Off-label prescribing in macular degeneration

Are doctors being pushed into prescribing an off-label drug?
Margaret McCartney investigates

The drug company Novartis stands to lose a hefty slice of income if most patients with macular degeneration in the United Kingdom are treated with the cheaper cancer drug bevacizumab (Avastin) instead of the more expensive eye drug ranibizumab (Lucentis), which, unlike bevacizumab, is licensed specifically for that condition (www.inpharm.com/news/1657822/novartis-lucentis-price-cut-switzerland). Both drugs are made by Roche, and the more expensive one is marketed in the UK by Novartis.

Novartis has produced research showing that patients do not like the idea of being given an unlicensed drug for their condition. And now some newspapers are claiming that doctors are being pushed into prescribing the cheaper drug. But are they really being pressurised to do so, and would it matter if they were? The background is this: bevacizumab costs about £85 (€98; $134) an injection, compared with £740 for ranibizumab (http://blogs.bmj.com/bmj/2011/06/28/james-raftery-avastin-lucentis-and-nice). Ranibizumab is licensed to treat macular degeneration; bevacizumab is not, but it has been proved to be just as effective in doing so.

Evidence that some places are seeking savings by turning to bevacizumab comes from the SHIP (Southampton, Hampshire, Isle of Wight, and Portsmouth) cluster of primary care trusts, which, unlike bevacizumab, is licensed specifically for that condition (www.inpharm.com/news/1657822/novartis-lucentis-price-cut-switzerland). Both drugs are made by Roche, and the more expensive one is marketed in the UK by Novartis.

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THE ART OF RISK COMMUNICATION  Gerd Gigerenzer

What are natural frequencies?

Doctors need to find better ways to communicate risk to patients

A 2011 Cochrane Review concluded that health professionals and consumers “understood natural frequencies better than probabilities.” A 2011 *Annals of Internal Medicine* article reported the opposite, that “natural frequencies are not the best format for communicating the absolute benefits and harms of treatment.” How should physicians deal with these contradictory messages?

As is often the case, the contradiction lies in the definitions, not in the data. Ulrich Hoffrage and I introduced the term “natural frequencies” in the late 1990s and conducted the first studies showing that they foster understanding of the positive predictive value among lay people, doctors, and medical students. What is a natural frequency? It is a joint frequency of two events, such as the number of patients with disease and who have a positive test result, and is an alternative to presenting the same information in conditional probabilities, such as sensitivities and specificities. Conditional probabilities tend to cloud the minds of many people, including health professionals, as the following problem illustrates (for convenience, probabilities are expressed in percentages).

Assume you use mammography in a certain region to screen for breast cancer. The following information is known:

- The probability that a woman has breast cancer is 1% (the prevalence).
- If a woman has breast cancer, the probability that she tests positive is 90% (the sensitivity).
- If a woman does not have breast cancer, the probability that she nevertheless tests positive is 5% (the false positive rate).

A woman tests positive. What is the chance that she actually has breast cancer? When I asked 160 gynaecologists this question at the beginning of a continuing medical education session on risk literacy, a majority (60%) believed the answer was 80% to 90% and 19% believed it to be 1%. Why? To compute the probability of cancer given a positive test result from probability information (fig, left), we need to use Bayes’s rule, a complex formula that entails three multiplications. Note that the four conditional probabilities at the bottom of the tree (left) do not add up to 100%. This is because they are normalised with respect to the prevalence of cancer or no cancer. With normalisation, the information about prevalence gets lost and then needs to be reintroduced by multiplying it by each conditional probability. Natural frequencies (fig, right), in contrast, do not require these multiplications. The four natural frequencies at the bottom of the tree (right) are not normalised but add up to the total number on the top, simplifying the use of Bayes’s rule.

So why did the *Annals of Medicine* article not find this advantage? Simply because it did not test natural frequencies. As shown in the figure, natural frequencies are joint frequencies, such as the number of women (nine) who test positive and who have breast cancer. These differ from simple frequencies, such as two in 10 people who test positive. Similarly, conditional probabilities and simple probabilities are not the same. What the *Annals of Medicine* article did was compare simple percentages (such as 2% of people who took a drug and had diarrhoea) and other formats against simple frequencies (20 in every 1000 people who took the drug and had diarrhoea), which it called natural frequencies. However, the computational advantage does not apply to simple frequencies.

It does not matter to a computer program whether the input is conditional probabilities or natural frequencies, but to a human being it clearly does. Healthcare providers need to know how to represent information so that their patients can actually understand what it means. Providing a helpful representation is a key skill in the art of communication of risk. Yet understanding test results is not a forte of most doctors themselves. To remedy the situation, every medical curriculum should teach an understanding of health statistics. This is not the same as teaching biostatistics (which corresponds to the left of the figure). For some people, natural frequency trees are ideal; for others, natural frequency grids that represent individuals by icons are best. Effective representations such as these are indeed available, but we need to teach them.

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Conditional probabilities (left) make it difficult to infer the positive predictive value, while natural frequencies (right) make it easy. The reason is that the representation simplifies the computation. Both formulas are versions of Bayes’s rule. The four probabilities (expressed in percentages) at the bottom of the tree are conditional probabilities; the four frequencies at the bottom of the right tree are natural frequencies. Natural frequencies are a form of intuitive statistics, corresponding to the way humans encountered information before probability theory was invented.
Probe GMC over Southall and Meadow hearings

The GMC should not support complaints from parents where it is alleged that they have abused doctors working in child protection

Professionals Against Child Abuse welcomes the result of the latest fitness to practise hearing concerning David Southall, which found him not guilty of serious professional misconduct. Given the evidence, we would question how the allegations ever reached a hearing, although the same applies to the earlier matters examined in fitness to practise hearings involving Professor Southall in 2004, 2006, 2007, and 2008.

We are seriously concerned as to how the GMC repeatedly alleged charges of serious professional misconduct against Professor Southall in the above hearings—as we were with its decision to discipline Roy Meadow in 2005. Both professors of paediatrics are internationally recognised experts in fabricated and induced illness. They were tried as much by politicians and the media as by the GMC, whose fitness to practise panels ordered their erasure from the medical register. Both successfully appealed and were returned to the medical register.

We are strongly critical of the alleged “expert” advice that the GMC used in deciding to hold hearings in both these cases. In the latest hearing, the GMC pursued complaints by parents of children about whom Professor Southall had given evidence that was intended to help social services protect the children. For reasons best known to themselves, the GMC and its expert pursued new complaints relating to administrative matters on issues such as record keeping and filing, which did no harm to the children or other parties. The hearing could have led to a potential finding of serious professional misconduct and erasure from the register.

In one case, David Southall copied a letter about a child from South Wales to a paediatrician in Gwent without the parents’ permission—the GMC had already found in 2007 that this breached confidentiality. This is despite the fact that the referring consultant from Great Ormond Street, Dr Dinwiddie, to whom the letter was later copied correspondence to an “unnamed” community physician in Gwent and that a Social Services child protection case conference also made recommendations to let “local hospitals” in Gwent know what was happening. In the second case, correspondence was found in David Southall’s departmental file and not in the main hospital records, long after the child was discharged and highly unlikely to return. The panel found in 2007 that this breached the integrity of medical records in North Staffordshire, even though the child was being followed in Berkshire and London and the correspondence was being copied to David Southall predominantly for courtesy purposes.

In both these cases pursuit of the complaint was supported by the GMC’s expert, who had also been called by parents as an expert witness in the case against Professor Meadow and had previously published criticism of Professor Southall’s work. However, he did not give evidence in the latest hearing to decide on the seriousness of the panel’s findings.

Since August 2009 the GMC has been able to close a complaint if it is thought to be vexatious. Yet what doctors will understand from the GMC’s actions against Professor Southall is that the GMC may pursue complaints from parents in alleged child abuse cases and will threaten the doctor’s career and personal life. It would seem that the GMC’s motive for progressing to hearings is not based on the seriousness of the alleged errors but more on the media and political reaction. Throughout all these cases the honesty and good faith of David Southall and Roy Meadow have never been questioned; yet the sanction of erasure that they both received was disproportionate when compared, for example, with doctors who access child abuse media (pornography), who get far lower sanctions.

The effects of the GMC’s actions against two high profile experts have been damaging to child protection. Paediatricians at all levels have become less willing to engage with child protection cases, and those who do are more likely to prepare reports that sit on the fence and do not help direct the courts. Although the GMC hearings have damaged the lives of David Southall and Roy Meadow, it is vulnerable children who are likely to have suffered most, because doctors will have been less willing to protect them.

At the 2008 annual general meeting of the Royal College of Paediatrics and Child Health members voted overwhelmingly in support of the motion that the college had grave concerns over the GMC’s procedures for dealing with cases related to child protection. The GMC is soon to close its own consultation on guidance to doctors in matters relating to child protection. But although this draft guidance deals with communicating with parents, it is short on the difficulties faced by paediatricians when parents deceive doctors or use complaints to the GMC as a means of dealing with allegations against them. Doctors dealing with child protection have become sadly too familiar with these scenarios, yet the GMC has clearly chosen to act on behalf of parents rather than to understand the needs of children. Until the GMC shows such understanding, paediatricians will remain wary of involvement in such cases and children will suffer.

We now believe that the GMC should be subject to an independent inquiry to examine how decisions were made that led to these inappropriate hearings so that in the future the GMC will not support complaints from parents where it is alleged that they have abused doctors and thus deter engagement in child protection. We submitted a lengthy complaint about the GMC’s actions to the parliamentary health select committee in 2008, but this matter was not seen as a priority. However, with the conclusion of the GMC’s cases against Professor Southall, a full and proper external inquiry now needs to be undertaken.

Politicians are quick to react in prominent cases where there has been failure to protect a child, but they showed no concern when two of the most prominent figures in child protection are subject to regulatory abuse with the consequent effects on child protection. Hansard shows that politicians went so far as to deny the existence of fabricated and induced illness.

We believe that the GMC also needs to be more transparent in its selection of experts to avoid inappropriate inquiries in child protection cases. Finally, Professionals Against Child Abuse considers that the GMC should now apologise to Roy Meadow and David Southall for the actions against them.

John Bridson is chairman, Professionals Against Child Abuse

References are on bmj.com

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Call for urgent action on climate change

On 17 October leading health professionals and experts in international security met at a BMJ conference in London on the health and security implications of climate change. They issued a statement calling on governments around the world to prioritise efforts to tackle the causes and effects of climate change.

Specifically they urge:
• The European Union to unconditionally agree a target to reduce greenhouse gas emissions domestically by 30% by 2020 and to prepare further targets towards 2050 that would incentivise the decarbonisation of the economy
• Developed countries to adopt more ambitious targets on greenhouse gas reduction, to increase their support for low carbon development, and to invest in further research into the effects of climate change on health and security
• Developed countries to identify the key ways in which climate change threatens health and democratic governance and to undertake mitigation and adaptation activities, including through supported and unsupported nationally appropriate mitigation actions
• All governments to enact legislative and regulatory change to stop the building of new coal fired power stations and to phase out the continuing operation of existing plants, prioritising those using the most polluting (and thus health damaging) lignite coal
• All parties at the climate change conference in Durban on 28 November to 9 December 2011 to strive to adopt an ambitious agreement on greenhouse gas reduction that is consistent with the target of restricting the global temperature rise to 2°C (or, more safely, 1.5°C) above preindustrial levels
• Establishment of a mechanism to ensure that all people can share equitably the benefits of a safe atmosphere without penalising those with the least historical responsibility for climate change
• All governments to incorporate the UN Security Council’s presidential statement from 20 July 2011 on the potential consequences of climate change on security into their short and long term security planning
• All governments to strive to adopt climate change mitigation targets and policies that are more ambitious than their international commitments.

To read the statement in full and see the signatories, add your signature, or for more information about the conference please visit http://climatechange.bmj.com/statement.

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LOBBY WATCH Jane Cassidy

Save Our Pubs & Clubs

What is its goal?
The Save Our Pubs & Clubs campaign wants to see an amendment to the public smoking ban, which it says has led to hundreds of pubs and clubs going out of business since 2007. It would like the United Kingdom to be brought into line with other European countries where smoking is still allowed in some licensed premises or in “comfortable” outdoor smoking rooms.

The television chef and pub owner Antony Worrall Thompson is the campaign’s patron. Supporters include the Working Men’s Club and Institute Union, 251 pubs and clubs, the artist David Hockney, and the musician Joe Jackson.

MPs who have pledged their support include Brian Binley (Conservative, Northampton South), Philip Davies (Conservative, Shipley), John Hemming (Liberal Democrat, Birmingham Yardley), Simon Kirby (Conservative, Brighton Kemptown), Greg Knight (Conservative, East Yorkshire), and David Nuttall (Conservative, Bury North).

A total of 86 MPs supported Mr Nuttall’s 10 minute rule bill to amend the smoking ban, debated in the House of Commons a year ago. And 36 MPs have signed Mr Binley’s early day motion calling for a review of the smoking ban.

Who’s backing it?
The campaign is run by the pro-smoking lobby group Forest (the Freedom Organisation for the Right to Enjoy Smoking Tobacco). Most of its money is donated by UK based tobacco companies.

Forest’s director, Simon Clark, told the Scottish parliament’s Health and Sport Committee in 2009 that Forest received about £250 000 (£285 000; $395 000) a year from three tobacco companies, Japan Tobacco International (JTI), British American Tobacco, and Imperial Tobacco Group.1

Individual smokers known as Friends of Forest contribute donations ranging from £10 to £2000 to register their support, says the organisation. However, it is not a membership group run by a committee; instead its role is to lobby politicians and the media.

The “best smoking area” category at this year’s Great British Pub awards event was jointly sponsored by Save Our Pubs & Clubs and JTI, the world’s third largest tobacco company.

So it’s just a “front” organisation for the tobacco industry?
Forest says that it lost funding from a tobacco company for pursuing a campaign against HM Customs and Excise in 2001. It insists that it represents the consumer, not the tobacco industry. It speaks its mind as it sees fit and guards its independence jealously, whatever the cost, it says.

However, Mr Clark also told the Scottish parliament that without donations from tobacco companies it would be very difficult for Forest to exist.

Forest is currently campaigning to stop the smoking ban being extended to parks, beaches, and other outdoor areas. It is also fighting the “denormalisation” of smoking, the use of “junk science by the tobacco control industry,” and discrimination against smokers, particularly in the workplace.

Does Forest have any more offshoots? 
Yes, the Free Society. This is billed as an initiative set up to fight “big government” attacks on personal lifestyle choices on a broad front that includes tobacco, alcohol, and food.

The war on tobacco has moved from education to censorship and coercion, says the society. Today the “war on tobacco” has been joined by the “war on obesity” and the “war on binge drinking,” it says.

“Genuine libertarians stick together and defend people’s right to do things they themselves are not that keen on. If you enjoy a drink but don’t smoke, you should still oppose the war on tobacco; if you smoke but don’t drink, you should oppose excessive regulation of alcohol, and so on,” it says.

Other areas of interest to the Free Society include motoring, in particular the excessive use of speed cameras and speed limits on motorways; closed circuit television cameras; compulsory identity cards; free speech; and global warming.

The Free Society co-hosts events with like minded libertarian groups such as the Institute of Economic Affairs, the Adam Smith Institute, the Democracy Institute, the Manifesto Club, Liberal Vision, and Privacy International.

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