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PERSPECTIVE PIECE

Schizophrenia: an ever-changing entity

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Schizophrenia is one of the most devastating mental disorders, both in terms of societal cost and individual patient suffering. It is frighteningly common, affecting 1% of the population worldwide. A frequently encountered question regarding schizophrenia is whether or not psychiatry truly *treats* this disease. In the 100 years since it was first described as a discrete disease entity, management of schizophrenia has changed dramatically, with shifts being seen across different generations of psychiatrists from institutionalisation, insulin therapy and lobotomies to community management, antipsychotic drug therapy and cognitive behavioural therapy. However, none of these treatment strategies, or any combination of these treatment strategies, have been successful in addressing the pathological processes underlying the disease itself. Therefore, I think it is reasonable to say that psychiatry *manages* schizophrenia, rather than treats it.

Schizophrenia is a multifaceted disorder that affects the individual on several different levels. Since *dementia praecox* was first described by Kraeplin in the early 1900s, definition and management of schizophrenia has moved from being focussed on the cognitive aspects of the disease, to focussing on the disordered dopamine pathways (delusions and hallucinations) seen in the disease. However, over the last 15 years, we have seen a shift in how this disease is regarded by clinicians and scientists. We are beginning to construct a syndromal framework of schizophrenia through which we are recognising, not only cognitive deficits and aberrant dopamine pathways, but also disordered development, neurostructural abnormalities and genetic susceptibility.

However, schizophrenia today is still diagnosed based on clinical presentation of the disorder. Positive symptoms (auditory hallucinations, passivity phenomena, persecutory delusions, etc.) and negative symptoms (avolition, social withdrawal, psychomotor retardation, etc.) are the backbone of how the diagnosis is made according to both the DSM-V and ICD-10. While recognising the practical basis behind a symptomatic approach to diagnosing schizophrenia, there is considerable controversy surrounding this approach, as clinicians and scientists look forward to an era of diagnosing schizophrenia – and other mental illnesses – based on aetiology, as opposed to nosology.

To illustrate this, Howes and Kapur (2014) drew a historical parallel in an editorial in the July issue of the *British Journal of Psychiatry*. They liken schizophrenia today to diabetes in the past – when diabetes mellitus and diabetes insipidus presented with similar symptomatology, though with completely different aetiology and responses to treatment. Does this represent a harbinger of our understanding of schizophrenia? Does schizophrenia represent a heterogeneous group of disorders that respond to different treatments that target its aetiology, and not its nosology?

Students in psychiatry are encouraged to formulate multi-axial differential diagnoses, which identify psychiatric disorders, personality disorders, medical disorders, social stressors and levels of global functioning. Differentials for a patient presenting with a schizophreniform disorder, according to this multi-axial framework, are varied and subjective, however the treatment remains the same. We are targeting an aberrant dopamine pathway, treating schizophrenia symptomatically, and we are not tackling the underlying cause of the disease. Therefore, in the same way a cardiologist manages angina with nitrates, a psychiatrist manages schizophrenia with antipsychotics. Inevitably, the patient is not cured.

However, a psychiatric renaissance is coming. In August 2013, two papers were published in the *British Journal of Psychiatry* identifying a link between attention deficit hyperactivity disorder (ADHD) and adult mental illness. Marian Hamshere *et al.* (2013) identified a shared polygenic risk for childhood ADHD and adult schizophrenia. In a separate study, Henrich Laarson *et al.* (2013) identified a two-fold increase in risk of bipolar affective disorder (BPAD) and schizophrenia in first-degree relatives of subjects with ADHD, suggesting a common genetic risk for ADHD, BPAD and schizophrenia. Previously, ADHD and schizophrenia had been viewed as aetiologically and pathologically separate disease entities, but this new evidence is exciting in that it suggests a common underlying cause and possibly, novel therapeutic targets that could potentially treat these disorders in their entirety.

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Furthermore, the Lancet published a paper in February 2013 (Smoller *et al.* 2013), identifying four loci that were seen significantly more often in patients suffering from one of five psychiatric disorders. These included BPAD, major depressive disorder, ADHD, autism spectrum disorder (ASD) *and* schizophrenia. Two of these loci were single-nucleotide polymorphisms (SNPs) affecting L-type voltage-gated calcium ion channel subunits. This is significant as it identifies a specific potential target for treating schizophrenia. This work was carried out by the Cross Disorder Group of the Psychiatric Genomic Consortium (PGC), an international group of clinicians and scientists, who are working together to identify the underlying cause of these mental illnesses, all of which are common and devastating disorders. It is a group that is driving the 'psychiatric renaissance', and in identifying these SNPs, they are slowly changing how schizophrenia and other disorders are viewed and how they are going to be managed in the future. However, as with all research, it unfortunately does not provide an overnight cure.

Nevertheless, the identification of calcium channel mutations common to these five disorders is a significant step forward in schizophrenia and mental health research. It is also important to recognise that there are several other loci being identified, and research in this area is flourishing. We are still decades away from having the technology to identify therapeutic targets as a fruit of the identification of these loci, but translational psychiatry – combining the work of neurologists, neuroscientists and psychiatrists – taking research from bench to bedside, offers a glimmer of hope in the development of potential treatment of the underlying aetiology of schizophrenia. In recent years, gene therapy has been approved for conditions exhibiting single-gene Mendelian autosomal recessive inheritance patterns. One such example is the use of ivacaftor in the treatment of the G551D mutation in the CFTR gene causing 4–5% of cystic fibrosis. This drug potentiates the affected chloride channel, increasing the likelihood of it being open, and increasing the transport of chloride across cell membranes. Where cystic fibrosis had previously been treated symptomatically, with physiotherapy, prophylactic antibiotic therapy and exogenous pancreatic enzymes, a small subset of patients with this disease can now be treated by tackling the cause, as opposed to the symptoms.

However, schizophrenia does not exhibit simple Mendelian inheritance patterns. It is a polygenic disorder, with environmental influences. Gene therapies, thus far, exhibit guarded efficacy, and cost health services hundreds of thousands of euro per patient per annum. In phase III trials, only 10% (Vertex Pharmaceuticals Incorporated, 2011) of patients treated with ivacaftor showed an absolute increase in lung function and it is estimated to cost $311,000 (O'Sullivan *et al.* 2013) per patient per annum. Schizophrenia is far more common than cystic fibrosis, and if a novel method of gene therapy were developed to treat it, even in a small population of patients, the cost to the health service would be crippling. When one considers that we still need to fully identify gene targets, develop gene therapy agents, pass drugs through clinical trials, and rationalise resource allocation for the distribution of this medication, it seems psychiatrists are fighting an uphill battle in the treatment of schizophrenia.

This is where it is easy to become cynical about scientific research, drug development and treatment strategies in general. Recent books written by Ben Goldacre (2012), Margaret McCartney (2012) and Robert Whitaker (2011), make it easy to become disillusioned with how treatments are developed, how diseases are diagnosed and how physicians manage their patients. Many would say 'psychiatry only manages schizophrenia – we can't treat it'. Ideas like this have been the fuel behind thousands of pages of writing, advocating a psychological approach to psychiatric disorders, and condemning the medicalisation of mental illness. I do not argue that these opinions are not valid, but I do not believe that they align themselves entirely with the available evidence.

In contemporary psychiatry the best practice, as evidenced by the most current literature recognises the importance of a holistic approach to the management of schizophrenia. We are encouraged to approach schizophrenia from a bio-psycho-social point of view, incorporating a solid understanding of predisposing, precipitating and perpetuating factors of the disease, in order to best manage it.

Best practice recognises the multi-dimensional nature of schizophrenia, identifying and stressing alterations in perceptions, thoughts, mood and behaviour, as well as the effects of schizophrenia on the family. Conversely, best practice also recognises the effects of the family on a patient with schizophrenia. It stresses that each patient will have a unique set of symptoms and experiences. It also stresses the varying course of the disease – some having a brief, responsive disease course, others, a protracted, refractory disease course. Importantly, current best practice guidelines remind us about the social stigma, lack of understanding and fear associated with schizophrenia. The UK National Institute for Health and Care Excellence (NICE, 2014) guidelines on psychosis and schizophrenia provide one such example of best practice guidelines.

The 2014 NICE Guideline makes recommendations on the exemplary management of schizophrenia based on the most up-to-date evidence available. It follows a trend that mirrors that which can be seen across every sub-speciality in medicine, that is the graduation toward the involvement of the multi-disciplinary team

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(MDT). By recognising not only the biological aspects of the disease, but the psychological and social aspects of schizophrenia, using an MDT approach facilitates the psychiatrist to manage the patient in the best way possible with the support of psychology, nursing staff, community psychiatry, social work and general practitioners.

The new guideline emphasises the importance of early recognition and treatment of schizophrenia with cognitive behavioural therapy, family systems therapy and anti-psychotic medication. As well as this, it recommends diligent follow-up in the community, with an emphasis on recognising medical conditions seen commonly in schizophrenic patients (diabetes, cardiovascular disease, weight gain) and recognising further mental health problems associated with their schizophrenia (depression, post-traumatic stress disorder, further episodes of psychosis). There are then recommendations of social interventions, including back-to-work schemes, sheltered living and educational activities.

Here in Ireland, the HSE published a document – 'A Vision for Change' (Expert Group on Mental Health Policy, HSE, 2006) with policy recommendations spanning all mental health in Ireland. The core message delivered in the document is that 'service providers should work in partnership with service users and their families, and facilitate recovery and reintegration through the provision of accessible, comprehensive and community-based mental health services'. Combining this message with the best practice guidelines, we can see a movement towards a holistic approach to the management of schizophrenia, incorporating the bio-psycho-social model of mental health-care delivery.

In summary, the overlying themes of current policy and guidelines emphasise the importance of early identification, early management and promoting recovery, through the support of the MDT. This describes an ideal where at risk patients are identified and managed in the community, under supervision of a consultant psychiatrist and psychiatric MDT. It promotes the integration of patients suffering from schizophrenia into the community, where they can lead normal lives, as anyone else with a chronic disorder does. Currently in Ireland, given the lack of mental health support services available, this remains an ideal – a goal to aspire to. However, combining this holistic approach to the management of schizophrenia with the movement in current research, we can see a realistic possibility for this system being implemented more efficiently in community care, thus improving the management of schizophrenia as a whole. And importantly, though we are 'managing' and not 'treating' this disease, it is difficult to argue that we are not providing the best service possible, given our current knowledge, resources and mental health infrastructure.

After I retire, if I am asked what I have noticed to be the most important change in medicine throughout my career (although my opinion now is somewhat premature) I hope I can say that the most important change I have seen is the elimination of schizophrenia as the disease we currently know. I believe that through the work of groups like the PGC, schizophrenia will be redefined as the schizophrenic syndrome, a heterogeneous group of disorders that can be treated without 'out-ruling an organic cause' because will we have found its organic cause. In fact, hopefully 'out-ruling organic causes' will disappear from the psychiatrist's lexicon entirely. The cynicism that exists about how psychiatrists can't treat schizophrenia will disappear – because the only reason it exists in the first place is that we simply do not understand the brain as well as we understand the other organs. It is an exciting time for psychiatry, particularly the study of schizophrenia. I am confident that how we currently manage schizophrenia is best practice, and that definitive treatment will become a possibility through the leaps we are making in research. The last 50 years have seen great steps forward in the symptomatic control of schizophrenia, and the coming 50 years hold the prospect of neurobiological understanding of the disease, and potential therapeutic targets found therein. In the interim, however, it is important to focus on respect, hope and dignity, rather than cynicism, stigma and marginalisation.

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