanced transcription of the aromatase gene or stabilization of the aromatase protein.[12,13]

Exemestane is a highly potent inactivator of aromatase activity. When given daily mg amounts to postmenopausal women, peripheral aromatase is almost totally blocked (>98%) and circulating estrogens are reduced to levels near the limit of detection.[6] Since estrogen levels in the circulation of postmenopausal women do not necessarily reflect those in the breast and local aromatase activity may be differentially affected by antiaromatase agents, it is important to determine the effects within the breast. Exemestane profoundly inhibits *in situ* aromatase activity both in breast cancers and surrounding nonmalignant breast.

While reversible Type II inhibitors appear effective when given acutely, more chronic use could increase aromatase levels such that estrogen biosynthesis resumes. In this scenario, irreversible inactivation caused by Type I agents may be superior. The potency and pharmacokinetics of triazole inhibitors, such as letrozole, appear to achieve highly effective inhibition of estrogen synthesis. Interestingly, there is a lack of complete cross-resistance between aromatase inhibitors and inactivators, suggesting that Type I inactivators do provide additional clinical benefit in patients relapsing on nonsteroidal inhibitors. This ability to potently block estrogen biosynthesis provides new options for the treatment of hormone-sensitive breast cancer in postmenopausal women.[6]

Exemestane has a favourable pharmacokinetic profile in humans. The drug exhibits linear pharmacokinetics in the dose range 0.5-800 mg and has a half-life of approximately 24 h, which allows once-daily administration. It has the added advantage of rapid washout should the patient need to discontinue treatment.[14,15] Absorption of exemestane is rapid and extensive (>42%). Average peak plasma levels of 18 ng/ml are achieved within 2 h following a single 25 mg dose. Steady-state plasma levels are reached in about 4 days with repeated administration. With a high volume of distribution, exemestane is extensively distributed into tissue. Clearance of exemestane is high, mostly through oxidation of the methylene group at position 6 *via* Cytochrome P450

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epirubicin

3A4 (CYP 3A4) isoenzyme and reduction of the 17-keto group by aldoketoreductases or both. CYP 3A4 is the principle isoenzyme identified in the oxidation of exemestane. Since exemestane selectively and irreversibly inhibits aromatase, it significantly lowers circulating estrogen concentration in postmenopausal women but it has no detectable effect on the adrenal biosynthesis of cortisol or aldosterone or other enzymes involved in the steroidogenic pathway.

In postmenopausal women with advanced breast cancer, administration of a 5 mg daily dose of exemestane significantly reduces plasma estrogen concentrations and maximal suppression (>90%) of estrogen levels was achieved with a 10-25 mg dose. A single daily 25 mg dose of exemestane also reduced whole body aromatization by 98%.

Although formal drug interaction studies are limited, *in vitro* studies have shown that exemestane does not inhibit any of the major CYP isoenzymes. The coadministration of exemestane with the CYP 3A4 inhibitor ketoconazole showed no significant effects on the pharmacokinetics of exemestane. A possible decrease of exemestane plasma levels by known inducers of CYP 3A4 cannot, however, be excluded.

Clinical profile

The clinical efficacy and safety of exemestane 25 mg once daily as a new hormonal therapy for postmenopausal women with metastatic breast cancer has been established in a large Phase III study and several Phase II studies. Several Phase I studies revealed dose-dependent plasma estrogen suppression, with maximal effects observed with a daily dose of 25 mg.[15-16] It is well tolerated and as a consequence, a maximum-tolerated dose has not been identified. Oral exemestane had been evaluated as second-line therapy in patients failing tamoxifen and as third-line therapy in patients failing both tamoxifen an megestrol acetate, tamoxifen and aminoglutethimide, or tamoxifen and a nonsteroidal aromatase inhibitor.

Phase II study data

Results of several Phase II trials indicate that oral exemestane is an effective second- or third-line agent in the treatment of postmenopausal women with advanced breast cancer, inducing an objective response in up to 28 and 26% of patients, respectively.

- In Phase II trials in postmenopausal women having progressed on antiestrogens, exemestane produced objective response rates in 22-28%, with overall clinical benefit rates (OR or SD ≥24 weeks) in 47-48% of postmenopausal women with advanced breast cancer.[17, 18]
- In Phase II studies in patients who had failed multiple hormonal therapies, exemestane 25 mg/day induced objective responses in 7-26% of patients and disease stabilization (≥24 weeks) in a further 11-19% of patients. The median time to response was 8-16 weeks and median time-to-progression was 9-12 weeks.[19,20]

Results of a Phase II multicentre, open-label study evaluating the antitumor activity and toxicity of exemestane in postmenopausal women with metastatic breast cancer who had progressive disease after treatment with a nonsteroidal aromatase inhibitor suggest a lack of complete cross-resistance between nonsteroidal aromatase inhibitors and steroidal aromatase inhibitors.[21] On the intent-to-treat analysis based on independent review, exemestane 25 mg produced objective responses in 7% of patients and an overall success or clinical benefit in 25%. The median durations of objective response and overall success were 58.4 and 37 weeks, respectively.

Furthermore, exemestane seems to be an attractive alternative to chemotherapy for treatment of patients with metastatic breast cancer after failure of multiple hormonal therapies (including reversible aromatase inhibitors), especially for those patients with predominantly soft tissue disease.[21]

Phase III study overview

The aromatase inhibitors and inactivators have been compared with megestrol acetate in four international, multicentre, randomized Phase III trials as second-line therapy following tamoxifen failure in postmenopausal women with metastatic breast cancer.[1-3] Each trial demonstrated both the clinical superiority of these third-generation aromatase agents over megestrol acetate and combined with a better safety profile. However, exemestane is the only agent with a prospectively proven survival advantage compared with megestrol acetate in second-line hormonal therapy after tamoxifen failure.

The Phase III randomized, double-blind multicentre study compared the efficacy, Pharmacodynamic effects and safety of exemestane 25 mg/day *versus* megestrol acetate 40 mg q.i.d. following tamoxifen failure in 769 postmenopausal women with advanced breast cancer.[3] Tumor response was confirmed by external peer-review and analyses were based on the intent-to-treat population; the minimum follow-up was >16 weeks, with a median follow-up of 48.9 weeks.

Prospectively proven survival benefit

Unlike the results reported with reversible aromatase inhibitors, this Phase III study prospectively showed a statistically significant prolongation in time to tumor progression (TTP) and time to treatment failure with the irreversible aromatase inactivator exemestane. Exemestane treatment was associated with 23% reduction in the relative risk of death and was found to induce tumor shrinkage, delay tumor growth and prolong survival. Treatment with exemestane produced a statistically significant improvement in the time to treatment failure, produced a trend towards superiority in tumor-related signs and symptoms and resulted in no change to quality of life. Median survival time was significantly longer with exemestane (median not yet reached) than with megestrol (123.4 weeks; $p = 0.039$), as were the median duration of overall

success (OR or stable disease ≥24 weeks; 60.1 *vs.* 49.1 weeks; p = 0.025), time to tumor progression (20.3 *vs.* 16.6 weeks; p = 0.037) and time to treatment failure (16.3 *vs.* 15.7 weeks; p = 0.042). in the same trial, exemestane was associated with a statistically significant improvement in physical functioning, global health and fatigue.

Study investigators concluded that compared with megestrol acetate, exemestane significantly prolongs survival in women with progressive advanced breast cancer who experience failure of tamoxifen therapy, while offering at least as much improvement in pain and tumor-related signs and symptoms as megestrol acetate and similar or improved outcomes for most quality of life domains.

The presence of visceral disease represents a major challenge in the treatment of advanced breast cancer and is usually an indication for treatment with cytotoxic chemotherapy. However, the latter is associated with significant toxicity. Data from the Phase III study shows that exemestane is active in patients with predominantly visceral disease. A subgroup of patients enrolled in the Phase III trial (n = 207) who had predominantly visceral disease achieved overall response rare in lung lesions (25%) and liver lesions (19%) were higher with exemestane than with megestrol (17 and 11%, respectively). Of note, the 1-year survival difference between exemestane and t he control arm in the Phase III study is similar in patients with predominantly visceral disease and in the overall population (6 and 7%, respectively, in favor of exemestane).

Tolerability

Evidence from noncomparative Phase II studies demonstrates that exemestane 25 mg/day is well tolerated in postmenopausal women with advanced breast cancer. Common adverse events (≥5% of patients) in these trials were typically mild-to-moderate in severity and included nauseas, hot flushes, dizziness, increased sweating and headache. Other less common adverse events, with an incidence ≥2%, were insomnia, pain, skin rash, abdominal pain, anorexia, vomiting, depression, alopecia, peripheral or leg edema, constipation and dyspepsia.

In the controlled Phase III trial, exemestane was better tolerated than megestrol acetate. More megestrol-treated patients (45.8%) reported adverse events considered drug-related or of indeterminate cause than exemestane-treated patients (39.1%). The most common adverse events (usually grade 1-2) with exemestane were hot flushes, nausea and fatigue, increased sweating and increased appetite. Greater weight gain was observed in megestrol-treated patients, especially in those patients overweight at study entry. Weight gain > 10% was noted in 4% of overweight patients treated with megestrol. Drug-related treatment withdrawals were also more common with megestrol than with exemestane (5.0 *vs.* 1.7%, respectively, p = 0.011).

Expert opinion

Metastatic breast cancer is a noncurable disease and it is important to extend the duration of control with hormone therapy, particularly in nonlife-threatening disease, as long as possible before using cytotoxic chemotherapy. Exemestane 25 mg/day is a well-established and potent therapeutic agent in postmenopausal patients with advanced breast cancer who experience failure of tamoxifen. Moreover, accumulating data regarding the efficacy and activity of aromatase inhibitors and inactivators has prompted a re-evaluation of contemporary approaches to the treatment of metastatic breast cancer. As a class of anticancer compounds, antiaromatase drugs are probably the most active hormonal agents in postmenopausal breast cancer patients and should be considered part of the treatment plan of any patient with estrogen receptor positive breast cancer. Preliminary evidence also suggests response to exemestane exceeds that obtained with tamoxifen as first-line treatment.[22,23] An interim report of a randomized Phase II trial examining the activity and safety of exemestane 25 mg/day *versus* tamoxifen 20 mg/day in the first-line treatment of metastatic breast cancer suggests that exemestane is well tolerated and has promising antitumor activity as first-line hormonal therapy.

Encouraging results in neoadjuvant setting

Results from the use of exemestane for neoadjuvant therapy are also encouraging. Study results confirm that exemestane is a highly specific and potent aromatase inactivator that is associated with significant responses in the neoadjuvant setting. A high response rate was noted in a 3-month study investigating the efficacy of exemestane as primary therapy in 13 postmenopausal women with histologically confirmed breast cancer without evidence of distant metastases.[6]

Compared with 65 historical control patients treated with tamoxifen, exemestane appeared to produce a much greater reduction in tumor volume. Ten patients had a partial response and two had a stable disease over the 3-month treatment period.

The median percentage reduction in clinical tumor volume was 85.5%, the median reduction in mammographic tumor volume 84% and the median reduction in ultrasound tumor volume 82.5%. At the outset of treatment, ten of 12 patients would have required mastectomy. However, following 3 months of exemestane 25 mg/day, two patients underwent mastectomy and ten had breast conservation with clear margins. Overall, 80% of patients were converted from the requiring mastectomy to breast conserving surgery. This compares with 63% change in 41 patients treated with tamoxifen who would have required a mastectomy. There have been no local recurrences in the series of patients treated with exemestane following breast-conserving surgery with a median follow-up of 27 months. Significantly different immunohistochemical changes were

observed between exemestane-treated patients and those receiving tamoxifen; with a significant reduction in proliferation and decrease in intensity of PgR expression (compared with an increase in tamoxifen) being observed in exemestane-treated patients.

These findings underscore the marked antitumor effect of exemestane which produces significant responses as neoadjuvant therapy. Its biological effects also differ from those of tamoxifen. These results, together with other confirmatory evidence, suggest that aromatase inactivators/inhibitors may be superior to tamoxifen in the neoadjuvant endocrine treatment of breast cancer, helping reduce the size of tumors and thereby allowing greater conservation of breast tissue.

Profound in situ *inhibition of aromatase*

Several prospective studies have found that a high plasma estrogen concentration in postmenopausal women is a risk-factor for subsequent breast cancer suggesting that aromatase inhibitors and inactivators may have a future role in help preventing breast cancer.[24] Exemestane induces profound *in situ* inhibition of aromatase, both peripherally and locally within the breast. Given the efficacy data regarding aromatase inhibitors and inactivators and the accumulating evidence that estrogens may be directly carcinogenic, there is considerable interest in the potential use of specific aromatase inhibitors as chemoprevention in women at high risk of developing breast cancer.[25] In this setting, drugs that reduce levels of estrogen rather than block their mechanism of action (such as SERMs) may have an added advantage.

Lack of cross-resistance between inhibitors & inactivators

No study has directly compared the clinical efficacy of the different third-generation antiaromatase agents and therefore it is not known whether there is any significant difference between these compounds. Of note, there is a lack of complete cross-resistance between aromatase inhibitors and inactivators. Considering research priorities in endocrine therapy, noncross-resistance between different classes of aromatase inhibitors should be better exploited and the relative clinical advantages of aromatase inhibitors and inactivators warrants investigation. The lack of cross-resistance between tamoxifen and aromatase inhibitors and inactivators in advanced disease suggests that sequential therapy could be beneficial in preventing the out-growth of tamoxifen-resistant micrometastases in some patients undergoing adjuvant therapy. The current evaluation of exemestane for adjuvant therapy and its potential role in prevention of postmenopausal breast cancer will likely extend the utility and contribution of antiaromatase therapy as a valuable palliative treatment option, conferring survival benefit and possible preventative outcomes in the management of breast cancer.

Five-year view

Role of aromatase inhibitors/inactivators in visceral disease

Inherent hormone sensitivity is a fundamental characteristic of most breast cancers. This sensitivity is gradually lost with evolution of the disease. Selecting the optimal hormonal sequence is therefore fundamental to exploit the full potential of endocrine manipulations. Patients with dominantly or fast-growing visceral metastases have not traditionally been considered candidates for endocrine treatments. However, data from a Phase II clinical trial suggests that exemestane has meaningful efficacy in tamoxifen-resistant patients with visceral disease.[17, 26] Objective responses were seen in 25% of cases with visceral metastases, increasing to 41% if SD cases (≥24 weeks) were included. The rates of successes observed were not different from the general population of patients treated.

Data from the Phase III trial show an overall success rate of 37.4% in all exemestane-treated patients and an overall success rate of 36.3% in women with visceral disease taking exemestane. With exemestane, the survival of breast cancer patients having predominant visceral disease was similar to that achieved in patients with less extensive disease; it was also longer than that achieved with megestrol.[27] Median survival time was significantly longer with exemestane (median not yet reached) than with megestrol (123.4 weeks; $p = 0.039$).

Adjuvant hormonal therapy

Adjuvant hormonal therapy for breast cancer primarily using the antiestrogen tamoxifen had a dramatic effect in reducing risk of relapse after surgery for early breast cancer. Third-generation aromatase inhibitors and inactivators have the potential to be even more effective if used earlier in the natural history of the disease.[28]

In metastatic breast cancer, antiaromatase agents including exemestane have shown superiority to tamoxifen and several multicentre studies are underway examining the role of antiaromatase agents in the adjuvant treatment of early breast cancer. The Tamoxifen and Exemestane Adjuvant Multicentre (TEAM) trial is an open-label, randomized, parallel-group comparative trial evaluating 5 years adjuvant exemestane treatment versus 5 hears adjuvant tamoxifen treatment in postmenopausal women treated for ER-positive moderate – and high-risk early breast cancer. A total of 4400 patients will be enrolled.

The TEAM study presents a unique opportunity to collect prospectively tumor samples from the surgical specimens and examine potential predictive markers for clinical outcome, such as the overexpression of the human epidermal growth factor receptor family where evidence supports a potential role for these to modulate ER function. The activation status of downstream targets of growth factor receptors, ER phosphorylation status and markers of ER activation are all planned areas of investigation.

Key Issues

- With the introduction of orally-active, potent and selective third-generation antiaromatase agents – anastrozole, letrozole and exemestane – treatment approaches to the management of advanced breast cancer are undergoing re-evaluation. These aromatase inhibitors are now challenging the conventional position of tamoxifen as standard first-line therapy for advanced breast cancer.

- Exemestane is an orally-active steroidal aromatase inactivator with a distinct mechanism of action, binding irreversibly to the substrate binding site of the enzyme to inhibit its activity and thereby reduce plasma estrogen levels. Reversible nonsteroidal aromatase inhibitors, such as anastrozole and letrozole compete for the substrate on the enzyme's active site, bind reversibly to the heme site of the enzyme and prevent product formation only as long as the inhibitor occupies this site.

- Unlike the results reported with reversible aromatase inhibitors, the prospective Phase III study evaluating the efficacy and tolerability of exemestane showed a statistically significant prolongation in time to tumor progression and time to treatment failure in patients treated with the irreversible aromatase inactivator exemestane. Exemestane treatment was found to induce tumor shrinkage, delay tumor growth and prolong survival.

- There is a lack of complete cross-reference between aromatase inhibitors and inactivators, suggesting that Type I inactivators may provide additional clinical benefit in patients relapsing on nonsteroidal inhibitors.

- No study has directly compared the clinical efficacy of t he different third-generation antiaromatase agents and therefore it is not known whether there is any significant difference between these compounds.

- The lack of cross-resistance between tamoxifen and aromatase inhibitors an inactivators in advanced disease suggests that sequential therapy should be beneficial in preventing the outgrowth of tamoxifen-resistant micrometastases in some patients undergoing adjuvant therapy.

The first results from the ATAC study of over 9300 women demonstrated that the reversible aromatase inhibitor anastrozole is significantly more effective and has important tolerability benefits compared with the current gold standard, tamoxifen, when given as adjuvant treatment to postmenopausal women with early breast cancer.[5] After an average of 33 months' follow-up, anastrozole monotherapy was found to be significantly more effective in preventing relapse than tamoxifen, with a 17% reduction in risk of breast cancer recurring with anastrozole treatment compared with tamoxifen. In the ATAC trial, both the overall incidence of thromboembolic events and that of deep vein thromboses were significantly reduced in the anastrozole group. However, women taking tamoxifen did have a lower risk of experiencing musculo skeletal disorders or types of fractures that are common in this age group when compared with those taking anastrozole.

Preventative properties of aromatase inhibitors & inactivators in breast cancer

Improved therapy has led to a decrease in mortality rates from breast cancer. However, there has also been a marked increase in the incidence of breast cancer. Therefore, preventative strategies are more important than ever. The major factors known to be involved in the epidemiology of breast cancer are estrogen-related. In postmenopausal women, obesity, hormone replacement therapy, high plasma estrogen levels and increased bone density are all related to the incidence of breast cancer, supporting the role of estrogen as a major etiological factor or agent of breast cancer.

The concept of chemoprevention based on antiestrogenic mechanisms was established by the NSAPB-PI study (tamoxifen 20 mg/day versus placebo, n = 13,388). This trial – designed to test the hypothesis that long-term treatment with tamoxifen is effective in preventing invasive breast cancer – reported an approximate halving of the incidence of breast cancer during a median 4-year exposure period.[29] However, tamoxifen is associated with significant side effects including an increase in both thromboembolic disease and endometrial cancer.

Some of the data regarding breast cancer prevention come form investigations into the effect of hormonal adjuvant therapy on contralateral breast cancer incidence. Data from the EBCTCG 1998 overview analysis show a 47% reduction in incidence following 5 years tamoxifen adjuvant treatment.[30] Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized study show that among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with the selective ER modulator raloxifene.[31] Thirteen cases of breast cancer were confirmed among 5129 women assigned to raloxifene compared with 27 among the 2576 women assigned to placebo. Investigators noted that raloxifene decreased the risk of ER-positive breast cancer by 90% but not ER-negative breast cancer.

Raloxifene increased the risk of venous thromboembolic disease but did not increase the risk of endometrial cancer.

These findings explain why other well-tolerated agents targeted at estrogen deprivation are under evaluation as chemo-preventative agents.[32] In particular, third-generation aromatase inhibitors have been shown to provide improved efficacy over tamoxifen in established disease.[33] Evaluation of first events in the intent-to-treat population from the ATAC study shows a markedly lower incidence of invasive contralateral breast cancer in anastrozole-treated patients (nine out of 3125) compared with those receiving either tamoxifen (30 out of 3116) or a combination of anastrozole and tamoxifen (23 out of 3125).

A strong rationale exists for the use of aromatase inhibitors in breast cancer prophylaxis.[24, 32] If estrogen molecules are carcinogenic initiators, the ability of aromatase inhibitors and inactivators to reduce estrogen to exceptionally low levels should provide a degree of protection beyond other hormonal agents. However, there may be a case for the utilization of different prophylactic agents according to hormonal risk, using SERMs in women with a low estrogen environment who face the greatest risk of osteoporosis, with aromatase inhibitors providing maximum preventative benefit in those facing the highest breast cancer risk. If genotoxic estrogens are in fact an important component of breast cancer incidence, then aromatase inhibitors would be expected to be more effective.

Results of a pilot prevention study evaluating the biologic effects of letrozole on the normal breast of postmenopausal women indicate that increased bone resorption will need to be addressed if aromatase inhibitors are to be successful prophylactic agents for breast cancer.[34] While enhanced bone loss in postmenopausal women, as a result of aromatase inhibitor therapy is problematic, it should be solvable.

Data on biomarkers of bone resorption indicate that strategies to restrict this may be necessary for acceptable chemopreventive use of aromatase inhibitors. Such strategies may include their combined use with bisphosphonates, tibolone or the targeting of women with particularly high estrogen levels, which is indicative of both low osteoporotic risk and high breast cancer risk.

Data from an evaluation of the effects of exemestane on bone and lipids in cycling and ovariectomized rats show the potent effect of exemestane in preventing bone loss and in lowering cholesterol and LDL levels.[35] Goss *et al.* noted that exemestane has also been shown recently in humans to prevent adverse side effects on bone and lipid metabolism in postmenopausal women. It was argued that these data could make exemestane a suitable therapy in women undergoing adjuvant breast cancer therapy or chemoprevention. The issue of long-term safety rather than efficacy may ultimately prove to be the key differentiation between aromatase inhibitors and inactivators.

Advanced breast cancer

In the case of postmenopausal women with hormone-sensitive advanced breast cancer, the indications are that aromatase inhibitors are rapidly becoming established as the first choice treatment over tamoxifen.

Information resources

With contributions from over 75 international experts, the book *Aromatase Inhibition and Breast Cancer*, Miller RM and Santen RJ (Eds), Marcel Dekker, Inc., London, UK (2001). provides a state-of-the-art assessment of drugs that inhibit the synthesis of estrogens and demonstrates how the endocrinological effects of the new generation of inhibitors translate into clinical benefits.

The second edition of the award winning *ABC of Breast Diseases.* Dixon MJ (Ed.), BMJ Books, London, UK (2000). Written by experts in the field, provides an invaluable source of advice on the important decisions regarding symptoms and treatment of both benign and malignant breast disorders.

Publishers of the major oncology and breast cancer journals have well presented, easily accessed and comprehensively archived on-line websites, providing access to abstracts and in some cases full text of published papers and presentations.

Recommended bookmarks include:

- www.jco.org
Journal of Clinical Oncology
- www.jnci.oupjournals.org
Journal of National Cancer Institute
- www.bmj.com
British Medical Journal
- www.elsevier.com
European Journal of Cancer
- www.cancerres.aacrjournals.org
Cancer Research, American Association for Cancer Research
- www.asco.org
American Society of Clinical Oncology
- www.jnci.oupjournals.org
Journal of the National Cancer Institute
- www.nsabp.pitt.edu
National Surgical Adjuvant Breast Cancer and Bowel Project
- www.nejm.org
The New England Journal of Medicine

Pharmaceutical companies provide a highly useful resource to current therapeutic developments and ongoing research and clinical initiatives. In many cases additional global resource links are provided:

- www.pharmacia.com
- www.astrazeneca.com
- www.novartis.com

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Aromatase Inhibitors for Breast Cancer – set to replace tamoxifen ?

Dr Stephen RD Johnston

Within the last 5 years third-generation potent oral aromatase inhibitors have become a standard treatment option for postmenopausal patients with oestrogen-receptor (ER) positive breast cancer. The non-steroidal inhibitors anastrozole (Arimidex), letrozole (Femara), and the steroidal aromatase inactivator exemestane (Aromasin), are 2-3 orders of magnitude more potent than previous inhibitors such as aminoglutethimide. In addition they are highly selective for the aromatase enzyme without affecting mineralo-corticoid or glucocorticoid synthesis. These drugs are indicated for the treatment of advanced metastatic breast cancer in ER-positive breast cancer that has recurred following previous tamoxifen therapy. Recent evidence has suggested that aromatase inhibitors are more effective and better tolerated than tamoxifen, both in the management of advanced breast cancer and in the adjuvant / neoadjuvant setting for early disease. Here we review the evidence for aromatase inhibitors as first-line endocrine therapy for postmenopausal breast cancer.

Background

In the UK breast cancer affects one in 9 women during their lifetime, and causes about 21,000 deaths per year (Quinn *et al*, 2001). Prevalence is about five times higher, with over 100,000 women living with breast cancer at any one time. Risk factors for breast cancers are multi-factorial, but include older age and hormonal factors such as early onset of menstruation, late menopause and greater age at first completed pregnancy. Use of exogenous hormones (either the oral contraceptives or hormonal replacement therapy (HRT) may increase risk, but the effects are not large and may disappear a decade after cessation (Collaborative Group on Hormonal Factors, 1996 and 1997). Lifestyle factors including obesity, diet, alcohol and smoking have all been linked, although the precise nature of these relationships remains unclear. A genetic inherited predisposition may occur in 5-10% of patients (McPherson *et al*, 2000).

Of the 35,000 new cases of breast cancer per annum in the UK the majority will present with primary early operable disease that is confined to the breast and / or axillary lymph nodes, which is of a size and in a position to render surgery possible. Women are at risk of either local or distant recurrence, and this risk is highest through the first 5 years, but still remains for up to 15-20 years after surgery. While attempts have been made to establish an individual's risk of recurrence from various different prognostic factors, in clinical practice tumour size, axillary lymph node involvement, and oestrogen receptor (ER) status provide the most significant and relevant information. Women with lymph node-positive disease have a 50-60% chance of relapsing within 5 years, whereas for those with node-negative disease the risk is only 30-35%. In addition high pathological grade (i.e. a grade III poorly differentiated tumours), together with the presence of lympho-vascular invasion are tumour factors likely to be associated with an increased risk of recurrence. Accurate staging and pathological assessment at the time of diagnosis influences whether subsequent adjuvant therapy with radiotherapy, chemotherapy or endocrine therapy is required. This is given both to prevent local recurrence at the site of the original tumour, and to eliminate any micro-metastatic disease which may remain after surgery, thereby increasing the chance of cure.

Current Treatment Options

Early Breast Cancer

The primary management of early operable breast cancer involves initial surgery (either breast conserving surgery or mastectomy), followed by radiotherapy either to the breast (i.e.. following wide local excision) or chest wall (i.e.. after mastectomy). The aim of combined loco-regional treatment with surgery and radiotherapy is to remove the primary breast cancer and reduce as much as possible the risk of local recurrence within the breast or on the chest wall. For women with early operable breast cancer, systemic drugs (either chemotherapy or endocrine therapy, or the combination of both) are used to further reduce the risk of recurrence, in particular the risk of metastatic recurrence (secondary tumours) at distant sites. These drug treatments may be given in the adjuvant setting (i.e.. following initial primary surgical therapy), or for large primary cancers in the neo-adjuvant setting (i.e.. before surgery is undertaken). The wider use of such therapies in the UK since the mid 1980's has almost certainly accounted for the significant and consistent fall in breast cancer mortality which has been observed since 1990 [Peto *et al*, 2000].

Advanced / Metastatic Breast Cancer

Systemic drug therapies are used to palliate symptoms of advanced disease through the effective control of tumour growth, consequently improving the patient's quality of life. Choice of therapy is dependent on several factors including prior treatments received in

the adjuvant and/or metastatic setting (Rubens *et al.* 1994), together with the likelihood of benefit balanced against a given drug's side-effect and tolerability profile. In the last decade significant gains in efficacy have been seen with new hormone, cytotoxic and biological therapies, with evidence that these drugs may significantly improve tumour response rates and quality of life, but also may impact on patient survival even in metastatic disease.

Treatments in advanced disease tend to be used in sequence, and patients with ER+ve breast cancer may initially benefit from endocrine therapy before chemotherapy is considered. Approximately two thirds of human breast carcinomas express oestrogen receptors (ER) and thus may be dependent on oestrogen for their growth. Routine immuno-histochemical assays on paraffin-embedded tissue that can be performed retrospectively on the excised primary tumour mean that this information should now be available for all breast cancer patients. For these patients endocrine treatment options when they develop locally advanced or metastatic breast cancer include tamoxifen, progestins, and oestrogen deprivation therapies such as LHRH agonists for pre-menopausal women, and aromatase inhibitors for postmenopausal women.

Hormonal Therapies for Post-menopausal Breast Cancer

Oestrogen is the main hormone involved in breast cancer development and growth. Tamoxifen is a non-steroidal oestrogen receptor (ER) antagonist which inhibits breast cancer growth by competitive antagonism of estrogen at the receptor site. Its actions are complex due to partial oestrogenic agonist effects which in some tissues (ie. bone) can be beneficial (Powles *et al.* 1996), but in others may be harmful increasing the risk of uterine cancer and thromboembolism (Fisher *et al* 1998). Although an effective treatment for breast cancer, the partial agonist effects may account for the development of tamoxifen resistance after prolonged treatment.23 In the past alternative therapies for endocrine sensitive breast cancer following failure of tamoxifen have included progestins such as megesterol acetate (Megace) or medroxyprogesterone acetate (Provera).

Oral aromatase inhibitors such as anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin) all reduce serum oestrogen levels in post-menopausal women by preventing the conversion of adrenal androgens (androstenedione and testosterone) into oestradiol (E1) and oestrone (E2) by the cytochrome P450 enzyme aromatase. While aromatase is highly expressed in the placenta and in the granulosa cells of ovarian follicles, it is also present in lower levels in several non-glandular tissues including fat, liver, and muscle. At the menopause mean plasma E2 levels fall from about 400-600 pmol/l to around 25-50 pmol/l. While oestrogens are synthesised in the ovary in premenopausal women, following the menopause oestrogens come solely from peripheral aromatase conversion, particularly in sub-cutaneous fat – indeed plasma E2 levels correlate with body mass index in postmenopausal women (Longcope *et al.* 1986). Aromatase inhibitors are indicated only for postmenopausal women to prevent the peripheral conversion of androgens into oestrogens, and on their own are not effective in reducing the much higher levels of circulating E1 / E2 seen in premenopausal women. Unlike tamoxifen they have no partial agonist activity. Anastrozole and letrozole are both non-steroidal aromatase inhibitors and have similar pharmacokinetics with half-lives approximating 48 hours (Lamb *et al.* 1998; Wiseman *et al* 1998) allowing a once daily schedule. The half-life of exemestane which is a steroidal aromatase inactivator is 27 hours (Lonning *et al.* 1998).

Clinical Efficacy

Advanced Disease

Between 1995-2000 the three 3rd generation aromatase inhibitors established themselves clinically when a series of RCTs in over 2000 women demonstrated clinical superiority over megestrol acetate as second-line therapy after tamoxifen (Jonat *et al.* 1996; Buzdar *et al.* 1996; Dombernowsky *et al.* 1998; Kaufmann *et al.* 2000). Although the benefit was often small, these trials confirmed a very low incidence of serious side effects with aromatase inhibitors, in particular less weight gain and thromboembolic events than with progestins. As such aromatase inhibitors became standard therapy for postmenopausal women with advanced breast cancer which relapsed or progressed after tamoxifen (Hamilton *et al* 1999). While pharmacodynamic studies in advanced breast cancer had suggested greater oestrogen suppression for patients treated with letrozole compared with anastrozole (Geisler *et al* 2002), an open randomised trial in over 600 patients suggested no overall significant differences in efficacy (Rose *et al*, 2002).

Recently trials have asked whether aromatase inhibitors should challenge tamoxifen as the first-line endocrine agent of choice. Previously, no first or second generation aromatase inhibitor had proved superior to tamoxifen (Smith *et al* 1981; Falkson *et al* 1996; Thurlimann *et al* 1996). In addition to comparing tolerability, the potential of these studies with the new 3rd generation aromatse inhibitors was to see whether the complete oestrogen blockade provided by these drugs could deliver greater control of hormone-sensitive breast cancer than tamoxifen, thus circumventing the problem of acquired resistance due to the partial agonist effects of tamoxifen (Johnston 1997). The first published data came from two parallel multi-centre double-blind randomised controlled trials in which anastrozole was compared with tamoxifen as first-line therapy in ER-positive breast cancer. The first study in 353 women showed that anastrozole significantly prolonged the time to disease progression from 5.6 to 11.1 months (p=0.005) (Nabholtz *et al.*, 2000). While there was no significant difference in

objective tumour response rate (21% anastrozole vs 17% tamoxifen), the clinical benefit rate (defined as the proportion of patient who responded or had stable disease for at least 6 months) was significantly better for anastrozole (59% vs 46%). By contrast, in the larger trial in 668 patients no difference was found between the treatments in terms of median time to progression (8.2 vs 8.3 months), response rate (33% both arms) or clinical benefit rate (56% both arms) (Bonneterre *et al*., 2000). The explanation for the different results may have involved a higher proportion of patients with unknown ER status in the second trial, and a subsequent combined analysis of women with just ER+ve disease from both trials confirmed a significant improvement in disease-free survival in favour of anastrozole (Bonneterre *et al* 2001). Short-term side-effects such as hot flashes, vaginal dryness and headaches were infrequent and similar in both trials in comparison with tamoxifen.

The largest single trial was conducted with letrozole in comparison with tamoxifen in over 900 women with advanced breast cancer (Mouridsen *et al* 2001). Patients treated with letrozole had a significantly higher objective tumour response rate (30% vs 20%, p<0.001), clinical benefit rate (49% vs. 38%, p<0.001) and prolonged time to disease progression (median TTP of 9.4 months vs 6.0 months, hazard ratio 0.72 (95% CI 0.62-0.83), p<0.0001). Of particular note in this trial, nearly 20% patients had received prior tamoxifen in the adjuvant setting, although had ceased more than a year (median 3 years) prior to development of metastatic disease – in this subgroup, re-treatment with tamoxifen had a low response rate of 8% compared with a 32% response rate with letrozole. The improvements in clinical efficacy for letrozole resulted in an early improvement in survival during the first two years, with 64% patients treated with letrozole alive at 2 years compared with 58% treated with tamoxifen (p=0.02) (Mouridsen *et al* 2003), although with longer follow up this difference was lost. The explanation for this may relate to the high number (>50%) of patients who prospectively crossed-over to the alternate treatment at the time of progression, as significantly more patients benefited from second-line letrozole after progression on tamoxifen than to second-line tamoxifen after letrozole. Again, there were no significant differences in toxicity between the two treatments.

A large European study comparing the efficacy and tolerability of the steroidal aromatse inactivator exemestane with tamoxifen as first-line therapy is still ongoing. Preliminary reports have suggested significantly higher response rates seen with exemestane than tamoxifen, although the final results from this trial are awaited (Dirix *et al*., 2001). Thus, the available data from the RCTs of the 3rd generation aromatase inhibitors in advanced disease suggests improved efficacy over tamoxifen, and as such both anastrozole and letrozole are licensed as first-line endocrine therapy in postmenopasual women with ER+ve advanced breast cancer. At the same time these trials were first reporting, large scale studies scheduled to recruit over 40,000 women had been set up to compare aromatase inhibitors with tamoxifen.

Adjuvant Therapy

For postmenopausal women with ER-positive early breast cancer adjuvant tamoxifen for 5 years following surgery is the current standard of care. It reduces the risk of death by around 25%, translating into an absolute 10 year survival improvement of more than 10% for patients with lymph-node involvement, and 5% for those without (Early Breast Cancer Trialists Group, 1998). This translates into many thousands of lives saved per annum and and is one of the major reasons for fall in UK breast cancer mortality seen over the last 10 years (Peto *et al*, 2000). The first randomised trial of the 3rd generation aromatase inhibitors recently reported that for postmenopausal women, anastrozole may be a more effective and better tolerated treatment option than tamoxifen (ATAC *et al*. 2002). In the trial 9366 postmenopausal patients with ER-positive early breast cancer were randomized in 3 treatment arms in which anastrozole was compared with tamoxifen, or with combined tamoxifen and anastrozole. Preliminary results after a median of 33 months follow up have shown a significant improvement in 3-year disease-free survival of 89.4% for anastrozole compared with 87.4% for tamoxifen (hazard ratio 0.83, 95% CI 0.71-0.96, p=0.013). There was also a significantly reduced incidence of contra-lateral invasive breast cancers (9 vs 30, p=0.001), suggesting an even greater effect for an aromatase inhibitor than tamoxifen in the possible chemo-prevention of breast cancer. Of interest, the combination of anastrozole with tamoxifen did not show any superiority to tamoxifen alone. A possible explanation for this is that tamoxifen saturates available receptors such that the activated tamoxifen-ER complex cannot then be further modified by oestrogen deprivation, and the anti-cancer effect remains the same as for tamoxifen alone

While further follow up of this trial is needed to see if overall survival is improved, the side-effect profile was significantly better for anastrozole with a reduced incidence of endometrial cancer (p=0.02), less vaginal bleeding and discharge (p<0.0001), fewer cerebrovascular events (p=0.0006), less hot flushes (p<0.0001) and a lower incidence of venous thromboembolic events (p=0.0006). However anastrozole was associated with more musculoskeletal events and a higher incidence of bone fractures (p<0.0001), raising concerns about the potential long-term effects of complete oestrogen deprivation on bone mineral density. Aromatase inhibitors have been associated with an increase in urine and plasma bone resorption markers (Heshmati *et al* 2002), and there is much interest to see whether combined therapy with bisphosphonates in the adjuvant setting may not only reduce aromatase induced osteopenia, but also prevent bone metastases and further improve survival.

These preliminary results are very encouraging and

for the first time offer an alternative adjuvant endocrine therapy for postmenopausal women in situations where there may be concerns about the potential risks of tamoxifen. There are several other large trials of adjuvant aromatase inhibitors (mainly with letrozole and with exemestane) in postmenopausal women, and while the design of these trials varies, several issues will be addressed including further direct comparisons with tamoxifen, the potential benefit of sequential therapy (tamoxifen then aromatase inhibitor) compared with tamoxifen alone, and maintenance therapy with an aromatase inhibitor after completion of 5 years tamoxifen. It is hoped these trials will establish the role and correct sequence for these drugs in the adjuvant setting.

Neoadjuvant Therapy

Endocrine therapy before surgery for early breast cancer is given to downstage large primary cancers in the hope of avoiding mastectomy (Cheung *et al* 2000). In small non-randomised studies in older women with large primaries preoperative anastrozole, letrozole and exemestane have each been reported to achieve high tumour regression rates compared with historical tamoxifen studies (Dixon *et al* 2000; Miller *et al* 2002). While no difference was found however in a small randomised preoperative trial comparing the aromatase inhibitor vorozole (no longer in development) with tamoxifen (Harper-Wynne *et al* 2002), superiority of letrozole over tamoxifen was seen in a randomised double-blind trial of either therapy for 4 months prior to surgery in older patients with ER and/or PgR positive inoperable or large operable breast cancers requiring a mastectomy (Eiermann *et al* 2001). Letrozole achieved a higher regression rate (55% vs 36%, $p<0.001$), and more patients had tumour regressions sufficient to allow breast conserving surgery (45% vs. 35%, $p=0.022$). An important finding in a subset of patients whose tumours were available for further analysis was that ER-positive tumours which over-expressed the growth factor receptors HER2 and/or EGFR responded were relatively resistant to tamoxifen (as has been demonstrated in the past), but were sensitive to letrozole, with 88% (15/17) tumours which responded to letrozole vs. 21% (4/19) for tamoxifen (Ellis *et al* 2001).

These results are however preliminary and require verification in further neoadjuvant trials currently under way. However they support an emerging concept of 'cross talk' between signal transduction pathways for steroid receptors and growth factors (Nicholson *et al* 2000), and provide a biological explanation for why aromatase inhibitors may be superior to tamoxifen..

Conclusion

The 3rd generation aromatase inhibitors have had a major impact in the management of ER-positive postmenopausal breast cancer over the last 6 years. In the advanced disease setting randomised trials have shown superiority and better tolerability for aromatase inhibitors compared with tamoxifen. While tamoxifen has been an effective therapy for some patients with large operable or locally advanced breast cancer to downstage ER-positive tumours, recent evidence suggests that aromatase inhibitor letrozole is significantly superior in this setting. Most significantly promising results have now been reported in the adjuvant setting for anastrozole, although the absolute benefit over tamoxifen in freedom from relapse is very small and no survival benefit has emerged yet. Despite this, both the FDA and EMEA have given approval for anastrozole as adjuvant treatment of post-menopausal women with ER-positive early breast cancer. While it is very probable that the early gain seen for anastrozole will improve with time, many feel that adjuvant tamoxifen should remain the standard of care for most patients with ER-positive early breast cancer until further long-term safety data (especially on bone) emerge. However for patients with a history of thromboembolism or in whom tamoxifen is poorly tolerated, adjuvant anastrozole is now a useful alternative, as supported by the recent American Society of Clinical Oncology evidence-based technology assessment (Winer *et al* 2002). The next few years will see further results from ongoing trials, but many feel that the significant benefits of aromatase inhibitors will result in it completely replacing tamoxifen, the mainstay drug treatment for the disease for the last 20 years.

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Abbreviated Prescribing Information

Soltamox 10mg/5ml is presented as a clear colourless solution for oral administration containing 10mg tamoxifen (as citrate) in each 5ml. **Therapeutic Indications:** Treatment of breast cancer. **Posology and Method of Administration:** Normally 20mg – 40mg once or twice daily by mouth. For high doses twice daily is recommended. **Contra-indications:** Pregnancy, use in children, hypersensitivity to tamoxifen or any of the ingredients. **Special Warnings and Precautions for Use:** Pregnancy must be excluded in premenopausal patients. Advise of the potential risks to the foetus, if pregnancy occurs during or within two months of cessation of therapy. Other primary tumours have been reported in clinical trials following treatment. The clinical significance remains unclear. Menstruation is suppressed in some patients. Any patients who have received tamoxifen therapy and have reported abnormal vaginal bleeding or patients presenting with menstrual irregularities, vaginal discharge and pelvic pressure or pain should undergo prompt investigation. When starting therapy, the patient should undergo an eye examination. If visual changes occur during therapy it is urgent that an investigation be performed. In cases of severe thrombocytopenia, leucocytopenia or hypercalcaemia, individual risk-benefit assessment and thorough medical supervision are necessary. There is a risk of venous thromboembolic events, which increase when tamoxifen is used in combination with cytotoxic agents. Blood counts, liver function test and serum calcium should be monitored regularly. Assessment of triglycerides in serum may be advisable. This product contains 19%v/v ethanol. Harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. It may modify or increase the effect of other medicines. It also contains glycerol which may cause headache, stomach upset and diarrhoea. **Interactions with other Medicaments and other forms of Interaction:** Coumarin-type anti-coagulants: When used in combination with Tamoxifen Solution a significant increase in anticoagulant effect may occur. Thrombocyte Aggregation Inhibitors: To avoid bleeding during a possible thrombocytopenic interval, these should not be combined with tamoxifen. Cytotoxic agents: When used in combination with Tamoxifen Solution there is increased risk of thromboembolic events. Bromocriptine: Tamoxifen increases the dopaminergic effect of bromocriptine. Hormone preparations: Hormone preparations should not be combined with tamoxifen. Pregnancy and Lactation: Tamoxifen must not be taken during pregnancy. Breast feeding is not recommended. **Effects on Ability to Drive and Use Machines:** None known. **Undesirable Effects:** ***Very common:*** Hot flushes, vaginal discharge, pruritus vulvae, vaginal bleeding. ***Common:*** Bone and tumour pain, fluid retention, increase in serum triglycerides, light-headedness, headache, corneal changes, cataracts and/or retinopathy (the risk for cataracts increases with duration of therapy), venous thromboembolic events, nausea, alopecia. ***Uncommon:*** Patients with bony metastases have developed hypercalcaemia on initiation of therapy, vomiting. ***Rare:*** Temporary anaemia, temporary neutropenia, temporary thrombocytopenia, changes in liver enzymes, fatty liver, cholestasis and hepatitis, hypersensitivity including angioneurotic oedema, skin rash, cystic ovarian swellings, uterine fibroids, endometrial changes, including hyperplasia and polyps and cancer, suppression of menstruation. ***Very rare:*** Severe neutropenia, pancytopenia, severe triglyceridemia, pancreatitis, agranulocytosis, liver cell necrosis, erythema multiforme, Stevens-Johnson-syndrome, bullous pemphigoid. **Overdose:** Overdosage of tamoxifen will increase the anti-oestrogenic effects. There is no specific antidote to overdosage and treatment should be symptomatic. **Shelf Life:** 24 months. **Special Precautions for Storage:** Do not store above 25°C. Protect from light. **Pack Size and NHS price:** 150ml £31.50. **Instruction for Use/Handling:** Keep out of the reach of children. **Marketing Authorisation Holder:** Rosemont Pharmaceuticals Ltd., Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE, UK. **Marketing Authorisation Number:** PL 00427/0121 **Legal Category:** POM. **Date of Preparation:** October 2002.

Tamoxifen and Dysphagia in Breast Cancer Patients: A Brief Literature Review

Mark Greener

Tamoxifen is established as the *British National Formulary's* adjuvant hormonal treatment of choice for women suffering from oestrogen-receptor positive breast neoplasms. Moreover, tamoxifen is also the current hormonal gold standard for women with metastatic oestrogen-receptor positive breast cancer.

Tamoxifen, an oestrogen receptor antagonist, is currently available as several branded and generic solid oral formulations and also as a liquid Soltamox. However, dysphagia – most commonly as an acute adverse event associated with radiotherapy – might mean that many women with breast cancer are unable to benefit from tamoxifen given as solid oral formulations. As a result, they might require the liquid formulation. This review aims to briefly summarise the clinical problem posed by dysphagia associated with breast cancer.

Dysphagia in women suffering from breast cancer can arise from several causes. For example, vincristine can be associated with dysphagia in patients receiving combination chemotherapy for metastatic breast cancer.[1] However, most of the literature focuses on dysphagia arising from either oesophageal and stomach metastasis or as an acute or chronic consequence of radiotherapy.

Direct oesophageal metastasis arising from a distant primary carcinoma is relatively rare. Nevertheless, clinicians need to remain alert for the possibility in patients that present with dysphagia and a history of a distant carcinoma. For example, in a review[2] of six patients aged between 68 and 74 years, currently the largest series in the literature, four subjects developed oesophageal metastasis from a primary breast neoplasm. The remaining patients suffered from primary lung cancers. On average, oesophageal metastasis occurred seven years after the initial diagnosis of the breast cancer. Three patients died from upper gastrointestinal bleeds. Surgeons managed the other patients using endoscopic dilation and stents.

The authors comment that oesophageal metastasis arising from breast carcinoma is usually submucosal .[2] This makes diagnosis difficult. Moreover, oesophageal metastasis usually presents as a mid-organ stricture. Less commonly, however, metastasis can arise in the gastroesophageal junction. In such cases, the metastasis can mimic achalasia,[3] further complicating the diagnosis. As a result, clinicians should consider oesophageal metastasis in patients that present with malignant dysphagia as well as a history of distant carcinoma,[2] such as breast neoplasms. Indeed, oesophageal obstruction and, therefore, dysphagia can be the presenting symptom of recurrent breast carcinoma. However, if clinicians attribute the dysphagia to a benign pathophysiology, treatment might be inappropriately delayed.[4]

A study[5] from the Netherlands Cancer Institute further underscores the importance of considering a cancerous origin for dysphagia in women with a history of breast carcinoma. The authors found that 27 patients developed stomach metastasis from primary breast cancer over 15 year's clinical experience. Most of these patients suffered from lobular rather than ductal breast carcinomas. Patients suffered non-specific symptoms such as nausea, vomiting, epigastric pain, melena and dysphagia. Endoscopies identified the metastasis in 13 of 22 patients. The authors added that non-surgical treatment produced a 32 per cent palliative response rate. Again this underscores the importance of not dismissing dysphagia and other non-specific gastrointestinal symptoms in patients with a history of breast cancer.

Clinicians should even consider the possibility of a cancerous origin for dysphagia several years following the initial diagnosis of breast carcinoma. Some oesophageal metastases arise decades after the primary cancer. For instance, one paper[6] reports the case of a 68 year old woman who presented with dysphagia and a history of both breast and colon cancer. A non-ulcerated stricture in the middle of the oesophagus arising from a poorly differentiated submucosal adenocarcinoma caused the dysphagia. The tumour was histologically similar to the breast cancer surgically removed 15 years before. Furthermore, the oesophageal adenocarcinoma was positive for both oestrogen and progesterone receptors.

An American study[7] confirmed the possibility of a long latency between the primary diagnosis and oesophageal metastasis. The study enrolled four patients who developed dysphagia as a consequence of oesophageal metastasis arising from breast neoplasms. Clinicians made the primary diagnosis of breast cancer between 8 and 22 years before. The authors add that endoscopic ultrasound can aid diagnosis of breast cancer that metastasises to the oesophagus.

In other cases, dysphagia can arise in breast cancer patients following radiotherapy, both as an acute side effect or a long-term complication. Indeed, oesophagitis, characterised by dysphagia, seems to be a relatively common acute side effect following post-mastectomy radiotherapy. In one study,[8] 20 per cent of 194 patients treated with post-mastectomy radiotherapy developed oesophagitis.

Radiotherapy can also lead to secondary squamous cell carcinomas, which again, can present as dysphagia. In one case,[9] a 60 year old woman underwent repeated radiotherapy for breast cancer 19 years and one year before presenting with dysphagia and weight loss. Further examination revealed multiple dysplastic foci as well as both in situ and invasive squamous cell carcinomas along the oesophagus. Mucosa between the dysplastic foci and carcinomas were normal. In common with the most recent breast cancer, oesophageal lesions were p53 positive. The normal mucosa was p53 negative. The authors suggest that the oesophageal lesions probably arose independently of the primary cancer from a field change, possibly caused by radiotherapy. As the woman showed a strong family history of cancer, the authors speculate that genetic factors might also contribute to the development of the secondary neoplasms.

Similarly, a French paper[10] reported the cases of three women, who did not have a history of tobacco or alcohol abuse. However, the women developed squamous cell oesophageal carcinomas between 8 and 11 years following mediastinal radiotherapy. The authors suggested that patients that present with dysphagia and histories of mediastinal radiotherapy should be considered for biopsy to check for squamous cell oesophageal carcinomas.

As this brief review illustrates, dysphagia can occur in women with breast cancer. Dysphagia is relatively uncommon as a symptom of oesophageal and stomach metastasis or secondary squamous cell carcinomas following radiotherapy. Nevertheless, clinicians need to be aware of the possibility that dysphagia might herald metastasis or a secondary neoplasm. However, the literature suggests that the commonest presentation is oesophagitis that causes dysphagia following post-mastectomy radiotherapy, which may occur in around a fifth of women.

Irrespective of the cause, dysphagia might mean that women with breast cancer are unable to tolerate the solid oral dosage forms of tamoxifen. Such women might be suitable for an oral tamoxifen solution. Currently, there is only one oral solution, Soltamax, available on the UK market. Considering alternative dosing forms of tamoxifen should allow more women to benefit from the gold standard hormonal treatment for oestrogen receptor positive breast cancer.

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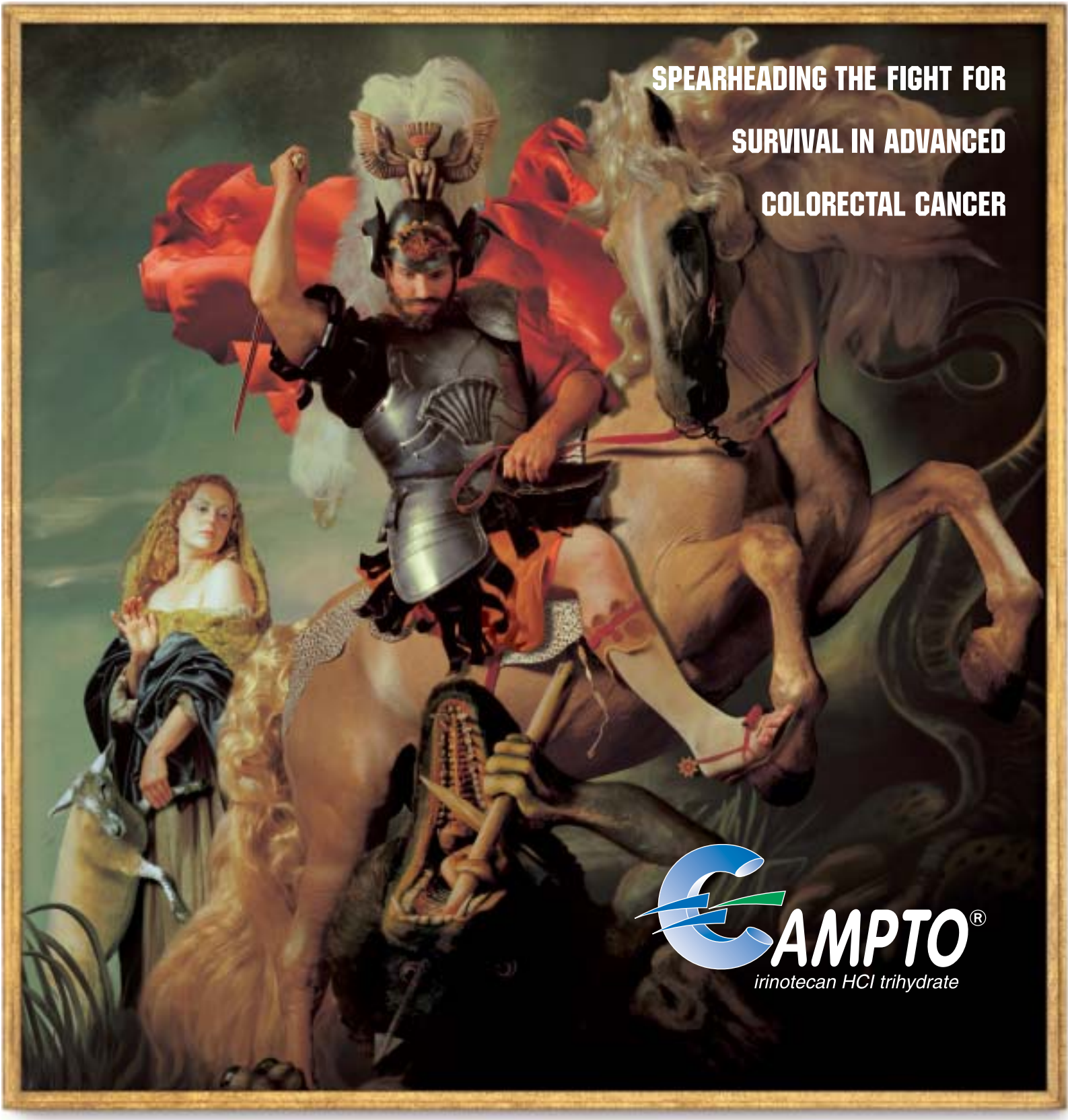

This image is a photographic reproduction of Rubens' painting SAINT GEORGE AND THE DRAGON

CAMPTO® (irinotecan hydrochloride trihydrate):
PRESCRIBING INFORMATION Presentations: Vials of concentrate for infusion containing either 40mg or 100mg irinotecan hydrochloride trihydrate. **Indications:** Treatment of adult patients with advanced colorectal cancer. **Dosage & Administration:** Solution must be prepared aseptically. Campto should be administered as an intravenous infusion over 30 to 90 minutes. In first line: combination therapy of 180mg/m^2 every 2 weeks followed by folinic acid and 5-fluorouracil; in second line: monotherapy 350mg/m^2 every 3 weeks. Prophylactic anti-emetics are recommended. ***Dosage Adjustments:*** Subsequent cycles should follow appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC and resolution of diarrhoea. Dose reduction of 15-20% recommended if patients experience grade 4 neutropenia, febrile neutropenia, thrombocytopenia, grade 4 leucopenia or grade 3-4 non-haematological toxicity. ***Impaired hepatic function:*** Monitor liver function regularly. Blood bilirubin levels (up to 3 times ULN) in patients with performance status ≤2, should determine the starting dose of Campto. Bilirubin up to 1.5 times ULN the recommended dosage is 350mg/m^2. Bilirubin 1.5-3 times ULN the recommended dosage is 250mg/m^2. Patients with bilirubin beyond 3 times ULN should not be treated with Campto. ***Impaired renal function:*** Not recommended. ***Elderly:*** Care due to the greater frequency of decreased biological functions. **Contraindications:** Chronic inflammatory bowel disease and/or bowel obstruction; severe hypersensitivity reactions to Campto; pregnancy; breastfeeding; severe bone marrow failure; WHO performance status >2. **Warnings and Precautions:** Use in units specialised in the administration of cytotoxic chemotherapy and under the supervision of an oncologist. Patients needing closer follow-up or particular risk of neutropenia weekly dosing schedule (125mg/m^2/week for 4 weeks, then 2 weeks rest) may be considered. Patients should be aware of the risks of acute cholinergic syndrome and neutropenia, and management of delayed diarrhoea (occuring >24 hours after the infusion). Loperamide should not be given prophylactically. Weekly monitoring of full blood counts recommended. Patients should not drive if dizziness or visual disturbances occur. Contraceptive measures must be taken during and for 3 months after therapy. **Interactions:** Care in patients receiving neuromuscular blocking agents. **Adverse reactions:** Delayed diarrhoea (requires immediate treatment with loperamide). Uncommonly, pseudomembranous colitis. Neutropenia, fever, anaemia, thrombocytopenia, nausea and vomiting, acute cholinergic syndrome. Infrequently intestinal obstruction, ileus or gastrointestinal haemorrhage, intestinal perforation, and increases of amylase and/or lipase. Transient increases in transaminases, alkaline phosphatase, bilirubin or creatinine. Dyspnoea, muscular contractions, cramps, paraesthesia, asthenia, reversible alopecia, dehydration, constipation; infrequently dehydration-related renal insufficiency, hypotension or circulatory failure. Mild effects include anorexia, cutaneous reactions, abdominal pain, and mucositis. Uncommonly, allergy and infusion site reactions, transient speech disorders associated with Campto infusions. **Pharmaceutical Precautions:** Do not mix with any other medications. Complete infusion within 12 hours of reconstitution, if stored at room temperature (22±4°C) or 24 hours, if stored at 2-8°C. Comply with prevailing cytotoxic handling guidelines when preparing or handling Campto. **Legal category:** POM. **PL Number:** 40mg: 0012/0302, 100mg: 0012/0303. **Basic NHS Price:** Campto 40mg; £53.00; Campto 100mg; £130.00. Further information is available on request from Aventis Ltd, 50 Kings Hill Avenue, West Malling, Kent. ME19 4AH. **Last revision of text:** Jan 2002.

Date of preparation: September 2002
ONC 602/06/01

Aventis

Current Thinking in the Management of Advanced Colorectal Cancer

Dr Rob Glynne-Jones

Colorectal Cancer is one of the commonest solid tumours in adults. The incidence in the United Kingdom is in the region of 36,000 cases per year. The overall 5 year survival lies in the range of 40-60%, but appears lower than in many other parts of Europe and the USA. Approximately 25% of patients present with advanced disease at diagnosis, and a large proportion of patients (50%) who undergo apparently curative surgery will eventually relapse with metastatic disease – most commonly in liver. The role of chemotherapy in this setting is to palliate symptoms, improve quality of life and hopefully extend survival.

Colorectal cancer has become an extremely exciting area to work in, and has provided some of the most intriguing pieces of research in the last decade. Current thinking in the management of advanced colorectal cancer is evolving rapidly. This article offers a simple framework to examine the major achievements in this particular field.

Systemic chemotherapy has been shown to extend median survival and improve quality of life in advanced colorectal cancer when compared to best supportive care (Scheithauer *et al* 1993). It is also accepted that survival and quality of life are improved if chemotherapy is initiated early in the course of the disease rather than waiting for symptoms to become obtrusive (Nordic Gastrointestinal Tumour Adjuvant Therapy Group 1992).

Although 5-fluorouracil (5FU) was developed 40 years ago, there was little widespread enthusiasm for this drug until the development of infusional and leucovorin-modulated regimens. However, even these more active 5FU regimens can only offer objective partial complete response is in the range of 20% - 30% as evidenced from the data in randomised controlled phase III multicentre trials. More recently combination chemotherapy with the addition of mitomycin c, oxaliplatin and irinotecan to 5FU-based regimens have created a firm rationale for the use of combination chemotherapy in colorectal cancer. In addition the oral fluoropyrimidines (capecitabine and UFT) - although they have not proved a major advance in improving overall survival or quality of life over intravenous 5FU - have demonstrated both similar efficacy and a clear patient preference.

Oral fluoropyrimdines

Capecitabine (Xeloda)

Xeloda is an oral tumour-activated fluoropyrimidine carbamate. Preferential conversion to 5-FU at the tumour site exploits the higher levels of thymidine phosphorylase found in tumour cells compared to normal cells. An outpatient oral regimen is simple, cheap and preferred by patients. The evidence of the CRO6 trial and the two phase III trials of Xeloda versus Mayo regimen (5FU/folinic acid), suggest response rates were 25% for infusional 5FU, 23% for De Gramont, 18% for Tomudex, 25% for Capecitabine and 17% for Mayo. These trials are not direct comparisons of capecitabine with 5FU but results are in the same ball park and suggest that there is very little difference in efficacy. One year survival being 37%, 40%, 18%, 57%, 57% respectively and two year survival 12%, 16%, 12%, 19% and 19% respectively. The evidence is that Xeloda as an oral agent is better tolerated with fewer side effects and less requirements for the use of hospital resources than the Mayo regimen. However, all regimens have approximate equal efficacy in terms of response rate and overall survival.

UFT

UFT is widely used in some European countries, although not in the UK. The evidence from randomised phase III studies appears to show a poor response rate when compared to 5FU/Leucovorin but with similar survival.

Irinotecan (Campto/CPT11)

Irinotecan is a derivative of camptothecin. It is the active metabolite SN38 which is cytotoxic through its interaction with the enzyme topo-isomerase 1 (Topo 1). Topo -isomerase 1 is required to relieve the torsion effects of tightening of DNA strands during the separation which occurs in mitosis or transcription. This process has similar effects to pulling apart one end of a double stranded rope. The enzyme Topo-isomerase 1 allows a single strand break in the DNA to occur and rotate around the intact strand before rejoining it. The activity of SN38 is to bind to the topo-isomerase 1 cleavable complex, which it then stabilises and prevents this action. Thus the DNA is unable to

replicate.

Irinotecan has been shown to be active as a single agent in patients who are both 5FU resistant and 5FU refractory. In an international landmark study (Cunningham *et al*, 1998) patients were randomised to single agent irinotecan 350mg/m2 every three weeks or best supportive care when they had failed conventional 5FU based chemotherapy. In a similar European trial, patients were randomised to infusional 5FU or single agent irinotecan (Rougier *et al* 1998). Both these trials confirmed a survival advantage of irinotecan of between 2 – 3 months. In addition symptoms were much improved with the use of irinotecan. Half the patients in the irinotecan arm were pain free at six months and generally had less weight loss and less malaise although formal quality of life appeared similar. Recognised side effects of irinotecan include nausea, diarrhoea, fatigue, asthenia, neutropenia and myelosuppression.

In addition two pivotal studies one in Europe and the other in United States (Douillard *et al* 2000, Saltz *et al*, 2000) have established the efficacy of irinotecan in combination with 5FU and folinic acid in the first line treatment of metastatic colorectal cancer.

The European trial was a permissive trial which compared the combination of irinotecan with infusional 5FU and folinic acid with the same 5FU /folinic acid regimen. Investigators could choose either the bi-monthly de Gramont regimen or the German weekly 24 hour infusional regimen (AIO). A total of 338 patients were randomised in the European study. Again the response rate was higher for the combination regimen (41%) compared to the control arm (23%), and both the duration of response and the time to progression and overall survival was also significantly increased from 14.1 to 17.4 months.

The Saltz trial randomised between standard Mayo regimen of 5 days of 5FU and folinic acid versus the same combination with irinotecan versus single agent irinotecan. There were approximately 220 patients in each arm. Interestingly the side effects in terms of diarrhoea were lower in the combination arm despite using the same schedule and dose of irinotecan suggesting that there is an antagonism in normal tissue when 5FU and irinotecan are used simultaneously. Response rate was almost double for the combination of irinotecan and the Mayo regimen versus the Mayo regimen alone (39% v 21%). There was significant improvement in overall survival.

A combined analysis of both trials confirmed the advantage to the combination of irinotecan and 5FU based chemotherapy over 5FU-based monotherapy alone.

However, despite evidence of an increased response rate and an improvement in survival in the randomised phase III trial, the duration of response remains short and the gain in survival modest.

Oxaliplatin (Eloxatin)

This is a platinum drug which acts in a similar way to cisplatin by forming DNA adducts, but these diaminocyclohexane (DACH) adducts are larger and require much more energy from the cell to remove. These adducts are not recognised by the mismatch repair (MMR) protein complex which appears common in some forms of colorectal cancer.

There appears to be synergism between oxaliplatin and 5FU. Since patients who progress on 5FU/folinic acid have responded when treated with a combination of oxaliplatin, 5FU and folinic acid. In contrast single agent oxaliplatin seems to have minimal activity - in the region of 10% (Machover *et al* 1996).

Side effects of oxaliplatin include nausea, fatigue, neutropenia, diarrhoea, cold dysaesthesias and a potentially long standing neuropathy.

Oxaliplatin in combination with 5FU has also been examined in phase III trials. A small underpowered trial compared the de Gramont regimen with oxaliplatin and de Gramont (De Gramont *et al* 2000). Only 400 patients were included in this trial. There was a significant increase in response rate (50% versus 22%) for the combination over 5FU-based chemotherapy alone. However, overall survival did not seem to be significantly improved. The crossover effect from second line treatment may well have blurred any apparent differences; probably because the trial was underpowered. A similar study using a chronomodulated 5FU/folinic acid with and without the addition of oxaliplatin (Giachetti *et al* 2000) also showed an increase in response rate and progression free survival. Overall survival was not significantly increased. It is important to note the high proportion of patients in this trial who proceeded to dissection of hepatic metastases. In addition in the control arm, the chronomodulated 5FU/folinic acid, 57% of the patients eventually received oxaliplatin as second line treatment which may account for why the control arm has a median survival of 19.9 months.

Mitomycin C

Mitomycin C has an uncertain action. It has been used as a single agent with minimal effect but in first line therapy in combination with 5FU has given rise to a response rate of 40% (Ross *et al*).

NICE Guidance

In the United Kingdom guidance on the treatment of advanced colorectal cancer and the use of irinotecan, oxaliplatin and tomudex issued by the National Institute of Clinincal Excellence (NICE Technology Appraisal Guidance no 33) has directed clinical practice. Funding is usually made available for drugs in the indications which NICE have approved, in contrast departments have had to find resources within their existing budgetary envelope if the proposed use lies outside NICE guidance.

NICE guidance **"does not recommend the routine use of Irinotecan or Oxaliplatin as combination chemotherapy in the first line treatment of colorectal cancer"**.

This guidance has been interpreted that not all patients should receive combination chemotherapy as

a matter of routine but respected the clinician's expertise and clinical decision making that there would be some patients who would require combination chemotherapy first line.

However, a number of clinical trials in advanced colorectal cancer have been published since NICE stopped taking evidence (just over two years ago). There have been some randomised phase III trials presented in public at international meetings. (FOLFOX versus FOLFIRI, German Oxaliplatin Study (Grothey *et al* etc), and a first line study comparing oxaliplatin and irinotecan (Goldberg *et al* 2002). The updated results from this study were published at the request of the data monitoring committee

The bi-monthly de Gramont regimen was combined either with irinotecan (Folfiri) or with Oxaliplatin (Folfox) in first line treatment (Tournigand C *et al*, 2001). Patients were randomised to Folfiri or Folfox and after progression, the other regimen was introduced as second line treatment. Both chemotherapy regimens produced a high initial response rate (56% and 54% respectively). Overall median survival was over 20 months and similar for both sequences. Although a small study (100 in each arm) and open to the criticism that the patients are selected and therefore not generalisable to the standard population with metastatic disease, this landmark study suggests that patients should benefit from the availability of all three drugs. The full publication is awaited with interest.

NICE guidance (technology appraisal) No 61 May 2003 recommends that oral therapy with either capecitabine or tegafur with uracil(in combination with folinic acid) is recomended as an option for the first line treatment of metastatic colorectal cancer. The guidance recommends that the choice of intravenous or oral therapy should be made jointly by the individual and the clinician after informed discussion between the clinician and the patient.

Surgical treatment of liver metastases

Early diagnosis of liver metastases (either solitary or multiple) is currently considered desirable, and many clinicians advocate a proactive surveillance programme, which involves regular CT scans. Liver resection remains the only chance of long-term remission, and sometimes even cure, for patients where disease is confined to the liver. The criteria of suitability for liver resection remains a matter of debate, and several factors are important in the decision. These mainly involve extent of liver involvement and the exclusion of extra-hepatic disease. Age and co-morbidity must also be taken into account. Overall patients undergoing successful liver resection for operable colorectal liver metastases have a three-year survival of approximately 60% and a five year survival of 30%. Currently it remains an important clinical question as to whether neoadjuvant chemotherapy using oxaliplatin can facilitate the resection of initially unresectable liver metastases.

Radio-frequency ablation

The advantages and indications for radio-frequency ablation as an alternative to surgery remain controversial. The criteria for radio-frequency ablation of liver metastasis are evolving. The following groups may be considered;- patients unfit for surgery but who have liver metastases 5cm or less in diameter; patients with recurrence following liver resection, unsuitable for further surgical excision; patients with localised liver metastases and small volume disease elsewhere. There are several prospective randomised trials (eg the CLOCC Trial) at an early stage or about to commence, which assesses the role of radio-frequency ablation in addition to combination chemotherapy.

Other ongoing studies explore the worth of preoperative 5FU and oxaliplatin in patients with colorectal potentially operable liver metastases. A further study compares combination versus monotherapy post resection chemotherapies (5FU versus 5FU/irinotecan).

Conclusions

We no longer have only a single effective drug (5FU). The oral fluoropyrimidines are available, and three other drugs (irinotecan, oxaliplatin and mitomycin C) with completely different mechanisms of action, which lack cross-resistance and have shown increased efficacy when combined with 5FU in first line therapy for colorectal cancer. The question remains as to which combinations are the best or whether three drugs may be more effective in downstaging patients with disease confined to the liver and facilitating hepatic resection.

In palliative terms it also remains unclear whether the sequential use of these new agents or the combined use early in the disease is more effective and which of these strategies offers the best quality of life. To some extent this question is being addressed in the FOCUS trial. Future studies will need to continue to address the question of the optimal combination and sequence of the three drugs oxaliplatin, irinotecan and 5FU.

It also remains questionable how generalisable these trials are to the general population where patients are often older and have a worse performance status than in the trials.

Nevertheless, impressive progress has been made recently in our understanding of colorectal cancer. We are now beginning to unravel the molecular biology involved in the development and progression of colorectal cancer, which will give us a much better guide in the future to providing both an individual prognosis and predicting which treatments will be most and least appropriate (Danenberg *et al* 1998, Lenz *et al* 2002). We are beginning to develop new targets for drug development as a direct result of this knowledge. Moloecular 'switches' which interfere with cell growth regulation, host-tumour interactions and tumour microvasculature or promote apoptosis have been developed to the level of clinical phase III trials. For all these reasons there is a growing optimism for the future.

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Opioids For Severe Chronic Pain in the Community *Friend or Foe?*

Eileen Mann

Opioids, occurring in their natural form as opium, have been used by mankind for thousands of years, and their use has always been fraught with problems and controversy. This is mainly due to their remarkable variety of pharmacological actions, which include analgesia, euphoria, lethal respiratory depression and the potential for addiction. From their earliest use, opioids have been associated with abuse and criminal activity. Even in modern medical practice they are sometimes seen as agents of last resort to ease terminal suffering and in the UK their image has recently been dramatically distorted by the Shipman murders. However, pain is the true scourge of mankind and strong opioids are currently still the best analgesics available. Unfortunately, stigma, myth and misinformation often overshadow our judgement when evaluating the role of these powerful drugs as a valuable strategy to relieve pain.

The purpose of this paper is to provide an overview of opioid drugs and to highlight the difference between strong and weak opioids. It will briefly trace the history of opioids, their current clinical application, their associated benefits and risks and examine some of the barriers to their effective use for chronic non malignant pain.

The term opioid is given to any substance that has morphine-like qualities whether it is synthetic, semi-synthetic or derived directly from opium. Strong opioids are characterised by their greater efficacy in relieving pain as well as their greater potential for causing hazardous side-effects. Weak opioids have lesser and variable analgesic efficacies with drugs such as codeine unable to perform better than placebo analgesia in some clinical trials (Bandolier 2003). Whilst the use of strong opioids to treat severe acute and cancer pain is now well established and accepted, we are still faced with inadequate evidence, politics, prejudice, myth and misconception in relation to the use of strong opioids for the alleviation of severe chronic non-malignant pain.

Treating severe acute pain in hospitals is relatively uncomplicated, safe and effective due mainly to the short duration of their use and the close observation available. In the community however, a whole new set of challenges must be recognised and the concerns about using strong opioids need to be debated and addressed. This article will therefore conclude with some hopefully practical reflections on how we can develop strategies to ensure patients suffering from chronic non-malignant pain are the focus of improved education, rigorous quality research and an evidence based approach to their management is applied in clinical practice.

History of opioids

Archaeological evidence suggests that even Neanderthal man may have stumbled upon the effects of opium over thirty thousand years ago. There is certainly evidence that the ancient civilisations of Persia, Egypt and Mesopotamia were aware of the properties of opium. Classical Greek physicians, such as Galen, had great regard for the medicinal properties of opium as seemingly a panacea for such conditions as varied as vertigo, deafness, fever, dropsy, melancholy and even pestilences. The complex attitude of society to potentially harmful mood-altering agents is reflected in the 8th century use and trade in opium by Islamic cultures in which the use of alcohol was prohibited. In England, 100 years ago, poppies were regularly grown on the Cambridgeshire Fens to provide "oblivion for the workingman and his family". However, the brewing lobby argued on the basis of weak evidence that their potions were less hazardous and opium production was subsequently banned (McQuay 1999). There are legal restrictions on the use of opium and subsequently all strong opioids in most countries today, but patients with chronic severe pain may suffer longer and unnecessarily if we prescribe and legislate badly (McQuay 1999).

Today we have a range of strong opioids, which include morphine, methadone, hydromorphone, oxycodone, buprenorphine, fentanyl and pethidine. The commonly used weak opioids ones are codeine, dextropopoxyphene, dihydrocodeine, pentazocine and tramadol . The most widely used opioid is morphine, which was isolated from the opium poppy in 1805 by the German pharmacist, Wilhelm Serturner. Well aware of its properties, he gave his discovery the name morphium after Morpheus, the Greek god of dreams

Although it cannot be denied that opioids used for recreation can be damaging to society and lethal to the individual, burdensome restrictions can impede rapid and effective administration for pain and lack of knowledge still hinders the appropriate use of these drugs (Marcer & Deighton 1988; Ferrell et al 2000). In our attempts to legislate for safety, are we in danger of excessively restricting the use of our most powerful analgesics in clinical practice? Despite some undeniable advances in the management of pain, 'opiophobia' continues to assert a powerful influence (Morgan 1985).

Extent of pain in the community

Epidemiological data suggests that inadequately treated pain is a huge problem in society, which will increase in an aging population in whom pain-inducing non-malignant pathologies accumulate. Studies of the incidence of pain within the community over the past 10 years range from 7% to 46.5% (Bowsher *et al* 1991; Elliot *et al* 1999). A more recent MORI poll conducted in 2001 suggests that almost one in four people in the United Kingdom suffer from chronic non-malignant pain, most commonly arthritis and low back pain. Of course a relatively modest proportion of this pain may be perceived as severe, but equally, severe pain is a great burden for the individual and often applies significant socioeconomic stresses to both the individual and their community.

Up until the early 1990's epidemiological and scientific research into pain was relatively under-developed. We could transplant hearts in the 1970's but pain control was then very poorly understood. Although times have fortunately changed, the recent rapid strides in the scientific understanding of pain and its management are not being matched by changes in clinical practice. Although there have been major advances in the treatment of acute pain, with many of these advances brought into the clinical arena, the following quote from a past president of the International Association for the Study of Pain defines the challenge of non-malignant chronic pain clearly:

"Despite recent advances that make it possible to relieve chronic non-cancer pain in 70-80% of patients, fewer than 10% actually obtain pain relief. That is a pitiful situation." Cousins (2001).

What this quote fails to state is that although the successful alleviation of severe non-malignant pain is often possible, it is not easy to achieve. Effective management usually involves a time-consuming long-term trial-and-error approach punctuated by regular detailed assessments. It is therefore hardly surprising that so often the term 'heart sink' springs to mind when a patient suffering many years of intractable pain once again turns to their hard-pressed General Practitioner desperate for help.

The arguments for strong opioids

The results of high quality randomised controlled trials do suggest certain selected patients with chronic non-malignant nociceptive (associated with a noxious stimuli) and neuropathic (associated with peripheral or central nerve damage) pain can indeed derive benefit from the use of strong opioids - even with long term use. In some incidences patients prescribed strong opioids have returned to work after many years of multiple failed treatments (Mak *et al* 2002). Other researchers have investigated the effects of established opioids on psychomotor, cognitive functioning and driving ability and indicated that these may not necessarily be compromised (Zancy 1995; Vainio *et al* 1995; Sabatowski *et al* 2002; Kalso *et al* 2002).

Much of the literature suggests that strong opioids should be trialled for any patient with nociceptive severe chronic pain who fails to benefit from appropriate balanced therapy such as the traditional combinations of paracetamol and / or a non-steroidal anti-inflammatory and / or weak opioids. For suffers of neuropathic pain, strong opioids may also provide benefit if the recognised adjuvants (antidepressants, anticonvulsants or local anaesthetic procedures) also fail to provide relief.

Databases such as those produced by the Cochrane Collaboration (www.cochrane.org), Bandolier (www.jr2.ox.ac.uk/bandolier/index.html) and The National Clearinghouse (www.guideline.gov) can help clinicians select evidence- based strategies to treat a variety of painful conditions. Although more research is urgently needed, these organisations regularly update guidelines based on meta-analysis of the latest data.

An excellent review of opioids for the management of non-malignant pain can be found in Beverly Collett's article in the BMJ (2001). In it she lists randomised controlled trials and prospective uncontrolled studies for nociceptive, neuropathic, idiopathic and unspecified pain. From the RCTs (adapted from Graven *et al* 2000) the conclusion drawn is that nociceptive pain responds well to opioid therapy. Neuropathic pain responds reasonably well but not as well as nociceptive pain, but for patients with idiopathic (no recognisable cause) pain the response was not very good. In many cases patients themselves indicate a positive preference for opioid analgesia. (Collett 2001).

Although adverse effects are reported with the use of strong opioids, for the most part these are predictable, quickly recognised and can be managed or controlled effectively (Schug *et al* 2002). In a monitored clinical setting, if adverse effects are found to outweigh benefit or if inadequate benefit is obtained, the opioid can be discontinued with confidence in the knowledge that at least the use of strong opioids has been explored. The trial itself may well convey to the patient that their reports of severe pain have been believed and taken seriously. This implied recognition of severity is often stated by patients as being very important in the management of chronic pain states.

Chronic pain syndromes are complex, although general trends are discernable and are often caused by nociceptive pathologies, which predispose to episodic severe pain with or without background persistent pain. The most common of these pathologies include rheumatoid arthritis, sickle cell disease, osteoporosis, vascular disease including venous ulcers, pancreatitis, and haemophilia. Neuropathic pain associated with nerve damage include conditions such as post herpetic neuralgia, diabetic neuropathy, post stroke pain, complex regional pain syndrome and phantom limb pain. Idiopathic (i.e. no cause found) pain continues to challenge our understanding but cognitive behavioural therapy might offer the most effective solution for these patients.

For the treatment of chronic non-malignant pain, strong opioids alone will never be a panacea. Complete relief of pain may be unachievable in some cases and improved function, mood elevation, quality of sleep and quality of life in general are acceptable goals to which the judicious use of strong opioids can contribute. Their therapeutic use in this setting should always be linked to realistic, achievable outcomes. This limiting of expectations may contribute to the safer use of these powerful drugs.

Musculo-skeletal low back pain appears to form a major category all its own. Acute back pain can, and all too frequently does, evolve into a debilitating chronic pain syndrome for some individuals. The consequences of this evolution can be dire reducing an individual's quality of life and inflicting significant socio-economic damage. The recognised approach to reducing the risk of this evolution is aggressive management of the acute event with optimal analgesia, education and a rapid return to full mobilisation. In this setting a very short course of strong opioids may have a useful role if other analgesia is failing. This suggestion is controversial as currently available evidence does not support the use of strong opioids and their use when not linked to a remobilisation program could certainly be problematic. As many patients suffering from this condition are fit, healthy and relatively young, their main goal is rehabilitation and a return to normal activity, not an increasing reliance on drugs. The utility of strong opioid for acute and even chronic low back pain therefore remains currently under debate (Bartleson 2002).

We are entering an exciting era of scientific discovery associated with the human experience and perception of pain. A diverse and complex array of chemical mediators manage and modulate our perception of pain in our highly flexible or "plastic" neural systems. Studies into cytokines may unlock some of the mechanisms of pathological pain (Watkins 2001). The discovery of NMDA receptors and central second messenger pathways is improving our knowledge of the 'wind up' phenomena (Salter *et al* 2002;) and complex brain imaging is enabling the study of neurological pain states such as post amputation pain (Nakamura *et al* 2002). Only in February of this year a team from Michigan published a fascinating article in Science on the discovery of a gene that may make us more or less tolerant of pain, biologically "sorting the marines from the wimps" as interpreted by several newspapers (Zubieta *et al* 2003).

Studies of spinal neural cell gene expression caused by pain show the expression of proteins responsible for rapid structural changes in cells, which may set the scene for the development of pain syndromes (Munglani 1996). Many clinical studies suggest that more aggressive pain management in the very early stages of a painful condition may be more useful than trying to close the 'gate' once pain has become established. Ineffective acute pain management may have damaging consequences (Hill 1994; Celeri *et al* 2000). The biopsychosocial model of pain continues to suggest that uncontrolled pain may leave an indelible imprint on our central nervous system, producing long term changes that upset our finely balanced homeostasis at a psychological, biological and cellular level (Melzack 1999; Carr 2002).

The case for the judicious use of strong opioids for the control of non-malignant severe chronic pain is strong, but the mixed actions of these drugs and the inability of pharmacological science to produce strong analgesics with fewer adverse effects means that clinical prescribers need to be vigilant and deal with a range of adverse actions.

The arguments for caution

Although the arguments for using strong opioids are powerful, it would be wrong to suggest they are suitable for everyone, in any situation and for all types of pain. The arguments for caution centre on the issues of addiction, dependence, tolerance, side effects and patient acceptance of incomplete relief of pain.

Addiction in this setting may be defined as dysfunctional opioid use that may involve adverse consequences, loss of control over opioid use and / or a preoccupation with obtaining opioids despite the presence of adequate analgesia (Compton *et al* 1998) Although addiction is so rare in acute pain as to be clinically insignificant (Porter & Jick 1980) the picture is not so clear-cut for patients with chronic pain. Estimates of addiction rates for these patients range between 3.2 and 18.9% (Nicholson 2003). We still have major gaps in our understanding of addiction and its complex interplay with genetic risk, exposure and adverse psychosocial environment. The complexity of addiction is reflected in current research which links addiction to multiple neurotransmitter systems within the limbic system of the brain and related areas of the brain associated with reward, anxiety and the relief of depression (Kalso 2002).

Analgesic tolerance is defined as the need to increase the dose of opioid to achieve the same level of analgesia. Analgesic tolerance may or may not be evident during opioid treatment and does not equate with addiction (Federation of State Medical Boards of the United States 1998). Studies on tolerance to opioids seem to indicate this is not a significant problem with many patients stabilised on a long-term course (Zenz *et al* 1992).

Physical dependence refers to the normal interaction between an organism and a drug that can lead to discomfort or adverse effects following its sudden withdrawal (WHO 1996). It is a predictable result of opioid use, and in itself does not equate with addiction (Federation of State Medical Boards of the United States 1998). Physical dependence must not to be confused with psychological addiction, which as previously stated, is the dysfunctional compulsion to continue to take a drug even in the knowledge that it is harmful. Again, studies suggest that the risk of physical dependence, and in some instances, even past psychological dependence, should not preclude opioid use (Ralphs *et al* 1994).

Side effects such as drowsiness and constipation can be a major problem with the use of strong opioids but may be an overemphasised reason to exclude their use. The same side effects are caused by weak opioids but this has not prevented these drugs from being frequently prescribed for very long periods. The fact that the efficacy data for many of the weak opioids, especially when used alone, is so poor (McQuay & Moore 1998; Oxford Pain Research Trust 2002) suggests that a step up to carefully titrated strong opioids may be more beneficial with ultimately less side effects than large doses of weak opioids.

If chronic non-malignant pain is established as being responsive to strong opioids, then a planned regimen of a long acting orally administered strong opioid is certainly worth considering. The clinician must be prepared to alter drug dose, frequency of administration, delivery method (e.g. patch technology if oral fails) or type of opioid to suit the individual and must be prepared to evaluate improvements in pain management and or function on a regular basis. Incorporating cognitive and behavioural strategies may also be useful. Opioids by injection are very rarely appropriate, helpful or safe in the community setting (Pither *et al* 2002).

The negative aspects of strong opioid use and their potential to cause side effects must be rationally balanced against the potential for serious adverse effects of non opioid drugs in common use. Paracetamol has a low therapeutic index (therapeutic dose/toxic dose) for an 'over the counter' drug. Relatively modest overdose can be and often is lethally hepatotoxic. NSAIDs have a very significant profile of adverse effects and cause an estimated 2000 deaths a year in the United Kingdom (McQuay 2002; Bandolier 2002). Conversely, there is scant evidence that strong opioids cause major organ toxicity when prescribed by experienced clinicians and titrated carefully to effect (Taub 1982).

Patient acceptance is also a potential barrier to the use of strong opioids. This may be due to the negative connotations associated with the names "morphine" or "diamorphine" and associations with addiction and criminality. The abuse of opioids and other drugs that affect the central nervous system has become a serious sociological problem. It seems to be a "pharmacological truth" that there is no health benefit without potential toxicity and therefore no absolutely risk-free drug. Government messages and 'Say No to Drugs' campaigns can promote feelings of guilt for taking a drug on the government's hit list. Finally, the effect of the Shipman murders on the public's perception of morphine may present a further obstacle to the rational use of these analgesics for chronic non-malignant pain.

The challenges in primary care

We have to face the unfortunate fact that education in pain management has been lacking for most health care professionals with only the very latest textbooks giving it a mention. Education and our increasing scientific understanding of the mechanisms of pain are keys to improvement. However, a realistic appreciation of the time constraints placed upon most practising clinicians and the breadth of the fields in which they must keep abreast, means that we have to find ways of bringing this information to them as succinctly and painlessly as possible.

One way might be to provide easy improved access to well-written and researched guidelines that are very simple to use and set out a basic plan of management such as those already mentioned. Work is currently underway in the UK where the Pain Society is producing a guideline or consensus document for use in this country (Pain Society 2003). This document will help clinicians to select effective and appropriate ways of using opioids in patients with chronic non-cancer related pain and should be available later this year. The Internet provides easy access to summaries of data, meta-analyses and straightforward guidance such as can be found on Bandolier. In addition, The United States has also produced *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (Federation of State Medical Boards of the United States 1998).

Successful treatment will always rely on thorough assessment and regular evaluation of therapy. Whether this will be possible within the current primary care environment is debatable. The average GP consultation of 7 minutes makes it hardly surprising that disillusioned patients with chronic pain resort to alternative therapies and even faith healers who have the time to listen to a tale of years of suffering.

With the development of extended roles in pain management for nurses and allied health professionals in many areas of healthcare, there might now be a case for such specialised pain clinicians to become a valuable resource within primary care. Healthcare professionals such as nurses or physiotherapists could undertake additional education and function as lead pain clinicians in the primary care environment. These community pain specialists would be able to liaise with, and be supported by, specialist pain clinicians in secondary care. They could recommend or even prescribe short trials of various analgesics, adjuvant therapies and supportive non-pharmacological strategies. They could certainly have more time than the average British general practitioner to develop contracts with patients to ensure that agreed goals are explicit and achievable, with the emphasis on pain control linked to more sophisticated endpoints such as enhanced function and improved quality of life.

Conclusion

We are in the era of the 'New NHS'. An era of higher patient expectation and a requirement to exercise evidence based care. An era of highly informed patients, up to 40% of whom may have used the Internet to search out information about their condition for themselves (Halligan 2001). The government is driving this change in focus with patients recognised as partners in their care and not

merely bystanders. Within this new clinical environment the management of chronic non-malignant pain must move forward. Patients living with pain need the best care currently available, and this may well include the intelligent, informed and controlled use of strong opioid analgesics.

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Acknowledgements: This paper acknowledges the valuable contribution made by Dr. B. Newman, Director of the Acute Pain Service, Poole Hospital NHS Trust, Dorset.

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A Comparison of Available Prostaglandin Analogues for the Treatment of Glaucoma

Mr Nitin Anand

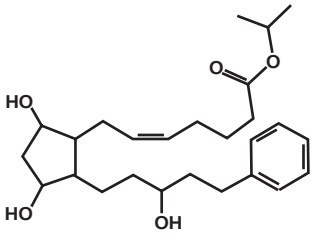
Glaucoma is one of the leading causes of irreversible blindness in the world, affecting more than 3% of people over 65 in the UK.[1] Glaucoma is defined as a condition characterised by damage to optic nerve fibres at the optic nerve head and retrograde loss of ganglion cells, leading to a gradual, characteristic loss of visual field. The disease is relatively symptom free in the early stages and a significant amount of vision may have been irretrievably lost before diagnosis takes place. Raised intraocular pressure (IOP) is the most important risk factor for the development of glaucoma.[2] In the normal eye IOP is maintained by the constant production and drainage of aqueous humour. Drainage of aqueous humour occurs predominantly through the trabecular meshwork, located in the angle of the anterior chamber formed between the anterior surface of the iris and the posterior cornea (trabecular route). A smaller portion (about 10%) of aqueous humour drains through spaces in the ciliary muscle bundles into the suprachoroidal space and leaves the eye through the sclera (uveoscleral route).[3,4] Primary open-angle glaucoma (POAG) is the most common form of the disease. In this condition the drainage system of the eye is apparently normal in structure but the drainage canals are blocked inside so that aqueous humour cannot drain away efficiently and IOP becomes raised.[4] POAG is a disease of the elderly and the severe loss of vision that it can cause will produce a significant deterioration in quality of life. A recent literature review has indicated that people with reduced visual acuity are 1.7 times more likely to have a fall and 1.9 times more likely to have multiple falls.[5]

Some people who do not have a high IOP still suffer from glaucomatous optic nerve damage and visual loss. This condition is referred to as normal or low-tension glaucoma. Conversely, other people have sustained high IOP but never suffer vision loss. This condition is termed ocular hypertension (OH).

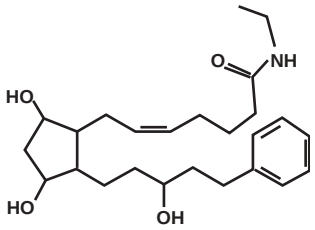
Medical treatment of glaucoma is currently targeted at reducing the intraocular pressure (IOP) either by reducing production of aqueous humour or by improving drainage. Until recently ophthalmic beta-blockers, such as timolol, have been the drugs of first choice, with additional agents added if adequate control cannot be maintained. In the past few years several new drugs have been introduced for the treatment of glaucoma including the topical carbonic anhydrase inhibitors, dorzolamide and brinzolamide, and the adrenergic α_2-agonist, brimonidine. Undoubtedly the most significant addition has been the prostaglandin analogue, latanoprost.

Latanoprost 0.0005%, given once daily, has been demonstrated to produce a greater reduction in IOP than timolol 0.5%, the reference beta-blocker, given twice daily.[6] As a result it has rapidly become established as the first choice medication for many glaucoma specialists. Latanoprost has now been joined on the U.K. market by two other prostaglandin analogues, travoprost and bimatoprost. The properties and clinical potential of these three prostaglandin analogues will be reviewed in this article.

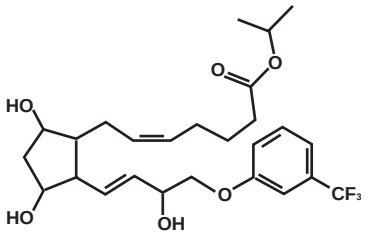
Figure 1. Chemical structure of the prostaglandin analogues



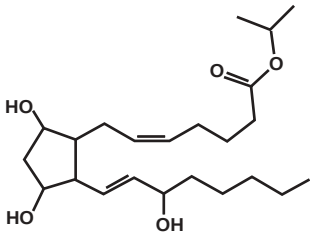
Latanoprost



Bimatoprost



Travoprost



PGF2α isopropyl ester

Table 1. Receptor Binding Affinity and Functional Potency of the Prostaglandin Analogues (adapted from Hellberg *et al*, 2001 and Sharif *et al* 2002)

Compound	Receptor Binding Affinity (K_i, nM)*		Functional Potency at the FP receptor (EC_{50}, nM)*
	FP	EP_1	
$PGF_{2\alpha}$	129+/-12	600	28.9+/-2.3
Latanoprost acid	92+/-14	2000	54.6+/-12.4
Travoprost acid	52+/-2	9540	3.2+/-0.6
Bimatoprost acid	83+/-2	95	5.8+/-2.6

*Lower numbers represent higher affinity and higher potency for the receptor

Latanoprost – the first prostaglandin analogue

The introduction of latanoprost was the culmination of many years of research into the use of prostaglandins as ocular hypotensive agents.[7]

Prostaglandins are a ubiquitous group of naturally occurring, hormone-like substances that have a great variety of physiological effects. Five naturally occurring prostaglandins have been identified, PGE_2, $PGF_{2\alpha}$, PGD_2, PGI_2 (prostacyclin) and thromboxane A_2. They produce their varied pharmacological effects via interaction with specific members of a family of distinct G-protein-coupled prostanoid receptors, designated EP_1, EP_2, EP_3, EP_4, IP, FP, DP and TP.[8,9]

Prostaglandins, and in particular $PGF_{2\alpha}$, have been shown to reduce IOP in a variety of animal models. However, poor ocular penetration meant that relatively high doses had to be used and unacceptable levels of ocular discomfort accompanied administration.[7] Modification of $PGF_{2\alpha}$, by adding an isopropyl ester group, increased corneal penetration and meant that much lower doses were needed. The ester is a pro-drug and is subsequently hydrolysed to $PGF_{2\alpha}$ in the cornea.[7] Further modification, by addition of a benzene ring to the side chain of $PGF_{2\alpha}$ isopropyl ester, resulted in the production of latanoprost, a molecule that has greater selectivity for the FP receptor, which is responsible for the ocular hypotensive effect (Figure 1).[7]

Although, in early clinical studies, latanoprost proved to be very effective and free from the systemic side effects associated with beta-blockers, it produced significant and unusual ocular side effects.[10-13] Conjunctival hyperaemia was seen more frequently with latanoprost than with timolol, but the incidence and severity were clinically acceptable. Increased eyelash growth (hypertrichosis) occurred in some patients[13] but of greater concern was a change in iris colour that affected up to 10% of subjects in some studies. This latter side effect is predominantly seen in people with hazel or heterochromic iris colour and appears to have no harmful consequences.[7,14] In view of the unusual ocular side effect profile, latanoprost was initially licensed only for second-line use when other ocular hypotensive agents proved to be ineffective. However, after six years of successful clinical experience with the drug a licence for first-line use was granted in Europe in 2002.

Stimulation of the FP receptor is considered to be primarily responsible for the IOP decrease seen with latanoprost and other prostaglandin analogues[15] and for the episcleral vasodilation which produces the conjunctival hyperaemic response.[16] It is also proposed that the stimulation of melanogenesis in iridial melanocytes, which is thought to lead to the observed changes in iris colour produced by latanoprost, is mediated by the FP receptor.[17] However, the pain and irritation produced by prostaglandins in the eye is thought to be mediated by EP_1 receptors.[18-20]

Pharmacodynamic Studies

The two newer prostaglandin analogues, travoprost and bimatoprost differ significantly from latanoprost in terms of their chemical structure (see Figure 1) and also in terms of their pharmacodynamic profile. The differences in pharmacodynamics observed can help to explain the variations in clinical efficacy and side effects that have been seen in clinical practice.

Using tissue or cell preparations rich in specific prostaglandin receptor sub-types the receptor binding affinity of the prostaglandin analogues for the FP and the EP_1 receptors can be studied.[21, 22] Latanoprost has a strong affinity for the FP receptor but a relatively weak affinity for the EP_1 receptor. Bimatoprost has a similar affinity for both receptor sub-types, providing the potential for EP_1 related side effects such as pain and inflammation. Travoprost has the strongest affinity for the FP receptor and has a very low affinity for the EP_1 receptor (Table 1).

Using similar techniques the functional potency of the prostaglandin analogues at the FP receptor can also be studied.[21-23] Latanoprost demonstrates greater potency than $PGF_{2\alpha}$, reaching approximately 80% of the maximal response for the receptor. Bimatoprost is similar in potency to latanoprost, while travoprost is the most potent of the molecules and is the only one that can achieve a maximal response at the receptor as concentration is increased (full-agonist effect).

Clinical Efficacy

In terms of clinical efficacy the relative performance of the prostaglandin analogues, observed in clinical

studies, appears to be in-line with that anticipated from the established pharmacodynamic profiles.

Latanoprost, bimatoprost and travoprost given once daily have all been demonstrated to reduce IOP to a significantly greater extent than timolol 0.5% given twice daily.[7,24-28] In clinical studies reductions in mean IOP from baseline ranged from about 30 to 35% for the prostaglandin analogues compared to 20 to 30% for timolol. The difference in mean IOP from baseline was generally statistically significantly lower for the prostaglandin analogues than for timolol. Falls in IOP of about 30% have similarly been found in clinical audits of travoprost and bimatoprost undertaken at the Calderdale and Huddersfield NHS Trust.[29]

In direct comparative studies travoprost and bimatoprost have generally been found to produce slightly greater reductions in mean IOP than latanoprost, although these differences have rarely reached statistical significance.[24, 30-32]

One interesting point to emerge from clinical experience is the variability of individual response to prostaglandin analogues. Patients who do not respond adequately to one prostaglandin analogue can demonstrate an improved response to one of the others. For example in one study in glaucoma patients judged to be failing on current therapy, 78% of patients on latanoprost and 64% of patients on bimatoprost showed an improved response when switched to travoprost.[33]

Side Effects

The side effects seen in clinical studies have also largely followed the pattern anticipated from the pharmacodynamic profiles of the molecules. Conjunctival hyperaemia and iris colour change are class effects, thought to be mediated by stimulation of the FP receptor,[16,17] while pain and irritation are thought to be mediated via the EP_1 receptor.[18-20] The mechanism for the other class related side effect of hypertrichosis has not been evaluated in detail.

In direct comparative studies[24,31,32] travoprost and bimatoprost have produced a slightly higher incidence of conjunctival hyperaemia than latanoprost. However, hyperaemia produced by all of the prostaglandin analogues is generally mild, reduces with time and has not resulted in significant patient distress or patient withdrawals in clinical studies. Conjunctival hyperaemia with prostaglandin analogues appears to be caused by an FP receptor mediated dilation of the episcleral blood vessels[16] and so is less serious for example than the inflammatory response seen with some other drugs, such as brimonidine.[34] Anecdotal reports and the results of clinical audits of prostaglandins at the Calderdale and Huddersfield NHS Trust suggest that, although the incidence of conjunctival hyperaemia may be slightly higher with travoprost, with time the hyperaemia decreases and is not of clinical concern. The incidence of intolerance appears to be higher with bimatoprost.[29] This is because ocular hyperaemia with bimatoprost, in these audits, was more likely to be accompanied by irritation and discomfort, possibly as a result of its greater affinity for the EP_1 receptor. In a recent twelve-week study comparing all three drugs 10.9% of patients on bimatoprost complained of eye irritation, compared to 6.6% for latanoprost and 4.3% for travoprost.[32]

The incidence of the other class-related side effects of hypertrichosis and iris melanocytosis are generally too low for trends between the various prostaglandin analogues to become clear in clinical studies. However, these effects generally cause patients few concerns unless they are treated unilaterally with one of the drugs. In order to minimise possible anxiety, it is recommended that patients should be warned about the potential for hypertrichosis, iris melanocytosis and transient conjunctival hyperaemia when prostaglandin analogues are first prescribed.

Response to treatment

Although mean IOP values and the extent to which IOP is lowered have generally been used as the main measure of clinical efficacy for ocular hypotensive agents, recent findings, from a large clinical study of advanced glaucoma patients, suggest that such an

Table 2. Summary of the Main Properties of the Prostaglandin Analogues

Attribute	Relative Performance (+++ = Best; + = Worst)		
	Latanoprost	Travoprost	Bimatoprost
Affinity for FP receptor	+	+++	++
Affinity for EP1 receptor*	++	+++	+
Functional potency at FP receptor	+	+++	++
Reduction of IOP	+++	+++	+++
Percentage responders	++	+++	+++
Conjunctival hyperaemia*	++	+	+
Ocular comfort	++	++	+
Stability	+	+++	++

*The lowest response is classified as best in this case

analysis may be inadequate to fully evaluate the relative clinical potential of different drugs.[35]

This study, which involved five hundred and ninety-one patients (789 eyes) with advanced glaucoma, convincingly demonstrated the inverse relationship between good control of IOP and progression of visual field loss. However, it was also demonstrated that when IOP was maintained consistently below 18 mmHg, progression of visual field loss could virtually be halted. These results indicate that consistent achievement of an IOP level of less than 18 mmHg should perhaps be a target for effective glaucoma management, if progression of visual field loss is to be minimised.

As a result of these findings recent clinical studies involving prostaglandin analogues have included a "responder" analysis in which the percentage of patients achieving a target IOP value has been reported. Unfortunately, the parameters used to define a successful response to treatment are not yet standardised, but most studies target an IOP value of 17 mmHg or less. All prostaglandin analogues studied in this way have generally been found to produce better responder rates than timolol.

In a study by Netland *et al* comparing travoprost, latanoprost and timolol over a twelve-month period, a responder analysis was conducted by looking at the percentage of patients with a 30% fall in IOP or a pressure </= 17 mmHg.[24] Judged in this way there was a significantly higher percentage of patients classified as responders with travoprost 0.004% (54.7%) than with latanoprost 0.005% (49.6%) or timolol 0.5% (39%). In addition the percentage of patients with all IOP readings below 18 mmHg at 4 pm was significantly higher for travoprost (45%) than for latanoprost (33%).[36] This time point, which was 20 hours post-dose, corresponded to the trough drug effect in this study.

In a one year study of bimatoprost 0.03% given once daily compared to timolol 0.5% given twice daily comparative figures for percentage of patients achieving an IOP value of </= 17 mmHg were 58% for bimatoprost and 37% for timolol.[27] In another study comparing bimatoprost and latanoprost, Noecker *et al* found that after six months a mean IOP value at 4 pm of </= 17 mmHg was found in 60% of bimatoprost treated patients compared to only 48% of those treated with latanoprost.[31]

Pharmaceutical characteristics

One final area of differentiation between the available prostaglandin analogues also needs to be mentioned as it can potentially have a significant effect on their clinical use. Latanoprost is temperature sensitive and is degraded by light.[37] As a result it is supplied commercially in opaque containers and needs to be refrigerated prior to opening. Refrigerated storage can be inconvenient in the pharmacy and for the patient, particularly if more than one bottle of drops needs to be dispensed at any one time, for example when a patient is going on holiday. Provision of eye drops in opaque containers also means that the quantity remaining is not clearly discernible. In contrast travoprost is stable to changes in temperature and to light. Commercially it is provided in clear plastic bottles which can be stored at room temperature. Each bottle is packed inside a foil pouch to minimise moisture loss during storage. There are also no special storage requirements listed on the product particulars for the commercially available preparation of bimatoprost and refrigerated storage prior to opening is not required. However the product is packed in opaque containers, although it is not obvious whether this results from light instability of the molecule or not.

Conclusion

The prostaglandin analogues are generally accepted as the most effective ocular hypotensive drugs available at the present time and a comparison of the main properties of the available prostaglandin analogues is presented in Table 2. Latanoprost, as the first molecule of this class introduced into the UK, and the first to receive first-line status, is currently the most widely used. However, travoprost and bimatoprost offer viable alternatives providing at least as good control of IOP, when measured in terms of mean values, but with a greater probability of achieving target IOP values below 18 mmHg than latanoprost. This latter finding could be significant where maintenance of visual field is concerned.

Both travoprost and bimatoprost have acceptable side effect profiles, typical of this class of drugs, although bimatoprost appears to have a higher potential for problems in clinical practice, possibly as a result of its greater affinity for the EP_1 receptor. They are also more temperature stable than latanoprost and do not require refrigerated storage prior to opening. However, bimatoprost is supplied in an opaque container, preventing a clear appreciation of the quantity of product remaining in the bottle.

The severe loss of vision that POAG can cause in the typical elderly patient produces a significant deterioration in their quality of life. However, frequent use of eye drops that may cause severe ocular or systemic side effects, such as non-selective beta-blockers or pilocarpine, can also detract from a patient's sense of well-being. Simple dosing, the low incidence of serious side effects and excellent efficacy mean that prostaglandin analogues can contribute to a marked improvement in the potential quality of life for glaucoma patients.

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Refer to Summary of Product Characteristics before prescribing.

TRAVATAN® 40 micrograms/ml eye drops solution (travoprost). **Presentation:** Plastic bottle containing 2.5 ml eye drops. Each 1ml of TRAVATAN® contains travoprost 40 micrograms (0.004%). **Indication:** Decrease of elevated intraocular pressure in patients with ocular hypertension or OAG. **Dosage and administration:** *Adults, including the elderly:* One drop in the affected eye(s) once daily in the evening. *Children and adolescents:* Not recommended. *Hepatic and renal impairment:* No dosage adjustment is necessary. **Contraindications:** Hypersensitivity to travoprost or any of the excipients. **Precautions:** TRAVATAN® may gradually change eye colour. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. Long term effects on melanocytes and any consequences are currently unknown. Change in iris colour occurs slowly and may not be noticeable for months to years. After discontinuation of therapy, no further increase in brown iris pigment has been observed. TRAVATAN® may gradually increase the length, thickness, pigmentation, and/or number of eyelashes in the treated eye(s). Exercise caution in patients with inflammatory ocular conditions and other types of glaucoma, aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, and in patients with known risk factors for cystoid macular oedema. Skin contact with TRAVATAN® must be avoided. Close monitoring is required in dry eye patients, or where the cornea is compromised. Benzalkonium chloride may cause irritation and is known to discolour soft contact lenses. Patients must remove contact lenses prior to application of TRAVATAN® and wait 15 minutes after instillation of TRAVATAN® before inserting contact lenses. **Side effects:** Commonly, ocular hyperaemia, eyelash changes, pruritus, discomfort and pain. Also dry eye, photophobia, foreign body sensation, flare, iris discolouration, cells and keratitis. Uncommon ocular effects include tearing, blurred vision, conjunctivitis, ocular irritation and fatigue, decreased visual acuity, lid oedema and margin crusting, sticky sensation, blepharitis, browache, conjunctival follicles and papillae, and iritis/uveitis. Systemic effects include headache, hypotension, bradycardia and periorbital skin discolouration. **Interactions:** Interactions of TRAVATAN® with other medications have not been specifically evaluated. **Incompatibilities:** None known. **Pregnancy and lactation:** *Pregnancy:* Do not use unless clearly necessary. *Women of child-bearing potential:* TRAVATAN® must not be used in women who may become pregnant unless adequate contraceptive measures are in place. *Breast-feeding women:* Not recommended whilst breast-feeding. **Driving:** If blurred vision occurs, the patient must wait until the vision clears before driving or using machinery. **Overdose:** Symptomatic treatment. **Pharmaceutical Precautions:** No special precautions for storage, 3 year shelf life, discard 4 weeks after first opening. **Instructions for use and handling:** The patient should remove the protective overwrap immediately prior to initial use. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In case of accidental contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately. **Legal Category:** POM. **Pack Size and Basic NHS Price:** 2.5ml £11.46. **GMS Price:** €19.17. **PL Holder:** Alcon Laboratories (UK) Ltd., Boundary Way, Hemel Hempstead, Herts HP2 7UD, United Kingdom. **PL Number:** EU/1/01/199/001-002. **Date of preparation of PI:** July 2003. **References: 1.** Whitson J T Expert Opin. Pharmacother. (2002) 3(7). **2.** Netland P A *et al*, A.J.O. 2001; 132: 472-484. **3.** Data on File. **Further information is available on request.**

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Considerations in Treating Seasonal Allergic Conjunctivitis

Dr Richard Wyse, Medical Director, Celsus UK

Seasonal allergic conjunctivitis (SAC) is a common disorder in the UK, affecting between 7.5%[1,2] and 21%[3,4] of the entire population. With several million people sufferers, SAC represents a huge national burden of disease (workdays lost, loss of quality of life etc). By its nature of presentation and management it is predominantly dealt with at the primary care level. During the SAC season patients will typically present to their GP with red, itchy, swollen eyes (Figure 1). Some may also complain of headache. Although most allergies develop during childhood, however it does commence late, between 18 and 35, in a significant number of people. As described in the recent Royal Society of Medicine report on seasonal allergic conjunctivitis and rhinoconjunctivitis,[5] GP's find SAC often also presents with associated nasal symptoms (itchy, runny or blocked nose, sneezing, rhinorrhoea), but they may present in isolation. An article in this journal[6] recently discussed options available to GPs for the treatment of allergic rhinitis, and emphasized how this related condition similarly creates a huge number of missed workdays, schooldays, and reduced activity days. Furthermore, ocular symptoms are often under-treated in patients with allergic rhinoconjunctivitis. It is important that GPs treat SAC and rhinoconjunctivitis effectively, especially as any referrals to secondary care are unlikely to generate consultations before the end of the allergen season.

The science

The prevailing view is that the prevalence of allergic disease has been increasing in the Western world in recent years. There is some evidence to support this.[7] The link between asthma and SAC is not well understood but, studying >400,000 patients, the ISAAC study[1] clearly showed that nearly half of children with SAC also show symptoms of asthma, and vice versa. Furthermore, recent government figures show that 33% of UK children will have suffered a wheezing episode by 12 years of age and 18% will have presented with rhinoconjunctivitis during the previous year.[5]

The science behind allergic eye disease has been very well reviewed by McGill *et al*,[8] and Church.[5] Histamine is the primary mediator of SAC. H_1 histamine receptor stimulation mediate symptoms of pruritus in the conjunctiva, whilst H_2 histamine receptors are more involved with vasodilation.[9,10] Within minutes of exposure to an allergen the resulting release of histamine causes dose-dependent itching, redness and oedema. Thus, H_1 anti-histamines act therapeutically by helping to prevent of activation of histamine H_1 receptors. Mast cells are pivotal to the development of symptoms in SAC since the allergic response is primarily related to mast cell activation and degranulation. Normally located nasally rather than temporally, ocular mast cells are an heterogeneous group; their normal function is homeostasis and control of the microvasculature. However, their numbers greatly increase during allergic episodes and they begin to migrate into more superficial parts of the eye; steroids can inhibit this migration but are far from ideal for use in SAC. When activated by allergic stimuli, ocular mast cells not only release histamine, cytokines, and eicosanoids, they also synthesise cytokines IL-4 and TNF-alpha,[11] which are central to the generation of the allergic cascade. Thus, by inhibiting degranulation, with its concomitant release of histamine and cytokines, mast cell stabilisation represents an important therapeutic approach by which the symptoms of SAC can be controlled pharmacologically.

The normal tear volume of approximately 10ml is temporarily doubled or tripled by the topical application of an ocular formulation. Excess drug may enter the systemic circulation via the nasolacrimal duct and nasal mucosa, by swallowing, and via the conjunctival vasculature.

Patient examination

For differential diagnosis, *itchiness* indicates allergy (*burning* would suggest dry eye, whilst *stickiness* would suggest bacterial conjunctivitis).

All patients presenting to their GP with suspected SAC need a basic eye examination. Whilst exclusion of red eye and dry eye is relatively straightforward,[5] when one suspects seasonal allergic conjunctivitis, often

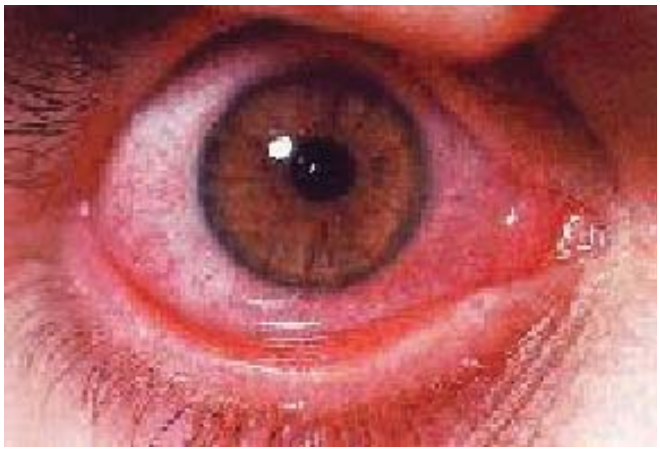

Figure 1

immediately due to concomitant nasal symptoms, the GP will be looking to confirm[12] whether the presenting conjunctival symptoms are in fact:-

- Seasonal allergic conjunctivitis
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (a paediatric condition that is chronic, more severe than SAC and PAC, and must be referred to an ophthalmologist)
- Atopic keratoconjunctivitis (a rare condition seen in adults, usually accompanied by atopic dermatitis), or
- Giant papilliary conjunctivitis (very rare, more associated with contact lens use or foreign bodies)

As well as the obvious seasonal timing, in identifying SAC, the main symptoms are likely to be bilateral itching, soreness, stinging and watering. Chemosis (conjunctival oedema) is also common, as is swelling of the eyelids. Unlike SAC, perennial allergic conjunctivitis will occur all year due to persistent exposure to the allergen responsible (typically house mites or cat dander). The patient's history may well reveal a pattern of increasing symptoms when outdoors for SAC, rather than indoors for PAC. If in doubt conjunctival and lid cultures would eliminate concerns of an infectious aetiology. Other diagnostic aids to consider[5] might be skin prick tests, serum IgE or RAST, although these may not always be practical in a GP setting.

Since patients presenting with SAC need a basic eye examination by their GP, this also offers a rare but excellent opportunity to identify other undiagnosed eye disease,[5] such as cataract, glaucoma or macular degeneration. Only simple equipment is required. Even more importantly for this predominantly young population of affected individuals, a retinal examination may reveal undiagnosed diabetes.

Treatment

Although often not practical for many patients, the first line of management is of allergen avoidance,[13] since it can reduce symptoms dramatically. Determining the nature of the offending allergen using standard techniques may be required.

Patients with mild to moderate SAC find that cold compresses and tear substitutes are fairly effective in soothing symptoms. Cold, artificial tears can be applied several times a day as required but a less toxic preservative-free formulation should be considered if their use becomes very frequent. If these strategies are insufficient to manage SAC to the patient's acceptability then pharmaceutical intervention will be required. Several therapeutic options are available in terms of drug class and mode of action. In short, mast cell stabilisers and anti-histamines (H_1 blockers) are both effective and safe, whilst steroids should be avoided whenever possible.

The pharmaceutical management of SAC focuses on the conjunctiva, cornea, sclera and the tear fluid. The most rapid and straightforward approach is the direct application of a topical agent (mast cell stabilisers, antihistamines, vasoconstrictors, anti-inflammatory drugs). The choice of therapy depends on patient history, previous pattern of response, prevailing eye health, likelihood of compliance, use of contact lenses, and cost and cost-effectiveness of therapy.

For mild SAC, drug treatment regimes should be topical only, using either an anti-histamine, vasoconstriction, mast cell stabiliser, or a combination of these therapies. For severe SAC, topical treatment should first be attempted, moving to a systemic approach if required. Although most SAC can be treated in primary care, severe cases of ocular allergy, especially those involving ocular pain or chronic red eye, or those that necessitate persistent use of topical or systemic steroids, should ideally also be referred to an ophthalmologist.

Topical treatments

Antihistamines

Topical anti-histamines (such as Levocabastine, Emedastine and Azelastine) have a rapid onset of action but may only be successful in managing about 50% of cases.[5] Topical application can be several times per day, they have a good long term efficacy and safety record, and is therapeutically more successful than using systemic anti-histamines.

Levocabastine is a selective H_1 anti-histamine enjoying rapid onset, prolonged action, and does not cause drowsiness.[14, 15] Emedastine is a selective H_1 antagonist that also offers additional beneficial effects on immunological activation.[16, 17] It also has a rapid action, can be used over long periods of time, and provides very good efficacy and symptom relief.[18] Azelastine also reduces the symptoms of SAC, acting for up to 6 hours,[19] and is at least as clinically effective as levocabastine,[20] but less so for itching.[21]

Vasoconstrictors

Topical decongestants (such as Phenylephrine, Antazoline), acting as vasoconstrictors, are often used in combination with anti-histamines. Whilst they do not influence the allergic response, they do decrease vascular congestion and eyelid oedema. While generally safe to use they are contra-indicated if narrow angle glaucoma is suspected.

Mast cell stabilisers

Mast Cell Stabilisers (such as Lodoxamide, Sodium Chromoglycate, and Nedochromil Sodium) have a slower mode of action than antihistamines, but can be highly successful in managing the symptoms of SAC.[5] They also have an excellent safety record. Lodoxamide is a potent mast cell stabiliser which lowers histamine and tryptase levels, and has similar efficacy to levocabastine,[22] but superior to sodium chromoglycate.[23] Nedochromil sodium also stabilises mast cells and inhibits histamine release (in this case from the mast cells), leading to improvement of the symptoms of SAC.[24-26]

Dual action drugs

Single agents with dual anti-histamine and mast cell stabilising actions (such as Olopatadine, and Ketotifen) are the most successful in terms of symptom relief. They are also longer acting. These two attributes both improve patient compliance. They have a good long term safety and efficacy record. Olopatadine, a new drug to the UK, but widely used with a good safety and efficacy record in the USA for several years, has been shown to possess both anti-histamine[27] and mast cell stabilising properties,[16, 28-31] rapid onset of action (within minutes), and provides extended symptomatic relief for up to 8 hours.[30, 32] It is also well tolerated by children,[33] which aids compliance. Wide US experience with Olopatadine has shown it to be "superior to each of the other drugs and other classes used in treating ocular allergy",[5, 27] particularly in reducing itching. A single drop of Olopatadine is "more effective than a two-week loading period of either mast cell-stabilizer or steroid. Compliance is aided by its comfort".[5, 34-35] A prospective, double-masked clinical trial showed Olopatadine to be more effective in relieving ocular itching than Ketotifen, and gave greater ocular comfort and patient satisfaction with treatment.[36]

Non-steroidal anti-inflammatories

NSAIDs relieve pruritus, but a high proportion of patients experience burning with topical use. Their use in conjunctivitis has mainly been confined to vernal keratoconjunctivitis,[37] although they have been also used in the context of SAC.[38]

Steroids

Topical steroids are good at reducing the ocular inflammatory response,[39, 40] and reduce the migration and maturation of mast cells in the conjunctiva and nasal mucosae.[5] However, they should only be used with caution, perhaps when a range of other treatments have already proved ineffective, and only for short durations (certainly shorter than the entire SAC season), since they raise intraocular pressure, permit opportunistic viral infections, and may promote cataract formation. Their use in SAC would always be preferably via collaboration with an ophthalmologist.

Systemic Treatments

The benefits of topical treatment of SAC generally outweigh systemic alternatives. Local drug concentrations are higher, there is less opportunity for drug interactions, and there are fewer side effects. Treat topical diseases topically.

Antihistamines

Oral anti-histamines do relieve symptoms of ocular allergy, but have a slow onset of action. Newer forms of antihistamines do not cross the blood-brain barrier, and so will cause less drowsiness. However, they may cause dry eye (which would counterproductively exacerbate the allergic symptoms under treatment).

Steroids

Systemic steroids are slow to act, often have significant side effects, and carry some of the risks (including glaucoma) of their topical use in treating SAC.

Health Economics – Patient Quality of Life versus Cost Effectiveness of Therapy

The national UK economic burden of SAC and rhinoconjunctivitis – the number of sufferers by the number of affected days – has never been calculated, but is likely (extrapolating from similar analyses elsewhere[41,42]) substantially to exceed £900 million.

Although rarely sight-threatening, SAC can have a profound effect on quality of life,[43] indeed, causing many days to be lost from work, from school, and during examinations. Typically, there is compromise of social life and any vision-related activities. The impact to employers is also considerable, as is the seasonal increase in the workload of GP practices. When considering alternative treatments for SAC it is therefore important to consider that the choice of therapy will impact in a very major way on patient comfort, quality of life and their ability to work. Although very little work has been done in this area, particularly in the UK, a quality of life score with seven components (itchiness, photophobia, redness, grittiness, epiphora, mucus discharge and swelling) was developed some time ago by Dart *et al*,[4] who used this approach to show that symptoms of SAC tended to be far more severe than PAC. Since then other quality of life scoring methods and approaches have been developed,[44–46] and these not only allow rational assessment of the severity of symptoms in patients with SAC, they also permit evaluation of the cost effectiveness and cost benefit of the various therapeutic alternatives available. Recent work[46] on the health economics of using Olopatadine to treat SAC suggests its superior efficacy may also "confer cost-effective advantages both in terms of the reduced number of patient days affected versus the severity of these symptoms on these days, and also from the perspective of improvements in patient quality of life-adjusted days".[5]

Conclusions

For its 2-3 month duration, SAC is a widespread and debilitating disease. Finding the right therapy for each patient needs insight from each GP into the mechanisms of the development of the disease, and the therapeutic options available. Topical rather than systemic treatment is strongly advised. Whilst there are currently no evidence-based protocols to follow, development of ocular allergic guidelines has been attempted.[47] Depending on presenting symptoms, dual action therapy appears to offer the most effective, safe, cost-effective front-line therapy.

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Evolution Not Revolution

PCT's Asthma, COPD and what's new in aerosols

This brief article brings together thoughts on asthma and COPD and what can be done to assist patients to make their lives as trouble free as possible.

The article covers the size of the issue, who we are talking about, some practical guides on areas of further investigation and options available to patients.

"Everyone acknowledges how hard pressed PCTs or practices are to find time to think about or discuss anything that is not on the "must do" list and this includes asthma. Yet out there in practices we know that asthma is a very real and common problem; it is a common reason for presentation out of hours; it is an important reason for school absenteeism, there is wide variation in diagnosis and management and many people continue to have symptoms. National statistics tell us that respiratory disease is the most common reason for a child to consult a GP, which is highly likely to be the result of a parental anxiety around undiagnosed or diagnosed asthma." NRTC, GPIAG.

"With asthma on the increase and becoming a common problem among children with ratios of 1 in 8 children in the age bracket of 2 - 15 years, as well as 1 in 13 adults aged 16 years and 8 million diagnosed asthmatics at some stage in their lives we have the 5th highest prevalence rate for asthma in the world (ISAAC study).

COPD is a major problem that is set to increase, estimated to become the fifth most common cause of death worldwide by 2020. True prevalence of COPD is difficult to estimate because of misdiagnosis (many patients with early diseases who are asymptomatic and unknown to their doctor)" Rachael Booker NRTC.

The life style of Asthmatics and COPD patients need not be restricted. There are many organisations who are attempting to address the management, education and symptom relief for both asthma and COPD patients. Many organisations work in the area of education while others address drug compliance and therapy or diagnostics. A brief internet search will return more pages and articles than it is possible to read on the subject. This article focuses on the area of therapy compliance and ease of use of devices for inhaled therapy for asthma and COPD. It is through education technical developments and new combination drug therapies and treatment regimes that patients will be able to reduce their treatment times and better manage their condition.

The internet based information can be informative for both patients on how best to deal with the issues concerning asthma and COPD. This is an ideal way to keep up to date with developments. In the UK there are many organisation such as the National Respiratory Training Centre, General Practice Airways Group, The

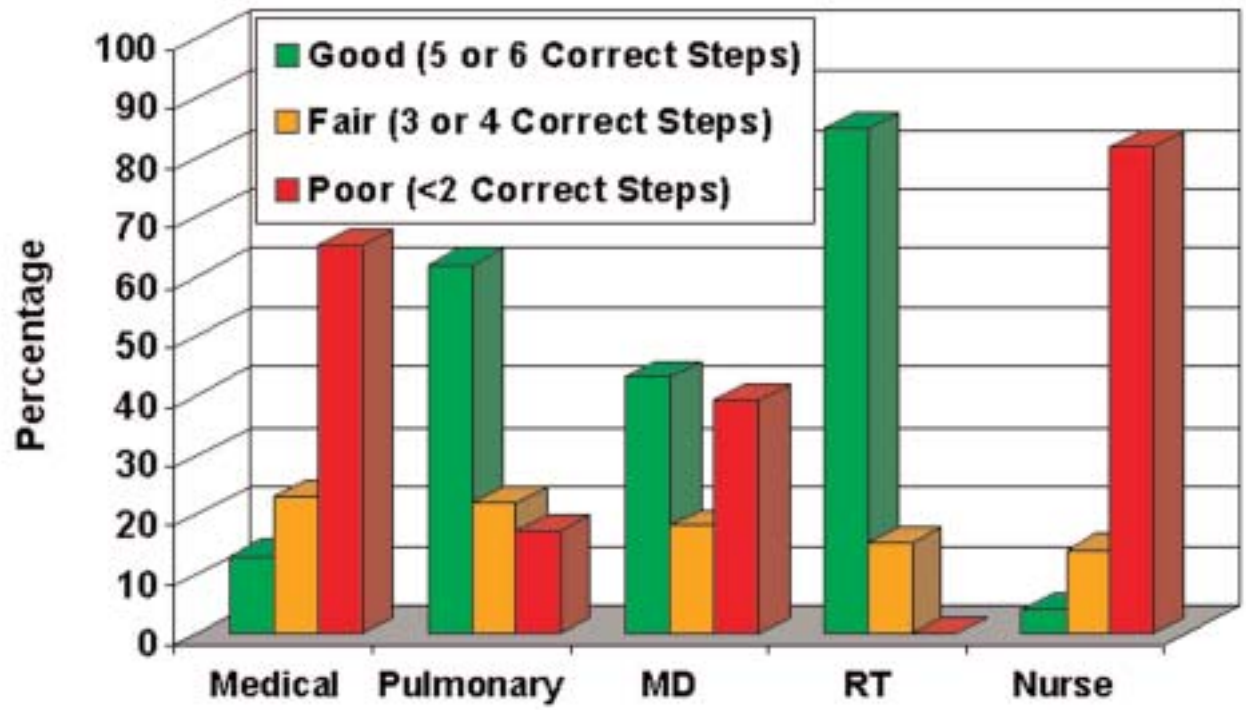


Figure 1. Interiano, *et al*. *Arch Intern Med* 1993; **153:** 81-5 Inhalation technique.

Medical = Medical Patients, Pulmonary = Pulmonary Patients, MD = Medical Doctor, RT = Respiratory Therapist, Nurse = Ward based Nurse.

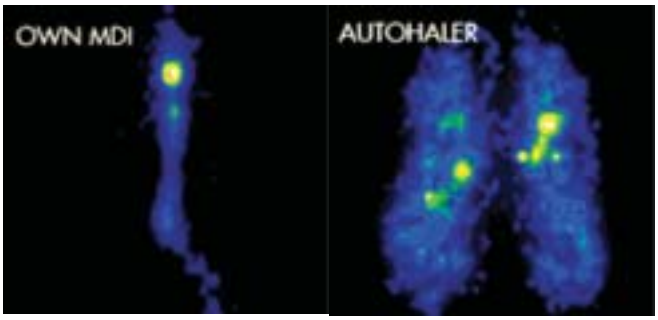
National Asthma Campaign, British Thoracic Society to name a few as well as many equipment and pharmaceutical companies all working to inform and educate users and therapists in the latest techniques. Each of these organisations try to educate, inform and describe ways patients can improve the quality of their lives. Other organisations bring improvements in care in the form of drug developments such as combination therapies so a patient can improve their compliance to therapy by taking their preventative with their bronchial dilator. Such is the approach offered by the Serevent dry powder inhaler from gsk. (Glaxo Smith Kline)

"Seretide Diskus also produced significant improvements in health status (as defined by the St George's Respiratory Questionnaire2) compared with patients receiving fluticasone but not salmeterol. The rate of moderate/severe exacerbations, considered an important cause for hospitalisation, were reduced by 25% for Seretide Diskus and by 20% and 19% in the salmeterol and fluticasone groups compared to placebo. Acute episodes of symptom exacerbation requiring oral corticosteroids were reduced by 39% for Seretide Diskus, 29% for salmeterol, and 34% for fluticasone compared to placebo. There were no significant differences between active treatments with respect to their effect on the rate of episodes of symptom exacerbation, time to first exacerbation, or number of hospital admissions." Seretide COPD study published in The Lancet.

Drugs companies have been working on designs of devices for inhalers for years to try and make them easier to use. As although the "puffer" (MDI Metered Dose Inhaler) was a breakthrough in its time being small and pocket size, it has always suffered from the problem of requiring an educated patient on the end of it able to use properly. Patient techniques are not always very good, and yet are very important for these devices to enable them to work properly (see figure 1).

Although this study is US-based and ten years old, it shows the stark difference education can have on inhalation technique. The difference between the

Figure 2



Self-taught patient **Autohaler**

percentage of Nurses with good technique and the Respiratory Therapists is clear evidence of the benefits of good inhalation education.

This demonstration was with a device that releases the drug to the patients only at the point they reach the correct inspiratory flow to optimally deliver the drug. These pictures are made possible by a patient inhaling a slightly radio active material in the device so a special type of camera can see where the drug has gone in the lung. (figure 2).

This image of the lungs using a normal MDI with a trigger mechanism showing drug in the stomach and throat as well as the lungs. (figure 3).

Other types of devices have been developed and are widely used to assist patients with the use of MDIs namely "Spacer Devices". Spacer Devices work by allowing the high-speed plume of drug to slow down in the chamber and to allow the particles to reduce in size while the propellant evaporates leaving just the drug to be inhaled. (figure 4).

Spacers / Reservoirs and Holding Chambers

- Slow down droplets;
- Control inhalation rate;
- Trap large droplets;
- Allow droplet evaporation yielding smaller particles;
- Exhalation diversion;
- Aid coordinated actuation and inhalation.

Maxair Autohaler

Mechanical device to synchronize actuation and inhalation. The difference between good technique and poor technique can be stark as demonstrated above a self-taught patient standard MDI. As reported in a presentation *Aerosol Drug Delivery Systems* give nby Richard Dalby, Ph.D. University of Maryland School of Pharmacy.

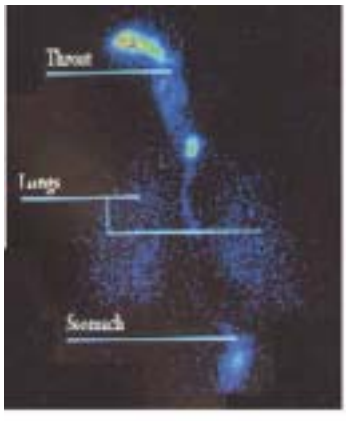
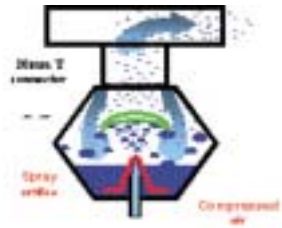


Figure 3

Figure 4

Figure 5. A Jet nebuliser using compressed air to generate a constant flow of aerosolised drug.



Nebulisers have always been known to be the easiest of devices to use as they generate a lot of drug to inhale without it impacting on the back of the throat. Their biggest drawback has been their size and non-portability, apart from being noisy and cumbersome. They have also in the past had a bad reputation as people relied on them to use in an emergency rather than taking their preventive medication this led to over reliance by some patients on nebulisers, resulting in serious problems for patients if they where away from their nebuliser when they had an asthma attack.

What next?

Luckily the development of new devices goes on as companies strive to find a way of removing the parts of disease management, which patients find reduces their likelihood of compliance to their therapy. In the area of portability, reduced treatment time and silent operation there are a wide-range of new devices now available to buy over the counter from Pharmacists. Companies like Omron Healthcare are running accredited training evenings for Pharmacists and practice nurses in conjunction with the National Respiratory Training Centre to increase the education and awareness of asthma and COPD. The success or failure of a device relies on the technology actually delivering a real benefit to a patient's lifestyle.

Produced by Adrian Gee-Turner. with contributions from Kiyotsugu Kuki Omron Japan, Gerry Franks OHI and Richard Dalby, PhD, University of Maryland School of Pharmacy.

	Medication is stored in inhaler		Independent
Type	 MDI	 DPI	 Neb
Principle	Pressurized gas CFC, HFA etc.	Inhale scattered dry powders	Ultrasonic Compressed air
Treatment time	Less than 0.3 sec	1 Breathing	10-20 minutes
Advantages	Portability No preparation required		Easy to Inhale
Disadvantages	Environmental impact of the propellant Difficult to synchronise	Certain inhalation speed is required	Cost Bigger Longer treatment
User	Child, Adult / Light symptom		Baby, Old Severe symptom

Figure 6. The options patients have at the moment

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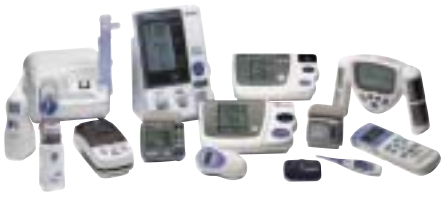

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COPD - The Challenge for Primary Care

Dr Michael Rudolf

COPD affects more than half a million people in the UK, is the sixth most common cause of death, and is responsible for 310,000 emergency medical admissions annually. At least 95% of people with COPD are smokers, and their lung function deteriorates at a rate faster than non-smokers. Early identification of these individuals is essential both to prevent disease progression and to ensure optimal management. Early diagnosis can only be accomplished with spirometry. The availability and correct use of spirometry in primary care are major challenges for improving COPD services.

Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressing disorder characterised by airflow obstruction that is not fully reversible and does not change markedly over several months. The vast majority of cases are due to cigarette smoking.

Diagnostic labels encompassed by COPD include chronic bronchitis, emphysema, and chronic obstructive airways disease. Although the clinical diagnosis of COPD is suggested by the presence of various symptoms, a confident accurate diagnosis can only be made by objective measurement of airflow obstruction with a spirometer.

Implementing COPD guidelines

Guidelines on the diagnosis and management of COPD were published by the British Thoracic Society (BTS) in 1997. In order to ensure dissemination of good practice following the publication of these guidelines, the BTS COPD Consortium was established. This is a unique partnership between the BTS, industry and the British Lung Foundation, with its main objectives being widespread promulgation of the guidelines and the development of programmes of activities designed to achieve high levels of awareness and understanding of COPD in primary care.

The success of these activities has been monitored by undertaking regular research in primary care to quantify the extent to which key recommendations in the guidelines were being implemented. In 2001, 93% of GPs and practice nurses were aware of the guidelines, and 59% of the nurses and 45% of the GPs rated themselves as confident or very confident in differentiating COPD from asthma. Interestingly, both groups identified smoking history, lack of bronchodilator reversibility and age of onset as important factors in distinguishing these conditions (see table 1).

Spirometry

A major feature of the Consortium's activities over the past six years has been encouraging the use and understanding of spirometry to diagnose COPD. There has been a significant increase in the number of primary care practices that claim to have a spirometer from 53% in 1998 to 62% in 1999, and to 78% in 2001. Although in 2001 74% of GPs and 80% of nurses correctly stated that spirometry was a key measurement to diagnose COPD, only 39% of the GPs and 55% of the practice nurses realised that spirometry was also a criterion for grading the severity of the disease. Furthermore, only 42% of both GPs and nurses rated themselves as confident or very confident in interpreting the results of spirometry to diagnose COPD.

If spirometry screening in primary care is to develop as a method of early diagnosis, there is clearly more work to do to improve both understanding and confidence in performing and interpreting this measurement.

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under 45	Uncommon	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Uncommon
Spirometry	Always abnormal	May be normal
Serial PEF	Minimal variation	Day-to-day and diurnal variation
Bronchodilator reversibility	Usually < 15%	Usually > 15%

Table 1. Differences between COPD and asthma

The burden of COPD

COPD is an enormous burden to patients and their carers, health care services, and the national economy.

Epidemiology

COPD is the sixth most common cause of death in England and Wales, with nearly 30,000 deaths attributed to this condition each year. It accounts for twenty times more deaths than asthma. More than half a million people in the UK (around 1% of the population) have been diagnosed with COPD, but as the condition is often under-diagnosed (or misdiagnosed as asthma), the true figure may be much higher. While prevalence rates of COPD seem to have peaked in men, they are continuing to rise steadily in women. This trend, taken together with the ageing of the population, is likely to increase the current burden of COPD in the UK.

Patients

COPD has a major effect on patients and carers, especially when the condition has progressed to moderate or severe disease. Breathlessness has a huge impact on a patient's daily activities, as it becomes progressively more incapacitating.

Ultimately, many patients become breathless at rest and thus effectively housebound. Systemic symptoms of the disease are often unrecognised, such as depression, weight loss and sleep disturbance.

Healthcare

In an average UK health district of 250,000, there will be over 14,000 GP consultations each year for COPD, over 2000 more than for asthma. Annual consultation rates for COPD per 10,000 population rise from 417 at age 45 – 64 to 886 at age 65 – 74, and to 1032 at age 75 – 84, values that are 2 - 4 times the equivalent rates for angina.

Between April 2000 and March 2001 there were approximately 310,000 emergency medical admissions in the UK due to COPD, accounting for nearly two and a half million bed days. Emergency admissions due to COPD have risen by over 50% between 1991 and 2000, and one in eight of all medical admissions are due to COPD in some regions.

Costs

The NHS spent £818 million to treat COPD in the UK in 1996/97. In 2000/2001, COPD in-patient admissions alone cost almost £600 million. These are only the direct medical costs. Indirect costs of COPD include an estimated 24 million working days lost per year with £600 million estimated social security costs and a further estimated £1.5 billion in lost productivity.

Natural history : need for early diagnosis

The healthcare costs of COPD rise considerably with increasing severity of the disease, and it has been estimated that the 15% or so of patients with the most severe form of the disease account for up to 70% of the total costs (predominantly those costs associated with in-patient hospital admission due to acute exacerbations). Accordingly anything that can be done to decrease the number or frequency of these exacerbations would potentially be of enormous benefit.

Recently introduced treatments for COPD (especially long-acting inhaled beta-agonist/inhaled steroid combinations and a long-acting inhaled anticholinergic) are undoubtedly effective in reducing exacerbations, and these drugs are becoming increasingly used in clinical practice for patients with established moderate to severe disease.

However, a far more effective, although more difficult, strategy for the future must be to prevent patients developing severe disease (and the exacerbations that occur in severe disease) in the first place. This will necessitate the much earlier identification of patients with COPD, while they have only mild or moderate disease. The natural history of COPD is one of progressive worsening in lung function (usually due to cigarette smoking) over many years. Even in non-smokers, the forced expired volume in one second (FEV1) falls slowly with age, such that by the age of 75 years it may be about 75% of its value at 25 years. But in susceptible cigarette smokers the FEV1 falls at a dramatically faster rate. Mild COPD is currently defined by an FEV1 that is 60 – 80% of its predicted normal value, moderate COPD by an FEV1 of 40 – 59% of predicted normal, and severe COPD by an FEV1 of less than 40%.

The majority of people with mild COPD will have little or no breathlessness, their only symptom may be a "smoker's cough" (which they may well regard as normal), and they will have no abnormal clinical signs on physical examination. However, their spirometry (measurement of FEV1) will, by definition, be abnormal, and performing lung function will be the only certain way of diagnosing them correctly.

Patients do not usually present to their GPs until symptoms appear, usually breathlessness (with or without some wheeze) on moderate exertion, but by this stage they will almost certainly have moderate or severe disease (by FEV1 criteria). As it is impossible to develop moderate or severe COPD without first having been through the mild and largely asymptomatic phase, any patient who is not diagnosed until these later stages of the disease has in effect been "missed" by the health services earlier in the natural history of his or her disease.

The enormous challenge for primary care is therefore to diagnose COPD in susceptible individuals much earlier in the natural history of their disease. Making an earlier diagnosis, doing more to stop patients smoking (still the single most important part of COPD management and the key to preventing further disease progressions and giving appropriate bronchodilator therapy can make an enormous difference.

Diagnosis of COPD

The symptoms of COPD will vary with the progression of the disease, and, as pointed out above, patients with

mild COPD may have minimal or even no symptoms. The single most important factor in making a diagnosis of COPD is to think of the disease in the first place.

A diagnosis of COPD should be considered in any individual over the age of thirty-five who is currently (or has been) a cigarette smoker and who has one or more of the following:

- Persistent breathlessness, worse on exertion.
- Chronic cough ("smoker's cough")
- Regular or persistent sputum production
- Frequent winter respiratory infections ("bronchitis")
- Wheeze or chest tightness

The presence of these symptoms can be extremely variable, and individual patients will rate the relative importance of these symptoms differently.

Physical signs on clinical examination are not helpful in making a diagnosis of COPD, and most patients with mild disease will have no abnormal signs. Once the possibility of COPD is being considered, a confident diagnosis can only be confirmed by spirometry. The criteria for diagnosing COPD are FEV_1: vital capacity ratio

< 0.7, and FEV_1 < 80% predicted normal. Peak expiratory flow (PEF) should not be used to diagnose COPD, although serial measurements of PEF may be helpful in differentiating COPD from asthma.

COPD is often confused with (and misdiagnosed as) asthma, with which it does share some superficially similar symptoms. However, the two diseases can usually be differentiated on clinical grounds and simple lung function measurements (see table).

The early identification of COPD depends not only on a high diagnostic suspicion and the need for confirmatory spirometry, but also the presentation of the potential patient in the first place. Many people with early COPD, even when they do have symptoms, do not visit their GP for diagnosis and advice. In a MORI poll of 866 adults, 61% of those currently smoking had symptoms which were possibly indicative of COPD, yet only a half of them had consulted their GP. In two out of three cases this was because they were unconcerned or unaware that the symptoms might be important, and in nearly one in four cases this was because they thought (probably correctly) that they would be advised to stop smoking.

If individuals with possible COPD are not going to self-present with their respiratory symptoms, other methods of identifying these cases needs to be developed.

Screening for COPD

Although mass screening for COPD with spirometry can be carried out, it is far more cost-effective when targeted at people with a much higher likelihood of having COPD. In a large "Know the Age of Your Lung Study" in Poland, free spirometry was offered to smokers who were over 39 years of age with a smoking history of more than ten-pack years. Of 11,027 subjects screened in pulmonary out-patient clinics in twelve cities, spirometric evidence of airway obstruction was found in 24%.

In a study carried out in two semi-rural general practices in the Netherlands, 651 smokers aged 35 – 70 had spirometry performed and completed a short questionnaire on respiratory symptoms. Of those not taking any drugs for a pulmonary condition, one in six had abnormal spirometry. Of those smokers who also had a chronic cough, 27% had FEV1 < 80% predicted. The authors of this study concluded that case finding for COPD (by targeted or opportunistic spirometry on smokers with a chronic cough) was achievable in general practice.

The advantages of early identification

There is no point in screening for COPD or having other strategies for earlier diagnosis unless effective remedial measures are available. There is such a remedial measure for COPD: smoking cessation reverses the accelerated decline in lung function that is the hallmark of the disease. Smokers who quit will not recover lost lung function, but the further rate in decline of FEV1 may reverse to that of a non-smoker. Smoking cessation at an early stage of the disease improves prognosis, irrespective of how many attempts it takes to stop. Furthermore, smokers are more motivated to quit if they realise that they are at risk of developing COPD, and there is evidence that the early diagnosis of abnormal lung function can significantly affect the success of smoking cessation therapy.

Irrespective of the success of smoking cessation, the earlier diagnosis of COPD will allow for appropriate treatment of symptoms (especially with bronchodilator therapy), and the identification of patients who may be suitable for other important therapeutic interventions such as pulmonary rehabilitation. Correctly diagnosing COPD will stop the misprescribing of asthma medications, identify patients for influenza vaccination, allow appropriate audit of both COPD and asthma, and ensure that more patients with COPD get the best possible treatment. New NICE guidance on the diagnosis and management of COPD will be appearing early in 2004. How to identify more patients with early COPD and ensure that spirometry in primary care is available to all who require it remains a pressing challenge for the organisers of primary care services.

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Shared Care Facilities in Urology

Dr John E T Pillinger

What is shared care?

Shared care involves the constructive collaboration between specialists, in this instance urologists, nurse practitioners and general practitioners.[1] In 1994, the late Professor Geoffrey Chisholm CBE chaired the first shared care initiative for BPH (benign prostatic hyperplasia), which discussed assessment, treatment and referral guidelines for GPs (general practitioners). The catalyst for this was the development of medical therapy for LUTS (lower urinary tract symptoms) and the concept that only the more severely affected patients may require surgical treatment. Following consultation with over 2,000 professionals, including Urologists, general surgeons, geriatricians, general practitioners and FHSA (family health service authority) advisers, it was agreed that screening for BPH was not generally practicable and a nomogram was devised, based on case finding in primary care.[2]

Do we need shared care Urology facilities in the UK?

Establishing need

Let us look at four common urological problems from a national perspective:

BPH

The UK has an estimated 2.5-3.4 million BPH sufferers.

Benign Prostatic Hypertrophy [BPH] has been shown to cause Lower Urinary Tract Symptoms [LUTS] in almost half of men aged over 65, of whom 51% report interference with at least one daily living activity.[3, 4]

In 1991 about one in six people in the UK were over 65, and by 2021 this proportion is expected to be nearly one in five, as estimated by the Family Policy Studies Centre.[5]

Drummond *et al* (1993) estimated the cost of BPH (including NHS and indirect costs) at between £62 and £91M in 1990, the largest component being in-patient treatment.[6]

Prostate Cancer

Prostate cancer is the second leading cause of cancer in UK men.

Prostate cancer is the second leading cause of cancer in men.[7]

In the UK, almost one cancer in seven and one in eight cancer deaths are due to prostate cancer.[7]

The death toll from prostate cancer amounts to nearly 10,000 men per year.[8]

This number is more than four times the number of deaths from cervical cancer in women), and over 19,000 men are newly diagnosed with this cancer every year in England and Wales (Table 1).[9]

These figures are likely to rise further with an increasing older population.[8]

Prostate cancer affects essentially men between 65 and 70 years, but also men as young as 55 years.[9] Survival rate at the age of 70 years is 50%.[10]

Diseases of the prostate adversely affect the quality of life (Table 2) of many middle-aged and older men, leading to mental distress in the sufferers.[11] Nevertheless, many men go untreated because of their reluctance to consult a doctor.[12] The reasons for this behaviour include:

- Perception that the symptoms of prostatic diseases occur naturally with age
- Embarrassment of discussing the symptoms, in particular with a person of the opposite sex
- Fear of diagnosis of cancer (Table 3).[12]

Another reason why prostate diseases remain under diagnosed and under treated is that most standard health checks do not include specific enquiry into prostate health.[12]

Erectile Dysfunction

Erectile dysfunction can affect one in 10 men at some point in their lives

Erectile dysfunction – the inability to attain or

Table 1. Newly diagnosed cases of prostate cancer in England and Wales[9]

Age	0-34	35-44	45-59	60-69	70-79	80+	All
No. of cases	0	18	1175	4720	8193	5229	19335

Many sufferers may go unreported because of low awareness of prostatic disease symptoms and reluctance to see a GP.

Figure 1. Shared Care Pathway for Highcliffe Urology Clinic

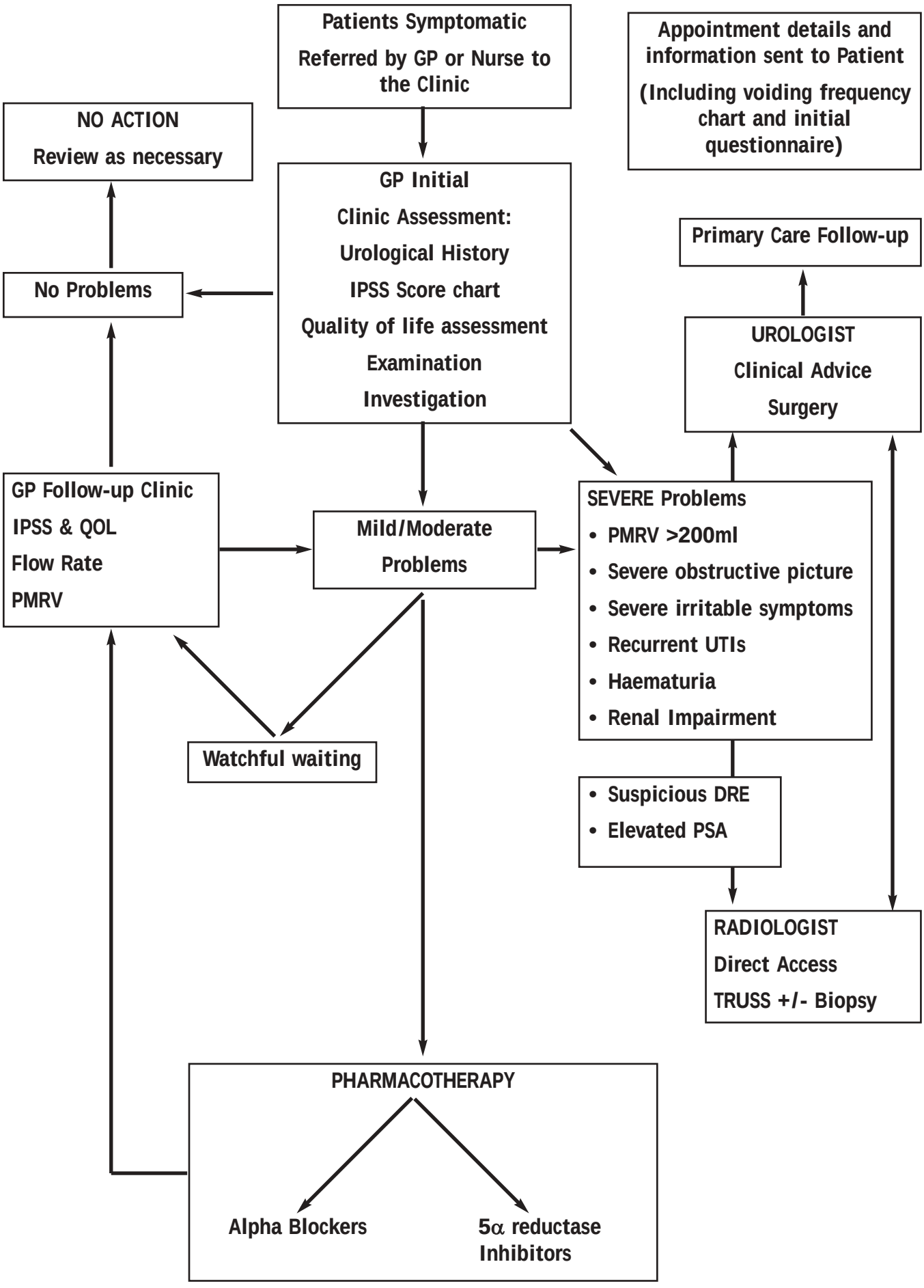

Table 2. Impact of prostatic disease on activities of daily life[12]

- **Limited fluid intake before travel or in evenings**
- **Inability to drive for more than 1-2 hours without a break**
- **Disruption of sleep**
- **Limitation on going to places without toilets**
- **Limitation on outdoor sporting activities**
- **Restricted leisure activities such as going to the cinema, theatre, etc.**

maintain an erection sufficient for completion of sexual activity – is a common complaint in men.

- Approximately one in 10 of men over the age of 16 years suffer from this condition at some point in their life.[13]
- In the UK, it is estimated that over 2 million men suffer from this condition.[13]
- The prevalence of erectile dysfunction increases in men > 60 years of age[14]

Although most patients think that erectile dysfunction is a natural consequence of ageing, it has been proved that erectile dysfunction itself is not-age related but result from conditions that are related to ageing.[15] For example, it is estimated that as many as half of male diabetic patients older than 50 years are affected by erectile dysfunction.[15] This condition can now be treated successfully if detected early enough.

Help for erectile dysfunction is not sought in time – delay can last over 40 years

Many men with erectile dysfunction do not seek help from their doctors because of embarrassment or because they believe that nothing can be done to help.[15]

As many as 40% of men who suffered from erectile dysfunction had not discussed their problem with anyone[16]

Up to 80% did not consult their doctors because they did not know that effective treatments were available[16]

Delay in seeking help can last from a few weeks to over 40 years[17]

Longer delay can be damaging to the patient: erectile dysfunction has negative impact on the patient's quality of life, reduces his feeling of self-esteem, and can lead to a breakdown in his relationship[16, 18, 19]

Continence Problems

Overactive bladder is a common problem that has considerable impact on patient's quality of life. In many cases, the underlying instability is compounded by urinary incontinence, which places a considerable burden on patients and the NHS.

The NHS is increasingly recognising the need to improve the management of urinary incontinence. In particular, the Older Person's National Service Framework requires the development of integrated continence services with a Director of Continence Services in place by 2004.

- UK prevalence - urinary incontinence
  - age 15-64 Men 2% Women 9%
  - age >65 Men 7% Women 12%
- There are no data that suggest that old age disadvantages incontinent people with respect to prognosis

Shared Care Facilities in Urology – Time to Re-think?

It is clear the present number of urologists cannot cope with the current urological workload. Furthermore workload pressures will increase due to many factors including demand for community based outpatient services, the ageing population, performance targets for the treatment of cancer and early retirement of existing consultants.

The Solution currently proposed by BAUS (British Association of Urological Surgeons) to meet these quality and workload demands is:

- An increase in consultant numbers from the present 1:117,000 to 1:80,000 of the population.
- Increased training time from 5 to 6 years (implemented).
- Introduction of sub-specialist training (in process of implementation).

Are these measures an appropriate and sufficient response to the expectations of patients, government and urologists?

It has been acknowledged that there are three gaps in service provision needing to be filled.

First the total **Manpower Gap** between demand and supply exhibited by long waiting lists and waiting times.

Secondly there is the **Inpatient-Outpatient Gap**, an increasing mismatch between the demand for outpatient services and inpatient operating. Urology is changing as more medical therapies become available.

Finally there is the **Time Gap.** It was acknowledged by BAUS in February 2001 that even with the new 6 year training programme the consultant to population ratio of 1:80,000 could not be achieved before 2010 and only then if a total of 30 new training posts were

to be approved, financed and implemented (15 in each year 2001 and 2002).

It has been argued that even if we were successful in training this number of urological surgeons, each with subspecialty skills, they might have difficulty maintaining those skills. All would be doing more outpatient work with less operating. Perhaps some would never have the opportunity to practice the skills learned and become office urologists by default.

How would plan the provision of Urological services for the NHS if we started from scratch with a clean sheet?

Shared care between urologists and GPs will ensure that patients benefit from optimal referral and treatment

Shared care has been shown to be convenient to the patient, cost effective and leads to the best working relationships between GPs, specialist nurses and urologists.[20, 21]

Specialist GP Urology services can be developed to achieve:

- Management of LUTs
- Direct access to trans rectal ultrasound scans
- Direct access to day case flexible cystoscopy
- Direct access to Urodynamics
- Prostate Cancer monitoring and treatment
- Management of Erectile Dysfunction
- An integrated continence service
- More appropriate use of the secondary sector, without damage to infrastructure
- Safe, Hospital-equivalent quality
- Reduced Cost
- Reduced Waiting times
- Low DNA rate
- Increased Patient Satisfaction

PCTs need to take action and focus on the disease area in an organised way

The strategy for the future of the NHS, as set out in 'The NHS Plan', specifically aims to improve quality of care, reduce waiting times, increase efficiency, and increase value for money. "The investment proposed has to be accompanied by reform...and the service redesigned around the needs of the patient"[22]

Nurses are already successfully delivering a range of protocol driven outpatient services both in the hospital and the community.

For GPs, the Plan states that 'there will be a bigger role for GPs in shaping local services, as more become specialist GPs'. RCGP (The Royal College of General Practitioners) views the initiative as a means of promoting portfolio careers and diversification of GPs, while maintaining their generalist expertise and role.

The RCGP prefers to use the term 'GPs with a special interest' (GPWsi).

The GP contract framework 2002 included the development of special interests as part of a new career structure model.[23]

However, despite the apparent political will to develop new roles for GPs, a broader range of services has been slow to develop.

Monitoring arrangements are essential to ensure accountability to the PCTs (Primary Care Trusts). A programme has to be developed to ensure audit arrangements are in place and that quality of the service is acceptable and outcomes comparable to traditional secondary care.

The ASCU (Association for Shared Care Urology)

A close collaboration will need to be established between family practitioners and urologists so that patients can benefit from an optimal referral and treatment pattern.[12] Family practitioners will have to update their knowledge and skills in the field of prostate health to ensure that they can identify potential sufferers and refer them to urologists promptly for appropriate evaluation and treatment.[12] Ideally, urologists must be prepared to provide appropriate help, information and even tuition to family practitioners.[12]

The ASCU was formed in 1998 to propagate discussion and develop high quality primary care strategies for health improvement. Association meetings were subsequently held in 2000 and 2001. The association has the support of BAUS and there are

Perception that symptoms are a normal feature of ageing
Fear of a diagnosis of cancer
Fear of surgery and its potential side-effects
Reluctance to discuss symptoms with a female family practitioner
Fear of ridicule, and embarrassment of discussing symptoms
Dislike of digital rectal examination
Reluctance to travel long distances from home for diagnosis and treatment

Table 3. Reasons why men with prostatic disease symptoms do not present to their doctor[12]

currently around 160 members, including consultants, nurses, managers and GPs. Progress has been hampered for a variety of reasons, not least the lack of clear training standards – until now..

The PGDipUrol (Postgraduate Diploma in Urology)

In October 2002, the PGDipUrol was launched by the Institute of Urology and Nephrology, Middlesex University & Rila Publications Ltd.[24]

This one year course gives GPs and nurses with an interest in developing community or hospital based shared care services the opportunity to become formally accredited in providing such services as:

- All aspects of the non-surgical investigation, diagnosis and management of urological disease;
- Endoscopic diagnostic procedures;
- Perhaps some carefully defined minor surgical procedures, both endoscopic and open;
- Urological ultrasound (abdominal);
- Urodynamics.

Possible advantages:

- Would help to fill the total workload gap and deal with the growing mismatch between inpatient and outpatient workload.
- Would fill the PCT driven need for patient centred, community-based services.
- A defined training programme with assessment and accreditation would ensure the provision of high quality, uniform and consistent urological care.
- The shorter training period would help to fill the time gap.

I sincerely hope that the PCTs, the ASCU, the BAUS and the RCN (Royal College of Nursing) will grasp this opportunity afforded them by the PGDipUrol framework to provide for our patients the well integrated, high quality shared care Urology service that they deserve for the NHS of the future.

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Special Interests: Respiratory Medicine; Male Health; Urology - including sexual health. The implementation of clinical guidelines and the development of new models for the delivery of primary care.

Durability of BPH Treatments and Surgical Considerations

Miss Mary Garthwaite & Mr Ian Eardley

Benign prostatic hyperplasia (BPH) is a chronic, progressive condition, which is common among ageing men. Estimates of prevalence range from 10-30% for men in their early 70's depending on the definition of BPH.[1] Clinically it is characterised by lower urinary tract symptoms (LUTS) which include frequency, urgency, a poor stream, a sense of incomplete emptying and nocturia. The mechanisms by which BPH causes symptoms remain undetermined, however, bladder outlet obstruction plays a key role.[2] If left untreated several complications can occur. These include acute urinary retention (AUR), recurrent urinary tract infections, hydronephrosis and renal failure. The aims of treatment are to alleviate lower urinary tract symptoms and to prevent complications arising. These aims need to be achieved whilst simultaneously minimising the side effects from the treatments themselves. Treatment options range from non-invasive pharmacotherapy, with the use of α–blockers or 5α reductase inhibitors, to invasive surgical techniques such as transurethral resection of the prostate (TURP). The emergence of minimally invasive surgical techniques, such as transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA), is adding yet another therapeutic option.[3]

Medical treatment

Selective α–blockers (tamsulosin, alfuzosin, prazosin, terazosin, doxazosin)

Human prostate, bladder base and urethral smooth muscle have a predominance of α1-adrenoreceptors. Stimulation of these receptors induces contraction. α1-adrenoreceptor antagonists (α blockers) are presumed to reduce the functional obstruction in BPH via a direct action on prostatic smooth muscle tension. α1-adrenoreceptor blockade has become an accepted treatment principle as evidence shows α blockers to be reliably effective at decreasing both the obstructive and irritative symptoms of BPH.[4,5] There have been numerous randomised control trials comparing individual α blockers to each other, in terms of efficacy and side-effects, but no significant difference has been found.[6] The side-effects of α blockers include dizziness, asthenia, postural hypotension and abnormal ejaculation.[4] Treatment withdrawal rates are similar for alfuzosin and tamsulosin (0.4mg dose), but higher for doxazosin, terazosin and tamsulosin (0.8mg dose).[4] Men with severe symptoms appear to benefit the most showing the largest reduction in overall symptom scores.[7,8]

5α -reductase inhibitors (finasteride, epristeride)

BPH is an androgen-dependent process. It is thought that a critical level of prostatic androgen is required to maintain the hyperplastic state of the gland. Withdrawal of the androgen will result in significant involutionary changes within the prostate leading to reduced gland size and consequently a decrease in outflow obstruction.[9] It has been shown that 5α-reductase inhibitors are effective in improving lower urinary tract symptoms and reducing the rate of complications in men with BPH, in particular those with larger prostates. When compared with α blockers their efficacy appeared to be slightly lower.[5] The most commonly reported side effects of the 5α-reductase inhibitor finasteride relate to sexual dysfunction and include reduced libido, impotence and decreased ejaculation.[10]

Combination therapy

The use of α blockers in combination with 5α-reductase inhibitors for the treatment of symptomatic BPH is currently under investigation. The limited research to date has not found any significant benefit with this approach.[11] The results from further, large scale, long-term studies are awaited.

Surgical treatment

TURP

Transurethral resection of the prostate (TURP) has been the gold standard treatment of symptomatic BPH for many years. TURP has been proven to reduce lower urinary tract symptoms associated with BPH and increase urinary flow when compared with 'watchful waiting'.[12, 13] There is a lack of data on long-term comparisons of TURP with medical therapy. The morbidity associated with TURP is not insignificant. A review of observational studies reported immediate surgical complications (12%), haemorrhage requiring intervention (2%), erectile dysfunction (14%), retrograde ejaculation (74%) and incontinence (5%).[14-16] Mortality figures for the first 30 days post-TURP range from 0.4% to 1.9% depending on the patient's age.[17] The reoperation rate is approximately 1% a year.[17] The treatment failures can be divided into three main

categories; acute urinary retention, development of a large bladder residual volume (>350ml) and deterioration to a severe symptom score.[12]

Minimally invasive therapies

The minimally invasive therapies attempt to treat patients without the need for general or regional anaesthesia. They thereby eliminate the morbidity risks associated with the more standard surgical procedure of TURP and the long-term side-effects or compliance issues associated with medical therapy.[18] They are potentially suitable for administration in an outpatient setting thus removing the requirement of an inpatient stay. A period of time post-procedure is needed to allow for resolution of the effects of treatment before the alleviation of symptoms is noted. The patient requires a catheter during this time. The two main techniques employed are transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA).[18] TUMT uses heat generated by microwave antennae in the urethra to coagulate prostatic tissue. TUNA uses radiofrequency energy through two intraprostatic electrodes to generate the heat required to coagulate the tissue. Other techniques include interstitial laser thermoablation and water-induced thermotherapy.[18] The relief of symptoms is thought to be based on two principles. Firstly, the reduction of obstructing prostatic tissue by the thermoablative effect and secondly, by the reduction in numbers, or the altered function, of receptors in the affected tissue.[19, 20] The reported adverse events for TUMT include the need for catheterisation for more than a week, persistent irritative symptoms, haematuria and sexual dysfunction. Those for TUNA are similar. As these treatments have only been introduced over the last decade there is a lack of follow-up data, making it difficult to evaluate the long-term effects of the treatments or to compare them with TURP and medical therapies. The limited evidence so far would suggest that the risks of major bleeding, incontinence and retrograde ejaculation are reduced compared with TURP.[6, 18]

Phytotherapy (Saw palmetto, rye grass pollen extract, α sitosterol plant extract)

The management of BPH with 'natural' agents continues to be of interest. Phytotherapeutic agents are derived from extracts of the roots, seeds, fruit or bark of various plants. Most preparations are made from a combination of these extracts. In the United States they can be bought over-the-counter and in many European countries they are available on prescription.[21, 22] They are often marketed to "promote prostatic health" with claims that they potentially help avoid prostatic surgery and may even prevent prostate cancer.[23] There is an lack of good experimental data with regard to these products, making it difficult to assess their potential as treatments for BPH and impossible to validate the claims made regarding their use.[6] The mechanisms of their action remain unclear.[22] Studies show that the composition of each extract is complex and variable, thus preventing comparison of the different preparations.[23] It is known that most extracts contain a combination of phytosterols, plant oils, fatty acids and phytoesrogens, however, it is unclear as to which of these compounds are 'active'.[21] It is accepted that there is a need for further research in order to ascertain the efficacy of these agents and address the issues of clinical safety.

Economics of BPH

As the ageing population increases in number so too does the economic burden of providing treatment for this condition. It is no longer acceptable for a treatment to be available merely because it works. Any decisions regarding the implementation of current or new therapies need to be accountable to the public as it is they who provide the money to pay for them. The two questions that must be answered are "how well does it work" and "does it provide a durable and validated cost-effective improvement in the quality of life?"[24] The difficulty in addressing the cost-benefit analysis of BPH treatment lies in attaching 'prices' to quality of life issues, such as incontinence, loss of sleep, impotence and sexual dysfunction.[25] A recent comprehensive economic evaluation of BPH treatment, associated with the CLasP (Conservative management, Laser therapy, transurethral resection of the Prostate) study, looked at costs to both the United Kingdom National Health Service and to the patient.[26] The evaluation assessed costs from the time of randomisation to the 7.5 month follow-up and therefore only gives data on the short term cost-effectiveness of the treatments. The conclusions reached indicated that transurethral resection of the prostate was more cost-effective than noncontact laser therapy in terms of symptomatic improvement. In men wishing to delay therapy, conservative treatment appears to be a cost-effective alternative. It does not include any data on medical therapy options.

As the economics of healthcare expenditure becomes an ever more important issue it is imperative that decisions, regarding treatment provision, are based on good quality clinical research, which includes a thorough assessment of the economic data available.

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Clinical BPH – Matching the Right Patient and the Right Treatment

Mr. Mark Speakman

An Overview

Clinical BPH is now better known as lower urinary tract symptoms (LUTS) secondary to BPH. In the past, this condition was known as prostatism. This was based on the assumption that all men who suffered LUTS developed this because of an enlarged prostate. The interplay between LUTS, bladder outlet obstruction (BOO) and benign prostate enlargement (BPE) was clarified more than 20 years ago. In recent years, however, it has been recognised that LUTS can occur secondary to multiple factors rather than just prostatic problems. These include primary abnormalities of the bladder or its nerve supply and numerous non-urological problems such as cardiac, endocrine, renal and central nervous system diseases. This wide breadth of disorders must be kept in mind when evaluating a patient with LUTS.

One of the difficulties with diagnosing and managing this condition is that it is a men's health problem. Men are notoriously poor at presenting with the early stages of this condition often due to the fact that they regard LUTS as a normal part of ageing rather than an illness and simply modify their lifestyle to cope with their symptoms. It is often not until they develop complications such as urinary tract infection, haematuria or retention, that they present. However, not all patients with LUTS will have a progression of their symptoms and not all patients will develop complications. The key issue is to discern which patients are at the greatest risk.

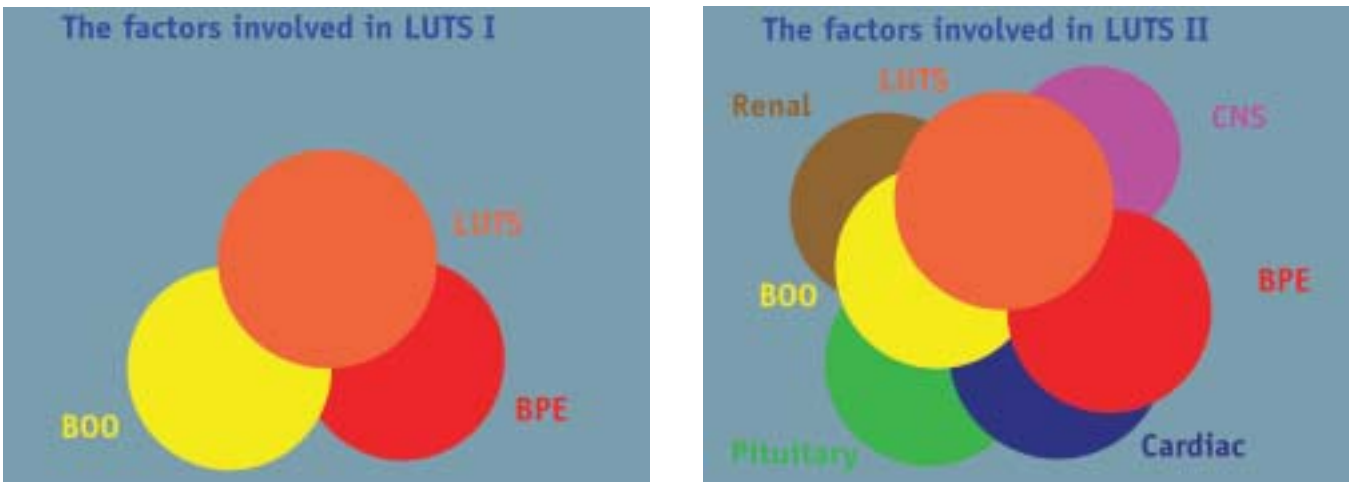
Symptom Assessment and Bother

The initial symptoms in prostatic obstruction are the obstructive or voiding symptoms such as weak urinary flow rate, hesitancy, intermittency and terminal dribbling. This may lead on to incomplete bladder emptying and ultimately to retention. The more bothersome symptoms, however, are the irritative or filling symptoms such as frequency, nocturia, urgency and urge incontinence.

The decision to treat a patient is most commonly based on the extent to which symptoms interfere with daily activities and thereby cause 'bother'. It is important to be able to quantify the severity of the symptoms with a recognised scoring system such as the IPSS (International prostate symptom score). This must be related to the bother experienced by the patient in order to judge the impact of this condition on the individual patient's quality of life. For example a farmer may have a very high symptom score but not be bothered because he can urinate in the field at any time; a bus driver is likely to be more bothered by considerably less severe symptoms.

By using symptom scores and bother factors the likely benefits can be balanced against the morbidity of the treatment which is offered. Although individual doctors may have prejudices about their preferred treatment plan, there is little doubt that the outcome is likely to be affected by choice and that patients should be given a broad range of information and a wide variety of choices to allow them to make an informed decision.

Fig 1: Diagrams to illustrate the interplay between lower urinary tract symptoms (LUTS) and the pathology causing them.



BOO= Bladder outlet obstruction; BPE= Benign prostatic enlargement; CNS= Central nervous system disorders;

Examination

Examination should follow a general history as well as a urinary symptom analysis. During abdominal examination the kidneys are rarely palpable and it must be remembered that percussion more easily identifies a distended bladder than palpation. Examination of the external genitalia is obligatory as many men with foreskin abnormalities, such as phimosis or with meatal stenosis do not mention this fact and commonly turn up in hospitals having been referred for prostatic problems.

Examination should be completed by a careful digital rectal examination, which cannot be replaced simply by a routine prostate specific antigen (PSA) test. The digital rectal examination as well as evaluating the size and any areas of irregularity in the prostate also allows assessment of the anal tone and any rectal abnormalities themselves.

Investigation

All men presenting with LUTS should have a urine dipstick test to exclude the presence of diabetes, identify the presence or absence of proteinuria, infection or haematuria. All male patients with haematuria should be referred for urological investigation.

Many general practitioners now have access to open access flow clinics or direct access to nurse-led prostate assessment clinics. These allow the ability to perform a simple flow test and post-micturition bladder scan, both of which can be helpful in deciding between treatment options. Evaluation of the flow test is more than simply recording the maximum flow rate. Tests that are performed with a voided volume of less than 150mls should be repeated and generally better accuracy comes from performing two or more evaluations. A good flow rate should be demonstrated by a bell-shaped curve on the flow trace and the development of a decreasing plateau at the end of the curve is an early sign of prostatic obstruction. Ultimately a very flat curve with a very poor maximum flow rate could indicate either severe prostatic obstruction or possibly urethral stricture.

When available post void residual scan following the flow test will allow the assessment of the amount of urine left behind in the bladder. A Residual volume of over 250mls increases the risk of complications such as renal failure secondary and infection and these patients should have the renal function estimated and their progress monitored more closely.

One of the most valuable, but under-utilised tests in patients with LUTS is the frequency/volume chart where a patient can record the volume and time of voiding throughout the day and night over a period of 3 or more days. This will accurately quantify the level of symptoms and will also identify nocturnal polyuria (where more than 35% of the 24-hour urine output occurs during the night) in patients with frequent nocturnal voids.

Prostate specific antigen (PSA) testing remains controversial in the United Kingdom, but is part of routine practice in most of Europe and North America. Although there is to date no strong evidence that the incidence of prostate cancer is higher in patients with LUTS than in patients of a similar age without bladder symptoms, the majority of patients now in the UK do undergo PSA testing before hospital referral. Age-specific PSA values should be used to decide who needs hospital referral and recent data from America have also shown that the PSA test can be used in selecting which treatment to use in which patient with BPH as well as its use as a diagnostic test for cancer.

Treatment

Traditional outcomes for the treatment of BPH included the measurement of such factors as symptom analysis, flow rate measurement, post-void residual volume, prostate size and urodynamic evaluations. It is now realised, however, that the principal aim of treatment for LUTS is to reduce or alleviate the LUTS, prevent complications and to minimise the adverse events of the planned treatment. It would be better to suggest therefore that modern outcomes for BPH treatment should assess the burden of LUTS, the rate of urinary retention, the rates of prostatectomy and the rates of adverse events.

Treatment choices for LUTS include conservative measures, such as reducing caffeine intake, increasing water intake, bladder drill and attention to bowel habit in particular the avoidance of constipation. Active treatments include phytotherapy, alpha adrenergic receptor blockers, 5-alpha reductase inhibitors, standard surgical treatments, such as TUIP, TURP or open prostatectomy and more recent surgical approaches such as laser prostate treatment. All treatments should be reviewed with regards to the strength of published studies with considering both subjective and objective improvement. Incidence of short and long term complications, their ability to be repeated and their long-term costs should be evaluated.

Benign prostatic enlargement can produce bladder outlet obstruction by two principal mechanisms; firstly a dynamic or muscular component or secondly a mechanical or static component. Drugs therefore can be effective by either relaxing the prostatic smooth muscle or reducing the prostatic bulk. The principal limitation of drug therapy is the development of side effects, which usually result from the undesirable effects of the drugs on non-target tissues with the same receptor such as the blood vessels. Patient preference will always be for a drug that has a good therapeutic effect with a low rate of adverse events. A severely bothered patient, however, might accept an effective treatment with more adverse events.

Alpha Adrenergic Receptor Blockers

Whilst this class of drugs has been available now for two decades or more, it is only since the early 1990s that drug therapy has improved. Multiple studies comparing drugs such as prazosin, indoramin, terazosin, doxazosin, alfuzosin and tamsulosin showed that there is no strong statistical evidence for any

Figure 2: Table illustrating the major risk factors for the development of complications secondary to benign prostatic enlargement

Risk Factors
• Age > 80 years
• Very slow flow rate
• Large residual volume
• Large prostate gland on DRE

greater efficacy with any of these agents when compared with each other. All of these drugs work in approximately 70-80% of patients and typically improve the symptom score by about 40% and improve the flow rate by between 15-40%. These drugs, however, have been shown to have an impact on quality of life measures such as the bother score at the end of the International Prostate Symptom Score. There are, however, significant differences in the side effect profiles of these drugs and the newer prostate specific agents have an improved patient profile. This is particularly evident in avoiding postural hypotension, which has been shown to be significantly better with the later drugs such as alfuzosin and tamsulosin. In one study, tamsulosin was shown to have no greater effect on blood pressure than placebo.

5-alpha reductase inhibitors

5-alpha reductase inhibitors work by a different mechanism causing reduction in prostate size and are therefore much slower in onset of action. Typically most patients taking alpha-blockers achieve a significant symptomatic benefit within 2 weeks or less whilst many patients on finasteride can take 3 months to achieve a strong symptomatic benefit. These drugs have been shown however to reduce the risk of acute urinary retention and to reduce the need for surgery.

The combination of medical therapies would seem, scientifically, eminently logical. The use of one drug that would relax the prostate and bladder neck and a second drug that would shrink the prostate seems logical. Until this year, however, the scientific evidence for this was poor. The most recent study presented by the National Institute of Health in America at this year's American Urology Meeting has, for the first time, shown that in certain patients, there can be genuine improvements when dual therapy is used. There is also increasing evidence that some patients with predominantly irritative symptoms can benefit from the use of the newer alpha-blocker therapies even in the absence of significant obstruction.

Surgical Treatment

In comparison to TURP all drug therapies are far less effective with regard to the improvement in flow rate. Whilst TURP can result in an improvement in flow rate by up to 140%, typically drugs such as tamsulosin and finasteride achieve improvements in flow rate which are more modest around 15-40%. However, this difference is less marked when we look at the symptomatic improvements. TURP has been shown to achieve a reduction in total symptom score of between 60-80% compared with 40-60% with tamsulosin and approximately 40% with finasteride. When we sub-divide the symptoms, however, between irritative (filling) and obstructive (voiding) symptoms, it becomes clear that this difference is even smaller for the more bothersome irritative symptoms. Recent good work from Australia has also shown that the greatest symptomatic benefits come in patients with the most severe symptoms. In addition, patients with mild symptoms, who will often see a symptomatic improvement with medication, may see deterioration in their symptoms with surgery.

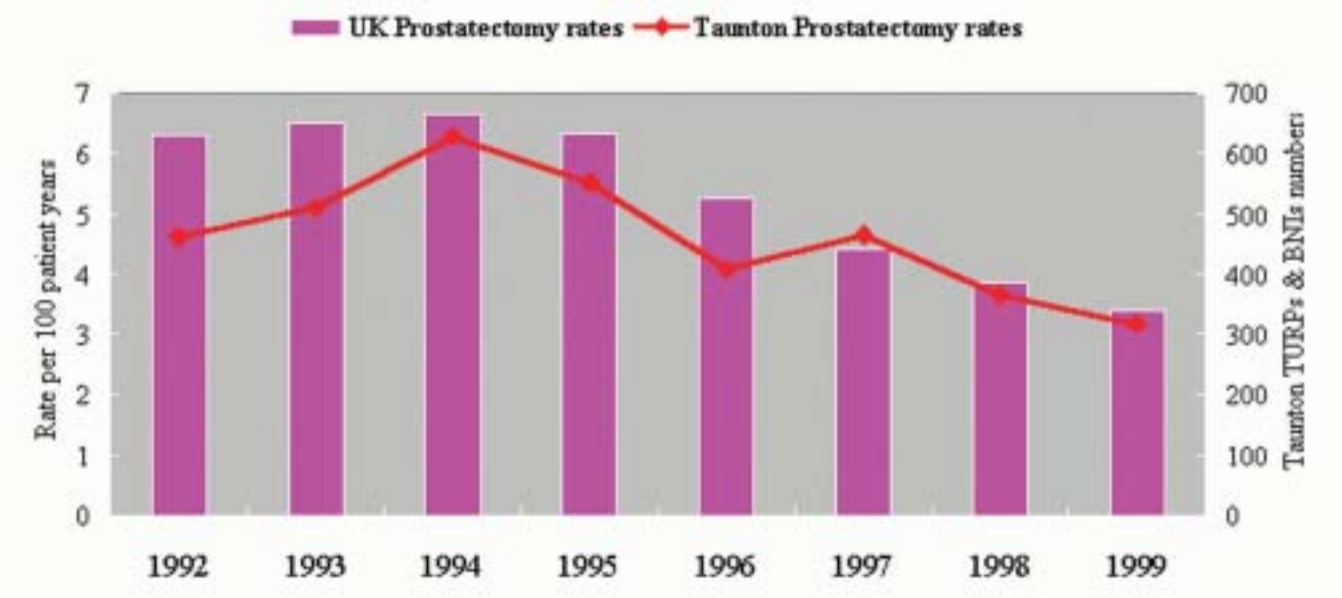


Figure 3. Graph to show how Prostatectomy rates have changed over a seven year period in the UK as a whole and in Taunton as a single centre.

Of greatest interest over the last few years, has been the evidence that drug therapy can reduce the risk of both acute urinary retention and the need for surgery. This data came out of a very large North American study using finasteride that showed a reduction in risk for retention and surgery of 57 and 55% respectively. There are not yet any long term placebo-controlled trials of alpha blockers, but there does appear to be some evidence from the analysis of other studies that alpha blockers, provided they are maintained for a long period of time, can achieve similar beneficial reductions. Certainly work from the General Practice Research Database in the UK has shown that the newer alpha-blockers with a low side effect profile have the same long interval from initiation of treatment to treatment failure as finasteride. They are statistically better than the older, less targeted, alpha-blockers. Recent work has also shown that the use of alpha-blockers such as alfuzosin and tamsulosin can improve the percentage of patients who have a successful trial without catheter after acute urinary retention.

In conclusion, patients with severe and bothersome symptoms who want early treatment effects will do better with alpha-blockers and their quicker onset of action. Patients at risk of acute urinary retention, such as men over 70 with poor flow rates, high symptom scores and large prostates with less bothersome symptoms would probably do better with drugs such as finasteride. The effect of increasing medical treatment of BPH has resulted in significant decreases in the number of prostatectomies in the United States, most of Europe and the UK. Comparison of data between 1994 and 2000 shows that the surgical operation rate has reduced by almost 50%.

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LUTS and the GP consultation – Let's Talk About Sex

Dr Mark Coombe

At last year's European Association of Urology annual conference, a survey of 14,000 men was announced in which a clear link was established between lower urinary tract symptoms (LUTS) and sexual dysfunction.[1]

The study's principal author, Dr Raymond Rosen – a professor of psychiatry and medicine at the University of Medicine and Dentistry in New Jersey – concluded that every man presenting to the GP with urinary problems should also be quizzed about his sex life.

Given that the study showed an association between LUTS and problems such as erectile dysfunction, ejaculation disorders and loss of desire, this seems like sensible advice. However, as most primary care practitioners know only too well, getting any patient to talk about their sexual performance is never easy, particularly with the added time constraints of the primary care consultation. When that patient is a middle-aged/elderly man who has only just managed to overcome the embarrassment of revealing his urinary difficulties, it can seem nigh on impossible.

Nevertheless, Prof Rosen's data clearly showed that men retain an active interest in matters sexual well into their late 60's and 70's. In fact 76 per cent of the 60 to 69-year olds reported sexual intercourse during the past four weeks.

Sexual dysfunction is therefore something that is likely to be of considerable concern to this group of patients. It may also play a significant role in our choice of therapy. It is well known that transurethral resection (TURP) of the prostate is associated with a high rate of retrograde ejaculation (70 per cent) and impotence (14 per cent).[2] Some medical therapies can also affect sexual performance. For instance the 5α-reductase inhibitor finasteride is associated with an increased incidence of erectile dysfunction, decreased libido and abnormal ejaculation,[3,4] while the α_{1A}-selective blocker tamsulosin has been linked to a dose-dependant increase in ejaculatory disorders.[5] For those patients who may already be concerned about their sexual performance it may therefore be more appropriate to choose a management option with negligible effect on sexual performance

The Consultation

It is important that we discuss our patient's attitudes to sex before prescribing LUTS therapy. But how do we get our LUTS patients to raise any concerns they have about their sex lives?

As is often the case when confronted with problems of this nature, it is a good idea to go back to basics and examine the way we are interacting with our patients. There may be ways in which our consultation technique can be improved or adapted to make it easier for patients to express all their concerns.

The GP consultation has undergone a considerable metamorphosis over the past few years with a greater emphasis on patient centred consulting behaviour. This is not always possible, but very desirable when the topic material is perceived by the patient as being sensitive or personal.

To cope with these ongoing changes in doctor/patient relationships, a number of stylised models have been adopted to provide a template for a more patient centred consultation. (see table 1). Although there are some key differences between these models, most work on the basis that the GP should first try to build a relationship with the patient, then try to collect data on their condition and finally agree a shared management plan. These three key stages are often referred to as the "Three Function Model" and will form the basis of much of the advice given here.[6]

Build the relationship

Patients with LUTS are notoriously reluctant to consult a GP. This may be through embarassment, not wanting to waste the GP's time, concern that their symptoms are a sign of something serious, or fear that they might need surgery. It is therefore important that those patients who do make it to the surgery are made to feel welcome and given every chance to air their concerns. You can achieve this through:

- Making it clear that you are listening throughout the consultation by offering empathic comments and not reading the patient's notes while he is speaking.
- Trying not to interrupt the patient's opening statement and once he has finished ask if he has any other concerns.
- Avoiding misunderstandings by summarising[7]– "So, you have to get up several times during the night, but you don't suffer any pain on going to the toilet?"

Above all, try to make the patient feel he has done the right thing in coming to see you.

The recent MSAM-7 study confirms that 79% of men (aged 50–79) are still sexually active [1]

Once Daily
Xatral® XL
alfuzosin hydrochloride 10 mg

Treats BPH – Respects sexual function

Xatral®XL (alfuzosin hydrochloride) Xatral® Prescribing Information – UK Presentation: Xatral XL tablets containing 10mg alfuzosin hydrochloride in a prolonged release formulation. Xatral tablets containing 2.5mg alfuzosin hydrochloride. **Indication:** Symptomatic relief of benign prostatic hypertrophy. **Dosage:** Initial dose should be taken before bedtime. *Adults.* Xatral XL – one tablet to be taken daily after a meal. Tablet should be swallowed whole. Xatral – one tablet (2.5mg) three times daily increasing to four tablets per day if required. *Elderly and treated hypertensive patients.* Xatral XL – no dose adjustment required. Xatral – one tablet (2.5mg) twice daily (morning and evening). *Renal insufficiency.* Xatral XL – no dose adjustment required in patients with mild to moderate renal impairment. Experience in patients with severe renal impairment is limited and cautious use in these patients is recommended. Xatral – one tablet (2.5mg) twice daily (morning and evening) adjusted according to clinical response. *Hepatic insufficiency.* Mild to moderate: single dose of Xatral 2.5mg per day, increasing to 2.5mg twice daily according to clinical response. **Contraindications:** Hypersensitivity to alfuzosin, history of orthostatic hypotension, co-administration with other alpha-blockers, severe hepatic insufficiency (Xatral), hepatic insufficiency (Xatral XL). **Warnings:** Postural hypotension with or without symptoms may occur in some subjects, in particular, patients receiving antihypertensive medications. These effects are transient and do not usually prevent continuation of treatment following dose adjustment. **Precautions:** Initiate treatment gradually in patients who have shown hypersensitivity to alpha blockers and in patients taking anti-hypertensive drugs. Continue specific anti-anginal therapy in patients with coronary insufficiency. Discontinue Xatral XL or Xatral if angina reappears or worsens. Withdraw 24 hours before surgery. **Side effects:** Most frequently observed side effects are faintness, vertigo, dizziness or malaise, headache, minor gastrointestinal disorders. Less frequently: tachycardia, chest pain, drowsiness, rash, pruritus and flushes. Palpitations, orthostatic hypotension and oedema have been reported. **Basic NHS Cost:** Xatral XL – 10mg blister packs of 30 tablets £23.80. Xatral 2.5mg blister packs of 60 tablets £22.80. **Legal Category:** POM. **Product Licence Number:** Xatral XL: PL 11723/0370. Xatral: PL 11723/0329. **Product Licence Holder:** Sanofi-Synthelabo, PO Box 597, Guildford, Surrey. **Further information available on request. Date of preparation of Prescribing Information:** 02/03. **Reference: 1.** MSAM-7 research, Data on file Sanofi-Synthelabo. The Ipsos Group, 2001.

XAT-03/052

Table 1. Examples of consultation models

Stott and Davis model[9] - every consultation should seek to explore four key areas:

- Management of presenting problems
- Modification of help seeking behaviours
- Management of continuing problems
- Opportunistic health promotion

R Neighbour- 5 checkpoints in a consultation:

Connecting

Summarizing

Safety netting- To ensure no serious pathology is missed

Handover- of presenting problem and management plan back to the patient

Housekeeping- remember to look after yourself

Byrne and Long model[10] - The consultation should move through six key phases:

- Establish a relationship with the patient
- Attempts to discover or actually discover the reason for the patient's attendance
- Conduct a verbal or physical examination or both
- Consider the condition
- Detail further treatment or further investigation
- Terminate the consultation

Pendleton et al model[11] - Each consultation should seek to complete seven tasks:

- Define the reason for the patient's attendance
- Consider other problems
- With the patient, choose an appropriate action for each problem
- Achieve a shared understanding of the problem with the patient
- Involve the patient in the management and encourage him or her to accept appropriate responsibility
- Use time and resources appropriately both in the consultation and in the long term
- Establish or maintain a relationship with the patient which helps to achieve the other tasks

Helman's focus model[12] - The consultation should answer the patent's six key questions:

- What has happened?
- Why has it happened?
- Why to me?
- Why now?
- What would happen if nothing were done about it?
- What should I do about it or who should I consult for further help?

Collecting data

Lower urinary tract problems can cause a wide array of symptoms ranging from weak stream and hesitancy to nocturia and urge incontinence. The condition may also be affecting the patient's emotional or sexual health. It is quite common, however, for the patient initially to focus on the symptom that concerns him the most or the one he feels most comfortable talking about.

It is therefore important to respond to all the

relevant cues the patient is offering you.

So, while the patient is speaking you should not only be listening to what he is saying, but also observing his manner,[8] physical posture, level of eye contact and tone of voice. You will then be able to respond to both the verbal and non-verbal cues. If the patient appears nervous or upset, point this out and ask if there is anything else bothering him.

At the beginning of the consultation use open-ended questions then use closed questions to focus in on specific problems.

If the patient appears hesitant there are a number of techniques you can use to encourage him along. These include:

- Encouragement – nodding or saying "go on"
- Legitimising his concerns – "no, it's not just a sign of getting old" "I don't think you're wasting my time" "Yes it's quite possible that the problems with your waterworks are affecting your sex life".
- Asking for more information – "So you're going to the toilet ten times a day. Do you find it difficult to pee when you get there? Any problems with dribbling. What about at night?"
- Direct questions about the patient's sexual performance. When doing this make it clear that sexual problems are common in men with LUTs and you are not singling out this patient in particular – "Sometimes these problems can also affect your love life. Some men have any problems getting an erection or sex becomes painful. Have you noticed anything like that?"
- Think of the family – "You're getting up four times a night. What does your wife think about that?" It may be that only at this point in the consultation that the patient tells you that he and his wife are now sleeping in separate beds.

Agree a management plan

Before negotiating a management plan with your patient you need to know what he wants and expects out of treatment. You will receive little thanks for improving a patient's flow rate if it is his nocturia that bothers him most. A patient with no interest in sex may well be delighted with the results of a TURP, while another may reject any therapy that is likely to interfere with his sex life. These matters need to be discussed up-front and the patient should be informed of all options and likely outcomes. Only then should the management plan be agreed.

Once agreed, it is a good idea to put the management plan in writing and include a contingency plan advising the patient on what to do if his symptoms return or he suffers unacceptable side effects.

Conclusion

LUTS is a condition fraught with embarrassment and irrational fears. Add sex into the equation and you have a recipe for reluctant patients who simply want to get out of your consulting room as quickly as possible. But it is important to remain clear that your patient's sexual performance may be at least as important to him as his urinary function. Using one of the more patient centred consultation techniques can help you ascertain both your patient's current level of sexual activity and their expectations for the future. You may then make your management options accordingly.

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AUR Review

New trends in the management of acute urinary retention

Alan McNeill, Western General Hospital, Edinburgh UK

Acute urinary retention (AUR) is a painful condition characterised by a sudden inability to micturate. This common problem was, in the past, considered an absolute indication for surgery (prostatectomy). Patients who managed to avoid surgery by having a successful TWOC (trial without catheter) remained at high risk of having surgery within a year. Although surgery is often successful, studies show that men who undergo prostatectomy after AUR are at increased risk of intraoperative complications, transfusions, postoperative complications and hospital death. Urethral catheterisation for AUR has also been shown to result in bacterial colonisation at a rate of 4% a day. It is therefore preferable that patients undergo a trial without a catheter (TWOC) after an episode of AUR to potentially avoid surgery. Moreover, new evidence is emerging indicating that α1-blockers improve the success rate of TWOC, resulting in a re-evaluation of the management of AUR. Primary prevention of AUR is a desirable goal given the extreme pain that patients can suffer and because of the potential morbidity following management of AUR. Various studies have indicated that AUR can be prevented with medical treatment. Indeed, studies aimed at assessing the role of α1-blockers in the prevention of AUR are underway.

Acute urinary retention (AUR) refers to the sudden inability to pass urine and is characterised by painful distension of the bladder. It is a very common condition; more than 1 in 10 men in their 70s will experience AUR within the next five years,[1] while the risk for men in their 80s is nearly 1 in 3. However, there is some evidence that the incidence may be declining,[2] an observation which may be partly explained by a trend towards earlier presentation of men with lower urinary tract symptoms.[3]

Risk factors

There are identifiable risk factors for the development of AUR, though its aetiology remains the subject of much speculation. Data from Olmsted County Study assessing 2,115 community-dwelling men, assessed the key risk factors for AUR as increasing age, severity of lower urinary tract symptoms (LUTS), peak urinary flow rate and increasing prostate size.[1] Other authors have suggested that PSA is the strongest predictor for BPH related outcomes including AUR, which perhaps reflects the fact that PSA is a good surrogate marker of prostatic size.[4-6] Also, men aged 40-79 years with a post-void residual (PVR) urine volume greater than 50ml are at a threefold greater risk of developing AUR.[7]

Aetiology

There are a number of presumed causes of AUR, suggested by published literature and anecdotal reports:

- Events that increase the resistance to the flow of urine, for example, urethral stricture or increase in muscle tone;
- Interruption of either the sensory innervation of the bladder wall or the motor supply to the detrusor muscle, or secondary to the influence of drugs;
- Events that lead to over distension of the bladder; for example, this is common in patients after operations under general anaesthesia, without catheterisation;[8]
- Prostatic infarction leading to increased a-adrenergic activity and neurotransmitter modulation are processes mooted by some authors to begin a sequence of events that result in AUR.[9-11]

Management

In my experience, the first presentation of a man with benign prostatic obstruction may be AUR. This highlights the importance of encouraging symptomatic men to present to their GP because if the patient's BPH is effectively treated and monitored, the risk of AUR may be reduced.

Acute urinary retention is treated by catheterisation, which may be done by GPs or by urologists. As already discussed, AUR can commonly lead to prostatectomy. However, given that urinary catheterisation prior to surgery may be associated with an increased risk of sepsis and bleeding due to bacterial colonisation,[12] it is preferable that men undergo a trial without a catheter (TWOC) after an AUR episode in the hope that they may avoid surgery altogether.

If the patient does have to undergo surgery, it is preferable if this is done without a urinary catheter in place. It is important that such a management strategy is considered because men undergoing prostatectomy after AUR are at increased risk of intraoperative complications, transfusion, postoperative complications and hospital death compared to men having the surgery to relieve LUTS alone.[13, 14]

Another reason for avoiding surgery for this condition, if possible, is that men having their prostatectomy because of AUR have slightly worse outcome in terms of symptom reduction and improvements in quality of life than those that undergo planned prostatectomies.[14]

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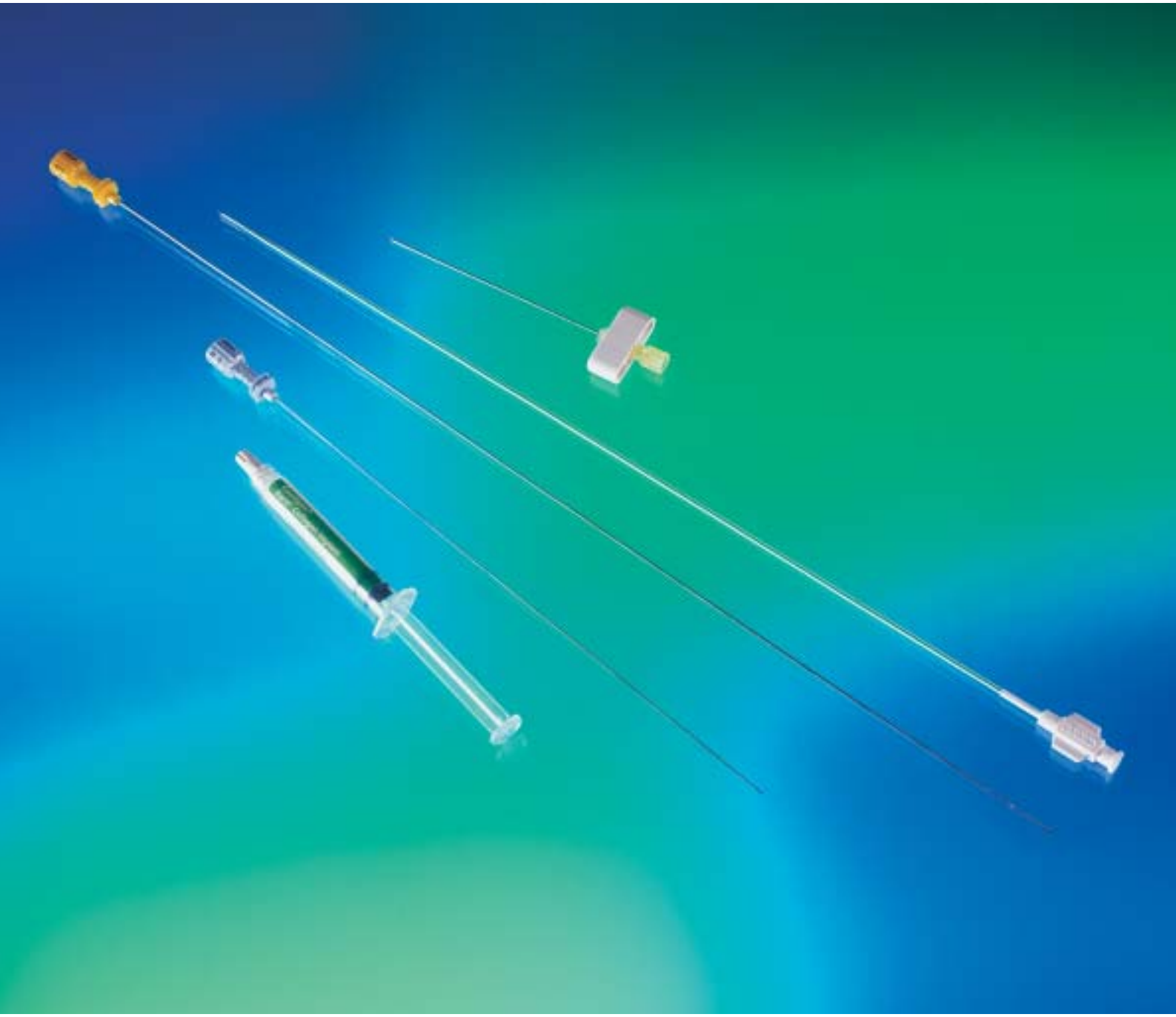

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TWOC

Recent evidence suggests that prolonged catheter drainage[15] may be associated with more successful TWOC and that α-blockers may improve the outcome of TWOC, findings that support the hypothesis that an acute inflammatory event precipitates an AUR episode.

Success rates of 23-28% have been reported with TWOC[16] with only around a third of patients needing surgery within six months.[17]

Role of α-blockers

It is assumed that bladder outlet resistance plays an important role in the aetiology of AUR. Given that α-blockers reduce bladder-neck and prostatic smooth muscle tone, it is a logical hypothesis that α-blockers could improve the chances of a successful TWOC. Caine, *et al.* tested this theory by treating a series of eight BPH patients with intravenous phentolamine (10mg) and/or 5mg oral qid phenoxybenzamine. Two patients with AUR voided without catheterisation.[18] In another small placebo-controlled study, involving 30 patients, TWOC following treatment with terazosin was successful in around 80% of patients compared to a 15% success rate in the placebo group.[19]

More recently, a prospective double-blind study looking at the effect of alfuzosin on the outcome of TWOC found that patients who received α-blockade did significantly better, with 55% of alfuzosin-treated patients experiencing a successful TWOC compared to only 29% in the placebo group.[20] Successful TWOC was defined as the return to spontaneous voiding and failure was defined as re-catheterisation within 24 hours. This data with alfuzosin has now further been confirmed in preliminary results from the ALFAUR study, which demonstrated the clear benefit to patients of receiving alfuzosin 10mg od prior to TWOC. In this study, the probability of successful TWOC in the alfuzosin was twice that of patients who received placebo.[21]

Data on the long-term outcome in patients who had a successful TWOC following α-blocker treatment is limited. In theory, continued use of α-blockers following an episode of AUR should be beneficial because of the effect on the sympathetic tone of the bladder neck and prostatic stroma allowing for better bladder emptying. A pooled analysis of 11 double-blind studies on alfuzosin supports longer term benefit[22] but this needs to be confirmed in a larger, prospective study.

Prevention

Because of the extreme pain that can be suffered during an episode of AUR, and the potential morbidity following management of AUR, primary prevention is clearly preferable for patients and clinicians, despite the problem not being life-threatening.

Various studies have indicated that AUR can be prevented with medical treatment. Use of the 5-alpha reductase inhibitor, finasteride, is associated with a reduction in risk of AUR.[23] Furthermore, phase III clinical data suggests that the dual 5-alpha reductase inhibitor, dutasteride, also reduces the risk of AUR. In addition, studies are ongoing aimed at assessing the role of alpha blockers in prevention of AUR.

Conclusion

Until recently, AUR was an absolute indication for surgery. Although prostatectomy is a successful procedure for AUR, patients are at increased risk of intraoperative complications, transfusions, postoperative complications and hospital death, indicating that, ideally, surgery is best avoided in the acute phase if AUR can be managed in an alternate way.

Recent and emerging evidence shows that some patients with AUR may avoid surgery by α-blocker treatment, suggesting that a TWOC after treatment with an α-blocker is an advisable course of action in all patients, apart from those who are very aged, presenting with painful AUR. Ongoing studies aimed at assessing the role of alpha blockers in the primary and secondary prevention of AUR may also provide evidence supporting a further role for this class of drugs in the management of this painful and distressing condition.

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Pitfalls in PSA Testing

Mr. P.H. O'Reilly

Prostate Specific Antigen (PSA) is a glycoprotein produced almost exclusively by the epithelial cells of the prostate. Since its introduction in 1987,[1] it has become one of the most successful and important tumour markers in medical practice. The result has been an enormous increase in the diagnosis of prostate cancer, and a growing concentration on early diagnosis and the potential for curative treatment. As with most clinical procedures, the test is not without its problems, and an understanding of the pitfalls in its usage is essential if the clinician is to interpret its results accurately to allow appropriate patient management.

Factors which influence PSA levels

A raised PSA is not necessarily diagnostic of prostate cancer. Elevation above 4ng/ml carries a 22% probability of cancer; elevation above 10ng/ml raises the risk of cancer to 63%.[2] So what other situations can cause an elevation in the absence of malignancy?

PSA Assay

More than 80 different Assays are available within Europe for PSA estimation, and it is important that the assay used is identified on the report, and the same assay used for follow-up investigations.

Different assays may have different upper limits of normal and different age-specific ranges. Thus a level of 4.3 using one kit may be normal, yet may be raised for another.

Age

PSA levels rise with age. In general, using the Hybritech assay for example, the PSA of a man in his 50s should be less than 3.5ng/ml, in his 60s, less than 4ng/ml, and in his 70s, less than 6.5 ng/ml. The latter age adjustment is vital to avoid needless referrals for suspected cancer, with all that might subsequently entail. Transrectal Ultrasound and Biopsy (TRUS and Bx) is not a pleasant experience, and carries a small sepsis rate even with the use of prophylactic antibiotics; sepsis can be a very serious complication in the elderly.

Prostate Volume

PSA levels can vary enormously in benign prostatic hypertrophy (BPH). Big prostates produce more PSA than small ones; indeed, some workers believe that PSA levels are directly linked with prostate volume, and can be of as much value as a digital rectal examination in determining prostate size.

Serial measurement of the PSA in this situation should reveal a steady or fluctuating PSA level, often between 4ng/ml and 10ng/ml, rather than a consistent rise. Nonetheless, prostate biopsies may be required to establish that the cause of the raised PSA is BPH and not cancer before non-interventional surveillance continues. A single set of benign biopsies confers an 80% reliance that the gland is benign. A second set of biopsies (as might be required, for example, for a sudden unexpected rise in PSA level) raises this to 95%.

Urinary tract infections

PSA levels are raised in uncomplicated urinary tract infections, and may be enormously high (eg 60ng/ml) in acute prostatitis. It is important that this is recognised; the last thing a patient with acute prostatitis needs in 12 needles thrust into the infected gland for biopsies! Further PSA estimation 3-4 weeks after an adequate course of antibiotics (eg. Ciprofloxacin 500mg bd for 6 weeks) should demonstrate a fall, eventually to within normal limits. Chronic prostatitis or non-bacterial inflammation can also give slightly raised levels.

Miscellaneous other benign causes of raised PSA

Transurethral Resection of the Prostate (TURP) and Transrectal Ultrasound and Biopsy both cause a significant temporary rise in PSA levels.

Prostatic infarction can raise PSA levels as high as acute prostatitis, and can be difficult to detect clinically without biopsy. One not infrequently sees such areas during transurethral resection of the prostate. Retention of urine and urethal catheterisation also elevate PSA levels.

Ejaculation raises the PSA. Since the half–life of the glycoprotein in approximately 2 days, if the patient attends the practice or clinic the morning after a night of passion, the PSA is likely to be raised.

Cycling can raise the PSA. The modern design of bicycle saddles mean that the prostate and perineum are given a severe bout of punishment and massage causing the same elevation asejaculation. The author recalls a patient who rode his bike from Blackpool to Stockport for his visit to the Prostate Assessment Clinic – information which only came to light when he was summoned back to the clinic for a repeat PSA after the first reading came back at 29ng/ml!

In this respect, it is important to note that a standard digital rectal examination (DRE) does not raise PSA. If the clinician does a DRE and feels there may be an abnormal hard area or nodule, and wants then to do a PSA, then there is no reason not to do just that. DRE may raise a sub-form of PSA known as free-PSA (see below), but that is not relevant to this situation

Causes of an artificially low PSA

Finasteride halves the PSA. Other drugs or herbs, eg PC-SPES or Saw-Palmetto may reduce it a little.

Clinical management

The point of PSA determination is to diagnose prostate cancer and discriminate it from benign conditions. There is unfortunately considerable overlap in PSA concentrations between patients with early, organ-confined cancer, and patients with BPH. Conversely, approximately 25% of patients with prostate cancer show no elevation of serum PSA. Thus, the threshold at which a TRUS & Bx become necessary are not clear and sensible clinical judgement allied to patient counselling and preference become essential. Some situations are clear-cut; the 80 year old with a PSA of 9 does not require biopsy. The 48 year old with a PSA of 4.8 does. But what of the 65 year old with the PSA of 8, and a benign-feeling prostate with a measured volume of 100ml? In this situation, initial biopsy followed by regular follow up if the biopsies are benign may be preferred. However initial surveillance and serial measurement of PSA levels with intervention if there is a consistent rise may be an equally acceptable management plan. Of course, if the patient himself decides at any time that he wants a biopsy to be certain of things, his wish should be granted.

Evidence is now accumulating to support the importance of PSA in early detection and potential cure. For example, the Surveillance, Epidemiology and End Results (SEER) database of 60,000 patients in the USA demonstrated major benefit from increased survival in men with Gleason score 5-7, where surgery was better than radiotherapy and both were better than watchful waiting.[3] More recently, a Scandinavian study of 695 men (median follow-up 6.5 years) demonstrated that death due to prostate cancer occurred in 31 (8.9%) of 348 patients assigned to watchful waiting, and in 16 (4.6%) of 347 assigned to radical prostatectomy.[4] Early diagnosis is beginning to pay dividends.

A further vexed question is the role of screening. There is concern that widespread PSA testing will diagnose clinically insignificant prostate cancer, and that the new cases discovered will not justify the huge expense of such a programme. Furthermore, men are not good at coming forward for screening. Our own analyses of the method of detection, and the role of the partner in diagnosis and management of prostate cancer reveals that a not insignificant number of men are first diagnosed by a PSA test instigated by their wife or partner. In a number of such cases, there is no doubt that the wife has saved her husband's life. One wonders if PSA were BSA ("breast specific antigen"), if national screening would be insisted upon by the women's health-lobby? Recent communications in the British Medical Journal[5] demonstrated clearly that things are changing and men increasingly want to be given the chance to manage their health in this respect. Two prospective randomised trials on screening are under way (ERSPC and PLCO) and we will have to await these results before making a judgement on this topic.

Improving the accuracy of PSA testing

It is clearly desirable to improve the specificity of PSA testing to increase its accuracy in detecting significant cancer. Several methods have been explored for this purpose.[6]

PSA Density

This is determined by dividing the PSA level by the prostate volume measured by transrectal ultrasound. The theory here is that prostate cancer secretes more PSA per volume than BPH. PSAD should therefore be

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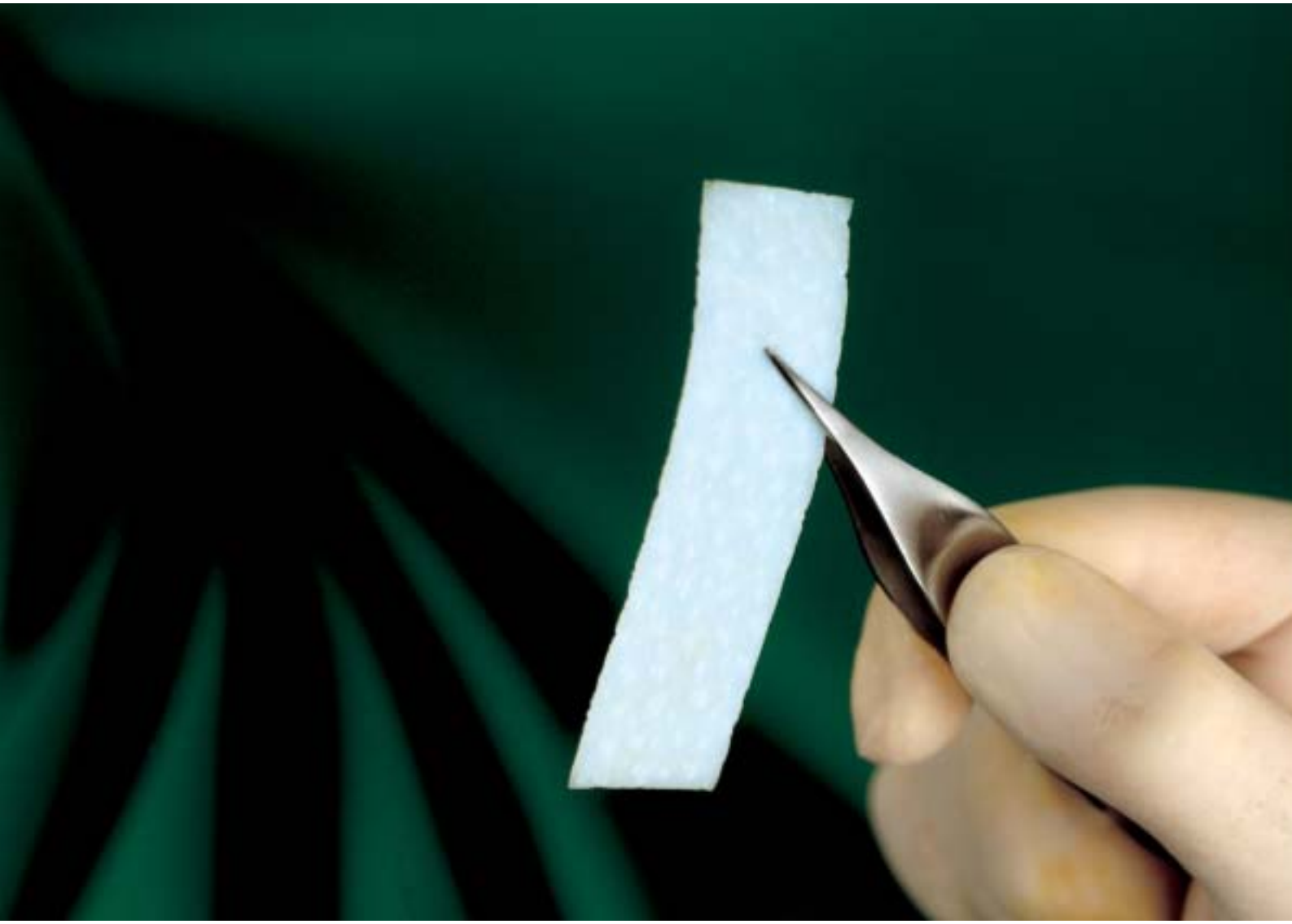

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higher in cancer patients. This practice has not been widely adopted however. TRUS is operator dependent, invasive and expensive, and can give false positive results from chronic prostatitis.

Free/total PSA ratio

PSA is mostly bound in serum to alpha-1-antichymotrypsin, a serine protease inhibitor. A small amount of PSA circulates in a free or unbound form. In cancer patients there is more complex bound PSA and less free PSA. Thus if the free/total PSA ratio is high, say above 0.25, the chance of cancer may be low; conversely if it is low, say 0.12, then the chance of cancer may be higher. Certainly in clinical practice, a marginally high PSA (say 5.2) and a low free/total PSA ratio (say 0.12) in a man of 58 would raise significant suspicions of the possibility of cancer and indicate the need for biopsy. This subject continues to be explored.

Complex PSA

Recent interest has been aroused by investigation of various complexed forms of PSA (cPSA). Results of studies have so far been divergent. Superior performance over total PSA and free/total PSA, total PSA but not free/total PSA, or neither, have all been found and studies are continuing.

PSA Velocity

Increase in PSA over time has also been investigated. This might be by PSA Velocity (PSAV), or PSA Doubling Time (PSADT). PSAV has been defined as an absolute annual increase in PSA . It is said that PSADT has advantages over PSAV in that it is independent of the initial PSA value, and is independent of the assay used so long as the same assay is used in a given patient (as mentioned above). Further developments are awaited.

Conclusions

There is no doubt that PSA testing has been one of the major developments in the management of prostate cancer in the last 20 years. It is leading to early diagnosis and curative treatment, but it is still not the perfect diagnostic tool. However, in men of 50 or over who have a 10 year life expectancy who have urinary tract symptoms or are undergoing medical checks, or who simply request it, the digital rectal examination and serum PSA are essential parts of their evaluation. The role of general screening is not yet clear. In men with a family history of prostate cancer, annual PSAs should be started at the age of 45. Further work into the various forms of the test should improve accuracy and specificity over the next few years.

It has been suggested that PSA can be regarded as standing for Promoting Stress and Anxiety. This is true to some extent; one sees it occasionally in men who have been treated by radical prostatectomy or radiotherapy and who are attending for their follow-up appointments. However, with proper usage and patient counselling, it might also be regarded as Preventing Serious Adversity. Current evidence suggests that increasing awareness of prostate cancer and its diagnosis both in the media and in primary care setting has reduced the level of psychopathology associated with its investigation and diagnosis, of which PSA testing is such an integral part. When this is accompanied by evidence that early intervention confers a significant survival advantage, it is clear that PSA testing is here to stay; it is up to the profession to explore every possibility to make such testing appropriate and accurate for the benefit of our patients.

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