EDITORIALS

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How medicine is broken, and how we can fix it

The chief medical officer's review on statins and oseltamivir may look for answers in the wrong places

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Last week there was extensive coverage of a leaked letter written by the chief medical officer (right) to the Academy of Medical Sciences. This letter focused especially on concerns around statins and oseltamivir (Tamiflu) and asked the academy for an "authoritative independent report looking at how society should judge the safety and efficacy of drugs."[1] The academy has since announced that it is convening a working group on the subject.

With any such report there are two major risks. The first is a focus on "trust" or even—as a worst case—false reassurance for well documented problems. We do not believe the academy will choose this path. But there is another, bigger risk: the academy may accept shortcomings in the evidence as somehow inevitable. Here there are good grounds for concern. The academy has already announced that its work "will explore how evidence that originates from different sources (e.g. randomised clinical trials and observational data) are used to make decisions about the safety and efficacy of drugs and medical interventions."[2]

Focusing solely on existing trials and observational studies would represent a failure of vision and ambition in an era when medicine has both the need and the opportunity to innovate. Well documented problems exist in the funding and prioritisation of research, the conduct of trials, the withholding of results, the dissemination of evidence, and its implementation with patients. Here we briefly examine six domains where the academy could call for simple practical improvements that would address legitimate concerns.

Publication bias—We conduct trials to detect modest differences, and spend vast amounts of money specifically to exclude bias, yet we allow that bias to flood back in through selective publication.[3 4] Eminent bodies writing reports will not fix this, but practical action will. We need new funding for simple systematic work to audit which trials are unreported, to highlight the best and worst performers, and to shine a light on withheld studies.[5]

Independent trials—A recent cohort study found that 97% of head to head trials sponsored by industry give results that favour the sponsor's drug.[6] Doctors and patients are right to want independent trials. On statins and oseltamivir, there are two clear opportunities, and here we declare our own conflicts. With colleagues, one of us (CH) first proposed a trial of oseltamivir in a pandemic in 2009; the other (BG) first proposed a trial of statins examining side effects over a year ago. In both cases we could have the answer by now.

PHOTOSHOT

Sally Davies: concerned about the public's health

Cost of trials—Replication will be possible only if the cost of conducting trials is radically reduced. Much of this cost is driven by disproportionate regulation around trials of routinely used treatments.[7] The National Institute for Health and Care Excellence's guidance on cholesterol argues for head to head trials in low risk populations; this would require over 100 000 participants, followed up for a decade. Such trials can practically be delivered only by reducing the expensive and disproportionate regulatory burden,[7] embedding them in everyday clinical care and gathering follow-up data from existing electronic health records.[8]

Better evidence—Treatments are routinely approved after trials with only surrogate outcomes.[9] Drugs are then extensively promoted, at the moment of approval, when evidence on real world outcomes is paradoxically at its weakest. We could encourage better evidence by, for example, compelling companies to follow-up all phase III trial participants until real world benefits emerge, considering routine randomisation for newly approved drugs when benefits are unclear, and bartering with either patent extension or choice of the start date for market exclusivity. These suggestions would come at minimal cost and deliver more comprehensive data on treatment effects.

Shared decision making—Concern over statins has been reawakened by the introduction of a financial incentive for general practitioners to prescribe the drugs to low risk patients. This is ill judged because patients' informed choices vary widely.[10 11] An incentive to prescribe a treatment that many adequately informed patients do not want undermines informed decision making and inflicts avoidable reputational harm on the profession. If instead we incentivise shared decision making then—for the same financial outlay—best practice will be recognised, rewarded, and laid down in the everyday templates of what doctors do.[12]

Declare conflicts of interest—Declaration of conflicts of interest is currently chaotic, inconsistent, and incomplete. We clearly need a central system of declarations, ideally maintained by the General Medical Council.[13] Conflicts, however, become particularly salient when evidence is unclear: when decisions about which treatment works best are made on the basis of a speculative, superficially plausible narrative about a drug's mechanism of action, or on the interpretation of weak, confounded, observational data when randomised trials are feasible. If we are able to generate better evidence and ensure that we see the complete evidence, then competing interests—although they must always be declared—will become less salient.

RCTs: transgressive once

We should remember that evidence based medicine, in its true modern incarnation, has a relatively short history and that when randomised trials were first introduced they were often regarded as a transgressive, expensive, unnecessary, and unwelcome challenge to medical authority.[14] The public is increasingly aware of the shortcomings we collectively tolerate in the evidence base for clinical practice. We now have the opportunity to use public frustration as fuel to update our implementation of evidence based medicine in the light of new technology and get our house in order. To restrict a review of these problems to the interpretation of inadequate existing data—as the academy apparently proposes—would be recklessly backward looking.

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These studies suggest that starting of PCA in emergency departments is likely to be beneficial for patients who have needed a bolus of intravenous opiate analgesia for initial pain management

Patient controlled analgesia in the emergency department

Reduces pain and increases autonomy

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Acute severe pain that follows injury or onset of illness alerts patients to the likelihood of tissue damage (nociception) and drives much emergency department attendance.[1] The prompt assessment and alleviation of pain is a quality benchmark for emergency departments internationally, and titrated intravenous opiates are the initial analgesic of choice for severe pain.[2 3]

Recent improvements in initial pain assessment and analgesic provision have occurred in UK emergency departments, but processes for referral to an inpatient team and time based standards for ward admission can interfere with effective pain management after the first dose of intravenous opiate. Recent surveys of patients and studies of care pathways suggest that current care is suboptimal in this regard.[4]

Two open label, multicentre, randomised trials of pain solutions in the emergency setting (PASTIES) by Smith and colleagues provide new evidence to help us tackle this deficiency.[5 6] The studies each enrolled patients who commonly require parenteral analgesia throughout the first day of an emergency admission—adults with acute non-traumatic abdominal pain and adults with acute traumatic injury. Both studies included only patients who required initial treatment with boluses of morphine. Participants in the intervention groups were given a patient controlled analgesia (PCA) device consisting of a volumetric pump safely delivering a fixed dose when a button is pressed, with a subsequent lockout period.

Patient centred analgesia

Patients in the control group received standard prescriptions for intermittent opiates.

One novel feature of these studies was the measurement of patients' own pain scores hourly for up to 12 hours. This allowed the authors to calculate the "area under the curve" for pain scores, a measure of total pain experienced in the emergency department and into the ward admission.

Divergent results

Interestingly, the studies reported different results. Adults with non-traumatic abdominal pain experienced significantly less pain overall when managed with PCA compared with usual treatment[5]; this observation was robust to sensitivity analyses. Participants in the PCA group spent 15% less time in moderate or severe pain throughout the 12 hour study period, received significantly more morphine, and had a 2.6-fold increase in the (adjusted) odds of being very or completely satisfied with pain management. In the study of patients with acute traumatic injuries, pain scores were lower and satisfaction scores were higher in those managed with PCA, but the differences were not statistically significant.[6]

The inconsistent results could be due to differing pain mechanisms in the two populations (visceral in abdominal pain, somatic in acute traumatic injury), a type 2 error in the study of acute traumatic injury (whereby the study failed to find an existing difference between treatments owing to methodological factors such as low power), or type 1 error in the abdominal pain study (whereby the study found a difference where none existed). As the confidence limits in the study of acute traumatic injury include a clinically relevant difference between the treatments, type 2 error seems more likely. The authors also acknowledge the strong possibility of a Hawthorne effect improving pain management in the control groups beyond the experience of patients in the "real world."

However, somatic pain from limb fractures differs from visceral pain in that management in the emergency department can include reduction of fractures and dislocations, plaster splintage, and regional nerve blocks, which may markedly reduce subsequent analgesic requirements. In both studies, the relative increase in satisfaction scores with PCA was greater than the relative reduction in pain scores, suggesting that patients attach more value to autonomy in pain management than to the magnitude of pain experienced.

Together, these studies suggest that starting of PCA in emergency departments is likely to be beneficial for patients who have needed a bolus of intravenous opiate analgesia for initial pain management, particularly when severe pain recurs during their stay in the emergency department. Patients with a similar clinical profile to those in the PASTIES studies are most likely to benefit; however, extrapolation to other groups is not unreasonable, particularly when a second bolus of intravenous opiate is being considered. The counter arguments include concern about serious side effects of opiates, although in practice these are rare. Among the 400 patients in these studies, just one had a serious adverse event—excessive drowsiness from which the patient recovered fully.

Both PASTIES studies appropriately excluded patients with a less favourable risk-benefit balance in relation to intravenous opiates. Pain management guidance from the UK's Royal College of Emergency Medicine also urges caution in the use of intravenous opiates in older adults,[7] but the PASTIES investigators safely included patients up to 75 years old. It is important to acknowledge that benefit from PCA occurs in the context of multimodal analgesia that enables opiate sparing.[8] The overall goal of emergency admission must be to treat the underlying illness or injury and reduce the need for parenteral analgesia.

We know that PCA devices are safe and effective in the postoperative setting, where they have been used extensively since the 1990s.[9] Cost effectiveness—although not described in PASTIES—is unlikely to be a major barrier for emergency departments, as the small investment in reusable equipment and set-up time is more than likely to be recuperated by reductions in the nursing time spent administering additional bolus opiates. The acronym for the PCA device should perhaps be reattributed to "patient centred analgesia," as these devices clearly deliver an autonomy that is highly valued by many patients.

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They found that acute rejection was rare overall and that risk did not differ between groups of participants treated with a generic or an innovator drug

Are generic immunosuppressants safe and effective?

Clinical experience is now reassuring and regulation is strict; now we need definitive evidence

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Diminishing grounds for concern

Increasing use of generic drugs is essential to maintain comprehensive and equitable healthcare, given current pressure on budgets. Concerns remain, however, about generic prescribing or compulsory substitution in certain drugs and classes of drug classes, including lithium, theophyllines, some anti-epileptic drugs, and the immunosuppressants evaluated in the linked study by Molnar and colleagues.[1 4]

Strict regulations govern market authorisation for generic drugs.[5] Regulators such as the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) require manufacturers to show bioequivalence between a generic and a proprietary version of the same drug.[6] Subsequent meta-analyses have found no difference in outcomes between generics and originators across several classes of drugs, including cardiovascular medicines.[7]

Strict regulation helps to limit concerns about prescribing of international non-proprietory name drugs and generic substitution. Several studies have reported that proprietary drugs and their generic equivalents differ by only a few percentage points on accepted measures of bioavailability (area under the plasma concentration curve or AUC) and peak exposure (maximum plasma concentration or C_{max}).[8]

Regulation of generic immunosuppressants is stricter still. As a precautionary measure, the EMA has narrowed the acceptable difference in AUC between generic and proprietary versions. Marketing authorisation is granted only when the AUC ratio of test and reference product falls within a 90% confidence interval of 90% to 111%, narrower than the 80% to 125% interval accepted for other drugs.[8] The summary of product characteristics also recommends that patients prescribed generic immunosuppressive drugs have their plasma concentrations monitored during the switch to minimise the risk of rejection.[9] This recommendation echoes normal clinical practice, as patients are monitored in a similar way during initial treatment with an immunosuppressant after a solid organ graft.

In view of the continuing debate about the safety and effectiveness of generic immunosuppressive drugs, Molnar and colleagues undertook a systematic review and meta-analysis of all studies published since 1980 that compared generic with innovator (originator) immunosuppressive drugs for people with a solid organ transplant.[4]

They found that acute rejection was rare overall and that risk did not differ between groups of participants treated with a generic or an innovator drug.[4] The standard of methods of the published studies, however, was variable, with most studies having inadequate length of follow-up. Treatment failure can take time to emerge and can be missed by short term studies.[10]

Bioequivalent, probably

Their analysis of pooled pharmacokinetic data showed that generic immunosuppressants are bioequivalent according to conventional regulatory criteria (90% confidence interval for the AUC ratio no wider than 80% to 125%), but they don't always meet the stricter EMA criteria (90% confidence interval no wider than 90% to 111%). The small number of patients in some studies probably contributed to this finding as lack of power leads to wide confidence intervals. Sample sizes would have to increase up to eightfold in some studies to achieve the tighter confidence intervals required by the EMA.[11]

For instance, the two trials of ciclosporin in recipients of kidney grafts had a mean number of 30 patients. In a pooled analysis, the AUC ratio failed to meet the EMA's criteria for bioequivalence. In a substantially larger pooled analysis of seven non-randomised studies (mean sample size 46), the EMA's criteria were met.

In most reported trials, the point estimates for AUC and C_{max} ratios were well within the expected range of being just a few percentage points higher or lower than 100%.[4] The problem might lie not with any clinically important difference between generics and originator immunosuppressants but with the poor quality of the available evidence and ensuing difficulties with interpretation.

We should also remember that the EMA's narrowing of the bioequivalence limits was designed to further protect patients who were unlikely to be monitored correctly after switching to a generic immunosuppressant.[12] Studies in patients who are correctly monitored could provide additional evidence that immunosuppressive generics, used in the correct manner and with precautionary monitoring in place, can indeed be bioequivalent to originator drugs and achieve similar long term outcomes.

Unfortunately, because of a relatively small number of eligible studies with hard to compare methods, and partly hampered by variable outcome reporting of crucial parameters, the study by Molnar and colleagues cannot establish with confidence whether or not generic immunosuppressive drugs are truly bioequivalent, effective, and safe.[4] We do know that generic immunosuppressive drugs, such as ciclosporin, have been on the market in Europe for more than 10 years and that pharmacovigilance systems have not identified any serious safety signals among the hundreds of thousands of doses prescribed and dispensed. While this observation is reassuring for clinicians and patients considering or undertaking a switch, bigger and better studies with longer follow-up are still required to fully examine any remaining concerns. In the meantime, clinicians could benefit from more education on the importance of monitoring plasma concentrations in patients who switch to a generic immunosuppressant. Monitoring is recommended by regulators, reassuring for patients, and might even improve adherence to treatment.[13]

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To facilitate meaningful international comparisons, future research would benefit from standardisation in the definition and classification of stillbirth

Protecting families from recurrent stillbirth

All pregnancies that follow a stillbirth should be managed as high risk

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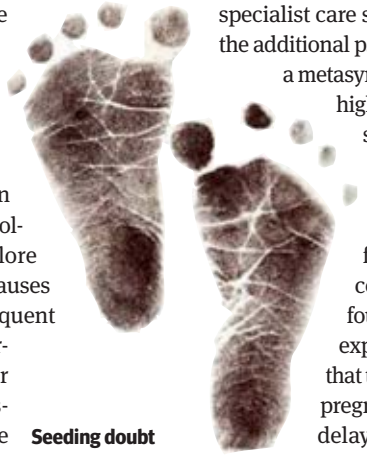
Stillbirth is a tragedy for parents and has enduring medical, psychological, social, and economic consequences. It remains a major problem in the United Kingdom; in 2013, 3286 babies were stillborn after 24 weeks of pregnancy, equating to one in every 240 births.[1] Since 2011, when the UK was ranked 33rd out of 35 high income countries for stillbirths, there has been a downward trend in the stillbirth rate, but this has not yet reached the lower levels seen elsewhere in Europe.[2]

Identification of pregnancies at increased risk of stillbirth can help to prevent stillbirths by directing additional antenatal care and intervention to those most likely to benefit. Consequently, identification of risk factors is highly desirable. In their meta-analysis of 16 studies of 3 412 079 women in this issue, Lamont and colleagues identify an increased risk of stillbirth in subsequent pregnancies after a previous pregnancy ended in stillbirth.[3] This approximately fivefold increase in risk is greater than that of stillbirth associated with pre-existing medical conditions, such as diabetes or hypertension.[4] Heightened antenatal surveillance is recommended in both of these maternal conditions and should be considered for women with a previous stillbirth.

Stillbirth has a variety of causes, only some of which, such as placental insufficiency, are likely to influence the risk in subsequent pregnancies. Other causes, such as umbilical cord occlusion are thought to be isolated. A substantial proportion of stillbirths (around 20%) remain unexplained.[5-7] Lamont and colleagues were unable to explore the contribution of specific causes of stillbirth to risk in a subsequent pregnancy.[3] If heightened surveillance is recommended for pregnant women with a history of stillbirth, it should be offered to all affected women not just those with an identifiable and potentially recurring cause.



Seeding doubt

In common with other studies of stillbirth, Lamont and colleagues' meta-analysis was limited by variations in the definition of stillbirth within individual studies, the classification system used, and the extent of adjustments for confounding factors. This may in part explain the considerable heterogeneity in their findings. To facilitate meaningful international comparisons, future research would benefit from standardisation in the definition and classification of stillbirth. An "unexplained" stillbirth should be reserved for those stillbirths without an identifiable cause despite thorough investigation, and they should not include those events that remained unexplained after inadequate or incomplete review.

Most studies in Lamont and colleagues' meta-analysis did not report rates of postmortem examination, placental histology, or chromosomal analysis, all of which reduce the proportion of stillbirths defined as unexplained. Without this kind of information, readers cannot deduce whether reported stillbirths were truly unexplained. Rates of postmortem examination continue to fall in the UK, a worrying trend that reduces the ability to identify or exclude recurrent causes of stillbirth.

Manage subsequent pregnancies as high risk

Current guidance from the UK's Royal College of Obstetricians and Gynaecologists recommends that women with a previous stillbirth are managed as high risk during a subsequent pregnancy.[8] Lamont and colleagues provide a biomedical basis for this recommendation. The need for specialist care should also take into account the additional psychological needs of parents; a metasynthesis of parents' experiences highlighted the challenges of subsequent pregnancies, particularly for mothers.[8] During pregnancy, conflicting emotions may co-exist as hope for the forthcoming pregnancy combines with grief and profound anxiety. Women who have experienced stillbirth may doubt that their bodies can sustain healthy pregnancies. To cope, parents may delay emotional attachment with their baby, or seek additional control. Interactions with health professionals gain heightened importance and may in themselves be therapeutic; additional support from health professionals is valued highly by parents.[9]

The death of a child is a life changing event that may occur with no warning signs or symptoms. Women can believe their body has let them down, and also feel guilty that they had not protected their child, or given their family another child. Parents recognise that the support they need in a subsequent pregnancy differs from that needed and received previously. Continuity of care by the same provider, and additional ultrasound scans provide parents with reassurance that their concerns will be heard and deviations from a healthy pregnancy detected. However, even these interventions do not remove the anxiety associated with a late stillbirth because there are no thresholds to reach, no point at which a stillbirth can be ruled out. Rather than trying to prevent or hide anxiety, care in a service dedicated to parents with a history of stillbirth exposes parents to other families with similar experiences and emotions, avoids awkward questions, and helps reduce feelings of isolation.

A substantial proportion of women using maternity services will have had a stillbirth in the recent past. Lamont and colleagues estimate that 8% of stillbirths are attributable to the risks associated with a previous event (population attributable risk),[3] which suggests that effective antenatal surveillance and intervention for this high risk group may reduce the overall burden of stillbirth. However, the authors stress that we still do not know whether the potential benefits of increased surveillance outweigh the potential harms to babies or mothers from unnecessary interventions. Critically, over 1100 parents and professionals contributing to the stillbirth Priority Setting Partnership identified care in a subsequent pregnancy as one of the top priorities for stillbirth research.[11]

If pregnancies after stillbirth should be managed as high risk then how to optimise biomedical and psychological outcomes for families is not yet clear. Finding out should be an urgent priority for researchers and clinicians.

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