TECHNICAL COMMENTARY

Treatments for high-risk of psychosis

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Introduction

The primary aims of early intervention are twofold: to prevent or delay future transition to psychosis in high-risk individuals with early symptoms, and to reduce symptom severity in individuals following a first episode of psychosis[1]. A key target of early intervention is "indicated prevention", for individuals at high risk of psychosis who have been identified with detectable signs of possible disorder, but do not meet any diagnostic criteria for disorder[2, 3].

There are two key approaches for identifying patients with early signs that may suggest an ultra-high risk (UHR) of developing psychosis. The first approach is based on Huber's Basic Symptoms (BS) which focuses on a detailed way of describing phenomenological (subjective) disturbances. Because the basic symptoms refer only to subtle subjectively experienced abnormalities, they may reflect an earlier phase in the disease process than the second approach, which identifies at risk mental states as a combination of: a Family History (FH) of psychosis plus non-specific symptoms and recent decline in functioning; recent onset Attenuated Psychotic Symptoms (APS) with decline in functioning; and Brief Limited Intermittent Psychotic Symptoms (BLIPS).

Whichever approach is utilised to identify those at UHR, a benefit of early intervention should a transition to psychosis occur is that the patient is already established in a treatment regime thus reducing the duration of untreated psychosis, which has been associated with increased illness severity[4].

Ethical considerations restrict trial design of randomised controlled trials, in terms of the implications of withholding treatments from "control" patients who are also at high risk of psychosis. Other issues with early intervention trials are the number of false positives identified by the screening tools and the consequent unnecessary treatments which may be administered; and the social stigma that may be attached to a pre-psychosis label[5].

Nonetheless, the domain of early intervention is a rapidly expanding field and shows promise in reducing the incidence or severity of schizophrenia, and also may prove to be more cost-effective than the ongoing inpatient expenses that can be associated with severe schizophrenia[3]. Determination of the most efficacious time scale for treatment would improve interventions at each stage of psychosis progression[5].

Early intervention paradigms for people at a high risk of psychosis are often combined, comprising both pharmaceutical and psychosocial therapies. Consequently, this table presents the evidence for interventions utilising either, or both, antipsychotic medications and/or cognitive or behavioural therapies for preventing transition to psychosis.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with early signs or symptoms of first episode psychosis or schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data were prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[6]. Reviews reporting

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less than 50% of items have now been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[7]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven systematic reviews that met our inclusion criteria[1-3, 8-11].

- Moderate to high quality evidence shows a medium-sized effect of reduced risk of psychosis for up to one year with any focused treatment for ultra-high risk groups, and a small effect for up to four years.
- Moderate quality evidence suggests a medium-sized effect of cognitive behavioural therapies, either alone or combined with antipsychotic medication, for delaying transition to psychosis for up to two years.
- Moderate to low quality evidence suggests some benefit of Needs Focused Intervention plus amisulpride over Needs Focused Intervention alone for improving functioning and reducing symptom severity in the short term, although there may be more weight gain with amisulpride.

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de Koning MB, Bloemen OJN, van Amelsvoort TAMJ, Becker HE, Nieman DH, van der Gaag M, Linszen DH

Early intervention in patients at ultra-high risk of psychosis: benefits and risks

Acta Psychiatrica Scandinavica 2009; 119: 426-442

View review abstract online

Comparison 1	**6 months of risperidone, 1-2mg + Cognitive Behavioural Therapy (CBT) + needs-based care vs. needs-based intervention only.** **Sample: UHR symptoms (identified by PACE and CAARMS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, unable to assess precision, direct) is uncertain of the benefit of risperidone + CBT + needs-based care.**
Transition to psychosis **Measured using BPRS and the Comprehensive Assessment of Symptoms and History**	
1 RCT, N = 59, not blind After 6 months of treatment *Significant effect favouring Risperidone + CBT + needs-based care over needs-based care alone for reducing the number of patients transitioning to psychosis, p = 0.03;* Risperidone + CBT + needs-based care = 3/31 patients transitioned (10%) Needs based care only = 10/28 patients (36%) *No significant difference between groups for transition to psychosis at 12 month or 3-4 year follow up;* 1 year post-treatment Risperidone + CBT + needs based care = 6/31 patients (19%) Needs based care only = 10/28 patients (36%) 3-4 years post-treatment Risperidone + CBT + needs based care = 10/31 patients (32%) Needs based care only = 12/28 patients (43%)	
Attrition	No attrition (0/59)
Consistency in results‡	Not applicable, 1 RCT only

Precision in results[§]	Unable to assess; no confidence intervals provided
Directness of results[‖]	Direct
Comparison 2	**1 year of olanzapine (5-15mg) + supportive therapy vs. placebo + supportive therapy.** **Sample: UHR symptoms (identified by COPS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, unable to assess precision, direct) is uncertain of the benefit of olanzapine + supportive therapy.**
Transition to psychosis **Measured by POPS**	
1 RCT, N = 60 During treatment - by 1 year *No significant difference between groups for transition to psychosis;* Olanzapine group = 5/31 patients transitioned (16%) Placebo group = 11/29 patients (38%) *No significant difference between groups for transition to psychosis at 2 year follow up;* Olanzapine group = 8/31 patients (16%) Placebo group = 13/29 patients (45%) Authors report that the treatment group showed significant improvement in functioning (SOPS total score), with no significant differences in changes in symptom scores (no data reported).	
Attrition	High attrition in both groups: 14/31 (45%) of treatment group and 19/29 (66%) of placebo group (difference NS).
Risks	Fatigue was reported at by 29% of the olanzapine group compared to 3% of the placebo group (significant difference, *p* value not reported). 56.7% of the olanzapine group gained more than 7% of their baseline body weight, compared to 3.4% of the placebo group ($p < 0.0001$).
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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Comparison 3	**6 months of Cognitive Therapy (CT) vs. monitoring.** **Sample: UHR symptoms (identified by adapted CAARMS, based on PANSS).**
Summary of evidence	**Moderte to low quality evidence (1 small RCT unable to assess precision, direct) is uncertain of the benefit of CT.**
Transition to psychosis **Measured by PACE and PANSS, prescription of antipsychotic or diagnosis of first episode psychosis**	
1 RCT, N = 58 At 1 year *Significant treatment effect of CT over monitoring for transition to psychosis p = 0.028;* CT group = 2/35 patients transitioned (6%) Monitoring group = 5/23 patients (22%) *No significant differences between groups for transition to psychosis at 3 year follow up;* CT group = 7/35 patients Monitoring group = 5/23 patients	
Attrition	Moderate attrition in both groups; 9/35 (25%) in CT group and 7/23 (30%) in Monitoring group.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 4	**1 year of comprehensive CBT (incorporating individual cognitive therapy, group intervention, cognitive remediation, psychoeducation, and family intervention) vs. supportive counselling (SC) in the Early Initial Prodromal Stage (EIPS).** **Sample: Initial prodromal stage (identified by 1 BS, GAF and family history measures).**
Summary of evidence	**Moderate to low quality evidence (1 medium-sized RCT, unable to assess precision, direct) suggests some benefit of comprehensive CBT over supportive therapy for preventing transition to late prodromal stage for up to 2 years post treatment, and transition to**

	psychosis for up to 1 year.
Transition from initial - late initial prodromal stage	
1 RCT, N = 128 *Significant treatment effect of CBT over supportive counselling for transition at end of treatment, p = 0.008;* CBT group = 3.2% transition SC group = 16.9% transition *Significant treatment effect of CBT over supportive counselling for transition at 1 year follow up, p = 0.019;* CBT group = 6.3% transition SC group = 20.0% transition	
Transition from initial prodromal stage to psychosis	
Significant treatment effect of CBT over supportive counselling at end of treatment, p=0.020; CBT group = 1.6% transition SC group = 13.8% transition	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 5	**12 weeks of Needs-Focused Intervention (NFI) + amisulpride vs. NFI in the Late Initial Prodromal Stage.** **Sample: Late initial prodromal stage (LIPS) (identified by APS and/or BLIPS).**
Summary of evidence	**Moderate to low quality evidence (1 small to medium-sized RCT, unable to assess precision, direct) suggests some benefit of NFI + amisulpride over NFI alone for improving functioning and reducing symptom severity in the short term.**
Acute treatment effects **Measured by overall functioning and symptom severity**	

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1 RCT, N = 102 *NFI + amisulpride group showed significantly improved symptom than NFI alone at end of treatment;* Data not reported	
Attrition	Moderate attrition: 26% of amisulpride group and 34% of NFI alone.
Risks	Significant increase in Body Mass Index in amisulpride group.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 6	**12 weeks of omega-3 fatty acids (1.5g/day) vs. placebo.** **Sample: UHR symptoms (defined by CAARMS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT unable to assess precision, direct) is uncertain of the benefit of omega-3 fatty acids.**
Transition to psychosis **Measured by PANSS + symptom frequency and duration + GAF**	
1 RCT, N = 81 *Significant treatment effect of omega-3 over placebo for transition to psychosis by end of treatment, p = 0.028;* Omega-3 group = 1/38 patients (2.6%) Placebo group = 8/38 patients (21.2%) There were also significant differences in changes from baseline on PANSS and GAF score, in favour of the treatment group (data not reported). *Significant treatment effect of omega-3 over placebo for transition to psychosis at 1 year follow up p = 0.006;* Omega-3 group = 2/41 patients (4.9%) Placebo group = 11/40 patients (27.5%)	
Risks	No side effects observed by end of treatment.
Consistency in results	Not applicable, 1 RCT only.

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Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 7	**2 years of integrated treatment (IT - including Assertive Community Treatment, family therapy and social skills training) vs. standard treatment (ST).** **Sample: schizotypal personality disorder.**
Summary of evidence	**Moderate to low quality evidence (1 small RCT unable to assess precision, direct) is uncertain of the benefits of psychosocial integrated treatments.**
Transition to psychosis **Measured by diagnosis of psychotic disorder**	
1 RCT, N = 73 *Small effect size favouring IT over ST for transition to psychosis at 1 year follow up;* IT group = 3/37 patients (8.1%) ST group = 10/30 patients (33%) IT group = less negative symptoms reported at 1 year. No differences on other measures of symptomatology. *Small effect size favouring IT over ST for transition to psychosis at 2 year follow up;* IT group = 9/36 (25%) ST group = 14/29 (48.3%) Multivariate analysis results; RR = 0.36, *p* = 0.02 No differences on measures of symptomatology.	
Attrition	Moderate attrition: 6/42 (14%) in the IT group and 8/37 (21%) in the ST group.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 8	**6 months of risperidone or haloperidol 0.5-2mg/day + psychoeducation + supportive psychotherapy. No control**

	group. **Sample: UHR symptoms (identified by CAARMS).**
Summary of evidence	**Moderate to low quality evidence (1 small observational study unable to assess precision, direct) is uncertain of the benefits of risperidone or haloperidol + psychoeducation + supportive psychotherapy.**
Transition to psychosis (no mention of measure)	
1 retrospective naturalistic study, N = 42 3/42 (7.1%) subjects developed psychosis by 1 year follow up	
Attrition	Moderate attrition; 10/52 (19%) were lost to follow up.
Risks	Mild and transient neuroleptic side effects.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided
Directness of results	Direct
Comparison 9	**8 weeks of second generation antipsychotics (many also received antidepressants) vs. antidepressants only.** **Sample: UHR symptoms (identified by APS + attenuated negative symptoms).**
Summary of evidence	**Low quality evidence (1 small observational study) is uncertain of the benefits of second generation antipsychotics.**
Transition to psychosis	
1 retrospective naturalistic study, N = 48 *Significant treatment effect favouring antidepressants only over antipsychotics for transition to psychosis up to 5 year follow up (mean = 2.5 years), p = 0.007;* Antipsychotic group = 12/28 patients (43%) Antidepressant group = 0/20 patients (0%) Note; baseline symptom profiles differed only on disorganised thinking which was more severe in the antipsychotic group.	

Treatment adherence	
Significant treatment effect favouring antidepressants over antipsychotics for transition to psychosis up to 5 year follow up, p=0.005; Antipsychotic group = 17/28 patients (61%) Antidepressant group = 4/20 patients (20%) Note; 11/12 converters to psychosis were non-adherent.	
Risks	Mild and transient neuroleptic side effects.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct comparison of antipsychotics to antidepressants (although some taking antipsychotics were also taking antidepressants).
Comparison 10	**Antipsychotics only vs. antidepressants only.** **Sample: UHR symptoms (identified by CAARMS). Choice of treatment was made by participants.**
Summary of evidence	**Moderate to low quality evidence (1 small observational study, unable to assess precision, direct) is uncertain as to the benefit of antipsychotic vs. antidepressants.**
Transition to psychosis	
1 retrospective naturalistic study N = 48 At 2 years Antipsychotic group = 10/35 (29%) Antidepressant group = 1/13 (8%)	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 11	**8 weeks of open label pilot: aripiprazole (5-30mg/day). No control group.** **Sample: UHR symptoms (identified by COPS).**

Summary of evidence	**Moderate to low quality evidence (1 small study, unable to assess precision, direct) is uncertain as to the benefit of aripiprazole.**
Prodromal symptoms **Measured by SOPS score**	
1 open label pilot, N = 15 At 8 weeks Improvement from baseline SOPS was significant with mixed effects analysis. Transition to psychosis No subject converted to psychosis during the trial period (0/15).	
Risks	Mean weight gain was 1.2kg. Acathisia emerged in 8/15 subjects.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 12	**8 weeks of glycine open label pilot (0.4g/kg).** **Sample: UHR symptoms (identified by COPS).** **Note; Glycine is an amino acid neurotransmitter that acts as a coagonist with glutamate at N-methyl D-aspartate (NMDA) receptors. It is not standard treatment for psychosis.**
Summary of evidence	**Moderate to low quality evidence (1 small study, unable to assess precision, direct) is uncertain as to the benefit of glycine.**
Severity of prodromal symptoms **Measured by SOPS score**	
1 open label pilot N = 10 At 16 weeks Improvement from baseline on SOPS total score was significant ($p < 0.001$) on all subscales except negative.	
Attrition	Moderate attrition: 3/10 (30%).

Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals provided
Directness of results	Direct

Hutton P, Taylor PJ

Cognitive behavioural therapy for psychosisprevention: a systematic review and meta-analysis

Psychological Medicine 2014; 44: 449-468

View review abstract online

Comparison	**CBT without antipsychotic medication for 6-12 months vs. monitoring or non-specific supportive therapy.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, imprecise, indirect) suggests CBT without antipsychotic treatment may reduce the risk of transition to psychosis for up to 2 years, with no differences in symptoms, functioning, study retention or quality of life.**

Transition to psychosis

A medium effect of reduced transition to psychosis for those receiving CBT for up to 2 years;

At 6 months: 6 RCTs, N = 800, RR 0.47, 95%CI 0.27 to 0.82, $p = 0.06$, $I^2 = 13\%$, $p = 0.33$

Excluding 1 non-blinded study: 5 RCTs, N = 672, RR 0.58, 95%CI 0.31 to 1.07, $p = 0.08$

At 12 months: 6 RCTs, N = 800, RR 0.45, 95%CI 0.28 to 0.73, $p = 0.001$, $I^2 = 0\%$, $p = 0.41$

Excluding 1 non-blinded study: 5 RCTs, N = 672, RR 0.48, 95%CI 0.30 to 0.79, $p = 0.001$

At 18-24 months: 4 RCTs, N = 452, RR 0.41, 95%CI 0.23 to 0.72, $p = 0.002$, $I^2 = 0\%$, $p = 0.47$

Excluding 1 non-blinded study: 5 RCTs, N = 672, RR 0.46, 95%CI 0.28 to 0.75, $p = 0.01$

Authors state that eight and 11 people need to receive CBT instead of, or in addition to, non-specific support for one person to avoid transition over the longer term

Symptoms

No differences in symptoms at 6 months or 2 years, small effect of improved symptoms for those receiving CBT at 1 year;

At 6 months: 4 RCTs, N = 473, *g* = -0.111, 95%CI -0.291 to 0.69, *p* = 0.226, I^2 = not reported At 12 months: 5 RCTs, N = 473, *g* = -0.248, 95%CI -0.462 to -0.033, *p* = 0.024, I^2 = not reported At 18-24 months: 2 RCTs, N = 168, *g* = -0.17, 95%CI -0.47 to 0.14, *p* = 0.28, I^2 = 0%, *p* = 0.58
Functioning
No differences in functioning; At 6 months: 6 RCTs, N = 472, *g* = -0.03, 95%CI -0.21 to 0.35, *p* = 0.84, I^2 = 52%, *p* = 0.10 At 12 months: 6 RCTs, N = 483, *g* = 0.03, 95%CI -0.21 to 0.27, *p* = 0.78, I^2 = 36%, *p* = 0.18 At 18-24 months: 2 RCTs, N = 168, *g* = 0.09, 95%CI -0.21 to 0.39, *p* = 0.56, I^2 = 0%, *p* = 0.39
Study retention
No differences in study retention; At 6 months: 4 RCTs, N = 612, RR = 1.08, 95%CI 0.82 to 1.41, *p* = 0.59, I^2 = 0%, *p* = 0.77 At 12 months: 6 RCTs, N = 800, RR = 0.99, 95%CI 0.80 to 1.23, *p* = 0.96, I^2 = 0%, *p* = 0.92 At 18-24 months: 6 RCTs, N = 544, RR = 0.95, 95%CI 0.79 to 1.15, *p* = 0.62, I^2 = 0%, *p* = 0.92 At 36 months: 1 RCT, N = 60, RR = 0.96, 95%CI 0.60 to 1.52, *p* = 0.85
No differences in quality of life; At 6 months: 2 RCTs, N = not reported, *g* = -0.09, 95%CI -0.35 to 0.18, *p* = 0.52, I^2 = not reported At 12 months: 2 RCTs, N = not reported, *g* = 0.00, 95%CI -0.28 to 0.28, *p* = 0.99, I^2 = not reported At 18 months: 1 RCT, N = 201, *g* = 0.11, 95%CI -0.22 to 0.44, *p* = 0.51

Risks	1 study reported no differences in mood or suicidal ideation. 2 studies reported no differences in any other adverse effects.
Consistency in results	Consistent
Precision in results	Imprecise for RRs, precise for *g*
Directness of results	Indirect (mixed control conditions)

Marshall M, Rathbone J

Early Intervention for psychosis

Cochrane Database of Systematic Reviews, 2011 Issue 6. Art. No.: CD004718. DOI: 10.1002/14651858.CD004718.pub3 View review abstract online	
Comparison 1	**1 year of olanzapine (5-15mg/day) + supportive therapy vs. placebo + supportive therapy.** **Sample: UHR symptoms (identified by COPS).**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) is uncertain of the benefit of olanzapine + supportive therapy.**
Leaving the study early	
No significant difference between groups at 1 year; Olanzapine = 17/31 patients (55%), Placebo = 10/29 patients (34%) 1 RCT, N = 60, RR = 1.59 95%CI 0.88 to 2.88, *p* = 0.13	
Transition to psychosis **Measured by POPS**	
No significant difference between groups by 2 years follow up; Olanzapine group = 8/31 patients (16%), Placebo group = 13/29 patients (45%) 1 RCT, N = 60, RR = 0.58 95%CI 0.28 to 1.18, *p* = 0.13	
Global state **Measured by CGI-severity of illness, average total score change**	
No significant difference between groups at 1 month; 1 RCT, N = 59, *d* = -0.20 , 95%CI -0.71 to 0.31, *p* = 0.45	
Global state **Measured by GAF-current, average total score change**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.17 95%CI -0.34 to 0.68, *p* = 0.52	
Mental state **Measured by SOPS-total average total score change**	

No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = -0.15, 95%CI -0.66 to 0.36, *p* = 0.56 No differences on subscale scores	
Mental state **Measured by PANSS-total average total score change**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.02, 95%CI -0.49 to 0.53, *p* = 0.93 No differences on subscale scores	
Mental state **Measured by YMS average total score change**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = -0.16, 95%CI -0.67 to 0.35, *p* = 0.54	
Mental state **Measured by MADRS average total score change**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.08 95%CI -0.43 to 0.59, *p* = 0.77	
Risks	No differences in adverse effects, apart from increased weight gain and fatigue in those receiving olanzapine.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise for all outcomes.
Directness of results	Direct
Comparison 2	**6 months of risperidone (1-2mg/day) + CBT + needs based specialised team (providing case management, supportive psychotherapy, family therapy, and accommodation, employment and education assistance) vs. needs based specialised team alone.** **Sample: UHR symptoms (identified by PACE and CAARMS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct)**

	is uncertain of the benefit of risperidone + CBT.
Transition to psychosis **Measured by BPRS and the Comprehensive Assessment of Symptoms and History**	
At 6 months *Medium treatment effect favouring risperidone + therapy over the specialised team alone;* 1 RCT, N = 59, RR = 0.27, 95%CI 0.08 to 0.89, *p* = 0.031, NNT 4, 95%CI 2 to 20 *No significant difference between groups at 1 year;* 1 RCT, N = 59, RR = 0.54, 95%CI 0.23 to 1.30, *p* = 0.17	
Global state **Measured by GAF-current, average endpoint score**	
No significant difference between groups at 1 year; 1 RCT, N = 59, WMD = 0.00, 95%CI -5.21 to 5.21, *p* = 1.00	
Mental state **Measured by BPRS psychotic symptoms -general**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.21, 95%CI -0.30 to 0.72, *p* = 0.43	
Mental state **Measured by SANS psychotic symptoms -negative**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = -0.06, 95%CI -0.57 to 0.45, *p* = 0.83	
Mental state **Measured by HRSA average endpoint score anxiety**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.06, 95%CI -0.45 to 0.57, *p* = 0.81	
Mental state **Measured by HRSD average endpoint score depression**	

No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.14, 95%CI -0.37 to 0.65, *p* = 0.60	
Quality of life **Measured by QOL average endpoint score**	
No significant difference between groups at 1 year; 1 RCT, N = 59, *d* = 0.04 95%CI -0.47 to 0.55, *p* = 0.89	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**6 months (26 sessions) of Cognitive Therapy (CT) + supportive therapy (including monitoring and case management) vs. Supportive therapy alone.** **Sample: UHR symptoms (identified by adapted PACE, based on PANSS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of CT.**
Transition to psychosis **Measured by PACE and PANSS**	
No significant difference between groups at 1 year; 1 RCT, N = 58, RR = 0.50, 95%CI 0.15 to 1.66, *p* = 0.62	
Leaving the study early	
No significant difference between groups at 1 year; 1 RCT, N = 58, RR = 0.98, 95%CI 0.44 to 2.16, *p* = 0.95	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise
Directness of results	Direct

Comparison 4	**Needs Focused Intervention plus amisulpride (mean dose 118 mg/day) vs. Needs Focused Intervention.** **Needs Focused Intervention includes psychoeducation, crisis intervention, family counselling, and assistance with education or work-related difficulties according to the patient's needs.** **Sample: prodromal at risk of psychosis.**
Summary of evidence	**Moderate to low quality evidence (1 small to medium-sized RCT, unable to assess precision, direct) suggests some benefit of NFI + amisulpride over NFI alone for improving functioning and reducing symptom severity in the short term.**
Mental state **Measured by PANSS**	
Trend effect for reduced PANSS general scores in the amisulpride group at 12 weeks; 1 RCT, N = 102, MD = -3.40, 95%CI -6.85 to 0.05, *p* = 0.054 *Improved positive symptoms (reduced PANSS positive scores) in the amisulpride group at 12 weeks;* 1 RCT, N = 102, MD = -2.10, 95%CI -3.69 to -0.51, *p* = 0.0097 *No significant difference for PANSS negative scores;* 1 RCT, N = 102, MD = -1.30, 95%CI -3.26 to 0.66, *p* = 0.19	
Depression **Measured by MADRS**	
No significant difference; 1 RCT, N = 102, MD = -1.10, 95%CI -4.49 to 2.29, *p* = 0.53	
Global state **Measured by GAF**	
Improved global state (reduced GAF scores) in the amisulpride group at 12 weeks; 1 RCT, N = 102, MD = -6.10, 95%CI -11.76 to -0.44, *p* = 0.035	
Leaving the study early	
Fewer participants in the amisulpride group left the study early; 1 RCT, N = 124, RR = 0.59, 95%CI 0.28 to 0.94, *p* < 0.00001	
Consistency in results	Not applicable, 1 RCT only.

Precision in results	Unable to assess.
Directness of results	Direct
Comparison 5	**3 months of omega-3 fatty acids (eicosapentaenoic acid 0.84g per day; docosahexaenoic acid 0.7g/day) vs. placebo.** **Sample: Adolescents at risk of 1st episode psychosis determined by cut-off points on PANSS subscales (4 or more on hallucinations, 4 or more on delusions, and 5 or more on conceptual disorganization), and the frequency of symptoms (at least several times a week) and their duration (more than one week).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of omega-3.**
Transition to psychosis	
A large effect of reduced transition to psychosis in the omega-3 group at 12 weeks; 1 RCT, N = 76, RR = 0.13, 95%CI 0.02 to 0.95, *p* = 0.045	
Risks	None reported
Consistency in results	Not applicable, 1 RCT only
Precision in results	Imprecise
Directness of results	Direct

Olsen KA, Rosenbaum B

Prospective investigations of the prodromal state of schizophrenia: review of studies

Acta Psychiatrica Scandinavica 2006; 113: 247-272

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Comparison 1	**1 year of comprehensive CBT (incorporating individual cognitive therapy, group intervention, cognitive remediation, psychoeducation, and family intervention) vs. Supportive Counselling (SC) in the Early Initial Prodromal Stage (EIPS).**

	Sample: Initial prodromal stage (identified by 1 BS, GAF and family history measures).
Summary of evidence	**Moderate to low quality evidence (1 small to medium-sized RCT, unable to assess precision, direct) suggests a benefit of CBT over clinical management for reduced transition rates and longer duration to transition.**
Overall transition to psychosis	
1 RCT N = 129 (109 in early prodromal stage), rater blinding unclear *Less transition to psychosis in CBT group by 1 year, significance unclear;* CBT group 5.3% transition Clinical management group 14.8% transition	
Duration until transition to psychosis	
Longer time to transition to psychosis in CBT group at 1 year; CBT group; 16.3 months Clinical management group; 9.2 months	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 2	**Cognitive therapy (CT) vs. monitoring.** **Sample: UHR symptoms (identified by adapted PACE, based on PANSS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, unable to assess precision, direct) is uncertain of the benefit of CT.**
Transition to psychosis **Measured by PACE and PANSS score**	
1 RCT, N = 58 *Significant effect reported (effect size not reported) favouring cognitive therapy over monitoring at 1 year;* Cognitive therapy group 6% transition	

Monitoring group 22% transition	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 3	**6 months of Risperidone + CBT + needs based intervention vs. needs-based intervention only.** **Sample: UHR symptoms (identified by PACE and CAARMS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, unable to assess precision, direct) is uncertain of the benefit of risperidone + CBT + needs based intervention**
Transition to psychosis **Measured by BPRS and the Comprehensive Assessment of Symptoms and History**	
1 RCT, N = 59 *Significant effect reported (effect size not reported) favouring antipsychotic + CBT over CBT alone at 6 months;* Antipsychotic group 10% transition CBT only group 36% transition *No significant difference between groups at 1 year;* Antipsychotic group 19% transition CBT only group 36% transition	
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 4	**Olanzapine + supportive therapy vs. placebo + supportive therapy.** **Sample: UHR symptoms (identified by COPS).**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of olanzapine.**
Transition to psychosis **Measured by POPS**	

1 RCT, N = 60, triple blind (including outcome raters) No significant difference between groups at 2 years.	
Risks	Significant weight gain in the antipsychotic group.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Preti A, Cella M

Randomized-controlled trials in people at ultra-high risk of psychosis: A review of treatment effectiveness

Schizophrenia Research 2010; 123: 30-36

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Comparison	**All focused treatments targeting UHR (pharmaceutical and/or psychosocial treatments) vs. various control conditions (e.g. placebo, monitoring, treatment as usual).**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, indirect) shows focused treatments may reduce risk of transition to psychosis within 12 months.** **Moderate quality evidence (imprecise) suggests the focused treatment may also reduce the risk of transition to psychosis for up to 2 to 3 years.**

Transition to psychosis

Significant medium effect of reduced risk of transition to psychosis over 1 year for treatment groups compared to the control groups;

5 RCTs, N = 337, RR = 0.364, 95%CI 0.222 to 0.599, $p = 0.0001$, $I^2 = 0\%$, $p = 0.682$

Significant small effect of reduced risk of transition to psychosis within 2 to 3 years for the treatment groups compared to the control groups;

4 RCTs, N = 256, RR = 0.636, 95%CI 0.440 to 0.919, $p = 0.016$, $I^2 = 0\%$, $p = 0.935$

Authors report possible publication bias for 2 to 3 year results

Consistency in results	Consistent
Precision in results	Precise for measures over 1 year, imprecise for 2 – 3 year follow-up.
Directness of results	Indirect comparison (mixed treatment conditions combined and mixed control conditions combined).

Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T

Early interventions to prevent psychosis: systematic review and meta-analysis

British Medical Journal 2013; 346:f185 doi: 10.1136/bmj.f185

View review abstract online

Comparison 1	**CBT vs. supportive counselling.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests reduced transition to psychosis at 12 months for those receiving CBT compared to supportive counselling. The evidence after 12 months is of lower quality due to possible study bias.**
Transition to psychosis	
Small to medium effect of reduced transition to psychosis in the CBT group after 6 months; < 6 months: 4 RCTs, N = 591, RR = 0.62, 95%CI 0.29 to 1.31, I^2 = 17%, *p* = 0.31 6-12 months: 5 RCTs, N = 645, RR = 0.54, 95%CI 0.34 to 0.86, I^2 = 0%, *p* = 0.64 > 12 months: 4 RCTs, N = 570, RR = 0.63, 95%CI 0.40 to 0.99, I^2 = 0%, *p* = 0.48 Authors report a high risk of study bias < 6 months and > 12 months. No differences were reported for psychotic symptoms, depression or quality of life.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**12 months + of risperidone (1-3mg/day) + CBT vs. supportive counselling.**

Summary of evidence	**Moderate to low quality evidence (small samples, imprecise, consistent, direct, possible bias) suggests some benefit of risperidone + CBT for reducing transition to psychosis at 6 months, but not by 1 year.**
Transition to psychosis	
Medium treatment effect favouring risperidone + CBT at 6 months; 2 RCTs, N = 130, RR = 0.35, 95%CI 0.13 to 0.95, I^2 = 0%, *p* = 0.44 *No significant difference between groups at 1 year or after 1 year;* *1 year:* 2 RCTs, N = 130, RR = 0.63, 95%CI 0.33 to 1.21, I^2 = 0%, *p* = 0.61 *> 1 year:* 1 RCT, N = 41, RR = 0.59, 95%CI 0.34 to 1.04 Authors report a high risk of study and publication bias. No differences were reported for psychotic symptoms, depression, mania or quality of life.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**6 months of risperidone (1-3mg/day) + CBT vs. CBT and placebo.**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of risperidone + CBT.**
Transition to psychosis	
No significant difference between groups; *At 6 months:* 1 RCT, N = 87, RR = 1.02, 95%CI 0.15 to 6.94 *At 1 year:* 1 RCT, N = 87, RR = 1.02, 95%CI 0.39 to 2.67 Authors report a high risk of study and publication bias. No differences were reported for psychotic symptoms, depression or quality of life.	
Consistency in results	Not applicable, 1 RCT only
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**6-12 months of olanzapine (8 mg/day) vs. placebo.**

Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of olanzapine.**
Transition to psychosis	
No significant difference between groups; 1 RCT, N = 60, RR = 0.43 95%CI 0.17 to 1.08 Authors report a high risk of study and publication bias.	
Risks	No differences in weight gain.
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Unable to assess.
Directness of results	Direct
Comparison 5	**3 months of omega-3 fatty acids vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of omega-3 fatty acids.**
Transition to psychosis	
A large effect of reduced transition to psychosis in the omega-3 group; < 6 months: 1 RCT, N = 76, RR = 0.13, 95%CI 0.02 to 0.95 < 12 months: 1 RCT, N = 81, RR = 0.18, 95%CI 0.04 to 0.75 Authors report a high risk of publication bias.	
Consistency in results	Not applicable, 1 RCT only
Precision in results	Imprecise
Directness of results	Direct
Comparison 6	**Integrated psychotherapy vs. supportive counselling.**
Summary of evidence	**Moderate to low quality evidence (1 small to medium-sized RCT, imprecise, direct) is uncertain of the benefit of integrated psychotherapy.**
Transition to psychosis	

A medium effect of reduced transition to psychosis in the integrated psychotherapy group; *6-12 months:* 1 RCT, N = 125, RR = 0.19, 95%CI 0.04 to 0.81 *< 12 months:* 1 RCT, N = 125, RR = 0.32, 95%CI 0.11 to 0.92 Authors report a high risk of study bias.	
Consistency in results	Not applicable, 1 RCT only
Precision in results	Imprecise
Directness of results	Direct
Comparison 7	**Integrated psychotherapy vs. standard care.**
Summary of evidence	**Moderate to low quality evidence (1 small RCT, imprecise, direct) is uncertain of the benefit of integrated psychotherapy.**
Transition to psychosis	
A medium effect of reduced transition to psychosis in the integrated psychotherapy group at 6-12 months only; 6-12 months: 1 RCT, N = 67, RR = 0.24, 95%CI 0.07 to 0.81 < 12 months: 1 RCT, N = 65, RR = 0.22, 95%CI 0.26 to 1.02 Authors report a high risk of study bias.	
Consistency in results	Not applicable, 1 RCT only
Precision in results	Imprecise
Directness of results	Direct

van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, McGorry P, Cuijpers P

Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups

Schizophrenia Research 2013; 149: 56-62

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Comparison	**Any treatment for UHR groups (pharmaceutical and/or**

	psychosocial treatments) vs. any control condition (e.g. placebo, monitoring, treatment as usual).
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, precise, indirect) shows that focused treatments may reduce risk of transition to psychosis for up to 1 year, and a small effect of reduced risk of transition to psychosis for up to 4 years.** **Moderate quality evidence (imprecise, or unable to assess) shows CBT or antipsychotic treatment may reduce the risk of transition to psychosis for up to 1 year.**
Transition to psychosis	
Significant medium effect of reduced risk of transition to psychosis over 1 year for all treatment groups compared to all control groups; 10 RCTs, N = 1112, RR = 0.463, 95%CI 0.334 to 0.642, $p = 0.001$, $I^2 = 0\%$, $p = 0.104$ Meta-regression showed no differences in overall results according to study quality, and trim and fill analysis for possible publication bias changed RR to 0.51. *Significant small effect of reduced risk of transition to psychosis within 2 to 4 years for the treatment groups compared to the control groups;* 5 RCTs, N = 614, RR = 0.635, 95%CI 0.438 to 0.919, $p = 0.016$, $I^2 = 0\%$, $p > 0.05$ *No differences in social functioning between groups;* 7 RCT, N = 823, RR = 0.096, 95%CI -0.127 to 0.319, $p = 0.400$ *Subgroup analyses revealed significant small to medium effect of reduced risk of transition to psychosis over 1 year for cognitive behavioural treatment groups compared to the control groups;* 5 RCTs, N = 672, RR = 0.52, 95%CI 0.0 to 0.79, $p < 0.05$, $I^2 = 0\%$, $p > 0.05$ *Significant small effect of reduced risk of transition to psychosis over 1 year for antipsychotic treatment groups compared to the control groups;* 3 RCTs, N = 190, RR = 0.55, 95%CI not reported, $p = 0.029$, $I^2 = 0\%$, $p > 0.05$ No subgroup analyses were performed for integrated psychological treatments (2/2 RCT reporting significant benefits) or omega-3 fatty acids (1/1 RCT reporting significant benefits).	
Consistency in results	Consistent
Precision in results	Precise where CI reported
Directness of results	Indirect (mixed treatment conditions combined and mixed control conditions combined)

Explanation of acronyms

APS = Attenuated positive symptoms, BS = Basic symptoms, BPRS = Brief Psychopathological Rating Scale, BLIPS = Brief Limited Intermittent Psychotic Symptoms, CAARMS = Comprehensive Assessment of At-Risk Mental States, CBT = Cognitive Behavioural Therapy, CI = confidence interval, CGI = Clinical Global Impression, COPS = Criteria of Prodromal Syndromes, CT = Cognitive Therapy, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect sizes), EIPS = Early intervention in the Initial Prodromal State, EPPIC = Early Psychosis Prevention and Intervention Centre, HRSA = Hamilton Rating Scale for Anxiety, HRSD = Hamilton Rating Scale for Depression, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), GAF = Global Assessment of Functioning, IT = integrated treatment, LIPS = Late Initial Prodromal State, MADRS = Montgomery and Asberg Depression Rating Scale, N = number of participants, NFI = Needs focused intervention, NS = non-significant, Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, QOL = Quality of Life Scale, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PACE = Personal Assessment and Crisis Evaluation, PANSS = Positive and Negative Symptom Score, PEPP = Prevention and Early Intervention Program for Psychosis, POPS = Presence of Psychotic Syndrome, QOL = quality of life, RCT = randomized controlled trial/s, RR = relative risk, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SC = supportive counselling, SOPS = Scale of Prodromal Symptoms, UHR = ultra-high risk, vs. = versus, , WQOLI = Wisconsin Quality of Life Index, WMD = weighted mean difference, YMS = Young Mania Scale

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[12].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[12].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[13]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[14].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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