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. 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.

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.

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.

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. Determination of the most efficacious time scale for treatment would improve interventions at each stage of psychosis progression.

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.

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[1]. 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)[2]. 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 eight systematic reviews that met our inclusion criteria[3-10].

- Moderate quality evidence suggests cognitive behavioural therapy may reduce the risk of transition to psychosis for up to two years when compared to monitoring or supportive therapy with no differences in symptoms, functioning, study retention or quality of life.
- Moderate quality evidence finds some advantages of ziprasidone plus needs-based interventions for improving attenuated psychotic symptoms when compared to needs-based interventions alone, cognitive behavioural therapy plus needs-based interventions, or risperidone plus cognitive behavioural therapy and needs-based interventions.
- There were no differences in rates of transitioning to psychosis between needs-based interventions with or without additional components (aripiprazole, olanzapine, ziprasidone, risperidone, glycine or D-serine, omega-3, cognitive behavioural therapy, integrated therapies, or family therapies).
- There were no differences between CBT, omega-3, or cognitive remediation and various control conditions for social functioning, and no differences between NMDAR modulators, CBT, omega-3, risperidone, family therapies, or cognitive remediation and control conditions for negative symptoms.

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Davies C, Cipriani A, Ioannidis JPA, Radua J, Stahl D, Provenzani U, McGuire P, Fusar-Poli P

Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis

World Psychiatry 2018; 17: 196-209

View review abstract online

Comparison	**Needs-based interventions (NBI) involving supportive psychotherapy, case management, brief family psychoeducation and support, medications other than antipsychotics, clinical monitoring and/or crisis management vs. NBI + other components (antipsychotics, other medications, cognitive behavioural therapy [CBT], integrated therapies or family therapies).** **Note: integrated therapies included individual CBT, group social skills training, cognitive remediation, and/or group family psychoeducation.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, imprecise, indirect) shows no differences between needs-based interventions with or without additional components (antipsychotics, other medications, CBT, integrated therapies or family therapies).**

Transition to psychosis

16 RCTs, N = 2,035 in the network meta-analysis

There were no significant differences between NBI and;

Aripiprazole + NBI: SMD = 0.94, 95%CI 0.15 to 5.73, $p > 0.05$

Olanzapine + NBI: SMD = 0.29, 95%CI 0.03 to 2.57, $p > 0.05$

Ziprasidone + NBI: SMD = 0.56, 95%CI 0.03 to 11.51, $p > 0.05$

D-serine + NBI: SMD = 0.64, 95%CI 0.15 to 2.68, $p > 0.05$

Omega-3 + NBI: SMD = 0.73, 95%CI 0.27 to 2.01, $p > 0.05$

CBT French & Morrison protocol (CBT-F) + NBI: SMD = 0.52, 95%CI 0.03 to 10.72, $p > 0.05$

CBT-F + risperidone + NBI: SMD = 0.21, 95%CI 0.04 to 1.08, $p > 0.05$

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CBT van der Gaag protocol (CBT-V) + CBT-F + NBI: SMD = 0.22, 95%CI 0.02 to 2.17, $p > 0.05$ Integrated psychological interventions: SMD = 0.06, 95%CI 0.00 to 1.90, $p > 0.05$ Family therapy + NBI: SMD = 0.17, 95%CI 0.01 to 2.69, $p > 0.05$ The results were similar at 12 months.	
Risks	No significant differences in acceptability.
Consistency in results‡	Consistent
Precision in results§	Imprecise
Directness of results‖	Indirect – network analysis

Davies C, Radua J, Cipriani A, Stahl D, Provenzani U, McGuire P, Fusar-Poli P

Efficacy and acceptability of interventions for attenuated positive psychotic symptoms in individuals at clinical high risk of psychosis: a network meta-analysis

Frontiers in Psychiatry 2018; 12: 187

View review abstract online

Comparison	**Any treatment for individuals at clinical high-risk vs. any other treatment.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, imprecise, indirect) shows ziprasidone + NBI was more effective for improving symptoms by 6 months than NBI alone, CBT French & Morrison protocol (CBT-F) + NBI or CBT-F + risperidone + NBI.**
Attenuated psychotic symptoms	
14 RCTs, N = 1,707 in the network meta-analysis *At 6 months, ziprasidone + NBI was more effective for improving symptoms than;* NBI alone: SMD = -1.10, 95% CI -2.04 to -0.15, $p < 0.05$ CBT-F + NBI: SMD = -1.03, 95% CI −2.05 to -0.01, $p < 0.05$ CBT-F + risperidone + NBI: SMD = -1.18, 95%CI -2.29 to -0.07, $p < 0.05$ There were no significant differences between any other interventions.	

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There were no significant differences between NBI and; Aripiprazole + NBI: SMD = -0.18, 95%CI -0.90 to 0.53, $p > 0.05$ D-serine + NBI: SMD = -0.10, 95%CI -1.05 to 0.84, $p > 0.05$ Omega-3 + NBI: SMD = -0.42, 95%CI -1.01 to 0.16, $p > 0.05$ CBT-F + NBI: SMD = -0.07, 95%CI -0.44 to 0.31, $p > 0.05$ CBT-F + risperidone + NBI: SMD = 0.08, 95%CI -0.50 to 0.67, $p < 0.05$ Family therapy + NBI: SMD = -0.41, 95%CI -1.22 to 0.41, $p > 0.05$ At 12 months, there was no evidence that any one intervention was superior over any others (NBI, integrated therapies, risperidone + CBT-F + NBI, olanzapine + NBI, aripiprazole + NBI, omega-3 + NBI, or CBT-F + NBI).

Risks	No significant differences in acceptability at 6 months. At 12 months, aripiprazole + NBI was more acceptable than olanzapine + NBI.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect – network analysis

Devoe DJ, Farris MS, Townes P, Addington J

Attenuated psychotic symptom interventions in youth at risk of psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 2018; 13: 3-7

View review abstract online

Comparison	**Any treatment for individuals at clinical high-risk of psychosis vs. any other intervention.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, indirect) finds no differences between CBT and control conditions for attenuated psychotic symptoms. Moderate to low quality evidence (small to medium-sized samples, inconsistent or imprecise or unable to assess, indirect) also finds no differences between omega-3, NMDAR modulators, risperidone + CBT, cognitive remediation or integrated treatments and control conditions.**

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Attenuated psychotic symptoms	
There were no significant differences between any intervention for up to 12 months; CBT: 6 studies, N = 500, SMD = -0.15, 95%CI -0.33 to 0.02, *p* = 0.09, I^2 = 0% Omega-3: 3 studies, N = 333, SMD = -0.31, 95%CI -0.88 to 0.26, *p* = 0.29, I^2 = 80% Risperidone + CBT: 2 studies, N = 146, MD = 0.19, 95%CI -0.92 to 1.31, *p* = 0.73, I^2 = 0% Cognitive remediation: 3 studies, N = 170, MD = 1.60, 95%CI -0.11 to 3.30, *p* = 0.07, I^2 = 0% Integrated treatment: 2 studies, N = 116, MD = 0.28, 95%CI -0.64 to 0.08. *p* = 0.13, I^2 = 0% NMDAR modulators: 2 studies, N = 43, MD = -1.19, 95%CI -4.19 to 1.80, *p* = 0.43, I^2 = 0%	
Consistency in results	Consistent, apart from omega-3.
Precision in results	Precise for CBT, imprecise for omega-3, unable to assess MDs.
Directness of results	Indirect – mixed control conditions.

Devoe DJ, Peterson A, Addington J

Negative symptom interventions in youth at risk of psychosis: a systematic review and network meta-analysis

Schizophrenia Bulletin 2018; 44: 807-23

View review abstract online

Comparison	**Any treatment for individuals at clinical high-risk of psychosis vs. any other intervention.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent or imprecise or unable to assess, indirect) finds no differences between NMDAR modulators, CBT, omega-3, risperidone, family therapies, or cognitive remediation and control conditions.**
Negative symptoms	
There were no significant differences between any intervention for up to 12 months; Risperidone: 2 studies, N = 146, MD = 0.41, 95%CI -4.45 to 5.28, *p* = 0.87, I^2 = 0% NMDAR modulators: 2 studies, N = 52, MD = -0.54, 95%CI -1.09 to 0.02, *p* = 0.06, I^2 = 0%	

Omega-3: 3 studies, N = 375, SMD = -0.06, 95%CI -0.46 to 0.35, p = 0.78, I^2 = 63% CBT: 3 studies, N = 236, SMD = -0.12, 95%CI -0.37 to 0.13, p = 0.37, I^2 = 0% Family therapy: 2 studies, N = 211, SMD = -1.17, 95%CI -3.29 to 0.95, p = 0.28, I^2 = 0% Cognitive remediation: 3 studies, N = 154, SMD = 0.21, 95%CI -0.12 to 0.53, p = 0.21, I^2 = 0% *A medium-sized, significant improvement in symptoms in pre-post analysis (no control);* Aripiprazole: 3 studies, N = 61, SMD = -0.66, 95%CI -1.03 to -0.30, p = 0.01, I^2 = 0%	
Consistency in results	Consistent, apart from omega-3.
Precision in results	Precise apart from family therapy, unable to assess MDs.
Directness of results	Indirect – mixed control conditions.

Devoe DJ, Farris MS, Townes P, Addington J

Interventions and social functioning in youth at risk of psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 13: 169-80

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Comparison	**Any treatment for individuals at clinical high-risk of psychosis for social functioning vs. various control conditions.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, precise, indirect) finds no differences between CBT, omega-3, or cognitive remediation and control conditions.**
Social functioning	
There were no significant differences between groups; CBT 6 months: 3 studies, N = 239, SMD = 0.06, 95%CI -0.35 to 0.46, p = 0.78, I^2 = 44%, p = 0.17 CBT 12 months: 4 studies, N = 321, SMD = -0.15, 95%CI -0.38 to 0.08, p = 0.20, I^2 = 6%, p = 0.36 CBT 18 months: 2 studies, N = 168, SMD = 0.20, 95%CI -0.10 to 0.50, p = 0.20, I^2 = 0%, p = 0.47 Cognitive remediation 2-3 months: 3 studies, N = 170, SMD = 0.13, 95%CI -0.18 to 0.43, p = 0.41, I^2 = 0%, p = 0.38 Omega-3 6 months: 2 studies, N = 309, SMD = 0.01, 95%CI -0.21 to 0.24, p = 0.91, I^2 = 0%, p = 0.85	

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Omega-3 12 months: 2 studies, N = 252, SMD = -0.08, 95%CI -0.33 to 0.17, p = 0.51, I^2 = 0%, p = 0.36	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Indirect – mixed control conditions.

Farris MS, Devoe DJ, Addington J

Attrition rates in trials for adolescents and young adults at clinical high-risk for psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 2019; 14(5): 515-527

View review abstract online

Comparison	**Attrition rates in trials of any intervention for clinical high-risk of psychosis vs. various control conditions.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, consistent, imprecise, indirect) finds no differences between groups in attrition rates.**

Attrition

The pooled overall trial attrition was 29.57%

There were no significant differences between groups;

CBT 6 months: 5 studies, N not reported, OR = 1.06, 95%CI 0.76 to 1.49, p > 0.05, I^2 = 0%

CBT 12 months: 5 studies, N not reported, OR = 1.02, 95%CI 0.74 to 1.42, p > 0.05, I^2 = 0%

CBT 24 months: 3 studies, N not reported, OR = 0.87, 95%CI 0.62 to 1.22, p > 0.05, I^2 = 0%

Cognitive remediation 2 months: 3 studies, N not reported, OR = 0.85, 95%CI 0.39 to 4.89, p > 0.05, I^2 = 0%

Interpersonal therapies 12 months: 2 studies, N not reported, OR = 1.06, 95%CI 0.38 to 2.98, p > 0.05, I^2 = 43%

Interpersonal therapies months: 3 studies, N not reported, OR = 0.77, 95%CI 0.46 to 1.29, p > 0.05, I^2 = 0%

Omega-3 6 months: 3 studies, N not reported, OR = 1.07, 95%CI 0.71 to 1.61, p > 0.05, I^2 = 0%

Omega-3 12 months: 3 studies, N not reported, OR = 1.53, 95%CI 0.68 to 3.43, $p > 0.05$, $I^2 = 0\%$	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect – mixed control conditions.

Hutton P, Taylor PJ

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

Psychological Medicine 2014; 44: 449-468

View review abstract online

Comparison	**CBT for 6-12 months vs. monitoring or non-specific supportive therapy.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, imprecise, indirect) suggests CBT 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.

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	**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	**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; *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	**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	

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No significant difference between groups by 6-12 months; 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	**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	

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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-sized 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

Explanation of acronyms

CBT = Cognitive Behavioural Therapy, CI = confidence interval, CT = Cognitive Therapy, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, NMDAR = glutamate, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial/s, RR = relative risk, SMD = standardised mean difference, UHR = ultra-high risk, vs. = versus

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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[11].

† 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[11].

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[12]. 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[13].

‖ 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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