Institute and Faculty of Actuaries

ISSN 2397-7221

Longevity Bulletin

From the Institute and Faculty of Actuaries

The pharmacology issue

Issue 12

September 2020

Contents

Introduction by the Editor

Two of the most important contributors in dealing with the Covid-19 pandemic are epidemiology and pharmacology. Epidemiology has helped to identify the spread of the infection and its mortality impact; pharmacology offers us tests and we hope, eventually, a vaccine.

Although the content of this edition was written before the pandemic started, the themes remain relevant.

These two fields have been great contributors to the longevity improvements of the 20th century. Pharmacology gave us antibiotics, largely eliminating known infectious diseases from the developed world, as well as a range of other drugs and medications with generally beneficial effects across many causes of death. Epidemiology gave us insights into the risks of smoking (followed by other damaging lifestyle behaviours), paving the way for major health advances through greater awareness of those risks; it then provided the 'vehicle' for the application of pharmaceutical discoveries, helping test which drugs and medications were efficacious.

This issue of the *Longevity Bulletin* has been designed around the theme of pharmacology, and given that understanding the claims of the pharmaceutical industry is largely a question of understanding the major tenets of epidemiology, we also consider some key aspects of epidemiology ('Researching research', page 9).

While the great 20th-century waves of pharmaceutical progress have been largely beneficial, there is increasing concern around particular aspects of pharmaceutical proliferation. One of these, the issue of opioids, has been a well-known contributor to increased mortality for some sections of the USA population (page 22), and is also problematic in the UK (page 16). Another interesting perspective is offered in the field of diabetes, where metformin has been of great help in managing the condition; on the other hand, we have seen the mass prescribing of statins lead to increased incidence of diabetes (page 25).

Finally, we consider whether 'you can have too much of a good thing' in this area – the issue of polypharmacy, where drugs usually tested in isolation are prescribed in increasing numbers, generally to the elderly, in a way that appears to be encouraged by existing health systems (page 3).

We hope you find this issue of the *Longevity Bulletin* interesting, and that it helps shed light on some of the positive and negative aspects of the pharmacological 'revolution' that has helped improve the field of medicine so much.

Our next issue will focus on the pandemic, with particular regard to the likely shape of life – and death – in a 'post-pandemic' world.

Matthew Edwards
Editor

Foreword by the President of the IFoA

It gives me great pleasure to introduce this issue of the profession's *Longevity Bulletin*, a publication that has been running for almost ten years now, helping 'longevity stakeholders' – not just actuaries – achieve a better understanding of the drivers behind mortality, morbidity and longevity.

While we like to think we understand a great deal about these subjects, the current pandemic has made us realise how much remains uncertain, unknowable, uncontrollable.

In my presidential address, I spoke about the importance of judgement and the embracing of diversity, experimentation and adaptation. Their importance have been underscored by the Covid-19 crisis. For some time, they have underpinned much of the work involved in the twin fields of pharmacological discovery and epidemiological research considered in this edition of the *Longevity Bulletin*. Experimentation speaks for itself in these fields, but adaptation has long been an important part of pharmacology, with many medicines being examples of 'repurposing' – finding a novel application for an existing and well-tested drug.

Diversity has also been seen in this crisis, with governments and organisations realising they needed many different skills, resources and approaches to cope well – and more fundamentally, different mindsets.

Finally, judgement. The crisis has brought out the importance of applying sound judgement quickly when data is incomplete, and the problem too complex to fully model and quantify – as has often been the case with many common conditions that pharmacologists and epidemiologists have grappled with.

Although the content of this issue predates the Covid-19 emergency, it remains an important and fascinating selection of topics covering both recent 'negatives' (the opioid crisis), well-known success stories (metformin for diabetics), and one area of growing concern – the problem of polypharmacy, or too many drugs. In one sense the pandemic puts these into perspective; in another, it makes us realise that chronic problems may end up more serious than temporary crises if they are allowed to grow unchecked, and their complexity not appreciated.

I hope all readers find this edition of the *Longevity Bulletin* useful and that it shows how we in the actuarial profession can apply our judgement and analysis in the unfolding catastrophe, trying to navigate through the uncertainty, in ways that serve the public interest – which is, of course, our raison d'être.

Tan Suee Chieh
President, Institute and Faculty of Actuaries

Too much medicine – reducing life expectancy?

Dr Malcolm Kendrick

This article could have been entitled 'polypharmacy', although that may not be a term many people are familiar with. Polypharmacy just means the prescribing of multiple medications. It is a subset of what many people believe to be a more generalised over-medicalisation of the population, an issue that is being addressed by the 'Too Much Medicine' initiative, driven from 2002 by the *British Medical Journal*:

> *'The BMJ's Too Much Medicine initiative aims to highlight the threat to human health posed by overdiagnosis and the waste of resources on unnecessary care. We are part of a movement of doctors, researchers, patients, and policymakers who want to describe, raise awareness of, and find solutions to the problem of too much medicine.*
>
> *Causes of too much medicine include expanded disease definitions, uncritical adoption of population screening, disease mongering and medicalisation, commercial vested interest, strongly held clinical beliefs, increased patient expectations, litigation, and fear of uncertainty and new technology. Winding back the harms of too much medicine invites clinicians to focus on those who are sick, and only intervene with those who are well when there is a strong case to do so.'* (BMJ, n.d.).

This is a relatively long-winded way of saying that preventive medicine may not be working, or, at least, that it entails significant risks. Marcia Angell, a long-time editor of *The New England Journal of Medicine*, has said that "I do think that we are an overmedicated society."(Angell, 2004).

She is one of an increasing number of people who feel that we have reached, or are perhaps long past, the point when we are in danger of doing more harm than good – using an ever-increasing number of medical interventions that can be damaging.

Are we all 'diseased' in the first place?

It is certainly true that if preventive medicine gets things wrong, the fallout may be monumentally damaging because of the huge numbers of people involved, for example in the treatment of high blood pressure, a 'disease' that, unless the blood pressure is extremely high, has no symptoms – it is often referred to as the silent killer.

Mahase (2019) estimates that, in 2015, 13.5 million people in the UK had high blood pressure, and the latest guidance from the National Institute for Health and Care Excellence (NICE) has lowered the level at which treatment should be started, adding another three quarters of a million people to those currently deemed 'hypertensive' (Lancet, 2019).

There is no doubt that treating blood pressure at very high levels is beneficial, but there is considerably more doubt about the benefits to be gained in using medication to lower 'mild to moderate' hypertension. Mahase (2018) states: "There is 'no evidence' that lowering hypertension thresholds to treat low-risk patients has any benefit, a new study has found. Researchers analysed nearly 40,000 low-risk patients across England and found that not only was there no benefit to treating such patients with anti-hypertensive medication, it also had the potential to cause 'harm'."

In an article published in the *Journal of the American Medical Association,* Sheppard et al. (2018) conclude that: "The findings suggest that physicians should be cautious when initiating treatment in low-risk patients with mild hypertension, particularly because such an approach may affect millions of individuals with little evidence of benefit."

This research, and other similar findings, has had little impact on NICE. It seems that every new set of guidelines they produce lowers the level of blood pressure meriting treatment ever further.

Alongside the many millions of people 'diagnosed' with hypertension, more than 60% of the adult population is now considered to have a raised cholesterol level. In 2017 raised total cholesterol was highest among women aged 55 to 64 (76%), and among men aged 35 to 54 (63%) (NHS Digital, 2018).

NICE guidelines on cholesterol lowering, if they were to be slavishly followed by all GPs, would mean nearly 20 million people being advised to take lifelong statins (cholesterol-lowering medication). This number is set to grow, as there is a move towards lowering the 'normal' cholesterol level even further.

While there is considerable overlap between those with raised blood pressure, and raised cholesterol, it has been estimated that well over 70% of the adult population will be advised to take blood pressure lowering and/or cholesterol lowering medication.

In addition to these two conditions, we have type II diabetes. Diabetes UK (2019a) estimates that the total number of people living with type II diabetes in the UK is nearly five million.

This is far from the end. In the last few years another condition has been identified, known as pre-diabetes. That is, people with a raised blood sugar level but at a level not high enough to be considered 'frank' type II diabetes. However, there is increasing pressure to start these people on medication. Diabetes UK (2019b) estimates that the total number of people with pre-diabetes in the UK is around seven million.

Taking all of these conditions together – raised blood pressure, high cholesterol level, diabetes, pre-diabetes – the majority of the population would appear 'diseased'.

Raised blood pressure	**14,000,000**
Raised blood cholesterol	**20,000,000**
Diabetes	**5,000,000**
Pre-diabetes	**7,000,000**

Of course there is considerable overlap here, with many people having two or three conditions simultaneously – hence the total of these figures is somewhat misleading. However, this list does not consider those diagnosed with thin bones (osteopenia and osteoporosis), nor the many millions who have conditions such as chronic kidney disease (CKD), anxiety and depression, atrial fibrillation etc.

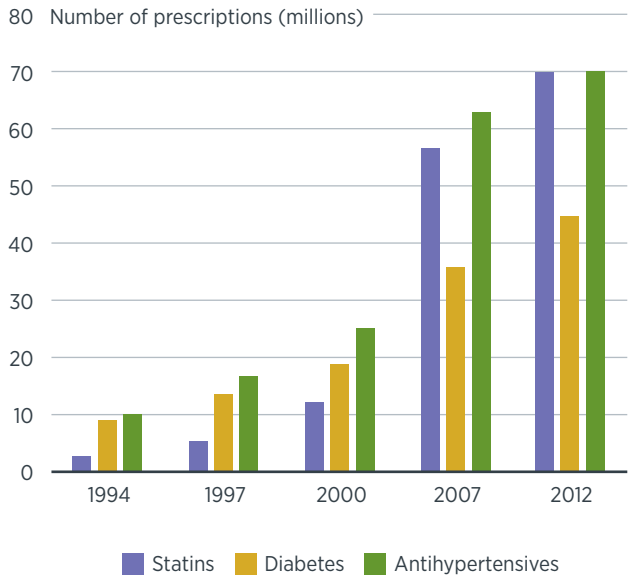
In addition to this, anyone who has suffered chest pain that is considered cardiac (from the heart) in nature, will also be put on a cocktail of different drugs. A statin, aspirin – or an equivalent anti-clotting drug eg clopidogrel – a beta blocker and another drug called an ACE-inhibitor (used for blood pressure lowering but it has other cardioprotective effects). These will all be lifelong.

Unsurprisingly, the lowering of targets, and the labelling of more and more conditions as diseases that require medications, has led to an ever-increasing number of drugs being prescribed. In their paper *The rising tide of polypharmacy and drug-drug interactions,* Guthrie et al. (2015) state: "Between 1995 and 2010 the proportion of adults dispensed more than five drugs doubled to 20% and the proportion dispensed more than ten tripled to 6%. The prescription of more than ten drugs was strongly associated with increasing age. The proportion of potentially serious drug-drug interactions more than doubled."

I work in rehabilitation medicine, usually with the elderly who have fallen and fractured their hips and suchlike. Three years ago, in a small-scale audit, the average number of medications being taken by these patients was 9.2. Earlier this year it was 11.1.

My personal record was a woman on 36 different drugs. I spend a large amount of my clinical time trying to reduce the number of medications that patients take – often with considerable benefit to their quality of life, but almost always to the displeasure of their own GP and relatives.

The graph below, although it does not show numbers of prescriptions per individual, does show an alarming increase in the number of prescriptions in the UK over the last 25 years:



Source: NHS Digital: Prescriptions Dispensed in the Community, ***https://digital.nhs.uk/data-and-information/publications/statistical/prescriptions-dispensed-in-the-community****. Graph reproduced with permission from James le Fanu.*

Quality Outcome Framework

The movement towards too much medicine can be seen in almost all countries around the world. However, in the UK, there is another factor which has driven polypharmacy at a faster rate than anywhere. This factor is known as the Quality Outcome Framework (QOF), introduced in 2004. It was calibrated using a points system, whereby GPs could achieve a maximum of 1,050 points – each point being financially rewarded.

550 points could be gained across 76 targets, for ten different medical conditions eg heart disease, high blood pressure, diabetes, CKD. In total, QOF makes up a quarter of a GP's total income. An example of some of the initial clinical indicators can be seen in the table on the following page:

QOF clinical indicators Secondary prevention in coronary heart disease (CHD)		
CHD indicator		**Points**
CHD 6	The percentage of patients with CHD in whom the last BP reading (measured in the last 15 months) is 150/90 or less	19
CHD 7	The percentage of patients with CHD whose notes have a record of total cholesterol in the previous 15 months	7
CHD 8	The percentage of patents with CHD whose last measured cholesterol (measured in the last 15 months) is 5mmol/l or less	16
CHD 9	The percentage of patients with CHD with a record in the last 15 months that aspirin, or alternative anti-platelet therapy, or an anti-coagulant is being taken (unless a contraindication or side effects are recorded)	7
CHD 10	The percentage of patients with CHD who are currently treated with a beta-blocker	7
CHD 11	The percentage of patients with a history of a heart attack (MI) (diagnosed before 2003 who are currently treated with an ACE-inhibitor or angiotensin II antagonist	7
CHD 12	The percentage of patients with CHD who have a record of influenza vaccination in the preceding 1 Sep to 31 March	7

The QOF indicators change each year in an ever-moving target. One of the most important effects is to drive up the number of medications that everyone will receive. GPs can ill afford to lose a quarter of their total practice income. This could result, in some cases, in zero partnership profit – after expenses have been deducted. EQ Accountants/Kreston UK Healthcare Group (2017) state that the net profit in an average GP practice is around 34%.

So, while QOF is still nominally voluntary, the system incentivises GPs to work extremely hard to gain every QOF point on offer. This means that GPs do not welcome other clinicians looking to reduce the number of medications that a patient may be taking.

It is interesting that in Scotland the QOF system has been abolished, with QOF money being redirected in the 'Global Sum' that is paid to practices. This happened in 2017, with the Scottish government implementing their decision to "completely abolish the existing burdensome system of GP payments, freeing up GPs to spend more time with patients".

There are, at present, no plans to abolish the QOF payment system in England and Wales, and the legacy of 'polypharmacy' driven by QOF remains very much in place in Scotland.

Polypharmacy – has it been beneficial or harmful?

Part of the problem here, ironically, is that the QOF system, and the thinking that underpins it, is not based on good-quality evidence. A comment that probably needs a little explanation and context.

For many years, medical practice was not evidence based. Some called it 'eminence'-based medicine, in that the opinions of those considered experts in their field tended to dominate medical management.

Over the years, evidence from controlled clinical studies has been gathered, and this has created an evidence base. This underpinned the creation of evidence-based medicine, directed in large part by researchers and thought leaders at Oxford University during the late 1980s and early 1990s.

Another organisation, the Cochrane collaboration, grew from this new thinking, starting life in 1993 under the leadership of Iain Chalmers. It was developed in response to Archie Cochrane's call for up-to-date, systematic reviews of all relevant randomised controlled trials in the field of healthcare.

These factors then slotted neatly alongside the concept of preventive medicine, which also had its intellectual heart in Oxford. The idea behind preventive medicine being that it is better to stop diseases at an early stage than have to deal with the devastating consequences later. Lowering blood pressure to prevent a stroke, lowering blood sugar level to prevent limb amputation – there are many examples.

This initiative was supercharged by trials demonstrating that lowering blood pressure reduced the risk of stroke, lowering cholesterol reduced the risk of cardiovascular disease (CVD), and suchlike. The scene was now set for the mass medication of tens of millions of people.

There were those who urged caution, for two main reasons. First, could we be certain that the evidence was free from commercial bias? Almost all the major trials on blood pressure lowering, cholesterol lowering, blood sugar lowering etc. were set up and run by pharmaceutical companies with a clear vested interest in proving the benefit of their particular medications.

Whether or not research is free from bias is obviously a critically important issue, but I am not discussing it in any depth here. I will just use one rather telling quote from Richard Horton, editor of *The Lancet*: "The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue . . . science has taken a turn towards darkness." (Horton, 2015).

The second problem is as follows. While there is evidence of benefit from individual drugs, there has been no attempt to establish whether combining medications creates an additive benefit. Or, to put this another way, it is almost unknown for researchers to evaluate the extent to which, as you combine more and more medications, the inevitable interactions, and possible adverse effects, cancel out the benefits of any individual medication.

For example, the benefits of giving a beta-blocker after a heart attack have been established. Not a massive benefit but clearly significant. The benefits of giving aspirin (or equivalent) has also been established. Likewise, the benefits of giving an ACE-inhibitor and a statin.

However, there has never been a trial to establish whether giving all four in combination is better than giving nothing at all. Or that giving four is better than giving three. When it comes to polypharmacy, the thinking is that all benefits will be cumulative. That, however, is what we call a guess.

Occasionally, worrying evidence emerges. The ACCORD study, completed in 2008, was a study designed to look at the benefits of adding in medication after medication to see whether polypharmacy would drive down blood sugar levels and improve outcomes in diabetic patients. It had been assumed that because a higher blood sugar level was associated with increased mortality, intensive lowering of the blood sugar level would be beneficial. In fact, cardiovascular and overall mortality did not go down, it increased. Whether this was due to polypharmacy itself, or by driving the blood sugar levels ever lower, is not clear. However, the central concept, that it must be better to aim for ever lower targets through multiple means, was contradicted. In the ACCORD trial, greater blood sugar lowering killed more people (Cheung, 2012).

In the same way, when intensive blood pressure lowering has been studied, problems have emerged. Chi et al. (2019) state: "Compared to the standard blood pressure target, pooled data from randomized controlled trials suggest that intensive strategy did not achieve a net clinical benefit when weighing the benefit of MACE [major adverse cardiac events] reduction against the risk of SAE [Serious Adverse Events] under the bivariate framework."

Or, as a colleague of mine put it rather bluntly: "We drop the blood pressure too low, our elderly patients get dizzy, fall over, break their hips – then die." (A particular challenge, over and above polypharmacy, is that most studies relate to younger populations and the findings are then assumed to be applicable to much older patients.)

The irony here is that evidence-based medicine has been the driving force behind polypharmacy, and yet there is no evidence that 'higher order' polypharmacy does any good. On a population level, if mass medication were truly beneficial, then we would have seen continuous material increases in life expectancy, particularly in cardiovascular disease, where the greatest efforts have been concentrated.

However, the long-term fall in CVD deaths is now reversing, as reported by the British Heart Foundation in 2019: "The number of people dying from heart and circulatory diseases before they reach their 75th birthday is on the rise for the first time in 50 years, according to our analysis of the latest national health statistics."(Mitchell, 2019).

Conclusion

We are suffering an epidemic of polypharmacy, driven by a combination of factors: preventive medicine, evidence-based medicine, QOF (in the UK), and major commercial interests. What has been the impact? We do not know for certain, but we do know that prescription drugs are powerful agents that should be used with caution.

Outlining the experience in the US, Light (2014) states:

> *'Few people know that new prescription drugs have a 1 in 5 chance of causing serious reactions after they have been approved. That is why expert physicians recommend not taking new drugs for at least five years unless patients have first tried better-established options, and have the need to do so.*

Few know that systematic reviews of hospital charts found that even properly prescribed drugs (aside from misprescribing, overdosing, or self-prescribing) cause about 1.9 million hospitalizations a year. Another 840,000 hospitalized patients are given drugs that cause serious adverse reactions for a total of 2.74 million serious adverse drug reactions.

About 128,000 people die from drugs prescribed to them. This makes prescription drugs a major health risk, ranking 4th with stroke as a leading cause of death. The European Commission estimates that adverse reactions from prescription drugs cause 200,000 deaths; so together, about 328,000 patients in the U.S. and Europe die from prescription drugs each year.'

While numbers of deaths (as opposed to, for instance, standardised mortality rate impacts) can be misconstrued, the message is telling.

As for polypharmacy itself, the data is scarce. Most researchers shy away from stopping any medication, for obvious reasons. It would be considered unethical to withhold any individual drug that has been 'proved' to provide benefit. Bit of a Catch 22.

In a paper entitled *The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug-therapy in disabled elderly people,* Garfinkel, Zur-Gil and Ben-Israel (2007) looked at trying to reduce the number of medications given to elderly and disabled patients. As many drugs as possible were discontinued. The main findings were that:

- Mortality rate over one year was reduced from 45% to 21%
- Referral rate to acute care facility was reduced from 30% to 11.8%.

The paper concluded: "Application of the geriatric-palliative mythology in the disabled elderly enable simultaneous discontinuation of several medications and yields a number of benefits: reduction in mortality rates and referral to acute care facilities, lower costs, and improved quality of living.'"

Reduced costs, improved quality of life and a reduction in overall mortality. It could be said that stopping drugs is the single most effective drug treatment currently available. This is an issue that needs to be tackled urgently.

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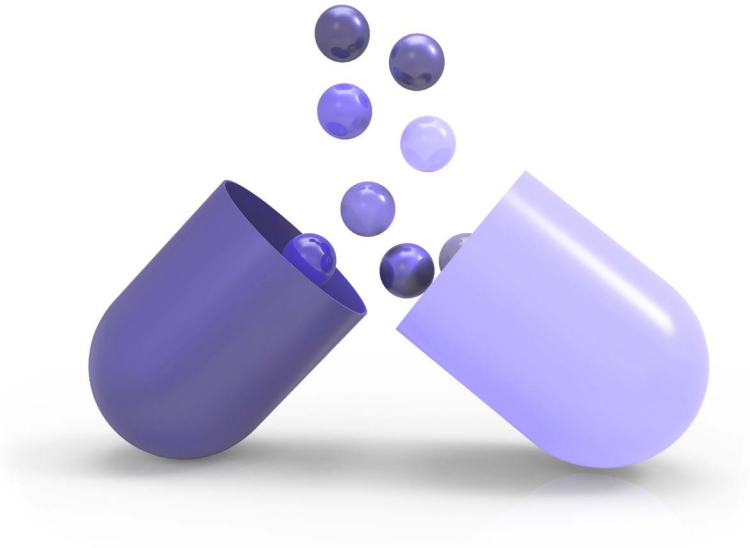


Researching research: the ups and downs of epidemiology

Matthew Edwards, Director, Willis Towers Watson and Dan Ryan, Chief Science Officer, COIOS Research

Introduction

It might reasonably be assumed that if a study is published in a prestigious medical journal such as *The Lancet*, the *BMJ* or *The New England Journal of Medicine* then the combination of rigorous study design, impartial analysis and independent peer review would render the output reliably 'cast iron'. While many might by now appreciate that, for instance, nutritional research is often highly flawed owing to problems with self-reporting, or research into vaping of little use because there is insufficient data so far, we might expect the claims of the pharmaceutical industry and public health bodies to be largely indisputable.

Why, then, have we been seeing statements such as the following from the current editor of *The Lancet* and a former editor of *The New England Journal of Medicine*?

- '. . . Much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable trends of dubious importance, science has taken a turn toward darkness.' (Horton, 2015).
- 'It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of the *NEJM*.' (Angell, 2004).

The problem can be summed up by the words from one of the most cited research papers of all time, *Why most published research findings are false* by John Ioannidis: "In modern research, false findings may be the majority or even the vast majority of published research claims." (Ioannides, 2005).

What has driven these concerns, and if these concerns are well-founded then how can we assess the validity of any published research?

In this article, we consider some of the ways in which epidemiological research can be misleading, or at least misunderstood, and (hopefully) provide readers with a firmer grasp on how to interpret the claims of pharma. Many of our observations are also likely to be of interest to readers working in data analytics.

The start of epidemiology

Skipping much of the interesting history of relevance here – for instance, the fascinating account of Snow's work on cholera and its association with particular water pumps in London (Stanwell-Smith, 2003) – we could say that epidemiology became a promising field of medicine in its own right during the 1950s, alongside fields such as the study of infectious diseases, organ transplants and cardiovascular surgery.

In 1954 Doll and Hill published their preliminary paper on the mortality of doctors, concluding their research, initiated in 1951, with an open letter to doctors to report their smoking habits, enabling a simple form of prospective study. The paper showed a clear and material relationship between smoking 'dosage' and lung cancer mortality, and marked a turning point in our understanding of the effects of tobacco (Doll and Hill, 1954). Hypertension was another area in which our understanding took great leaps forward due to early epidemiological studies.

The field has since mushroomed, with two particular ambitions: seeking morbidity and mortality improvements via a better understanding of 'lifestyle' (a term that was just entering common usage in the 1960s), and the assessment of pharmaceutical discoveries.

But how, back then – in the infancy of the field – would one interpret epidemiological results and make a judgement on their meaningfulness?

The Bradford Hill criteria

In 1965 Bradford Hill (co-author of the paper referred to above) published *The environment and disease: association or causation?* in which he introduced what have generally been known since as 'the Bradford Hill criteria' (Hill, 1965). A testament to their strength is that they have remained the standard criteria to distinguish association and causation ever since; when the *Journal of the Royal Society of Medicine* reprinted the original article in 2015 to mark the 50th anniversary, it was only the language that seemed slightly dated, not the concepts therein.

The criteria were as follows:

- **Strength (effect size):** The larger the association between 'dose' and response, the more likely that it is causal.
- **Consistency (reproducibility):** Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
- **Specificity:** Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation.
- **Temporality:** The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
- **Biological gradient (ie dose response relationship):** Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect (like a catalyst). Or, an inverse proportion may be observed.
- **Plausibility:** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
- **Consistency** ...between epidemiological and clinical findings increases the likelihood of an effect. (Strictly speaking, Bradford Hill used the term 'coherence', not consistency.)
- **Experiment:** Do preventive actions taken on the basis of an assumed causal association alter the outcomes?
- **Analogy:** What are the effects of similar factors?

The rise and plateauing of epidemiology?

If the prospects for epidemiology seemed so bright 60 years ago, and the principles for understanding the analyses so clear and, apparently, well-accepted, then how could anything go wrong?

The field boomed in the 1970s, with university courses established and the conduct of epidemiological studies moving from statistically numerate medical doctors to those trained as specialists in the field. Although this might be regarded as a good thing, this shift necessarily meant less consideration of clinical reality and the underlying biological mechanisms, in line with a concern Bradford Hill had voiced that this new branch of medicine was becoming overly statistical.

Access to data became problematic: many of the early studies were conducted using data from hospitals or mental institutions (the latter providing the ability to enforce large-scale changes, for instance in areas such as diet, in a way that would be impossible to achieve under any respectable ethical framework). These data sources dried up as review boards were set up, and regulatory and administrative hurdles increased. When recalling his study of food additives and cancer based on patient data from 66 Boston-area hospitals, the US epidemiologist Professor A.Z. Smith stated: "One year of my career was invested in contacting hospitals, completing redundant forms about informed consent and privacy, assuring sceptical clinicians of the value of epidemiologic research such as mine, and writing letters repeatedly awakening slumbering administrators to the urgency of my request." (Rothman, 2007).

Owing to the number of hurdles, the attraction of the epidemiological path in universities began to wane, and a gradual shift got underway as 'talent' moved to the pharmaceutical sector, with its own vested interests (discussed below as a likely source of bias).

On the other hand, during this period health datasets started to be created, with the aim of furthering epidemiological research. Probably the earliest such dataset, and certainly one of the most well-known in the medical community, was the Framingham study initiated in 1948 with just over 5,000 subjects (Mahmood et al., 2014). (Framingham is a small town near Boston.) Data collection activities in many countries started to gather pace in the 1980s and 1990s – for instance, in the UK what is currently known as the Clinical Practice Research Datalink (CPRD), covering around five million lives at the primary care level, started in 1987 (then as the General Practice Research Database, GPRD) with the aim of facilitating longitudinal studies.

However, attractive as such datasets are for many purposes, the data is often much less rich, reliable or consistent than lay readers might assume and, even if the datasets are assumed to be accurate, the observational studies they enable can be highly misleading, as we discuss below.

Another point of consideration is a form of the 'diminishing returns' problem. Given the available data and the associated limitations, each decade has felt less illuminating than the previous one. From the initial work on smoking, and other early breakthroughs allowing tangible improvements in public health policy (for instance, tuberculosis management in the 1950s), we have come to the point where the public perception of epidemiology is perhaps diminished by continually conflicting claims regarding the harms or benefits of aspirin, broccoli, coffee and so on (the list could probably be extended alphabetically to Z without much difficulty, and interactions may also be allowed – eg 'broccoli coffee' (Nagesh, 2018).

Furthermore, quantification of the reputed harms or benefits of risk factors – with typical effects shown in the order of 10-20% for particular causes of death – shows life expectancy impacts of the order of a few weeks compared with the massive life expectancy impact implied by the smoking studies of circa 5-10 years (for a 50-year old). (Although, given ageing populations and the escalating costs of dealing with co-morbidities, small evidence-based improvements could still be beneficial at a societal level.)

But this 'waning' of the epidemiological lodestar may be set for a reversal with the increased extent of genetic information available, with datasets such as the UK Biobank facilitating studies that take into account genotype variations. TwinsUK's dataset (available at **https://www.twinsuk.ac.uk**) provides an interesting resource to enable comparisons between identical genotypes (identical twins have always been a source of fascination to researchers with particular regard to the 'nature v nurture' debate).

Finally, the focus of many health systems on more extensive and detailed electronic health records (EHR), of which the above datasets are good early examples, should provide opportunities for medical insight – and were such datasets to be combined in some way with social media or other lifestyle data, allowing an accurate assessment of behavioural traits, the 'undiscovered heterogeneity' problems in some study designs might be largely overcome.

Bias

The principal challenge of all research, and particularly that involving human subjects, is bias. Multiple factors conspire so that incorrect associations are drawn, or so that research may not be replicable or even applicable to the wider population of interest to the epidemiologist or clinician. Let us explore some of the more common and insidious examples that researchers need to constantly guard against.

Observer bias

Observer bias reflects the reality that all studies pass through a 'human filter'. Whether this plays out through differences in interpretation between observers or the manner in which the analysis (or equivalent) is carried out, the effect is to introduce a degree of unexpected variation that could be systematic in nature. Such bias can be minimised by extensive training and making the observers aware of inherent biases, but such biases remain a substantial risk.

We should remember that the observer does not just observe, but in many studies is also the individual who either directly selects the study subjects or otherwise influences their selection through their choices. Almost every study will consider a sample from the wider possible population; selection bias describes the likelihood that the process of selecting this sample could distort how representative it is of the wider population. Guidelines for selection and randomisation of allocation to different arms of a study can limit the likelihood of selection bias, and indeed in some circumstances the study organisers may wish to deliberately over-sample particular groups in the population for whom the study is likely to have greater significance.

Bias in trial completion

If we look instead from the perspective of the interviewee, one key challenge is a particular issue for longitudinal cohorts in which subjects are interviewed on a number of occasions. The risk of such studies is that some individuals may not present themselves for subsequent interviews by dropping out of the study, and, moreover, that there may be a systematic bias in those who do so. It is probable that the groups the researcher may be most interested in, for example those who are not adhering to their medications in a study of individuals with mental illness, are those most likely to miss subsequent follow-up meetings due to their mental health issues (which may include a lack of confidence and trust in healthcare professionals). This could compromise the validity and the applicability of any such study to the wider population that was meant to be investigated.

Sponsored research

Primary research studies can be incredibly expensive, requiring extensive resources to follow up subjects and ensure that data is accurately recorded and analysed. As such, a continual challenge for researchers is securing adequate and appropriate sources of funding. The difficulty for researchers and reviewers is in objectively assessing whether there are omissions or biases in research that has been sponsored by an entity that would benefit from particular conclusions, or whether such assessment reflects internal but unsubstantiated biases and expectations. Sponsored research is not necessarily bad research, and indeed may be the only way in which certain research topics are addressed and better understood.

Lack of commercial benefit

This aspect can also subtly present itself through the absence of large studies relating to questions that are of no commercial benefit to likely sponsors (generally, pharmaceutical companies) – hence the enormous imbalance between the high numbers of cancer survival or diabetes management studies concerning particular medications, and the low numbers of equivalent scale studies concerning, for instance, extreme dietary restriction.

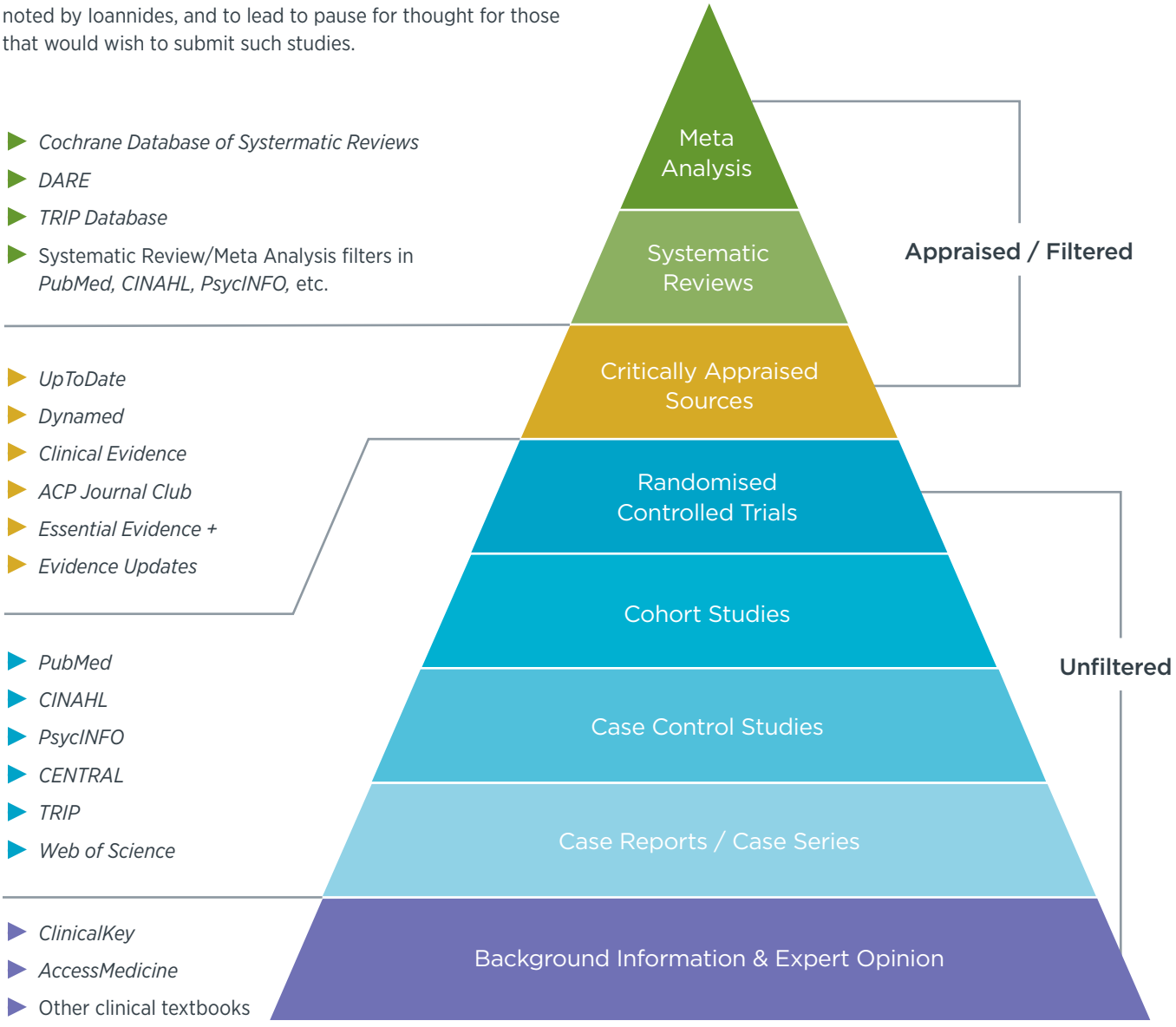
Side-effects of the peer review process

Finally, evidence-based medicine is typically a reflective process, building on the successes and failures of prior studies. While every research study strives, and is expected, to be novel and to add to the sum total of human knowledge, the nature of the peer review process can inhibit research questions that challenge current orthodoxies. Indeed while it is widely and correctly held that peer-review increases the rigour and validity of submitted research, the review process may well lead to either the rejection or the tempering of research findings, as noted by Ioannides, and to lead to pause for thought for those that would wish to submit such studies.

Hierarchy of evidence

The hierarchy of medical evidence has been long established, and is most often expressed in the ubiquitous pyramid shown [below]. Following on from the previous section, higher layers are meant to represent increasing internal validity as the risk of bias is reduced (if not eliminated). The efforts taken to allow for confounding factors increase the likelihood that the phenomenon being observed is relates to the 'cause and effect' mechanism of interest.

However, the dividing lines are not always clear cut. For example, while a cohort study tracks the experience of many individuals over time to assess the longitudinal impact of risk factors or treatment context, carefully selected case controls may provide stronger explanatory power. The supposed top layer of the unfiltered studies, the randomised control trial (RCT), particularly the double-blinded version, ensures that there should be similar heterogeneity in each of the intervention arms.



However, the results of the trial will only hold true if the selected population from which participants are drawn is representative of the population to which the treatment or intervention is applied. A multiplicity of different factors, from age to nutrition to attitudes towards adherence, may mean that reality could be firmly divorced from the output of an individual trial. This problem is particularly manifest in the safety (let alone the efficacy) of medications in the presence of other medications, since trials generally seek to investigate the treatment in question in isolation – hence the growing problem of polypharmacy, addressed earlier in this issue.

Meta-analyses and systematic reviews are normally placed at the top of the pyramid because of the explanatory power credited with bringing together many individually rigorous studies. Indeed, rapid increases in computational ability and online access to datasets promote and encourage more and more meta-analyses. However, the sheer number of studies involved is likely to preclude a clear expert understanding or allowance for heterogeneities in approach, and the meta-analysis should not blind scientists to the quality of the underlying studies. The role of meta-analyses may be better suited to guiding future avenues of research rather than acting as a 'kitemark' of evidence-based medicine.

Case study

Bias risk in observational studies

A very interesting question is the degree of bias likely to be present in observational studies, in which studies are constructed 'retrospectively' through the analysis of historical datasets, such as the Clinical Practice Research Datalink, rather than set up on a prospective basis. The study would typically split records according to the patients' apparent use of a particular treatment.

There is a high possibility that the 'taking this medication' group are behaviourally distinct from the 'not taking the medication' group, and that this behavioural difference regarding healthy lifestyle aspects not controlled for in the data is likely to contribute to a marked mortality differential in its own right (common datasets of this type would often not distinguish heavy from light smokers, heavy from light drinkers, or exercisers v non-exercisers, for example).

The most famous (or rather, infamous) example of this bias relates to advice recommending hormone replacement therapy (HRT), following the results of the 1985 Nurses' Health Study. This was an observational study that found a 42% reduction in cardiovascular risk associated with HRT, while an equivalent randomised controlled trial (RCT) conducted some years later showed a 29% increase in cardiovascular risk from HRT.

The difference was seen as largely attributable to other healthy behaviours in those women who had decided to have HRT (Kolata, 2003; Tai, Grey and Bolland, 2014; Zahl and Mæhlen, 2015).

Other studies have looked at this matter from the perspective of adherence within the placebo groups of RCTs – ie what is the mortality of 'placebo taking' v 'placebo neglecting' individuals? Such studies have shown very striking differentials, of the order of 50% risk reduction in respect of adherence – which is acting here as a marker for general healthy behaviour (Wilson, 2010; Stetler, 2014).

Danaei, Tavakkoli and Hernán (2012) looked at the differences between observational and RCT studies of the mortality of statin users which showed an approximately 30% differential – ie statin users in observational studies seemed to enjoy a '30% + *k*' mortality benefit compared with non-users, while RCTs demonstrated that this margin was simply *'k'*%. Again, this seems to broadly quantify a healthy behaviour effect not allowed for elsewhere in the observational data.

Quantifying the problem

Can problems such as the above forms of bias, or evidentiary gaps, be quantified in terms of overall impact or cost? A formal answer would be laborious to the extreme, and of course would not itself be impervious to some of the forms of bias already noted. A high-level 'market consistent' quantification, relating, in particular, to how commercial bias might be valued, can be gleaned by considering the settlements paid out by pharmaceutical companies over the years for their acknowledged improper activities in this field (largely relating to conducting and/or interpreting drug-use trials inappropriately, in a way that in hindsight has been judged to be aligned with their commercial interests rather than drug efficacy or even safety).

Good Jobs First's Violation Tracker for the pharmaceutical industry (Good Jobs First, 2020) shows a total of over $40 billion of penalties since 2000, with the largest four pharmaceutical companies (Pfizer, GSK, Johnson & Johnson and Merck) averaging over $4 billion each.

While a large proportion of this relates to mis-selling, such mis-selling can generally happen only in a context where the underlying studies have not been conducted properly and have not justified whatever claims may have been made for the products in question.

Conclusion

While the above may have dwelt more on the various flaws and problems inherent in the field of epidemiology, it remains a vital field of exploration to quantify the morbidity and mortality effects of a large number of things spanning lifestyle, medication and other forms of treatment.

If a reader were to want a simple 'sense-check' list with which to approach apparently impressive claims made by any paper, we would suggest the following as a useful starter (noting that the Bradford Hill criteria listed above are themselves an excellent reference point):

- **Impact** – what is the all-cause mortality impact if the results are correct? For very many findings published in recent years, the impact on life expectancy is negligible. Many studies also look at endpoints other than morbidity/mortality (for instance, cholesterol measures), which make the results even less useful.
- **Applicability** – related to the practical issue of impact above, there is the related point of whether the results are generalisable. Where the drug might reasonably have a particular beneficial impact on the group analysed, and assuming this can be regarded as causative rather than merely associative (see below), what about, for instance, older individuals with other conditions and/or taking other medication?
- **Data bias** – how might bias be present in data selection, or in the operation of confounding factors? Data bias can be present in almost undetectable ways; for instance, operating a pre-trial period to determine if any individuals suffer side-effects from the medication.
- **Commercial bias** – given the penalty sums noted above, it is clearly the case that pharmaceutical companies have been prepared to adopt questionable approaches to justify the promulgation of drugs that may earn them in the order of $100 billion.
- **Association or causation** – very few study types allow us to safely infer causation, although association may be sufficient in a typical insurance underwriting context (as opposed to the much wider question of changing future treatment guidelines, for which we would need to be certain of some causative relationship).
- **Biological plausibility** – are the results plausible regarding the underlying biological process involved and, similarly, are they consistent with clinical evidence and the wider question of a plausible fit to an evolutionary perspective on what is likely to 'work'?

Finally, we should note that many of these points, just as many of the Bradford Hill criteria, are useful in broader 'big data' analytical contexts. Here, too, actuaries and others must ponder complex studies and be alert to the potential for problems such as data bias, establish whether causation can be shown (if that is necessary), and consider whether the findings tie in with day-to-day reality (hence the question of biological plausibility above becomes the old tyre-kicking question, 'Would an underwriter believe this result?').

Proper appreciation of models requires attention to the real world underlying these models, and this point harks back to Bradford Hill's concern noted earlier – epidemiology (to a large extent, the modelling of medical data) is more likely to be misleading when it becomes a purely statistical enterprise, divorced from its underlying reality.

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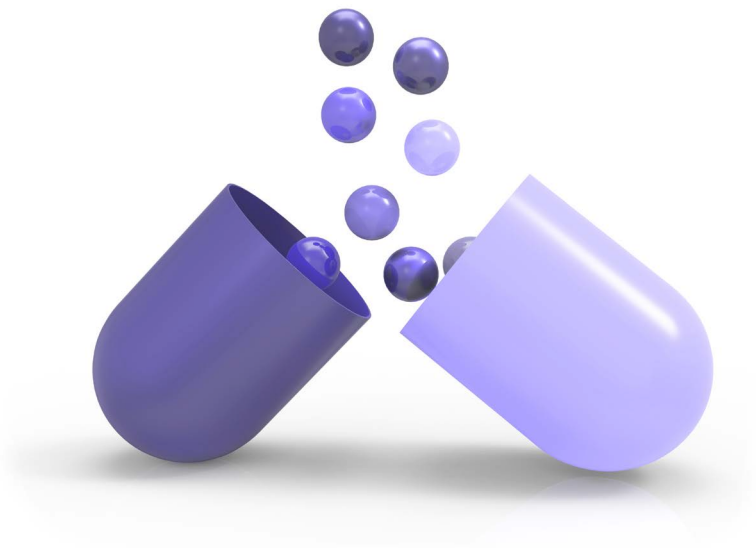

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Dan introduced the concept of disease-based models of mortality using electronic health records and was a key contributor to the development of the Pandemic Emergency Facility with the WHO and World Bank.

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The opioid epidemic in the United Kingdom

Dr Chris Martin, Director of Modelling at Crystallise

Background

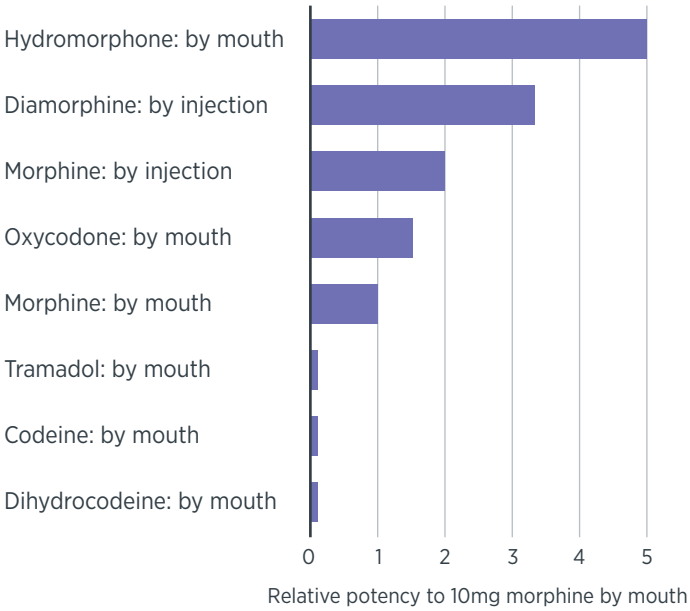
Opiates are naturally occurring morphine-like narcotic substances most commonly derived from the opium poppy (*Papaver somniferum*). The term 'opioids' refers to drugs that act upon opioid receptors including naturally occurring 'opiates' and synthetic derivatives. Morphine was first isolated at the beginning of the 19th century by Friedrich Wilhelm Serturner, who named it after Morpheus (the god of dreams) because of its tendency to induce sleep. In 1831 he won the Moynton prize from the Institute of France and the title of 'Benefactor of Humanity' but died ten years later in 1841 chronically addicted to morphine – depressed and severely withdrawn.

Opioids are a very important class of drugs medically. They are not only effective analgesics for the short-term treatment of acute pain but are also used to reduce pain, coughing and diarrhoea in end-of-life care, as well as being useful for the treatment of acute breathlessness in acute heart failure. Unfortunately, all opioids are highly addictive – oxycodone, in particular (Remillard, Kaye and McAnally, 2019).

Opioids cause the release of dopamine in the brain, which generates a feeling of pleasure and activates the brain's 'mesolimbic reward system' in the mid-brain (Kosten and George, 2002). Repeated activation of this 'reward system' in the absence of significant pain generates a motivation for repeated use of the drug (craving). The dependence is not merely psychological; opioids also have physical effects, such as a reduction in bowel motility (constipating agent), suppression of coughing (anti-tussive), and vaso-dilation, causing a reduction in blood pressure. Repeated use leads to changes in the concentration of enzymes that mediate the effects of the opioids, so that the normal physiological and psychological 'status quo' is maintained in the continued presence of the opioids. Therefore, in order to maintain beneficial effects over time, the dose must be increased. This drives the characteristic dose 'escalation', where users seek larger and larger doses. If the opioids are then withdrawn, the user experiences the reverse of the beneficial effects including agitation, anxiety, a lack of a sense of wellbeing, diarrhoea and muscle pains (Kosten and George, 2002).

Unlike the USA and most other countries, heroin is used medicinally in the United Kingdom where it is prescribed under the name 'diamorphine'. Its effects are similar to morphine but are more intense, therefore requiring lower doses. The relative strengths of different opioids are shown in Figure 1.

Figure 1 Relative potency of different opioids relative to 10mg morphine by mouth.



Source: Prescribing in palliative care. British National Formulary 6 November 2019.

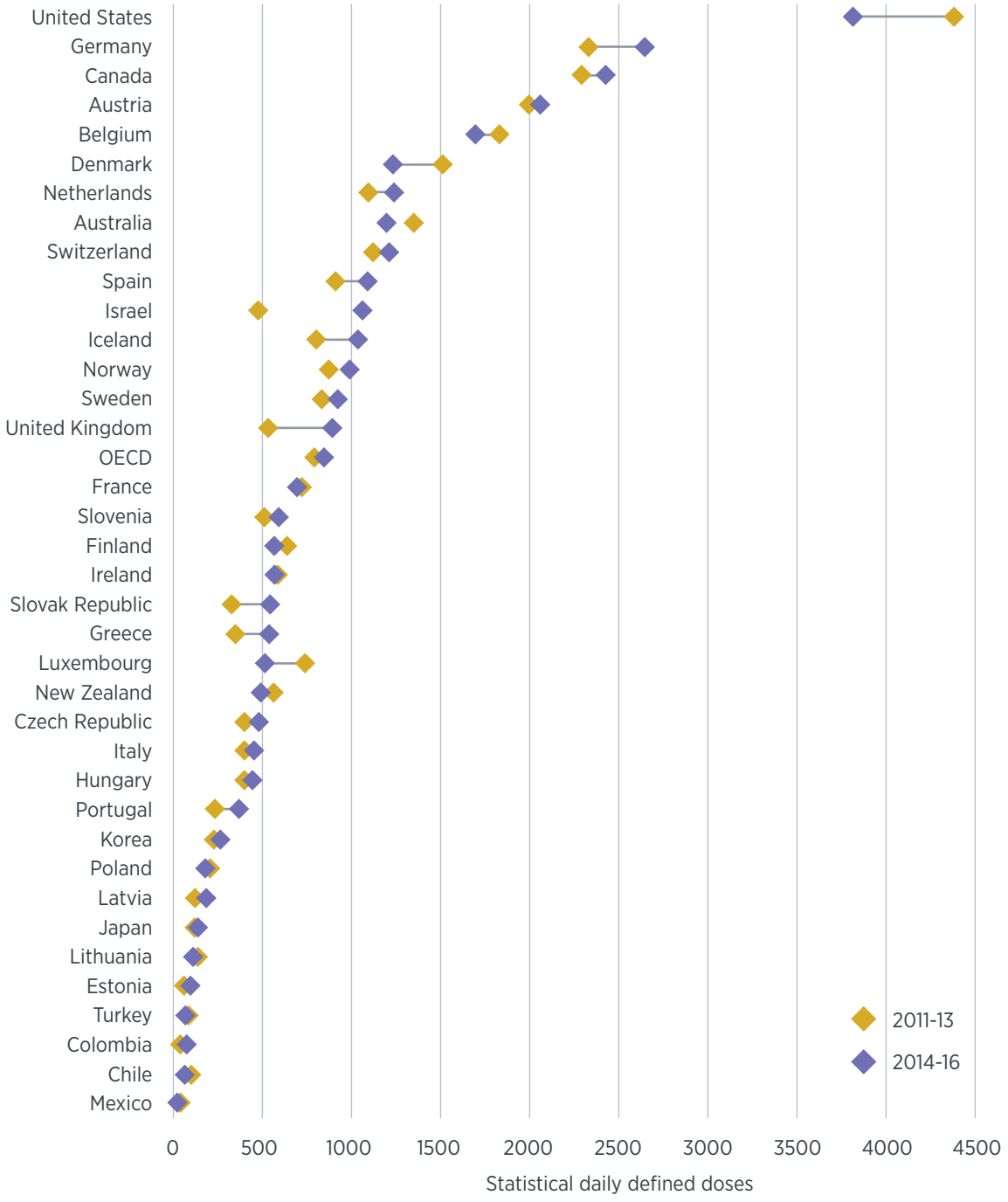
Prescriptions

For most of the 20th century, opioid analgesics were generally used in a limited fashion in healthcare for severe acute pain and end-of-life care. The sharp rise in the abuse of prescription opioids began in the mid-1990s and continues to the present time. In 1995 a slow release formulation of oxycodone (OxyContin) was produced, and like all new formulations of a drug, it enjoyed a patent allowing exclusive marketing for a period of 20 years. It was initially believed that the slow release formulation would reduce the tendency of addiction by avoiding the rapid peaks in blood levels associated with the 'high' feeling that addicts crave. By the early 2000s it was clear there was an emerging problem of addiction to

prescribed opioids, with OxyContin at its centre. In 2003 the US Food and Drug Administration wrote a warning letter to the manufacturer, Purdue Pharma, explaining that its marketing materials downplayed the risks and harms of the product, and promoted its use beyond the indications for which it was proven to be safe and effective, including for non-malignant pain. In September 2019 Purdue Pharma filed for bankruptcy protection as a result of the large number of lawsuits accusing the firm of fuelling the opioid crisis (FDA, 2019; Van Zee, 2009).

While the USA has been particularly hard hit, other OECD countries are also experiencing a crisis with opioid addiction and associated deaths. Figure 2 shows that the UK is slightly above the OECD average for the rate of prescribing of opioids, with an increase between 2011–2013 and 2014–2016 (whereas in the USA there was a fall, but from a much higher starting level).

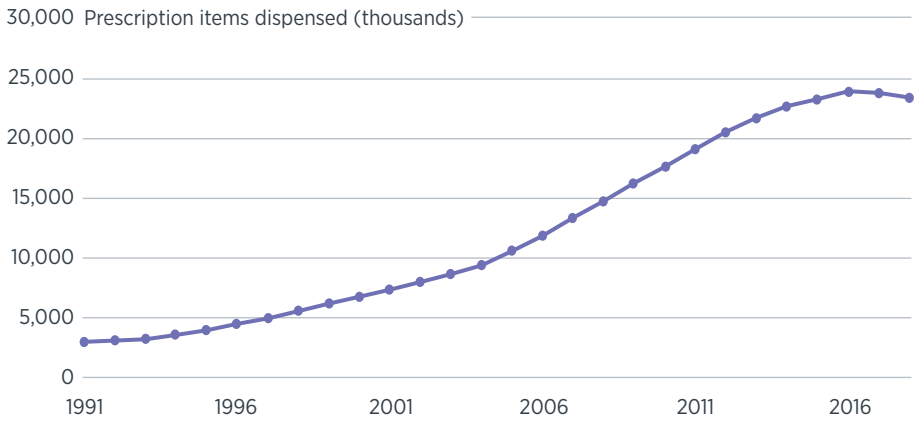
Figure 2 Mean availability of analgesic opioids in OECD countries 2011-13 and 2014-16. S-DDDs per million inhabitants per day.



Source: OECD, Addressing Problematic Opioid Use in OECD Countries, 2019.

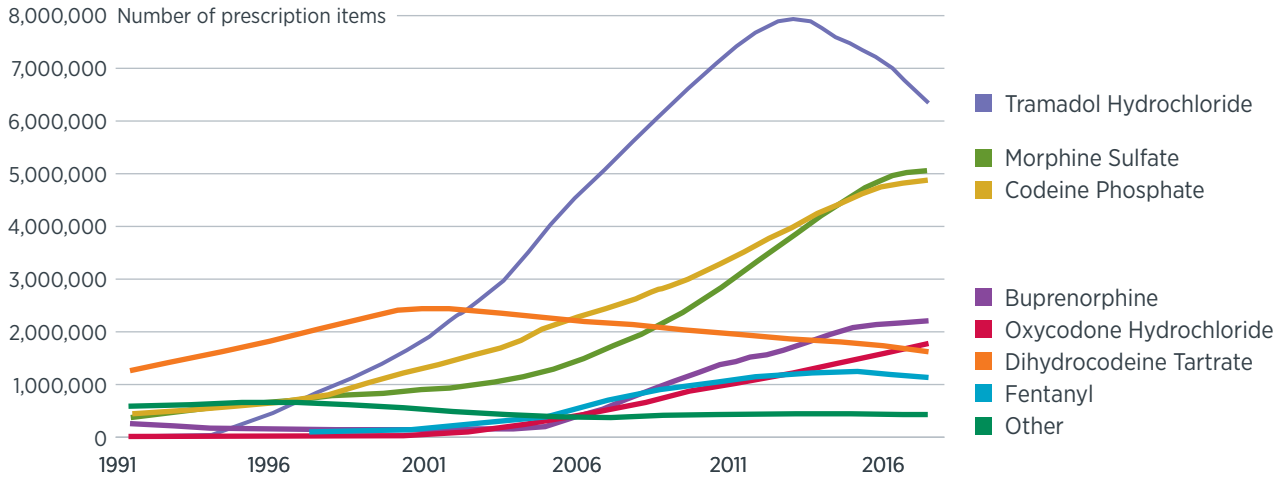
In England and Wales there was a steady rise in the number of prescriptions issued for opioids up to 2016, although it now appears to be falling (Figure 3). The fall is largely due to a reduction in the number of prescriptions for tramadol (Figure 4), one of the less potent opioids.

Figure 3 Prescription items dispensed for opioid analgesics in England and Wales between 1991 and 2018.



Source: NHS prescription cost analysis. ***http://qna.files.parliament.uk/qna-attachments/1105736/original/237626 table formatted.xlsx***

Figure 4 Prescriptions for opioids 1991 to 2018 in England by type.



Source: ***https://www.parliament.uk/business/publications/written-questions-answers-statements/written-question/Commons/2019-03-27/237626/***

Patterns in prescribing

In England in 2017–2018, 5.6 million adults (12.8%) were prescribed an opioid painkiller. Prescriptions for women are 50% higher than for men (15.3% of women and 10.1% of men) and the number increases with every age group. The oldest age group (90+ years) received nine times as many prescriptions as 18- to 24-year-olds.

Deprivation correlates with the number of prescriptions for opioids and long-term use, with the most deprived quintile being prescribed 60% more prescriptions than the least deprived quintile. Other predictive factors include living in rural areas and the size of the GP practice, with larger practices prescribing more (Curtis et al., 2019; Taylor et al., 2019).

Over half a million people in England received a continuous supply of opioid analgesics between April 2015 and March 2018. Of 498,000 prescriptions of opioids that were started in June 2015, 64% received a prescription for only one month, but 3% had a continuous supply until May 2018 (Taylor et al., 2019). This reveals a pattern of high prescribing in general, but mostly for short periods of time. However, because of the high prescribing rate, it leaves substantial numbers of people receiving long-term prescriptions, with the attendant risks of addiction, side effects and over-dosage.

We saw from Figure 1 that there is a marked difference in potency between different types of opioid, and Figure 4 suggests a relative increase in the use of morphine. The number of strong opioid users has increased steadily, from 9,479 in the year 2000 to 53,666 in 2010, which is a 466% increase (Zin, Chen and Knaggs, 2014). If the relative potencies of opioids are taken into account, then the total equivalent dose is 27% higher in 2018 compared with 1998 than that implied by the increase in prescriptions alone (Curtis et al., 2019).

Using the Clinical Research Practice Datalink, one study between 2000 and 2010 found that 87.8% of prescriptions for potent opioids (morphine, fentanyl, buprenorphine and oxycodone) were for non-cancer patients, and 47% of prescriptions in non-cancer patients were for morphine (Zin, Chen and Knaggs, 2014).

Deaths

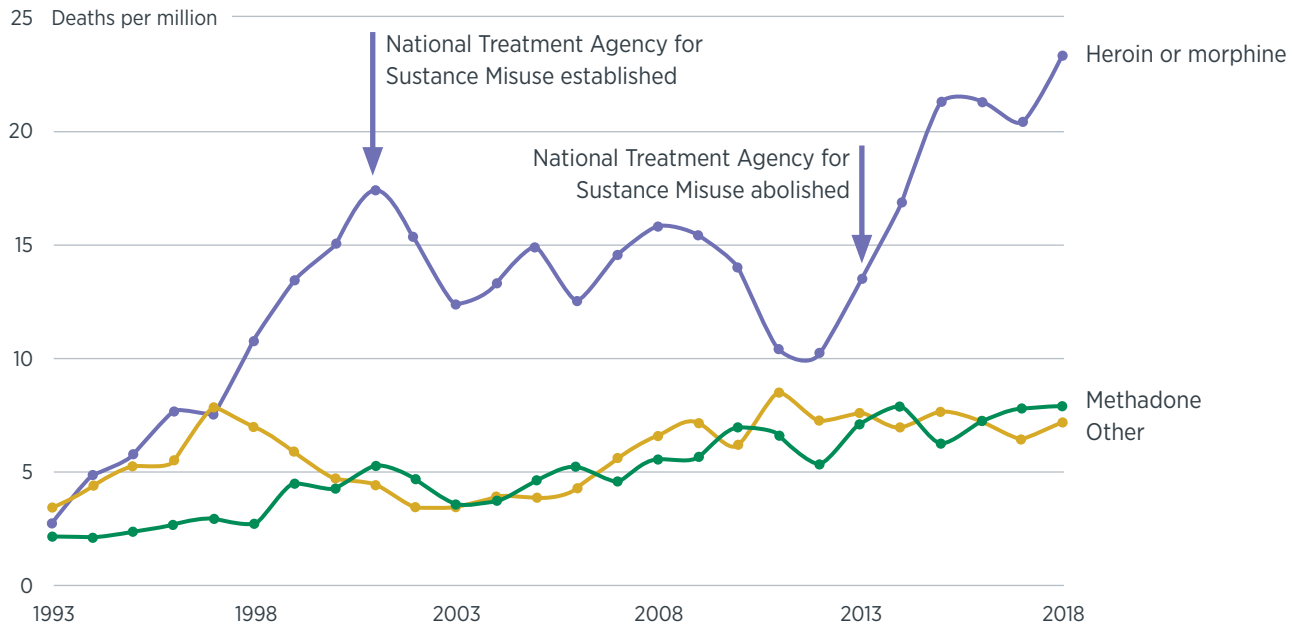
Opioids are sedative and higher doses induce sleepiness and ultimately unconsciousness. One of the most dangerous effects is respiratory suppression. The opioids attach to receptors in the respiratory rhythm-generating system in the pons, part of the brain-stem. As a result, death in overdosage is most commonly due to a simple failure to breathe. Over-dosage, however, is not the only way that opioids kill. Chronic users are at increased risk of death from accidents, violence, suicide and infections (Bech et al., 2019; Bjornaas et al., 2008).

Deaths from opioid use have risen across the OECD countries, with the most severely affected country being the United States with nearly 400,000 deaths between 1999 and 2017 (Hererra and Wahal, 2019). In the USA it has contributed to the fall in life-expectancy at birth in recent years. In England and Wales it has accounted for over 35,000 deaths between 1993 and 2018, with the mortality rate attributed to morphine and heroin doubling in the past 20 years (Figure 5).

Comparing Figures 5 and 3, it can be seen that the correlation between the number of prescriptions for opioids and the number of deaths from opioids is modest. This is, at least in part, because the supply of illicit opioids is a very significant driver of consumption.

In 2001 the National Treatment Agency for Substance Misuse was established to co-ordinate the management and treatment of substance misuse across England. Between 2001 and 2012, the year before the agency was abolished, the mortality rate related to morphine and heroin misuse fell more than 40%. Responsibility for co-ordinating this care was passed to Public Health England, and local authorities, who had no prior experience or infrastructure in place, assumed responsibility for delivering treatment. Local councils have experienced severe budgetary constraints in the era of austerity, and between 2013–2017, the budgets for substance misuse treatment fell by 16% (Institute for Alcohol Studies, 2017). Since 2013 the mortality rates have more than doubled. It is difficult to draw a direct link between these reforms, budgetary cuts and the rise in mortality as there are potentially many confounding factors, including variations in the supply of illicit sources of these drugs.

Figure 5 Age standardised mortality per million people by type of opioid death, standardised to the European standard population 2013.



Source: ONS, Deaths related to drug poisoning in England and Wales (2019).

What to do about it?

Public Health England produced a series of recommendations that fall into five broad categories. These are:

1. **Better data.** Increasing the availability and use of data on the prescribing of medicines that can cause dependence or withdrawal to support greater transparency and accountability and help ensure practice is consistent and in line with guidance.
2. **Clinical guidelines.** Enhancing clinical guidance and the likelihood it will be followed. They recommend that NICE review the place of opioids in its guidance and place a greater emphasis on withdrawal management.
3. **Patient information.** Improving information for patients and carers on prescribed medicines and other treatments and increasing informed choice and shared decision making between clinicians and patients. This includes a recommendation to make warnings on packaging clearer.
4. **Greater provision of treatment.** Improving the support available from the healthcare system for patients experiencing dependence on, or withdrawal from, prescribed medicines, including a helpline and associated website.
5. **Research.** Further research on the prevention and treatment of dependence on, and withdrawal from, prescribed medicines.

In April 2019 the Health and Social Care Secretary, Matt Hancock, picked up on the recommendation regarding labelling and announced that all prescribed opioid medication packages would be required to display a prominent warning that they can cause addiction. This decision follows the recommendations of the UK Commission on Human Medicines (CHM) Opioid Expert Working Group, who are conducting a review of the problem; warnings began to appear before the end of 2019 (MHRA, 2019). This brings it in line with the regulations for codeine and dihydrocodeine available in over-the-counter preparations.

In an observational study of opioid prescribing in primary care between August 2010 to February 2014, the investigators made some recommendations to reduce risk in the prescribing of opioids in general practice (Mordecai et al., 2018). They suggested the establishment of a national database of patients being prescribed high doses of potent opioids to facilitate monitoring and reduce the risk of dose escalation, and to provide data for further research in this high-risk group.

Summary

Since the early 1990s there has been a major increase in the number and strength of prescriptions for opioid analgesics in the UK, mirroring the experience in other OECD countries. There has also been a substantial rise in deaths associated with opioid use since the 1990s, despite there being a significant fall in these deaths between the founding of the National Treatment Agency for Substance Misuse in 2001 and its abolition in 2013. Strategies suggested to mitigate the problem include better information, including the establishment of a national database of high users of prescribed opioids, enhanced guidance and information for patients and professionals, greater provision of treatment, and more research. Since late 2019, it has been compulsory for all prescriptions for opioids to carry a prominently displayed warning label (MHRA, 2019).

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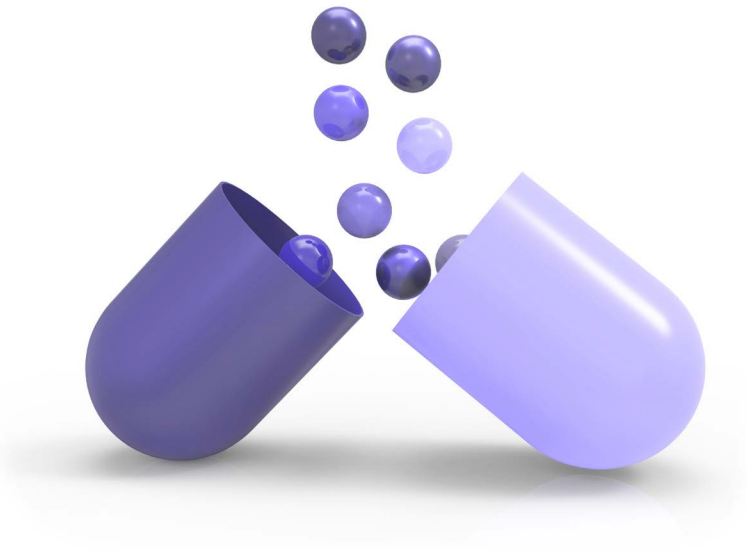
Biography

Chris Martin is a modeller, health informatician and former GP in the NHS. He has worked in a number of specialities including psychiatry, medicine, surgery, oncology, nephrology and obstetrics as well as general practice. After doing research in aspects of primary healthcare, he completed a Masters and then a PhD in Health Informatics with a focus on modelling mortality by cause of death. He initially began modelling morbidity and mortality for decision support in clinical practice but for the past decade has worked in longevity modelling for annuities.



The opioid epidemic in the United States

Dr Magali Barbieri, French Institute for Demographic Studies (INED) and University of California, Berkeley

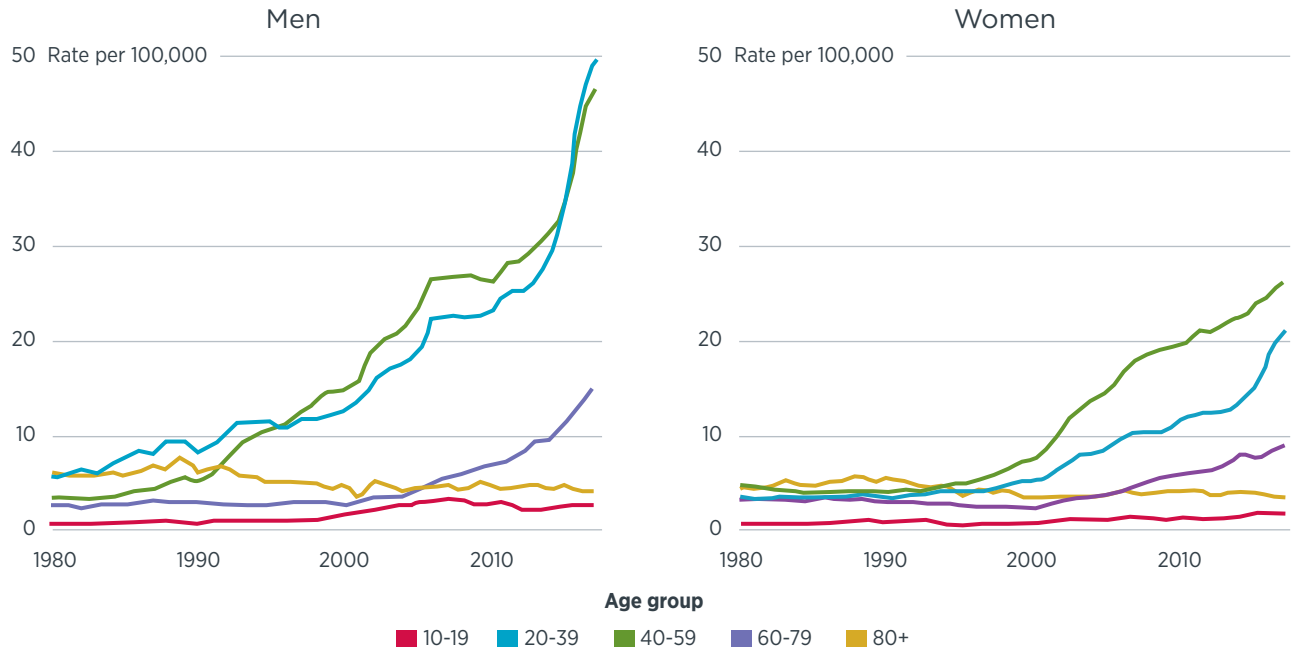
Background

In 2010 life expectancy at birth in the United States stopped increasing, and since 2014 has fallen for men. Recent data would suggest that this small decline in survival for men has been driven largely by the 'overdose epidemic', which refers to the substantial increase in the number of drug-related deaths.

Overdose mortality has risen steadily since around 1980, when the death rate from this cause was around 4 per 100,000.[1] By 2017 the rate had increased to 22 per 100,000[1], accounting for almost one-third of all deaths from external causes (which also include accidents, suicides and homicides). In the 1990s and 2000s, the pharmaceutical industry launched aggressive sales campaigns encouraging physicians to prescribe highly-addictive opiate-based pain relievers (OxyContin in particular) to their patients (Haffajee and Mello, 2017).

Adults aged 20 to 60, and especially white, low-educated men (those without a high-school diploma, equivalent to GCSEs) were most severely affected by the epidemic in its initial phases (Figure 1 shows the relative age group impacts). Since 2010, however, opioid mortality has increased rapidly in the black population as well (Alexander, Kiang and Barbieri, 2018). In 2017 overdoses accounted for 25-30% of all male deaths at ages 20-40, 20% at ages 40-50 and slightly below 10% at ages 50-60. Overdose mortality at ages 60-80 has also increased, perhaps due to the ageing of the birth cohorts affected by the upsurge in opiate addiction in the 1990s. However, as the contribution of other causes – mainly cancers and cardiovascular diseases – also increases steadily after age 60, the share of overdose deaths in overall mortality is small at advanced ages (below 2%).

Figure 1. Age-specific mortality from overdose by sex and age group, 1980-2017[1]



1 | Calculated by the author from the National Center for Health Statistics Mortality Multiple Cause Files available at: **https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm**

Drivers of the problem

The overdose epidemic began among economically disadvantaged populations in which the proportion of people in poor self-rated health and reporting chronic pain has increased steadily in surveys since the 1990s (Case and Deaton, 2017). These populations are concentrated in the south-west of the country, but also, and above all, in its former industrial heartlands to the south and east of the Great Lakes. It is in these regions, ravaged by the recession of the late 2000s, that the pharmaceutical companies focused their marketing campaigns (Monnat, 2019). The epidemic then spread across the entire country, affecting life expectancy everywhere.

In 2010, when the federal government restricted access to prescription opioids, those addicted switched to the illicit drug market and demand for heroin soared (Alpert, Powell and Pacula, 2017). The situation particularly deteriorated when synthetic opioids started flooding the market. Such synthetic drugs (fentanyl and other substantially similar drugs) are eighty times more potent than heroin or cocaine (deShazo et al., 2018). Because they are much cheaper to produce, they are mixed with heroin and cocaine, unbeknown to the users who continue to consume their regular doses, unaware of the increased risk associated with the substance. The death toll from opioid abuse reached 70,000 in 2017 (Scholl et al. 2019), more than the deaths from traffic accidents, suicides, homicides and HIV-AIDS combined. The problem now affects all American states.

Mitigation

Recognising the severity of the situation, the US authorities have implemented a series of measures to curb the epidemic. They include programmes to:

- monitor prescription drugs
- introduce abuse-deterrent formulations of pharmaceutical pain relievers
- stop the most toxic products from entering the country (across the borders or through the mail)
- promote the use of naloxone, an effective fentanyl antidote
- increase the number of addiction-rehabilitation centres
- facilitate access to substance-abuse treatment (Pitt, Humphreys and Brandeau, 2018).

2018 data from the Centers for Disease Control and Prevention (CDC, 2020) showed a 4% decline in the number of drug-related deaths compared to the year before, suggesting that these programmes had been successful in stopping the epidemic. However, more recent, though scattered, evidence appears to indicate a resurgence in the number of overdose deaths in 2019 (CDC, 2020) and further increases in 2020 (American Medical Association, 2020). Indeed, it has been difficult for law enforcement agencies in the United States to counter the expansion of the Mexican drug cartels. Furthermore, the American healthcare system is ill-equipped to prevent substance abuse and provide the long-term care necessary for a full recovery from drug addiction and it is likely that the few resources available to deal with the problem have been further reduced in 2020 due to the disastrous consequences of Covid-19. Combined with the increased social isolation and economic hardships associated with the widespread shelter-in-place policies implemented to control the spread of the virus, the situation has created the perfect cocktail for a new surge in addiction.

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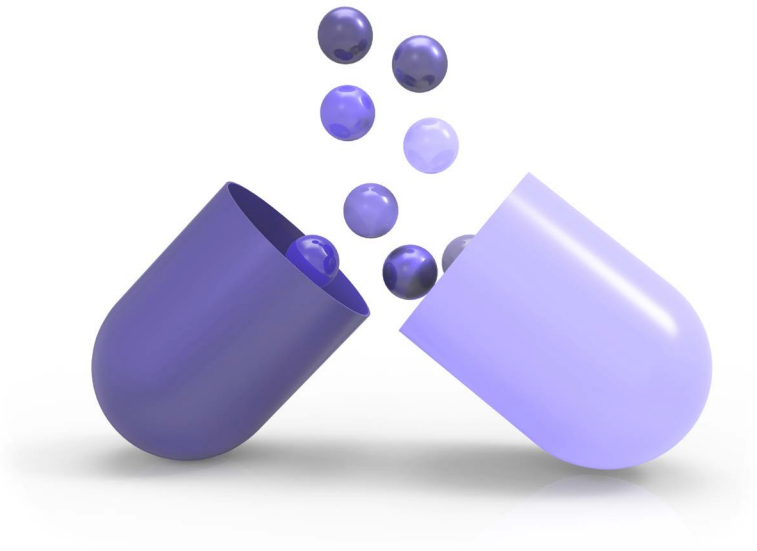
Magali Barbieri received her PhD in Demography at the University of California, Berkeley, in 1990. She currently holds a joint research position at the French Institute for Demographic Studies (INED) in Paris, France and in the Department of Demography at the University of California, Berkeley. At Berkeley, she leads the Human Mortality Database (HMD) project and is working on developing an HMD-like database for all US states and counties in collaboration, the United States Mortality DataBase. Magali has maintained an active research career, publishing articles in top demography and other internationally ranked journals.



Pharmacology and diabetes: swings and roundabouts

Nicola Oliver, Director of Life and Health, Medical Intelligence

Introduction

Pharmaceutical innovation is a key driver in extending life expectancy. For instance, around 40% of the mortality improvements in heart disease are believed to be as a result of pharmaceuticals (Unal et al., 2004), and today, innovation in cancer treatment continues to extend survival.

However, it is also recognised that pharmaceuticals can produce unwanted effects, to the point where they may cause disease. As an example, a class of drugs known as COX-2 inhibitors, commonly prescribed for joint pain, has been found to increase the risk of myocardial infarction and stroke.

In this article, we examine two classes of commonly prescribed drugs and their impact on diabetes. One, a drug used to help control diabetes (metformin), the other to help control blood lipids (statins).

Diabetes treatments - history

The first historical mention of what we now know as diabetes mellitus was over 3,000 years ago. The Ebers Papyrus is a record of ancient Egyptian medicine and, among other things, describes a condition thus: '. . . to eliminate urine which is too asha' (asha meaning plentiful or often). The following mixture was prescribed for treatment: 'A measuring glass filled with water from the bird pond, elderberry, fibres of the asit plant, fresh milk, beer-swill, flower of the cucumber, and green dates'.

Insulin

Thankfully, significant progress has been made since pond water and beer swill were prescribed for diabetes! Much of this progress naturally followed increased understanding of the pathophysiology of both type 1 and type 2 diabetes. Indeed, by the 5th century AD, people in India and China had worked out that there was a difference between type 1 and type 2 diabetes. They noted that type 2 diabetes was more common in heavy, wealthy people than in other people.

In 1922 Frederick Banting administered the first dose of canine insulin to a 14-year-old boy, Leonard Thompson, which heralded the advent of commercial production of insulin. By 1923 insulin was commercially available in the United States. The discovery of insulin was undoubtedly a breakthrough in the history of diabetes, saving millions of patients and also improving their quality of life, particularly those with type 1 diabetes.

Metformin

Goat's Rue or French Lilac (*Galega officinalis*) is a flowering plant containing guanidine that has been used to treat diabetes since the early 1900s. The active ingredient is known to be guanidine, and it is from this compound that metformin was derived. Metformin is the most widely used oral diabetic medication and is on the World Health Organization's List of Essential Medicines (which lists the most effective and safe medicines needed in a health system). Its main mode of action is to decrease glucose production by the liver and increase the insulin sensitivity of body tissues, though its full mode of action is not fully understood.

Metformin was first described in 1922 by Emil Werner and James Bell but the high-profile development of insulin overshadowed the continued development of metformin as a potential anti-diabetic drug. However, interest resumed in the 1940s and 1950s and French diabetologist Jean Sterne was the first to try metformin on humans for the treatment of diabetes. Metformin became available in France in 1957, in the UK in 1958, but not until 1995 in the US. The delayed approval in the US was as a result of the withdrawal of phenformin, a drug in the same class as metformin, after it had been marketed and prescribed extensively throughout the 1960s and 1970s. Phenformin was found to be associated with many cases of fatal lactic acidosis. Because it belonged to the same drug family as phenformin, metformin's reputation was tarnished.

Subsequently, many other classes of oral and injectable anti-diabetes drugs were developed.

It's abundantly clear that without pharmaceutical innovation, people with diabetes would still be experiencing lower life expectancy and complications at rates seen in the past. Before insulin therapy, type 1 diabetes was always fatal within months, or even weeks. In addition, the widespread use of easily administered oral drugs has transformed the lives of people with type 2 diabetes; in particular, the impact of metformin, a drug that is now under investigation for its anti-ageing properties. A closer examination of the benefits of this cheap and widely prescribed drug is presented here.

Metformin

Modes of action

As previously mentioned, metformin is an orally administered drug used for lowering blood glucose concentrations in patients with type 2 diabetes, particularly in those who are overweight and obese. There are several mechanisms by which metformin exerts its anti-hyperglycaemic action.

System	Mode of action
Hepatic	Inhibits glucose output from the liver
Muscle	Increases glucose uptake into muscle
Gut	Decreases intestinal absorption of glucose

Mitochondria, the power generators of the cell, are now known to be central to metformin's mode of action. Metformin acts as an energy disruptor, resulting in the effects outlined in the table. The disruption of mitochondrial metabolism sensitises cells to apoptosis (the process of cell death) and opens new therapeutic avenues in cancer treatment – another avenue of investigation in metformin's potential use.

Side effects

There are few significant adverse effects associated with metformin use. Indeed, it is highly unlikely to induce hypoglycaemia, something that is seen with the use of other anti-diabetic drugs.

One of the more serious conditions that may occur is lactic acidosis in which levels of plasma lactate increase. Elevated plasma metformin concentrations (that occur in individuals with renal impairment) and a secondary event or condition that further disrupts lactate production or clearance (eg cirrhosis or sepsis) are typically necessary to cause metformin-associated lactic acidosis (MALA). Lactic acidosis, in which there is an excessively low pH in the bloodstream, is considered a medical emergency. For this reason, metformin is not usually prescribed to those with existing kidney disease as these individuals are already compromised in terms of lactate clearance. However, the reported incidence of lactic acidosis in clinical practice has proved to be very low (<10 cases per 100,000 patient-years).

Impact

The first inkling that metformin could exert significant positive effects was through analysis of the UK Prospective Diabetes Study (UKPDS, 1998). The UKPDS was a randomised multicentre trial of glycaemic therapies in 5,102 patients with newly diagnosed type 2 diabetes. It ran for 20 years (1977 to 1997) in 23 UK clinical sites.

In the 1998 analysis, it was observed that intensive glucose control with metformin appeared to decrease the risk of diabetes-related measures in trials (for instance, HbA1c, a standard blood glucose measure) in overweight diabetic patients and was associated with less weight gain and fewer hypoglycaemic attacks than insulin and sulphonylureas.

Patients allocated metformin, compared with the conventional group, had risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality. At the time, the researchers concluded:

> *'Since metformin seems to give risk reduction of diabetes-related endpoints in overweight patients with type 2 diabetes, does not induce weight gain, and is associated with fewer hypoglycaemic attacks than sulphonylurea or insulin therapy, it could be chosen as the first-line pharmacological therapy in such patients.'*

Additional analysis was published by Holman et al. (2008). In this post-trial monitoring, the researchers were keen to ascertain whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes (eg amputations, strokes, renal failure).

Among patients in the metformin group, as compared with overweight patients in the conventional-therapy group, the significant reductions in relative risk that were observed during the interventional trial for any diabetes-related outcome, diabetes-related death, myocardial infarction, and death from any cause were maintained.

At 10 years, the risk reduction for any diabetes-related end point was 21%, for diabetes-related death 30%, for myocardial infarction 33%, and for death from any cause 27%. The trial showed the extended effects of improved glycaemic control in patients with newly diagnosed type 2 diabetes, some of whom were followed for up to 30 years.

The question of life expectancy with metformin use was explored in a paper by Bannister et al. (2014). In this publication, the authors used retrospective observational data from the UK Clinical Practice Research Datalink from 2000 in order to compare all-cause mortality of diabetic patients treated first line with either sulphonylurea or metformin monotherapy with that of matched individuals without diabetes.

Remarkably, the observed survival in diabetic patients initiated with metformin was 15% lower (survival time ratio [STR]=0.85, 95% CI 0.81–0.90) in matched individuals without diabetes and 38% lower (0.62, 0.58–0.66) in diabetic patients treated with sulphonylurea monotherapy.

This study indicates that those with type 2 diabetes initiated with metformin monotherapy had longer survival than matched non-diabetic controls. The researchers suggest that those with diabetes treated with metformin monotherapy can expect their survival to be at least as good as that of the non-diabetic population while on this specific regimen.

Conclusion – metformin

Metformin is now attracting the attention of researchers in fields other than diabetes, as it has been shown to have anti-cancer, immunoregulatory and anti-ageing effects. The anti-cancer effects of metformin are purported to be two-fold: directly, by affecting the inflammatory processes that play a significant role in tumour progression, and indirectly, by modifying the blood glucose and insulin levels which can influence the survival of cancer cells.

In conclusion, metformin, a cheap and easily administered drug, has transformed the lives of millions of people with diabetes and holds promise for its future application in other chronic diseases.

Cholesterol and statins

History

Since it was first isolated from gallstones in 1784, cholesterol has fascinated scientists in many areas of science and medicine. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol research.

During the 19th century, arteriosclerosis was well recognised, with the first report that cholesterol was related to atherosclerosis appearing in 1910 from German pathologist Rudolf Virchow, who identified that human atherosclerotic plaques contained cholesterol.

The lipid hypothesis was born in the 1950s (although controversy now exists in this area), and by the 1970s the race was on to find a chemical that would inhibit a crucial enzyme involved in the synthesis of cholesterol. Finally, in the 1980s, Lovastatin was approved.

Today

Today, statins are widely prescribed for both primary and secondary prevention in cardiovascular disease. In the UK, they are recommended for those with a 10% or greater risk of developing CVD within the next 10 years, following assessment using the cardiovascular risk measurement tool QRISK2. (However, before offering statins for primary prevention, GPs should discuss the benefits of lifestyle modification, and optimise all other modifiable CVD factors if possible.)

There is considerable debate regarding the benefits of statin use, particularly in primary prevention. This article does not present this aspect of statin use; instead, the focus is on the side effects of statin use and, in particular, the potential association between statin use and increased risk of diabetes.

Side effects

In 2019 the American Heart Association issued a scientific statement (AHA, 2019) regarding the safety of statins and associated adverse effects. Using data primarily from randomised controlled trials, supplemented with observational data where necessary, their scientific statement provides a review of statin safety and tolerability.

In it, they identify that there is an increased risk of certain conditions when taking statins, as set out in Table B.

Table B. Statin side-effects (AHA, 2019)

Condition	Risk
Risk of statin-induced serious muscle injury	<0.1%
Risk of serious hepatotoxicity	≈0.001%.
Risk of statin-induced newly diagnosed diabetes mellitus	≈0.2% per year of treatment

In US clinical practices, roughly 10% of patients stop taking a statin because of subjective complaints, most commonly relating to muscle symptoms. (Interestingly, a strong predictor that you'll experience muscle aches when taking statins could be whether or not you read about the potential side effect.)

Statins and diabetes

The precise mechanism(s) of diabetogenesis with statin therapy are unclear, but impaired insulin sensitivity and compromised β cell function may be involved. Statins reduce biosynthesis of the vital coenzyme CoQ10 in the liver, and this may cause mitochondrial dysfunction and energy depletion leading to insulin resistance.

The JUPITER trial (a well-regarded study in statin history) reported a 25% increase in diabetes risk with rosuvastatin 20 mg, over a median follow-up of 1.9 years, compared with those on placebo (Narla et al., 2009). Since then, several meta-analyses have confirmed a smaller but significant increase with various statins.

Observational studies have provided additional insight into the supposed statin/diabetes link. A population-based cohort study (Macedo et al., 2014) aimed to assess the effect of statins on the development of diabetes mellitus. Using data from the Clinical Practice Research Datalink, the researchers followed up every patient aged 30–85 years old who started taking a statin between 1989 and 2009 and matched them with up to five non-statin users.

This large study comprised 2,016,094 individuals: 430,890 people who received a statin, matched to 1,585,204 people not prescribed a statin. Mean follow-up time was 5.4 years for statin users and 3.9 years for non-users. Overall, this study found that statin use was associated with a 57% increased risk of T2DM (HR 1.57; 95% CI 1.54-1.59), which was found to increase with longer duration of use.

In addition, analysis of data from the US-based Diabetes Prevention Program Outcomes Study (Crandall et al., 2017) reported that statin use was associated with 36% greater diabetes risk irrespective of treatment group (95% CI of 1.36 (1.17 to 1.58).

Zigmont et al. (2019) published the results of a retrospective cohort study which sought to understand the risk of (inter alia) new onset diabetes (NOD) for a cohort of individuals that reflect real-world prescribing patterns, and the paper added increased evidence of the association between statins and diabetes. The participants in this study were drawn from a retrospective cohort of employees and dependent spouses enrolled in a private insurance plan in the US Midwest.

Those using statins for two or more years had elevated risk of NOD development, with a hazard ratio of 3.3 (95% CI: 1.84, 6.01). Those using statins for less than two years did not have a statistically significant increase in the risk of NOD. As with previous studies, duration of use was associated with increased risk in a dose-dependent manner, which is suggestive of a causal relationship. This study did not observe any differences by statin class or intensity of dose.

Conclusions – statins

There is little doubt that statins play a role in an increased risk of diabetes. The question is, has the use of statins been responsible for the increasing incidence of diabetes? A key risk factor for type 2 diabetes is the presence of obesity; prevalence trends indicate clearly the association between rising obesity rates and diabetes. In 1993 the percentage of people in England classified obese was 15%; by 2016 this had almost doubled to 29% (NHS Digital, 2017). Over a similar time period, the number of people diagnosed with diabetes in the UK has also doubled (Diabetes UK, 2019).

Statin prescribing prevalence rates increased sharply between 1995 (2.36 per 1,000 person-years) to 2013 (128.03 per 1,000 person-years) (O'Keeffe, Nazareth and Petersen, 2016). Research evidence certainly points towards a causal relationship between statin use and diabetes risk. But how much of the increase in diabetes rates is as a result of statin use is challenging to quantify. Type 2 diabetes is a multifactorial disease, with complex interactions between various environmental, behavioural and genetic factors, making the contribution of each single factor difficult to assess. It is, however, fair to say that some of the increase in diabetes cases may have arisen as a result of the use of statins.

Overall conclusion

Pharmaceutical innovation has, without a doubt, transformed the lives of millions of people, not just with diabetes, but other chronic and life-limiting conditions such as cancer and heart disease. In the case of insulin administration alone, without the scientific breakthrough that led to its commercial production, a diagnosis of type 1 diabetes would still be associated with an extremely poor prognosis.

Metformin has also transformed the lives of many millions of people with type 2 diabetes and has the potential to help many more as the drug's anti-cancer and anti-ageing properties are better understood.

However, the adverse side effects of some drugs can, and do, result in additional health problems, as we have discovered with statins and diabetes. The wider implications of this issue, and those of other adverse drug reactions, and interactions, cannot be underestimated.

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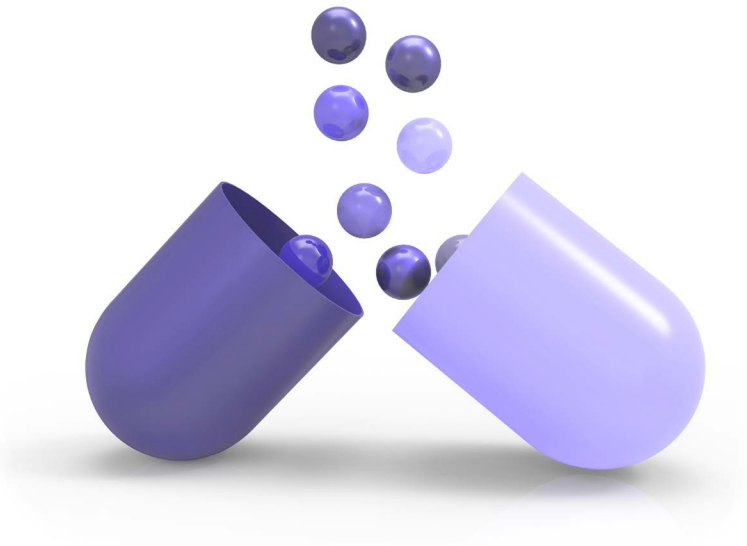
Nicola's background includes a long career in the UK National Health Service, where she specialised in public health. This followed many years in senior roles in intensive care nursing and paediatrics. Nicola has also studied epidemiology and statistics at the London School of Hygiene and Tropical Medicine.

Nicola is an affiliate member of the Institute and Faculty of Actuaries and is chair of the IFoA Diabetes Working Party.



Recent developments

Continuous Mortality Investigation (CMI) update

The coronavirus pandemic is an extreme mortality event that has occurred on a global scale. Given that the pandemic fundamentally relates to mortality and morbidity, the Continuous Mortality Investigation (CMI) is producing material that it hopes subscribers will find informative. In particular, the CMI is doing the following.

- From April the Mortality Projections Committee increased the frequency with which it publishes its **mortality monitors**, releasing them weekly rather than quarterly. (These monitor the progression of mortality rates and mortality improvements in the general population of England and Wales based on provisional weekly deaths data released by the ONS.) The monitors show that, compared to 2019, there have been around 60,600 excess deaths in the UK from the start of the pandemic to the week of 4 September 2020, leading to an abnormally high negative mortality improvement over 2020. As weekly excess deaths have now fallen, the Committee has decided to reduce the frequency of the monitors. However, the Committee has released software that allows users to monitor excess deaths on a weekly basis if they wish. If there are any further peaks in deaths then the frequency of the monitor will increase again.
- Given how extreme the mortality improvement for 2020 is likely to be, the Mortality Projections Committee is also considering the approaches it could take to modify the CMI Mortality Projections Model for the data observed in 2020. The Committee will provide further information on the possible modification approaches later in 2020.
- The CMI is also considering how to modify our experience analyses methods to allow for the exceptional mortality in 2020. We have set up a working party (led by Steve Bale) to develop a consistent approach across CMI committees and intend to consult on this in the autumn.
- The Annuities and Assurances Committees have contacted data contributors who submit either pension annuities in payment, term assurances or whole of life assurances data to the CMI to gauge their ability to continue to submit data within the data submission deadlines. Both committees have also asked data contributors about the possibility of accelerating the submission of experience data for 2020, to enable them to report on the impact of the coronavirus pandemic on insured lives.

Tailoring the CMI Model for different populations

The CMI encourages users of the CMI Mortality Projections Model to consider adjusting the parameters of the Model so that the mortality improvements that it generates are appropriate for the population being modelled. CMI_2018, for the first time, and CMI_2019 allow users of the model to add a constant addition (that tapers to nil between ages 85 – 110) to the historical age-period component of mortality improvements. This new parameter (the 'initial addition to mortality improvements' or 'A') adjusts both the level of the initial age-period component and the historical mortality improvements and enables users to easily apply a simple adjustment for their population.

To assist users of the model, the CMI has published analyses of mortality improvements in various datasets. These include published mortality improvements in the Annuities, Assurances and SAPS datasets (based on mortality data collected by the CMI investigations) as well as mortality improvements in the general population of England and Wales (based on the total population as well as the population divided into socio-economic subsets as measured using the Index of Multiple Deprivation, or IMD).

Working Paper 127 shows that observed mortality improvements were clearly higher in the least deprived socio-economic groups, measured by IMD, over 2001–2018. However, in the CMI datasets analysed, the results are less clear-cut. While observed mortality improvements in the SAPS and Annuities datasets tended to be higher than in the general population, this was not true of all time periods and not all of the differences were statistically significant.

Charts 1 and 2 show five-year trailing averages of lives-weighted mortality improvements in the SAPS and England and Wales datasets. Chart 1 shows the observed five-year mortality improvements over 2006-17 for SAPS and England and Wales, and Chart 2 shows the difference (SAPS minus England and Wales). The shaded areas show the 95% confidence intervals.

Chart 1: Five-year average mortality improvements, males and females combined ages 65-100

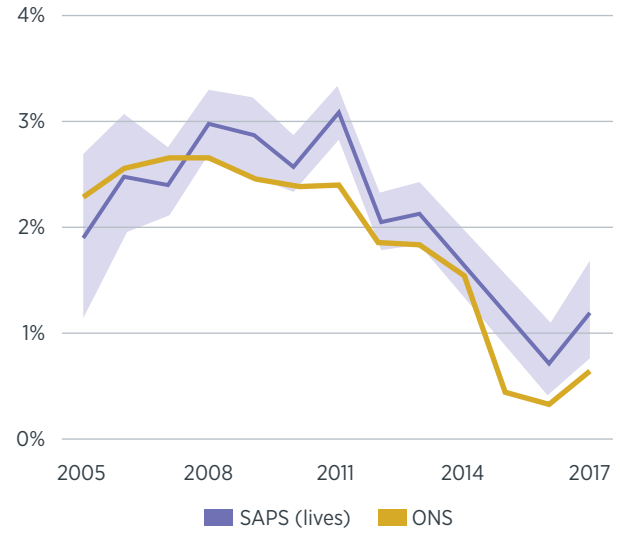
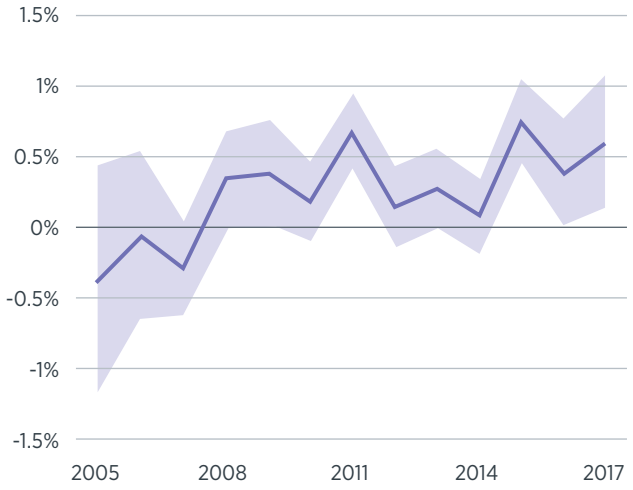


Chart 2: Difference in five-year average mortality improvements (SAPS minus England & Wales), males and females combined ages 65-100



*Source: CMI **Working Paper 127** (Chart 5E and Chart 5F)*

Chart 1 shows a similar pattern for mortality improvements in the SAPS and England and Wales datasets – both have relatively high mortality improvements at the start of the period and falling improvements since 2011. The SAPS mortality improvements show higher levels of volatility due to the smaller population size. Chart 2 shows that the five-year average mortality improvement for SAPS has been consistently higher than that for England and Wales since 2008, although this difference has not always been statistically significant. Working Paper 127 also included an analysis of mortality improvements in socio-economic subsets of the general population of England and Wales (split by IMD) for males and females respectively, shown in Charts 3 and 4 below. These show that observed mortality improvements have been higher for less deprived groups (IMD 8-10) than for more deprived groups (IMD 1-3) and that since 2011 all three socio-economic groups have experienced a slowdown in mortality improvements.

A key challenge in measuring mortality improvements in CMI datasets is the lack of consistency of the datasets over time. For example, we may only have data for a particular life office or pension scheme for part of the period being analysed. To control for this in the analysis of the SAPS dataset, the mortality improvement in year Y is calculated based only on pension schemes that have contributed data for the period 1 January Y – 1 to 31 December Y + 1. This attempts to control for two factors – consistency of the dataset over time as well as possible late-reported deaths in the dataset.

Chart 3: Five-year average mortality improvements, males ages 65-89

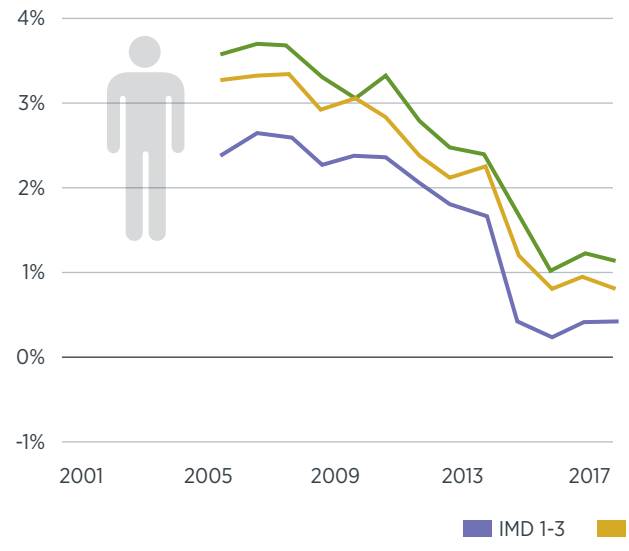
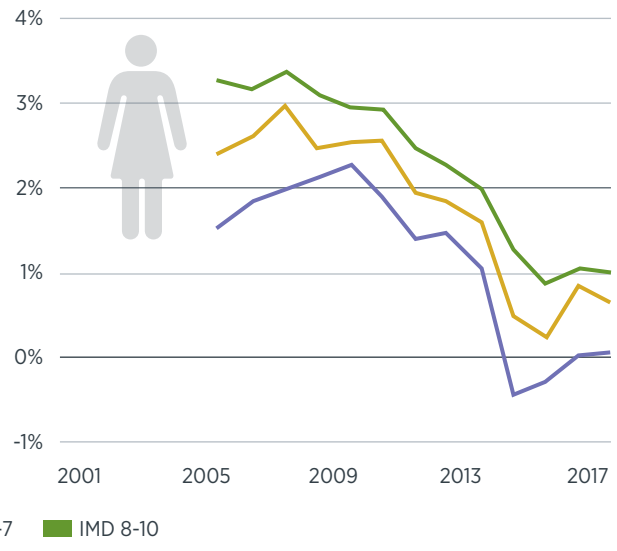


Chart 4: Five-year average mortality improvements, females ages 65-89



In **Working Paper 128** the Annuities Committee published analysis of experience of pension annuities in payment in 2015–2018. Although this is a very short period over which to assess mortality improvements, the dataset is highly consistent across these four years. This analysis suggests that mortality improvements for annuitants have been a little higher than mortality improvements in the population of England and Wales although this is, at least in part, a consequence of lower experience in 2018, which is subject to greater uncertainty as it incorporates an allowance for late reporting of deaths. The average mortality improvements for the England and Wales and Annuities datasets for the period 2016–2018 are shown in Chart 5. The range represents the 95% confidence interval.

Chart 5: Average mortality improvements for 2016-2018, males and females ages 65-100

Compared to the standardised mortality rate approach used above, the Assurances Committee has used a different approach; in **Working Paper 132** it assessed the experience for 2011–2018 using an Actual / Expected (A/E) approach. This analysis looked at the A/E by calendar year in the term assurance dataset for both genders and both smoker statuses combined. The analysis showed that there is a slight downward trend in A/E for the dataset once improvements observed in the general population are allowed for (ie improvements in the term assurances dataset were marginally higher than in the general population), although the results were not statistically credible. However, even if the results of the analysis were credible, it would still be difficult to compare this with the other analyses due to the different age range and the very different features of term assurances; for example, the strong effects of policy duration and the existence of smoker-differentiated rates.

Other recent work published by the CMI

The following summarises recent work published by the CMI.

- The Mortality Projections Committee published CMI_2019 in March 2020 alongside **Working Paper 129**. Mortality improvements over 2019 were relatively high – the mortality improvement in 2019, based on provisional weekly deaths data, was 3.8% for males and 3.9% for females. These high levels of improvements led to an increase in the initial rates of improvement at most ages in CMI_2019 compared to CMI_2018, which led to a small corresponding rise in cohort life expectancies at most ages compared to CMI_2018. Subscribers were surveyed for their views on the CMI Mortality Projections Model, and the results of this survey and feedback from the Committee were published in **Working Paper 135**.
- The Annuities Committee released proposed '16' Series tables for pension annuities in payment for consultation alongside **Working Paper 130**. The volume of data used to construct the proposed tables is materially higher than the volume of data used to graduate the '08' Series tables. More significantly, the latest dataset provides increased granularity by product, enabling the Committee to propose separate tables for different types of annuities (individual internal, individual external and pension buy-out) as well as composite tables. In each case, tables have been produced for ages 20–120, on both lives- and amounts-weighted bases for each gender. After considering the feedback received during the consultation period, the Committee released final '16' Series tables alongside **Working Paper 134**.
- The Annuities Committee also released **Working Paper 133**, which included analysis of 'all offices' experience of life annuities for the period 2013–2018. This working paper compared experience in the life annuities dataset to a version of the '08' Series tables (modified for the recommendations of the High Age Mortality Working Party) using an A/E analysis.
- The Income Protection Committee released proposed 'IP11' Series claim inception and termination tables alongside **Working Paper 131**. The proposed tables are based on data for 2007-2016, which are unchanged from the data underlying the 'all offices' results issued alongside Working Papers 96 and 124.
- The SAPS Committee released **Working Paper 126** in November 2019; this presents an analysis of the mortality experience of data received by 30 June 2019, covering the period 2011–2018, and also includes details of the initial socio-economic data that has so far been collected for SAPS pensioners. The SAPS Committee will be carrying out further analysis of the IMD data collected later in 2020.

Upcoming work from the CMI

The following summarises work to be published by the CMI in the near future.

- Following release of 'All offices' experience of pension annuities in payment in 2015-2018, in **Working Paper 128**, the Annuities Committee is carrying out analysis of mortality by socio-economic status in 2020, as a substantial proportion of that data included IMD deciles, generated using the **'CMI postcode mapping tool'**.
- The Income Protection Committee will collate the responses to the consultation it is running (see above) and provide further information in due course.
- The Assurances Committee is in the process of constructing draft '16' Series term tables, which would cover term assurances data for the period 2015–2018. These tables will be released alongside a working paper for consultation later in 2020.
- The CMI is working in collaboration with the Society of Actuaries in Ireland to calibrate a version of the CMI Projections Model to population and deaths data for the Republic of Ireland. Initial results of the analysis were presented at the Life Conference in Dublin in November 2019, with a joint paper due to be released soon.

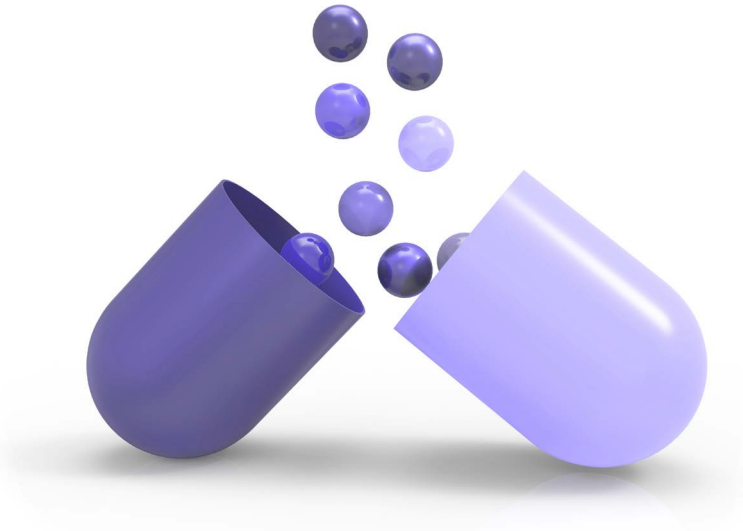
Continuous Mortality Investigation

Institute and Faculty of Actuaries

The Continuous Mortality Investigation (CMI) carries out research into mortality and morbidity experience, providing outputs that are widely used by UK life insurance companies and pension funds.

The CMI is funded by annual subscriptions from organisations that require access to our work for commercial purposes. Most new research is available only to employees of subscribers and to researchers for non-commercial use. However, papers relating to methodology may be made more widely available.

If you have any questions about the CMI or are interested in becoming a subscriber to the CMI's outputs, please email us at **info@cmilimited.co.uk**



Actuarial Research Centre
Institute and Faculty of Actuaries

IFoAFoundation
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IFoA commissions research project on diabetes mortality and morbidity risk

The IFoA's Actuarial Research Centre (ARC) is pleased to announce that Pacific Life Re, PartnerRe, Swiss Re Zurich Insurance Group and Legal & General have joined forces with the IFoA to commission research on 'diabetes mortality and morbidity risk'.

Independent academic guidance for this research is being provided by City's Business School, City, University of London. The overarching aim of the project is to develop a deeper understanding of the mortality and morbidity risks associated with a diagnosis of type 1 or type 2 diabetes and the impact of recent improved treatments. The insurance industry underwrites customers with diabetes based on a range of factors, medical expertise and various medical studies. It is hoped that the research undertaken in this project will help the insurance industry appreciate and use current data and studies when considering diabetic risks.

The hope is that the research will ultimately lead to improved access to insurance products for individuals with diabetes.

Further details are available on the IFoA website, where updates on the project will also be shared as they become available. **https://www.actuaries.org.uk/learn-and-develop/research-and-knowledge/actuarial-research-centre-arc**.

The website also provides information about the ARC's full range of world-class research programmes and projects that bring together industry, academia and practitioners to develop models, insight and practical tools for the benefit of actuaries, institutions and society in general.

The IFoA Foundation – Actuaries supporting others

The IFoA Foundation is the new charity of the actuarial profession. Being an actuary has always meant giving back, opening doors for the next generation and helping to solve some of the biggest challenges facing society. The IFoA Foundation seeks to continue this legacy.

It has three objectives:

- **Rewarding excellence:** Providing recognition, prizes and awards for excellence in actuarial examinations and academic research
- **Supporting our community:** Giving scholarships, bursaries and grants to university students, those studying for the actuarial examinations, and others in financial hardship; plus supporting publications, courses and conferences
- **Addressing future challenges:** Supporting the IFoA's public interest responsibilities and partnering with other charities on financial education

Recent activities have included support for university and school prizes, school mathematics competitions, sponsoring university conferences, and actuarial examination and research prizes. The Foundation will continue to support these activities while at the same time developing others, particularly outside the UK. The principal focus will be on encouraging future generations of actuaries and supporting activities that make a significant impact on society.

The Foundation formally launched on 17 August 2020. To continue and extend its work, the Foundation is actively fundraising and seeking donations from our community. Ideas and suggestions for raising funds are welcome. To find out more about the Foundation, including how you can either support or benefit from it, please visit the Foundation website at: **bit.ly/ifoafoundation**

The IFoA Foundation is a Scottish Charity, registration number SC049518.

Annals of Actuarial Science (AAS) and the *British Actuarial Journal (BAJ)*

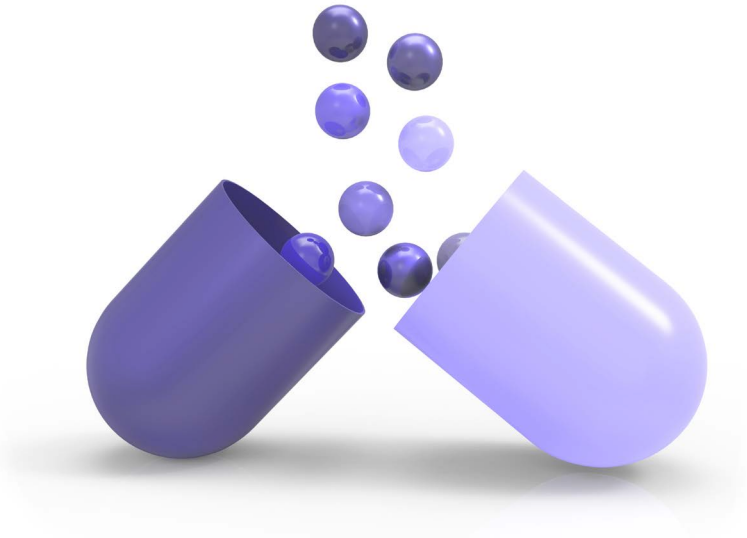
AAS attracts and peer-reviews articles of theoretical and applied research on all aspects of actuarial science from authors worldwide (**http://bit.ly/ifoa2531**).

Vol. 14 no. 2 (Sep 2020) is a Special Issue based on papers presented at Longevity 14: The Fourteenth International Longevity Risk and Capital Markets Solutions Conference, held in Amsterdam in 2018. All papers are available individually on the website before September as 'FirstView' articles. These include:

- Identifiability in age/period/cohort mortality models
- Longevity trend risk over limited time horizons
- Asymmetry in mortality volatility and its implications on index-based longevity hedging
- An investigation into the impact of deprivation on demographic inequalities in adults.

The *BAJ* publishes papers presented at the sessional research meetings of the IFoA as well as papers of interest to practitioners (**http://bit.ly/ifoa9125**). Recent papers and discussions include:

- E-cigarettes: no smoke without fire?
- Managing uncertainty: principles for improved decision making
- Saving for retirement: rules of thumb
- A review of the risk margin – Solvency II and beyond.



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