

Title: Early intervention for incipient insanity: early notions from the 19th century English literature

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Abstract

Aim: Early intervention programs in mental illnesses started to bloom in the 1990s and they have been established worldwide during the past twenty years. However, the concept of early intervention has emerged during the 19th century but it did not receive much attention. The aim of this review is to identify the difficulties appeared during that period of time which could provide insight into the modern development of early intervention initiatives.

Methods: A narrative review which focused on English literature about early intervention for insanity during the 19th century was undertaken.

Results: Some physicians during the 19th century recognized that treatment would be the most effective at the early stage of the mental illness and they had emphasized the importance of early intervention. However, due to a number of factors, such as the limited use of asylums, people's lack of knowledge about mental disorder and the timely quest of effective treatment, the development of early intervention did not attract much attention during that period of time.

Conclusion: During the past two hundred years, understanding toward mental illness has advanced and more effective treatments, such as the use of anti-psychotic medications, have been developed. Reflecting on the past experience and difficulties might shed light on the refinement of today early intervention in mental disorder.

Keywords: Early intervention, psychopathology, psychotherapy.

Introduction

Early intervention programs have been established to alleviate the impact of mental illnesses such as psychosis. They specifically aim at identifying and treating emerging mental disorders at the earliest opportunity. Previous research has suggested that these programs lead to better long-term outcome because some factors active in the early stage of illnesses may be malleable to interventions.¹

The modern era of early intervention efforts began around the 1990s with pioneering early intervention programs such as the EPPIC program in Melbourne and an early-identification-and-treatment program in Norway.²⁻³ These initiatives were rooted in the view that delayed treatment of psychosis is associated with less satisfactory clinical outcome, as evidenced by observations reporting the relationship between poor outcome and long duration of untreated psychosis (DUP). Early intervention has been suggested to produce better treatment response⁴ and reduce long-term morbidity.⁵ On the other hand, a longer duration of illness prior to treatment was associated with a longer time to remission.⁶ Such findings provided a compelling rationale for the development of early intervention programs in many localities around the world over the past two decades. Some examples included the Prevention and Early intervention Programme for Psychoses (PEPP) in Canada,⁷ the Lambeth Early Onset (LEO) Team in the United Kingdom,⁸ the Early Psychosis Intervention Program (EPIP) in Singapore,⁹ the Early Assessment Service for Young People with Psychosis (EASY) in Hong Kong,¹⁰ and an intensive early intervention program (the OPUS trial) in Denmark.¹¹

In view of recent developments in these intervention programs, the historical origins of the concept of “early intervention” deserve more attention. At the end of the 18th century, psychiatry as a medical specialty caring for mental disorders was beginning to emerge in Europe; however, understanding of mental disorders was rudimentary.¹² There were few efforts to systematically classify mental illnesses; most serious conditions were grouped under “insanity” that was either present or absent.^{13 -14} As a result of this dichotomous approach, patients were not recognized as “insane” until their symptoms had become entrenched; at this point, their disorders had probably been deteriorating for some time. The national statistics in the 1820s showed that only a small proportion of patients were admitted to asylums in England, one of the reasons was that asylums had mainly played a custodial role.¹² Despite these predicaments, the idea that mental disorders were divisible into a number of symptoms which could combine to give rise to different disorders began to take shape.^{13,15}

In this historical context, whether the idea of early intervention of insanity had been considered by practitioners during this period becomes an important issue. If the ideas were present, it would then be important to examine what obstacles had led to the subsequent abatement of this approach until recently. In this context, an exposition of the ideas and practice in relation to early intervention in the late 19th century is important.

An initial exploration revealed that by the end of 19th century, a number of psychiatrists, such as William Charles Ellis, had expressed concerns over the situation that for many patients admitted to the asylums, “the golden opportunity to receive treatment had already been missed”.¹⁶ Since scientific evidence and cohort studies were sparse at that

time, notions were largely based on clinical impressions. Contemporary clinicians believed that insanity in the early stage was different from chronic insanity in terms of curability; and that applying treatments at early stage of disorders might slow down or even stop deterioration. This concept was based on observations that many mental illnesses generally progress and deteriorate if no intervention was given.⁵

This article reviews the English-language literature regarding the notion of early intervention for insanity in the 19th century. By examining the evolution of this important concept, it is hoped that the issues and difficulties that appeared during that period could be identified and understood, thus shed light on the modern development of the early intervention initiatives.

Views towards insanity and its causes at the beginning of the 19th century

Before the 19th century, there was no recognizable descriptive psychopathology and insanity was simply understood as an “all-or-none” condition; a systematic descriptive psychopathology did not appear until the late 19th century.¹⁷ Definition of insanity and its symptoms has never been easy because this disorder exhibits itself in various forms. Due to its diversity, some contemporaneous physicians, such as Arnold, pointed out that different varieties of insanity required different methods of cure.¹⁸

Since the 18th century, the belief that abnormal mental states and behavioral patterns are the result of brain diseases have become generally accepted.¹⁹ During the 19th century, more sophisticated notions about the causes of insanity have been proposed. For example, multiple aetiological factors involving both bodily causes and mental causes have been described; the former includes brain abnormality and other physical issues, the latter

included psychological factors such as “over-application of mind” and “excesses of passion”.¹⁸ Based on the observation that a particular form of mental disorder seemed to be transmitted in families, Prichard pointed out that the condition is hereditary;²⁰ Ellis expressed a similar view.²¹ It was proposed that some of the causes of mental disorders are “capable of removal”, provided this could be done with “proper caution and attention to the natural constitution”.²¹ Even for the individuals who inherited a liability to such diseases, they “ought most carefully to avoid those circumstances which will have a tendency to produce (the disorders)”.²¹ In Arnold’s book of 1806, he devoted an entire chapter to the prevention of insanity; examples of his suggestions included “exercise, self-regulation of emotions, attention to the operations of the imagination and rational views of religion”.¹⁸

Views towards “incipient insanity” and “early intervention” in 19th century

From the 19th century literature, it is apparent that physicians generally had the idea that, without any treatment, mental illnesses would deteriorate over time. This view is implicit in their suggestions that patients should be admitted to asylums to receive medical remedies as soon as possible.

Prichard has expressed that “the ultimate tendency of insanity is to pass into a state of mental decay... but before the transition into this deplorable state has completely taken place, there is, in most cases of protracted mental derangement, a stage of uncertain duration...”.²⁰ He had the idea that transitions would be observed in mental disorders as the condition pursued its deteriorating course.

Ellis proposed that insanity can be divided into two classes; “incipient insanity” and “chronic insanity”.²¹ He emphasized that “relief of symptoms, or even cure, should only be

expected when the disorder is incipient”; this was based on his idea that it would be “impossible to restore mental manifestations once brain lesion takes place”.²¹ It could be seen that Ellis believed that in patients with chronic insanity, the disorder has resulted in irreversible damages of the brain.

Esquirol also viewed insanity in terms of different stages and subtly underscored the earliest stage. He wrote that insanity has its period of incubation; “and often in the history given by friends, it is discovered that the first act of insanity which frightened them, had been preceded by many symptoms, which escaped all observation”.²² The state that he described could be understood as the prodromal phase of mental illness. A similar view is observed from Winslow, who raised the concern that many symptoms of cerebral disorder had escaped observation before development of the disease started.¹⁶ He also put forward the idea that the majority of cases of mental disorders would have been cured had they been treated in the early stage.¹⁶

It could be concluded that the 19th century psychiatric writings did recognize the critical nature of incipient insanity and the importance of treating this disease at an early stage. However, despite these opinions from experts in the field of mental health, little progress was made on early intervention in 19th century.

Treatments of insanity in 19th century

Historians of psychiatry had suggested different perspectives regarding the role of treatment in the 19th century. One view was that asylums had primarily a custodial function.¹² However, others emphasized efforts in therapeutic treatment of the mental condition.²³⁻²⁴ Treatments of mental disorders could be broadly grouped into two

categories: “therapeutical treatment” and “moral treatment”; the former focused on the physical and the latter focused on psychological causes of insanity.¹⁹⁻²⁰ The development and the uses of these treatments were based on the contemporaneous physicians’ observations and understanding of the aetiology of mental illness.

Physical treatment

A wide variety of medicines had been employed for different purposes. For example, purgatives or laxatives were used because intestinal problems were viewed as related to some cases of insanity, emetics and digitalis were used to induce vomiting and to control “the maniacal excitement” in patients.²⁰ Bleeding was also a treatment that was usually resorted to in order to remove the excess blood from patients’ sanguineous circulation since insanity was believed to be related to heightened circulation of blood.²⁰⁻²² Cold application had also been used in treating maniacal diseases as maniacs were said to be “consumed by an internal heat”.^{21, 22, 25}

Given such wide range of medicinal treatments at that time, opinions were mixed among physicians at that time.²⁰⁻²¹ Ellis emphasized that they might not be always effective when the mental disorders were unrelated to physical causes. In order to treat the diseases arose from psychological factors, “moral remedies” would be required.²¹

Moral Treatment

As defined by Carlson and Dain, moral treatment referred to “therapeutic efforts which affected the patient’s psychology”.²⁶ Tuke stated that “if the opinion that the disease originates in the mind, applications made immediately to it... are the most likely to be

attended with success”.²⁵ Ellis mentioned similar view by suggesting that “(in the cases induced by moral causes,) the grand object to be attained, with a view to ultimate cure, is the removing the cause by moral treatment”.²¹ Tuke suggested employing the principle of fear in the management of patients; he believed that when a sufficient level of fear is excited, “madness is capable of entire control”.²⁵ However, it was emphasized that “fear should never be excited exceedingly, such as with chains and corporal punishments”.²⁵ While physical force was originally the only means to keep psychotic patients in control, milder methods were suggested in the early 18th century and they were believed to be effective as well.²⁰ Tuke’s suggestion of providing the patients with a humane environment and treatment became the cornerstone of the changes in the care and environment provided to patients with mental illnesses during the first half of the 19th century.²⁷

Difficulties of launching early intervention for insanity in 19th century

During 19th century, conditions for admission to the asylums were set out by the Lunacy Act; patients had to be certified as insane before they could be admitted to asylums, a compulsory reception order was also required from a local magistrate.²⁸ It was observed that not only the patients’ families and friends, but also the magistrates, showed reluctance to send the patients to asylums even though they had received a certificate of insanity from the doctors.¹⁶ Many early cases thus went untreated and by the time the patients were admitted to asylums, they often “become incurable, and remain in the asylum for life”.¹⁶

Apart from the rarity of admission of incipient patients to the asylums, another reason of treatment delay laid in patients and people around them. Esquirol wrote that “the insane often combat their false ideas and unusual determinations, before any one perceives

the disorder of their reason, and the internal struggle which precedes the outbreak of insanity".²² From the perspectives of people around the patients, the symptoms might be regarded as "healthy exaggerations, eccentricities or extravagances of natural conditions of thought" instead of abnormal mental states relating to the brain.¹⁶ Even though people interacting with the patients might have observed their changed behavioral patterns and mental states, "mental disorder" was seldom the first explanations that came up to their minds to account for such changes. Since people at that time did not have much understanding toward insanity, many patients were probably left untreated during 19th century.

Psychiatrists during the 19th century had already remarked upon the possible consequences of delays in treatments and advocated early intervention of mental disorders. Ellis, who wrote the third report of the Hanwell County Lunatic Asylum for 1833, pointed out that "the neglect of proper remedies in the early stages of the disease" had led to irreversible impairment in patients' brains, by the time such situation occurred, the cases often became incurable.¹⁶

During the 19th century, patients seldom received timely intervention during their incipient insanity. The lack of effective treatment is potentially another factor which hindered early intervention efforts. Despite a wide variety of treatment methods proposed, there was no systematically robust method to ascertain efficacy.

Since some physicians at that time applied different treatments to the patients, by the time they had found a relatively effective method, a long period of time had often elapsed. One of the cases described in Esquirol's book demonstrated this situation; a female

patient's condition did not ameliorate until more than a year after her admission to the asylum.²² During that period of time, Esquirol tried different treatments, such as application of tepid baths, laxative drinks and blister, however, no appreciable effect was observed.²² This type of cases illustrated that during the 19th century, and in some cases even today, the quest for workable treatments could sometimes be a lengthy process in itself.

Early intervention for psychosis nowadays

The quest for effective treatment did not cease and new doctrines emerged from time to time. One of the important trend in the early 20th century was a notable increase in popularity of psychoanalytic approaches, which emphasized the role of early psychological (especially psychosexual) factors on formation of mental illness.²⁹ The notion of psychoanalysis was popular among the educated classes in Europe and the United States and it was the mainstream psychotherapy employed at that time.²⁹ Despite its growing prevalence, there were skepticisms about both the simplified account for the causation of mental illness, as well as the effectiveness of the approach.²⁹ Eysenck, a German psychologist, evaluated the outcome of different types of psychotherapies used during the early 20th century; one of his conclusions was that there was no evidence that psychoanalysis significantly facilitated patients' recovery.³⁰ Nevertheless, with the further development of psychoanalytic practice in private clinics, the emphasis of psychiatry had shifted from psychotic disorders to milder anxiety and mood disorders.²⁹ This trend, together with the lack of effective treatment, left the idea of early intervention for psychosis neglected for decades, until interest toward it grew again in the 1980s.³¹

Strong initiatives advocating the concept of early intervention of psychosis emerged as understanding towards the natural course of psychotic illness increased. For instance, a review conducted by Wyatt showed that early intervention with anti-psychotic medications in psychotic patients could reduce long-term morbidity;⁵ another study showed similar result, first-episode patients were found to have a better treatment outcome than chronic patients.³² Based on the hypothesis that influences during early phase of psychosis show better effect, Birchwood emphasized the importance the “critical period”.³³ Hence, a growing number of early intervention programs have been developed since the 1990s, evidence of their efficacies in improving clinical outcome is emerging. For example, the TIPS study in Norway and the EPIP in Singapore demonstrated a significant reduction in DUP after commencement of local early intervention programs.^{9,34} The OPUS trial in Denmark found that comparing with patients receiving standard treatment, those who received integrated treatment achieved a better clinical outcome.¹¹ Another early intervention project in Sweden showed that first-episode psychotic patients who received “need-specific treatment” had a better symptomatic and functional outcome than a historical group of patients who received standard care.³⁵

There are still challenges in putting early intervention into practice in the modern era.³⁶ Since one of the prerequisites of this concept is to identify incipient features in patients, the problem of false positives may arise; many people who do not need psychiatric care might be referred.³⁷⁻³⁸ The costs and benefits of interventions at this stage are also much debated currently.³⁹ A recent study analyzed the cost-effectiveness of the intensive early-intervention program in Denmark (OPUS), no significant difference was found between the costs of early intervention and standard treatment.⁴⁰⁻⁴¹ As Csillag et al.

argued that the evidence of the benefits of early intervention programs is still inconclusive currently, more analyses on the implementation of the services are needed before reaching a conclusion.⁴²

Conclusion

We took a retrospective view of the ideas of early intervention for insanity by reviewing English language literature during the 19th century. A number of common themes that are emphasized in modern early intervention approaches have already been proposed in the early developments of mental health care. Concerns over delays in treatment of insanity have been clearly voiced. The notion of delivering treatment as early as the mental illness commences has been in existence at that time. At the core of these ideas lies the belief that early symptoms are less intractable, but if neglected, could give rise to deteriorations that are less malleable at a later stage. This idea is consonant with the concept of critical period in modern early intervention theories.

It could be observed that the difficulties in embarking on early intervention of psychoses could be grouped under three dimensions; i.e. lack of efficacious treatment facilities to manage people with early symptoms of psychosis, admission to asylums was a last resort, the lack of understanding toward insanity in patients and in people around them, effective treatments were also not available to clinicians then. These limitations resulted in a generally late commencement of treatments, perpetuating an impression that insanity was a chronic and hardly curable disease. During the past two hundred years, major advancements have been made in the understanding toward the aetiology of mental illnesses and robust treatment programs combining pharmaceutical and psychosocial

interventions have been developed. However, there are still gaps and needs for refinements in carrying out early intervention of psychosis in the 21st century, such as lack of appropriate treatment settings, pessimistic views of outcome, and negative perception of mental health services. Reflecting upon modern early intervention efforts in the context of past ideas and approaches provides an important perspective that may shed light on somewhat neglected continuity between early and modern aspirations in better health care for the early stages of psychotic disorders.

Table 1. Onset of mental illness as described by authors in the 19th century.

Year	Author	Description of illness onset
1837	J. C. Prichard	The course of mental illness is a process of mental decay. Early symptoms, including impaired memory, judgement and attention, could be regarded as the prelude of the state of dementation (p.66). ²⁰ Symptoms of different forms of insanity are not noticeably distinct from each other at the onset of illness (p. 67). ²⁰
1838	W. C. Ellis	Insanity is divided into “incipient insanity” and “chronic insanity”; the illness is possible to be treated in the former while irreversible damages are established in the latter (p. 147). ²¹
1845	E. Esquirol	Mental illness starts with a period of incubation during which early symptoms are prone to be overlooked. The early indication of the illness might be a change of habits, preferences and passions (pp. 54-55). ²²
1860	F. Winslow	Early symptoms, such as deviations from healthy thought, impairment of intelligence and trivial loss of motor ability often escape observation (p. 27). However, this is the stage at which “easy and speedy cure” could be expected if treatment is delivered (p.80). ¹⁶

Reference

1. Marshall M, Rathbone J. Early Intervention for Psychosis. *Schizophrenia Bulletin* 2011; 37: 1111-1114.
2. Larsen TK, McGlashan TH, Moe LC. First-episode schizophrenia: I. Early course parameters. *Schizophrenia Bulletin* 1996; 22: 241-256.
3. McGorry PD, Edwards J, Mihalopoulos C et al. EPPIC: An evolving system of early detection and optimal management. *Schizophrenia Bulletin* 1996; 22: 305-326.
4. Lieberman J, Jody D, Geisler S et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry* 1993; 50: 369-376.
5. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin* 1991; 17:325-351.
6. Loebel AD, Lieberman JA, Alvir JMJ et al. Duration of psychosis and outcome in first-episode schizophrenia. *The American Journal of Psychiatry* 1992; 149: 1183-1188.
7. Malla A, Norman R, McLean T et al. A Canadian programme for early intervention in non-affective psychotic disorders. *Australian and New Zealand Journal of Psychiatry* 2003; 37: 407-413.
8. Craig TKJ, Garety P, Power P et al. The Lambeth Early Onset (LEO) Team: randomized controlled trial of the effectiveness of specialized care for early psychosis. *BMJ* 2004; 329: 1067
9. Chong SA, Mythily S, Verma S. Reducing the duration of untreated psychosis and changing help-seeking behaviour in Singapore. *Social Psychiatry and Psychiatric Epidemiology* 2005; 40: 619-621.

10. Chen EYH. Developing an early intervention services in Hong Kong. In: Ehmann T, MacEwan GW, Honer WG, eds. *Best Care in Early Psychosis Intervention: Global Perspectives*. London: Taylor & Francis, 2004; 125-130.
11. Petersen L, Jeppesen P, Thorup A et al. A randomized multicenter trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ* 2005; 331: 602.
12. Shorter E. *A history of psychiatry: From the era of the asylum to the age of Prozac*. John Wiley & Sons, Inc.; 1997. Chapter 1, The birth of psychiatry; p.1-8.
13. Berrios GE, Luque R, Villagrán JM. Schizophrenia: A conceptual history. *International Journal of Psychology and Psychological Therapy* 2003; 3: 111-140.
14. Berrios GE. Epilepsy and insanity during the early 19th century. *Arch Neurology* 1984; 41: 978-981.
15. Berrios GE. Classifications in psychiatry: a conceptual history. *Australian and New Zealand Journal of Psychiatry* 1999; 33: 145-160.
16. Winslow F. *On obscure diseases of the brain, and disorders of the mind: their incipient symptoms, pathology, diagnosis, treatment, and prophylaxis*. Philadelphia: Blanchard & Lea; 1860
17. Berrios GE. Descriptive psychiatry and psychiatric nosology during the nineteenth century. In: Wallace ER, Gach J, eds. *History of Psychiatry and Medical Psychology*. New York: Springer, 2008; 353-379.
18. Arnold T. *Observations on the nature, kinds, causes, and prevention, of insanity*, Vol. II. 2nd edn. London: Richard Phillips; 1806.

19. Bynum WF. Rationales for therapy in British psychiatry: 1780-1835. *Medical History* 1964; 18: 317-334.
20. Prichard JC. A treatise on insanity and other disorders affecting the mind. Philadelphia: Haswell, Barrington, and Haswell; 1837.
21. Ellis WC. A treatise on the nature, symptoms, causes, and treatment of insanity with practical observations on lunatic asylums, and a description of the pauper lunatic asylum for the county of Middlesex, at Hanwell, with a detailed account of its management. London: Samuel Holdsworth, Amen Corner, Paternoster Row; 1838.
22. Esquirol E. Mental maladies; a treatise on insanity [E. K. Hunt, trans]. Philadelphia: Lea and Blanchard; 1845.
23. Wright D. Getting out of the asylum: understanding the confinement of the insane in the nineteenth century. *Social history of medicine* 1997; 10: 137-155.
24. Scull A. The insanity of place/the place of insanity: essays on the history of psychiatry. London and New York: Routledge; 2006.
25. Tuke S. Description of the Retreat, an institution near York, for insane persons of the Society of Friends: containing an account of its origin and progress, the modes of treatment, and a statement of cases. York: W. Alexander; 1813.
26. Carlson ET, Dain N. The Psychotherapy that was moral treatment. *The American Journal of Psychiatry* 1960; 117: 519-524.
27. Borthwick A, Holman C, Kennard D et al. The relevance of moral treatment to contemporary mental health care. *Journal of Mental Health* 2001; 10: 427-439.
28. Killaspy H. From the asylum to community care: learning from experience. *British Medical Bulletin* 2006; 79 & 80: 245-258.

29. Shorter E. A history of psychiatry: From the era of the asylum to the age of Prozac. John Wiley & Sons, Inc.; 1997. Chapter 5, The psychoanalytic hiatus; p.145-189.
30. Eysenck HJ. The effects of psychotherapy: an evaluation. *Journal of Consulting Psychology* 1952; 16: 319-324.
31. McGorry PD. An overview of the background and scope for psychological interventions in early psychosis. In: Gleeson JFM, McGorry PD, eds. *Psychological Interventions in Early Psychosis: A Treatment Handbook*. Chichester: John Wiley & Sons Ltd, 2004; 1-22.
32. Lieberman JA, Alvir MJ, Woerner M et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophrenia Bulletin* 1992; 18: 351-371.
33. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *The British journal of psychiatry* 1998; 172: 53-59.
34. Larsen TK, McGlashan TH, Johannessen JO et al. Shortened duration of untreated first episode of psychosis: changes in patient characteristics at treatment. *The American Journal of Psychiatry*; 158: 1917-1919.
35. Cullberg J, Mattsson M, Levander S et al. Treatment costs and clinical outcome for first episode schizophrenia patients: a 3-year follow-up of the Swedish 'Parachute Project' and two comparison groups. *Acta Psychiatrica Scandinavica* 2006; 114: 274-281.
36. McGorry PD, Yung AR. Early intervention in psychosis: an overdue reform. *Australian and New Zealand Journal of Psychiatry* 2003; 37: 393-398.
37. Yung AR, McGorry PD, McFarlane CA et al. Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin* 1996; 22: 283-303.

38. Warner R. Problems with early and very early intervention in psychosis. *British Journal of Psychiatry* 2005; 187: s104-s107.
39. Mihalopoulos C, Harris M, Henry L et al. Is Early Intervention in Psychosis Cost-Effective Over the Long Term? *Schizophrenia Bulletin* 2009; 35: 909-918.
40. Hastrup LH, Kronborg C, Bertelsen M et al. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomized controlled trial (the OPUS study). *British Journal of Psychiatry* 2013; 202: 35-41.
41. Nordentoft M, Melau M, Iversen T et al. From research to practice: how OPUS treatment was accepted and implemented throughout Denmark. *Early Intervention in Psychiatry* 2015; 9: 156-162
42. Csillag C, Nordentoft M, Mizuno M et al. Early intervention services in psychosis: from evidence to wide implementation. *Early Intervention in Psychiatry* 2015.