

Early Intervention in the Prodrome of Psychosis

Clare Holt, 1. Sophie Butler 1, Mark Agius 2, 3

1. Eastern Deanery, 2. Department of Psychiatry University Of Cambridge, 3. SEPT: South Essex Partnership University NHS Foundation Trust.

Abstract

One approach to intervening early in a psychotic illness is to initiate appropriate treatment in the prodromal phase of the illness with the aim to prevent or delay the first psychotic episode. Although still somewhat experimental, due to the growing evidence base, a number of clinics dedicated to this approach have been set up. We describe the identification of the prodrome, and explore the present evidence for its treatment.

Keywords: psychosis, prodrome, at risk mental states, medication, psychological interventions

Background

The prodrome can be considered either the earliest form of a psychotic disorder, or a syndrome conferring increased vulnerability to psychosis, i.e. an 'at-risk mental state' or 'precursor state'. This phase of the illness has achieved significant attention because it is a potential target for improving the outcome of psychosis. The aim is to prevent the patient from developing the first psychotic episode through appropriate interventions (1-3).

Early intervention depends not only on suitable treatment options but also on the correct identification of this phase. The features of the prodrome (if present) are variable and non-specific and it can most easily be defined retrospectively: it can therefore be difficult to identify it in a predictive way. The development of preventive strategies requires a shift to a more prospective framework. This can be done by observing the onset of a psychotic illness and observing how the symptom pattern of psychosis changes with time.

The Prodromal symptoms which are most commonly described in first episode studies, in descending order of frequency, include the following (4).

- Reduced concentration, attention.
- Reduced drive and motivation, anergia.
- Depressed mood.
- Sleep disturbance.
- Anxiety.
- Social withdrawal.
- Suspiciousness.
- Deterioration in role functioning.
- Irritability.

There are not discrete diagnostic indicators for this phase as these symptoms are not specific to psychosis and estimates of the duration of the prodrome vary from a mean of two years (4) up to 5 years (5). Various scales have been created in an effort to identify progression of prodromal symptoms and stratify patients at risk. These look at symptom development as well as a variety of behavioural, emotional, and environmental factors.

In recent years, rating scales, such as CAARMS (developed by McGorry and Yung's team in Melbourne), SIPS, and SOPS (Developed by McGlashan's team in Yale) have been developed for patients at ultra high risk and hence aid the investigation into the point of conversion to full-blown psychosis (6-8). McGorry and Yung (8) also introduced the term 'At Ultra

High Risk of Developing Psychosis', as a way of designating prospectively patients who appeared to be in the prodromal stage of psychosis. Yung was able, by using the criteria developed for use with her CAARMS scale – including a strong family history of psychosis, attenuated signs of psychotic symptoms, and Brief Limited Episodes of Psychosis (Blips) – to identify a group of patients 40% of whom were likely to become fully psychotic within 12 months (8).

German colleagues tend to divide the prodrome into phases. According to Wolbrock (9), the late initial prodromal state (LIPS) is characterised by more overt psychotic symptoms such as ideas of reference and paranoid ideation. This is in contrast to the early initial prodromal state (EIPS) which involves vaguer symptoms such as thought disturbances along with a known family history of schizophrenia or peri/pre-natal complications.

Various studies have been carried out to identify interventions that might delay the onset of full-blown psychosis in patients in the late phase of the prodrome. Our group recently carried out a meta-analysis of all the trials of treatment in the prodrome of schizophrenia (10,11). The treatments studied are summarised in the table 1 below:

Table 1

Paper	Year	Intervention	Control
McGorry et al 12	2002	Risperidone + CBT	Needs based Tx (antidepressants + psychotherapy, not antipsychotic)
Woods et al 13	2007	Aripiprazole	No control
Morrison 14	2002	CBT	Non-patient population
Morrison 15	2004	CBT	Monitoring
Nordentoft 16	2006	"Integrated care"	Standard Copenhagen Care
Nordentoft 16	2006	"Integrated care"	Standard Copenhagen Care
McGlashan 17,18	2006	Olanzapine	Placebo
Cornblatt 19,20	2007	Antidepressants	2nd Gen Antipsychotic
Bechdoff 21	2007	CBT	Supportive counselling
Berger 22	2007	Omega3-fatty acids	Placebo
Ruhrmann et al 23	2007	Amisulpride	Needs-focussed intervention
Amminger et al 24	2007	Omega3-fatty acids	Placebo

The interventions were wide-ranging – from pharmacological treatments such as antipsychotics or antidepressants to non-pharmacological methods such as CBT. Of the studies listed above, two were excluded from the meta-analysis – Woods et al (13) and Morrison et al (14) – because there was a lack of an adequate control. With the exception of the study using olanzapine (17), the remaining studies reached statistical significance (i.e. $p < 0.05$) with respect to slowing down the conversion to acute psychosis. Even the olanzapine study 'tended towards significance', indicating that this drug may also have a role in the treatment of patients during the prodrome.

Clearly the idea that intervention in the prodrome may improve the overall prognosis of patients with schizophrenia is exciting. However, there is still much work to be done before the treatment of patients so early in their illness is likely to become accepted as routine practice. As discussed earlier, even the definition of the prodrome is not clear-cut. This makes it challenging not only to identify patients for treatment, but also to know at exactly what point interventions would be most beneficial. In addition, the modes of potential treatments are extremely varied, so more research is required to better define which type of intervention is best.

In considering possible treatments it is important to weigh up the benefits of delaying psychosis against any harmful effects of the intervention. When it comes to pharmacological treatments, the

ethics of giving drugs with considerable adverse effects to patients that may not necessarily go on to develop psychosis has already been questioned (22). As part of our meta-analysis (10,11) we considered the adverse effects of the drugs used in the various studies. We found that low dose risperidone (1-2mg) showed few extra-pyramidal adverse effects and full-dose olanzapine showed the considerable adverse effect of weight gain. Amisulpride was associated with hyperprolactinaemia and aripiprazole with early akathisia.

Thus, even if pharmacological treatments are promising in terms of their effect of delaying psychosis, there are still issues around overall safety. It is interesting that McGorry et al achieved significant results even using a lower dose of risperidone than is usually used to treat psychosis. It is the opinion of the present authors that if pharmacological measures are to be used in the treatment of psychosis, further research is required to determine the optimum dose of drug that is still effective, but has minimal side-effects. In addition, further investigation into treatments with less adverse effects treatments such as CBT or antidepressants, as used by Cornblatt and others (19,20,25), or omega fatty acids would be useful. If, as current studies suggest, these interventions are of similar effectiveness to drug therapies, they may provide a safer alternative to pharmacological methods.

Conclusion

The effectiveness of attempts to prevent the development of psychotic illness by intervening in the prodrome remains a goal to be achieved rather than a proven treatment policy. Current trials are relatively small and we await the development of techniques for delivering safer and more effective treatments. However, CBT, the use of anti-depressants and omega fatty acids appear promising.

How should this influence management by the general practitioner? It is clear that the point at which conversion to full psychosis occurs is an artificial dividing line, and both Pantelis et al (26) and Koutsouleris et al (27) have shown that grey matter loss, and hence cell damage, occurs during the prodromal phase. This implies that, if a general practitioner is presented with a patient who may be psychotic, but the symptoms are such that the GP is not completely convinced that the patient is fully psychotic, he should still refer the patient urgently for evaluation, as loss of time while symptoms become 'classical' may only lead to an increased duration of untreated psychosis (DUP) and further detriment to the patient. It will then be for the specialists to decide how each individual patient is best treated.

GP comment

What have I learned from this paper?

1. There may be a prodromal phase before the psychosis becomes clearly evident, during which the patient can present with a number of symptoms, including reduced concentration, attention, drive and motivation, depressed mood; sleep disturbance, and anxiety; social withdrawal, suspiciousness, deterioration in function and irritability. This may last up to 5 years.

2. Although the situation currently remains unclear, early referral for specialist assessment and, if appropriate, treatment might improve the long-term prospects for the patient. It is clear that there should be in place clinical pathways of referral or early intervention in psychosis either directly to the Consultant Psychiatrist or via the Mental Health Community Teams if this is to work effectively in Primary Care.

Dr P.A.H. Cliffe,
General Practitioner, Surrey.

References

1. Jackson HJ, McGorry PD Dudgeon P Prodromal symptoms of schizophrenia in first episode psychosis; prevalence and specificity. *Comprehensive Psychiatry* 1995; 36:241-250. (published erratum in comprehensive psychiatry 37;75.).
2. Yung AR, McGorry PD The prodromal phase of first episode psychosis; past and current conceptualisations. *Schizophrenia Bulletin* 1996; 22: 353-370.
3. Yung AR, McGorry PD *The initial prodrome in psychosis; descriptive and qualitative aspects Aust NZJ of Psychiatry* 1996; 30;587-599.
4. McGorry P et al. Early *Psychosis training pack module 1*; recognition Gardiner-Cauldwell. P1-29.1997.
5. Hafner H et al Prodrome, onset and early course of Schizophrenia. In *The Epidemiology of Schizophrenia* ed. Murray R et al. Cambridge. Cambridge University Press p124-147.2003.
6. Hafner H et al. IRAOS; an instrument for the retrospective assessment of the onset of schizophrenia. *Schizophrenia Research* 1992; 6, 209-223.
7. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes; preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* 2002; 159:863-865
8. McGorry PD, Yung AR, Phillips LJ The 'close in' or ultra high risk model; A safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophrenia Bulletin* 2003; 29; 771-790.
9. Wolbrock T, Falkai P, Gaebel W Implementing early detection and intervention in psychosis; the german approach. In Ehmann T, Macewan GW, Honer W editors *Best care in early psychosis intervention* . London and New York Taylor and Francis p157-166.2004.
10. Agius M, Kelly C, Zaman R Metanalysis of medical and non medical treatments of the prodromal phase of psychotic illness, the so-called at risk mental states. *European Neuropsychopharmacology* 2008; 18 suppl 4 S441
11. Kelly C, Hadjinicolaou AV, Holt C, Agius M & Zaman R: Meta-Analysis of Medical and non-medical treatments of the prodromal phase of psychotic illness in at-risk mental states. *Psychiatr Danub*. 2010 ;22 suppl 1 ; 56-62
12. McGorry PD, Yung AR, Phillips LJ, et al. Randomised controlled trial of interventions designed to reduce the risk of progression to first episode psychosis in a clinical sample with subthreshold symptoms *Archives of General Psychiatry* 2002; 59:921-928.
13. Woods SW, Tully EM, Walsh BC, Hawkins KA, Callahan JL, Cohen SJ, Mathalon DH, Miller TJ, McGlashan TH, "Aripiprazole in the treatment of the psychosis prodrome. An open-label pilot study", *British Journal of Psychiatry*, (2007) 191(suppl . 51), s96- s101.
14. Morrison AP, Bentall RP, Walford FL, Kilcommons A, Knight A, Kreutz M, Lewis SW, "Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals Study design and interim analysis of transition rate and psychological risk factors", *British Journal of Psychiatry*, (2002), 181 (suppl. 4 3), s 78- s 84
15. Morrison AP, French P, Walford L et al A randomised controlled trial of cognitive therapy for prevention of psychosis in people at ultra-high risk. *Schizophrenia Research* 2004; 67; 7.
16. Nordentoft M, Thorup A, Petersen L, Øhlenschlaeger J, Melau M, Christensen T, Krapup G, Jorgensen P, Jeppesen P, "Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment", *Schizophrenia Research*, (2006) 83 ; 29– 40

17. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, et al The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophr Res.* 2003; 61(1):7-18
18. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. "Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis", *Am J Psychiatry*, (2006) 163:790–799.
19. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E, "The Schizophrenia Prodrome Revisited: A Neurodevelopmental Perspective", *Schizophrenia Bulletin*, (2003) 29(4):633-651.
20. Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, et al..Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry.* 2007 ;68(4):546-57
21. Bechdolf A, et al, "Randomized controlled multicentre trial of cognitive behaviour therapy in the early initial prodromal state: effects on social adjustment post treatment." *Early Intervention in Psychiatry* 2007; 1: 71–78
22. Berger G, Dell'Olio M, Amminger P, Cornblatt B, Phillips L, Yung A, et al Neuroprotection in emerging psychotic disorders. *Early Intervention in Psychiatry* 2007 ; 1: 114–127
23. Ruhrmann S, Bechdolf A, Kühn KU, Wagner M, Schultze-Lutter F, Janssen B, Maurer K, Häfner H, Gaebel W, Möller HJ, Maier W, Klosterkötter J; LIPS study group, "Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis", *British Journal of Psychiatry*, (2007) 191 (suppl. 51), s 88 - s 95.
24. Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE. Long-Chain -3 Fatty Acids for Indicated Prevention of Psychotic Disorders A Randomized, Placebo-Controlled Trial *Arch Gen Psychiatry.* 2010;67(2):146-154
25. Walker EF, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, et al. The relation of antipsychotic and antidepressant medication with baseline symptoms and symptom progression: a naturalistic study of the North American Prodrome Longitudinal Sample. *Schizophr Res.* 2009 ;115(1):50-7
26. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, et al Neuroanatomical abnormalities before and after onset of psychosis :a crosssectional and longitudinal MRI comparison. *Lancet* (2003) 361:281-288.
27. Koutsouleris N, Schmitt GA, Gaser C et al Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. *British journal of Psychiatry* (2009) 195:218-226.