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META-ANALYSIS OF MEDICAL AND NON-MEDICAL TREATMENTS OF THE PRODROMAL PHASE OF PSYCHOTIC ILLNESS IN AT-RISK MENTAL STATES

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SUMMARY

Introduction: *There are now many existing studies which assess the treatments available for 'at risk mental states', as patients who are believed to be in the prodromal phase of psychotic illness are referred to. However, concerns regarding side effects of possible treatments remain.*

We here conduct a meta-analysis of the studies available up to October 2010. The aim of this study is to decide what would be the best treatment for 'at high risk patients'.

Results: *All the available studies examining potential treatments during the prodromal phase of psychotic illness were collected. They all showed comparable efficacy, which reached statistical significance, excluding the one study using olanzapine, which in fact 'tended towards significance'.*

Discussion: *Treatments appear promising but a balance needs to be kept between adverse events and effectiveness of preventing psychosis.*

Conclusion: *It is necessary to search further for treatments in order to identify effective treatments with fewer adverse side effects in this phase of psychotic illness.*

Key words: *at risk mental state - anti-psychotics - anti-depressants - Omega3 poly-unsaturated fatty acids - cognitive behaviour therapy*

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Introduction

There are now several studies of treatment for 'at-risk mental states' as patients who are believed to be in the prodromal phase of psychotic illness are referred to. Such treatments aim to prevent the onset of a full first psychotic episode. Treatments which have been studied so far include low dose risperidone combined with cognitive behaviour therapy (CBT) (McGorry et al. 2002), full doses of olanzapine (McGlashan et al. 2006), amisulpiride (Ruhrmann et al. 2007), Omega3 poly-unsaturated fatty acids (Berger et al. 2007, Amminger et al. 2010), aripiprazole (Woods et al. 2007), antidepressants versus atypical antipsychotics (Cornblatt et al. 2003, Berger et al. 2007), and CBT alone in two trials (Bechdolf et al. 2007, Morrison et al. 2002). Each of the studies alone is small, but if brought together, the studies now demonstrate that several hundred patients with 'at risk mental states' have been studied under trial conditions for several hundred months of treatment.

Aim

The aim of this study was to study these trials collectively in order to comment on the efficacy and tolerability of these treatments during the prodromal period, in preventing the onset of psychotic illness.

Methods

All studies of Early Intervention in the Prodrome of Psychosis up to October 2010 were critically reviewed. The outcomes of these studies in preventing psychosis were compared using odds ratios plotted as a 'forest plot'. Side effects of the various agents were compared using bar charts.

Results

The studies by Woods et al. 2007 and Morrison et al. 2002 could not be included in the forest plot because of the lack of proper control groups in either study. All studies compared showed comparable efficacy, which reached statistical significance, excluding the study using olanzapine, which 'tended towards significance'. P values shown here, are the ones quoted in the original studies. Thus, for the amisulpride study $p<0.01$ ($p=0.006$) (Ruhrmann et al. 2007), for the risperidone study, $p=0.03$ (McGorry et al. 2002), for the Morrison CBT study, $p=0.028$, after 6 months therapy and 12 months monitoring (Morrison et al. 2002), for the Nordentoft study at 12 months, $p<0.01$ ($p=0.009$), but statistical significance was lost at 24 months (Nordentoft et al. 2006), while for the olanzapine study (McGlashan et al. 2006), $p=0.08$.

Table 1. Studies identified from literature search

Paper Authors	Year	Journal	Title	Control	Intervention	Duration
McGorry et al.	2002	Arch Gen Psychiatry	Randomized Controlled Trial of Interventions Designed to Reduce the Risk of Progression to First-Episode Psychosis in a Clinical Sample with Subthreshold Symptoms	Needs based Tx (antide-pressants + psychotherapy, not anti-psychotics	Risperidone + CBT	26 weeks
Woods et al.	2007	British Journal of Psychiatry	Aripiprazole in the treatment of the psychosis prodrome	No control	Aripiprazole	8 months
Morrison	2002	British Journal of Psychiatry	Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals (EDIE)	Non-patient population	CBT	6 months
Morrison	2004	British Journal of Psychiatry	Cognitive therapy for the prevention of psychosis in people at ultra- high risk	Monitoring	CBT	12 months
Nordentoft	2006	Schizophreni a Research	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	Standard Copenhagen care	Integrated care	1 year
Nordentoft	2006	Schizophreni a Research	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	Standard Copenhagen care	Integrated care	2 years
McGlashan	2006	Am J Psychiatry	Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis	Placebo	Olanzapine	1 year
Cornblatt	2007	J Clin Psych	Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents.	2nd Gen Antipsychotic	Anti-depressants	6 months
Berger	2007	EIPsych	Neuroprotection in emerging psychotic disorders	Placebo	Omega-3 fatty acids	3 months
Ruhrmann et al.	2007	British Journal of Psychiatry	Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis	Needs-focused intervention	Amisupride	1 year
Amminger et al.	2010	Arch Gen Psychiatry	Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial	Placebo	Omega-3 fatty acids	3 months

Study Information

The studies using Omega3 poly-unsaturatedfatty acids also gave significant results; p=0.028 (Berger 2007) and p=0.007 (Amminger et al. 2010). Antidepressants appeared to be more effective than atypical antipsychotics (p=0.007) (Cornblatt et al. 2003, Berger et al. 2007, Cornblatt et al. 2007), but it is noteworthy that there was a marked problem with compliance in the antipsychotic group. The main measure of success in trials of treatment in the prodrome is a reduction in the conversion rate from prodrome to first psychotic episode.

Table 2. Summary of statistical outcomes of trials of treatment during the prodromal phase of psychotic illness

	Control	Intervention	Duration (months)	Patients analysed	Control group size
McGorry et al. (2002)	Needs based Tx (antide-pressants + psychotherapy, not antipsychotics)	Risperidone + CBT	6.5	59	28
Morrison (2004)	Monitoring	CBT	12	58	23
Nordentoft (2006)	Standard Copenhagen care	"Integrated care''	12	67	30
Nordentoft (2006)	Standard Copenhagen care	"Integrated care''	24	65	29
McGlashan (2006)	Placebo	Olanzapine	12	33	19
Cornblatt (2007)	2nd Gen Antipsychotic	Antidepressants	6	48	28
Berger (2007)	Placebo	Omega-3 fatty acids + antipsychotics	3	76	38
Ruhrmann et al. (2007)	Needs-focused intervention	Amisupride	12	102	44
Bechdolf (2007)	Supportive counselling	CBT	12	113	59
Amminger (2010)	Placebo	Omega-3 fatty acids	3	76	38

	Progression to Psychosis	Intervention group size	Progression to Psychosis	p value	Odds ratio	CI lower (95%)	CI upper (95%)
McGorry et al. (2002)	10	31	3	0.016	0.19	0.05	0.80
Morrison (2004)	5	35	2	0.028	0.22	0.04	1.24
Nordentoft (2006)	10	37	3	0.009	0.18	0.04	0.72
Nordentoft (2006)	14	36	9		0.36	0.13	1.02
McGlashan (2006)	11	14	5	0.080	0.40	0.10	1.68
Cornblatt (2007)	12	21	0.5	0.007	0.03	0.00	0.59
Berger (2007)	8	38	1	0.013	0.10	0.01	0.86
Ruhrmann et al. (2007)	35	58	31	0.006	0.30	0.12	0.72
Bechdolf (2007)	8	54	1		0.12	0.01	0.96
Amminger (2010)	11	38	2	0.007	0.14	0.03	0.67

The formula used in this spreadsheet can be found on page 251 of Woolson, R.F. (1987) Statistical Methods for the Analysis of Biomedical Data. New York NY: John Wiley and Sons, Inc.

Summary of Statistical Outcomes

Table 3. Transition rates for the various trials using antipsychotic treatment, expressed as a table

	Control	Treatment	N
BT (Morrison) - 12m	22%	6%	58
Risperidine + CBT (McGorry - 6m	37%	10%	59
Risperidine + CBT (McGorry - 12m	36%	19%	
Olanzapine (McGlas han) - 24m	35%	16%	60
"Integrated treatment" (Nordentoft) - 12m	28%	8%	62
'Integrated treatment" (Nordentoft) - 24m	44%	28%	
Bechdolff - 12m	14%	2%	128
Omega 3FA + antipsychotics (Burger) - 3m	21%	3%	76
Omega 3FA (Amminger) - 3m	29%	5%	76

When assessing these studies, it is necessary to consider the side effects caused by the treatments. This is important in order to ensure that the treatment is safe and less likely to cause adverse events or symptoms when compared to the prodromal illness itself. It is for this reason that there has been much controversy with regards to the ethics of these proposed treatments (Bentall et al. 2002, Agius et al. 2008).

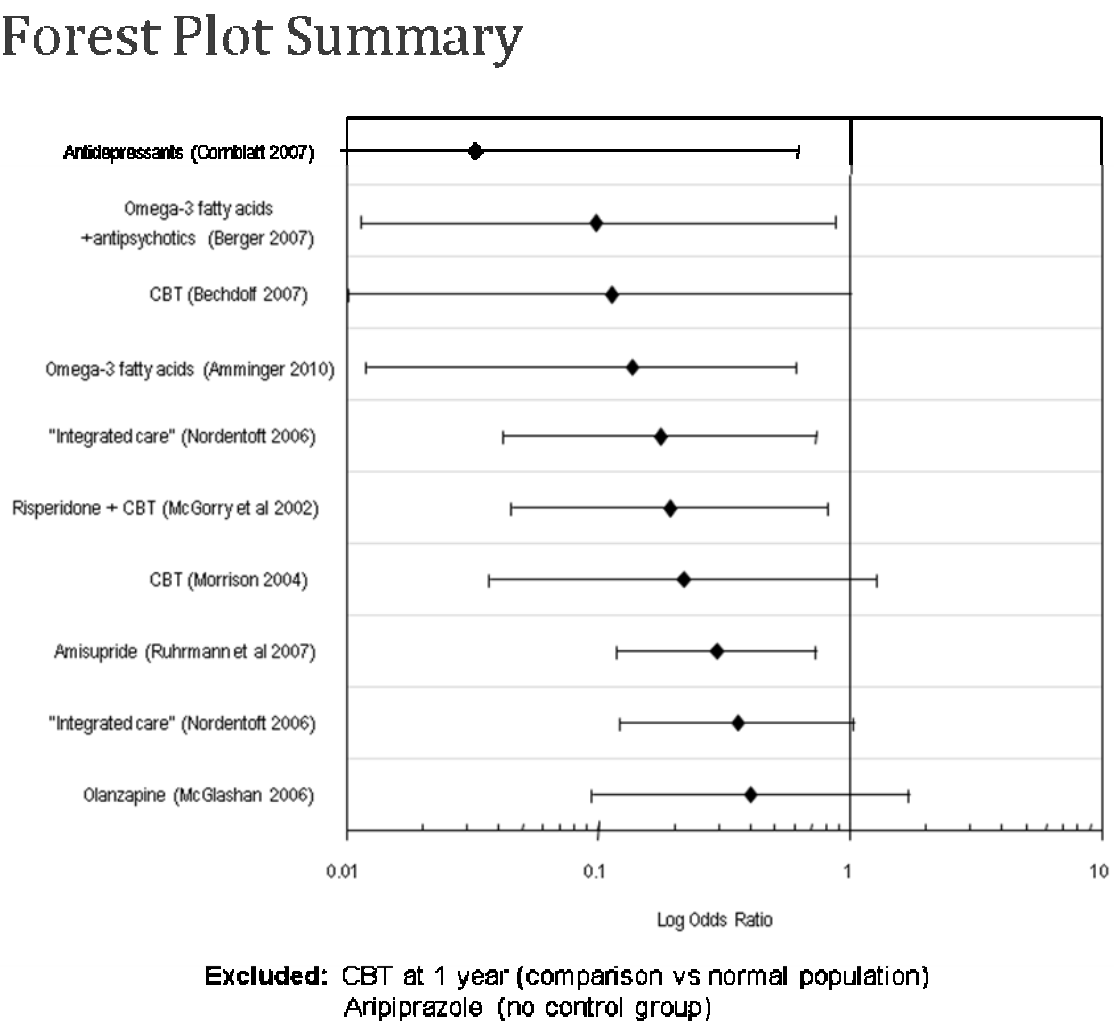

Figure 1. Forest Plot demonstrating Odds Ratios for different trials of treatment in the prodromal phase

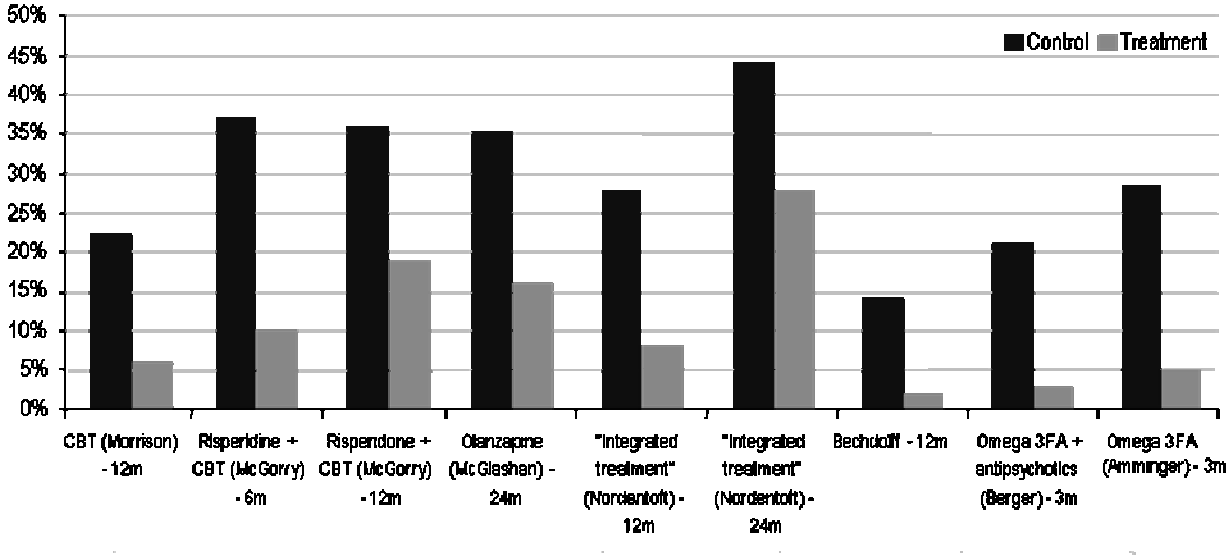

Figure 2. Transition rates for the various trials using antipsychotic treatment, expressed as bar charts

Table 4. Side effects of Amisulpride in Ruhrmann 2007 trial, expressed as a table

Side effects	Amisulpride	Control
Prolactin	81.8%	20.6%
Extapyramidal S/Es	34.4%	65.6%
Liver alanine aminotransfera	4.9%	0.0%
BMI inc amisulpride	2.6%	0.0%

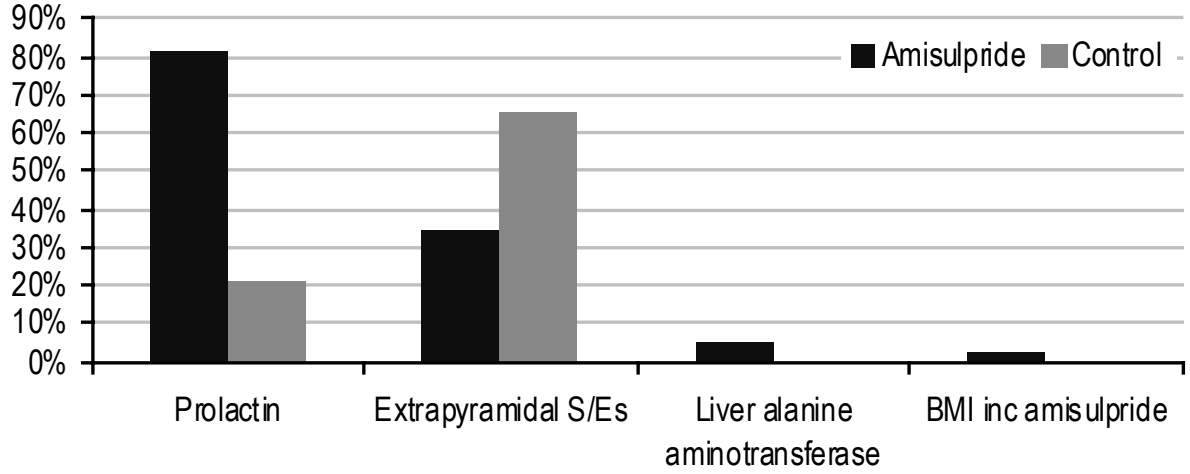

Figure 3. Side effects of Amisulpride in Ruhrmann 2007 trial in bar chart form

Tabele 5. Side effects of Amisulpride, Aripiprazole, Olanzapine and Risperidone, expressed as a table

Side effects	Intervention	Control
BMI (amisulpride)	2.6%	0.0%
Prolactin (amisulpride)	81.8%	20.6%
Akathisia (aripiprazole)	61.5%	n/a
Fatigue (olanzapine)	29.0%	3.9%
Weightgain (olanzapine)	61.3%	17.2%
Stiffness (risperidone)	12.0%	0.0%

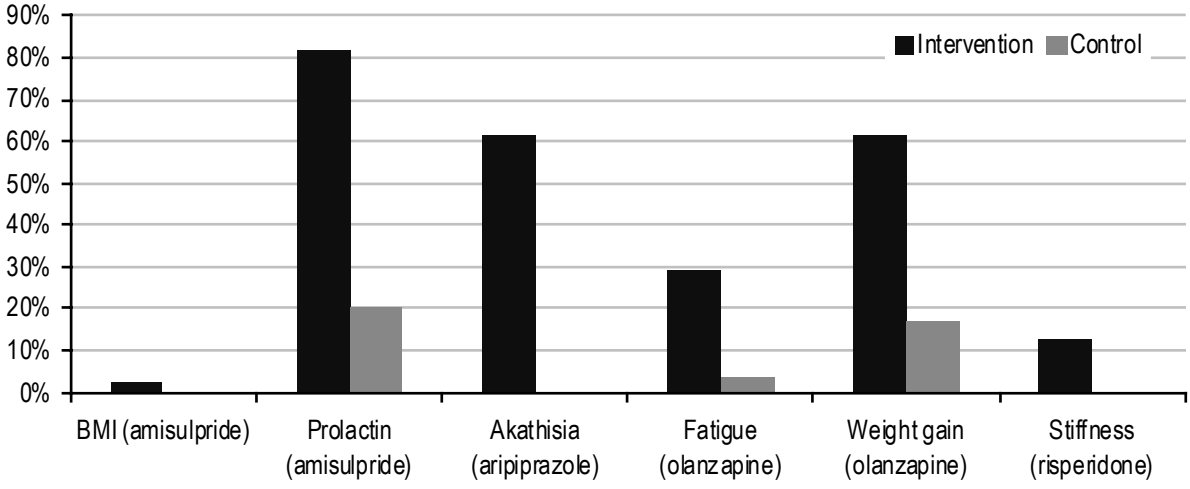

Figure 4. Side effects of Amisulpride, Aripiprazole, Olanzapine and Risperidone trials in bar chart forms

Low dose risperidone (1-2mg) showed few extra-pyramidal side effects. Full dose olanzapine showed an important side effect of weight gain, amisulpride caused hyperprolactinaemia in a substantial number of patients, while aripiprazole caused akathisia early in the treatment, which however improved by the end of the study.

Comment

One approach to intervening early in a psychotic disorder is to interfere in an appropriate manner in the prodromal phase of the illness. In this case, the aim is to prevent the patient from developing the first psychotic episode by offering appropriate interventions, which may be psychological or pharmaceutical. This approach, which is one of 'indicated prevention', is at present experimental. However, as a result of a number of trials around the world, a number of clinics dedicated to this approach have been set up. The analysis of the trials which has been carried out above shows that interventions during the prodrome may indeed prevent the development of full blown psychotic illness in some patients.

It is not possible to distinguish, in terms of efficacy, between those studies which used CBT alone and those which used medication.

The reported side effects were of the same entity which would have been expected if the medications had been used in fully psychotic patients.

Omega3 poly-unsaturated fatty acids appear to be a very promising intervention because of their low adverse effect profile and strong beneficial effects as indicated in the studies by Berger et al. and Amminger et al. (Berger et al. 2007, Amminger et al. 2010). In the latter study, which was designed as a double blind controlled trial against placebo with 3 months treatment and 40 months observation, the difference between the groups in terms of cumulative risk of progression to full-threshold psychosis was 22.6% (95% confidence interval, 4.8-40.4) (Amminger et al. 2010). Furthermore, it was observed that Omega3 poly-unsaturated fatty acids also significantly reduced positive symptoms (P=0.01), negative symptoms (P=0.02), and general symptoms (P=0.01)(Amminger et al. 2010). Another conclusion drawn from this study is that Omega3 poly-unsaturated fatty acids improved general functioning when compared to placebo (P=0.002) (Amminger et al. 2010). The incidence of adverse effects was the same and minimal in the two treatment groups (Amminger et al. 2010). Hence, long-chain Omega3 poly-unsaturated fatty acids reduce the risk of progression to psychotic disorder and could suggest a safe and effective method of prevention in young patients 'at 'Ultra High Risk' of progressing to psychosis. What is particularly interesting about this study is that the effect of the Omega3 poly-unsaturated fatty acids appeared to continue after their administration had been stopped and throughout the study observation period. Since there is great need of interventions to use in the prodromal period, one might postulate in the future the use of a combination of Omega3 poly-unsaturated Fatty acids and Cognitive Behaviour Therapy as long term prevention of the development of psychotic illness in the at risk mental state period.

Conclusion

Much controversy has been raised about whether antipsychotics should be used in the prodromal phase of psychotic illness. This meta-analysis has been carried out in order to elaborate on this point based on the available information.

The most important issue in deciding what the most effective treatment is for prodromal psychosis is whether the potentially beneficial effects of neuroprotection conferred by medication, outweigh the possible side effects. In this context, the use of antidepressants and Omega3 poly-unsaturated fatty acids, as well as Cognitive Behaviour Therapy, offer new possibilities that are both effective and safe. It would be useful to have data on the use of low dose, rather than full dose olanzapine or amisulpride as other possible alternatives.

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