> The costs of inefficiencies are swallowed by the NHS. The sign might say "NHS pharmacy," but it is Pantone 300 blue lipstick on a corporate pig

NO HOLDS BARRED Margaret McCartney

Bring pharmacists into the NHS

Community pharmacists should work directly for the NHS, mainly in general practices, and not in private chemist stores. This intervention would be radical and unusual, directing people back towards the NHS rather than to private business.

I visited a local chemist's shop recently. On the counter were some healing crystals and on the shelves a plethora of homeopathic preparations. Nearby a sign, in official NHS Pantone 300 blue, offered NHS services such as stop smoking and repeat prescription orders.

Most pharmacies now have little rooms to accommodate confidential conversations, but a lot of wares—from cough mixtures[1] to topical agents for insect bites[2]—do brisk trade without good evidence of effectiveness.

Pharmacists in the community have been plagued by corporate conflicts of interest in much the same way as GPs have under the Quality and Outcomes Framework, pushed to meet targets for drug reviews even when inappropriate.[3] Many pharmacists working for large chains are demoralised, as happens to us all when judged by standards that we know are not in patients' best interests.

The NHS 111 system directs many patients to pharmacists. In some areas pharmacists are already working in GP surgeries. Many things that GPs do could be done by pharmacists, from helping with drug reviews and checking inhaler technique to dealing with inquiries about out-of-stock drugs (a continual source of on-call time wasting).

Teaming up with a pharmacist employed by and sited inside a private company are the vested interests of the employer and disrupted communications back to the NHS.

Corporate pharmacy chains often restrict which wholesalers they use, creating work for the NHS. For example, this week a pharmacy phoned me to say that it had run out of lithium and asked whether I could prescribe an alternative. But a different pharmacy, with a different supplier, had no difficulty dispensing the drug. The costs of these inefficiencies are transferred back to patients and swallowed by the NHS. The sign might say "NHS pharmacy," but it is Pantone 300 blue lipstick on a corporate pig.

As GPs move to a contract with a lighter form of the Quality and Outcomes Framework, ever closer to a salaried rather than a contractor model, we should reassess the situation. If remote general practices can dispense, practices with a pharmacist working on the same team most certainly can.

The idea that private companies should do NHS dispensing ignores the uncounted problems of corporate firms. Could we at least consider testing the idea of bringing high street pharmacists into the NHS fold?

Margaret McCartney is a general practitioner, Glasgow
margaret@margaretmccartney.com
Follow Margaret on Twitter, @mgtmccartney

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BODY POLITIC Nigel Hawkes

The travesty of expensive insulin

A bad precedent for future drug pricing

Almost a century after its discovery insulin remains out of reach of millions of people, against the wishes of its discoverers. It's simply too expensive a drug for a disease that makes no distinctions of class, colour, or birthplace.

Many people agree that this is shameful.[1 2] It also sets a terrible precedent for newer biological drugs and raises awkward questions about the patents system and drug market. Many other drugs even a quarter of insulin's age are now available as cheap generics. With insulin, constant reinvention and marginal improvements, combined with barriers to market entry, have enabled a few companies to maintain their grip and generate huge profits. It's as if Bayer still owned the rights to aspirin and charged us a fiver a pill.

It's as if Bayer still owned the rights to aspirin and charged us a fiver a pill

thebmj.com

Feature: Big profits for insulin manufacturers (*BMJ* 2010;341: c7139)

US election

The price of drugs has become a key issue in the US election. Donald Trump, Hillary Clinton, and Bernie Sanders have called for a new law to allow Medicare, the federal health insurance system for people aged 65 or over, to negotiate prices directly with companies. Trump claims this would save $300bn (£210 bn) a year, but Medicare spends only about $80bn a year on drugs. For the Republican candidate to suggest such a change, though, is interesting.

The issue is hot because two small companies recently imposed huge arbitrary price rises. Turing Pharmaceuticals and Valeant Pharmaceuticals International were quickly disowned by the Pharmaceutical Research and Manufacturers of America (PhRMA), but the price hikes drew attention to the large and widening gap between what the US and what most of the rest of the world pays for drugs. "Break up the insulin racket," a *New York Times* article by an endocrinologist, brought the price of insulin into the mix.[3]

Many poor Americans with diabetes find it hard to pay for insulin. A recent *JAMA* study found that US prices had tripled from 2002 to 2013, while other diabetes drugs had fallen in price.[4] And even people with insurance or in Medicare pay top-ups.

PhRMA said that the prices quoted in the *JAMA* paper were misleading because they didn't take account of rebates. But if a market is so opaque, why should we believe it?

There is no doubt, however, about the effect of insulin prices in poor countries. The life expectancy of a child with type 1 diabetes in sub-Saharan Africa is just a year. True, insulin cannot be copied and

ACUTE PERSPECTIVE David Oliver

The department of spin

Some say don't shoot the messenger. The professionals leading government communications offices are simply politicians' minions. I don't believe that.

During the current crises in healthcare, ministers may be the lightning rod for our anger. But we need to stop letting the Department of Health's press office off the hook, challenge and expose its partial truths. The messages it pumps out, inconvenient facts omitted, seep into the media and public consciousness and are often loaded against the services and professionals it claims to support . If you don't believe me, check the @DeptHealthPress tweets from April and May, when the junior doctors' industrial dispute was playing out and gaping holes were exposed in NHS workforce planning, funding, and deteriorating performance. Media relations staff made a timeline of the junior doctors' dispute, which failed to mention that it was the department that (twice) had to be exhorted to the mediator, Acas, and terminated January's talks.[1] The word "imposition" did not feature.

The press office claimed that evidence for the weekend mortality effect was "overwhelming"[2]—even though its existence, causes, and

The messages are often loaded against the services and professionals it claims to support

solutions have prompted considerable academic debate, with authors and editors disputing the spin.[3]

Press officers also said that, by the end of this parliament in 2020, the number of doctors trained by the NHS will have increased by 11 000 and that this government had already overseen an increase of more than 10 000 hospital nurses and doctors.[4] They also made big promises about increases in the GP workforce as part of April's *Forward View*.[5]

Strangely, the press office omitted mention of parliamentary committees flagging the disastrous failure of NHS workforce planning, with

STEVE MCCRAKEN

produced for pennies, but by now we might have hoped to do a lot better.

Evergreening?

It's easy to point fingers. The three companies that dominate the market, Novo Nordisk, Eli Lilly, and Sanofi, have pursued a policy of product improvement that critics characterise as "evergreening": animal insulin disappeared in favour of human insulin created by recombinant DNA techniques, and human insulin is now being replaced by analogue insulin. Each change brought improvements in performance whose importance is contested, as well as prolonging patent protection and sustaining prices. The extra cost of analogue insulin to the NHS over 10 years has been estimated at £625m.[5]

Modern drugs are always costly, largely because the US market is so skewed in pharma's favour. But they usually leave behind a trail of affordable generics that do the job very nearly as well. That is a strong justification for the drug industry. With insulin, though, this hasn't happened.

If we're not careful, this story will be repeated with today's best new drugs, many of which are biologicals. The industry has successfully sold the story that biologicals are costly to make (once true, now much less so) and that biosimilars, unlike generics, must be trialled to ensure equivalent performance (true, but the trials are simpler and less costly). Combine that with the arthritic performance of the NHS in using a biosimilar version of infliximab[6] and you're laughing if you're an investor in the drug industry. If you're a patient, especially in a poor country, prospects are much less rosy.

Nigel Hawkes is a freelance journalist, London

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22 000 nursing and 4000 medical vacancies.[6 7] Silence reigned over gaps in trainee recruitment to posts in key medical specialties—including for those overpromised new GP trainees.[8]

The department's public relations staff said that the NHS had received the sixth biggest funding increase in its history.[9] The chief economist at the King's Fund showed this to be nonsense.[10] Soundbites can't save a service already facing deficits and under further pressure to save money despite rising demand, diminishing performance, and real terms cuts to social care.

The spinners claimed that agreeing a new contract with one depleted workforce—junior doctors—would "deliver a seven day NHS."[11] Problem solved, then.

In 2013 the head of the DH press office said, "We have to be transparent and honest with the public. You can't hide stuff and hope that nobody notices."[12] For the sake of open democracy and the future NHS, it's vital to challenge the department at every turn. Its apolitical civil servants are supposed to work for us taxpayers—not for party headquarters.

David Oliver is a consultant in geriatrics and acute general medicine, Berkshire
davidoliver372@googlemail.com

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THEBMJ.COM BLOGS David Payne

Time to pause Scotland's "named person" policy

"They fuck you up, your mum and dad. They may not mean to, but they do." Was Philip Larkin right, and, if so, are state funded parenting classes the answer? Or should we be offering all children, regardless of their background, access to a state guardian from birth to age 18 to help safeguard their wellbeing?

One apparent problem; two potential solutions. John Ashton, outgoing president of the UK Faculty of Public Health, told the *Times* that 10-15% of school leavers are in trouble emotionally or mentally, with one child in 10 having a mental health problem.

It's not just parents from disadvantaged backgrounds who struggle to raise children, he adds, saying, "There's some terrible parenting among wealthy people who neglect their children and spoil them in other ways."

Are state funded parenting classes the answer?

Ashton wants to see the public health role of midwives strengthened and antenatal classes extended. The prime minister, David Cameron, talked of state run parenting classes and of them being seen as an "aspirational thing for families to attend."

The move, first mooted in January, is likely to enrage those who fear "a nanny state," said much of the news coverage. In Scotland, where the government is due to introduce a "named person" policy from 31 August, the rage has already erupted.

What does being a named person entail, and why does every child need one? It is, the Scottish government website says, "a central point of contact if a child, young person or their parent(s) want information or advice, or if they want to talk about any worries and seek support. They can also, when appropriate, reach out to different services who can help."

What types of professionals are we talking about here? GPs are not mentioned. In the case of preschool children, health visitors are suggested. At school it will be a teacher. But the types of teachers most talked about include head teachers, principal teachers, and guidance teachers. It's not clear how many children will be allocated to them, but health board and local authorities will have a statutory duty to provide one until a child reaches 18.

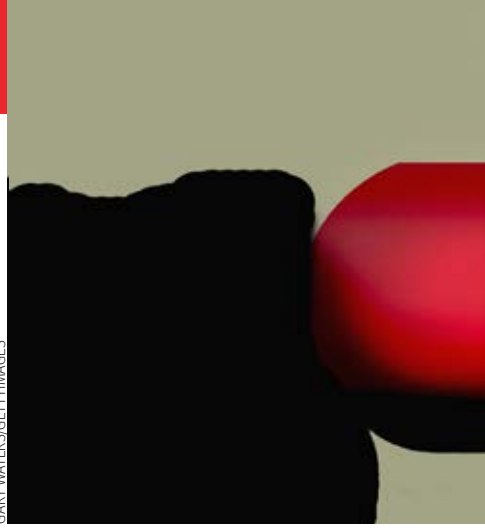
But is the legislation yet more "ill conceived nannying," designed to control the lives of ordinary Scots who don't need or want it? In a sense, the question has already been answered. A Survation poll of 1024 adult Scots earlier this month found that 64% thought it was an "unacceptable intrusion" into family life.

David Payne is digital editor, *The BMJ*

ANALYSIS

Drugs for rare diseases: bridging the evidence gap

Post-approval studies seldom cover the deficit of knowledge about orphan drugs, find **Roberta Joppi and colleagues**



GARY WATERS/GETTYIMAGES

Developing medicines for rare diseases is difficult. Small target populations limit the potential to recover investments in research and development, and even when medicines get to clinical trials, there may be too few patients to support adequately sized trials. Trials for these drugs often also have other shortcomings—for example, the use of placebo as control, surrogate endpoints instead of hard clinical outcomes, or an inadequate length of follow-up. As a result, orphan drugs—those intended for rare diseases (box)[1]—are not only few but often have insufficient evidence of efficacy and safety at the time of approval.[2]

Regulation introduced in Europe in 2000 aimed to encourage research and development into orphan drugs.[1] The regulation did not substantially improve the evidence underlying their approval[2-4] but allowed regulators to grant marketing authorisation trusting that post-marketing research would bridge the gap of knowledge on their safety and effectiveness. To check whether those expectations are being met and the missing data provided, we examined the evidence generated in the 10 years after marketing authorisation for orphan products approved in a single year.

Licensing of orphan products with no or incomplete proof of their efficacy may unduly harm patients and waste health service resources

Pre- and post-marketing available evidence

We analysed all six orphan products authorised by the European Medicines Agency (EMA) in 2004 (table) and conducted a literature search for studies of these drugs up to December 2014. We systematically searched MedLine, Embase, and Cochrane databases for published randomised clinical trials, observational studies, and meta-analyses of the selected products using their name or MESH term(s), and their authorised or designated indication(s). After a library search, two reviewers independently screened abstracts and full texts, and separately extracted data. Discrepancies were solved by consensus. We considered 10 years sufficient time to answer the clinical questions still open at the time of approval. It is also the period covered by patent and the special protection reserved for licensed orphan products, and companies should still be interested in increasing the evidence relating to their products.

Here, we summarise the evidence available before and after approval for each of the drugs.

Anagrelide

Anagrelide was authorised for the treatment of essential thrombocythaemia on the basis of two compassionate use programmes verifying platelet count reduction in 1176 patients overall. Three further studies (the intended phase II, single arm, pivotal study; another uncontrolled study; and a randomised comparative trial against hydroxyurea) were either stopped early or reported unreliable efficacy and safety data according to good clinical practice inspectors.[5]

Of the eight post-marketing studies,[6-13] three compared anagrelide and hydroxyurea. In the largest phase III trial anagrelide was worse than hydroxyurea in preventing arterial and venous thrombotic events, serious haemorrhage, and death in 809 patients with essential thrombocythaemia (odds ratio =1.57; 95% confidence interval 1.04 to 2.37; P=0.03).[6]

Two further trials primarily examined reduction in platelet count. However, one small trial also reported no thrombotic events with anagrelide and 11 with hydroxyurea.[7] In one non-inferiority trial anagrelide seemed to be as effective as hydroxyurea in preventing thrombocythaemia related clinical events, though the wide confidence intervals indicate that it could be much better or much worse than placebo (hazard ratio=0.92; 95% CI 0.57 to 1.46).[8]

How the evidence changed—At the time of approval it was known that anagrelide reduced platelet count but not what its effects were on thrombotic or haemorrhagic complications of essential thrombocythaemia or whether it was better than other platelet reducing agents. Post-marketing studies indicate that anagrelide is probably worse than hydroxyurea in reducing thrombocythaemia related vascular events but no regulatory action has been taken.

Cladribine

Cladribine was approved for patients with hairy cell leukaemia on the basis of two single arm studies reporting inconsistent overall response rates (97% and 19%). No overall survival figures were collected.[14]

After marketing approval two studies[15 16] found no difference in response rates and toxicity with the daily and weekly schedules of cladribine. Another phase II single

KEY MESSAGES

- Authorisation of drugs for rare diseases with unmet treatment needs relies on post-marketing research to cover incomplete information
- However, questions about safety and effectiveness are seldom settled in the post-marketing phase
- Ongoing uncertainty about these drugs may harm patients and waste health system resources

Definition of "orphan medicinal product"

European regulation No 141/2000 says that a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

a) That it is intended for the diagnosis, prevention, or treatment of a life threatening or chronically debilitating condition that affects ≤5 in 10 000 persons in the EU when the application is made or for which marketing is unlikely to generate sufficient return on investment without incentives

b) And that no satisfactory method of diagnosis, prevention, or treatment of the condition has been authorised in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by the condition

arm study[17] assessed responses and bone marrow minimal residual disease in 36 patients given five daily cladribine doses followed one month later by eight weekly rituximab doses. Persistent disease was reported in 12/27 evaluable patients (44%) given cladribine, while none had persistent disease after rituximab.

How the evidence changed—Post-marketing studies did not help clarify clabribine's relative efficacy and place in therapy with respect to rituximab or the inconsistent findings on the response of the disease.

Ibuprofen

Ibuprofen solution (Pedea) was approved for patent ductus arteriosus in preterm newborns on the basis of a meta-analysis of six randomised controlled trials comparing it with indomethacin.[18] The meta-analysis, which was conducted by the company itself, concluded that ibuprofen and indomethacin were equivalent with regard to ductal closure (75% *v* 73%, odds ratio=1.14, 95% CI 0.73 to 1.77), requirement for surgical ligation (11.7% in both groups, odds ratio=1.00, 0.55 to 1.81), and perinatal mortality (10.1% *v* 9.1%, hazard ratio=1.11, 0.55 to 2.24). The regulatory dossier also included a dose-range study[18] and a double blind randomised trial of prophylactic ibuprofen versus placebo in neonates with gestational age less than 28 weeks.[18] Of the 47 infants who reached 36 weeks of gestational age, none in the ibuprofen group and five in the placebo group required surgery. Ibuprofen was not recommended for prophylactic use because the possible small advantage in avoiding surgery was counterbalanced by higher risks of renal failure and pulmonary adverse events without a survival advantage. The trial was stopped at 60% of recruitment.

After the marketing authorisation, five small single centre trials,[19-23] two systematic reviews with meta-analyses,[24 25] and one observational study[26] were published. One of the trials found that continuous infusion of ibuprofen was more effective and just as safe as the bolus dose; in a second trial ibuprofen proved as effective as indomethacin, while in two trials paracetamol was as effective as ibuprofen but safer. In the last trial ibuprofen caused more renal impairments than placebo in neonates with gestational age less than 27 weeks and in low birthweight infants. The observational study found that oral ibuprofen caused no fewer neurological or cognitive impairments than intravenous ibuprofen.[26]

Of the two meta-analyses, one showed that oral ibuprofen gave a higher ductal closure rate than intravenous ibuprofen but the rate was similar to intravenous indomethacin.[24] The second meta-analysis concluded that ibuprofen was as effective as indomethacin and possibly there was less risk of necrotising enterocolitis and transient renal insufficiency.[25]

How the evidence changed—At the time of approval ibuprofen was known to be no better than indomethacin for patent ductus arteriosus. Post-marketing data showed its renal toxicity in newborns with gestational age less than 27 weeks. Information about the long term neurological and pulmonary safety of ibuprofen relies on one observational study. The news was that paracetamol was as effective as ibuprofen but less toxic, but this was never taken into account.

EU regulation stipulates that new medicines are approved on the basis of proved quality, efficacy, and safety, but few licensed orphan products meet these criteria

Mitotane

Mitotane was approved for advanced adrenal cortical carcinoma on the basis of 18 uncontrolled studies, mostly retrospective case series.[27] Only a few studies had evaluated the efficacy of mitotane on survival with

Evidence available before and after marketing for six orphan drugs approved in 2004

	Best available evidence		Type of evidence (GRADE level)	
Orphan drug (disease)	Before	After	Before	After
Anagrelide (essential thrombocythaemia)	Platelet count reduction	More vascular events than with adequate comparator*	Case series (4)	Superiority RCT (2b)
Cladribine (hairy cell leukaemia)	Inconsistent response rates (19-97%)	56% responses after cladribine became 100% after rituximab†	Case series (4)	Case series (4)
Ibuprofen (patent ductus arteriosus (PDA))	As effective as indomethacin in closing PDA	As effective as indomethacin in closing PDA, but less necrotising enterocolitis and transient renal insufficiency†	Meta-analysis of RCT (1a)	Systematic review with meta-analysis of RCT (1a)
Mitotane (adrenal cortical carcinoma)	Response rate 20-30%	Response rate 48.6%†	Case series (4)	Case series (4)
Porfimer sodium (Barrett's oesophagus)	More frequent ablation of dysplasia as add-on to omeprazole	Reduced risk of adenocarcinoma as add-on to omeprazole‡	RCT (1b)	RCT (1b)
Zinc acetate (Wilson's disease)	Prevents progression of disease	None†	Case series (4)	None

Case series means uncontrolled studies. RCT=randomised controlled trial. GRADE rating of evidence ranges from 1 (highest) to 5.
*Post-marketing trial shows worse efficacy.
†Evidence unchanged.
‡Post-marketing studies show better efficacy but drug withdrawn for safety reasons.

respect to activity, and their results were contradictory.

The post-marketing research included one randomised trial,[28] two single arm studies (one phase I[29] and one phase II[30]), and one observational study.[31] The randomised trial[28] showed no difference in overall survival in patients treated with mitotane-etoposide-doxorubicin-cisplatin or mitotane-streptozocin (14.8 months and 12.0 months, respectively; hazard ratio=0.79, 95% CI 0.61 to 1.02; P=0.07). The phase I, single arm trial of the combination of mitotane and cixutumumab was terminated on account of toxicity.[29] The phase II uncontrolled study[31] found complete response in only 5/72 patients. The observational study[31] showed that only patients receiving early specialised care survived longer.

How the evidence changed— None of the studies showed any survival benefit with mitotane.

Porfimer sodium

Porfimer was approved for photodynamic treatment of Barrett's oesophagus. Clinical data in the regulatory dossier came from one randomised trial and two single centre, uncontrolled studies.[32] In the controlled trial complete ablation of dysplasia was more common with porfimer plus omeprazole than omeprazole alone (76.8% *v* 38.6% at 24 months).

Three randomised trials were published post-marketing,[33-35] together with two dose escalation studies[36] and one observational retrospective study published as an abstract.[37] In one trial porfimer plus omeprazole reduced the risk of adenocarcinoma more than omeprazole alone (13% *v* 20%, P=0.006 at two years and 15% *v* 29%, P=0.004 at five years).[33] The second trial found argon plasma coagulation and porfimer sodium equally effective in eradicating Barrett's mucosa.[34] The final trial[35] found no difference in efficacy and safety of photodynamic treatment with 5-aminolaevulinic acid or porfimer.

How the evidence changed— Post-marketing studies confirmed the better efficacy of porfimer as an add-on to omeprazole and contributed slightly to defining its role in treatment relative to other options such as 5-aminolaevulinic acid and argon plasma coagulation. Unfortunately, porfimer was withdrawn from the market in 2012 because of reports suggesting it caused deep vein thrombosis.[32]

Zinc acetate dehydrate

Zinc acetate dehydrate was approved for Wilson's disease, an autosomal recessive defect in hepatic excretion of copper, on the basis of long use in clinical practice as a maintenance treatment. Other zinc salts had long been used to reduce the intestinal absorption of copper. The marketing authorisation was granted on the basis of data accumulated over more than 40 years.[38] Most came from a cohort of 148 patients treated with zinc since the 1980s.[39] The evaluation was based on an overall clinical impression of lack of disease progression.

The dossier also included uncontrolled studies and one trial using zinc sulphate (the two zinc salts are pharmacologically comparable and they are dealt with as such in the European public assessment report).[38] The one non-randomised trial of zinc sulphate versus penicillamine was in 67 newly diagnosed patients, 56 of whom had symptoms.[38] Improvement was reported in 15 patients in the zinc group and 14 in the penicillamine group, and deterioration in, respectively, two and three patients from the two groups.

How the evidence changed—Post-marketing studies suggest that zinc has similar efficacy to penicillamine in Wilson's disease and lower toxicity than other copper chelators. Despite this, no post-marketing head to head trials have been done.

Need for change

Our analysis shows that post-marketing clinical research did not satisfactorily cover the deficit of knowledge about orphan products at the time of their licensing in 2004. Furthermore, manufacturers were not obliged to carry out further studies. Despite lack of evidence, the original regulatory decisions were not revised and all the products except porfimer are still on the market. The US Food and Drug Administration also approved these drugs with no post-marketing commitments, and all of them are still on the US market.

Whenever the efficacy or safety of an orphan product is not clear, the EMA should require further clinical research

The present situation is concerning. Licensing of orphan products with no or incomplete proof of their efficacy and safety, sometimes even relative to other available treatments, may unduly harm patients and waste health service resources.[40] EU regulation stipulates that new medicines are approved on the basis of proved quality, efficacy, and safety, but few licensed orphan products meet these criteria.[41] Moreover, the regulation on orphan products allows market exclusivity only for new products that are shown to be "clinically superior" to competitors already on the market.[1] This is difficult to achieve without comparative trials that have clinically meaningful outcomes.

These problems apply to any medicine approved on the basis of insufficient evidence, not just orphan products.[40] Moves to abridge and simplify the evaluation of new medicines, such as conditional approvals and adaptive licensing, should therefore be approached with caution.[42] Whenever the efficacy or safety of an orphan product is not clear, the EMA should require further clinical research—for example, to prove real clinical benefit in the long term instead of surrogate advantages in a limited time frame. Evidence should be provided well before the 10 year market protection expires. If the company does not comply with the EMA's requests, the agency should withhold its marketing authorisation, engage an independent institution to complete the requested studies, and in the meantime ensure the drug is available to currently treated patients through an expanded access programme.

Roberta Joppi, researcher
roberta.joppi@guest.marionegri.it
Chiara Gerardi, researcher
Vittorio Bertele', researcher
Silvio Garattini, director, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; and Pharmaceutical Department, Local Health Unit of Verona, Italy

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Noshir Hormusjee Wadia

Pioneer in Indian neurology

Noshir Hormusjee Wadia (b 1925, q Grant Medical College, Mumbai, 1950; MRCP Lon), d 10 April 2016.

Noshir Hormusjee Wadia was born to a Parsi family of modest means. He eschewed the family's timber business and became a doctor. In 1950 he graduated from Mumbai's Grant Medical College and Sir JJ Hospital with a degree in general medicine.

Neurology and independence

As a graduate student, Wadia was keenly interested in neurology, but the scope for specialisation in the subject did not exist in India at the time. So when he travelled to England to sit the examination for membership of the Royal College of Physicians (MRCP), Wadia was determined to make the most of it. In London he signed up for a three month course on neurology. After obtaining his MRCP, Wadia decided to undergo further training. He joined the department of neurosurgery at Newcastle General Hospital, after which he was appointed regional medical officer at the National Hospital for Nervous Diseases in Maida Vale, London, in 1953. This gave him the opportunity to work with some of the finest neurologists in the UK—including Russell Brain. Wadia demonstrated exemplary medical acumen there and was soon appointed registrar to Brain.

After four years in the UK, Wadia returned to India at the age of 32. In 1957 he joined his alma mater—as honorary assistant neurologist at the JJ and lecturer in neurology at Grant Medical College. At a time when neurology was considered a separate discipline at many leading institutions around the world, Wadia was given the mandate to set up one of the first departments in India. A few months later, Gajendra Sinh and Jimmy Sidhva joined the JJ, and together the three doctors built a formidable neurosciences unit. The department grew from six to 45 beds over 25 years. Wadia's accounts of the early years of the department show the scale of the challenges that faced him. He strived to bring in new technologies and best practices, which enabled the unit to build a formidable reputation. In 1973 he set up another neurology department at a private hospital, Jaslok Hospital and Research Centre, which is now recognised for postgraduate studies.

Research and an Indian perspective

Wadia is credited with having identified two unique Indian diseases—a new variant of hereditary ataxia with slow eye movements, and adult poliomyelitis due to a new virus (enterovirus 70) associated with pandemic acute haemorrhagic conjunctivitis. His studies included neurological complications of manganese poisoning in Indian miners, the high prevalence of craniovertebral anomalies in India, Wilson's disease, tuberculosis presenting primarily as spinal meningitis, and nutritional disorders of the nervous system—all of which he reported and published.

Wadia's former students V Peter Misra and Shanti Vijayaraghavan said that when he returned to India he immediately noticed that the prevalence of neurological diseases was different from the rates in the standard textbooks. So he researched, planned, and edited a multiauthored book, Neurological Practice: an Indian Perspective. Wadia supported patients and their families. He was founder, trustee, or member of numerous societies, and the founder member of the Indian Epilepsy Association. He also supported societies for multiple sclerosis, muscular dystrophy, Parkinson's disease, and motor neurone disease.

Numerous honours—including the Padma Bhushan, India's third highest civilian award bestowed on him in 2012—recognised Wadia's many accomplishments.

Teaching career

Wadia trained nearly 100 neurologists over half a century. Many of his "boys and girls" have gone on to hold pivotal positions as clinicians and academicians around the world. He would be generous with his time and advice whenever students approached him. He helped students obtain scholarships for further studies and used his connections around the world to help them undertake further training. Misra and Vijayaraghavan were among the many whom Wadia counselled and assisted by introducing them to faculty at institutes overseas.

Wadia is credited with having identified two unique Indian diseases

One unfortunate incident in Wadia's life brought together doctors from across the world. In 1961, as he was returning from a neurology event in Buenos Aires, he was forcibly detained in Portugal as retaliation for India's invasion of Goa. Dorothy Russell, a renowned British neuropathologist, wrote a letter to *The BMJ*, "In December 1961, Dr N H Wadia, an Indian neurologist well known to many in England after having worked as registrar in two London teaching hospitals, was detained in Portugal for two months in the notorious Caxias prison as a reprisal for the Indian annexation of Goa . . . Continued pressure from medical bodies and eminent neurologists in this and other European countries, the USA, and Chile helped to hasten Dr Wadia's release."

Wadia leaves his wife, Piroja; two stepsons; and four step-grandchildren.

Jeetha D'Silva, Mumbai
j.dsilva@gmail.com

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DPP-4 INHIBITORS

Inclusion of EXAMINE study in DPP-4 meta-analysis

The main criterion in Salvo and colleagues' meta-analysis on increased risk of hypoglycaemia was that trials studied the effect of adding one dipeptidyl peptidase-4 (DPP-4) inhibitor or placebo to sulphonylureas (Research, 7 May).

It is unclear why the EXAMINE study was included—a cardiovascular outcome study comparing alogliptin with placebo, plus standard care for type 2 diabetes. It did not compare adding alogliptin or placebo to sulphonylureas or assess specific drug combinations.

Treatments and doses other than alogliptin and placebo could change during the study at the investigators' discretion. Moreover, standard care differs between countries. In Europe, 4 mg glibenclamide daily is recommended; in the US, 8 mg glimepiride can be used.

The EXAMINE results probably reflected patients' baseline characteristics. A major follow-up bias makes it unsuitable for this meta-analysis. And the authors state that results would be similar after excluding it, but it accounts for 35.8% of the pooled analysis.

Denis Boucaud-Maitre (denis.boucaud@gmail.com)

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Authors' reply

The methodological problem Boucaud-Maitre raises was discussed in the selection process, and we decided to include this trial for various reasons. EXAMINE probably better reflects real life situations than other studies because no action on standard care was taken before the trial, and the glucose lowering regimen could be modified in the follow-up period according to patients' clinical status (eg, hypoglycaemia events).

It was a "pragmatic trial" in primary care in patients with type 2 diabetes, and it offered high quality information for our meta-analysis. We asked the authors how many patients in the alogliptin and placebo groups used sulphonylureas at baseline and the corresponding number of hypoglycaemia events. Consequently, we conducted an intention-to-treat analysis. We do not believe that a different kind of analysis (eg, per protocol) would have greatly altered the EXAMINE result because most treatment changes would have occurred after a hypoglycaemic event.

Francesco Salvo (francesco.salvo@u-bordeaux.fr), Nicholas Moore, Mickael Arnaud, Philip Robinson, Emanuel Raschi, Fabrizio De Ponti, Bernard Bégaud, Antoine Pariente

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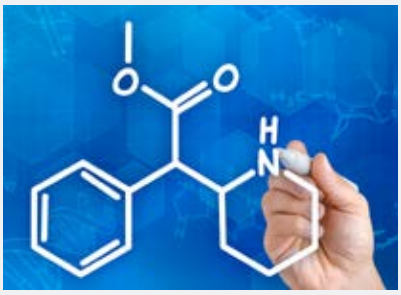
LETTER OF THE WEEK

Heart safety of methylphenidate in adults



Shin and colleagues showed an increased risk of arrhythmia from methylphenidate in children and young people with attention-deficit/hyperactivity disorder (ADHD) (Research, 4 June). We were recently notified of a spontaneous adverse drug reaction of ventricular extrasystoles in an adult patient who had taken only methylphenidate. Treatment was stopped and cardiological evaluation seven months later gave normal results. The causality (imputation) score was deemed likely.

To investigate this adverse drug reaction, we used VigiBase, WHO's global individual case safety report (ICSR) database. Among the 9 573 704 reports between 1978 and 2016 in which both age and sex were known, 18 329 concerned methylphenidate, 30 having been registered as ventricular extrasystoles. After medical review of these 30 reports, 27 were included. Most (22) cases occurred in children and young people, but five were in adults.

These case reports from another international database are in agreement with the work of Shin and colleagues. Thus we emphasise the potential risk of cardiac arrhythmia in general and of ventricular extrasystoles in particular, not only in children and young people but also in adults, during exposure to methylphenidate. Although this serious adverse drug reaction is rare as indicated by the number of reports on VigiBase, it should be taken into account because of the widespread exposure to methylphenidate.

François Montastruc (francois.montastruc@univ-tlse3.fr), Guillaume Montastruc, Jean-Louis Montastruc, Alexis Revet

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PRE-ECLAMPSIA RISK FACTORS

Pre-eclampsia paper raises aspirin dilemma

Bartsch and colleagues quantify risk factors for pre-eclampsia (Research, 23 April), but clinicians face a dilemma following the recommendations.

Firstly, NICE states that women with chronic kidney disease (CKD) and systemic lupus erythematosus (SLE) are high risk, qualifying to start aspirin. But in the paper CKD and SLE don't fall in the high risk category, as more than one risk factor is needed. UK obstetricians will find it difficult not to start aspirin in patients with CKD or SLE when these are the only risk factors present.

Secondly, the findings will generate debate in managing and investigating small for gestational age fetuses, as RCOG guideline 31 recognises SLE and CKD as a major (single) risk factor qualifying aspirin use before 16 weeks.

Junaid Rafi (drjunaidrafi@hotmail.com)

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Authors' reply

WHO, NICE, and the USPSTF find aspirin prophylaxis appropriate in high risk women, listing chronic kidney disease (CKD) and systemic lupus erythematosus (SLE) as "high risk" factors for pre-eclampsia. We estimated the absolute risk, aiming to quantify it and compare it with a threshold that may warrant aspirin prophylaxis.

CKD and SLE were not among the solitary risk factors to warrant this. At a 10% relative risk reduction (RRR) the threshold number needed to prevent (NNP) for CKD is below 200, but its upper 95% confidence interval crosses the NNP of 250. If aspirin conferred a 30% or 50% RRR against pre-eclampsia, the NNP for CKD falls significantly below 250—an adoptable solitary risk factor. For SLE, however, it did not fall below the threshold at any RRR, largely because of wide confidence intervals from the few studies on pregnancy outcomes.

Some clinicians may still feel comfortable deeming CKD and SLE important enough solitary risk factors to warrant aspirin prophylaxis.

Joel G Ray (rayj@smh.ca), Emily Bartsch

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