EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials
See http://resources.bmj.com/bmj/authors/types-of-article/editorials for more details

Response on bmj.com

"It is wise to consider all of the many serious conditions caused by use of hormonal contraception including the increased risks of suicide and breast cancer." Ellen CG Grant, retired medical gynaecologist, Kingston-upon-Thames, Surrey
Visit the article online and click "Respond to this article" to have your say.

Is an EMA review of hormonal contraception and thrombosis needed?

Sufficient evidence exists to recommend lightest tolerable second generation pill for all indications

Frans M Helmerhorst professor in clinical epidemiology of fertility
F.M.Helmerhorst@LUMC.nl
Frits R Rosendaal professor in clinical epidemiology, Leiden University Medical Center, 2300 RC Leiden, Netherlands

BSIP, B BOISSONNET/SPL

French drug authority L'Agence Nationale de Sécurité du Médicament recently banned Diane-35

Four recently reported deaths in women using the Diane-35 contraceptive and a lawsuit against the French drug authority (L'Agence Nationale de Sécurité du Médicament) after it banned Diane-35 led the authority to request that the European Medicines Agency (EMA) review the safety of combined oral contraceptives.[1 2] Of particular concern were third and fourth generation drugs, including Diane-35 and its generics. This review was granted on 7 February 2013.[3 4] The Dutch College for the Evaluation of Medicines (Dutch "EMA") decided that a new study on Diane-35 was in order.

Most oral contraceptives are combination preparations, containing a progestogen, to prevent ovulation, and an oestrogen to prevent breakthrough bleeding. Since the introduction of the pill, the oestrogen dose, in the form of ethinylestradiol, has been reduced (heavy *v* light pills) and the type of progestogen has changed several times (indicating the generation). The categorisation is imprecise and incomplete. For example, cyproterone acetate, the progestogen in Diane-35, does not belong to a generation. Furthermore, the categorisation assumes that all side effects of oral contraceptives are class effects. In our recent network meta-analysis of all combined oral contraceptives (unpublished data), we found that the risk of venous thrombosis depended on the dose of oestrogen and the type of progestogen, even within generations.

Many studies have shown that oral contraceptive users have an increased risk of venous thrombosis (deep vein thrombosis, pulmonary embolism) and arterial thrombosis.[5 6] Venous thrombosis is more common than arterial thrombosis, but in young women the incidence of these side effects is low. Even the "safest" oral contraceptive increases the risk of venous thrombosis, however, and the risk is twice as high for oral contraceptives containing a third generation progestogen, drospirenone (sometimes called fourth generation), or cyproterone acetate.[5] This knowledge is not new—the increased risk for pills containing third generation progestogens, cyproterone acetate, and drospirenone has been known since 1995, 2001,[7] and 2003, respectively.[8]

The EMA's public report at the beginning of the review states that Diane "works by blocking the effects of a class of hormones called androgens,"[3] and that this is responsible for its supposed benefits on acne and hirsutism. However, as early as 2004 (and in three updates) a systematic review concluded that all types of monophasic combined oral contraceptives are effective against acne.[9]

All combined oral contraceptives are equally effective in preventing pregnancy. Their side effects (such as weight gain[10]) and benefits (in terms of acne and hirsutism) are also similar, so the only rational strategy is to use the safest one with regard to venous thrombosis. The common arguments that the risk of thrombosis is low or that the risk of thrombosis during pregnancy is higher than when using oral contraceptives are flawed. Millions of women in Europe use oral contraceptives, so use of the pill with the best safety profile in terms of thrombosis would probably prevent thousands of thrombotic events and hundreds of deaths a year. Because the pill with the safest thrombosis profile is as effective at preventing pregnancy as the less safe ones, the risk of thrombosis in pregnancy is irrelevant in the choice of oral contraceptive. The safest oral contraceptive is one that contains the lowest tolerable dose of ethinylestradiol (lowest dose that prevents breakthrough bleeding—30 µg[11]) together with the second generation progestogen, levonorgestrel.

Sufficient evidence is already available on which clinicians and regulatory agencies can base their decisions, so lengthy evaluations, let alone new studies, are not needed.

In his 2011 *BMJ* editorial, Nick Dunn recommended prescribing an oral contraceptive that contains levonorgestrel unless "there is a persistent reason to use another type."[12] Because oral contraceptives containing levonorgestrel and the lowest tolerable dose of oestrogen are also adequate for the treatment of acne or hirsutism, we can see no reason to use another type. Third and fourth generation oral contraceptives are widely overprescribed.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2013;346:f1464

bmj.com Neurology updates from BMJ Group are at www.bmj.com/specialties/neurology

Cognitive deficits and mild traumatic brain injury

New study identifies risk factors and raises questions about the nature of any implied causal association

V F J Newcombe academic clinical fellow in emergency and intensive care medicine
D K Menon professor of anaesthesia, Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

Between 7% and 33% of patients who have "mild" traumatic brain injury (sometimes called concussion) develop persistent post-concussion syndrome, which may last weeks to months after injury.[1] More than 15% have a measurable cognitive deficit at one year.[2 3] There is growing interest in the syndrome of post-traumatic encephalopathy,[4 5] which may follow a blast injury or repeated sports related concussion. However, despite this growing literature on the cognitive consequences of mild traumatic brain injury, our knowledge of risk factors that predispose people to sustaining such injury is limited.

In a linked paper, Nordström and colleagues examine the associations and temporal associations between a history of concussion, cognitive function, academic achievement, and measures of social wellbeing in a cohort of more than 300 000 Swedish conscripts.[6] Given the paucity of data on premorbid neurocognitive testing in traumatic brain injury, this paper draws on an impressively large dataset that allows comparison of neurocognitive function before and after such injury in a nationwide cohort of Swedish men.

The results complement an earlier study from the same group, which examined the association between cognitive performance and incidence of a subdural haematoma.That study concluded that low global intelligence in adolescence was a risk factor for subsequent development of a subdural haematoma.

Although the current study investigates a more common diagnosis, case ascertainment was probably less precise than the more clearly definable endpoint of subdural haematoma. The case ascertainment of "concussion" that the authors used was based on the *International Classification of Diseases* and probably represents the best epidemiological approximation achievable in the administrative databases that were searched. However, a substantial proportion of patients with mild traumatic brain injury are never admitted to hospital or seen in the outpatient setting. Therefore, this study probably underestimated the incidence of this condition in the study population. Conversely, the approaches used may not have fully excluded subjects who sustained a moderate or severe injury. Cross correlating multiple sources of data could mitigate against this source of confounding, which is common when administrative datasets are analysed.[8]

JAMES DAVIES/ALAMY

Poor cognitive performance linked to concussion

Despite these caveats related to case ascertainment, Nordström and colleagues' study provides unique insights into the epidemiology of mild traumatic brain injury. Unsurprisingly, poor cognitive function, low educational status, and other risk factors were associated with mild traumatic brain injury. However, surprisingly, the association between cognitive function and concussion did not depend on the temporal association between the two and was just as common when poor cognitive performance preceded concussion. In addition, similar cognitive scores were seen before and after injury in twins discordant for mild traumatic brain injury, which suggests that both genetic and environmental influences contributed to the low cognitive function found. Other strong independent (but not unexpected) risk factors for development of mild traumatic brain injury included a previous episode of brain injury, hospital admission for intoxication, and low education and socioeconomic status. Surprisingly, the analysis found no significant differences in cognitive performance before and after the index event in men who sustained an injury.

These results are important for several reasons. Firstly, they identify potential risk factors for mild traumatic brain injury and could help guide attempts to investigate prevention strategies, perhaps through education initiatives (particularly in accessible populations such as the military conscripts investigated here). Secondly, they provide a context for interpreting studies that measure cognitive function after injury only and compare it with matched controls from the general population, with the assumption that those with brain injury have similar pre-injury characteristics to the general population. The results of this study suggest that such assumptions may be incorrect. Finally, those who subsequently sustained a mild traumatic brain injury had similar cognitive performance to that of those who had previously sustained such an injury, which implies that the injury itself may not reduce cognitive function. However, the tests used (word recollection; visuospatial geometric perception; logical and inductive performance; and mathematical and physics problem solving) have not been validated as sensitive measures of changing performance in cognitive areas thought to be affected by mild traumatic brain injury. These tests may therefore have missed important changes.

It is important that additional studies attempt to replicate these findings. Suitable populations for such studies include other military cohorts and cohorts of people who practise contact sports, which are associated with a relatively high incidence of mild traumatic brain injury. Such studies must take account of "gaming" by soldiers and sportspeople, who allegedly choose to perform suboptimally on pre-injury cognitive screening to hide evidence of any post-injury cognitive decrement, thus enabling them to stay with their units and teams. Although it may not be easy to control for such confounding, more studies like the current one will increase our understanding of the epidemiology, pathophysiology, and outcome impact of traumatic brain injury.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2013;346:f1522

Underlying the debate about the precise wording of the regulations is the much more important question as to the government's intentions on the role of markets in the NHS

Regulating the NHS market in England

The government must make its intentions clear as it rewrites the regulations on competition

Chris Ham chief executive, King's Fund, London W1G 0AN, UK C.Ham@kingsfund.org.uk

The government's draft regulations on procurement, patient choice, and competition, published in February, have opened up old wounds in the debate about NHS reform. The regulations set out in detail how commissioners should procure NHS services under section 75 of the Health and Social Care Act 2012. The stated aim of the regulations, which will be enforced by Monitor as the economic regulator, is to ensure that the NHS Commissioning Board and clinical commissioning groups act to protect patients' rights and to prevent anti-competitive behaviour.[1]

The government claims that the regulations follow from commitments given during the passage of the 2012 act and are consistent with the "Principles and rules for cooperation and competition" put in place by the previous administration. Its critics contend that they go much further and represent a major extension of market principles in the NHS. In this they are supported by legal advice, which argues that commissioners of NHS services will be expected to make greater use of tendering, with competition becoming "the norm for placing NHS contracts."[2]

The government's critics comprise general practitioner leaders who are worried that clinical commissioning groups will have to use tendering to procure all services; Liberal Democrat MPs and peers who fear this will make it more difficult to promote integrated care; and opposition politicians who interpret the regulations as confirmation that ministers are hell bent on opening the NHS up to the private sector. In the face of these concerns, the government has announced that it will amend the regulations to ensure that they are not open to misinterpretation. Statements made by ministers indicate that this means commissioners will not have to tender all services, Monitor will not force commissioners to tender competitively, and competition will not take precedence over cooperation and integration.[3]

The decision to make these changes less than a month before the provisions of the 2012 act come into effect is embarrassing for the government. It reflects both the influence of the Liberal Democrats within the coalition and the need to retain the support of GP leaders, who will play a key role in the work of clinical commissioning groups. If these leaders had walked away at this stage, the edifice on which the reforms are based might well have crumbled to the ground even before it had come into being.

Underlying the debate about the precise wording of the regulations is the more important question of the government's intentions regarding the role of markets in the NHS. On this question there is room for legitimate doubt in the light of the debate on the 2012 act and the amendments made after the work of the NHS Future Forum. Particularly important was the change to Monitor's role from an original duty to promote competition to a revised duty to protect and promote the interests of people who use healthcare services, and in so doing to prevent anti-competitive behaviour.

These amendments may have watered down Andrew Lansley's ambitious plans to apply market principles to the NHS, but the architecture of economic regulation set out in part 3 of the 2012 act remains in place. A key element in this architecture is the role that the Office of Fair Trading (OFT) and the Competition Commission will play in the future NHS. In the debate about the regulations, the involvement of the OFT in assessing the proposed merger of two NHS foundation trusts in the south of England has gone largely unnoticed. The OFT is also investigating the proposed merger of an NHS foundation trust and an NHS trust in Torbay, which is designed to bring about closer integration of services in an area well known for its innovative approach to the care of older people.

The question this raises is whether this kind of market regulation is needed in the NHS in addition to the new role of Monitor? There are many differences between healthcare and the industries that OFT and the Competition Commission regulate, and there is a danger that regulators with experience in other sectors will adopt an approach that is not sensitive to these differences. Overexuberant regulation of mergers could delay the implementation of service changes that may benefit patients—for example, by preventing the full integration of care as is being proposed in Torbay.

It is worrying that fundamental questions of this kind are unresolved so close to the date of implementation of the reforms. Evidence that competition in healthcare is beneficial is both equivocal and contested.[4 5] Even where benefits can be delivered, these have to be set against the considerable transaction costs involved in contract negotiations between commissioners and providers and the work of the regulators. The well known limits to markets in healthcare mean that planning, collaboration, and clinical networks[6] should also play a major role in bringing about improvements in care.

Where markets are used, regulators need to be sensitive to the different forms of competition in healthcare. Competition in the market has a role in situations where patients have the time and inclination to decide where to obtain treatment—for example, when receiving planned care. Competition for the market should be the preferred approach when commissioners want different providers to work together under long term contracts to deliver integrated urgent care and care for groups such as older people and those with complex needs.[7] A nuanced approach that combines the right kind of competition alongside planning, collaboration, and clinical networks, where appropriate, is most likely to deliver the desired results.

If GP leaders and Liberal Democrats are to withdraw their opposition, the government needs to provide reassurance on its intentions with regard to regulating the NHS market. To avoid doubt, ministers must be explicit about the place of markets in the NHS, including the role of the OFT and Competition Commission, when they publish the revised regulations. Without absolute clarity on these questions, there is a risk of uncertainty and misinterpretation by the commissioners and regulators tasked with making the regulations and the 2012 act work in practice.

There is also every possibility that old wounds will not heal and will cause even deeper rifts within the coalition, which will create political difficulties for the government as well as unwelcome confusion for the NHS.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2013;346:f1608

The new UK antimicrobial resistance strategy and action plan

A major societal, political, clinical, and research challenge

Anthony S Kessel honorary professor, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK
Mike Sharland professor in paediatric infectious diseases, Paediatric Infectious Diseases Research Group, St George's University London, London SW17 0RE, UK
mike.sharland@stgeorges.nhs.uk

This week the chief medical officer highlighted in her report how the rise of antimicrobial resistance (AMR) poses a threat to healthcare delivery in the United Kingdom.[1] This will be followed shortly by the Department of Health's new UK Five Year Antimicrobial Resistance Strategy and Action Plan, which will reflect the need for a clear change in the understanding and response to AMR by the public, the NHS, and the government in the UK. The rise of AMR as a serious health threat is due to the international spread of multidrug resistant (MDR) Gram negative bacteria, the global overuse of antibiotics in humans and animals, and the almost complete lack of new antibiotic development.[2] All of these are now of direct concern to the NHS.

The 85% reduction in rates of meticillin resistant *Staphylococcus aureus* (MRSA) bloodstream infections seen in England between 2003 and 2011 has been remarkable. MRSA is now responsible for less than 2% of all bloodstream infections in England. Less remarked on has been the inexorable rise in the number of bloodstream infections attributable to Gram negative organisms (particularly *Escherichia coli*), which now comprise more than half of the around 100 000 of these infections reported in England annually.[3] Most large NHS hospitals now identify 50-100 times more patients with Gram negative bloodstream infections than those with MRSA, with antibiotic resistance rates of 10-20% and mortality rates of 30% reported for MDR forms.[4] In England the successful introduction of conjugate pneumococcal vaccine means that the number of reported *Klebsiella pneumoniae* bloodstream infections in England is now higher than for *Streptococcus pneumoniae*.

In many European countries AMR rates are much worse. In 2011 the European Centre for Disease Prevention and Control reported a significant increase in multidrug resistant *E coli* and *K pneumoniae* (for example, resistance to third generation cephalosporins, fluoroquinolones, and aminoglycosides) in more than a third of European Union/European Economic Area countries.[5] *Klebsiella* is an important pathogen in the spread of resistance. Many antibiotic resistance genes group together in plasmids easily transferred between bacteria, with particular clones carrying multiple resistance genes (for example, OXA-48 and CTX-M15). Many EU countries are now reporting *Klebsiella* MDR rates of 25-40%.

UK antimicrobial resistance strategy: seven action areas and likely stakeholder involvement in the health sector

Seven key areas of focus	Stakeholders
Promote responsible evidence based prescribing	Individual prescribers, NHS providers, national and local commissioning boards, ARHAI, PHE, Department of Health, professional bodies
Improve infection prevention and control	Individual clinical staff, NHS providers, national and local commissioning boards, ARHAI, Department of Health, PHE, professional bodies
Raise public and professional awareness of antimicrobial resistance threat and promote behaviour change	Professional bodies, Department of Health, ARHAI, patient groups
Research programme into new diagnostics, alternatives to antibiotics (such as antiseptics), pathogenesis, effective behavioural change to improve infection prevention and control and prescribing practice	NIHR, universities, Department of Health, ARHAI
Facilitate development of new antimicrobials, vaccines, and immunomodulators	Department of Health, drug industry, European Union
Improve surveillance and data linkage	PHE, ARHAI, Department of Health
Encourage international collaboration and data sharing and learning from best practice internationally	Department of Health, PHE

ARHAI=Department of Health Expert Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection; PHE=Public Health England. NIHR=National Institute for Health Research.

Globally, rates of MDR Gram negative bacterial infection can be even higher.[6] This has inevitably led to a rapid rise in the use of carbapenem antibiotics (for example, meropenem) as empirical treatment for suspected sepsis. In turn, this has led to a rapid increase in hospital outbreaks of carbapenemase producing organisms, which are usually sensitive to only one or two older less effective antibiotics. In the UK, there has also been a sharp rise in meropenem use and increasing reports of carbapenemase producing organisms. Only one or two new antibiotics that target Gram negative organisms are likely to be marketed in the next decade (http://antibiotic-action.com), which raises the concern that virtually untreatable infections will threaten routine NHS care.[7]

The new UK strategy is an important step in recognising and responding to these concerns. At its core the strategy recognises that AMR, infection prevention and control, and antimicrobial stewardship are closely interconnected and all need to be strengthened. The seven aims (table) reflect that all individuals and organisations have unique roles and responsibilities. Enhanced infection prevention and control are crucial to limiting the spread of MDR Gram negative bacteria, both into and across the NHS.

New challenges will include screening (by rectal swab) and isolation of any patient admitted to the NHS who has received inpatient care outside the UK, with rigorous control of any outbreaks of multidrug resistant infection inside the NHS. Acute trusts and their boards will need to consider how to strengthen infection prevention and control practice using new methods of organisational and behavioural change.

Antimicrobial prescribing needs to be more evidence based and more efficiently targeted. New NHS initiatives to provide antimicrobial stewardship guidance in secondary care (Start Smart then Focus) and primary care (TARGET antimicrobial toolkit)[8] need to develop into more formal quality indicators.

This strategy makes the UK the first country to explicitly announce its intention to develop national outcome measures in AMR using specific drug-bug combination resistance rates (for example, rates of *E coli* resistance to third generation cephalosporins). This is a brave move and should be welcomed. The chief medical officer has taken a clear leadership role by tackling the international dimensions of the problem, adding AMR to the Department of Health risk register and calling for AMR to be added to the national risk register (National Security Risk Assessment) to promote cross government action. Important areas that will be covered include antimicrobial use in animals and new initiatives to encourage the development of novel antimicrobials.[1]

The wider application of molecular microbiology, particularly whole genome sequencing, to detect clonal spread of MDR Gram negative bacteria within hospitals is providing a rapid explosion of new data. It is still unclear if this will lead to effective new control policies. The research agenda is extensive, but the NHS information technology and National Institute of Health Research infrastructures are well placed to provide global leadership in this area.[9] New technology focusing on rapid diagnosis of specific bacteria and resistance genes, along with combination biomarkers indicating bacterial or viral infections, especially if adapted to near patient testing, could have a major impact on targeting appropriate antibiotic treatment. Improved surveillance by Public Health England, using large dataset linkage combined efficiently with observational studies focused on clinical outcomes, including all infection related deaths, will also help to define new targets for intervention.

Competing interests are in the version on bmj.com.

Provenance and peer review: Not commissioned; externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2013;346:f1601