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Letter

How to put psychiatrists back at the centre of medicine's innovation

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Since Hippocrates and Galen, practising doctors have been the lynchpins of medical innovation. In the modern era, all the major classes of drugs we use to treat mental illnesses were discovered, in the 1950s, by practitioners, not pharma companies.[1] But this rich vein of innovation has dried up. In the past five decades, there has not been a mechanistically novel psychiatry treatment for anxiety, depression, bipolar disorder or schizophrenia approved in the UK or Europe.[1] True, many new molecules have been invented and sold as medicines by pharma companies, but these are all derivatives of the first clinician-discovered drugs. There have only been two mechanistically novel psychiatry medicines in the past 50 years (cholinesterase inhibitors for dementia and orexin antagonists for insomnia).[1] This presents psychiatry with major problems, as our current treatments fail in a significant percentage of cases, and the number of patients with mental illness is growing; however, for-profit psychiatry drug development has effectively dried up.[1] We need to do something different, and this Letter presents three easily implementable approaches that I hope the Royal College of Psychiatrists (and other similar bodies) might endorse.

First we need to accept that the major reason for this lack of innovation is that the modern commercial drug development process is excessively lengthy and costly. It takes about 13 years to develop and license a psychiatry treatment and costs about a billion dollars from chemistry laboratory to marketing authorisation.[1] In this process, psychiatrists have been relegated to recruiters of patients and to almost mindless fillers-in of rating scales. Worse, in many trials, clinical outcomes are assessed by raters without psychiatric training (and this role might even be taken over by artificial intelligence soon).

Part of the problem of time and costs is the supposition that randomised controlled trials (RCTs) are at the apex of clinical decision-making, whereas Sir Michael Rawlins, the previous head of the Committee for the Safety of Medicines, the Medicines and Healthcare Products Regulatory Agency, and the National Institute for Health and Care Excellence pointed out that they are but one of several equally relevant forms of evidence.[2] He argued RCTs are poor value for money as they use outmoded frequentist (not the more powerful Bayesian) statistics. Worse, they have limited generalisability, because they exclude patients without comorbidity, unlike real-world patient populations. Yet, despite Rawlins's protestations, regulatory bodies still insist on RCTs. This too often leads to clinical guidelines, treatment algorithms and local prescribing committees considering RCTs as the only acceptable evidence. But we as medical practitioners know that every time we prescribe we are doing an $n = 1$ experiment with the question 'will this specific patient respond or not?'. Collecting such data in select clinical locations with Bayesian analysis would be a powerful way of putting research back into the hands of prescribers, with huge cost savings, allowing funding of many more studies. Two examples of the power of this approach were given in a recent paper by Szigeti et al.[3]

A second channel for new therapeutic insights would be to formally collect data from off-licence prescribing, such as that which led to the discovery that selective serotonin reuptake inhibitors worked in anxiety disorders.[4] Yet in UK psychiatry, off-licence prescribing is unnecessarily difficult and bureaucratic.[5] Strangely, general practitioners don't have such difficulties: a good example is amitriptyline, for which over 10 million scripts a year are prescribed[6] off-licence for pain and sleep. The Royal College of Psychiatrists should encourage psychiatrists to use their pharmacological knowledge and clinical experience to explore the rational use of medicines off-licence, provided they collect outcomes from this, ideally using modern electronic databases.

Another important development would be to revise the current research funders' prioritisation of mechanistic studies. This has constricted funding for new clinical research indications for established and upcoming drugs, further depleting clinicians' involvement and expertise, and should be revised.

These two approaches would quickly build up a knowledge base that could inform prescribers of possible new areas of treatment efficacy that would probably never be examined by the pharma company with the original marketing authorisation. A good example of this type of research is that of baclofen for alcohol dependence in France.[7] The Royal College of Psychiatrists (or another professional organisation) could set up its own data collection network at very little expense. Added value could be obtained by linking with the UK Biobank.

The third approach is to enhance serendipity. Most doctors see hundreds patients on different medicines, and some of these are likely have benefits for indications other than those they have been prescribed for. But we are not encouraged to collect such information, and the progressive disdain that many journals have for case reports limits sharing of useful insights. By contrast, we are encouraged to collect and share details of drug adverse effects via the yellow card scheme. I have long argued for a parallel (pink card) scheme that would allow unexpected therapeutic discoveries to be reported.[8] In addition to providing useful national data, this would encourage doctors to think more creatively about possible new uses for old medicines.

This scheme could also be rolled out for patients to contribute their own personal discoveries of medicines' unexpected utility (over the years, many patients have written to me to tell me they have found off-licence medicines very helpful and better than licensed ones). Currently, patients can use the yellow card scheme to report adverse effects, so why not encourage them to report positive outcomes as well? A systematic collection of these reports

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would help direct research into new treatment targets and could even be advanced by modern biological techniques such as stem cell transcriptomics.

Today, innovation in psychiatric medicines is moribund. In the past decade, in Europe and the UK, only one new psychiatric medicine has been approved, compared with more than 50 new anticancer medicines.[9] The Royal College of Psychiatrists needs to help to remedy this dire situation. Supporting these three simple suggestions to utilise the intellectual power of its membership would be a good start.

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