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EDITORIAL

Special Issue: Psychosis from early intervention to treatment resistance

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Psychotic disorders are central to mental health service provision and a common theme of academic research programmes in Ireland, which explore the neurobiological and psychosocial risk factors underpinning the development and progression of these illnesses. While we await the discovery of novel pharmacological treatment targets for psychotic disorders, it is important to employ our existing management strategies to optimal effect. In this special issue on psychosis, a selection of clinical research studies and reviews from Irish researchers, and often of Irish populations, are brought together which span the trajectory of psychotic illness from early intervention to treatment resistance. The topics include the characteristics and course of first episode psychosis cohorts, real-world evaluation of early intervention services, management strategies for treatment resistant schizophrenia and neurobiological research into social stress. The current editorial provides an overview of these papers and highlights the initial steps of the Irish Psychosis Research Network towards developing an integrated clinical research network focusing on the treatment and research into psychotic disorders.

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Schizophrenia has long been considered the heartland of psychiatry (Bebbington & McGuffin, 1988), although clearly the boundaries between this diagnosis and related psychotic disorders such as affective psychosis are blurred when it comes to aetiopathogenesis and management. It is easy to be concerned about the lack of progress psychiatry has made in managing this potentially devastating disorder when our most effective pharmacotherapy, clozapine, was developed in 1961. However, this must be considered in the light of the enormous benefit that the application of dopamine antagonists in treating psychotic illness has had in recent decades, the effectiveness of which stunned contemporary psychiatrists on their introduction and facilitated the implementation of deinstitutionalisation and development of community care. The quest for better biological treatments has had several dawns, often false, over the years, but continues unabated with optimism now pointing variously towards modulating glutamatergic, cholinergic, neuropeptide and inflammatory systems (Girgis *et al.* 2019).

In the absence of novel mechanisms of action on the immediate horizon, it especially behoves current researchers and clinicians to ensure that our existing tools are being used optimally. This includes using the best medications in the right doses at the optimal times, the correct application of targeted psychological interventions and social supports to maximise recovery in established illness and the development of services to detect psychotic illness and intervene effectively at the earliest stage in order to minimise the likely malign effects (neurobiological and psychosocial) of progressive illness. This special issue on psychosis brings together a selection of clinical research papers from Irish researchers spanning the trajectory of psychotic illness along the theme 'from early intervention to treatment resistance'.

Early intervention

In the accompanying editorial in this issue, Power (pp. 243–248) outlines how early intervention for psychosis (EIP) services have developed internationally over the past two decades. Against this backdrop, EIP services in Ireland commenced in 2005 with the DETECT (Dublin and East Treatment and Early Care Team) service launched by the late professor Eadbhard O'Callaghan, and gradually progressed with services established elsewhere by local clinicians, usually with only fractions of the ideal service provision due to resource constraints. We are now reaching a point where rollout of early intervention services nationally appears feasible. A Model of Care was approved and launched in 2019 consisting of enhanced clinical resources within child and adolescent and adult mental health services, mostly adopting a hub-and-spoke model of specialist

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care for first episode psychosis with plans to extend to early detection of at-risk cases. Despite inevitable resource challenges, feasible plans are crystallising and Irish mental health services appear finally on course to move towards best internationally recognised practice in optimising care for this critical stage of psychotic illness.

Linked to the existing early intervention clinical services in Ireland are active research programmes and several of these present research from their services in the current special issue. There is a rich history of high-quality epidemiological research into first episode psychosis from Irish research groups, and Waddington and Russell (pp. 293–303) review the complex challenges of psychosis research from the 'real world setting' of the Cavan Monaghan First Episode Psychosis Study. The longitudinal follow-up of first episode psychosis patients for up to 15 years enabled an array of clinical and functional measures to be assessed and provided evidence that a dimensional approach more realistically reflects the various diagnostic subgroups within the broad psychosis phenotype than traditional categorical classifications. The challenges of developing such a clinical research programme and the need to undertake this as a part of an academic collaboration is outlined in an accompanying paper by Russell *et al.* (pp. 317–322).

Murray and O'Connor (pp. 265–269) describe a retrospective appraisal of a pilot early intervention service which was embedded into the home treatment team in the urban South Lee Mental Health Services compared to standard community mental health teams (CMHT). The authors demonstrated a positive service impact in fewer hospital admissions and less bed usage in those patients presenting to the EIP service than standard CMHT care. A 5-year retrospective review of the longer-established EIP programme in the North Lee Mental Health Services by Lalevic *et al.* (pp. 271–277) reports low rates of hospital admission and high rates of medication adherence. A minority of patients completed the more specialised psychosocial interventions of cognitive behavioural therapy, behavioural family therapy for psychosis and physical health monitoring, and better resourcing was identified as a requirement to enhance engagement.

Examining characteristics of a standard urban service prior to specialised EIP introduction, Clarke *et al.* (pp. 249–258) present a retrospective review of clinical services provided for first episode psychosis patients in the Dublin Southwest Mental Health Service. Most patients received appropriate pharmacotherapeutic interventions, keyworker support and psychoeducation, but only a minority received more specialised treatment for first episode psychosis such as cognitive or family behavioural therapy. Deficits were noted in the physical health monitoring of these patients who were prescribed antipsychotic medication for the first time. Such baseline assessment before implementation of specialised early intervention programme services represents a valuable health service research initiative that could readily be replicated in other representative services to monitor the impact of the clinical care programme when implemented.

Treatment resistance

At the other end of the trajectory of illness course for schizophrenia are those patients with treatment resistance, which affects one-third of patients and can be detected over the course of the first antipsychotic treatment trial. Lally and Gaughran (pp. 279–291) provide a comprehensive overview of this common therapeutic challenge including a review of the epidemiology and predictive factors for treatment resistance. Their review covers practical advice for clinicians in the optimal use of clozapine, including augmentation strategies and alternatives, as well as novel psychotherapeutic strategies. Highlighting the real-world effectiveness of clozapine in standard care, Kirwan *et al.* (pp. 259–263) present a mirror-image study of clozapine initiation in a Galway catchment area service and demonstrate marked reductions in number of admissions and number of hospital days in patients after they commenced this treatment.

Pathophysiology of psychosis

Important progress has been made in understanding the neurobiological factors underpinning the development and progression of psychotic illness in recent years. How the brain responds to psychosocial stress is the topic of a systematic review by Dauvermann and Donohoe in this issue (pp. 305–315) who examined studies investigating hypothalamic pituitary adrenal axis dysfunction in response to induced psychosocial stress. There is consistent evidence that patients with chronic schizophrenia display a blunted cortisol response to acute social stress exposure, with more mixed evidence for such an effect at first episode psychosis and in genetically at-risk individuals.

In addition to many examples of clinicians researching psychotic illness and health service provision for such disorders in Ireland, several university-affiliated academic research programmes concentrate on aspects of schizophrenia and related psychoses through local clinical research and with international consortia. These employ a host of diverse investigative techniques, including epidemiology, molecular genetics, proteomics, lipidomics, neuroimaging, cognition and psychological interventions (Emsell *et al.* 2013; Kelleher *et al.* 2013; McCarthy *et al.* 2014; O'Donoghue *et al.* 2015; Donohoe *et al.* 2018; English *et al.* 2018; Kincaid *et al.* 2018; Madrid-Gambin *et al.* 2019; Mothersill *et al.* 2018; Föcking *et al.* in press). Given this broad thematic convergence on clinical

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research into psychosis, academic clinicians and research colleagues throughout the island have recently established the Irish Psychosis Research Network (http://www.psychosisireland.ie), which seeks to foster collaborative links between disciplines, institutions and the public in order to advance clinical research and service development for psychotic disorders. This website is in development and is an ongoing project open to input from patient groups, trainees, clinician and researchers alike.

This is an exciting time for psychosis research and clinical service provision. Between initiatives to advance high-quality collaborative research and clinical developments such as EIP service rollout to translate the fruits of research activity into enhanced clinical care, there is every reason to be hopeful for more optimal clinical outcomes for our patients with psychosis and their carers in future years. This special issue on psychosis provides a flavour of some of these strands of clinical research which we hope will be both informative and inspiring for colleagues interested in the causes and management of psychotic illness.

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Conflicts of Interest

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was not required for publication of this editorial.

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