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AN UPDATE ON: META-ANALYSIS OF MEDICAL AND NON-MEDICALTREATMENTS 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 July 2016. The aim of this study is to decide what would be the best treatment for 'at high risk patients'.*

Results: *18 studies were selected for inclusion; 12 showed significance, 5 did not and one tended towards significance. Both antipsychotic medication and psychological intervention show mixed results with cognitive behavioral therapy and olanzapine/amisulpride coming out on top. Omega 3 poly-unsaturated acid also shows promising and consistent results.*

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 – Omega 3 poly-unsaturated fatty acids – cognitive behaviour therapy*

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INTRODUCTION

Before the onset of frank psychotic disorders there exists a preceeding at risk-mental state (ARMS), identified by attenuated positive symptoms, intermittent psychotic states, and familial risk for psychotic illness in addition to recent and dramatic decline in functioning (Yung et al. 1996). To date these remain the most reliable way of determining those at risk, more recent advances in looking for measurable biomarkers include EEG indices (Duffy et al. 2015) and hippocampal T2 MRI relaxation time (Berger et al. 2008). This has been built upon with the use of low dose lithium, showing that there a significant difference (p=0.018) in relaxation time, this has been the first use of a biomarker to measure the effect of intervention in this group (Berger et al. 2012). These patients are prone to progressing at a rate of around 40% (Cannon et al. 2008, Yung et al. 2003) although significant differences have been found within the studies below, some being as low as 8%, this represents significant differences in methodology. Being able to avert this progressing cohort would avoid significant suffering for patients and loved ones, and potentially maintaining a higher cognitive, emotional and social functioning. Currently pharmacological treatment is conventional antipsychotics which come with significant side effects with the advantage of a relatively low cost. Recently one study of cost-effectiveness the van de Gaag (2012) CBT study showed £550 saved per averted psychosis compared to routine care, perhaps indicating improved efficiency of delivering this treatment.

In 2010 a meta-analysis was conducted of all the pharmacological and psychological treatments conducted in ARMS patients, this paper represents the updated version of the original meta-analysis. Treatments which have been studied so far include pharmacological in the form of amisulpiride, risperidone and olanzapine; psychological in the form of cognitive behavioral therapy and integrated psychological intervention, Family-aided Assertive Community Treatment; and supplementary, principally omega 3 fatty acids. Each of these studies alone are 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 analyze trials that tested interventions in at risk mental state patients collectively and comment on the efficacy and tolerability of pharmacological and non-pharmacological treatments during the prodromalperiod, primarily looking at the rates of transition to psychotic illness.

METHODS

All studies of Early Intervention in the Prodrome of Psychosis up to July 2016 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.

The search criteria were:

- ((conversion rate) OR (risk OR prodrome)) AND (schizophrenia or psychosis) AND (treatment).

For the National Center for Biotechnology Information (NCBI) database (PubMed) of clinical trials and:

- Prodrome;
- Prevention AND pyschosis;
- Ultra-high AND risk;
- At AND risk AND mental AND state.

For the Cochrane Database of systematic reviews

The search methods returned 769 clinical trials and 2 systematic reviews. These were analyzed for inclusion based on the population being under investigation designated as ARMS, an attempt to have a control group, and use transition rates as the primary outcome measured.

Odds ratios and confidence intervals were calculates so that these could be plotted on a forest plot.

For the trials using anti-psychotic medication, any comment on the tolerability or side effects was taken and turned into histograms for easy comparison.

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, Morrison et al. 2015 did include a control. There was an additional small open label glycine study for ARMS that lacked control groups or a significant patient number (Woods et al. 2013). Of the 18 studies that are now analyzed, 12 achieved significance in their intervention one study, using olanzapine, 'tended towards significance'; and five produced insignificant values (Table 1).

P values shown here, are the ones quoted in the original studies, table 2 uses calculated significance values. 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 12months 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), $p=0.08$. The studies using Omega 3 polyunsaturated fatty 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.

As of 2010 there has been a total of 8 studies that fit with the inclusion criteria, their stated significance values show that there has been less success. CBT with treatment as usual (Van der Gaag et al. 2012, $p=0.03$), Integrated psychological intervention (Bechdolf et al. 2012, $p=0.008$) and Omega 3 fatty acids (Amminger et al. 2015, $p=0.02$). The other 5 studies did not achieve significance, respirodone with cognitive therapy (McGorry et al. 2013, $p=0.60$ and Yung 2011, $p=0.92$) was the only subsequent use of pharmacological agents. The McGorry and Yang significance values compare the CBT + risperidone group to the standard therapy and risperidone and placebo groups, the significance values shown below show the intergroup differences calculated using two-tailed chi-squared test. The final psychological therapy interventions all failed to achieve significance CBT (Addington et al. 2011, $p=0.059$ and Morrison 2012, $p=0.73$) and FACT (MacFarlane 2015, $p=>0.05$).

Side effects of anti-psychotic medication were secondary outcomes in the olanzapine (McGlashan et al. 2006), risperidone (McGorry et al. 2002, 2013; Yung et al. 2011), apripiprazole (Woods et al. 2007) and amisulpride (Ruhrman et al. 2007) trials. Results of these are shown below except the Yung et al. 2011 and McGorry et al. 2013 trial, they showed insignificant differences between the patient and control groups for a range of psychic side effects and weight gain.

Finally of the two systematic reviews Marshall and Rathbone (2011) came to similar conclusions about the six studies preventing conversion but also include results regarding the effect on the severity of first episode psychosis symptoms, and Bošnjak et al. 2016 gives a good protocol of how to evaluate the safety of prodromal treatments (Table 3, 4, 5, 6, Figure 1, 2, 3).

Table 1. Studies identified from literature search

Paper	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 (antidepressants + psychotherapy, not antipsychotics	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 Schizophrenia 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	Amisulpride	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
Yung et al. 2011 J Clin Psychiatry	Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis.	Cognitive or sup-portive therapy with placebo	Cognitive therapy with risperidone	6 months
McGorry et al. 2013 J Clin Psychiatry	Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome.	Cognitive or sup-portive therapy with placebo	Cognitive therapy with risperidone	12 months
MacFarlane et al. 2015 Schizophr Bull	Clinical and functional outcomes after 2 years in the early detection and intervention for the prevention of psychosis multisite effectiveness trial.	Community Care	FACT	2 years
Morrison et al. 2012 BMJ	Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial.	Mental state monitoring	CBT and mental state monitoring	12 months
Bechdolf et al. 2012	Preventing progression to first-episode psychosis in early initial prodromal states.	Supportive counseling	Integrated psychologica l intervention	24 months
Van der Gaag et al. 2012 Schizophr Bull	Cognitive behavioral therapy for subjects at ultrahigh risk for developing psychosis: a randomized controlled clinical trial.	Treatment as usual	CBT with treatment as usual	18 months
Amminger et al. 2015 Nat Commun	Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study.	Placebo	Omega 3 fatty acids	6 years
Addington et al. 2011 Schizophr Res	A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis.	Supportive therapy	CBT	18 months

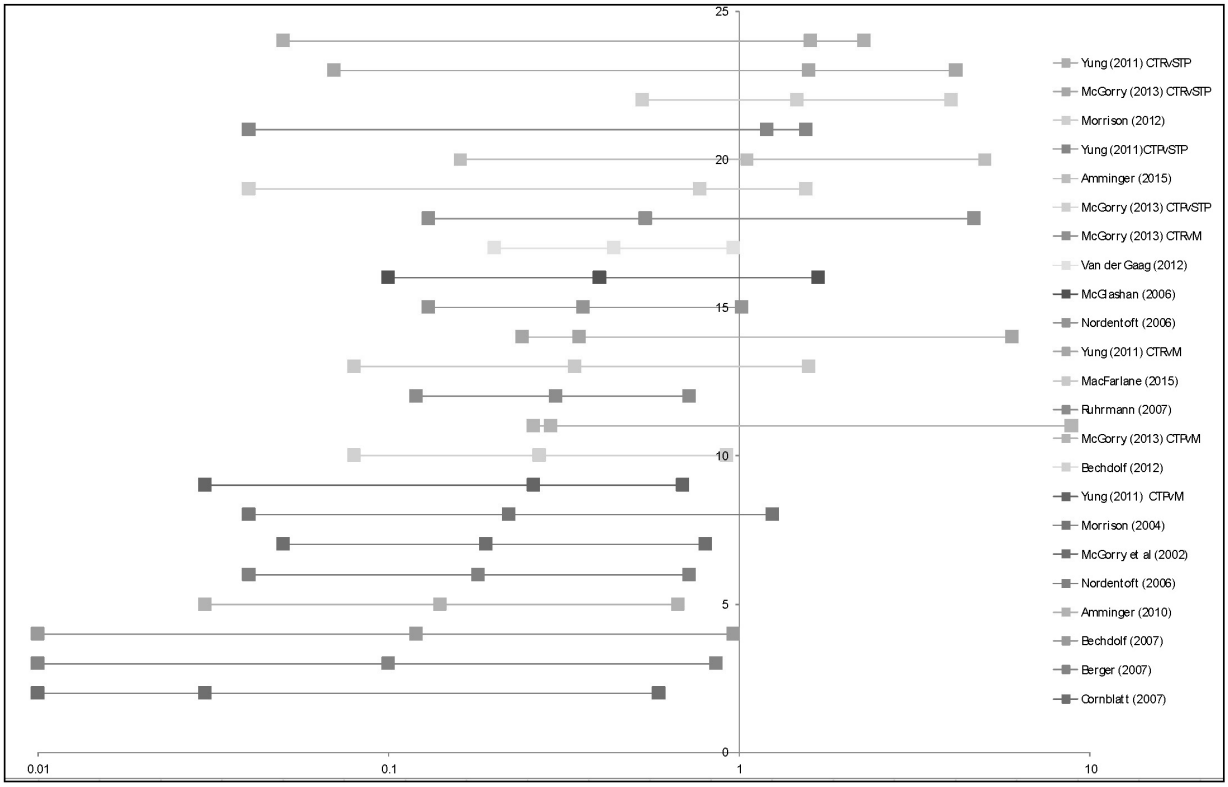

Figure 1. Forest plot of all included studies, except Woods (2007) and Morrison (2002)CTR: cognitive therapy and low dose resperidone; CTR: cognitive therapy and low dose resperidone; M: monitoring; STP: supportive therapy and placebo

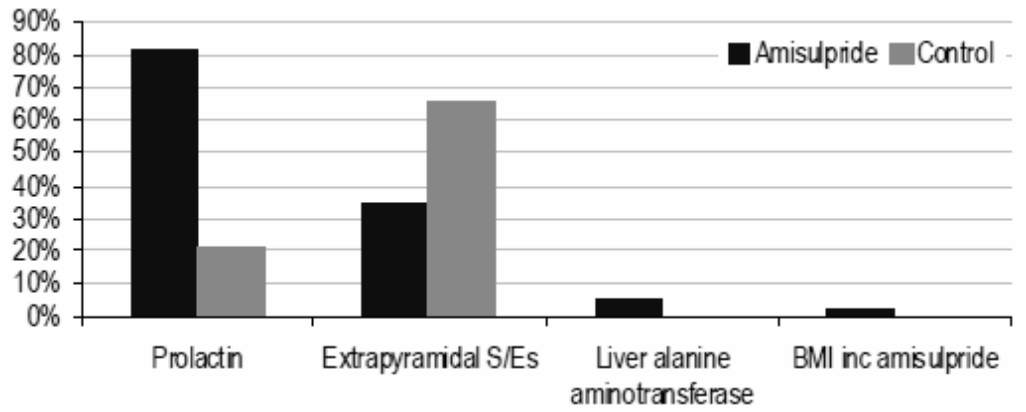

Figure 2. Side effects of Amisulpride in Ruhrmann et al. 2007 trial in bar chart form

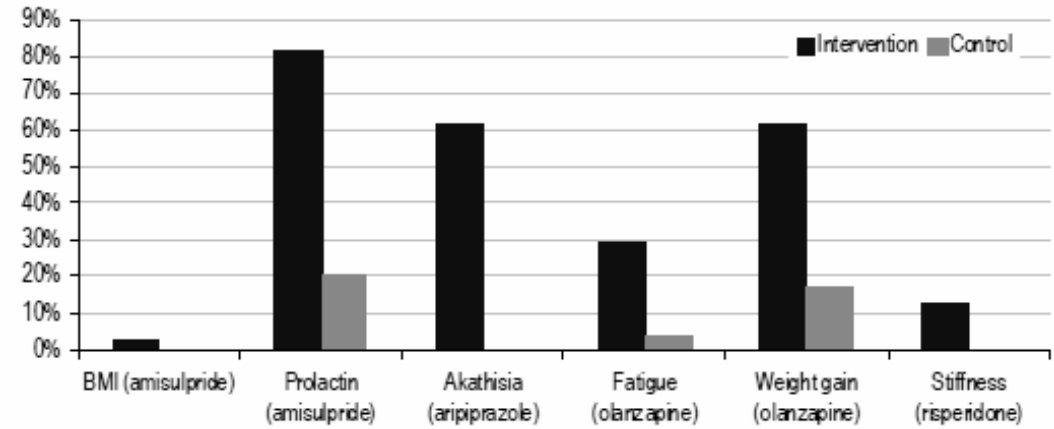

Figure 3. Side effects of Amisulpride, Aripiprazole, Olanzapine and Risperidone trials in bar chart form

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

Paper	Control	Intervention	Duration (months)	Patients analysed	Progression in Control
McGorry et al. 2002	Needs based Tx (antidepressants + psychotherapy)	Risperidone + CBT	6.5	59	10/28
Morrison 2004	Monitoring	CBT	12	58	5/23
Nordentoft 2006	Standard Copenhagen care	"Integrated care"	12	67	10/30
Nordentoft 2006	Standard Copenhagen care	"Integrated care"	24	65	14/29
McGlashan 2006	Placebo	Olanzapine	12	33	11/19
Cornblatt 2007	2nd Gen Antipsychotic	Antidepressants	6	48	12/28
Berger 2007	Placebo	Omega-3 fatty acids + antipsychotics	3	76	8/38
Ruhrmann 2007	Needs-focused intervention	Amisulpride	12	102	35/44
Bechdolf 2007	Supportive counselling	CBT	12	113	8/59
Amminger 2010	Placebo	Omega-3 fatty acids	3	76	11/38
Yung 2011	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	6	115	2/78M
Yung 2011	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	6	115	2/28STP
Yung 2011	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	6	115	2/78M
Yung 2011	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	6	115	2/28STP
McGorry 2013	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	12	115	4/78M
McGorry 2013	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	12	115	3/28STP
McGorry 2013	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	12	115	4/78M
McGorry 2013	Cognitive or supportive therapy with placebo	Cognitive therapy with risperidone	12	115	3/28STP
MacFarlane 2015	Community Care	FACT Not RCT, CHR and CLR	24	337	16/250
Morrison 2012	Mental state monitoring	CBT and mental state monitoring	12	228	7/144
Bechdolf 2012	Supportive counseling	Integrated psychological intervention	24	128	12/62
Van der Gaag 2012	Treatment as usual	CBT with treatment as usual	18	201	22/94
Amminger 2015	Placebo	Omega 3 fatty acids	720	81	16/40
Addington 2011	Supportive therapy	CBT	18	51	3/24

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 standard pharmacological agents for full blown or psychosis or psychological therapies to attenuate the effect of developing symptoms. 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. Currently there is mixed results on the efficacy of CBT, Morrison et al. (2012) and Van der Gaag et al. (2012) had conflicting results for the use of CBT. Morrison et al. (2012) would seem to be more powerful as they excluded for current or previous antipsychotics. However other forms of psychological intervention such as FACT and IPI don't appear particularly efficacious. The reported side effects were of the same entity which would have been expected if the medications had been used in fully psychotic patients, interestingly Yung (2011) and McGorry (2013) found no difference in side effects between patients and controls. Omega 3 poly-unsaturated fatty acids appear to be a promising intervention because of their low adverse effect profile and strong beneficial effects as indicated in the studies by Berger et al. 2007 and 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 Omega 3 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).

Table 3. CTR: cognitive therapy and low dose resperidone; CTR: cognitive therapy and low dose resperidone; M: monitoring; STP: supportive therapy and placebo. Values were calculated using tables from Woolson (1987)

Paper	Progression in Intervention	p value	Odds ratio	CI lower (95%)	CI upper (95%)
McGorry et al. 2002	3/31	0.016	0.19	0.05	0.80
Morrison 2004	2/35	0.028	0.22	0.04	1.24
Nordentoft 2006	3/37	0.009	0.18	0.04	0.72
Nordentoft 2006	9/36	0.000	0.36	0.13	1.02
McGlashan 2006	5/14	0.080	0.40	0.10	1.68
Cornblatt 2007	0.5/21	0.007	0.03	0.00	0.59
Berger 2007	1/38	0.013	0.10	0.01	0.86
Ruhrmann et al. 2007	31/58	0.006	0.30	0.12	0.72
Bechdolf 2007	1/54	0.000	0.12	0.01	0.96
Amminger 2010	2/38	0.007	0.14	0.03	0.67
Yung 2011	4/44CTP	0.244	0.26	0.03	0.69
Yung 2011	4/44CTP	0.934	1.20	0.04	1.55
Yung 2011	2/43CTR	0.771	0.35	0.24	6.01
Yung 2011	2/43CTR	0.656	1.60	0.05	2.27
McGorry 2013	4/44CTP	0.640	0.26	0.29	8.85
McGorry 2013	4/44CTP	0.700	0.77	0.04	1.55
McGorry 2013	3/43CTR	0.821	0.54	0.13	4.67
McGorry 2013	3/43CTR	0.884	1.58	0.07	4.14
MacFarlane 2015	2/87	0.235	0.34	0.08	1.58
Morrison 2012	10/144	0.730	1.46	0.53	4.03
Bechdolf 2012	4/65	0.019	0.27	0.08	0.92
Van der Gaag 2012	12/102	0.030	0.44	0.20	0.96
Amminger 2015	4/41	0.020	0.16	1.05	5.02
Addington 2011	0/27	0.059	0.00	0.05	0.56

Table 4. Transition rates for the various trials using antipsychotic treatment, expressed as a table

Paper	Control	Treatment	N
BT (Morrison) - 12m	22%	6%	58
Risperidine + CBT (McGorry) - 6m	37%	10%	59
Risperidine + CBT (McGorry) - 12m	36%	19%	0
Olanzapine (McGlashan) - 24m	35%	16%	60
“Integrated treatment”" (Nordentoft) – 12m	28%	8%	62
“Integrated treatment”" (Nordentoft) - 24m	44%	28%	0
Omega 3FA + antipsychotics (Burger) - 3m	21%	3%	76
Omega 3FA (Amminger) - 3m	29%	5%	76
CT + respiridone (McGorry) – 12m	10%	8%	87
Omega 3FA (Aminger) - 6yr	40%	10%	81

Table 5. 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 aminotransferase	4.9%	0.0%
BMI incamisulpride	2.6%	0.0%

Table 6. 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%

Amminger returned to this cohort and showed similar results five years later (Amminger et al. 2015). Another conclusion drawn from this study is that Omega 3 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 Omega 3 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 Omega 3 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 acombination of Omega 3 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 Omega 3 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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Conflict of interest:

Mark Agius is a Member of an advisory board to Otsuka, Japan.

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