Can We Rely On Science?

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Special Issue Supplement

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Can we rely on science?
Special Issue Editorial

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EDITORIAL

Science commands an enormous amount of respect in society at large. Indeed, scientists and their endeavours have helped enlighten the world over the last several hundred years. However, in the past decade or so there have been numerous concerns about the quality of the science papers that are driving policy in numerous different settings.

In 2010 a paper by two world leading economists in an eminent journal reported that economic growth of a nation slows dramatically when a government's debt exceeds 90% of a country's annual economic output. The study was cited by politicians and policymakers worldwide, helping to justify that reducing public spending would help drive economic growth. However, in 2013 a Harvard student found simple errors in the paper when trying to verify the findings, and the paper was later retracted with the authors fervently denying they were selective in their selection of data, and admitted a coding error1. In the realm of healthcare there have been unfounded concerns voiced about the Measles Mumps and Rubella vaccine (MMR)2 and difficulties in highlighting genuine concerns with an experimental drug3 due to the influence of a drug companies. Indeed, in a recent Economist article it was suggested that, “the false trails laid down by shoddy research are an unforgivable barrier to understanding”4.

This Scottish Universities Medical Journal supplemental edition ‘Can we rely on science?’ focuses upon some of these issues. Firstly, in the article, ‘The State of Science and Unreliable Research’5, your Associate Editor will look at the current challenges to high quality clinical and scientific research, including the competitiveness of science and academia, publication bias, the weaknesses of peer-review and ‘hidden’ data-sets.

Secondly, Dr David Christmas (Consultant Psychiatrist) will report about the influence that drug companies and the pharmaceutical industry has upon medical research67. In his two article series, Dr Christmas will consider both the problems that the current level of involvement the pharmaceutical industry causes and will suggest solutions to improve the relationship between scientists, clinicians and industry. Finally, Iain Hyndman explores the Human Genome Project (HGP) in a personal view/commentary article. The HGP was the largest collaborative research project carried out in human history, whose long-term effects have incredible potential to aid the lives of millions of patients worldwide8.

This supplement hopes to inform our readers about some of the important non-clinical factors that drive evidence based practice. As always we welcome comments and suggestions about our publication and welcome submissions for future main issues, online platform and supplements.

References
All references available on the online edition of this paper.
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The State of Science and Unreliable Research
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ABSTRACT
Scientific endeavours in all fields have helped develop and shape society across the globe. In the past decade the sheer quantity of research and data has been staggering, with 90% of all data being obtained since 2011. In the face of this sheer quantity of research and data there are legitimate concerns that quality may be being compromised for a number of different reasons. There are concerns that the peer-review process is not as effective as it should be, that papers reporting negative results only account for a small proportion of mainstream journal articles, and that the competitiveness of science and academia is discouraging verification studies particularly in basic sciences and promotes exaggeration and cherry-picking of results.

Such concerns are legitimised by the tenfold increase in retractions from mainstream journals in the past decade. In addition to wasting time and resources such flawed research may place patient lives in jeopardy. Indeed, between 2000 and 2010, 80,000 patients took part in clinical trials based upon research that was later retracted (either due to error or improprieties). This paper aims to discuss some of the areas including the competitiveness of science and academia, publication bias, the weaknesses of peer-review and ‘hidden’ data-sets.

Key Words: scientific research; peer-review; clinical research

Introduction
Scientific endeavours in all fields have helped develop and shape society across the globe. In the past decade the sheer quantity of research and data has been staggering, with 90% of all data being obtained since 2011. In the face of this sheer quantity of research and data there are legitimate concerns that quality may be being compromised for a number of different reasons. There are concerns that the peer-review process is not as effective as it should be, that papers reporting negative results only account for a small proportion of mainstream journal articles, and that the competitiveness of science and academia is discouraging verification studies particularly in basic sciences and promotes exaggeration and cherry-picking of results.

Such concerns are legitimised by the number of article retractions in mainstream journals. Retractions have steadily increased since the first retraction in 1977, with a ten-fold increase in the past decade. In addition to wasting time and resources such flawed research may place patient lives in jeopardy. Indeed, between 2000 and 2010, 80,000 patients took part in clinical trials based upon research that was later retracted (either due to error or improprieties). This paper aims to discuss some of the areas including the competitiveness of science and academia, publication bias, the weaknesses of peer-review and ‘hidden’ data-sets.

“Trust but Verify”
The concept that identical experiments always get the same result, no matter who performs them, is a cornerstone to scientific research and aims to prove a hypothesis as fact. Achieving perfect verification of all studies is clearly not achievable due to limitations of basic science research describing new findings, but it should be possible for the majority of
Science experiments (in all scientific fields) to be replicated and verified based upon the methods described by authors. However, this appears not to be the case.

In 2012, Amgen (an American drug company) attempted to replicate 53 pre-clinical oncology studies they considered landmark papers in the basic science of cancer. Even when liaising closely with authors of the relevant papers, only 11% of the papers findings were replicated, a result described by the authors as “shocking”. In 2011 Bayer (a German drug company) only managed to replicate a quarter of 67 seminal studies in an analysis of early in-house projects in the research fields of oncology, women’s health and cardiovascular diseases. Such work underlines the importance of confirmatory validation studies, which should also aim to complement the knowledge on a particular therapeutic target and hone researchers techniques. Indeed, the difficulties in the reproducibility of early stage scientific research may be part of the reason for the fall in the success in newly developed Phase II clinical trials in recent years.

It should be noted that a difficulty in reproducibility does not amount to fraud, but merely shows that particular novel techniques assessing unexplored scientific avenues in basic science may be prone to a greater degree of variability and error than expected. Another potentially contributing factor may be that papers do not adequately report all research resources (including antibodies, model organisms etc.), without which it is challenging to reproduce experiments even when the underlying science is sound. Indeed, a recent study reported that more than half of 238 biomedical papers in 84 journals failed to identify all the resources required to verify their work. Another review of 351 randomly selected papers in high-impact journals found that only 143 papers were subject to any data availability policies, and adhered to the data availability instructions in their respective journal.

Thus, it is important to promote verification. Adequately verifying scientific techniques will be of benefit for drug companies as their investments in early stage therapeutic products would be more likely to succeed at Phase II trials and for scientists as scientific techniques will develop over-time and provide greater weight to research findings. However, promoting verification is not easy. Many academic researchers would prefer to embark on novel research that is more likely to advance their own career and junior researchers may feel that replication is a challenge against a papers authors. More importantly, in the current climate the costs associated with verification studies alongside a desire for novel research by funding bodies may prevent some work being replicated.

Despite these barriers, in the discipline of psychology the journal Perspectives on Psychological Sciences will shortly have a section devoted to replication and verification studies. There is also the newly formed Reproducibility Initiative through which life scientists can pay to have their work verified by an independent laboratory, giving the papers methods and findings more weight thus incentivising replication. The Initiative is currently reviewing the findings of the 50 highest-impact cancer papers published between 2010 and 2012, following a grant from the Laura and John Arnold Foundation. Dr Elizabeth Iorns, the co-director of the Reproducibility Initiative, noted “The lack of reproducibility in cancer studies is a major obstacle in the development of viable therapies to cure cancer.” It is hoped that this initiative will help improve the reproducibility of work in other science and healthcare fields.

Science – A Competitive Industry
Science is a competitive industry. Full professors in America earned on average $135,000, and with 6 applications from new PhDs for every academic post in the US, the stakes are
The pressure to publish work in high-impact journals is crucial, as high-impact publications are important for being successful in the academic job market and subsequently obtaining and maintaining funding for research. The pressure to ‘publish or perish’ appears to have an effect upon some researchers overall scientific conduct. A 2009 meta-analysis covering 18 fraud surveys [six targeting biomedical scientists directly], found that 2% of those participating admitted to having falsified, fabricated or modified data at least once themselves. Although this figure is reasonably low, an alarming 14% reported to have noticed this behaviour in colleagues. The author also proposed that as these surveys ask sensitive questions and have other limitations, these figures are likely to be a conservative estimate of the true prevalence of scientific misconduct. Cherry-picking, selectively reporting data that supports a desired outcome, may be much more common than deliberate fabrication. A fine balance must always be found about reporting data that is relevant and important to the narrative of a paper, and data that is not. Massaging the data so they favour a particular finding/hypothesis walks a tightrope, between sloppy science and scientific misconduct depending on the circumstances.

Such cases have the potential to have a hugely detrimental impact for all involved in scientific research. Firstly, upon honest researchers by preventing those researchers obtaining funding for their work and tainting institutions with a fraudulent tag. Secondly, scandals in sensitive scientific areas including stem-cell work and oncology may erode public confidence in science and their research more widely. Finally, clinical work involving patients based upon flawed research may be placing lives at risk.

There are several approaches that are currently attempting to address some of the concerns associated with research integrity. Firstly, it is becoming increasingly stressed that the responsibility of maintaining academic integrity should fall with the senior investigator. In a recent Nature editorial it was noted that this individual has a unique position of trying to develop, “a laboratory environment that provides a strong foundation in best practice in research and research ethics, and to be a compelling role model for trainees.” Secondly, there has been recent work at both a national level and international level to support research integrity. In the UK, the UK Research Integrity Office provides support and advice for individuals and institutions throughout the research process and offers advice for those who feel that they may have witnessed research malpractice. Furthermore, international guidelines have been developed from the 2nd Worldwide Research Integrity Conference, aiming to raise awareness of science ethics and to lobby governments and institutions to design and implement policies to promote research integrity. The guidelines note the importance of reporting and raising irresponsible research practice. Finally, the guidelines stress to researchers that despite the huge pressure they can be placed under to cherry-pick or fabricate results, irreducible findings will be discredited in the long-run and the potential implications of fabrication can be career ending. Finally, journals can promote integrity and transparency in the practise and presentation of research by developing and implementing rigorous standards for data presentation, author contributions and statements of authors’ conflict of interests. Although there is more work to do in this area, the fact that there is increased awareness and interest in this area hopefully will improve the overall climate for researchers working in the ‘publish or perish’ climate.

**Publication Bias**

Yet another challenge facing science is publication bias. Journals yearn for papers that prove a hypothesis or describe a novel intervention or treatment. Indeed, negative results, where a hypothesis/treatment is shown to be incorrect, account for only 14% of published papers, down from 30% in the 1990s. However, publishing negative results, where a hypothesis is
shown to be incorrect, remains crucial. Failing to publish these results creates a false impression and bias in the literature. Other scientists may waste valuable time and resources on treatments that have already been shown to be ineffective. The importance of publishing negative studies is even more important in the area of clinical research, as patients may be treated with medications/therapies that have already been shown in unpublished data to be of no benefit and/or harm. Furthermore, not publishing negative data undermines all of the efforts made to minimise bias in individual trials.\(^{15}\)

There have been numerous efforts to try and address this. Firstly, in the US there are moves to enforce legislation requiring all results of clinical trials funded by the state to be posted on clinicaltrials.gov within 12 months of completion\(^{16}\). To date, this legislation appears to have been widely ignored\(^{16}\) and up to a third of clinical trials financed by the National Institute for Health remain unpublished after 51 months\(^{5}\). Secondly, closer to home, the AllTrials.net campaign, started 12 months ago, has called for all trials on all uses of all currently prescribed treatments to be registered, with their full methods and results reported\(^{17}\). The campaign is widely supported by medical and academic organisations, and has obtained the support of some in the pharmaceutical industry including GlaxoSmithKleine. This unfortunately will only include research carried out from 2014 and beyond, meaning that previous trial data will continue to skew the evidence base. However, efforts are continuing to include historical data. Thirdly, the British Medical Association has passed a motion noting that withholding trial results constitutes research misconduct\(^{18}\) with the General Medical Council reviewing their position\(^{15}\). Finally, for individual researchers, many journals now have online only publication meaning they have more space to publish papers with negative results.

**The Challenges of Peer-Review**

Peer-review is often reported to be the ‘gold-standard’ of vetting the quality of scientific work\(^4\). However, there are numerous examples of research that passed this standard subsequently being retracted due to clear fraud or unethical conduct. The most commonly quoted examples include Hwang Woo-suk who carried out fraudulent work on stem-cells published in *Science*\(^{19}\) and Andrew Wakefield whose work in the 1998 *Lancet* led to the MMR vaccine scandal\(^{20}\). Importantly, these cases extend the highest impact journals, which have rejection rates in excess of 90%.

Work by John Bohannon, a Harvard biologist, found that a pseudonymous paper on the effects of a chemical derived from lichen to treat cancer cells was accepted by 157 of 304 journals the work was submitted to\(^{21}\). This was despite the fact that the paper had numerous deliberate errors in study design, analysis and the interpretation of results\(^{20}\). This study only focused upon open access journals, which generally charge a fee to publish. Although this study only focused upon lower impact journals, similar problems have been found in well-established and respected journals such as the *BMJ*\(^{22}\). Indeed, an internal *BMJ* study took a paper about to be published in the *BMJ*, and inserted eight deliberate errors before sending it to 420 potential *BMJ* reviewers: 221 (53%) responded\(^{22}\). The results were stark, the median number of errors spotted was two, nobody spotted more than five, and 16% didn’t spot any\(^{22}\). Another concern voiced refers to referees who use anonymity to prevent publications in their field of research\(^{23}\).

There have been several suggestions as to how the process of peer-review can be improved. Firstly, various short-term peer-review training programmes have been shown to be of some limited benefit\(^{24,25}\), although the value of longer interventions needs to be assessed\(^{24}\). Secondly, the *BMJ* has implemented a process of open review where anonymity is
removed. In addition to removing concerns about reviewers being deliberately obtrusive, the BMJ editorial board felt this was ultimately ethical – placing authors and reviewers in equal positions and increasing accountability. A randomized controlled trial found that open review made no significant difference to the quality of reviews and it was acceptable by both authors and reviewers. Although there was a higher tendency to recommend acceptance, the fact that the editors retain total control as whether to publish means that this increase is less important. Clearly open review may not be suitable for all journals, particularly in specialist areas where clinicians and scientists may know each other very well. An intermediate solution to accountability has been tried in other journals, where reviews although anonymous are published online. This approach has been shown to affect reviewers as any comments they make on a specific paper is available to view, meaning that openly hostile or inappropriate reviews become less common and authors receiving such reviews are more supported by other researchers.

Electronic pre-publication prior to final publication is another approach used by some journals. Articles are uploaded online a few weeks before becoming incorporated into the journals database and this provides a window where general readers can make comments. This approach allows journals to provide researchers an additional setting to receive further feedback to develop and improve their article. It should be noted that the Editorial Board have the final say whether comments require to be addressed not by the authors. This approach has worked well for the Cochrane Collaboration as protocols have been changed and meta-analysis adjusted following comments for its clinical readership.

It is unclear if such approaches would have prevented some of the fraudulent papers of the past being published, but will certainly help to improve peer-reviews standing in the scientific community.

**Conclusion**

The status of science and research is based upon the idea that findings from research will be right most of the time and will correct its errors as and when they arise. However, with recent high profile scandals in the world rocking public confidence in science it is important to review the status quo. It is hoped that attempts to improve the quality of peer-review, address publication bias, promote verification and prevent fraud will over the coming years strengthen trust once again in scientific endeavours.

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Has the pharmaceutical industry commandeered evidence-based medicine? 1) Problems

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ABSTRACT

The pharmaceutical industry has come under increasing scrutiny in recent years because of its practices. For example, financial penalties imposed by the US Government and other agencies on pharmaceutical companies between 1991 and July 2012 exceed $30 billion. More worryingly, in recent years there has been increasing attention on some of the failures of multiple parts of the wider system including pharmaceutical development, safety monitoring and regulation.

This paper will examine some of the techniques used by the pharmaceutical industry to market their drugs, and examine the reliability of some of the claims and counter-claims being made regarding the impact that such practices have upon evidence based medicine.

Key Words: pharmaceutical company; research malpractice; Big Pharma

Introduction

The pharmaceutical industry has come under increasing scrutiny in recent years because of its practices. For example, financial penalties imposed by the US Government and other agencies on pharmaceutical companies between 1991 and July 2012 exceed $30 billion (1). It is often argued that because cases take many years to court, these reports are describing out-dated and corrected practices. However, settlements between November 2010 and July 2012 account for approximately one-third of this ($10.2 billion) and the recent bribery scandals in China admitted by GlaxoSmithKline1 suggest that problematic practices have not been completely eradicated.

Are the pipelines drying up?

Of concern is the announcement in the last few years that many companies are withdrawing funding into research and development into brain disorders, citing the high risk of experimental drugs failing to reach market (2). However, many commentators have called into question the current process of drug development; highlighting the fact that most drug classes have come about because of serendipitous discovery rather than planned development (3). The current approaches to drug-discovery for CNS disorders have arguably struggled to deliver on their promises over the last two decades.

Failures of regulation

More worryingly, in recent years there has been increasing attention on some of the failures of multiple parts of the system: pharmaceutical development; safety monitoring; and regulation. For example, Rofecoxib (Vioxx) was withdrawn from the market by the FDA after concerns about cardiac safety, but the manufacturer (Merck) had played down such risks for

1 http://www.bbc.co.uk/news/business-23402154
a long time beforehand. In fact, it is likely that the use of Vioxx resulted in over 2,000 excess deaths in the USA alone (4).

More recently, after a reanalysis of efficacy data by the Institute for Quality and Efficiency in Health Care, IQWIG (the German equivalent of NICE), the antidepressant Reboxetine was reported to be not only ineffective but harmful (5). There are still withheld data regarding Tamiflu (Oseltamivir) which leave considerable doubt over its effectiveness and safety, despite most countries continuing to stockpile the drug in an attempt to militate against pandemic flu. Recently, substantial concerns over publication bias have led to a reconsideration of the evidence for efficacy of the melatonergic antidepressant Agomelatine (6).

The need for transparency in trial reporting has, hopefully, reached a crescendo with the British Medical Journal announcing that they would not be publishing trials unless the raw data were made available to researchers.3

This paper will examine some of the techniques used by the pharmaceutical industry to market their drugs, and examine the reliability of some of the claims and counter-claims being made regarding the impact that such practises have upon evidence based medicine.

Collaboration or covert marketing?

In 2012, the Ethical Standards in Health & Life Sciences Group published ‘Guidance on collaboration between healthcare professionals and the pharmaceutical industry’, a document endorsed by most of the UK Royal Colleges (7) at the time. Some of the problems with this document have been highlighted (8) with The Lancet withdrawing their support for the guidance shortly after publication; closely followed by the BMA4.

The guidance, however, provides a useful framework for critically exploring some of the claims made, and also affords opportunities to reflect on the compelling evidence that contradicts most of the claims.

1. “Industry is responsible for the vast majority of medicines research and development (R&D) in the UK…”

This may be true for the UK, but in the USA more than half of new compounds were discovered by Universities and/ or biotechnology companies, and later transferred to pharmaceutical companies (9). Further, most drugs are marketed internationally so the ‘origin’ of a particular drug is less relevant. The importance of UK-based R&D is an important symbol for the pharmaceutical industry, so it’s a shame that Novartis and Roche have threatened to pull out of the UK5 and Pfizer has closed its research plant in the UK6.

2. “It takes 10 to 15 years to develop a new medicine and typically costs £550 million to do all the work necessary before a medicine can be licensed for use.”

This often-repeated figure comes from research (sponsored by the pharmaceutical industry) conducted in 2003 (10), but these costs have been challenged, along with the assumptions used, resulting in protracted debates about how to determine the costs of drug discovery (11-14). More conservative estimates have suggested much lower figures (15).

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3 http://dx.doi.org/10.1136/bmj.e7305
4 http://dx.doi.org/10.1136/bmj.e7304
7 http://www.bbc.co.uk/news/business-12335801
Whatever the real costs, a significant proportion of industry spend in recent years has been on incremental improvements to existing drugs, rather than new ‘breakthrough’ compounds. Only about 10% of new drugs offer significant benefits over existing drugs (16). For these ‘me-too’ drugs (a drug that is structurally very similar to already known drugs) and ‘evergreening’7, the development process is much shorter, and consequently, much cheaper. Evergreening also has the important consequence of delaying the entry of generic drugs into the market (17). Other examples of patent-extension include the licensing of unusual doses – for example, a 23mg dose of Donepezil which offered no additional benefits but could not be made up of generic 20mg and 5 mg tablets (18).

Finally, the high costs of drug discovery are often used to justify the high prices of new drugs. Industry claims that more money is spent on drug development than promotion are easily deconstructed, suggesting that promotion is the largest component of the costs of drugs (19).

3. “...the results of controlled clinical trials are made available in the public domain through clinical trial registries and portals, peer reviewed publications, medical meetings and company websites.”

This claim is spurious. As discussed above in the case of Reboxetine, unfavourable clinical trial data are often withheld by pharmaceutical companies because they are not obliged to produce it when submitting applications to regulatory bodies. In addition, despite the existence of trial registries and mandatory reporting, approximately 50% of trials used in support of marketing approval are never published (20). Further, there is compelling evidence of publication bias for antidepressants and antipsychotic drugs (21, 22). There is convergent evidence that studies sponsored by industry are more likely to report positive results (23, 24). Despite apparent mandatory reporting of data from trials in registries within one year of completion, most trials fail to comply (25, 26) and fewer than half of such studies are ever published in peer-reviewed journals (27). In summary, anywhere between 25% and 50% of trial data involving patients never reaches the light of day.

4. “Industry plays a valid and important role in the provision of medical education.”

This suggestion is not supported by the evidence. Unfortunately, industry-sponsored medical education creates clear conflicts of interest (28) and has been shown to be biased (29). In 2005, the House of Commons Health Committee concluded that: “The pharmaceutical industry’s promotional efforts are relentless and pervasive. The evidence presented showed the lengths to which the industry goes to ensure that promotional messages reach their targets, and that these targets include not only prescribing groups, but patients and the general public.” (17).

Many doctors fall foul of the ‘third-person effect’, i.e. they believe that others are more susceptible to influence than themselves (30). It is commonly assumed by people that they are immune from the influence of promotional strategies, but it is not the case – we are all vulnerable to such tactics (31).

5. “Whilst medical representatives are employed to promote medicines, they can be a useful source of information for healthcare professionals and are another vital feedback mechanism to the companies they represent.”

7 “Evergreening involves extending the patented life of a branded product, typically by reformulating the drug, for instance by using a different drug delivery system, changing a dosage form, or presentation (e.g. from tablet to capsule).” (17)
There is no evidence to support the claim that information from industry is consistently reliable, accurate, or free from bias. Information from pharmaceutical companies is associated with higher prescribing frequency, higher costs, and lower prescribing quality (32). Large conferences organised by independent groups provide ample opportunity for industry to gain contact with doctors and influence the scientific programme through satellite meetings (33).

The main reason for having representatives is to influence the prescribing patterns of doctors. The influence of medical reps on prescribing has been demonstrated repeatedly (34). In addition, the 'gifts' commonly-received (such as pens, notepads, etc.) and free samples all impact upon behaviour (35-38).

With regards to feedback, there are already well-established mechanisms by which health professionals can supply post-marketing data on the drugs they use; for example, the Yellow Card Scheme⁸, managed by the Medicines and Healthcare products Regulatory Agency (MHRA). Giving feedback to representatives from pharmaceutical companies is unlikely to result in safer or better drugs since the information is not shared between companies or reported centrally.

6. “Industry is able to provide factual information to patients about the medicines they have been prescribed including patient information leaflets and websites.”

Direct to Consumer Marketing (DTCA) is not permitted in the UK and many other countries. It has been shown to have no clear benefits and results in increased prescribing of advertised drugs (39). As discussed above, the information from drug companies is often of low quality. Such schemes are typically used to generate demand for a product (40) and/or galvanise support among patients groups. Such a process is often called ‘astroturfing’ because of its ability to generate an artificial ‘grass-roots’ community. The funding of patient groups by the pharmaceutical industry is concerning to many (41).

7. “Strict rules govern adverse event reporting. Companies have pharmacovigilance teams dedicated to post-marketing surveillance...”

This would be reassuring if it wasn’t for a number of high-profile examples where either information about safety was withheld by the company, e.g. Vioxx (42), or Rosiglitazone (43); or marketing was initiated to downplay potential risks of the drug, in the case of Olanzapine (44). This claim is perhaps most concerning given that it is offering false reassurance of safety when the track record of the pharmaceutical industry suggests that active attempts at hiding or downplaying risks are often employed. Further examples of drugs where risks outweigh benefits include Reboxetine, which turned out to be ineffective and harmful, largely due to the fact that 74% of the patient outcome data held by Pfizer had never been published (5).

Regulatory bodies, historically, have not been quick at removing potentially dangerous drugs from the market. For example, Benfluorex (Mediator) is estimated to have resulted in over 1,000 excess deaths before it was removed from the market (45).

Conclusions

The pharmaceutical business is just that – a business. Whilst its products have the potential to improve health and benefit patients, the magnitude of benefit to public health is difficult to quantify. Whilst some studies have suggested that many of the recent gains in life

⁸ https://yellowcard.mhra.gov.uk/
expectancy can be attributed to new drugs (46), these assumptions have been challenged (47).

Critics will argue that the business element of the industry has led to some of the practices described above, with a focus on profit, sales, and marketing over genuine improvements in patient benefits. Further, the need to maximise profit over a relatively short period of time leads to the suppression of concerns over risks associated with novel compounds.

The number and size of fines imposed on the pharmaceutical industry in recent years would suggest that many of the more questionable practices are not products of a bygone age. The wider implications include the overpromotion of new drugs that offer little benefit over existing drugs, and the risk of patient harm that is downplayed for as long as possible, in order to maximise the return to shareholders.

Evidence-based medicine, rather than providing a mechanism to challenge questionable claims has become another tool through which covert advertising and promotion furthers the industry’s aims, rather than benefiting patients. We will look at some of the other techniques, and discuss solutions in the second paper.

References


Has the pharmaceutical industry commandeered evidence-based medicine? 2) Solutions

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ABSTRACT

Evidence-based medicine, rather than providing a mechanism to challenge questionable claims has become another tool through which covert advertising and promotion furthers the industry’s aims, rather than benefiting patients. This paper will review how some of the techniques used by pharmaceutical companies affect evidence based medicine, before suggesting potential solutions to some of these challenges.

It may be some time before confidence can be fully restored in academic medicine, and clinicians and patients can be reassured that published study outcomes are free from influence. There are changes occurring which are moving towards greater transparency, and some pharmaceutical companies are speaking the right language, but only time will tell whether the pharmaceutical industry are prepared to shake off their chequered past and change for good.

Key Words: pharmaceutical company; research malpractice; Big Pharma

Introduction

In the first paper we saw how some of the claims made by the pharmaceutical industry don’t stand up to scrutiny. Some additional issues have the potential to impact significantly on the safety of our medicines. First, selective publication leads to an exaggeration of benefits whilst harms are downplayed. This has led to cases where licensed drugs were only found to be harmful long after deaths were occurring. Second, regulatory authorities are not given (or are not demanding) enough information to make fully-informed decisions on the medicines they are approving – full, detailed, patient-level data is held by the drug companies and rarely released. This makes it impossible for researchers to determine the true benefits and risks of particular treatments.

Before discussing some solutions, it makes sense to discuss some other techniques that are used to ‘muddy the waters’ when trying to determine the safety and efficacy of medicines.

Subversion of Evidence-Based Medicine

Off-Label Marketing

Off-label marketing, the promotion of drugs for conditions that the drug doesn’t have a license for, is relatively common. Indeed, a significant proportion of drug company financial penalties relates to off-label marketing and some of the largest corporate fines include penalties for off-label promotion (1).

Although it is not-permitted, off-label marketing can generate significant additional revenue for the company. Whilst a company cannot easily promote study findings outside of its
marketing license, conference presentations and posters provide a platform for the display of data relating to non-licensed indications and can still be cited in advertising for the drug (2). Continuing Professional Development, and educational seminars, provides another way in which companies can propagate off-label data by asking key-opinion leaders (KOLs) to talk about their experience of the drug to fellow professionals (3).

The release of company-confidential material as part of litigation proceedings in the US has highlighted the role that off-label marketing plays in the overall release of a new drug; in many cases, it will be an active part of the promotional strategy. For example, off-label promotion formed part of the advertising strategy for Quetiapine and companies have been fined for the off-label selling of Paroxetine (Paxil®) (4), Olanzapine (Zyprexa®) (5), and Semisodium Valproate (Depakote®) (6).

Ghost-Writing

Ghost-writing is the practice whereby a company will typically ask an external medical writing company to draft papers that are favourable to the company’s product. They will then invite prominent researchers or key-opinion leaders to become authors, in an attempt to increase the credibility of the paper. The original author(s) are rarely acknowledged, hence their description as ‘ghosts’. A variation is ‘guest’ authorship, when a physician or researcher who has made little contribution to the scientific work is credited as an author.

Ghost-writing is common, but can be difficult to spot. A common clue is the use of the term ‘editorial assistance’ in the acknowledgements section. Very often, this person will have had a much more prominent role in drafting the paper and will commonly work for a medical writing firm. The large depression study STAR*D resulted in approximately 124 papers, at least 45 of which acknowledge Jon Kilner (who is also a science fiction author) as providing ‘editorial assistance’. Standard rules about authorship do not necessarily protect against ghostwriting (7).

A number of studies have been examined in connection with ghost-writing. One of the most prominent is Study 329, a placebo-controlled study of Paroxetine (Paxil) for depression in adolescents which was later determined to have been written by Sally Laden, who worked for the medical writing firm Scientific Therapeutics Information (STI) (8).

Fixing the problem

There are numerous possible solutions to the challenges currently facing evidence-based medicine which hopefully will begin to re-establish trust in academic medicine and clinical research.

Improved disclosures of conflicts of interest

Potential conflicts of interest have been described in the drafting of the Diagnostic and Statistical Manual of Mental Disorders in both the recent versions: DSM-IV and DSM-5 (9, 10). They have also been identified in the groups producing clinical practice guidelines (11-14).

It is not just professionals that have ties with the pharmaceutical industry. Third sector organisations also have significant amounts of their funding coming from industry (15). The overall effect is that it is sometimes difficult to determine where particular interests lie, and

2 http://kilnerwriter.net/bookspage.htm
how those interests are influencing the scientific literature. Undisclosed interests are particular concerning (16). For example, a group of scientists published a review of research on vagus nerve stimulation (VNS), a controversial treatment for depression (16). However, the authors omitted they are paid advisers to the company that manufactures a device for VNS that was approved in 2007 by the U.S. Food and Drug Administration (16).

In a response to the problem, the US has introduced what is known as the ‘Sunshine Act’ where pharmaceutical companies have to disclose all payments to doctors. These payments will be made available on publicly-accessible websites. However, it is worth bearing in mind that disclosure doesn’t automatically remove a conflict of interest. Furthermore, it is possible that biases may be magnified by disclosure (17), through mechanisms such as “strategic exaggeration” and “moral licensing” (18).

**Comparative trials should be the norm**

Pharmaceutical companies do not have to demonstrate that their new drugs are better than existing treatments, they only have to demonstrate that they are better than placebo. This marker of success is often much easier to achieve. This is particularly true in the USA where placebo-controlled trials are mandated by the FDA. Such an approach, whilst ensuring that drugs demonstrate efficacy, results in a number of consequences.

First, where it is known that a particular type of intervention is better than placebo it raises ethical issues about whether it is appropriate to offer people dummy medication (19). Second, placebo-controlled trials are usually conducted across a number of different sites in different populations. This can result in differences between subgroups being obscured in the overall need to demonstrate efficacy for the average patient. In extreme cases, drugs that appear efficacious for one gender may offer little benefit for the other.

**Better evaluations of the benefits of new medications**

We saw in the first paper that the benefits of new medications often seem small. Over time, we are seeing fewer and fewer completely novel drugs, or drugs that offer major gains over existing agents. In recent years, the French industry journal *Prescrire* has found it increasingly difficult to award drugs that offer genuine incremental advances in care (20). Only 1-in-10 new drugs offers "a statistically significant difference in primary clinical endpoints" (21).

Consequently, as drug costs remain high but gains become smaller, there is an increasing need for health services to ensure that public funds are spent in the most effective and efficient way possible.

**Value-based pricing**

Value-based pricing for branded drugs will come into effect in 2014. NICE has always evaluated treatments on the basis of gains in utility – i.e. quality of life and function was an important measure when assessing the benefits of an intervention. Under the new rules, when considering new treatments, NICE will look at costs that extend beyond those borne by the NHS to include costs to carers and costs relating to employment (22). This means that if a treatment improves quality of life to a similar degree to other drugs, but improves other outcomes more, it may be considered more favourably by NICE.

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Some have voiced concerns that drugs that are second to market (i.e. ‘me-toos’) may be disadvantaged, but value-based pricing means that they will be unable to charge more than existing drugs unless they can demonstrate additional benefit (23).

**Full disclosure of data from Clinical Study Reports (CSRs)**

Since November 2010, the European Medicines Agency (EMA) has released almost two million pages of clinical trial information in response to requests from research groups and other agencies, as part of its 2010 access-to-documents policy. The policy aims to give access to non-clinical and clinical information (including clinical study reports) that have been submitted by pharmaceutical companies as part of their applications for marketing-authorisation. Such apparent transparency has been welcomed by medical researchers, particularly given EMA’s history of being unwilling to disclose data on the grounds of commercial sensitivity (24). However, the moves are being actively resisted by some pharmaceutical companies (see below).

**The AllTrials campaign**

The AllTrials campaign was established in early 2013 as a collaboration between: Bad Science (led by Ben Goldacre), the British Medical Journal, the Centre for Evidence-based Medicine, the Cochrane Collaboration, the James Lind Initiative, Public Library of Science, and Sense About Science. The campaign calls for all clinical trials to be registered and their results reported, and it has produced detailed plans for this aspiration.\(^4\)

The aspiration to ensure full disclosure of clinical study reports is an important step in ensuring that decisions can be made about healthcare interventions. It has been estimated that less than 50% of clinical trial outcomes are in the public domain; i.e. published in peer-reviewed literature (25). Importantly, clinical study reports (CSRs) contain much more detailed information about harms of medication.

We have seen in the first paper that selective publication and withholding of clinically-relevant information leads to poor decision-making. Reboxetine was considered to be an effective and safe antidepressant on the basis of published studies, but it was only when the German equivalent of NICE obtained unpublished data did it emerge that reboxetine was ineffective and potentially harmful (26). The problem was that 75% of patient data had never been published.

**Pharmaceutical company sign-up to the AllTrials campaign**

A few drug companies have publicly announced their support for the AllTrials campaign for clinical data transparency. GlaxoSmithKline was one of the first to announce their commitment to providing trial data\(^5\) in early 2013, but it has gone on to be caught up in bribery scandals in China\(^6\). Roche has also declared a greater willingness to share clinical trial data (27), although there remains some scepticism given Roche’s unwillingness to disclose data regarding Oseltamivir (28, 29).

**Is Big Pharma resisting change?**

Two pharmaceutical companies (AbbVie and Intermune) are challenging the EMA’s plans to provide access to clinical information (including CSRs) that were submitted as part of

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\(^4\) [http://www.alltrials.net/all-trials/](http://www.alltrials.net/all-trials/)


applications for marketing-authorisation. Most, it should be noted, have not launched legal proceedings. At a meeting hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA), a representative from AbbVie (a research-based company that split from Abbott in early 2013), claimed that information about adverse effects “is confidential commercial information because if released other companies could use it to help them get products approved.” The Head of the Dutch board which evaluates medicines went on to question whether AbbVie really thought that adverse events are commercially sensitive information and Hans Georg Eichler, the EMA’s chief medical offer said “I have been a regulator for many years and I am totally flabbergasted.”

A willingness to resist indication creep and expanding disease definitions

Many people are concerned by the gradual expansion of disease definitions so that previously-normal health states are now considered to be disease and requiring of treatment. As a general rule, medicine tends to expand disease rather than contract it (13). Some examples include hypertension and hypercholesterolaemia (where the benefits of treatment for those in low risk groups have been questioned) (30) and metabolic syndrome and diabetes where the number of potential ‘customers’ might be huge but benefits unknown (31).

A related phenomena is indication creep – the use or promotion of a drug for off-label indications (32). This has been discussed above, and while not necessarily bad medicine (eg: amitriptyline for neuropathic pain) it may be related to drug companies trying to maximise profits by widening the therapeutic indications for their drugs (eg: Levodopa for restless legs syndrome). Despite being common, it may be very difficult to change current practice (1).

Other related approaches include the use of online and self-diagnosis tools to reach a larger range of consumers, many of whom would never had known that they were unwell until they’d filled in on online form, often on a drug company’s website (33).

An acknowledgement that in many cases lifestyle and behavioural interventions can be just as effective as drugs

In some conditions where drugs are becoming increasingly used, and in particular those conditions where boundaries between disease states and normality are becoming blurred (e.g. hypercholesterolaemia and hypertension), there is very good evidence that lifestyle changes can be just as effective as drugs (34). This requires a greater effort on behalf of the patient, but the risks associated with such interventions may be lower than those associated with drug treatment.

Summary and Conclusions

We have seen that evidence-based medicine is a powerful tool for improving care but it is not perfect and current systems do not offer sufficient protection from influence from companies that have financial interests in ensuring that their message is promoted. The historical record does not support the view that pharmaceutical companies are changing quickly. Systems are changing in response to concerns from academics and other interested parties, but we are still not in a position whereby we can be confident that all the data arising from clinical trials is in the public domain.

It may be some time before confidence can be restored in academic medicine, and clinicians and patients can be reassured that published study outcomes are free from influence. There

7 http://www.alltrials.net/2013/2338/
are changes occurring which are moving towards greater transparency, and some pharmaceutical companies are speaking the right language, but only time will tell whether the pharmaceutical industry are prepared to shake off their chequered past and change for good.

References

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This article aims to inform medical students and clinicians about the Human Genome Project (HGP). The article discusses the barriers that have been broken down to allow for wider access to genetic testing and the potentially negative effects that an increase in genetic testing may have on patients. It is hoped that by contrasting the triumphs of the HGP (such as personalised medicine) with the potential pitfalls of the project (such as genetic discrimination), readers will develop an enhanced understanding of the HGP.

Key Words: human genome project; genetics

Introduction

If you were to take a group of medical students and ask them to identify the single greatest breakthrough in medical science, I am quite certain that the Human Genome Project (HGP) would not feature highly.

The reason is quite simple: people do not know what it is. The HGP was a scientific project that boasted the aim of sequencing all 3 billion base pairs in the human genome – the blueprint of life. It began formally in 1990 and was declared complete in 2003. The HGP remains the largest collaborative research project in human history and it is therefore surprising that future doctors know little about a study which has its roots in all walks of medicines (genes play a role in virtually all diseases). The scale and impact of the HGP is made even more impressive when you consider that DNA itself is a relatively new discovery: the double helix structure was only discovered in 1953 by James Watson and Francis Crick. Now, 60 years on, we all have a basic understanding of DNA and the world is a better place for it. Or is it? With genetic testing becoming more widely available, how can we ensure that this information is used appropriately and ethically so as to prevent discrimination on a genetic basis? In this article I consider the breakthroughs and drawbacks of the HGP and the challenges that lie ahead.

Angelina and BRCA

Since its completion, the HGP has helped us to identify the root of many monogenic diseases. Monogenic (or Mendelian) diseases offer the best chance of predicting life-time risk of disease or providing personalised therapy as the single gene mutation involved often makes for an easier predictive or therapeutic target.

Earlier this year Ms Jolie elected to have a double mastectomy to reduce her risk of developing cancer after discovering that she carries the BRCA1 gene. BRCA 1 & 2 are good at predicting life-time risk of breast or ovarian cancer (a female carrier of a mutation on one of the genes has a 50-85% risk of breast cancer and a 15-60% risk of ovarian cancer). However, as with everything in medicine, predicting disease is not as straightforward as this and indeed Genome Wide Association Studies (GWAS) have shown that there are other genetic factors which have a role in determining the risk of developing cancer, and that only a small number of genetic variants with a role in BRCA1/2-related cancer have been identified to date. However the complexity of genetics should not be seen by medical
students as a reason to run for the hills but rather as an exciting area of research in which there is still much more work to be done, with the BRCA genes representing a piece in the puzzle of targeted drug therapy.

**Monopoly: one winner, many losers**

Indeed if ever there was a time for BRCA testing to become more popular, it is now. On the 13th of June 2013 the US Supreme Court ruled that the previously patented BRCA genes were no longer eligible for patent, as they are a naturally occurring biological material. This was a major breakthrough for American women as BRCA testing previously cost $3,340 when Myriad Genetics held their legal monopoly on the gene. Just hours after the announcement, competing companies stated that they would offer the test at a cost as low as $995. It is hoped that the dissolution of other gene patents will follow this historic move and thus genetic-based medicine will become more widely available by way of competition driving prices down. The counter argument is that by allowing these molecules to remain patentable, we provide researchers with financial incentive to discover new and innovative gene therapies that will ultimately benefit patients. Whatever your own opinion, affordable genetic testing is the only way that patients will be able to fully reap the benefits of personalised medicine.

**What exactly is ‘personalised medicine’?**

Personalised medicine is the art of tailoring treatments to individuals based on their genetic profile. Personalised medicine has the potential to revolutionise clinical decision-making and prescribing, and could mean the development of new drugs targeted at a particular group of people, such as a specific race or even individuals with certain blood properties. It could even mean better use of drugs already in use or which failed in trial stage. There have been many developments in the field of personalised medicine in recent years.

However, the usefulness of personalised medicine is limited by the fact that we still have so much to learn about the human genome, and indeed knowledge is only acquired with time. We need only look at cystic fibrosis to see that identifying disease-causing genes is only part of the solution to treating the disorder. It is almost 25 years since the most common mutation in cystic fibrosis - ΔF508 - was identified and only now are therapies being developed that can treat the disease by targeting the faulty gene directly. Indeed when I sat in on an asthma clinic recently I heard the doctor tell the patient that the reason for changing her medication yet again was “more out of desperation, than scientific rationale” - she had not responded to all of the other recommended treatments and the genetic testing that she underwent for specific beta2-adrenergic receptor mutations had come back negative. It would seem that genetic testing is not as clear-cut as it is often made out to be and there are still many questions to be answered.

**Opportunity for Discrimination**

There is another side to genetic testing, a darker side where the threat of discrimination looms. Indeed there are some who fear that genetic testing could lead to discrimination by employers who may wish to select against those employees with a genome that may affect their ability to work. The theoretical potential for discrimination is huge, however it is very unlikely that this kind of discrimination would ever be legal. There is however a real risk of genetic testing affecting health insurance. There are insurance companies who would just love the chance to use the results of your genetic test to charge you a higher premium, despite the fact that we are unsure of just how much each “risky” gene actually elevates the risk of disease. In order to protect individuals from being charged more, there are a number of regulatory frameworks in place although there is debate over how much a risky genome
would actually increase premiums, with some suggesting that the increase in cost would be very small indeed.\textsuperscript{12}

The Council of Europe's Convention on Human Rights and Biomedicine sets out the laws relating to medical research and states that it “bans all forms of discrimination based on the grounds of a person’s genetic make-up and allows the carrying out of predictive genetic tests only for medical purposes.”\textsuperscript{13} At present the United Kingdom has not signed the treaty however it is recognised that the United Kingdom’s regulation of medical research with respect to genetic testing is consistent with the European framework.\textsuperscript{14} There is currently a moratorium in the UK - a temporary ban agreed to last until at least 2017 - which forbids insurance companies from requesting that a person undergoes a genetic test when purchasing life or critical illness insurance and also allows an individual the right to withhold the results of previous genetic tests when buying premiums up to a certain value.\textsuperscript{15} But what will happen in 2017? Is genetic testing a ticking time-bomb waiting to blow up in our faces? One way to stop the mass introduction of genetic testing would be to follow Germany’s lead and to only allow medical doctors to carry out genetic tests, as described in their Genetic Diagnosis Act (GenDg).\textsuperscript{16} This may serve to curb the recent increase in whole genome sequencing which has now become more popular on account of its ever-decreasing price-tag.

There are number of other concerns also relating to genetic testing. For example, whilst an individual may purchase a genetic test to learn of their susceptibility to one condition there may be other conditions to which they learn they are susceptible, despite them not wanting to know this ‘additional’ information.\textsuperscript{17} There are also likely to be implications for all family members if one member is found to be susceptible to a disease\textsuperscript{18} and so the impact of the result should be fully considered before the test. There are also concerns that the increase in genetic testing could lead to a greater number of abortions, with many prospective parents potentially choosing to abort children with profound disabilities (as is already often the case with diseases such as Down’s Syndrome). It is clear that genetic testing is an ethical and legal minefield with many considerations.

**Conclusion**

Twenty years after its completion, the HGP remains a hot topic that divides opinion. There are clearly many benefits to be reaped from genetic testing but at what cost to patients? I believe that if genetic testing is to become more commonplace then it must be tightly regulated to protect individuals from discrimination.

There have been many breakthroughs in medicine as a result of the HGP, such as the beginnings of personalised medicine. Indeed, personalised medicine has the potential to prevent 100,000 deaths caused by adverse drug reactions each year in the US.\textsuperscript{19} Ultimately, your opinion of the HGP is likely to be as individual as your DNA, but ponder this: where would the HGP feature on your list of the greatest breakthroughs now?

**References**

All references available on the online edition of this paper.