Translating animal research into clinical benefit

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Translating animal research into clinical benefit
Poor methodological standards in animal studies mean that positive results may not translate to the clinical domain

Most treatments are initially tested on animals for several reasons. Firstly, animal studies provide a degree of environmental and genetic manipulation rarely feasible in humans. Secondly, it may not be necessary to test new treatments on humans if preliminary testing on animals shows that they are not clinically useful. Thirdly, regulatory authorities concerned with public protection require extensive animal testing to screen new treatments for toxicity and to establish safety. Finally, animal studies provide unique insights into the pathophysiology and causes of disease, and often reveal novel targets for directed treatments. Yet in a systematic review reported in this week’s BMJ Perel and colleagues find that therapeutic efficacy in animals often does not translate to the clinical domain.

The authors conducted meta-analyses of all available animal data for six interventions that showed definitive proof of benefit or harm in humans. For three of the interventions—corticosteroids for brain injury, antifibrinolytics in haemorrhage, and tirilazad for acute ischaemic stroke—they found major discordance between the results of the animal experiments and human trials. Equally concerning, they found consistent methodological flaws throughout the animal data, irrespective of the intervention or disease studied. For example, only eight of the 113 animal studies on thrombolysis for stroke reported a sample size calculation, a fundamental step in helping to ensure an appropriately powered precise estimate of effect. In addition, the use of randomisation, concealed allocation, and blinded outcome assessment—standards that are considered the norm when planning and reporting modern human clinical trials—were inconsistent in the animal studies.

A limitation of the review is that only six interventions for six conditions were analysed; this raises questions about its applicability across the spectrum of experimental medicine. Others have found consistent results, however. In an overview of similar correlative reviews between animal studies and human trials, Pound and colleagues found that the results of only one—thrombolitics for acute ischaemic stroke—showed similar findings for humans and animals. In our systematic review of 76 highly cited (and therefore probably influential) animal studies, we found that only just over a third translated at the level of human randomised trials. Similar results have been reported in cancer research.

Why then are the results of animal studies often not replicated in the clinical domain? Several possible explanations exist. A consistent finding is the presence of methodological biases in animal experimentation; the lack of uniform requirements for reporting animal data has compounded this problem. A series of systematic reviews has shown that the effect size of animal studies is sensitive to the quality of the study and publication bias. A review of 290 animal experiments presented at emergency medicine meetings found that animal studies that did not use randomisation or blinding were much more likely to report a treatment effect than studies that were randomised or blinded.

A second explanation is that animal models may not adequately mimic human pathophysiology. Test animals are often young, rarely have comorbidities, and are not exposed to the range of competing (and interacting) interventions that humans often receive. The timing, route, and formulation of the intervention may also introduce problems. Most animal experiments have a limited sample size. Animal studies with small sample sizes are more likely to report higher estimates of effect than studies with larger numbers; this distortion usually regresses when all available studies are analysed in aggregate. To compound the problem, investigators may select positive animal data but ignore equally valid but negative work when the problem, investigators may select positive animal data but ignore equally valid but negative work when planning clinical trials, a phenomenon known as optimism bias.

What can be done to remedy this situation? Firstly, uniform reporting requirements are needed urgently and would improve the quality of animal research; as in the clinical research world, this would require cooperation between investigators, editors, and funders of basic scientific research. A more immediate solution is to promote rigorous systematic reviews of experimental treatments before clinical trials begin. Many clinical trials would probably not have gone ahead if all the data had been subjected to meta-analysis. Such reviews would also provide robust estimates of effect size and variance for adequately powering randomised trials.

A third solution, which Perel and colleagues call for, is a system for registering animal experiments, analogous to that for clinical trials. This would help to reduce publication bias and provide a more informed view before proceeding to clinical trials. Until such
improvements occur, it seems prudent to be critical and cautious about the applicability of animal data to the clinical domain.

6. Macleod MR, O’Collins T, Horky LL, Howells DW, Donnan GA.


Exercise and menstrual function

Up to four fifths of women who exercise vigorously may have some form of menstrual dysfunction

The risks to sportswomen of exercise related menstrual dysfunction and impaired bone health are important and under-recognised. Exercise related menstrual dysfunction may include any abnormality along the continuum of luteal phase deficiency, anovulation, oligomenorrhoea, amenorrhoea, and delayed menarche. Such dysfunction is multifactorial in origin, with a high degree of individual variation, but its main underlying mechanism is hypothalamic inhibition with suppression of gonadotrophin releasing hormone pulsatility (the frequency at which pulses of the hormone are released by the hypotalamus).

This hypothalamic suppression has a variety of causes in sportswomen, including the physical and psychological stress of training and competition, caloric deficiency, low body mass, low body fat, inadequate leptin values, and altered peripheral hormone metabolism. Relative hyperandrogeism and genetic influences may also have a role. The consequences can include musculoskeletal injuries (in particular stress fractures), infertility, and the general medical consequences of hypo-oestrogenism.

When menstrual dysfunction (in particular amenorrhoea) occurs in sportswomen in combination with low bone mass and energy deficit, the syndrome is termed the “female athletic triad.” This is a complex and poorly understood disorder seen in females who exercise intensively. 2-12 Athletes in lightweight sports (distance running, gymnastics, lightweight rowing) are at high risk, although the syndrome can arise in relation to any sport. The energy deficit is usually related to eating disorders and is partly influenced by peer pressure. Genetic, neurochemical, and psychodevelopmental factors may also contribute, along with the physical and psychological effects of training and competition. The long term effects tend to be greatest in young girls who start intense exercise before menarche. These girls have an increased chance of delayed menarche, impairment of growth and pubertal progression, subsequent menstrual dysfunction, and suboptimal bone health.13-14

Secondary amenorrhoea occurs in up to 44% of women who exercise vigorously, compared with 2-5% of the general population.1 5-6 Athletes who present with amenorrhoea are at the severe end of the spectrum of exercise related menstrual dysfunction. Subtle menstrual disturbances are more common, occurring in nearly four fifths of very active women. The impact of this on bone mineral density is unclear,9-9 and there is no evidence that women whose menstrual function recovers develop chronic infertility.

No specific threshold at which exercise leads to menstrual dysfunction has been defined because contributing physiological and psychological factors produce considerable individual variation. However, women who run more than 50 miles each week have a significantly increased incidence of amenorrhoea.10

Screening may be useful in women who exercise vigorously. Dietary, medical, and training histories should be taken from any apparently physically fit woman presenting with recurrent or resistant injuries to soft tissue or bone (in particular stress fractures). Women with eating disorders are often reluctant to disclose their diet, however. Urinalysis to detect ketonuria will suggest inadequate caloric intake, and thyroid function tests (yielding normal or raised thyroid stimulating hormone and reduced free thyroxine) will indicate a hypometabolic state.

Women who are amenorrhoeic will need the standard investigations. In women with suspected luteal phase deficiency basal body temperature should be monitored, surges in luteinising hormone measured with ovulation predictor kits, multiple samplings of serum progesterone taken, and ideally, endometrial...