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Invited Review

Early psychosis research at Orygen, The National Centre of Excellence in Youth Mental Health

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Abstract

Specialised early intervention (SEI) programs have offered individuals with psychotic disorders and their families new hope for improving illness trajectories and outcomes. The Early Psychosis Prevention and Intervention Centre (EPPIC) was one of the first SEI programs developed in the world, providing services for young people experiencing their first episode of psychosis. In this review, the history of the EPPIC model is first described. This is followed by a discussion of clinical research emerging from EPPIC, including psychopharmacological, psychotherapeutic trials and outcome studies. Neurobiological studies are also described. Issues pertaining to the conduct of clinical research and future research directions are then described. Finally, the impact of the EPPIC model on the Australian environment is discussed.

Introduction

"The good-news stories in medicine are early detection, early intervention".

Thomas R. Insel

Historically, psychosis has been associated with poor outcomes [1]. However, the early 1990s saw growing optimism regarding the potential for better outcomes [2] partly related to the emergence of a new generation of efficacious antipsychotic medications with fewer subjective and neurological side-effects as well as a growing view that there could be lower morbidity with earlier interventions [2].

In this paper we review both the clinical trials and observational studies conducted through the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne Australia. Although full-threshold psychosis is the main focus, we briefly touch on our work with individuals at "ultra high risk" (UHR) of psychosis who were treated through the Personal Assessment and Crisis Evaluation (PACE) clinic. EPPIC and PACE are embedded within Orygen Youth Health (OYH), which is closely tied to the translational research institute Orygen, The National Centre of Excellence in Youth Mental Health.

Evolution of EPPIC

In the early 80s, it became obvious that the needs of patients with first-episode psychosis (FEP) aged 15–45 years and their families were strikingly different from those with longer-term illnesses. Issues included grief and pessimism pertaining to diagnosis, exposure to frightening adult institutions and chronic populations, suitability of medication types and dosage, and age-appropriateness of psychosocial interventions [3]. Clinicians and researchers joined forces to tackle these issues and consequently, the first early psychosis intervention service was established in Australia. Core treatments at EPPIC included low-dose antipsychotic therapy, reduced dependence on inpatient care, a stronger focus on optimal recovery [1], and were accompanied by proactive strategies for early detection, prevention of secondary morbidities, and intensive outpatient recovery-focused care, with treatment spanning a maximum of 2 years [1]. PACE opened soon thereafter, providing a low-stigma clinical setting for young people with sub-threshold psychotic symptoms thought to be at risk of psychosis [1,4].

A number of research programs have evolved from EPPIC and PACE, dealing with specific issues surrounding early illness stages; including: (i) preventing and delaying illness onset; (ii) minimising the duration of untreated psychosis (DUP); (iii) determining best pharmacological treatments; (iv) coping with illness onset;

(v) preventing the second psychotic episode; (vi) facilitating psychosocial recovery; and (vii) understanding biological substrates of illness. These issues will be discussed in the context of our work over the past 20 years.

Preventing and delaying illness onset

We have developed UHR criteria [5,6] to identify those who were at greater likelihood of developing a psychotic disorder based on: (i) genetic vulnerability (family history of psychosis and/or patient has a schizotypal personality disorder and has experienced a decline in mental state and functioning); (ii) attenuated or transient psychotic symptoms) or (iii) brief intermittent psychotic episodes [4,7-10]. Initial estimates of transition rates in the UHR group were around 37% over a 12-month period [5,6]; although more recent estimates indicate that the rate of transition over a year are lower, ranging between 8–28% [11-13]. A 10-year follow-up of 416 PACE clients has indicated a transition rate of 34.9%, with the risk for transition being greatest in the first 2 years after service entry. Transition related to the duration of symptoms prior to service entry, baseline functioning, negative symptoms and thought disorder [12]. Alterations to brain structure may also occur between the transition from the prodromal state to full-threshold psychotic disorder [14].

The first intervention trial for UHR patients was conducted at PACE between 1996 and 2000 comparing a specific preventative intervention (SPI, cognitive behaviour therapy (CBT) + low dose risperidone; n=31) and a needs-based intervention (NBI, supportive therapy) [15]. At the end of 6 months of treatment, there were significantly more transitions in the NBI than the SPI group (p=.026); however, these between-group differences were lost 6 months post-treatment (p=.016). Post hoc subgroup analyses indicated that differences at 6 months post-treatment were only found for those who adhered to their medication regimen [15]. The improvements in symptoms and functioning in both groups were maintained to 3-4 year follow-up [16]. Limitations included small sample size, lack of blinding to randomisation, and that the treatment may have not been long enough to delay transition over the longer term [16].

A second trial was undertaken to determine what combinations of pharmacological and psychotherapy would delay transition and promote better outcomes [17]. Young people from PACE were randomised to one of three groups: (cognitive therapy plus risperidone, n=43; cognitive therapy plus placebo, n=44; and supportive therapy plus placebo, n=28) [18,17,19]. A further group who refused randomisation were also followed-up (*Monitoring*, n=78). The three randomised groups and the fourth monitoring group did not differ significantly from one another in terms of transition rates at 6 [18] and 12 months [19]; however, all groups demonstrated significant improvements over time in terms of symptomatology, functioning, and QoL [19,18]. A major

limitation of this study was that the transition rates were considerably lower than what was forecasted; reflecting a recent international trend [11-13]. This may have made the study underpowered to detect differences. The cohort may also have been less ill and/or had lower vulnerability to psychosis [19]. Alternatively it could indicate that a combination of supportive therapy and case management may be sufficient for the management of early illness stages, and that antipsychotic medications are not necessarily the best first-line treatment [19].

In those who are UHR who transition to full-threshold disorder there may be excessive synaptic elimination [20] and reductions in grey matter in right medial temporal, lateral temporal, inferior frontal cortex, and bilaterally in the cingulate cortex [14]. After illness onset there can be reductions in grey matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri [14]. We have examined the neuroprotective features of both lithium [21] and omega-3 fatty acids [22] in UHR participants. In a pilot study, the effects of low-dose lithium on hippocampal T2 relaxation time and proton magnetic resonance spectroscopy (^{1}H-MRS) were compared to treatment as usual (TAU). It was concluded that there was some support that low-dose lithium may have neuroprotective effects on hippocampal cells in UHR [21]; however, a larger randomised control is needed. Preliminary research evidence has demonstrated positive effects of long-chain omega-3 polyunsaturated fatty acids on transition rates, positive, negative and global symptoms, and functioning in those at UHR [23]. Given this evidence and the need for more benign treatments for those at UHR, we have recently undertaken an international multicentre 6-month trial of 1.4g day omega-3; statistical analyses are currently been undertaken [22].

Thus, it may be possible to delay the onset of psychotic disorder and ameliorate symptoms; however, further work is needed in this area to examine which combinations of treatments maximise outcomes.

Minimising the duration of untreated psychosis

Delay in initiating treatment after the onset of a first episode can be 12 months or longer [24-27]. This may be due to delays in help-seeking [28], but may also be related to the age of onset, gender, mental health literacy and stigma [29-31]. Although the definition of treatment initiation varies across studies [32], a longer DUP has been associated with deleterious effects on short- [27,33,34] and long-term [35,36] outcomes. In one observational study of 354 FEP patients treated at EPPIC, DUP was found to correlate with poorer outcomes 12 months post psychotic symptom stabilisation [34,36]. In a cohort of 636 FEP patients treated at EPPIC, a longer

DUP was associated with poorer premorbid functioning, schizophrenia spectrum disorder, and younger age onset of psychosis [37]. At discharge from the service (average of 18 months), longer DUP was associated with lack of remission of positive psychotic symptoms, lack of vocational engagement, persistent substance use, more severe illness and poorer global functioning [37]. In a longer 8-year follow-up study of EPPIC patients, positive symptoms, functioning and QoL were markedly worse when the DUP exceeded 3 months, even after controlling for confounding variables such as gender and premorbid functioning [38]. Thus, delays in receiving treatment for acute psychotic symptoms may result in lasting morbidity [24].

Quasi-experimental designs have been employed to delineate the effects of early detection strategies on DUP and outcome [39]. A number of interventions targeting DUP have been documented, including GP education campaigns [40,41], modifying service configuration [34,42,33] and multi-focused campaigns [43-47].

We considered whether the EPPIC service model facilitates treatment access and reduces DUP. In a study comparing DUP of EPPIC clients to DUP of those treated at a generic adult mental health service, the mean DUP of EPPIC clients was 6 months compared to 15 months in the adult service; however, no formal statistical analyses were conducted [42]. We also conducted a pilot community education campaign [43] where the intervention region (n=58) received interventions targeting young persons, general practitioners as well as by facilitating access to care, while the control region (n=40) accessed EPPIC services. Surprisingly, the mean DUP of clients from the intervention region (M=313.8, SD=558.6) was longer compared to those from the control region (M=254.4, SD=379.7) indicating different distributions of DUP in the two regions despite no reduction of DUP in the intervention [43]. The unexpected findings from these studies may reflect that for some there may be a reduction of treatment delays, but there may be other cases who have not previously been detected with longer DUPs [33,34,43]. These results could also indicate that service configuration alone is insufficient to promote changes in help-seeking and subsequently reduce DUP [48]. The findings of these multifocal interventions, yielding both positive [49,46] and negative [43,47] outcomes, highlight the need for future work in this area.

Treating symptoms

During FEP and in the subsequent critical years following illness onset, individuals require phase-specific treatments that maximise outcomes [50]. A combination of pharmacological and psychological therapies should be offered [50]. Delineating the best combinations of therapies has been part of core research conducted at EPPIC.

Pharmacological trials

The use of both typical and atypical antipsychotics for young people with FEP has been controversial. Although efficacy has been demonstrated in numerous clinical trials, these drugs do have [51] significant side-effects, such as weight gain [52] and changes in lifetime metabolic and lipid parameters [52,53] We have investigated the utility of quetiapine, risperidone and clozapine (CLZ) for FEP.

Quetiapine has demonstrated efficacy (doses range from 300 mg/day–750 mg/day) for chronic schizophrenia [54,55]. The appropriate dosage for FEP was unclear. A dosing RCT was conducted comparing 200 mg/day of quetiapine to 400/mg day in a cohort of 141 FEP patients [56]. The trial design comprised: (i) a double-blind, fixed-dose, 4-week comparison of the two doses; and (ii) a single-blinded, naturalistic flexible dose 8-week comparison. Patients receiving 200mg/day had significantly lower levels of anhedonia-asociality, better social and global functioning, and fewer side-effects compared to those receiving 400mg/day; despite no significant differences in symptoms, and response and remission rates [56]. In the flexible dosing arm of the study, dosing between groups was similar, with an average dose of 268 mg/day; therefore, low dose quetiapine is an appropriate treatment option for FEP [56]. It was also recommended that clinicians should avoid rapid escalation of quetiapine as this could lead to issues of poor tolerability and subsequent poor adherence [56].

An early EPPIC study was conducted to examine the value and feasibility of low dose (2mg/day) risperidone [57]. This was potentially important in order to maximise safety and adherence, with a strong sense that excessive doses were routine practice at the time. After the initial treatment phase (Phase I, Days 1–35, open-label), Phase II (Days 35–42) involved participants being divided into two treatment response groups: (i) ‘fast responders’ and (ii) ‘slow responders’. In Phase II, fast responders were maintained on 2mg/day risperidone, while slow responders were randomly assigned to either: (i) maintenance on 2 mg/day risperidone; (ii) increase in risperidone to 3 or 4 mg/day; or (iii) adjunctive lithium titrated to therapeutic levels (0.6–1.2 mmol). Ninety-six participants entered Phase I of the trial and 65.6% completed this phase. Significant improvements in BPRS total and BPRS-PS scores were seen from baseline to Week 4. At the end of Phase I, 26 were slow responders and 37 fast responders. Slow responders who had 3–4mg/day of risperidone had superior outcomes on BPRS-PS at the end of Phase II compared to those receiving low dose or combination therapies. Limitations of the study included a large number of responders in the first phase, as well as attrition reducing the power to test the efficacy of the treatment regimens for slow responders in Phase II. This study has provided

further evidence that low-dose strategies may be beneficial for FEP; however, larger trials for many antipsychotic medications are warranted [57].

Some FEP patients fail to respond to initial antipsychotic medications, leading to enduring positive symptoms 12 months after treatment initiation [58]. A pilot study was conducted to determine the relative and combined efficacy of clozapine (CLZ) with cognitive behavioural therapy (CBT). A four-arm design was used: (i) CLZ; (ii) CLZ plus CBT (CLZ+CBT); (iii) thioridazine (TDZ); and (iv) TDZ+CBT. A manualised CBT program was delivered twice-weekly for 12 weeks [59]. TDZ was used as a control because of its similar side-effect profile to CLZ. Treatment was achieved earlier for those on CLZ, and symptom remission was achieved by 52% on CLZ and 35% on TDZ. Combining CBT+CLZ had minimal benefit compared to CLZ alone; however, there was a therapeutic advantage of TDZ+CBT over TDZ with response time being reduced and greater likelihood of symptom remission. The benefits of the use of CLZ were highlighted, especially for less well-resourced clinical services where CBT was not yet available [60].

We also examined whether adjunctive high dose ethyl-eicosapentaenoic acid (2 g E-EPA) could enhance the effects of antipsychotics. Essential fatty acids (EFA) are often depleted in chronic schizophrenia [61], independent of treatment [62-64]. A 12-week, randomised, double-blind, placebo-controlled trial was conducted to determine the benefits of 2 g E-EPA in 80 FEP patients [65]. Although there were no differences in symptomatology between the two treatment groups at 12 weeks, there was evidence that adjunctive E-EPA accelerated treatment response, particularly around Week 6 with a subset of those on E-EPA requiring less medication in the mid-treatment phase. Fewer extrapyramidal and other side-effects were also noted [65]. The lack of sustained benefits in symptomatology may have been due to a ceiling effect, many participants achieved remission with antipsychotic medication alone [65].

Coping with illness onset

After detection of FEP, the goal of treatment is to encourage engagement and implement pharmacological and psychosocial treatments [66]. The devastating subjective impact of FEP on young people may be related to the potential loss of social roles, hopes and aspirations for lives and goals [67,68], stigma, social isolation and discrimination, [67] as well as the distress and trauma associated with symptoms and

treatment [68]. As the clinical and psychosocial deterioration can peak within the first 5 years of illness onset [69], this represents a critical period for interventions including psychosocial treatments [70,71].

At EPPIC, we attempted two psychosocial interventions to help young people navigate through the first episode: Cognitively-Orientated Psychotherapy for Early Psychosis (COPE) and Active Cognitive Therapy for Early Psychosis (ACE).

COPE was an 18-session program designed to facilitate disorder adjustment and manage the comorbidities that present after a psychotic episode [72]. Therapy tools included psycho-education and cognitive techniques for dealing with self-stigmatisation, self-stereotypes, insight, depression and anxiety [72,73]. A pilot study compared three groups: (i) COPE plus treatment as usual (TAU) at EPPIC (*n*=44); (ii) refusers of COPE but who had TAU (*n*=21); and (iii) a control group who only received inpatient care (*n*=15) [73]. The COPE group differed significantly from the controls in terms of insight, illness adaptation, negative symptoms and QoL. The COPE group differed from the refusers with respect to better illness adaptation, but had more severe depressive symptoms [73]. Over a year, the initial between-group differences were largely lost, with the exception that the COPE group showed greater illness adaptation than the control group [74]. High attrition in the refusal and control groups may have reduced the power to detect between-group differences [74]. Consequently, the COPE manual was adapted with a stronger emphasis on a phase-oriented approach and moving beyond the engagement and assessment phases [74]. The effectiveness of the revised COPE was assessed in a separate RCT [75]. . Several reasons were offered for the lack of treatment effects at 12 months, including difficulty in surpassing the standards of care provided by EPPIC where many of the elements of COPE may have been offered anyway, not assessing medication compliance, and that COPE patients may have received an inadequate dose of therapy [75].

ACE was designed for the acute phase of illness and incorporates a thorough assessment of psychotic and non-psychotic illness features [75] . Therapy was delivered with a maximum 20 sessions over 14 weeks. Those receiving ACE (*n*=31) were compared to a befriending group (*n*=31). There was improved mid-treatment functioning (6 weeks post-baseline) in the ACE versus befriending group, indicating that the therapy accelerated the rate of recovery from psychosis; however, this was not replicated at end of treatment or 1-year follow-up [75]. The approach nevertheless has merit. If a medication were shown to speed recovery in this way and potentially reduce duration of inpatient care, it would be widely employed. Issues such as determining optimal

doses of therapy, duration of sessions, and period of time for delivery of therapy were considered key directions for future research [76].

Relapse prevention

Up to 82% of FEP patients relapse within five years [77]. This compromises well-being, psychosocial recovery and increases the risk of chronic illness [78]. Although several studies have focussed on psychosocial therapies for relapse prevention in chronic schizophrenia [e.g., 79,80], little had been done for FEP. **Episode II** was the first relapse prevention trial designed for FEP patients who had achieved remission of positive psychotic symptoms [81]. The effectiveness of a multimodal individual plus family-based psychosocial relapse prevention therapy (RPT) was compared to treatment as usual (TAU) [81,82]. Family therapy was informed by previous work on behavioural family therapy for schizophrenia [83,84] and family interventions for FEP [85]. Forty-one FEP patients were randomised to RPT and 40 received TAU [82,86]. Sixty-three carers also participated (RPT *n*=32; TAU *n*=31) [86]. At 7-month follow-up (end of treatment), relapse rates in the RPT group were significantly lower and relapses were delayed compared to the TAU group [82]. Similar effects were seen at 12 months; however, these differences were not maintained at the 18-, 24-, and 30-month follow-ups [86]. Carers had better appraisals of negative symptoms and greater positive personal experiences of care-giving in the RPT group [87].

There were some perplexing patient outcomes in Episode II. The RPT group had more severe negative symptoms and poorer functioning at 30 months compared to the TAU group; these findings were in the context of significantly better medication adherence [86]. After controlling for medication compliance, the differences between RPT and TAU groups in functioning disappeared, but the between-group differences in negative symptoms remained. Both groups had equal access to psychosocial and vocational activities; no between-group differences regarding dose of antipsychotic medications were seen, thus these factors could not account for differences in fluctuations in functioning. It was speculated that FEP patients whose positive symptoms stabilised were more treatment adherent. The potential negative effects of long-term antipsychotic medication on recovery (including symptoms and functioning) has also been raised in a recent trial [88].

Psychosocial interventions

The onset of mental illness unfortunately coincides too often with the time in a person's life that developmental milestones are achieved and protective elements of social inclusion are established. Social drift

or decline often occur following illness onset [89,90] and can result in loss of protective elements including social supports, procurement of formal education and forging of a career [91]. Interventions that target psychosocial aspects of illness can assist with recovery and social inclusion. Consequently, **vocational recovery** has been a prominent research program at EPPIC. In 2005–2006, a pilot study focused on the benefits of individual placement and support (IPS) [92]. Forty-one young people from EPPIC participated; 20 received IPS+TAU and 21 received TAU [92]. The IPS group were significantly more likely to gain employment, work more hours per week, hold employment for a longer duration, and be less reliant on welfare benefits at 6-month follow-up [92]. This preliminary evidence supporting the benefits of IPS led to a larger effectiveness study of IPS [93]. In this newer study, participants were followed up for 18 months after a 6-month period of IPS+TAU or TAU on a range of outcomes (e.g., demographic, psychopathological, economic, social cognitive and neurocognitive); the statistical analyses for this study are currently being undertaken [93].

Social cognition can also impact on functional outcomes after a first episode of psychosis [94]. Social cognition training may be a promising way in which to promote psychosocial recovery [94]. We have conducted preliminary work examining the feasibility of a 10-week group-based social cognition and interaction training (SCIT) intervention [95]. Twelve young people with FEP participated in the program; assessments were conducted pre and post SCIT. SCIT was well-tolerated with high retention. Significant improvements were seen over time in terms of emotion recognition, and social and occupational functioning [95].

Both the vocational and social cognition interventions highlight the importance of not only considering symptom outcomes, but the importance of psychosocial recovery in young people with FEP.

Neurobiological studies

EPPIC and its long-term collaborators at the Melbourne Neuropsychiatry Centre have led groundbreaking work on the neurobiology of FEP. Reduced whole brain volume [96] and hippocampal volume [96] have been observed in clients with FEP. Bilateral grey matter reductions in the insular cortex (especially in the short insula) were associated with the severity of positive and negative symptoms 1–4 years after illness onset [97]. FEP patients were noted to have enlarged pituitary volumes that may relate to activation of the hypothalamic-pituitary-adrenal (HPA) axis [98]. Olfactory identification deficits have been found at illness

onset, indicating abnormal orbital frontal cortex functioning, and correlating with negative symptoms[99]. Neurocognitive deficits in object working memory [100] and story recall have also been noted [101,102].

First-episode schizophrenia (FES) has also been a specific research interest. Relative to controls, people with FES were observed to have reduced volumes in the bilaterial anterior and posterior insula cortices [103], and bilateral thinning of the paralimbic anterior cingulated cortex [104]. Those with FES also had significantly less grey matter in the Heschl gyrus (HG), planum temporale (PT), and caudal superior temporal gyrus bilaterally compared to those with early affective psychoses or healthy controls [97]. The anterior genu of the corpus callosum, which has important connections with the frontal cortex, was also reduced in FES [105]. There was greater prefrontal surface contraction localised to the right superior frontal gyrus and bilaterally to the middle frontal gyri [106]. In the early stages of FES, the left hippocampus was noted to be particularly vulnerable; with bilateral volume reductions noted in later stages of illness [107,108]. Among those with FEP, a progressive decline in visuospatial associative learning ability [109] was associated with anomalies in the right medial temporal lobes.. At illness onset under-activation of the dorsolateral prefrontal cortex [110] and left paracingulate cortex [111] were also noted. Impaired spatial working memory dysfunction in FES suggested impairments in a diffuse network including the prefrontal, temporal and parietal cortices [112].

Medication can impact on brain structure and functioning. For example, atypical antipsychotic medications may reduce pituitary gland volume in a dose-dependent manner, suggesting that they may enable those with FEP to cope better with illness-related stress [113]. Over the first 8 weeks of treatment with antipsychotics, there can be increased activity of the lateral prefrontal cortex; these changes may be associated with medications and/or reduction in positive psychotic symptoms [114]. Elevations in myoinositol (mI) and creatine/phosphocreatine (Cr/PCr) were also identified in FES patients treated with antipsychotic medications [115]; however, increased Cr/PCr was more likely due to illness effects whereas the elevation of mI, a second messenger, could be a consequence of antipsychotic treatment [115]. Quetiapine treatment was associated with increases in brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) and changes in these growth factors correlated with improvements in positive symptoms [116].

E-EPA augmentation has positive effects on neurobiology of the brain. On the basis of the spectroscopy and magnetic resonance imaging, E-EPA augmentation was inferred to impact glutathione availability, modulate the glutamine/glutamate cycle, and anticipated to result in oxidative stress reduction in FEP [117,118]. Such changes were noted to be associated with a decrease in negative symptoms [117,118].

In summary, evidence suggests that a neurodevelopmental insult, as well as brain changes, are associated with the emergence of psychosis, particularly in those with schizophrenia [119,120]. The normal neurodevelopmental course during adolescence and early adulthood may be altered related to disease pathophysiology [106]. There also may be a relationship between stress, HPA axis functioning, and the hippocampus during onset of psychotic disorders [121].

Emergent issues

A number of issues remain open regarding treatment for young people who are at risk of psychosis or who have had a first episode of psychosis.

Timing and staging of interventions: The timing of the window of opportunity for intervention which may maximise outcomes is not always clear. Clinical staging, an approach developed by our group, may aid this [122,123]. Within the clinical staging framework, an individual is considered to have a disorder that exists on a continuum ranging from Stage 0 (an at-risk stage) to Stage IV (late or end-stage disease) [124]. This framework can allow clinicians to select treatments relevant to the stage of illness that are effective and less harmful [123]. .

Ethics of intervening early: The pre-psychotic phase can be associated with erosion of developmental achievements and potential [125]; however intervening early has been contentious. Recently, transition rates have been steadily declining not only in Australia, but worldwide [11,126,13]. This may be due to increased community awareness that may lead to earlier detection and provision of care[127]. The altering of referral pathways may lead to a higher number of 'false positives' being included in samples of more recent studies [13]. One ethical issue pertains to whether intervention for individuals who are 'false positives' is intrusive, causes stigma and inconvenience, or if the benefits of intervention are outweighed by the harms [125]. Much of this controversy has been focused on medication; however, the issue pertains to the risk/benefit ratio of any intervention and the correct sequence. Regardless of whether an individual makes the transition to psychosis, a range of potential advantages exist including: (i) minimisation of social withdrawal, impaired functioning and distress; (ii) fostering of engagement and formation of foundations for later therapeutic interventions if needed; and (iii) treatment of comorbidities such as substance use [10]. If the individual does develop full-threshold psychosis, DUP is curtailed [10].

Is DUP a malleable causal risk factor? Longer DUP has been found to be associated with poorer short- and long-term outcomes [33,34,36,38,43,37]. However, the strength of the association may be no more than modest [37] and association does not necessarily mean causality [125]. Alternatively, DUP may serve as a proxy for other factors, such as more severe illness type and an insidious onset with more severe negative symptoms [125]; although our research has indicated that there are specific iatrogenic effects of DUP on outcome [36]. There have been mixed findings regarding the effectiveness of interventions designed to reduce DUP; this is in part due to whether interventions are multifaceted and/or target help-seeking or reduce delays in service access [28].

What are the best treatments for those who develop FEP? The optimal dose and duration of antipsychotic medication still requires demarcation and one size probably does not fit all. The possibility of whether a subgroup of patients exist who may not require antipsychotic treatments while providing adjunctive intensive psychosocial interventions is being examined in a double-blind RCT [128]. The right time to discontinue or at least reduce the dose of antipsychotic medications is also yet to be resolved, but is a research question strongly in focus now. It is also important to identify early the subgroup of patients that may be treatment-resistant and require additional treatment options [60]. Alternatively, natural pharmacological agents (e.g., E-EPA) can add to the neuroprotective properties of antipsychotics; the benefits of other agents such as N-acetyl cysteine (NAC), which has shown promising effects in chronic patients [129], and cannabidiol [130] should also be considered.

Pharmacological therapies may assist recovery from acute symptoms but do not assure functional recovery or prevent relapses [131]. We have preliminary evidence of the effectiveness of IPS on vocational outcomes [92] and social cognitive training [95]; however, there is more scope for such interventions. There were some positive findings for interventions targeting adjustment to illness [75,73,72,74,132] and relapse prevention [133,81,82,87,86]; however, improvements were not seen in all domains. Such interventions were delivered in addition to TAU at EPPIC, so one possible conclusion is that these interventions only have limited efficacy over and above TAU. It has been also difficult to determine which components of therapy are having an effect. Examining ways in which to increase the reach of more effective psychological interventions is an important research goal.

The short-term gains of integrated biopsychosocial interventions also appear to diminish over time, at least in a substantial subset of patients. A recent meta-analysis of psychosocial interventions for FEP indicated

that only modest efficacy can be demonstrated, especially for individual therapies [71]. The HORYZONS online social networking system is based on Moderated Online Social Therapy (MOST), and is an adjunctive novel intervention to sustain and maximise the benefits of early intervention over the longer term [134]. On the basis of promising pilot data on the acceptability, safety and preliminary efficacy of HORYZONS in 20 FEP patients [135] a larger trial is currently being undertaken at EPPIC.

What happens after early intervention? In the spirit of personalised care, we need to identify the characteristics associated with a positive long-term response to early intervention; as well as those related to a poor response and a need for continued care beyond 18 months in a specialised service particularly given the questions around the optimal duration of interventions [136]. These issues are currently being examined in a long-term follow-up study of 661 patients treated at EPPIC between 1998 and 2000. A comprehensive assessment of outcome is being undertaken, focussing on symptomatology, functioning, neurocognition, physical health, substance use, QoL and service utilisation after EPPIC.

EPPIC today

Over the last two decades the EPPIC model has been refined and carefully documented. This model, based on our experiences as well as the available evidence and international consensus, now comprises three core functions (acute care, early detection, and recovery) with sixteen components [118,119]. Crucially, this new model includes provision for a cohort of UHR or potentially prodromal cases. Both EPPIC and PACE are now part of Orygen Youth Health, where early intervention models of care for young people have been expanded to also cover the spectrum of potentially severe mental disorders such as mood and personality disorders [137]**.** Research continues at Orygen, as well in countless international settings, pursuing discovery and innovation, addressing gaps and uncertainties, and actively shaping clinical practice. The recent focus on early intervention in the United States and the investment in the cluster randomised controlled trial Recovery After an Initial Schizophrenia Episode (RAISE) is an exemplar of international efforts in this area [138].

The Australian context

EPPIC has been a blueprint for service reforms and the establishment of early intervention services in Europe, the UK, Asia and the US [120]. Until recently, the EPPIC model had not yet been up-scaled widely in Australia. However, in 2010, the Australian Government funded the national roll-out of the EPPIC model across Australia. These new SEI services are to be delivered through headspace, an enhanced primary care platform

providing integrated mental and physical health, as well as vocational and drug and alcohol services to young people aged between 12–25 years in youth-friendly, stigma-free community-based settings. Early psychosis services are to be added to eight regional headspace clusters across Australia, providing young Australians experiencing a first episode of psychosis access to youth-specific services offering evidence-based care and focusing on recovery and remaining well.

Conclusion

The focus on early intervention for psychotic disorders has a long history within Australian. To date, treatment and outcome studies have shown mixed results, with some definitive, some highly indicative, and certain inconclusive findings. The early psychosis paradigm that has evolved from the research and reform over the last two decades has provided proof of concept of the value of early intervention in these serious and disabling disorders and led to the establishment of dedicated early psychosis services in hundreds of centres world-wide. Early intervention, a keystone of pre-emptive psychiatry, is now being adopted across the full diagnostic spectrum, particularly with a focus on adolescents and emerging adults, and this exciting new field promises to improve the experience, prospects and outcome for those facing the onset of a potentially serious mental illness, on a much larger scale than could have been envisioned in psychiatry even a decade ago.

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