Non-drug industry funded research

Poor access to drugs leaves important clinical questions unanswered

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In May 2004, the European Clinical Trials Directive came into force. The directive made it mandatory for all clinical drug trials to follow the good clinical practice guidance, and it fuelled existing concerns that financial and organisational constraints were making it almost impossible to conduct independent trials not funded by the drug industry. In the accompanying paper, Berendt and colleagues show that the decrease in the number of new clinical trials registered each year in Denmark began well before 2004, and the decrease was similar for independent and industry sponsored trials.[1] In 2006, two years after the enforcement of the EU directive, the number of independent trials actually increased. Similar results have been reported in Sweden, Norway, and Italy.[2] The consistency of these findings, despite differences in registration and classification systems, supports their validity and generalisability.

So can we feel reassured about the future of independent therapeutic research? Certainly, clinical research not sponsored by the industry is alive and active. Yet, if we consider the role that independent researchers should have in directing therapeutic research towards its primary mission—meeting the needs of patients and health systems—the overall picture is more complex. The data above do not tell us how the relevance and potential impact of the independent trials compare with industry sponsored trials. For instance, the Italian data show that phase III trials, multicentre trials, and international trials are less likely to be independent.[2]

The trials that showed the efficacy of aromatase inhibitors for early, hormone dependent, postmenopausal breast cancer provide an example of how the aims of industry sponsored trials may differ from those of independent trials. These trials compared the use of aromatase inhibitors with the conventional regimen of five years of tamoxifen.[3-6] The first published analyses of these trials, which in two cases were interim analyses that led to the premature cessation and unblinding of the trial, were conducted at median follow-ups of 2.2 to 2.7 years. All four trials found that aromatase inhibitors significantly improved disease-free survival, which is a plausible but not validated surrogate end point for overall survival in early breast cancer.[7] In contrast, no significant effect was seen on overall survival.

Because early breast cancer has a long natural history and aromatase inhibitors may have delayed effects, decisions on the use of these drugs in this setting should be based on reliable information on their long term efficacy and safety.[8] However, crossover of the control group to aromatase inhibitors in all but one[3] of these studies may hamper their ability to provide this information.[8] Furthermore, for ethical reasons, it is no longer acceptable to conduct a trial in which tamoxifen is given for five years as the control. Consequently, despite the inclusion of more than 20 000 patients in the above trials, aromatase inhibitors are being used to treat early breast cancer on the basis of inadequate information, and this information might never become available.

These trials were industry sponsored, but were conducted by some of the most prestigious and reliable international research groups in the area, and were virtually flawless from a methodological and statistical viewpoint. However, their design and results fit much better with the expectations of their sponsors than those of the patients and of the health systems that must sustain the costs of the new treatments.

Drug companies autonomously devise the strategies for the clinical development of promising new drugs and have the resources to implement these strategies. These are usually designed to pursue the registration of the drug by both the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products as quickly as possible, perhaps with an unrestricted indication. These aims are best met by conducting very large international trials on unselected populations. The large size provides high power against marginal treatment benefits, and—most importantly—in early interim analyses.

Independent researchers are left with no option but to join these large studies because the new drug is not available for use in independent studies. Truly independent trials are possible only after the drug has been approved for clinical use, but then the costs can be prohibitive. More importantly, the characteristics of the original trials (unselected patients, early results on surrogate end points of questionable validity) leave important questions unanswered, and these questions cannot be answered by second generation trials because of ethical constraints. Therefore, truly independent research is condemned to focus on less important questions (such as combinations and delivery strategies).

So what can be done? As Berendt and colleagues suggest, the ability of academic researchers to handle problems related to the guidance on good clinical practice can be improved by allocating relatively modest resources to dedicated units.[1] However, individual researchers and academic institutions have no power to influence the clinical research plans of drug companies. The medical

research community has some power, and it should rethink the terms of cooperation with industry in clinical trials, taking into account a wider clinical and public health perspective.[8] But it is up to governments, health systems, and regulatory agencies to identify new paths for drug development and to set new standards for the approval of new drugs. It is ironic that our health systems risk bankruptcy for the skyrocketing costs of drugs that were developed on their own patients using strategies that ignore the patients' needs and priorities.

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Overprescribing proton pump inhibitors

Is expensive and not evidence based

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Proton pump inhibitors are one of the most frequently prescribed classes of drug in the world because they combine a high level of efficacy with low toxicity. In 2006, expenditure on these drugs was £425m (€595m; $872m) in England[1] and £7bn globally.[2] Yet studies consistently show that proton pump inhibitors are being overprescribed worldwide in both primary and secondary care.[3-9] Between 25% and 70% of patients taking these drugs have no appropriate indication. This means that, at the very least, £100m from the National Health Service (NHS) budget and almost £2bn worldwide is being spent unnecessarily on proton pump inhibitors each year.

The first generic proton pump inhibitor (omeprazole) was introduced in 2002 and now comprises more than four fifths of all prescriptions for proton pump inhibitors in the United Kingdom. In the five years since the introduction of omeprazole, precriptions for proton pump inhibitors have doubled, although the reasons for the this rise are not obvious.[1] Despite this substantial increase in drug usage, the decrease in price means that overall expenditure on proton pump inhibitors has been falling in recent years.

Effective and less expensive alternative drugs, such as H_2 receptor antagonists are available for many patients. Yet prescriptions for proton pump inhibitors have superseded those for all other acid inhibiting agents and now account for over 90% of the NHS drug budget for treating dyspepsia.[1] Proton pump inhibitors cost more than other agents, which is partly why prescribing guidelines have been drafted in several countries. The National Institute for Health and Clinical Excellence (NICE) published its guidelines on proton pump inhibitors in 2000. Its recommendations for using these drugs—particularly in the long term—are relatively selective.[10] If prescriptions were restricted to the recommended indications, expenditure on proton pump inhibitors would be far less than 90% of the total dyspepsia drug budget. But what is the evidence that well established guidelines are not followed?

Although it might be assumed that overprescribing occurs mainly in primary care, evidence of inappropriate use of proton pump inhibitors in secondary care is abundant. In hospital inpatients taking proton pump inhibitors in Australia,[3] Ireland,[4] and the UK,[5] 63%, 33%, and 67% of patients did not meet their country's criteria for taking the drug. In a series of hospital inpatients in Michigan, USA, 20% of patients were taking a proton pump inhibitor on admission and another 40% were prescribed the drug during their hospital stay (mostly for prophylaxis). At discharge, half the patients were taking a proton pump inhibitor—more than double the number who were taking the drug when admitted.[6] In this study, 90% of patients did not need to take these drugs unless having gastro-oesophageal reflux at some time in the past is accepted as a reasonable indication.

Problems have been identified at the interface between primary and secondary care. A study from New Zealand found that 40% of hospital inpatients were taking proton pump inhibitors inappropriately.[7] Two thirds of these patients were still taking the drugs on discharge and most were still taking them six months later. In a UK centre, the suggested length of treatment with a proton pump inhibitor was specified in fewer than one hospital discharge letter in five.[5] Only a third of letters indicated a date for the prescription to be reviewed and only half specified why the drug was started.

Studies in primary care have come largely from Europe. In a Swedish cohort of patients who had been taking proton pump inhibitors for four years, 27% were able to discontinue the drug altogether.[8] A prospective audit of a series of patients admitted as a medical emergency to a hospital in Wales found that a quarter of patients were taking a proton pump inhibitor. In only half of the patients was the indication for the drug deemed appropriate.[9] The audit was repeated six months after the

NICE guidelines were disseminated to local practitioners. This repeat audit found that the same proportion of admitted patients were taking a proton pump inhibitor and again that only half of these had a recommended indication.

Proton pump inhibitors have been a tremendous therapeutic advance. Especially in the long term, they have transformed the lives of patients with previously intractable symptoms of gastro-oesophageal reflux with its associated complications, and they have also proved valuable for patients who are at risk of iatrogenic upper gastrointestinal pathology. A short term trial of a proton pump inhibitor is also a good option for treating a wide range of acid-peptic conditions. But the drugs are clearly being overused.

Some people will point to their combination of superior efficacy and high safety as a justification for using them in preference to drugs such as H_2 receptor antagonists. Yet, side effects should not be overlooked. An increase in the prevalence of pneumonia and *Campylobacter* enteritis is reported, as well as a doubling of the risk of infection with *Clostridium difficile*.[11] Acute interstitial nephritis and osteoporosis are unusual but recognised consequences of treatment with proton pump inhibitors.[12] Such effects are fortunately rare. The adverse effect of overprescription on drug budgets around the world is the real problem. Quite how to motivate doctors to follow guidelines is a matter of considerable importance.

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Home haemodialysis

Wide variations in availability exist, and the UK lags behind some other countries

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Home haemodialysis was pioneered in the United States and United Kingdom in the early 1960s. By 1971, 58.8% of patients on dialysis in the UK and 32.2% in the US received dialysis at home, mostly overnight three times a week. In 2005, these figures were only 2.7% and 0.6%. The poor availability in the UK is in spite of recent guidance from the National Institute for Health and Clinical Excellence (NICE) recommending that "all suitable patients should be offered the choice between home haemodialysis or haemodialysis in a hospital/satellite unit."[1] Estimates of the proportion of people eligible for home haemodialysis range from about 5% to 20%. In 2006, it was reported that the 44 units in the UK that offer home haemodialysis provided it to only 0.6-11.1% of patients; the remaining 21 units had no such programme.[2] This variation is mirrored in the US—in 2004, 0.2-2.4% of patients on haemodialysis were dialysed at home in 32 states, and no patients were on home haemodialysis in 18 states.[3]

So, how effective is home haemodialysis and why is its use declining? Home haemodialysis improves survival, quality of life, and the opportunity for rehabilitation compared with haemodialysis delivered to outpatients in a hospital or satellite unit; it is also more cost effective, mostly because of lower staffing costs.[4] It encourages independence, responsibility, and confidence in patients; it eliminates travel to a unit three times weekly; it is more convenient and comfortable; it allows patients to set their own schedule; and it reduces the risk of infection.[4] Most importantly, it allows more frequent and longer treatment, which further improves quality of life,[4 5] and seems to reduce mortality and admission to hospital.[5] Short daily sessions of dialysis almost normalise blood pressure, reduce left ventricular mass, and may improve anaemia and phosphate balance. Long nightly sessions of dialysis improve phosphate balance enough to eliminate the need for phosphate binders, and they also increase the clearance of toxic middle molecules (molecules that are larger than urea and creatinine).[5]

Disadvantages of home haemodialysis include the space needed for equipment and supplies, possible plumbing and electrical modifications, increased cost of utility bills, and the need for someone else to be in the home during treatment.[4]

As far as possible, patients should be self sufficient and independent. The importance of involving patients in their own dialysis care was recognised 40 years ago. Recently, the importance of self management of patients in chronic diseases in general has been emphasised.[6] As a result, the Department of Health developed a national initiative for England, which was based on the concept of the "expert patient."[7] However, this initiative does not seem to have been extended to patients on dialysis.

A wide variation in the use of home haemodialysis is also seen in other high income countries. In 2003, New Zealand and Australia had the highest use (58.4 and 39.0 patients per million population), followed by France, Finland, Scotland (8.7), Sweden, Canada, the Netherlands, and England and Wales (6.2); these figures were 4.6 for the US and less than 0.5 for Greece, Iceland, Norway, and Portugal.[8] Differences cannot be explained by variations in the use of other types of treatment, the prevalence of diabetic nephropathy, healthcare expenditure per capita, or population density. Interestingly, Finland had almost no home haemodialysis in 1998, but since a unit in Helsinki started a programme in 1997,[9] its use in 2003 was exceeded only by New Zealand, Australia, and France.[7] This proves that expansion of home haemodialysis is possible.

Reasons for the decline in the use of home haemodialysis include the increasing proportion of sick elderly patients and patients with diabetes who are more likely to have complications; lack of patient education; lack of experience among nephrologists, nurses, social workers, and administrators; and lack of available programmes at many dialysis units.[4]

So what has been the response to this decline? Home haemodialysis and more frequent haemodialysis are beginning to increase in the US. This has been sparked by reports of the benefits of more frequent haemodialysis for patients,[5] development of equipment that is easier for patients to use, and interest in providing home haemodialysis by the two companies that provide care to around two thirds of all patients on dialysis in the US (Fresenius and DaVita). These two companies now have more than 2000 patients on home haemodialysis. Between 2004 and 2005, the number of patients on home haemodialysis in the US increased by 7% and has probably risen by another 20-30% since 2006. The National Institutes of Health is undertaking a randomised controlled trial of more frequent haemodialysis compared with conventional haemodialysis three times a week.

Governments of the Netherlands, Australia, and British Columbia already endorse and support home dialysis and more frequent haemodialysis. In the UK, the 2007 report from the Royal College of Physicians and the Renal Association[10] hardly mentions home haemodialysis apart from a reference to the NICE guideline and a comment about developing services in line with good practice, as described in the national service framework for renal services for England,[11] which recommended implementing the NICE guideline on home haemodialysis by 2006. The challenge now is for the UK to reappraise the availability of home haemodialysis in line with the guidelines supporting it and with its uptake elsewhere.[12]

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Reducing hospital admissions

Guidance should be evidence based and take a holistic view of patient care

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In March 2007, the National Health Service (NHS) Institute for Innovation and Improvement published a *Directory of Ambulatory Emergency Care for Adults*.[1] The directory lists conditions that can be clinically managed outside hospital, with appropriate and prompt access to diagnostic services and specialist advice.

Admissions to hospital are an increasing source of pressure on health system resources internationally. In the NHS, changes to commissioning arrangements have increased the drive to reduce hospital admissions.[2] Unplanned admissions make up 36.7% of hospital admissions in the United Kingdom (4 659 054 emergency admissions in 2005-6).[3] The Department of Health has introduced a national target to reduce the number of emergency bed days by 5% by 2008.[4]

Most of the evidence on the cost effectiveness of reducing admissions comes from the United States. Ways to reduce admissions include case management, observation units for the evaluation of acute conditions, and the provision of home health care.[5 6] Research from other countries, such as Australia, highlights the international relevance of reducing avoidable hospital

admissions.[7] Therefore, the development and implementation of the directory in the UK is relevant to policy makers and clinicians in other countries.

The directory lists 49 clinical conditions for which admission to hospital could be avoided in 10-90% of cases. It advises that emergency admission to hospital should be limited to acute illnesses that can be managed only in a hospital bed. We support the principle that admissions should be appropriate, and we welcome evidence based guidance that helps clinicians to reduce inappropriate admission to hospital.

However, the derivation of the proportion of cases that should be managed in ambulatory care is unclear. One systematic review of the appropriateness of hospital admissions in the UK found that 6-20% of emergency medical admissions were inappropriate, depending on the appropriateness tool used, the sample, and the admitting specialty.[8] Similarly, a study in the US found that, depending on the method used, 2.3-12.4% of emergency medical admissions in people over 65 were inappropriate, and these admissions were not related to the overall numbers of medical admissions.[9]

The management of urgent medical problems has progressed since these studies were published. None the less, it is hard to reconcile these data with proposed reductions of up to 90% in admissions for some common causes of emergency admission—including chest pain, first epileptic seizure, and abdominal pain—especially when the evidence for these reductions is not referenced.

The directory refers to the concept of ambulatory emergency care, the implication being that emergency care is provided but the patient is not admitted to hospital. The use of this term is unfortunate, as it may be confused with ambulatory care sensitive conditions—admission can be avoided in these conditions if appropriate care is provided in the primary care setting.[10] A considerable body of work exists in the US, and a growing amount is being done in the UK, on ambulatory care sensitive admissions.[11] Some of the admissions listed in the directory—such as chronic obstructive pulmonary disease, congestive cardiac failure, and urinary tract infection—are ambulatory care sensitive. Initiatives to reduce admissions for these conditions are in place in primary care and community care, the resources needed to manage them without hospital admission are available, and their inclusion in a directory of ambulatory emergency care seems appropriate. However, other conditions—such as pulmonary embolism—for which the directory recommends 60-90% of admissions should be avoided, fit less well with the traditional concept of treatment in ambulatory care. The recommendation to treat patients with pulmonary embolism as outpatients is based on a consensus guideline and case control studies or cohort studies, not randomised controlled trials.[12]

Decisions on admission to hospital are usually made with a holistic view of the patient's current state of health, existing comorbidities, available social support, and the patient's concerns and expectations. The recommendations in the UK's directory pertain to an ideal situation, uncomplicated by these factors. The reductions in admissions proposed are based on many assumptions, such as the provision of diagnostic facilities that allow the needs of patients to be assessed reliably at the point of access; a decision on management involving providers of medical and social care; and the availability of services and infrastructure to implement alternatives to hospital admission.

The directory underplays many challenges encountered in day to day clinical care, including uncertainties in diagnosis and appropriate management; difficulties in effective communication between social services and medical services; the availability of appropriate alternatives to admission; the importance of information and knowledge of services among admitting clinicians; and the effect of incentives (such as time targets in the accident and emergency department) on the admitting clinicians.

Emergency admissions are expensive, they create difficulties for those responsible for planning and delivering services, and they are distressing for patients and their families. Well thought out evidence based initiatives to reduce inappropriate emergency hospital admission are to be welcomed. Future guidance, in the UK and internationally, should explicitly reference evidence on which recommendations are based, and should incorporate perspectives from social services, primary care, patients, and carers.

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Diabetes, cognitive impairment, and dementia

Are strongly linked, but the precise mechanisms are unclear

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The *Dementia UK* report, published earlier this year on behalf of the Alzheimer's Society predicts that by 2050, 34 million people worldwide will have dementia, and 71% of these people will live in developing countries.[1] Currently, nearly 700 000 people have dementia in the United Kingdom, and worldwide this figure approaches 18 million. Dementia costs the UK economy around £17bn (€24bn; $35bn) each year, but the human cost to patients, their families, and their friends is incalculable.

Over the past 15 years, several studies have indicated that diabetes mellitus, particularly type 2 diabetes, is associated with an increased risk of cognitive impairment and dementia.[2-4] If these studies are correct, then the future burden of dementia may be even greater than estimated as the prevalence of type 2 diabetes continues to rise.

Early data that linked type 2 diabetes with cognitive impairment came from cross sectional cohort studies that were generally of poor methodological quality.[4] However, a recent systematic review of prospective observational studies identified 25 articles that assessed the link between diabetes and cognitive impairment.[3] Although the studies did not usually subclassify the type of diabetes, the demographics of the people included suggest that they mainly had type 2 diabetes. Overall, people with diabetes had a 1.2-1.7 times greater decline in cognitive performance than those without diabetes. Moreover, people with diabetes were 1.6 times more likely to develop dementia. Perhaps predictably, given the association between diabetes and cardiovascular disease, diabetes conferred a 2.2-3.4 times greater risk of vascular dementia, but people with diabetes were also 1.2-2.3 times more likely to develop Alzheimer's disease. Most of the studies excluded people with cognitive impairment at baseline assessment and did not provide information on those lost to follow-up, who may also have had poorer cognitive function, so these studies may underestimate the risk of cognitive impairment associated with diabetes.

Why might diabetes increase the risk of cognitive impairment? In people with type 1 diabetes, cross sectional studies have suggested a direct association between cognitive function and retrospectively estimated exposure to severe hypoglycaemia.[5] However, the DCCT/EDIC (diabetes control and complications trial/epidemiology of diabetes interventions and complications) study found no association between the frequency of severe hypoglycaemia, over an average period of 18 years, and any decline in cognitive function in 1144 people with type 1 diabetes. It did, however, find an association between higher mean glycated haemoglobin concentrations and a moderate decline in motor speed and psychomotor efficiency.[6]

Microvascular disease is the hallmark of protracted poor glycaemic control in people with diabetes, so the association detected in the DCCT/EDIC study might be a consequence of cerebral microvascular disease. Direct in vivo evaluation of the cerebral microcirculation is difficult in humans and requires sophisticated neuroimaging techniques, which preclude the study of large numbers of people. The microvasculature of the retina, however, offers a window into the status of the small vessels of the brain, and studies in people with and without diabetes have shown an association between retinal microvascular abnormalities and cognitive function.[7-9]

Shorter term changes in blood glucose concentrations may also affect cognitive function in people with diabetes. In one experimental study, an increase of blood glucose to 16.5 mmol/l for one hour was associated with specific impairments in working memory, attention, and mood in adults with type 2 diabetes.[10] Moreover, in a multicentre randomised trial, stricter glycaemic control over 26 weeks improved working memory in 141 adults with type 2 diabetes.[11] The relatively short timescale of these interventions (relative to the time it takes for microvascular changes to occur) imply that functional consequences of hyperglycaemia, such as altered cerebral blood flow or possibly osmotic changes in the brain, are likely to impair cognition.

Substantive longitudinal data are not available in people with type 2 diabetes to explore the relation between long term glycaemic control and cognitive function. Moreover, type 2 diabetes is a complex disorder that is not restricted to deranged glucose metabolism, so the cognitive impairments seen in people with this diabetes probably result from interactions between many other factors besides hyperglycaemia. Genetic predisposition, hypertension, dyslipidaemia, macrovascular disease, depression, and drug therapy could all contribute to cognitive impairment.

Dissecting out the relative importance of these factors is challenging. To facilitate this process, the UK Medical Research Council has funded a major prospective study of the risk factors for cognitive impairment in more than 1000 people with type 2 diabetes (the Edinburgh type 2 diabetes study; ET2DS). Ongoing multifactorial randomised controlled trials in people with type 2 diabetes have also included cognitive function as an outcome measure in a subset of participants.[12] Studies like these should help to clarify the relation between type 2 diabetes and cognitive impairment, so that appropriate preventative and therapeutic strategies can be developed.

All references are in the version on bmj.com