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EDITORIAL

How change comes: translating biological research into care

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Summary Thousands of papers have been published on the biological associations with psychosis yet this has had a limited impact on the routine clinical care of people with psychosis. Cognitive dysfunction, genetics and neuroimaging are the research areas likely to integrate into clinical practice in psychosis most rapidly. Clinical and academic collaborations in partnership with patients and carers are necessary to make progress, along with an acceptance that not all new approaches will necessarily prove effective in the longer term. Most discoveries do not just jump from bench to bedside, but require active interactions between scientists and clinicians.

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Over recent decades there has been a tremendous expansion of knowledge pertaining to the biological associations of mental health problems. There have been thousands of papers showing findings significant to a *P*-value of <0.05. Topics that were hardly researched a decade ago, such as cognition, now have a volume of emerging literature that it would take many hours to read through. A recent feature in the *British Medical Journal*[1] raises the question of what the current emphasis on translational research will yield in practice for patients and how far it can be speeded up and given direction. This is a particular challenge in neuroscience and psychiatry. Certainly, from the clinical viewpoint in the field of psychosis we have to acknowledge that, other than the introduction of clozapine and the atypical antipsychotics, biological research has not had a direct impact on care in a meaningful manner. Despite this, there are a number of avenues in schizophrenia research that show promise, with most hope resting with cognition, the genetic revolution and neuroimaging.

Cognitive dysfunction

Cognitive dysfunction in schizophrenia is arguably one of the most important aspects of the condition. Although a person may live a full and meaningful life continuing to experience auditory hallucinations, impaired cognition is associated with significant functional disability affecting an individual's ability to work, run their home or establish meaningful relationships. On the academic front, researchers have been developing increasingly user-friendly tools to measure cognitive function so that theoretically these could now be incorporated into the clinic. Notwithstanding these advances in assessment of cognition, the multiple pharmacological trials on cognitive enhancement in schizophrenia have all proven equivocal to date.[2] On the other hand, several types of psychological interventions such as cognitive remediation show promise – but they have yet to be standardised for dissemination.[3] It appears that for the foreseeable future, interventions in cognition in schizophrenia will use a combination of pharmacological and psychological approaches. The first UK clinic to specifically address cognition and schizophrenia has just opened, initially research-funded, in the Maudsley Hospital in collaboration with the Institute of Psychiatry.

Genetics

The genetic revolution has yet to yield a definitive genetic profile for schizophrenia. The hope for a 'gene for schizophrenia' has been dashed. In all likelihood schizophrenia will in part be explained by dozens of genes, each contributing a small increase in risk.[4] The predictive value of any single gene or copy number variants for an individual at risk of schizophrenia or in the early stages of the illness is yet to be determined, although this is what we aspire towards in the coming decades. In therapeutics, pharmacogenetic analysis shows some promise. Pharmacogenetics is the study of how DNA sequence variations in specific genes may affect drug response and drug toxicity. Increasingly in general medicine, applications for drug licensing include

pharmacogenetic testing. Pharmacogenetic *HER2* testing to target treatment is now established as part of the assessment for people with invasive breast cancer with the use of trastuzumab recommended only for those individuals with positive test results.[5] It may be time for psychiatry to catch up. Pharmacogenetics has been encouraging in some dimensions such as the predictive genes for response to clozapine, although it is not a recognised approach to the routine management of schizophrenia.[6] Genes that govern pharmacokinetics such as the cytochrome P450 (CYP450) genes have the potential to inform the management of people with treatment-resistant illness and complex treatment histories, with studies on cost-effectiveness awaited. It is hoped that knowing someone's CYP450 gene profile may help identify early those who do not respond because they metabolise the drug too extensively, or those who are too vulnerable to side-effects because they poorly metabolise the medication when given in regular doses.

Neuroimaging

There have been huge advances in quality and capability in both structural/anatomical and functional neuroimaging systems. As in the case of cognition, there have been hundreds of papers linking different imaging findings to symptomatology and prognosis in schizophrenia. There have been attempts to include neuroimaging in routine care; magnetic resonance imaging scans, for example, are now routine for all individuals with a first episode presenting to the South London and Maudsley Trust as part of a research collaboration intended to inform the next National Institute for Health and Clinical Excellence guidelines. However, apart from such sporadic examples there has been no generalised move towards introduction of even structural neuroimaging into general clinical care. Neither has the exact clinical role of functional imaging yet been clarified.

Psychopharmacological research

Psychopharmacological research too has recently been slow to translate to clinical care. The successful industry developments have largely been 'me-too' drugs, whereas other more novel approaches have faltered before the final hurdle, although often not before major investments by pharmaceutical companies. Participation in this process has been somewhat stilted in UK mental health, with a relative paucity of clinical trial activity. Translational pharmacological research in the clinic focuses more on ways to improve tolerance of treatment stalwarts such as clozapine or on 'add-on' approaches, such as minocycline, but no 'add-ons' yet provide the levels of evidence required for widespread use.

Bridging the gap

These examples demonstrate the challenge; none of these technological advances are yet making it to the clinic to be of benefit to individual patients. The question we as clinicians and academics need to ask ourselves is: why has it taken longer in psychiatry and how will this happen? Several reasons may explain these differences. First, it is quite likely that our current diagnostic criteria bundle together heterogeneous diseases into ICD or DSM labels. As a result, when biological tests are developed for explaining/predicting these entities, the tests have modest utility. Second may well be the non-medical 'culture' of psychiatry. Although psychiatrists are trained with other medical students, over time they come to rely less on biological tests and medical interventions and rely more on 'clinical judgement.' As a result there is a greater gulf to be bridged in transferring new possibilities from the bench to the bedside. Nonetheless, things are changing. Sometimes, major changes in practice will provide a stimulus for this. The introduction of atypical antipsychotics led to a new definition of function and different ways of thinking as well as highlighting the importance of physical health in serious mental illness that overall resulted in improved care.

It is time to take this recent wave of advances and move them into specialist clinics. For clinicians to do this in true partnership with patients and carers it is necessary to make clear the limitations of the existing evidence while working to push the boundaries of care further. This requires all participating parties to be aware of the established dogma and understand that although the proposed interventions may be beneficial for some individuals, they may as yet have insufficient evidence to become part of standard care at the level of national guidelines. This is a boundary with which we are struggling in our own institution, but we are sure these dilemmas are not ours alone.

The introduction of academic health sciences centres in the UK provides an opportunity to bridge the gap. The aim is to provide greater collaboration between clinical and academic interests across medicine with a view to increasing research productivity and accelerating clinical advances. It is vital that mental health practitioners and researchers enter into these partnerships on an equal footing. To try to achieve this, Kings Health Partners have adopted a model that organises clinical care and academic endeavour along dove-tailing clinical academic groups (CAGs) according to area of expertise (e.g. 'Psychosis', 'Mood, anxiety and personality disorders' and 'Medicine'). Links across CAGs are encouraged because of course there is a high level of comorbidity, but the aim is that CAGs will clarify care pathways for people with particular types of presentation and overall provide a better level of service. Only time will tell whether this brings translational medicine a bit closer but the hope is that it will.

Examples from psychiatry

Clinical–academic collaborations have previously been shown to work in psychiatry, for example in Toronto (Professors Gary Remington, Tony Cohn and others) where the academic interest in physical health in psychosis meant that a metabolic clinic with an endocrinologist was established 2–3 years earlier than in most centres across the globe. This started out as a cutting edge development but has since become routine clinical care rolled out internationally with a sound evidence base. This sums up the benefits of active clinical–academic translation; the end-point should not be so different but we should get there

sooner. Essentially one starts a service that takes research findings and puts them into practice and then uses that experience to define services so they can be generalised as standard clinical care while generating further evidence for future developments.

Another example within psychiatry is that of Professor Pat McGorry in Australia whose research led him to understand the importance of early intervention in psychosis. From there he provided a structure for services to identify and treat people at the early stages of their illness. His service has been adopted worldwide as an example of best practice and has provided an enormous amount of research evidence regarding the early treatment of schizophrenia. It has also been a huge local agent of change in the field of youth mental healthcare across Melbourne. In recognition of this wide-ranging impact, Professor McGorry was awarded the Australian of the Year award this year; a highly prestigious honour whose previous recipients include Nobel Laureates and international athletes.

Examples from other branches of medicine

The best examples of translational medicine remain in other branches of medicine. Some of the most successful clinical–academic collaborations have been in the field of oncology. Memorial Sloan-Kettering Cancer Center in New York works on the premise that 'better understanding of cancer prevention, dissemination of the latest research findings, and exchange of scientific knowledge will make a difference today and in the future'.[7] Similarly, the University of Texas MD Anderson Cancer Center's mission is to 'eliminate cancer through outstanding programs that integrate patient care, research and prevention, and through education'.[8] Both are regarded as top oncology centres globally because of these strong links between treating clinicians, emerging research and education. The clinical and academic concentration also allows for measurement of the practical and economic impact of clinical advances. For example, MD Anderson have calculated that knowledge gained through research discoveries there translates into improved treatments and economic effects that have an impact on the US economy to the tune of $20 billion in annual spending and more than 112 500 permanent jobs.[9] On the more general side, the Mayo Clinic targets 'virtually every type of complex illness' (https://healthmanager.macyoclinic.com/about.aspx). The combination of patient care and medical research alongside professional and public education means that they are recognised globally as innovators in medical practice. Time will tell how well psychiatry adapts to these models.

Conclusions

Clinical–academic collaborations have latterly been more prominent in the USA than in the UK.[9,10] This was not always the case; the old Maudsley was an excellent example of academic research integrating almost completely into clinical practice. It is interesting to speculate as to why this faded somewhat. Clinical–academic activity thrives in the grey zone between the National Health Service (NHS) and the university and may have been stifled by the increasing boundaries between the two. In recent decades, UK clinicians and trusts have had to focus on meeting one set of goals set by the Department of Health, whereas academics were striving towards different targets set by the Higher Education Funding Council for England. These polar systems of accountability may have led to conflicting priorities instead of fruitful collaboration. Happily, the two systems are converging here once more. Additionally, the market-driven model of funding in the USA may have more rapidly rewarded clinical–academic collaborations; research and teaching raises the profile of the associated clinical centre and creates a brand that prospective patients and carers seek out, thus increasing clinical activity. In this context the effect of increasing market forces within the NHS on university departments of psychiatry will be interesting to observe.

We have concentrated in this article on biological therapies as it seems that there is a quicker path from research to care for psychological therapies. Our colleague David Clark has a very efficient system for trialling complex psychological interventions to determine their suitability and effectiveness in clinical practice. Psychological interventions move from the metaphorical bench to couch-side in a relatively short time. Well-known examples include the improving access to psychological therapies (IAPT) model, cognitive–behavioural therapy in psychosis and cognitive remediation. This may partially relate to the greater palatability of psychological therapies, or the perception that there will be a lesser risk of harm from talking approaches to care. However, at least some of this greater speed reflects the relative paucity of translational work in biological therapies and perhaps a reluctance to partner with industry.

It is important that all parties with an interest, be they service users, carers, clinicians, academics or service providers, are aware that accelerating the rate at which laboratory findings are applied in clinical practice will increase the frequency of approaches that ultimately prove to be of little benefit, although it remains important before we move to this level that we are confident that the innovations have little risk of harm. One example of an innovative service that proved ineffective is the introduction of assertive outreach teams. This was an intuitively attractive idea but the research evidence post-introduction has not found it to be an effective or cost-effective model.[11]

It is inevitable that some interventions will not fulfil their early promise. Abandoned treatment paradigms from the past include insulin shock therapy and sleep deprivation. However, robust and early evaluation of effectiveness will allow such red herrings to be identified earlier and more promising treatments to be better resourced. It is inspiring to think of the very early advances in biological psychiatry such as the introduction of chlorpromazine or the use of electroconvulsive therapy. These changed the face of psychiatry with electroconvulsive therapy and medications with similar functions to chlorpromazine still mainstays of clinical practice. We as clinicians and scientists may hope that working together we can usher in the next wave of advances in the management of psychotic disorders and other psychiatric conditions.

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