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LETTERS

CARBAMAZEPINE IN PREGNANCY

Levetiracetam and lamotrigine are better options

Nulman's statement that carbamazepine is the antiepileptic drug of choice in pregnancy does not reflect evidence based clinical practice.[1] Carbamazepine is contraindicated in one of the most common epilepsies—idiopathic generalised epilepsy.

Randomised controlled trials have shown lamotrigine to be the best choice for partial onset epilepsies in the general population because it is as effective and better tolerated than carbamazepine,[2] and no significant differences between the two drugs are seen on cognitive function after fetal exposure.[3] Furthermore, the incidence of major congenital malformations is slightly lower with therapeutic doses (100-200 mg) of lamotrigine than with carbamazepine (400-1000 mg).[4]

As evidence of major congenital malformations and neurodevelopmental delay accumulates, alternatives to valproate—the first line drug for idiopathic generalised epilepsy[5]—are increasingly being prescribed in women of childbearing age. Evidence also suggests that children exposed to levetiracetam score more highly on developmental assessments than do those exposed to valproate, and no major congenital malformations have been reported for monotherapy with levetiracetam.[4]

The ideal antiepileptic for women of childbearing potential is one that has no effects on fertility, no teratogenicity, sustained efficacy during pregnancy, and no interactions with oral contraceptives. Unfortunately such a drug is far from being found.

However, current knowledge indicates that carbamazepine is not a reasonable option for women of childbearing age with idiopathic generalised epilepsy. Finally, whenever the type of epilepsy is in doubt, avoid narrow spectrum drugs such as carbamazepine and use other broad spectrum drugs such as lamotrigine and levetiracetam.

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Competing interests: None declared.

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Cite this as: *BMJ* 2011;342:d279

Author's reply

In response to Iniesta,[1] many pregnant women with epilepsy are treated with carbamazepine, which is prescribed according to their type of seizure (other than idiopathic generalised epilepsy). Lamotrigine has similar malformation rates to carbamazepine at doses of 200 mg, but it behaves differently at doses higher than 400 mg and is associated with oral clefts (relative risk 10.4, 95% confidence interval 4.3 to 24.9).[2] These findings need clarification, and cleft palate is challenging to diagnose prenatally. Only one cohort study reported on the long term neurodevelopmental outcomes of lamotrigine.[3] The investigators assessed 84 young children using the Bayley scales of infant development, not exactly a cognitive test. Favourable long term neurodevelopmental outcomes have been reported in a significantly larger number of older and younger children exposed to carbamazepine and tested with age appropriate neurocognitive tests.[4 5] Although promising, levetiracetam needs further study.

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Competing interests: None declared.

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Cite this as: *BMJ* 2011;342:d282

FEBRILE NEUTROPENIA

National guidelines are urgently needed

Febrile neutropenia is a medical emergency that is associated with morbidity and mortality if not managed appropriately with urgency.[1] Guidelines define fever as either a single oral temperature of 38.3°C or 38.0°C for one hour and neutropenia as a neutrophil count $\leq 0.5\times10^9$/L or $\leq 1.0\times10^9$/L, with a predicted decrease to $\leq 0.5\times10^9$/.[2 3]

Christie Hospital guidelines stratify risk on the basis of counts $<1.0\times10^9$/L, $<0.5\times10^9$/L, and $<0.01\times10^9$/L and suggest applying this stratification only at specialist centres.[3] The Department of Health (DoH) report and practice at most specialist units offering chemotherapy include a treatment plan and patient information on side effects, helpline numbers, and a facility for direct admission to the unit.[4] Data from the National Confidential Enquiry into Patient Outcome and Death suggest that high risk patients are not optimally informed.[5] Diagnosis of febrile neutropenia requires rapid performance of a full blood count, and DoH guidance mandates administration of intravenous broad spectrum antibiotics within one hour. Timely and specialist clinical assessment and prompt management of high risk patients would be suboptimal in primary care.

The DH report (2009) requested that the National Institute for Health and Clinical Excellence urgently develop a national guideline on the clinical management and prevention of febrile neutropenia,[4] but this is still awaited. A regional re-audit (2010) on the management of febrile neutropenia across 17 hospitals reported considerable variation, in the absence of national guidance that would apply to district hospitals and specialist centres.

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Competing interests: None declared.

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REFERENCE INTAKES OF VITAMIN D

Need to be implemented in UK

Recent recommendations from the Institute of Medicine (IOM, US/Canada) for vitamin D intakes set dietary reference intakes for adults at 600 IU/day.[1] Implementation of these guidelines would considerably improve the situation in the UK, which is the only European country with no recommendation for healthy adults.[2 3] Also, recommendations for vulnerable groups such as pregnant women are lower (400 IU/day) in the UK,[3] and even these are not achieved.[4] The Scientific Advisory Committee on Nutrition has prioritised a review on vitamin D, but this will probably take two to three years to complete. The UK cannot continue to do nothing while awaiting the outcome. Because of a more northerly location, lack of an effective food fortification policy, and the limited provision of supplementation, the UK population has a greater need for supplemental vitamin D than the Americans. Thus, immediate endorsement of the IOM recommendations on vitamin D in the UK is urgently required and would unquestionably be safe.

Controversially, the IOM based its recommendations solely on the effects of supplementation on bone health, largely discounting evidence on other diseases.[5] The IOM provided an exhaustive list of research recommendations. In our opinion, efforts should focus on distinguishing the causal from the coincidental in reported vitamin D-health outcome associations and on establishing whether dosages much higher than currently recommended are required and safe for implementation at the population level.

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Competing interests: None declared.

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SECRETS OF THE MMR SCARE

UCL's response

UCL takes any allegation of research misconduct seriously, and we will certainly investigate those raised in the *BMJ*.[1] However, we have not seen all the related articles yet so can give only a general institutional response to the issues raised so far.

The Royal Free Medical School was not part of UCL when the relevant research was conducted. It is over a decade since this research was carried out, and major institutional changes mean that circumstances are now very different. Important changes include reorganisation of ethics approval processes and a merger of previously separate research and development activities at UCL, University College Hospitals NHS Foundation Trust, and the Royal Free Hampstead NHS Trust.

This merger has increased integration, improved exchange of information across the NHS-university boundary, and helped establish common processes and standards. The availability of substantial additional resources has helped improve regulatory processes and the monitoring and audit of research.

After the General Medical Council's findings in January 2010, UCL initiated a review of its research governance structures and processes to test their robustness in the context of the case. This ongoing review aims to identify lessons that can be learnt and ensure that everything possible is in place to prevent a similar situation in the future.

Regarding the *BMJ*'s request for UCL to investigate Wakefield's research papers, we acknowledge the need to look closely at the research of someone alleged to have carried out research misconduct and for this process to be subject to external scrutiny. We are carefully considering how to conduct this investigation in light of the complex legal, practical, and logistical aspects involved.

We are determined to learn from the mistakes made in this case. Unfortunately, it will never be possible to have a system that guarantees to prevent research misconduct, and it is vital that governance procedures avoid obstructing valuable research. Our objective is to continue refining a structure and processes that provide all reasonable safeguards while facilitating the highest quality research.

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Competing interests: None declared.

1 Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ* 2011;342:c7452. (5 January.)

Cite this as: *BMJ* 2011;342:d460

Piltdown—hoax or fraud?

The *BMJ*'s revelations about Wakefield and the mumps, measles, and rubella (MMR) scare are shocking. I am stunned by the BBC's silence considering how much air time they gave Wakefield when the MMR scare was developing, especially on Radio 4 news. This should prompt us to try to educate people about the difference between a consensus of well conducted studies and a handful of anecdotes, however heart rending.

I am interested in the reference to the Piltdown man "hoax." Godlee wrote: "I am struck by Deer's comparison . . . between Wakefield's fraud and Piltdown man, the paleontological hoax that led people to believe for 40 years that the missing link between man and ape had been found."[1]

Why was the Piltdown skull a hoax and not a fraud? Why soften the impact of the deliberate, calculated, and effective Piltdown fraud, which deceived the scientific community for 40 years, by likening it to a schoolboy prank?

It is horrible to learn that we have been deceived, but better to admit it and guard against it happening again. This is the lesson we must all learn from the MMR vaccine scare. It's a shame we didn't learn it from the pertussis vaccine scare in the 1980s, when so many children were harmed as a result of their elders believing something that wasn't true.

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Competing interests: SFH's daughter was infected with pertussis in 1987 as a result of being denied vaccination on a paediatrician's advice because of a media generated pertussis vaccine scare.

1 Godlee F. The fraud behind the MMR scare [editor's choice]. *BMJ* 2011;342:d22. (6 January.)

Cite this as: *BMJ* 2011;342:d469

TREATMENT ABROAD

A long journey to healing

This news article highlights a growing trend among UK patients to travel abroad for treatment.[1] Interestingly, there have been no reports of people travelling outside the country for treatment of mental disorders. Recently, a team from East London NHS Foundation Trust visited Bangladesh to share knowledge and skills with Bangladeshi mental health professionals. The team met a few patients from London receiving treatment for mental health problems in Bangladesh, who gave a mixed response about the treatment they had received. One patient reported having been forcibly held in a mental health facility and having seen violence used in a private clinic. Most of these patients will come back to the UK, and it is important that their GPs have some knowledge of this treatment episode to arrange appropriate follow-up.

Both primary and secondary care could look into the reasons for such practice. Some GPs in Newham, East London, are already aware of this situation and would like to know more about psychiatric care pathways in Bangladesh. A recent paper looked at these care pathways.[2] A non-judgmental approach to patients and their families by their doctors might help gather more information about the treatment and even establish contact with the Bangladeshi professionals treating them. Local services could mount an awareness campaign among clinicians in the UK and abroad to establish better communication because people are likely to continue travelling overseas for such treatment.

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Competing interests: None declared.

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Cite this as: *BMJ* 2011;342:d447

ASSISTED DYING DEBATE

Try another approach, *BMJ*

Delamothe's observations article offers evidence from trials and surveys in favour of his preferred policy solution: that doctors should be allowed to become involved in assisted dying.[1] I, too, sympathise with such a policy, but I take issue with both him and Godlee, who seem to consider that this controversial policy change is justified exclusively by "rational" research evidence.[2] Are these the same *BMJ* editors who had the insight to publish a paper on the dangers of the unchecked march of rationalism in a previous Christmas issue?[3]

As a family doctor, I support professional assistance with dying in carefully defined and monitored circumstances because I believe that such actions are morally justified, humane, and resonant with the personal values and professional codes of conduct which define my identity.

Good policy making should not be equated with the "evidence pipeline": it entails the rhetorical deliberation over what is right and reasonable.[4] In policy issues with "high issue polarisation"—that is, fundamental differences in values between stakeholders—research evidence tends to be used selectively and instrumentally to back up particular value based positions.[5] If the *BMJ* wants to do something original in 2011, it should make a new year's resolution not to try to answer questions about values by reaching for its traditional comfort blanket of epidemiological evidence. Scholarly articles on religious and moral philosophy as applied to the assisted dying question would be most welcome.

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Competing interests: None declared.

1 Delamothe T. Half truths and one and a half truths about assisted dying. *BMJ* 2010;341:c7282. (22 December.)
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Cite this as: *BMJ* 2011;342:d451

Put everything out in the open

In this debate on assisted dying,[1] as in all other ethical debates, the idea that anyone comes to the table completely neutral is preposterous. Whether we have a previously formed strong belief one way or the other, we all bring our own cultural and experiential baggage.

There is a worrying trend of assuming that the views of people who subscribe to a religious belief in the traditional sense are inherently less objective. In fact, those of a religious persuasion might more likely be people of integrity, but they are not less likely to be people of integrity than anyone else.

Broadly, religion can be thought of as the paradigm through which we interpret the world. Those who do not subscribe to one of the traditional religions will still have their own paradigm, be it some form of humanism, atheism, or scientific rationalism.

To be seen as legitimate, any group considering ethical issues must not only represent people from both sides of the debate but also bring a range of paradigms. For this to be assured, members need to be honest about the personal views behind what they bring to the table. They should then try to be as objective as possible in their deliberations, but we only have their word that they are being so.

The same honesty and openness about where you are coming from is necessary for neutral comment pieces in medical journals.

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Competing interests: SHMcC's beliefs about the world are based in Christianity, and he is opposed to allowing assisted dying.

1 Delamothe T. Half truths and one and a half truths about assisted dying. *BMJ* 2010;341:c7282. (22 December.)

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Let's get the words right too

How we use words is important, particularly in the debate about what is variously referred to as assisted dying, assisted suicide, euthanasia, or plain killing.[1] Words can be used, perhaps unconsciously, for emotional as well as intellectual effect. Thus Delamothe describes Care not Killing as an outfit, an offensive term suggesting a ramshackle (possibly violent) organisation. Similarly, disabled people were accused of "hijacking" the debate for daring to get attention and argue their case.

"Assisted dying" is another example of word misuse. It sounds kinder than "killing," but the debate is not about helping people to die naturally: it's about assisting people to end their life, or ending it for them. Thus "assisted suicide"

and "voluntary euthanasia" are much more precise descriptions. "Assisted dying" is unfair to those who help dying patients without recourse to euthanasia.

"independent Commission on Assisted Dying" gives further examples of curious word choice. A commission is a group given the task of investigating something, usually by an official body. This group was commissioned by Demos, a think-tank, and is funded by high profile pro-euthanasia campaigners. "Independent" means free from outside interference but not necessarily unbiased. Several commissioners, including the chairman, have expressed prior preferences for legalising assisted suicide. The commission will "investigate the circumstances under which it should be possible for people to be assisted to die." "Should" implies that such circumstances exist, ignoring the fundamental question of whether assisted suicide should be allowed at all.

Delamothe appeals for more facts in the debate. I appeal for careful and precise language also: call a spade a spade and suicide and euthanasia by their proper names.

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Competing interests: AB previously and briefly worked in palliative care. He is a member of his hospital's clinical ethics committee, but this letter represents his views alone.

1 Delamothe T. Half truths and one and a half truths about assisted dying. *BMJ* 2010;341:c7282. (22 December.)

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What of virtue and integrity?

The arguments for and against assisted dying continue.[1] Deontological and utilitarian arguments abound, but what of virtue and integrity? How many doctors are going to be happy actively helping to end the life of a patient? And what will be the impact for those who are not happy but feel duty bound to follow a change in the law?

Lifton's comprehensive book examining the stories and experiences of Nazi doctors details what happens when doctors have to do things that compromise their integrity as healers and become killers.[2] Few of these doctors took pleasure in their "work," most developing strategies to cope with their compromised integrity.

It behoves us as a profession to look to the lessons of history and explore what happens when integrity is compromised. In our increasingly utilitarian evidence based healthcare service, we need to research the impact on the mental, physical, and emotional health of doctors who assist people to die in jurisdictions where this is legal.

This research should be extended to look at the impact on the relatives of those whose family member has been assisted to die. Assisting someone to die is seen by many as killing. What is the impact on doctors, patients, and society when carer becomes killer? Good ethics begin with good facts. Let us as a profession ensure that we have these essential facts on which to base our arguments.

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Competing interests: RAK is opposed to euthanasia, and hence assisted suicide.

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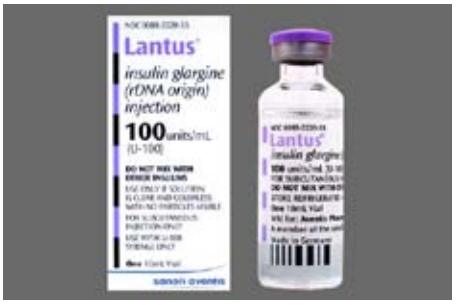

INSULIN MANUFACTURE

Marketing insulins

Cohen and Carter point out the lack of evidence that analogues are better than human insulin and conclude that marketing accounts for their success.[1] We have been here before.

In the 1970s, human insulin was thought in some unspecified way to be better than animal insulin, and Novo and Eli Lilly started a race to make and market it. The result was a tie, but in blind trials neither investigators nor patients could distinguish human from purified pork insulin. In a rational society consumers would have been left to choose which insulin to use. Because human insulin cost twice as much, many would have chosen to continue with animal insulin. However, between 1984 and 1988, 80% of patients in England were switched to human insulin, driven by propaganda and bribery. Advertisements portrayed human insulin as "natural" and "the logical choice" (Novo) or "outstandingly pure and less immunogenic than" animal insulin (Lilly). Drug reps claimed that human insulin would soon become cheaper. Some consultants switched all their patients to human insulin, a decision rewarded by research funds or trips to international meetings.

It is no surprise that analogues have not improved glucose control in most patients. Managing type 1 diabetes is, like becoming a champion golfer, a complex task in which coaching and perseverance are essential. Giving an ordinary golfer the most expensive clubs will not make him or her a champion, and changing a teenager with diabetes and a glycated haemoglobin of 12% to analogues will not result in the target of 7% being miraculously reached. However, the champion golfer or expert patient with type 1 diabetes may obtain a small but worthwhile advantage from a change of clubs or insulin.

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Competing interests: None declared.

1 Cohen D, Carter P. How small changes led to big profits for insulin manufacturers. *BMJ* 2010;341:c7139. (15 December.)

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INDUSTRY SPONSORED BIAS

NICE may be biased too

John-Baptiste and Bell characterise the purported differences in health economic analyses as an industry driven bias.[1] No consideration is given to the possibility that National Institute for Health and Clinical Excellence (NICE) appraisals are biased in the other direction.

Most people involved in health economics know that analyses ultimately boil down to two main considerations—the data selected for input to the model and the assumptions framing the model. Readers unfamiliar with health economics may be surprised that choosing different datasets often makes little difference. Some aspects of data that seem clinically relevant are unimportant in health economic terms. For example, in the health economics of the use of β interferons in relapsing-remitting multiple sclerosis, the effect on relapse prevention has little effect on health economics.

In multiple sclerosis, therefore, the health economics swing almost entirely on disability prevention. The crucial question becomes whether a model will look at outcomes seen only during the phase III trial, or whether it will estimate the future disability effects, and if so for how long into the future? These choices have a huge effect on health economics and essentially determine the outcome. The NICE appraisal of β interferon in multiple sclerosis, and the differences between company commissioned and NICE commissioned reports, swung almost entirely on different choices of time horizon. Both choices—to include a narrow or a broad time horizon—are legitimate scientific and health economic choices, as are similar questions and choices for other treatments. Unfortunately, there is no good way of resolving them when the knee jerk response assumption is that the industry view must be mistrusted and people are unwilling, or unable, to consider alternative points of view.

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Competing interests: MJT is a fellow of the Faculty of Pharmaceutical Medicine, fellow of the Faculty of Public Health, and past author of industry submissions to NICE.

1 John-Baptiste A, Bell C. Industry sponsored bias in cost effectiveness analyses. *BMJ* 2010;341:c5350. (13 October.)

Cite this as: *BMJ* 2011;342:d474