FDA ON ROSIGLITAZONE

More on advisory committee decision

Your readers may be interested in additional background concerning the recent US Food and Drug Administration (FDA) advisory committee meeting on rosiglitazone.1 In July 2007 a joint meeting of two FDA advisory committees voted 20-3 that rosiglitazone increased the risk of acute myocardial ischaemia and 22-1 that rosiglitazone remain on the market, without ever describing the drug’s benefits or explaining how they exceeded its cardiovascular risks.2

In July 2010 the FDA convened the same committees to consider again the fate of rosiglitazone.3 In an unprecedented move, FDA’s Center for Drug Evaluation and Research (CDER), which originally approved rosiglitazone and has defended its continued marketing, invited not only the current members of these committees but also all members from the 2007 meeting, even though they were no longer active members of either committee. Of the 32 advisers who voted at the 2010 meeting, 16 (50%) attended the 2007 meeting, and 15 of them had voted that rosiglitazone remain on the market (one attendee was a temporary non-voting invitee).

FDA advisory committee vote on market withdrawal of rosiglitazone by whether adviser had previously voted to keep rosiglitazone on market

<table>
<thead>
<tr>
<th>Voted in July 2010</th>
<th>Voted in 2007 to keep rosiglitazone on market</th>
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<tbody>
<tr>
<td>Withdraw from market</td>
<td>10</td>
</tr>
<tr>
<td>Keep on market</td>
<td>7</td>
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The addition of these former members substantially biased the results of the vote on whether rosiglitazone should be withdrawn from the market (table). Members voting for the first time were 4.4-times (95% confidence interval 1.1 to 17.0; P=0.01) more likely to vote that rosiglitazone be withdrawn from the market than were members who had voted previously to keep it on the market.

By inviting these former members to participate in the 2010 meeting, CDER biased the outcome of the vote in favour of rosiglitazone remaining on the market. Had these former members not been included, the vote would have been 10 out of 17 (59%) in favour of rosiglitazone withdrawal, with an additional three in favour of severely restricted distribution.

PREVENTING DEMENTIA

Targeting depressive symptoms is unlikely to help

Ritchie and colleagues urge moving from observational epidemiology to public health interventions to reduce dementia and propose reducing depressive symptoms.1 This is a poor example except as an opportunity to reflect on the pitfalls of inferring modifiable risk from correlation.

Depressive symptoms are related to a host of antecedent and cross sectional correlates ranging from economic to psychological variables. They similarly correlate with physical health, physical role functioning, all cause mortality, and mortality associated with specific health conditions. Isolating an association between depressive symptoms and a specific health outcome risks making too much of a spurious association or positing a specific mechanism when others are just as plausible and more testable.

Most increases in depressive symptoms do not represent depressive disorders for which evidence based treatments exist. Moreover, most treatment for depression in the community is inadequate or inappropriate.7 Non-syndromal depressive symptoms are not appropriate targets for treatment with antidepressants, though initiating treatment in people with symptoms but who do not have major depression probably contributed to a twofold to fourfold increase in antidepressant use.1

The ENRICH-D4 trial was a multimillion dollar trial with negative results of enhanced care for depressive disorders among patients with recent myocardial infarction with the aim of preventing re-infarction and reducing mortality.8 A systematic review and meta-analysis concluded that, despite an association between depression and cardiovascular outcomes, routine screening for depression in patients with heart disease was not warranted.9 Perhaps we should consider the folly of jumping from correlation to large scale interventions not only for depressive symptoms and cardiovascular outcomes but also for depressive symptoms and dementia.

BRIDGING THEORY AND REALITY GAP

Ritchie and colleagues may be overoptimistic about their programmes to prevent dementia1 given the huge gap between theoretical programmes derived from observational studies and findings from randomised clinical trials.

Indeed, observational studies have frequently shown a association of dementia with several modifiable factors—hypertension, hyperlipidaemia, and diabetes being putative risk factors and physical activity, antihypertensive treatment, and hormone replacement treatment potential protective factors.7,9 The association of these factors with dementia has also been confirmed in meta-analyses, and the biological mechanisms are partly supported by neuroimaging and neuropathological studies.5 However, to date, randomised clinical trials of therapeutic interventions that target these modifiable factors, such as antihypertensive treatment, oestrogen treatment, and lipid lowering treatment, have been largely inconclusive.1

The progress in understanding the aetiology of dementia has not been successfully translated...
into any effective intervention programmes for the general population. Systematic reviews of observational studies have shown an age dependent association of dementia with some risk factors, especially vascular factors; possessing these factors at midlife but not in late life is more evidently associated with an increased risk of dementia. Thus intervention measures implemented at middle age, such as controlling high systolic blood pressure, could reduce the risk of dementia.

Thus, a life course approach and the multifactorial nature of dementia need to be borne in mind when designing prevention programmes. In this way, intervention measures targeting multiple modifiable factors from midlife may be effective in reducing the risk of dementia.

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We found that only 27% of out of hours admissions were adequately handed over the following morning. As a result, patients were missed on ward rounds, delaying appropriate treatment and investigation. No critical incidents resulted in long term harm, but several near misses occurred.

The current reduction in working hours and shift patterns must end to prevent serious consequences to patient care.

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1 Eaton L. Working time directive puts patients’ lives at risk, surgeons claim. BMJ 2010;341:c4212. (5 August.)

WHEN IS RESTRAINT APPROPRIATE? An American view

As an American surgeon recently returned from Scotland, the one revelation about care in the UK that most reliably incites incredulity in the United States is that restraint is not used in routine clinical care. When I told colleagues in the UK that restraints were regularly used in US intensive care units (ICUs), they were initially surprised but then seemed to accept it in the same spirit as they accept that handgun ownership is commonplace in the US—as an example of casual American brutality.

Sokol’s article raises the question, Do restraints work? I would ask: Do restraints result in lower rates of equipment dislodgement than diligent nursing care alone? Do restrained patients require less sedation, resulting in lower rates of delirium and perhaps earlier extubation and discharge from the ICU, or do restraints themselves agitate patients, leading to more sedation and resulting in the opposite effects on delirium and length of stay?

Retrospective studies hint that restraints do not improve outcomes or reduce undesirable effects (such as unplanned extubation) in ICUs, a position congruent with my experience in the UK. But US practice is unlikely to change quickly unless questions of this sort are studied prospectively in an organised fashion.

To consider the placement of soft wrist restraints a violation of a patient’s basic human rights seems disingenuous when doctors might be making judgments for the same patient about whether a tumour is resectable, a limb salvageable, or chemical paralysis warranted. We doctors do a lot of things that infringe on people’s autonomy and are much more dangerous than restraint. This is morally acceptable because we are trying to help. Restraint should not be treated differently. The challenge is not determining whether restraint is ever appropriate but defining when it serves the end of beneficence.

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1 Sokol DK. When is restraint appropriate? BMJ 2010;341:c4147. (4 August.)

Cite this as: BMJ 2010;341:c4702

MEDIA TRAINING FOR RESEARCHERS

A win-win situation

Greenhalgh raises the issue of media training for researchers. We as healthcare professionals are generally rubbish at this bit of the job. It’s a bolt-on extra: a respite from the day job of preventing disease, treating sick people, or managing a health system. It is also a different language from NHS speak, which, although it may have many different dialects, be they medical or managerial, is all gibberish to a journalist and the general public.

This generation of young NHS hopefuls are the latest in a long line of healthcare professionals who struggle to translate knowledge and information into pithy, accurate, eyecatching news headlines. We need to continue to value this skill and to encourage talent wherever it is spotted. No business in its right mind would be without an effective media strategy—it sells your brand, which develops consumer trust and loyalty. If people trust you, they are more likely to subscribe to what they hear you say.

In public health, trust in the NHS brand is invaluable because it means that messages going through the media will be picked up and acted on. Healthier actions equal a healthier population equals less pressure on the NHS to treat preventable conditions, which leaves more time to learn with the media. It’s a win-win situation.

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1 Greenhalgh T. “We need a short quote”: media training for researchers. BMJ 2010;341:c4493. (18 August.)

Cite this as: BMJ 2010;341:c4853

RISKS OF WORKING TIME DIRECTIVE

Shorter shifts and more frequent handover

Surgeons claim that the working time directive puts patients’ lives at risk. Hospital trusts’ requirement to provide 24 hour acute patient care under the European Working Time Directive and the 48 hour working week has resulted in many junior doctors working more frequent, albeit shorter, on-call shifts, with more handovers between shifts. Such systems reduce continuity of patient care and increase the risk of adverse incidents.

We investigated the frequency and quality of handover of out of hours urology admissions over two months in 2009. Seventy three patients were admitted between 5 pm and 8 am and were not seen by a middle grade urologist. Twenty patients had their cases handed over orally or in writing, but 53 patients had no handover at all. In only seven of the 20 cases handed over were essential details given and clinical urgency indicated.