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Wrong questions, wrong answers? Are we getting the drugs we need?

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Introduction

While medicines usually promote health, they can also be expensive and cause harm. It is, therefore, important that needed medicines are developed, and that they are safe, effective and affordable. Unfortunately, progress towards this goal is inconsistent. We argue that forces other than commercialisation need to be considered, and that there is a need to advocate for a drug development process that fills important gaps, reduces clinical uncertainty and promotes the rational use of medicines.

The trouble with drug development

To maximize clinical benefit and minimize harm to patients, clinicians are increasingly aspiring to an 'evidence-based' or 'rational' approach to prescribing (1). The relevance and quality of the evidence available about pharmacotherapies is, therefore, essential to good clinical care. Ideally, drug discovery and clinical research ('drug development') should serve to advance medical knowledge and improve the prevention and management of disease. In reality, however, it is increasingly apparent that drug development is failing in fundamental ways and that there are major gaps in the evidence available to clinicians stemming from (for example) (2):

- measuring new agents against placebo rather than "gold standard" therapy (where this is not appropriate) or assessing non-inferiority rather than superiority (particularly in phase III/IV studies);
- not asking questions about substantive outcomes such as survival or cost-effectiveness;
- using surrogate outcome indicators which do not always reflect clinical outcomes and have not always been validated sufficiently;

- testing new drugs in populations which differ, for example genetically, from those who will be receiving the intervention;
- continuing to rely on randomised controlled trials and meta-analyses to study responses that do not necessarily reflect real-world clinical practice nor the complexity of diseases that are biologically heterogeneous.

This has two major effects. On the one hand there are some areas of practice in which there has been relatively limited progress (e.g. pharmacotherapy for pancreatic cancer, Alzheimer's disease and malaria). There are also areas in which progress has been made but where research has produced uncertainty as to what constitutes optimal treatment. In the case of breast cancer, for example, there are now a large number of effective agents including hormonal response modulators, cytotoxics, monoclonal antibodies and angiogenesis inhibitors. While this has improved outcomes for women with breast cancer, it has also created uncertainty regarding the use of early data and surrogate endpoints in drug approval and clinical practice; optimal combinations and sequencing of therapy; the duration of therapy; the use of maintenance therapy and the relevance to the choice of therapy of prior adjuvant therapy and individual patient characteristics (2). Similar problems can be found in many clinical areas including the treatment of rheumatoid arthritis, multiple myeloma, schizophrenia and viral hepatitis.

It is essential, therefore, that we not only conduct more pharmaceutical research, but also take a more critical approach to the research that is done. This, in turn, requires an understanding of the range of factors (other than medical utility) that might influence the focus, direction, quality and integrity of drug discovery and clinical research.

What research is done, and why?

Medical research has two broad epistemic and moral goals: to advance biomedical knowledge and improve human health. In recent years, however, it has become increasingly clear that the research agenda is shaped by a range of influences, including:

- The source of funding for research,
- The institutional context in which research is done,
- Advances in understanding of health, diseases, diagnostics and therapeutics,
- The regulatory environment,
- Information technologies,
- Changing consumer expectations,
- The forces of globalization and
- The increasing influence of 'payers' or 'purchasers'.

This, in turn, has major ethical, scientific, medical and public health implications.

For the most part, debate surrounding influences on drug discovery and clinical research has concerned itself with the impact of commerce, particularly the pharmaceutical industry, on the goals and conduct of research. While major distortions of research are now rare, practices of ongoing concern include the development of drugs which are very similar to existing products and the manipulation of drug doses, study populations, or the lengths of studies in order to more likely obtain the outcome of (commercial) interest (2). All of these practices are, in turn, shaped by a rapidly changing commercial and regulatory environment in which "blockbuster" drugs are going off-patent, pipelines are relatively empty and regulators are demanding ever more information (3).

It is increasingly difficult, however, to draw practical and moral distinctions between commercial and academic research. Many research institutes, universities and academic medical centres now position themselves as 'partners' with private industry and share control over the design, conduct or dissemination of research (4), and increasingly government funding bodies and research institutions demand that researchers consider the commercial possibilities of their research and the concordance of their research with commercial and political interests (5). Many of the criticisms of commercially-funded research therefore apply increasingly to government funded academic research being conducted in public institutions such as universities and health services.

Clinical research is also no longer practiced primarily in Europe, North America and Japan, with increasing numbers of clinical trials being conducted in Asian countries (e.g. China and India), South America (especially Brazil), Latin America and the countries of Eastern Europe and the Russian Federation (6). While this geographical shift in international research activity (driven largely by pharmaceutical companies) is welcomed by developing world governments and supported by major international research organizations such as the National Institutes of Health, and while the quality of this research, undertaken in support of registration in U.S., European and Japanese markets, is usually good, it can be difficult to be clear about the validity and generalizability of research results which are derived from populations with different genomic profiles (e.g. polymorphisms in particular enzymes), diets, comorbidities, life expectancies, and so on (7, 8).

The research that is being done is also being influenced by new scientific paradigms—which influence both the questions asked, and the methods used, in clinical research. The established hierarchies of research evidence, which privilege systematic reviews and meta-analyses of randomized controlled trials (RCTs) are, for example, challenged by scientific insights which have established that diseases and responses to therapies are much more heterogeneous (e.g. genetically) than previously thought. (9). In this context, RCTs are difficult and expensive to conduct (especially where more than one aberrant pathway or target has been identified and where combinations of targeted agents may be necessary) and meta-analyses have little meaning. Indeed, it may be the case that the focus will need to shift away from randomised,

controlled trials and towards other clinical research designs as well as basic research since there will simply be too many drug combinations to test empirically in trials.

The other major change in research over the past few decades is that it is no longer practiced in the rarefied climes of laboratories but rather in the full glare of public attention. Consumer groups, for example those concerned with HIV-AIDS and multiple myeloma, are increasingly interested in ensuring that pharmaceutical research generates the products and clinical outcomes that matter to them (10). Likewise, the agencies that fund clinical research, or approve and fund the products of this research, unquestionably influence the research agenda through demands for evidence of comparative effectiveness, cost-effectiveness and long-term safety.

Avoiding commercial myopia

It is perhaps understandable that attention has focused on the way that industry interests might bias the type of drug discovery and clinical research being done. But it is now increasingly clear that commercial interests are not the only influence on drug development. This means that researchers, clinicians and policymakers need to address the full range of influences on drug development and clinical research, the impact these have upon the quality and relevance of research activity and the ways in which these may impede or facilitate rational prescribing and evidence-based practice.

Getting the drugs we need

This reflection might, in turn, highlight a range of different strategies for getting the drugs we need (some of which are already being explored), such as:

1. Generating more epidemiological information (and increasing the impact of existing information) about the unmet needs of target communities, and better aligning drug development with the burden of disease;

2. Improving government funding of drug development so that, in addition to facilitating commercial drug development, it is in the public interest and meets the needs of populations under-served by industry;

3. Developing new mechanisms to encourage industry to invest in areas of unmet need;

4. Increasing collaboration between academia and industry, as well as between different companies, to streamline drug development processes and avoid repeating costly mistakes;

5. Encouraging the epidemiology, biostatistics and information technology communities to rethink hierarchies of evidence and research designs, and to develop information systems that support every stage of the drug development process, including post-approval cost-effectiveness evaluations and pharmacogenomic and biomarker research;

6. Encouraging national and global harmonisation and integration of research, regulatory and reimbursement processes so that these processes can be made more efficient and so that "value" (benefit-risk) considerations can be given as much weight as considerations of efficacy and safety;

7. Rethinking the roles that consumers, advocacy groups and purchasers can play at each stage of the drug development process.

More generally, we need not (only) more drugs discovered and more clinical research, but also to systematically explore new models of drug development, into which are built the necessary incentives and disincentives to ensure that industry, academia and government all work together towards producing the drugs we need.

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