LETTERS

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SECOND GENERATION ANTIDEPRESSANTS

Fluvoxamine: winner or loser?

Your recent editorial praises the review by Gartlehner and colleagues,[1 2] which is similar to an earlier one by this team.[3] However, the two papers differ strikingly regarding the efficacy of fluvoxamine compared with other antidepressants. In the 2008 review, fluvoxamine lost 11 of 11 comparisons; in the 2011 review, it won 11 of 12 comparisons (see figure).

One possible explanation for the difference might have been new research that became available by the time of the second review. The sampling time was 1980 to April 2007 for the first review and 1980 to August 2011 for the second one. A quick search found only one paper in the references of the 2011 paper with "fluvoxamine" in the title that was published after April 2007.[4]

The abstract includes the comment: "There were no large differences between fluvoxamine and any other antidepressants in terms of efficacy and tolerability."

It is surprising that such a neutrally worded paper would appear to have lifted fluvoxamine from being a 11/11 loser to a 11/12 winner.

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Competing interests: None declared.

1 Lester H. Choosing a second generation antidepressant for treatment of major depressive disorder. *BMJ* 2012;344:e1014. (14 February.)
2 Gartlehner G, Hansen R, Morgan L. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder. An updated meta-analysis. *Ann Intern Med* 2011;155:772-85.
3 Gartlehner G, Gaynes B, Hansen R. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med* 2008;149:734-50.
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Author's reply

Straton raises an interesting point, but his conclusion loses sight of an important factor in any statistical analysis—uncertainty.[1] All fluvoxamine comparisons (in our 2008 and 2011 reviews) are encompassed by substantial uncertainty, as shown by the wide credible intervals in the forest plot. It may seem intuitive to focus on the point estimates and to count winners and losers, but this approach is fundamentally flawed because it ignores the lack of precision of these results.

For our 2011 review, we used network meta-analysis, a statistical method used to estimate the comparative efficacy of drugs that have not been compared directly (as is the case for many fluvoxamine comparisons). We added about 20 new studies to the 2011 review, all of which can affect the estimate of a particular comparison. It is therefore not surprising that this new evidence changed the results. That all of the fluvoxamine point estimates switched from one side of the forest plot to the other is pure coincidence but still in line with what can be expected given the statistical uncertainty.

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1 Lester H. Choosing a second generation antidepressant for treatment of major depressive disorder. *BMJ* 2012;344:e1014. (14 February.)

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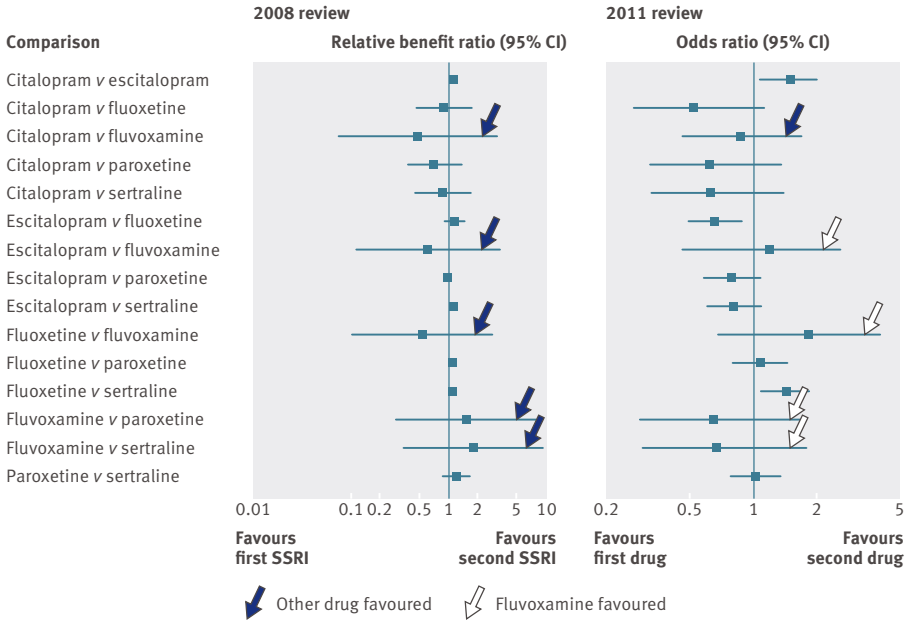

Adapted from *Ann Intern Med* 2008;149:734-50 and *Ann Intern Med* 2011;155:772-85

MENTAL HEALTH

Access to specialist services is missing

It is good to see the National Institute for Health and Clinical Excellence (NICE) focus on improving the experience of adults who use NHS mental health services, but, crucially, access to specialist services is missing.[1] Although the government's current mental health strategy "No Health without Mental Health" emphasises the equal status of mental health needs, the NHS cost saving agenda under the quality, innovation, productivity, and prevention programme (QIPP) has led to sharp unforeseen reductions (up to 50%) in "out of area" admissions into many specialist and secure services. Large numbers of people with serious mental illnesses, such as those in prison and homeless people, are now left untreated. The admission target of 14 days set by Lord Bradley's review on people in prison with mental disorders has been sidelined. This would not happen for equivalent groups with—for example, rare cancers—in need of urgent specialist care.

Reading the NICE guidance we can only strongly support assertions that high quality healthcare is a right and a necessity for all, and that continuity of care, advocacy, and social inclusion are important. It is good that discrimination in mental health is acknowledged, and the needs of the severely ill and the previously detained are emphasised, including access to care, prompt referral, assessment within three weeks, and the avoidance of delays. Even practical plans for admission to hospital are covered, with information about 24 hour access to services.

But how is all this put into practice? Areas suggested for future research include factors associated with late access to services. Such research should cover not only the standards of care, but also the duties of service commissioners and others with gate keeping powers. Only they can ensure prompt non-discriminatory access to specialist care.

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1 Kendall T, Crawford MJ, Taylor C, Whittington C, Rose D; on behalf of the Guidance Development Group. Improving the experience of care for adults using NHS mental health services: summary of NICE guidance. *BMJ* 2012;344:e1089. (1 March.)

Cite this as: *BMJ* 2012;344:e2285

Treat negative symptoms of schizophrenia early on

Kendall's editorial highlights important problems in the management of negative symptoms in schizophrenia.[1] These highly prevalent symptoms are among the most disabling features of schizophrenia,[2] and by their very nature hinder engagement with psychosocial therapeutic strategies. This may partly explain why progress on effective treatment has been so frustratingly slow.

As well as investment in trials of therapeutic approaches, consideration should also be given to strategies that focus on reducing negative symptoms through early identification of psychosis. There is already evidence of an association between duration of untreated psychosis and negative symptoms in the first year after presentation.[3] Furthermore, the TIPS project, which reduced delays to treatment using a targeted education campaign, showed a reduction in negative symptoms that was sustained five years later.[4] A further approach could include widespread education on the importance of identifying and treating negative symptoms, which might improve both the management of these debilitating symptoms and treatment outcomes.[5]

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Competing interests: None declared.

1 Kendall T. Treating negative symptoms of schizophrenia. *BMJ* 2012;344:e664. (28 February.)
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Cite this as: *BMJ* 2012;344:e2297

ALCOHOL AND MORTALITY

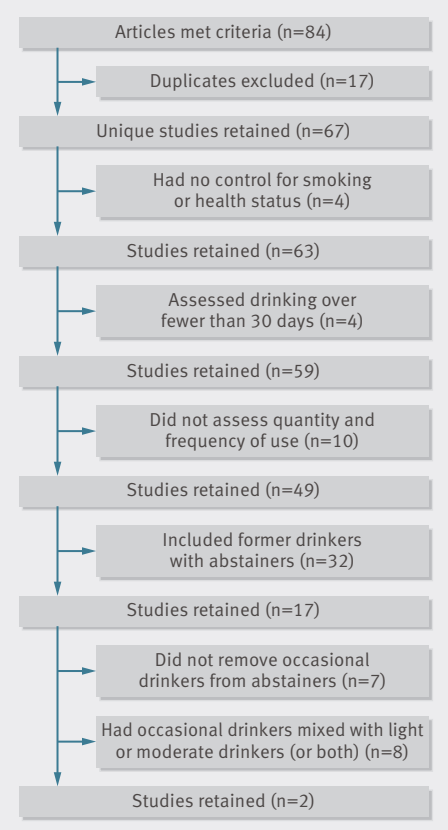
How good is the science?

Ronksley and colleagues asserted that the association between moderate alcohol consumption and reduced mortality risk was "beyond question."[1] We reviewed all 67 studies that generated the 84 articles in their meta-analysis. All but two had at least one of six serious methodological problems, and these two had mixed findings (figure); see http://carbc.ca/Portals/0/News/FeatureSupplement201203.pdf for bibliography).

(1) No control for smoking or health status: A conservative criterion because Naimi and colleagues found moderate drinkers to be healthier than abstainers on 27 risk factors for heart disease[2]

(2) Drinking assessed over fewer than 30 days: A much longer time period is needed to assess lifetime risk of morbidity and mortality

(3) Failure to assess quantity or frequency of consumption: Both are needed to estimate Ronksley's dependent variable of average daily consumption



(4) Former drinkers counted as abstainers: Former drinkers often abstain because of ill health so would make moderate drinkers appear healthy by comparison[3]

(5) Occasional drinkers counted as abstainers: Drinkers also tend to reduce consumption with increasing age and frailty.[3 4] Counting occasional drinkers as abstainers may make moderate drinkers seem healthier

(6) Occasional drinkers combined with moderate drinkers: Occasional drinkers may have enhanced health status owing to other health protective factors.[4] Combining the two groups may make moderate drinkers seem healthier.

We therefore suggest that it is premature to draw firm conclusions from this literature, and that strong competing hypotheses remain to explain the association of health benefits with moderate drinking. The possibility of uncontrolled confounding from other lifestyle factors [2] is supported by meta-analyses finding biologically implausible benefits from moderate drinking—for example, protection against cirrhosis.[5] We hope future studies will avoid these errors and provide a clearer answer to this important question.

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Competing interests: None declared.

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Cite this as: *BMJ* 2012;344:e2276

Authors' reply

Stockwell and colleagues adopted an extreme methodological position, proposing to dismiss an entire body of literature on the basis of the presence of predictable limitations in individual

studies. This dogmatic and dichotomous approach to the evaluation of epidemiological studies is counterproductive to scientific epistemology.

Arguably, an alternative means of exploring the impact of specific methodological shortcomings is through stratified meta-analyses. Within our review, this approach found that several of the apparent biases proposed by Stockwell and colleagues result in minimal changes to the pooled relative risks. Furthermore, their group says little about the strong mechanistic data from randomised trials within our companion review that show a biological effect of alcohol on cardiovascular and inflammatory biomarkers.[1] Finally, Stockwell and colleagues write from the perspective of their affiliation with a centre for addictions. Concern about alcohol from this perspective is justified, given the well documented harms of excessive alcohol consumption. However, worries and advocacy emanating from those concerns need to be distinguished from the scientific question of whether alcohol can be cardioprotective when consumed in moderation.

We reject the notion that an entire body of observational literature should be discarded outright because of limitations inherent in all observational epidemiology, particularly in light of the compelling mechanistic data within our companion review. From an epistemological perspective, the real question is not a dichotomous decision of whether alcohol is harmful or beneficial, but rather what to do with a body of knowledge that is substantial but less than pristine. We hope that our linked reviews continue to inform open minded dialogue around the potential health effects of alcohol—both positive and negative—and the potentially nuanced implications in clinical and public health practice.

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Competing interests: None declared.

1 Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011;342:d636.

Cite this as: *BMJ* 2012;344:e2294

ILLEGALLY PRODUCED ALCOHOL

Perhaps not such a great threat to public health in the UK

We disagree with this alarming picture of increasing availability of illegal alcohol in the UK market and its potential impact on health owing to various contaminants.[1]

The World Health Organization estimates that unrecorded consumption in the UK is relatively stable, at 2 L (or less) of pure alcohol per person (2.0 L in 2000, 1.7 L in 2004, 1.7 L in 2009).[2 3]

According to HM Revenue & Customs,[4] the illicit beer market is not increasing, with estimates of 6% in 2007-8 and 2008-9, and 5% in 2009-10. Illicit beer mainly comes from diversion or drawback fraud, so substantial differences in beer composition are unlikely to lead to more pronounced detrimental health effects.

The discussion about the health effects of illicit spirits neglected basic principles of regulatory toxicology and risk assessment.[1] For example, the legislative limit for methanol in vodka is not a toxicological threshold but a technological threshold based on good manufacturing practices. Toxicological thresholds for higher aliphatic alcohols also cannot be exceeded in home produced spirits.[5]

Unless there is empirical evidence, we should assume that unrecorded alcohol in the UK has similar health effects to recorded alcohol. Alcohol prices in the UK are currently comparably low, so that even the marginalised consumer has little incentive to switch to surrogate alcohol products. We see no need for a policy on unrecorded alcohol (except as a way to reduce fraud), and efforts in the UK should focus on measures that have been shown to reduce total alcohol consumption, such as price increases.

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Competing interests: None declared.

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Cite this as: *BMJ* 2012;344:e2251

Authors' reply

We were surprised by Lachenmeier and Rehm's response to our editorial. Of course efforts should focus primarily on legally sold alcohol, and we have recently published a systematic review to inform such policies.[1]

However, the World Health Organization's quoted estimates for unrecorded consumption are now several years old. More recent data from the UK government suggest a growth in the scale of the problem, and we think it would be complacent not to flag up the potential public health consequences, which may not be trivial in some sections of the community.

The question of beer that the authors raise was not mentioned by us, and we agree that it is not a concern. However, we presume that they do accept that illegally produced spirits are less likely to be subject to the quality standards applied in commercial production. We made it clear that these products can contain a range of toxic alcohols, not that they will always do so, and discussed the circumstances in which this was more likely. We are fully aware that manufacturing standards and toxicological thresholds vary, but we did not feel it necessary to include this detail in a short editorial.

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Competing interests: None declared.

1 Bryden A, Roberts B, McKee M, Petticrew M. A systematic review of the influence on alcohol use of community level availability and marketing of alcohol. *Health Place* 2012;18:349-57.

Cite this as: *BMJ* 2012;344:e2255

ATRIAL FIBRILLATION

Proposed screening is too simple and not focused enough

A recent consensus conference organised by the Royal College of Physicians of Edinburgh recommended opportunistic pulse checking of people over 65 years by GPs, followed by electrocardiography for those with an irregular pulse.[1] The aim is to identify people at an increased risk for stroke and adequate anticoagulation treatment of those detected.

However, this cheap and simple approach

will probably not achieve its goal of preventing as many strokes as possible. A high proportion of strokes occur in people with paroxysmal atrial fibrillation only, and opportunistic pulse checks are unlikely to identify such short lasting episodes. Moreover, the accuracy of electrocardiography in identifying atrial fibrillation is far from ideal in primary care, as shown in the SAFE trial.[2]

The focus on people over 65 years ignores the fact that many younger people with atrial fibrillation have a high risk of stroke, if certain risk factors are present as expressed in the CHA2DS2-VASc score.[3] The human and economic burden of stroke in this younger age group is particularly high.[4]

Such a screening programme should focus more on risk than on age groups and make use of more sophisticated but still relatively low priced methods, such as 24 hour electrocardiography, to increase sensitivity. Training in and assistance with new methods should be provided by cardiology experts in secondary care.

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Competing interests: None declared.

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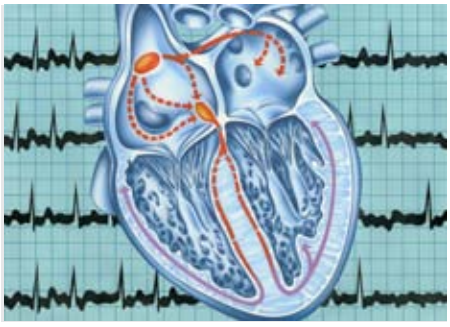
Cite this as: *BMJ* 2012;344:e2257

Atrial fibrillation, rheumatoid arthritis, and cardiovascular risk

Lindhardsen and colleagues' study found that increased risks of stroke and atrial fibrillation were associated with rheumatoid arthritis in the Danish population.[1] The incidence rate ratio of stroke for people with rheumatoid arthritis was 1.33 (95% confidence interval 1.22 to 1.46) for women and 1.34 (1.19 to 1.51) for men. The findings are similar to the increased risk of cardiovascular disease in patients with rheumatoid arthritis reported in the QRISK2 study,[2] where the adjusted hazard ratio for women was 1.50 (1.39 to 1.61) and 1.38 (1.25 to 1.52) for men. The QRISK2 algorithms also include terms for atrial fibrillation, which had overall adjusted hazard ratios of 3.06 (2.39 to 3.93) in women and 2.40 (2.07 to 2.79) in men in the QRISK2 study. These results support the



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inclusion of atrial fibrillation and rheumatoid arthritis in the calculation of cardiovascular risk.

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Competing interests: See www.bmj.com/content/344/bmj.e1257/rr/574632.

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Cite this as: *BMJ* 2012;344:e2259

UNRELIABILITY OF BIOPSIES

No more fine needle aspiration biopsies?

Should these results be confirmed,[1] in the future we should avoid all diagnostic methods that sample only a small fraction of a tumour, preferring total excision instead.

This would mark the end of fine needle aspiration biopsies, pipelle biopsies, colonoscopy biopsies, brush cytology biopsies, and so on.

A high grade invasive carcinoma could be hiding only millimetres away from retrieved reassuring tissue.

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Competing interests: None declared.

1 Mayor S. Biopsies from one tumour have more genetic differences than similarities, finds study. *BMJ* 2012;344:e1714. (7 March.)

Cite this as: *BMJ* 2012;344:e2261

CHANGES IN THE NHS

Going to hell in a hand cart?

Three small points for us all to consider.[1] Firstly, only England is changing its NHS as part of the current parliamentary mess. The rest of the UK is wisely treading a very different path and delivering more effective care.

Secondly, the focus on objectives by management may not be the best way to provide the best care. As Deming said in his foreword to Walton's book: "Understanding of a stable system discloses the devastation of people wrought by the annual appraisal of performance, futility of management by the numbers, management by MBO [management by objectives]."[2] He goes on to say: "teamwork in a company, except for putting out fires, is impossible under the existing annual appraisal of performance. Everybody, once the fire is conquered goes back to his own life preserver, not to miss a raise in pay."

Thirdly, Deming famously said "Export anything to a friendly country except American management." North American business schools (or their European clones) are training NHS managers and observers. Yet Deming implored the Japanese to avoid the seductive approach of American business schools' teaching because it would lower quality. The leading car manufacturer in the world learnt painfully the price of ignoring this advice.

I suspect the NHS is going to hell in a hand cart for exactly the same reason.

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Competing interests: None declared.

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Cite this as: *BMJ* 2012;344:e2288

FEAR OF DEATH

Not universal

In her thoughtful article, Heath states "Everyone is afraid of death or dying," but I'm not sure that this is true.[1] I certainly have no immediate wish to die. However, from the perspective of my nearly 73 years of life and nearly eight years of retirement, I have no fear of death. I have had an excellent and lucky life, I have done many of the things that I wanted to do, and I am content that many of the things I haven't done will now never get done. I'm a lot more afraid of dementia than of death.

Also, my dear late wife, when she was dying of ventilatory failure after 29 years of multiple sclerosis and aware that she was dying, was not in the least afraid, but rather relieved. Perhaps age brings these thoughts, but Mozart, in a famous letter to his father and in the prime of life, was also not in the least afraid of dying.[2]

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Competing interests: None declared.

1 Heath I. Who's afraid of whom? *BMJ* 2012;344:e1595. (7 March.)
2 Wolfgang Amadeus Mozart. *Wikipedia* http://en.wikiquote.org/wiki/Wolfgang_Amadeus_Mozart.

Cite this as: *BMJ* 2012;344:e2301