Antipsychotics and the risk of venous thromboembolism

A higher risk—so treatment should be tailored according to individual risk factors

Patients with schizophrenia have an increased risk of venous thromboembolism (VTE), and this might be associated with the use of antipsychotics, especially low potency drugs such as chlorpromazine and thioridazine. Among atypical antipsychotics, clozapine has consistently been associated with VTE in young patients with psychiatric illnesses, but evidence from large observational studies has suggested that other atypical antipsychotics carry a similar risk, especially among new users and elderly patients. So far, however, the possibility that the underlying psychiatric disorders themselves—and not the antipsychotics—are associated with VTE has never been excluded. This could occur, for example, by the increased concentrations of adrenaline seen during psychotic excitation increasing blood coagulation.

In the linked study, Parker and colleagues report a large population based case-control study that included primary care patients aged over 16 who were taking antipsychotics. In almost 99% of cases the reason for prescription of antipsychotics could not be ascertained. Most antipsychotics used were conventional agents, with prochlorperazine—probably given for nausea and vomiting—accounting for almost 80% of all prescriptions. The authors found that the use of antipsychotics was associated with a significantly increased risk of VTE (odds ratio 1.32, 95% CI 1.23 to 1.42). The validity of the findings is strengthened by the large sample size and the low potential for exposure and outcome misclassification because of the detailed source of data and adjustment for a large number of confounders.

The highest risks were for quetiapine (nearly fourfold increased risk) and for low potency antipsychotics rather than high potency ones. New users of antipsychotics seemed at greater risk than continuing users, and the effect was not seen in those who stopped taking the drug. These findings indicate that VTE is directly linked to the use of an antipsychotic, and that the risk of VTE increases early after starting the drug.

The mechanisms by which antipsychotics contribute to VTE remain elusive. Venous stasis can be exacerbated by excessive sedation. The metabolic abnormalities (dyslipidaemia, increased plasma concentrations of leptin and glucose, hyperhomocysteinemia, and weight gain) documented especially among users of atypical antipsychotics may be associated with decreased fibrinolytic activity, but they take months or years to manifest and occur only in long term users. Patients on conventional antipsychotics and clozapine have shown high levels of circulating lupus anticoagulant and anticardiolipin antibodies, but these are seldom associated with thromboembolism.

Changes in platelet function, plasma coagulation, or fibrinolysis are likely to be responsible for the increase in thrombotic events because VTE occurred early and during treatment of short duration; in addition, the risk of VTE was higher when antipsychotics were injected. Conventional agents, including chlorpromazine, fluphenazine, flupentixol, trifluoperazine, and haloperidol, have been associated with enhanced aggregation of platelets. Inhibition of 5-hydroxytryptamine 2A platelet receptors by clozapine, olanzapine, and risperidone can modulate receptor density and affinity but does not uniformly enhance platelet adhesion and aggregation. An effect of antipsychotics on platelets is supported by recent experimental findings.

Although VTE is treatable it has a three month mortality rate of 15-18%, and evidence is accumulating that the use of antipsychotics is an established risk factor for VTE. However, consistent with previous estimates, Parker and colleagues found a low absolute risk of antipsychotic related VTE (four extra cases of VTE per 10 000 patients treated over one year), and doctors should consider this risk when making clinical decisions. The rarity of such adverse events does not justify antithrombotic prophylaxis for patients on antipsychotics without other medical conditions for which such preventive treatment is indicated.

Despite their association with serious risks and few data to support their efficacy antipsychotics are widely used, and in 2008 they became the top selling drug class in the United States, ahead of lipid regulators and proton pump inhibitors. Despite efforts to improve non-drug based interventions, antipsychotics are often used, especially for the treatment of agitation in people with dementia.

In clinical practice we need to be able to identify the best candidates for antipsychotic treatment, such as those people with the lowest vascular risk profile who may respond short term and low dose treatment with antipsychotics because of individual pharmacogenetic characteristics, and those who may be more susceptible to developing side effects as a result of individual vascular risk factors possibly interacting with antipsychotics.
Is it time to revisit orphan drug policies?
Yes, for equity’s sake

The number of new treatments for rare disorders—so called orphan drugs—has increased over the past decade. This is a testament to the success of the Orphan Drug Act in the United States and the Orphan Drugs Regulation in Europe. The large number of treatments in late stage development indicates that this success is likely to be sustained. However, this poses a substantial challenge for healthcare systems because the prices charged for these drugs make it impossible for them to meet conventional measures of good value. Increasingly, access to orphan drugs is likely to be restricted, causing political problems for governments and reducing the return to manufacturers from their research investment.

To date, many healthcare payers have exempted orphan drugs from formal value assessment, arguing that society values equal opportunity for people with rare and common conditions enough to justify the high costs. Until now this has been assumed, rather than being based on robust evidence.

In the linked survey, Desser and colleagues asked a representative sample of the Norwegian general population whether society should pay more to treat rare diseases than it does for common diseases. They found that although respondents supported equality of access to health care for people with rare diseases they did not support providing care for people with rare diseases when the cost of that care was at the expense of people with common conditions. The implication from this study is that funding policies that take resources from the national healthcare budget to fund these treatments are not what the public wants.

Desser and colleagues’ study mirrors results emerging from two citizens’ juries held in Canada. After two and a half days of deliberation, the juries opted to take a health maximisation approach, most readily achieved by providing a sufficiently effective intervention to the largest number of patients. A preference for treating small numbers of patients was expressed only if the patients were severely ill and the treatment could produce substantial health gain to all of them, bringing them back to normal functioning. Relatively few patients with orphan conditions would meet these criteria.

The current model of developing and funding orphan drugs is not fit for purpose if it cannot deliver treatments at a price that healthcare systems can afford. In the short term, modifications to the system may help contain the excess health burden of funding orphan drugs. For example, drugs with multiple indications, such as imatinib and sildenafil, could be excluded from special funding schemes because the return on the investment is made by patients with non-orphan diseases receiving the drug. In addition, changes in clinical practice that would optimise cost effectiveness, rather than clinical effectiveness, might help. For example, doses of enzyme replacement therapy aimed at improving clinical outcomes rather than achieving biochemical targets might be more cost effective and affordable. Finally, the commercial attractiveness of the orphan drugs market, as shown by major drug companies’ moves to enter the market, suggests that there is room for more aggressive price negotiation.

In the long term, a fundamental change in the funding model will probably be needed, and lessons might be learnt from the strategies adopted for neglected diseases in resource poor countries. The high level of uncertainty about the sustainability of demand for new products is similar for orphan diseases and neglected diseases.

New treatments for neglected diseases are being developed through product development partnerships that bring together civil society (represented by academia), the public sector (government), and the private sector. These partnerships achieve superior development timelines and greater cost efficiency than purely public or private endeavours. As these technologies have moved to the later stages of development, advanced market commitments are being used to create a market of sufficient value to stimulate research, development, and the manufacture of new drugs. Advanced market commitments provide industry with the security of demand needed to invest in manufacturing capacity and healthcare systems and the security of supply needed to plan the large scale introduction of new technologies.

The parallel between the challenges of developing and implementing treatments for neglected diseases in developing countries and treatments for orphan diseases in developed countries is increasingly strong; the question is whether the solutions developed for neglected diseases can be adapted for orphan diseases.

Decision makers will probably be reluctant to take up the fiscal challenge of orphan drugs. Each orphan drug treats a small number of individuals. Each individual provides a persuasive human story that supports funding treatment. Experience has shown the power of individual stories in healthcare funding debates. However, if decision makers wish to act on society’s values, Desser and colleagues’ results indicate that they will need to make hard choices to ensure that the anonymous many are not harmed to benefit the identifiable few.

Competing interests: In the past three years CMcC has served on advisory boards for Celgene and GlaxoSmithKline, which manufacture orphan drugs; CMcC serves as a scientific adviser to the Biotherapies Development Association, which promotes academic and policy debate around access to oncology treatments including orphan drugs, receives funding from pharmaceutical companies, and has met CMcC’s expenses for attending three workshops; DM has received non-personal funding from the Canadian

12 Kuehn BM. Questionable antipsychotic prescribing remains common, despite serious risks. JAMA 2010;303:1582-4.
The global spread of bacteria carrying the New Delhi metallo-β-lactamase-1 (NDM-1) enzyme through India, Pakistan, and the United Kingdom—and now half a dozen other countries—has sparked much media coverage. The outbreak’s importance stems from the broad resistance to all antibiotics except tigecycline and colistin seen in bacterial strains carrying the gene for NDM-1 and from the ready transmission across borders. The original report of NDM-1 cautioned against medical tourism, suggesting the costs of contracting treatment resistant infection outside the UK might well outweigh the savings of lower priced care abroad. The naming of NDM-1 after New Delhi—it’s purported place of discovery—further vexed Indian government officials worried about potential fallout for the country’s burgeoning medical tourism industry. This added drama has distracted attention from what ought to be the main plot of this story.

Modern advances in health care, from organ transplants to cancer chemotherapy, are reliant on effective antibiotics and vulnerable to resistance. Multidrug resistant strains are no longer an isolated phenomenon, nor confined by political borders. To India’s credit, the government is preparing a policy on rational use of antibiotics. Healthcare leaders gather on 22 September 2010 for the World Medical Tourism and Global Healthcare Congress in Los Angeles, and these topics ought to be on their agenda.

Restricting medical tourism will not result in effective quarantine. Foreign travel alone resulted in healthy Swedish volunteers becoming colonised with extended spectrum β-lactamase-producing bacteria. Nor are outbreaks of resistant strains limited to hospitals in low income and middle income countries. Meticillin-resistant Staphylococcus aureus (MRSA) was first reported in the UK in the 1960s and has since spread worldwide. Antibiotic use and resistance levels vary widely even among countries in the European Union.

With a dearth of novel antibiotics in the pipeline, the conservation of existing ones is imperative. Infection control and rational antibiotic use are central to such efforts, but it is also susceptible to the failure of collective action. No hospital can remain an island if other community institutions are not doing their part in infection control. The spread of NDM-1 also suggests that globalisation has redefined the bounds of community. To tackle antibiotic resistance, all involved must “think globally, act locally.”

Hospitals engaged in medical tourism can make a difference. These institutions seek to deliver the latest in medical advances to patients. In 2007, 750 000 Americans travelled abroad for treatment, and 417 000 non-citizens came to the United States seeking medical care. By 2012, the global market for medical tourism is projected to rise to $100bn (£63.8bn; €76.1bn). Delivering high quality care depends on keeping antibiotic resistance in abeyance.

Hospitals engaged in medical tourism are often beacons of quality care in their local healthcare systems. However, in otherwise resource-limited settings, these hospitals can present concerns of health inequity, where patients who can pay receive the best of care, but others just outside their doorsteps cannot. This is, of course, still true in the United States, even after recent healthcare reforms. But such hospitals are particularly well positioned to show leadership in reducing the spread of resistant pathogens.

Increasingly, accreditation organisations like Joint Commission International work with institutions seeking globally recognisable certification on quality measures like infection control. In 2007 only 125 hospitals were accredited abroad for treatment, and 417 000 non-citizens came to the United States seeking medical care. By 2012, the global market for medical tourism is projected to rise to $100bn (£63.8bn; €76.1bn). Delivering high quality care depends on keeping antibiotic resistance in abeyance.

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Hospitals engaged in medical tourism can lead by example. These institutions could pledge to a process to improve infection control and to measure performance for accountability. Such efforts in relation to coronary artery bypass graft surgery have led to the voluntary reporting of risk adjusted outcomes in an online report card.  

How can institutional commitments translate into collective action? The World Health Organization’s World Alliance for Patient Safety and the Institute for Healthcare Improvement’s 5 Million Lives Campaign offer some lessons. Eight hospitals in different countries used a shared surgical safety checklist and lowered death rates and complications as part of the WHO’s Safe Surgery Saves Lives campaign. The 5 Million Lives Campaign enlisted more than 4000 hospitals in the United States to undertake interventions to minimise medical harms. The campaign developed a methodological approach to track progress, including the use of triggers to identify adverse events. A system of monitoring will help ensure that accountability will follow commitment. From reducing MRSA infection rates to preventing surgical site infections, such tools can provide a foundation for stronger infection control efforts. For the medical tourism industry, crisis could turn into opportunity. Will they and others rise to the challenge?  

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work. One author (RNV) was a member of Action on Antibiotic Resistance (ReAct) and was chair of the WHO/World Alliance for Patient Safety working group on antimicrobial R&D. AH is the executive director of ReAct and served as a member of the WHO/World Alliance for Patient Safety working group on rational use of antimicrobials. AH also works part time for the Swedish Strategic Programme against Antibiotic Resistance (Strama)/Swedish Institute for Infectious Disease Control.

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Hip resurfacing

Despite safety warnings, it remains an effective option in certain subgroups

Metal on metal hip resurfacing is a type of hip replacement or arthroplasty where the head of the femur is preserved and shaped to receive a metal cap or resurfacing. This is different from a total hip replacement where the femoral head is excised and the prosthesis sits in the femoral shaft.

Recent results for hip resurfacing in several national joint registries and the orthopaedic literature have raised concerns. On 22 April 2010 the Medicines and Healthcare products Regulatory Agency (MHRA) issued a device alert for all metal on metal hip replacements, most of which will be hip resurfacings. This, together with reports in the lay press, have raised concerns among patients and healthcare professionals.

Total hip replacement, as distinct from hip resurfacing, is one of the most successful surgical procedures in terms of quality adjusted life years, second only to smoking cessation in terms of cost-benefit analysis using these measures.

Despite this, about one in 10 patients is dissatisfied with their outcome. The worst results in terms of implant survival have been seen in young, physically active men. The 2004 Swedish arthroplasty register reported that a 73.5% implant survival rate at 13 years in 3122 men under 50 years of age compared with 95.7% in 30809 women older than 75. With current technology, younger patients are therefore destined to need multiple hip replacements in their lifetime. Functional outcome deteriorates after multiple revisions in these people. Consequently, surgeons try to avoid total hip replacement in younger patients. Hip resurfacing can delay this process by adding an additional step before total hip replacement.

The national joint registry for England and Wales reported a three year revision rate for all hip resurfacings of 4.5% (95% confidence interval 4% to 5%; n=1 1770) compared with 1.3% (1.2% to 1.4%; n=86 524) for total hip replacement with a cemented femoral stem. However, in men under 55 the three year revision rates were similar for hip resurfacing (3.7%, 3.0% to 4.7%; n=3 131), uncemented total hip replacement (3.3%, 2.6% to 4.2%; n=3 407), and cemented total hip replacement (2.5%, 1.7% to 3.7%; n=1 136). Overall, the variation in performance between the different resurfacing designs was far more striking. The best, in terms of survival, was the Birmingham Hip Resurfacing manufactured by Smith and Nephew, Memphis, TN, USA (3.3%, 2.9% to 3.9%; n=6 746) and the worst was the Articular Surface Replacement manufactured by Depuy, Warsaw, IN, USA (7.5%, 5.9% to 9.5%; n=13 332). This last design is no longer marketed in the United Kingdom.

In the Australian national joint replacement registry the overall eight year revision rate for total hip replacement was 4.9% (4.7% to 5.2%; n=147 422), and for hip resurfacing it was 6.1% (5.3% to 6.9%; n=12 093). In men under 55 years...
with osteoarthritis, and in the absence of infection, the seven year revision rates were similar for these procedures. Women have significantly poorer results for hip resurfacing and this is because they tend to have smaller components implanted. Smaller components (femoral head diameter ≤44 mm) had a four times greater risk of revision at seven years than larger components (femoral head diameter ≥55 mm). The biomechanical basis for this difference is unclear.

Preoperative planning using radiographs should allow surgeons to identify who would be likely to receive smaller components so that alternative types of hip replacement can be considered. Alterations to the selection criteria for hip resurfacings have been successful in the past. An increased risk of femoral neck fracture was seen in perimenopausal and postmenopausal women as a result of hormone related bone density changes. Excluding these patients successfully reduced this complication.10

Perhaps the most worrying complication of metal on metal hip replacements is the development of pseudotumours. They seem to be related to excessive wear states in these metal on metal hip joints and subsequent metal ion hypersensitivity reactions, which can in extreme cases severely damage the tissues around these artificial joints. The concerns over this complication largely prompted the MHRA device alert. Although it is potentially disastrous, this complication is thankfully rare, affecting about one in 1000 metal on metal hip replacements. The risk of an implant becoming infected after any type of joint replacement is also troubling and has formed part of the informed consent for these operations for many years. The risk of infection after joint replacement is 10-20 times that of developing a pseudotumour. Polyethylene wear debris produced by traditional total hip replacements also results in an inflammatory reaction that is behind most cases of eventual failure of these implants, although this occurs over a longer time period.

Hip resurfacing is a technically demanding procedure, and metal on metal implants do not tolerate poor positioning.11 12 Certain designs are much more sensitive to poor positioning than others, and this is likely to be related to design differences. The basic science behind our understanding of how large head metal on metal joint replacements work is incomplete, and more work is needed on how they function in the human body rather than in the laboratory. Retrospective studies assessing the risk of cancer after metal on metal joint replacements from the late 1960s and early 1970s have been reassuring.13

Direct comparison between hip resurfacing and total hip replacement might not be justified. The two designs differ considerably and they might have different indications. The threshold for revision of hip resurfacing, particularly in the current climate, may also be lower than that for revision of a total hip replacement. The number of hip resurfacing procedures being performed has reduced dramatically as surgeons and patients become alarmed by the headline figures. Yet a closer look at the data shows that the operation is effective in young men in whom the orthopaedic community has been struggling to find reliable longer term treatment strategies. The combination of hip resurfacing followed by total hip replacement when the resurfacing fails remains an attractive and rational option.


Oil, health, and health care

Future health and prosperity require that we prepare for life without cheap oil

The April 2010 oil leak in the Mexican Gulf illustrates the risks being taken to extract oil from inaccessible fields, and in June a Lloyd’s 360° risk insight report said, “We have entered a period of deep uncertainty in how we will source energy for power, heat and mobility and how much we will pay for it.” The reason why such damaging extraction methods are pursued, and why Lloyd’s are telling us we face a “new energy paradigm” rather than normal market volatility, is that oil discoveries peaked 40 years ago, and oil supply is probably at its maximum, with decline soon to follow. This has substantial implications for transport, food, jobs, health, and health care. Yet many people still haven’t heard of “peak oil” and few are discussing it.

The International Energy Agency says that we are running out of time to build the skills, systems, and infrastructure needed for a prosperous future. They forecast a depleted energy supply in the next decade. Energy availability underpins economic growth, and without the opportunity for future repayment of debt the financial system as we know it could stop working.

The science of peak oil is not difficult. Nation by nation, oil discovery has risen then declined in a bell shaped curve.
Health care is rationed and some conditions cannot be treated. Exponential growth in world population, debt, environmental damage, and rate of depletion of natural resources all link back to this energy rich, highly versatile, and easily transportable fuel. There is nothing equivalent to replace it.

Until 2005, the United Kingdom was a net exporter of North Sea oil and gas. Now the UK relies increasingly on imports. Government forecasts for fuel supply include a major portion yet to be determined. On March 22 the Department for Energy and Climate Change held a seminar, under Chatham House rules, examining “potential future oil supply constraints.” Jeremy Leggett of the UK industry peak oil taskforce, commenting to the Guardian, said “Government has gone from the BP position—‘40 years’ supply left, the price mechanism works, no need to worry’—to ‘crikey.’” It is too early to say how this might be reflected in the new coalition government’s policies.

Some cities in the UK are aware of peak oil implications. For example, leaders in Bristol commissioned a report in 2009 on the implications of peak oil. This has helped stimulate work to develop a Bristol Energy Company and a local currency, to analyze the vulnerabilities of the current food supply system, and to adopt a “climate change and energy security framework.” Incorporating peak oil preparedness into England’s official local government planning mechanisms—local transport plans and local development frameworks—is an uphill struggle because central government policies still favor the needs of big food corporations, construction industries, and the road lobby above the need for resilient local systems.

The healthcare conclusions in Bristol’s peak oil report are that oil is a primary raw material for many drugs, equipment, and supplies; that transport for patients, staff, deliveries, and services is heavily oil dependent; that currently suppliers are not required to provide business continuity plans around fuel supply shortages; and that rising oil costs would seriously affect health service budgets. On the positive side, the report noted the resilience afforded by the following facts: most people live within a mile of their nearest general practice; the NHS is used to responding to emergencies and making rapid changes; walking, cycling, and locally grown food are good for health; and the NHS Carbon Reduction Strategy for England does acknowledge peak oil. What this means is that health care will change, whether we like it or not, and that carbon reduction, fuel depletion, and financial stringencies have to be looked at together.

Experts on peak oil and health experts have examined this challenge together at three workshops, and some common themes emerge. These concern the need for simpler more robust systems that are capable of local maintenance, and the importance of fairness regarding access to food, water, transport, and essential health care. The box summarizes possible features identified as characteristic of a healthy prosperous society in the future. Because the workshops explored success not failure the goals may appear idealistic. The alternative could be very different.

Until recently, peak oil was mainly seen as a crackpot theory promulgated by doom merchants who hate progress. This probably reflects the influence that corporate public relations and pressure to preserve confidence in global markets have on the mainstream media. The Bristol peak oil report and Chris Martenson’s Crash Course are the first steps towards changing this attitude.

Summary outcomes from three future forecasting workshops examining effects of peak oil on health and health care

Features of a society that has successfully reduced its reliance on fossil fuel:

**Healthcare facilities, equipment, supplies**

All essential drugs are now produced without petrochemicals, some locally

Energy intensive and high cost methods of diagnosing and treating illnesses are a thing of the past

The most essential and best value aspects of modern health care have been preserved; those of only marginal benefit have been abandoned

All NHS estate is a net energy generator

Every NHS facility is accessible on foot, by bicycle, and by public transport

Digital infrastructure is used for high priority communication, including that between patients and health services

Landline telephone and radio are important

**Health and recreation**

Health and physical resilience are highly valued, and it is regarded as normal to safeguard health through the way that we live and work

Physical activity is for most people a non-negotiable part of everyday life, food is plainer but healthier, and local breweries are numerous

Local drama, art, music, dance, and celebration are commonplace

**Land and the built environment**

Towns and cities have high density housing—more lodgers, more boardroom houses, and more shared housing

All land and space that can be is used for food production. Many more people are employed in food growing and preparation, and people’s involvement with food is far greater

Many people work from home, or from shared “work cafes”

**People**

Communities have a network of registered volunteer carers and emergency helpers

Everyone participates in training within the local community

Everyone does some form of volunteering work for their local community

Health professionals work closely with informal carers

Every community has an emergency plan

Health care is seen as a community resource with priority given to those with greatest needs

**Rules**

There are local exchange trading schemes and local currencies

Legal structures are different, limited liability is gone, drivers of growth are gone, and the ability of an individual to pursue economic challenges is gone

The norm is for systems designed for the prosperity of the community and the preservation of non-renewable resources

Health care is rationed and some conditions cannot be treated.

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