

LSE Research Online

C. Csillag, M. Nordentoft, M. Mizuno, <u>D. McDaid</u>, C. Arango, J. Smith, A. Lora, S. Verma, T. di Fiandra, P. B. Jones Early intervention in psychosis: from clinical intervention to health system implementation

Article (Accepted version) (Refereed)

Original citation:

Csillag, Claudio and Nordentoft, Merete and Mizuno, Masafumi and McDaid, David and Arango, Celso and Smith, Jo and Lora, Antonioand Verma, Swapna and di Fiandra, Teresa and Jones, Peter B. (2017) *Early intervention in psychosis: from clinical intervention to health system implementation*. Early Intervention in Psychiatry. ISSN 1751-7885

DOI: 10.1111/eip.12514

© 2017 John Wiley & Sons Australia, Ltd

This version available at: http://eprints.lse.ac.uk/85134/

Available in LSE Research Online: February 2018

LSE has developed LSE Research Online so that users may access research output of the School. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LSE Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain. You may freely distribute the URL (http://eprints.lse.ac.uk) of the LSE Research Online website.

This document is the author's final accepted version of the journal article. There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

Title page

Early Intervention in Psychosis: From Clinical Intervention to Health System Implementation

Authors:

Claudio Csillag, Mental Health Centre North Zealand, University of Copenhagen, Denmark

Merete Nordentoft, Mental Health Centre Copenhagen, University of Copenhagen, Denmark,

Masafumi Mizuno, Toho University School of Medicine, Japan

David McDaid, London School of Economics and Political Science, UK

Celso Arango, Hospital General Universitario Gregorio Marañón, Universidad Complutense, School of Medicine, CIBERSAM, IiSGM, Madrid, Spain

Jo Smith, University of Worcester, UK

Antonio Lora, Lecco Mental Health Department, Italy

Swapna Verma, Institute of Mental Health, Singapore

Teresa di Fiandra, Health Ministry, Italy

Peter B. Jones, University of Cambridge, UK

Corresponding author: Claudio Csillag, Mental Health Centre North Zealand, Dyrehavevej 48, 3400 Hilleroed, Denmark. Phone + 45 3864-3107. Email: claudio.csillag@regionh.dk

Running title:

Implementation in Health Systems

Abstract and keywords

Abstract

Aim

Early Intervention in Psychosis (EIP) is a well-established approach with the intention of early detection and treatment of psychotic disorders. Its clinical and economic benefits are well documented. This paper presents basic aspects of EIP services, discusses challenges to their implementation and presents ideas and strategies to overcome some of these obstacles.

Methods

This paper is a narrative review about the evidence supporting EIP, with examples of successful implementation of EIP and of cases where major obstacles still need to be overcome.

Results

Experience from successfully implemented EIP services into the mental healthcare system have generated evidence, concepts and specific strategies that might serve as guidance or inspiration in other countries or systems where EIP is less well developed or not developed at all. Previous experience has made clear that evidence of clinical benefits alone is not enough to promote implementation, as economic arguments and political and social pressure have shown to be important elements in efforts to achieve implementation.

Conclusions

Users' narratives, close collaboration with community organisations and support from policy-makers and known people within the community championing EI services are just a few of the approaches that should be considered in campaigns for implementation of EI services. Fast progress in implementation is possible.

Key words:

Early intervention in psychosis (EIP); evidence-based medicine; health planning; implementation; mental health services

Introduction

Early Intervention in Psychosis (EIP) is a well-established approach with the intention of early detection and treatment of psychotic disorders. The rationale is that detection and treatment of psychotic symptoms, behavioural problems and psychosocial deficits in early stages reduce the long-term adverse impact of these severe mental disorders and contribute to preventing relapses and improving functioning. EIP services mainly target young people with psychotic symptoms, but they are also aimed at people who are at ultra-high risk for developing psychosis. EIP relies on the concept of clinical staging of psychosis, in which early and milder clinical phenomena differ from those that accompany illness extension, progression and chronicity ¹.

The aim of this paper is to present the local and national experiences, views and suggestions presented by leading specialists in EIP from several countries during a symposium at the IEPA 10, held by the IEPA Early Intervention in Mental Health in Milan, Italy, in October 2016.

EIP programmes originated from research showing convincing evidence of an association between shorter Duration of Untreated Psychosis (DUP) and benefit on relevant outcomes at 12 months, including positive and negative symptoms, depression, anxiety, overall functioning, and social functioning ^{2–4}.

Specialized assertive outreach teams are at the core of EIP services. Staff members in these teams have a reduced caseload compared to conventional mental health service teams ⁵. They are usually multidisciplinary and include psychiatrists, community psychiatric nurses, clinical psychologists, social workers, occupational therapists, employment support specialists, and peer support workers, among others.

Importantly, clinical management is not limited to pharmacological intervention. Interpersonal problems, social skills, vocational and educational issues, functional recovery, physical health, substance abuse, suicidal ideation, and financial problems are also the focus for multidisciplinary intervention.

Teams practice assertive outreach by actively promoting contact and engagement with the patient, including outreach efforts in community settings and in patients' homes. Family members are generally actively encouraged to be involved.

Besides this set of characteristic elements, EI services relate to external factors in specific ways, which can vary according to different national contexts. Primary and secondary health care professionals, schools and the police are encouraged to make direct referrals ⁶. Promotion to raise community awareness and education of local stakeholders in the health care system and other services relevant to the mental health of young people are often connected to EIP services ⁷.

Evidence

EIP services have shown that it is possible to shorten the duration of untreated psychosis, and that some positive effects, for instance on employment participation, have persisted for at least 10 years ⁸. Besides reducing the need for hospitalisation, including bed days, and increasing retention in care, EIP services have also been shown to improve social functioning ⁹ and user satisfaction ^{5,10,11}.

Results of one early trial, the Lambeth Early Onset (LEO) trial, a pioneer among EIP programmes, reduced the number of readmissions in psychiatric wards and decreased dropout rates significantly ¹².

Convincing results were also seen in OPUS, a randomised trial which was described in a Cochrane Review from 2011 as the largest study and the study with highest quality at the time of the review ¹³. OPUS compared EIP with standard care and demonstrated an incremental improvement in a health system that already had a good standard of care. Thus, results showed clear effects on psychotic symptoms, negative symptoms, social functioning, substance abuse, and burden of illness experienced by family members ^{14,15,16}.

It is not only people who already have symptoms who can benefit from EIP programs. An additional focus on people at ultra-high risk has also been associated with fewer admissions to hospital and less compulsory treatment ¹⁷.

But there is still uncertainty regarding EIP services. While we know that increasing the focus of a health system, including primary care, on EIP can greatly improve early identification of people with at-risk mental states or first episode psychosis ¹⁸ as a cost-effective measure, we do not know, for instance, for how long specialist services should be offered. Beneficial effects on symptoms and function seen after two years of specialized and intensive services in the OPUS trial were not sustained after five years (i.e. after three years of standard treatment), except for the ability to stay independently which was better in OPUS patients up to seven years after inclusion ¹⁸. On the other hand, an EI program from Canada suggests that a five-year program might have long-lasting effects ¹⁹. More recently the Danish OPUS II trial compared five years versus two years of specialised EIP services, and results showed no difference between groups regarding negative symptoms or on other psychopathological dimensions, functional level, labour market affiliation, cognitive function, or hospital admissions; as authors suggest, the results cannot serve as a basis for recommending EIP services for five years, but they do not contradict the early intervention paradigm ¹⁹.

Another unknown effect of EIP services is the long-term impact on physical health and mortality due to somatic diseases, which are associated with worse measures among people with psychotic disorders in relation to the general population ^{20,21}.

Health system implementation

If EIP programmes are to deliver expected results, they need to be implemented and conducted as they have been originally intended to do, which can be measured by instruments to assess how strictly the delivered program adheres to the proposed model. These fidelity measures are supported by research evidence showing that best results are actually achieved with the highest levels of fidelity to models ²².

Adherence to the originally designed programme means not only including essential features of good practice; it means also that other inappropriate types of practice should be avoided ²³.

<u>Australia</u>

One of the first fidelity measure instruments was based on the core components of the Early Psychosis Prevention and Intervention Centre (EPPIC), in Australia ²⁴. Essential elements in the Australian model include aspects such as community awareness and ease of access to service – without which patient enrolment would risk being compromised – and continued staff development and training; clinical parameters include case management, medical and psychological treatments, and functional recovery, among others.

EIP services in Australia has expanded throughout the country with The Headspace National Youth Mental Health Foundation, created and expanded to around 30 centres from 2006 to 2009 ²⁵, and currently implemented in about 100 centres across Australia. This foundation offers a specific EIP service, the Youth Early Psychosis Program (hYEPP) ²⁶.

Besides Australia, there are examples of widespread implementation in a handful of countries including England and Denmark, Norway, Canada and parts of Asia, and more recently in the United States – elsewhere service availability remains restricted to research-based teams ²⁷. Adequate implementation is not just a question of disseminating information on the effectiveness and cost effectiveness of EIP services, it is also about careful planning of the implementation and operationalisation.

England

In England, a rapid increase in implementation of EI programmes occurred after 2001, promoted by a National Service Framework (NSF) for mental health, which included EIP ²⁸. Is was later promoted by EIP policy implementation guidance ²⁹, and by the revised Initiative to Reduce the Impact of Schizophrenia (IRIS) guidelines, originally published in 1999 and revised in 2012 ³⁰.

These guiding policies were based on existing evidence at the time and embraced the vision of people committed to early intervention in psychosis. Services adhered reasonably to the proposed models, as a mean fidelity score of 6.44 (range from 1 [lower degree of fidelity] to 10 [higher degree of fidelity]) showed in 2005 ³¹. The number of teams providing comprehensive coverage across England to young people (14-35 years) with a first-episode psychosis rose to 178 by 2010.

But this widespread and policy-based dissemination and implementation of EIP programmes came under threat as constraints on public expenditure arising from the 2008 economic crisis began to have an impact within the National Health Service (NHS). There was a gradual dilution of some teams and incorporation of others into general community mental health teams. This was in spite of the National Institute for Health and Care Excellence (NICE) recommendation ³² that anyone with a first-episode psychosis should receive timely access to an EIP service, and accumulating evidence of cost savings associated with EI programmes ¹⁷. Significant cuts were seen in over 50% of EIP services, with a decrease in coverage from 95% to only 69% of NHS Trusts offering EIP services in 2016 ³³.

It seems that this decline is now being reversed. In 2016, a new EIP national policy was implemented in England, known as EIP National Access and Waiting Time (AWT) policy standard 34 , which states that 50% of people experiencing a first episode psychosis should start a NICE-approved EIP care package within two weeks of referral for assessment. Most EIP services (N = 125, 87%) are standalone specialist teams with their own management structure, working with people aged from 14 to 35 years (N = 90, 63%), and the new EIP AWT policy requires EIP services in England to extend their services to all people with an FEP aged up to 65 years. Most (n = 128, 89%) report working with people for a maximum of 3 years 35 .

Furthermore, a sophisticated prediction tool, the Psymaptic ³⁶, which is freely available online, generates high-quality data on the expected incidence of clinically relevant cases of psychotic disorder in England, allowing more effective local planning with an appropriate allocation of resources. It provides a basis to negotiate increasing funding where need is demonstrably greater than expected. Together with an increase in funding in EIP programmes, these and other initiatives can be considered the second wave of systematic and improved EIP implementation in England.

Denmark and Norway

A similar development can be seen in Denmark, where EIP services have been transferred from a research-based setting into a nationwide service embedded in the general healthcare system.

Since the initial positive OPUS results ¹⁴, EIP services have been implemented throughout the country. Between 1998 and 2013 Denmark had a tenfold increase in the numbers of EI teams. Financing the implementation of EIP services as the standard for care depended initially on specific governmental grants. In 2016, health experts and the regional health authorities agreed on a treatment package for people with psychosis, which sets the EIP programme approach as the standard for people with a psychotic disorder. As in England, this new development includes a timeframe to initiation of the treatment package: an individual is entitled to be evaluated within one month of referral ³⁷.

In Norway, the development of early intervention services in mental health started around 1990, and in the mid-nineties the TIPS-project (Early InTervention In PSychosis) was launched. Early intervention strategies are the core element in Norwegian guidelines for

assessment, treatment and follow-up of non-affective psychosis, and in 2016 a nationwide 3.3 million Euros implementation project has been launched ³⁸.

United States and Canada

A different and more recent example of implementation and expected maintenance of EIP services is the Recovery After an Initial Schizophrenia Episode: Early Treatment Program (RAISE-ETP), launched in 2008 in the United States by the National Institute of Mental Health (NIMH). This is a high-quality initiative with demanding fidelity measures embedded since its inception, in order to facilitate its replication in current US settings ³⁹. The results from the initial experiences of RAISE influenced federal and state agencies' support for widespread implementation across the country, and, by 2018, more than 100 EIP teams are expected to be fully implemented and operational ⁴⁰.

Canada has also seen an increase in EIP services. Specialized services emerged in the late 1990s and now exist in most provinces, but are not universally available, especially in remote or rural areas ⁴¹. Even though the delivered services are heterogeneous throughout the country, the Canadian Consortium for Early Intervention in Psychosis, established in 2012, promotes the adoption of national standards ⁴².

Implementation challenges

There are many obstacles to the widespread implementation of EIP services. Recognition of the specific needs of patients with early psychosis is a necessary starting point, but a more general acknowledgment that psychotic disorders can potentially have fatal consequences, being associated with reduced life expectancy compared to the general population, might also be lacking. There is a need to communicate effectively with politicians and administrators to convey more insight and knowledge about this patient group. It is also important to communicate effectively with relatives, health professionals in general, medical graduates, as well as other professionals, such as school teachers ⁴³. In Japan, for example, the school system is gradually but steadily incorporating educative and training activities for high school students to teach them deal and help peers with mental health problems.

Even when there is a perceived need to address the problem, insufficient funding might hinder the implementation of EIP services - as shown by a known and well-documented funding gap ^{44,45}. When political and budgetary obstacles are minimized or removed, the structure of the mental health system might itself be a major barrier to implementation - for example in countries where a reliance on institutionalisation and the social isolation of people with psychotic disorders is more common ^{46,47}.

Spain

A country that currently has to contend with many difficulties during initial efforts to implement EI services into the health system is Spain. Political interest is almost non-existent, and there is a lack of commitment and political involvement in preventive measures. There is almost no coordination between mental health specialists and primary care, welfare services or

educational institutions; it is difficult to offer integrated treatment, instead, treatment is offered in a fragmented manner through different services and in different sites, with no guarantee of continuous care. Access to psychosocial services is rare, and facilities are not adapted to the needs of young people. The organization of resources is inappropriate to operate EI services, with long waiting lists and long periods of time between visits ⁴⁸.

Against this scenario, some research-based programmes have emerged in Spain. These programmes are mostly funded by research grants, where family associations also contribute with funding and initiatives, such as efforts to educate the public and to train teachers and professionals in primary care services on concepts about early psychosis. An important institution in this context is the Fundación Manantial, created on the initiative of relatives' associations ⁴⁹.

Examples of intervention programmes on first-episode psychosis include the Programa Asistencial de Fases Iniciales de Psicosis (PAFIP), at the Marqués de Valdecilla University Hospital, in Santander ^{50,51}, and the Programa de Intervención en Psicosis Adolescente (PIENSA), based at the Gregorio Marañón Hospital, in Madrid ^{52,53}.

Italy

Another country with limited development and implementation of EIP services is Italy, in spite of the traditional focus of regional health care services on care provided through community mental health centres ⁵⁴. This might in part be explained by the country's regional variability: only some regions have successfully implemented EIP programmes, mainly inside the network of community mental health centres ⁵⁵. The central government is now putting efforts into the coordination and promotion of services, with the provision of a framework and the promotion of continuous and even compulsory monitoring of services. A research funding mechanism prioritises projects that are immediately applicable to the national system ⁵⁶.

Discussion

Different approaches might be used to overcome the variety of obstacles impeding widespread implementation of EIP services within healthcare systems. Embedding EIP services within publicly funded health systems might be considered an essential component of an implementation strategy. This has been achieved in only few countries, such as England, Denmark, Norway and Singapore. By evaluating the impact of embedding these services within existing mental health services, it is possible to demonstrate that EIP service models can be adapted to operate in contexts and countries where implementation had previously been limited ⁵⁴.

It is also important to look at the context in which EIP services could be delivered. For example, in Italy, where only a small number of specialist EIP services have been sustained, the recent large scale GET UP PIANO trial has assessed the impact of providing training for community mental health service mental health staff to provide EIP services. This study

concluded that it is feasible to provide EIP specialist services activities within the existing staff and infrastructure of the community mental health centres that are found throughout the country ^{54,57}. Potentially this might help both with the diffusion and sustainability of EIP services at a time when the health service is under substantial financial pressures.

Another way in which implementation might be facilitated could be through changing structures so that contact with services is perceived to be less stigmatising. This could be done by encouraging collaboration and co-location of staff in the same premises or by conducting joint training events ⁵⁴. Other general strategies that might facilitate the implementation of EIP services include introducing payment mechanisms to promote development of EIP capacity, widening access and coverage, monitoring the fidelity in the delivery of services and promoting the emergence of champions to raise awareness about early psychosis and the benefits of EIP services.

It is critical to share evidence on effectiveness as well as positive experiences in countries where implementation, appropriate coverage and acceptable fidelity and quality criteria have been met. This can help to generate a set of ideas and specific strategies that might serve as inspiration or guidance for implementation.

Cost effectiveness

The clinical evidence about the benefits of EIP is well documented and can be used by health professionals, policy makers, users and relatives to promote EIP services. There is also a growing evidence base on cost effectiveness. Economic arguments should also be considered essential elements of efforts to promote EIP services, including in countries with no or only incipient EIP services. It is probable that EIP is cost-effective in high income country contexts, with lower costs and better outcomes, compared to standard treatment, even without considering the impact on employment or on issues such as education and housing needs ⁵⁸. Despite services being more costly during the initial 12 months of support, there is some evidence that the main elements of EI can be cost-effective; indeed, the highest fidelity models show no advantage at one year ⁵⁹. By 24 months the overall costs to the healthcare system can be significantly lower than those of conventional mental health services. This economic advantage may increase further by 36 months ^{17,60,61}.

As the majority of the costs of living with psychosis do not fall on health systems, the economic case can be strengthened further if analyses consider the impact of EI on other sectors of the economy, such as education, employment, housing and justice. For instance, EI has been associated with significant net savings per recipient from improved employment and education outcomes during a three-year period ⁶². Economic analyses using modelling techniques can also be used to rapidly help to point to mid to longer economic benefits beyond the health sector ⁶². Such approaches can be particularly valuable in the absence of previous local empirical data on cost effectiveness as well in extrapolating longer term costs and benefits beyond those seem in clinical trials ⁶³.

Social pressure

It is not just a question of generating and communicating evidence on EIP. After more than 20 years of efforts to secure the development and the financing of EIP services in countries like England and Denmark, it has become clear that evidence alone is not sufficient. Experience shows that politicians respond to individual narratives, stories of young users and their family members who benefited from and campaigned for EIP services - or are in need of their benefits. Passionate stories can exert an immense impact, especially if they are part of organised public affairs campaigns. Service users and family members could be involved much more closely from the very beginning of EIP services campaigns. They may benefit from help in developing skills to communicate with policy makers and the media, as well as in setting up sustainable organisations and networks.

Fostering close connections to NGOs and with community organizations that support people with psychosis and other mental health needs is therefore a good starting point to promote El services.

Two types of alliances have been shown to have a powerful impact in campaigning for EIP services – with users and family members and with NGOs and community organisations. Besides, experience suggests that forging partnerships with professionals with a background in administration, fundraising or marketing might be helpful in order to implement changes in a healthcare system. This might lead to sophisticated approaches based on implementation science models, which might, for example, incorporate monitoring minimum service fidelity criteria, national dataset reporting and benchmarking.

Avoid thinking only at a clinical level

There is the key role and importance of EIP leaders providing leadership within and across countries. Without the championing of evidence, political efforts engaging politicians and civil servants, reciprocal support between countries from key EIP international leaders, even some of the most successful EIP service roll outs and implementations would probably not have happened.

The experience gathered from countries that have succeeded in implementing and sustaining EIP services shows that clinicians should avoid thinking only at a clinical level, and instead, consider an approach involving the mental healthcare system as a whole, as well as the primary and secondary care sectors, and wider social support systems.

Finally, attention must be paid to facilitating a continued high level of fidelity, which means not only initial adherence to the designed EIP model, procedures, and staff training, but also continued funding and monitoring of all these components.

Acknowledgements

This paper is based on a symposium held during the 10th International Conference on Early Intervention in Mental Health, held by IEPA Early Intervention in Mental Health in Milan, Italy, from 20 to 22 October, 2016. ⁵⁶ Otsuka Pharmaceutical Europe Ltd and H. Lundbeck A/S has offered financial support in relation to this report and the meeting that preceded it in the form of consultancy and secretarial services. The organisation of the meeting was carried out independently of this support and neither of the companies have had influence on the discussions and conclusions, which reflect the views of the Expert participants. Otsuka Pharmaceutical Europe Ltd and H. Lundbeck A/S have reviewed this report for factual accuracy only. Claudio Csillag received a grant from IEPA to report from the symposium.

Table 1. Timetable of implementation in England

- 1999 Initiative to Reduce the Impact of Schizophrenia (IRIS) guidelines
- 2001 Rapid increase in EIP services
- 2010 178 EIP teams
- 2012 Policy implementation guidelines by Mental Health Network NHS Confederation
- 2014 NICE guidelines on EIP: anyone with a first-episode psychosis should have access to EIP service
- 2016 Effects of financial crises in 2008 led to fall in coverage from 95% to 69% of NHS Trusts offering EIP services.
- 2016 National Access and Waiting Time (AWT) policy standard: EIP care should be offered within two weeks of referral.

EIP: Early Intervention in Psychosis. NHS: National Health Service. NICE: National Institute for Health and Care Excellence

Table 2. Facilitators and barriers to the implementation of EIP services

Facilitators

Research evidence

- EIP experts promote evidence of clinical and economic benefit
- Maintain a high level of fidelity

Political

 Adoption by health authorities of EIP services according to guidelines/clinical evidence

Communication and stakeholders

- Service users and family members should be closely involved from the very beginning
- Family associations can contribute with funding and initiatives
- Champions can raise awareness about early psychosis
- Individual narratives of users and families that benefit from EIP programs can have a great impact

Economic, structural and administrative

- Embedding EIP services with publicly funded healthcare systems
- Payment mechanisms to promote development of EIP capacity
- Changing structures of health services, so contact is perceived as less stigmatizing
- Central coordination in countries with regional variability in healthcare
- Partnerships with professionals in administration, fundraising or marketing

Barriers

Research evidence

 Avoid thinking only at a clinical level;
consider an approach involving the mental healthcare system as a whole

Political

- Lack of political interest
- Lack or recognition of specific needs of patients with early psychosis

Communication and stakeholders

- Lack of effective communication with relatives, other health professionals and other professionals, such as school teachers
- Lack of effective communication with politicians and administrators

Economic, structural and administrative

- Constraints in public finances, insufficient funding
- Obstacles in healthcare system structure (e.l. emphasis on institutionalization)
- Poor coordination between mental health specialists and primary care
- Poor access to services
- Facilities poorly adapted to the needs of young people

References

- 1. McGorry PD, Killackey E, Yung A, America N. Early intervention in psychosis: concepts, evidence and future directions. *World Psychiatry*. 2008;7(3):148-156. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2559918&tool=pmcentrez&rendertype =abstract. Accessed November 21, 2014.
- 2. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association Between Duration of Untreated Psychosis and Outcome in Cohorts of First-Episode Patients. *Arch Gen Psychiatry*. 2005;62:975-983.
- 3. Fraguas D, Del Rey-Mejías A, Moreno C, et al. Duration of untreated psychosis predicts functional and clinical outcome in children and adolescents with first-episode psychosis: a 2-year longitudinal study. *Schizophr Res.* 2014;152(1):130-138. doi:10.1016/j.schres.2013.11.018.
- 4. Fraguas D, Merchán-Naranjo J, del Rey-Mejías Á, et al. A longitudinal study on the relationship between duration of untreated psychosis and executive function in early-onset first-episode psychosis. *Schizophr Res.* 2014;158(1-3):126-133. doi:10.1016/j.schres.2014.06.038.
- 5. Nordentoft M, Rasmussen JO, Melau M, Hjorthøj CR, Thorup A a E. How successful are first episode programs? A review of the evidence for specialized assertive early intervention. *Curr Opin Psychiatry*. 2014;27:167-172. doi:10.1097/YCO.00000000000052.
- 6. Marshall M, Lockwood A, Lewis S, Fiander M. Essential elements of an early intervention service for psychosis: the opinions of expert clinicians. *BMC Psychiatry*. 2004;4:17. doi:10.1186/1471-244X-4-17.
- 7. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull*. 1996;22(2):305-326. http://www.ncbi.nlm.nih.gov/pubmed/8782288. Accessed December 15, 2014.
- 8. Ten Velden Hegelstad W, Haahr U, Larsen TK, et al. Early detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study. *Schizophr Res*. 2013;143(2-3):337-343. doi:10.1016/j.schres.2012.10.027.
- 9. Dieterich M, Irving CB, Park B, Marshall M. Intensive case management for severe mental illness. *Cochrane database Syst Rev.* 2010;(10):CD007906. doi:10.1002/14651858.CD007906.pub2.
- 10. Melle I, Johannesen JO, Friis S, et al. Early Detection of the First Episode of Schizophrenia and Suicidal Behavior. *Am J Psychiatry*. 2006;163(5):800-804. doi:10.1176/ajp.2006.163.5.800.
- 11. Harris MG, Burgess PM, Chant DC, Pirkis JE, McGorry PD. Impact of a specialized early psychosis treatment programme on suicide. Retrospective cohort study. *Early Interv Psychiatry*. 2008;2(1):11-21. doi:10.1111/j.1751-7893.2007.00050.x.
- 12. Craig TKJ, Garety P, Power P, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*. 2004;329(7474):1067. doi:10.1136/bmj.38246.594873.7C.
- 13. Marshall M, Rathbone J. Early intervention for psychosis (Review). *Cochrane Database Syst Rev.* 2011;(6).
- 14. Petersen L, Jeppesen P, Thorup A, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331:602. doi:10.1136/bmj.38565.415000.E01.
- 15. Thorup A, Petersen L, Jeppesen P, et al. Integrated treatment ameliorates negative symptoms in first episode psychosis-results from the Danish OPUS trial. In: *Schizophrenia Research*. Vol 79.; 2005:95-105. doi:10.1016/j.schres.2004.12.020.
- 16. Jeppesen P, Petersen L, Thorup A, et al. Integrated treatment of first-episode psychosis: Effect of treatment on family burden: OPUS trial. *Br J Psychiatry*. 2005;187. doi:10.1192/bjp.187.48.s85.
- 17. Valmaggia LR, McCrone P, Knapp M, et al. Economic impact of early intervention in people at high risk of psychosis. *Psychol Med*. 2009;39(10):1617-1626. doi:10.1017/S0033291709005613.

- 18. Perez J, Jin H, Russo DA, et al. Clinical effectiveness and cost-effectiveness of tailored intensive liaison between primary and secondary care to identify individuals at risk of a first psychotic illness (the LEGs study): a cluster-randomised controlled trial. *The lancet Psychiatry*. 2015;2(11):984-993. doi:10.1016/S2215-0366(15)00157-1.
- 19. Albert N, Melau M, Jensen H, et al. Five years of specialised early intervention versus two years of specialised early intervention followed by three years of standard treatment for patients with a first episode psychosis: randomised, superiority, parallel group trial in Denmark (OPUS II). *BMJ*. 2017;356:i6681. http://www.ncbi.nlm.nih.gov/pubmed/28082379. Accessed July 19, 2017.
- 20. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry*. 1997;171:502-508. http://www.ncbi.nlm.nih.gov/pubmed/9519087. Accessed March 31, 2015.
- 21. Nordentoft M, Wahlbeck K, Hällgren J, et al. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PloS one [electronic Resour.* 2013;8(1):e55176-e55176. doi:10.1371/journal.pone.0055176.
- 22. Drake RE, Goldman HH, Leff HS, et al. Implementing evidence-based practices in routine mental health service settings. *Psychiatr Serv*. 2001;52(2):179-182. http://www.ncbi.nlm.nih.gov/pubmed/11157115. Accessed December 20, 2014.
- 23. Monroe-DeVita M, Teague GB, Moser LL. The TMACT: a new tool for measuring fidelity to assertive community treatment. *J Am Psychiatr Nurses Assoc*. 2011;17(1):17-29. doi:10.1177/1078390310394658.
- 24. Hughes F, Stavely H, Simpson R, Goldstone S, Pennell K, McGorry P. At the heart of an early psychosis centre: the core components of the 2014 Early Psychosis Prevention and Intervention Centre model for Australian communities. *Australas Psychiatry*. 2014;22(3):228-234. doi:10.1177/1039856214530479.
- 25. History Orygen, The National Centre of Excellence in Youth Mental Health. https://www.orygen.org.au/About/History. Accessed July 20, 2017.
- 26. Who we are: Headspace. https://headspace.org.au/about-us/who-we-are/. Accessed July 20, 2017.
- 27. Csillag C, Nordentoft M, Mizuno M, et al. Early intervention services in psychosis: from evidence to wide implementation. *Early Interv Psychiatry*. 2016;10(6):540-546. doi:10.1111/eip.12279.
- 28. Department of Health. A National Service Framework for Mental Health. London; 1999.
- 29. Department of Health. The Mental Health Policy Implementation Guide. London; 2001.
- 30. Mental Health Network Nhs Confederation. IRIS Guidelines Update September 2012. 2012;(September):1-32.
- 31. Pinfold V, Smith J, Shiers D. Audit of early intervention in psychosis service development in England in 2005. *Psychiatr Bull.* 2007;31:7-10.
- 32. Psychosis and Schizophrenia in Adults: Prevention and Management | Guidance and Guidelines | NICE. London: NICE; 2014.
- 33. Crisp N, Smith G, Nicholson K. *Old Problems, New Solutions Improving Acute Psychiatric Care for Adults in England.*; 2016. http://www.rcpsych.ac.uk/pdf/Old_Problems_New_Solutions_CAAPC_Report_England.pdf.
- 34. NHS England, the National Collaborating Centre for Mental Health, National Institute for Health and Care Excellence. Implementing the Early Intervention in Psychosis Access and Waiting Time Standard: Guidance. 2016:57. https://www.england.nhs.uk/mentalhealth/wp-content/uploads/sites/29/2016/04/eip-guidance.pdf.
- 35. Royal College Psychiatrist. *Audit of Early Intervention in Psychosis.*; 2016. http://www.rcpsych.ac.uk/workinpsychiatry/qualityimprovement/nationalclinicalaudits/earlyinterventionpsychosis.aspx. Accessed August 31, 2017.
- 36. Psymaptic Psychiatric Mapping Translated into Innovations for Care. http://www.psymaptic.org/. Accessed December 27, 2014.
- 37. Danske Regioner. Pakkeforløb for Incident Skizofreni (in Danish). 2016.
- 38. Vylder JD. Police victimization increases risk for psychotic experiences: Data from 4 U.S. cities. *Early*

- Interv Psychiatry. 2016;10(S1):67. doi:10.1111/eip.12396.
- 39. About RAISE ETP. https://raiseetp.org/. Accessed March 31, 2015.
- 40. Robert H, Patrick M, Nordentoft M. Plenary Session. Raise 2.0 Establishing a National Early Psychosis Intervention Network in the U.S. *Early Interv Psychiatry*. 2016;10(S1):4. doi:10.1111/eip.12394.
- 41. Iyer S, Jordan G, MacDonald K, Joober R, Malla A. Early Intervention for Psychosis. *J Nerv Ment Dis.* 2015;203(5):356-364. doi:10.1097/NMD.00000000000288.
- 42. Nolin M, Malla A, Tibbo P, Norman R, Abdel-Baki A. Early intervention for psychosis in Canada: What is the State of Affairs? *Can J Psychiatry*. 2016;61(3):186-194. doi:10.1177/0706743716632516.
- 43. Fiorillo A, Sampogna G, Del Vecchio V, et al. What is the current status of training and practice of early intervention in psychiatry? Results from a survey in 35 countries. *Early Interv Psychiatry*. 2015;9(1):70-75. doi:10.1111/eip.12085.
- 44. Hewlett E, Moran V. Making Mental Health Count: The Social and Economic Costs of Neglecting Mental Health Care, OECD Health Policy Studies.; 2014.
- 45. Mcdaid D, Park A-L. Counting all the costs: the economic impact of co-morbidity. In: *Comorbidity of Mental and Physical Disorders*. Basel: Karger; 2015:23-32.
- 46. Mizuno M, Nemoto T, Tsujino N, Funatogawa T, Takeshi K. Early psychosis in Asia: Insights from Japan. *Asian J Psychiatr*. 2012;5(1):93-97. doi:10.1016/j.ajp.2012.02.004.
- 47. Mizuno M, Suzuki M, Matsumoto K, et al. Clinical practice and research activities for early psychiatric intervention at Japanese leading centres. *Early Interv Psychiatry*. 2009;3:5-9. doi:10.1111/j.1751-7893.2008.00104.x.
- 48. Arango C, Bernardo M, Bonet P, et al. Cuando la asistencia no sigue a la evidencia: el caso de la falta de programas de intervención temprana en psicosis en España. *Rev Psiquiatr y Salud Ment*. 2017;10(2):78-86. doi:10.1016/j.rpsm.2017.01.001.
- 49. Fundación Manantial. http://www.fundacionmanantial.org/en/quienes-somos-areas.php.
- 50. Pelayo-Terán JM, Gajardo Galán VG, de la Ortiz-García de la Foz V, et al. Rates and predictors of relapse in first-episode non-affective psychosis: a 3-year longitudinal study in a specialized intervention program (PAFIP). *Eur Arch Psychiatry Clin Neurosci*. October 2016. doi:10.1007/s00406-016-0740-3.
- 51. Crespo-Facorro B, de la Foz VO-G, Ayesa-Arriola R, et al. Prediction of acute clinical response following a first episode of non affective psychosis: results of a cohort of 375 patients from the Spanish PAFIP study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;44:162-167. doi:10.1016/j.pnpbp.2013.02.009.
- 52. Hospital Gregorio Marañón Programa Piensa. http://www.madrid.org/cs/Satellite?cid=1354258504306&language=es&pagename=HospitalGregori oMaranon%252FPage%252FHGMA_contenidoFinal.
- 53. Calvo A, Moreno M, Ruiz-Sancho A, et al. Psychoeducational Group Intervention for Adolescents With Psychosis and Their Families: A Two-Year Follow-Up. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):984-990. doi:10.1016/j.jaac.2015.09.018.
- 54. McDaid D, Park A, lemmi V, et al. Growth in the use of early intervention for psychosis services: An opportunity to promote recovery amid concerns on health care sustainability. *London Sch Econ*. 2016;(January).
- 55. Cocchi A, Cavicchini A, Collavo M, et al. Implementation and development of early intervention in psychosis services in Italy: a national survey promoted by the Associazione Italiana Interventi Precoci nelle Psicosi. *Early Interv Psychiatry*. September 2015:n/a-n/a. doi:10.1111/eip.12277.
- 56. From Clinical Intervention to Health System Implementation IEPA 10. http://www.iepaconference.org/program/sponsored-symposium/. Published 2016. Accessed December 7, 2016.
- 57. Ruggeri M, Bonetto C, Lasalvia A, et al. Feasibility and Effectiveness of a Multi-Element Psychosocial Intervention for First-Episode Psychosis: Results From the Cluster-Randomized Controlled GET UP PIANO Trial in a Catchment Area of 10 Million Inhabitants. *Schizophr Bull*. 2015;41(5):1192-1203.

- doi:10.1093/schbul/sbv058.
- 58. Hastrup LH, Kronborg C, Bertelsen M, et al. Cost-effectiveness of early intervention in first-episode psychosis: Economic evaluation of a randomised controlled trial (the OPUS study). *Br J Psychiatry*. 2013;202:35-41. doi:10.1192/bjp.bp.112.112300.
- 59. Radhakrishnan M, McCrone P, Lafortune L, et al. Cost-effectiveness of early intervention services for psychosis and fidelity to national policy implementation guidance. *Early Interv Psychiatry*. August 2017. doi:10.1111/eip.12481.
- 60. Tsiachristas A, Thomas T, Leal J, Lennox BR. Economic impact of early intervention in psychosis services: results from a longitudinal retrospective controlled study in England. *BMJ Open*. 2016;6(10):e012611. doi:10.1136/bmjopen-2016-012611.
- 61. McCrone P, Knapp M, Dhanasiri S. Economic impact of services for first-episode psychosis: a decision model approach. *Early Interv Psychiatry*. 2009;3(4):266-273. doi:10.1111/j.1751-7893.2009.00145.x.
- 62. Park A-L, McCrone P, Knapp M. Early intervention for first-episode psychosis: broadening the scope of economic estimates. *Early Interv Psychiatry*. 2014;(June 2010):1-8. doi:10.1111/eip.12149.
- 63. McDaid D, Park A-L. *Comorbidity of Mental and Physical Disorders*. Vol 179. (Sartorius N, Holt RIG, Maj M, eds.). Basel: S. KARGER AG; 2014. doi:10.1159/000365941.