Appendix A: Summary of evidence from surveillance

2021 surveillance of psychosis and schizophrenia in children and young people: recognition and management

(2013 NICE guideline CG155)

Overall surveillance proposal

We will not update the guideline at this time. We will monitor the evidence base for new evidence in the areas indicated below.

About this document

Studies were considered for inclusion using criteria defined by the guideline review protocols and are summarised from the information presented in their abstracts. More detailed summaries, including numerical data, are provided for studies assessed as having an impact on guideline recommendations or that indicate that the evidence base should be monitored.

Only CG155 guideline sections for which new evidence has been identified are discussed. Recommendations from NICE guidelines are referred to in the format *guideline number- recommendation number* e.g., CG155-1.1.1.

1.1 General principles of care

Surveillance proposal

Recommendations in this section should not be updated. We will add a link to decision-making and mental capacity (NICE guideline NG108) from 'Making decisions using NICE guidelines' which is linked to from CG155's recommendations page.

Previous surveillance

Evidence identified by the 2015 Evidence Update was assessed as being consistent with recommendations in this section. Evidence identified by the 2016 surveillance review was assessed as being consistent with recommendations in this section.

2021 surveillance

Referral from primary care

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

None identified

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

None identified.

Intelligence gathering

A topic expert highlighted shared decision-making is difficult for some people with psychosis unless they receive support, e.g., help remembering facts about treatment. They note that Principal 2 of the Mental Capacity Act (2005) (cross-referred to by CG155-1.1.2) requires practitioners to help a person make their own decision and that CG155 should cross-refer to NG108's recommendations about supporting decision-making.

Another topic expert noted that there is stigma attached to the recognition of serious mental illness and that most screening tools are devised for the 'western' British patient, which may not reflect the patients' family background.

Impact statement

One topic expert highlighted CG155 does not contain recommendations about supporting people to make shared decisions and notes this is important as schizophrenia can temporarily impair capacity. We have added decision-making and mental capacity (NICE guideline NG108) to NICE's webpage 'making decisions using NICE guidelines' which is linked to from CG155's recommendations page.

Comments about stigma and western screening tools are addressed by CG155-1.1.18. This recommends people working with those with schizophrenia should take into account the stigma and discrimination associated with schizophrenia. CG155-1.1.20 also recommends that health and social care professionals should have competence in assessment of people from diverse ethnic and cultural backgrounds.

We identified 1 ongoing trial relevant to section 1.1; the Early Youth Engagement in First Episode Psychosis (EYE-2) Randomised Controlled Trial. We will track its progress and assess its impact when it publishes.

New evidence is unlikely to change guideline recommendations.

1.2 Possible psychosis

Treatment options for symptoms not sufficient for a diagnosis of psychosis or schizophrenia

Surveillance proposal

Recommendations in this section should not be updated. We will monitor the evidence base about the use of antipsychotics for preventing transition to psychosis in children and young people with sub-diagnostic symptoms.

Previous surveillance

Two RCTs investigating cognitive behavioural therapy (CBT) as an add on to treatment as usual identified by the 2015 Evidence update (p.10) reported mixed results but overall benefit for CBT which was assessed as supporting recommendations in section 1.2. Evidence identified by the 2016 surveillance review was assessed as being consistent with recommendations in this section.

2021 surveillance summary

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

Two systematic reviews (1) (10 RCTs, n=1128, mean age 22.3 years) and (2) (26 RCTs, mean age 19.8 years) reported CBT for psychosis (CBTp) is effective for reducing transition to psychosis. The conclusions of these studies supports CG155.1.2.5 to offer CBT to people in high-risk mental states.

Two studies (3)(4) (n=304, mean age 19.3 years) report results from the NEURAPRO RCT which found omega-3 polyunsaturated fatty acid (PUFA) plus cognitive behavioural case management (CBCM) is no better than CBCM alone in reducing transition. These studies support the decision to not make any recommendations about use of omega-3 PUFAs to treat possible psychosis.

Two Cochrane Reviews (5) (n=1145) and (6) (n=780) investigated the effectiveness of specialised early intervention teams for people (age range: 16-35 years) with first episode psychosis (FEP) and early onset psychoses. Their findings support CG155-1.2.1 and 1.3.1 to refer all children and young people with possible psychosis and a first presentation of sustained psychotic symptoms to a specialist mental health service, either CAMHS or an early intervention in psychosis service.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

A network meta-analysis (7) of young adults (mean age 20.1 years) reports that there is a lack of evidence for superiority of one treatment over another for preventing transition to psychosis. This study compares combinations of psychosocial, psychological and pharmacological interventions and includes: needs-based interventions (NBI); omega-3 plus NBI; antipsychotics plus NBI; integrated psychological interventions; family therapy plus NBI; D-serine + NBI; CBT and CBT plus NBI plus antipsychotics. NBI includes supportive psychotherapy; case management; brief family psychoeducation; medications other than antipsychotics; and crisis management and monitoring. Integrated psychological therapies (IPT) were the most successful at reducing transition (OR range=0.39-0.06) but no comparison was significant. IPT may be comprised of several components, including individual family CBT, manualized group social skills training, computerised cognitive remediation, and psychoeducational multi-family group sessions.

See impact statement for rationale for monitoring the evidence base in this area.

Intelligence gathering

Four topic experts indicated recommendations about possible psychosis are a high priority for maintaining currency and provided us with new evidence. One commented that from clinical experience antipsychotics can be helpful for reducing symptoms in some children and young people at high risk of transition if psychological interventions have failed. We identified evidence-based guidelines for the pharmacological treatment of schizophrenia from the British Association for Psychopharmacology (2020) which notes that whilst antipsychotics 'can be considered for symptom relief' in people in high risk mental states this should be treated as a 'short-term therapeutic trial'. This is based on expert opinion or extrapolated from recommendations about other populations, and notes that there is 'clinical uncertainty' about this use of antipsychotics.

Impact statement

New evidence for CBT is mixed: 2 systematic reviews suggest it is effective for preventing transition; and a network meta-analysis suggests there is no significant difference between psychosocial, psychological, pharmacological therapies or combination therapies. However, the meta-analysis identified, does not assess adverse events from treatment using antipsychotics. The meta-analysis also finds IPT was the most successful at preventing transition which can include family CBT.

CG155-1.2.5 recommends individual CBT based on 6 RCTs that suggested it may have a beneficial effect on transition rates. CG155-1.2.6 recommends not offering antipsychotic medication for people with sub-diagnostic symptoms of psychosis. This was based on a consideration of side-effects which the guideline committee acknowledged were extensive and could outweigh benefits in cases were psychosis was not confirmed. Whilst intelligence indicates some practitioners might use antipsychotics for sub-diagnostic symptoms it also indicates there is minimal evidence to safely support making a recommendation. On balance new evidence favours CBT over other therapies and does not indicate the superiority of antipsychotics, a finding consistent with previous surveillance. We will monitor the evidence

base for evidence about the effectiveness of antipsychotics for preventing transition to full psychosis in children and young people with sub-diagnostic symptoms.

Results from the NEURAPRO trial report omega-3 fatty acids are ineffective in preventing transition to psychosis and addresses CG155 research recommendation 2. We will therefore stand this research recommendation down.

New evidence is unlikely to change guideline recommendations.

1.3 First episode psychosis and 1.4 subsequent acute episodes

Surveillance proposal

Recommendations in these sections should not be updated. The evidence base should be monitored for emerging evidence about the relative effectiveness of lurasidone and about adding CBT to standard care.

Treatment options – antipsychotic medication

Previous surveillance

A cohort study was identified by the 2015 evidence update (p.13-20) that reported metabolic changes caused by olanzapine are greater in children than adults. This triggered an update to CG155-1.3.14 and -1.3.15 about choice of antipsychotic medication. The 2016 surveillance review was assessed new evidence as consistent with recommendations. Topic experts highlighted the then ongoing IMPACT trial investigating antipsychotic-induced weight gain in children (see p.20-22). The impact of the published results is discussed in this document in evidence addressing research recommendation 6.

2021 exceptional review about monitoring for type 2 diabetes

The exceptional review noted that recommendations about testing for diabetes in people taking antipsychotics were inconsistent across guidelines. All NICE recommendations about adults and children taking antipsychotic medication will be amended to say that HbA1c or fasting blood glucose should be measured.

2021 surveillance summary

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

Four studies (8–11) from the 'Tolerance and Effect of Antipsychotics in Children and Adolescents with Psychosis (TEA)' trial compared quetiapine-extended release with aripiprazole in children with FEP (n=113, age 12-17 years). They reported no significant

difference, and that quetiapine is associated with significantly greater weight gain, heart rate increase and QT-interval prolongation.

A network meta-analysis (12) (average age 14.1 years) reported all antipsychotics except ziprasidone were superior to placebo for treating children with schizophrenia; and that clozapine was the most efficacious but is associated with significant weight gain.

These studies support current recommendations to not offer a named antipsychotic CG155-1.3.11); to base choice of antipsychotic on a consideration of benefits and side-effects (CG155-1.3.14); to consider treatment with antipsychotics an explicit, time limited therapeutic trial (CG155 1.3.18); to monitor their benefits and side-effects (CG155-1.3.19) and to retain research recommendation 4.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

Two studies (13,14) report results from the same RCT that investigated the effectiveness of lurasidone in children (age: 13-17 years) with exacerbation of acute symptoms. Goldman (n=326) compared PANSS at 6-weeks for lurasidone 40mg per day and 80mg per day with placebo and reports a reduction of - 18.6 with 40 mg day ($p < 0.001$ vs. placebo; effect size = 0.51) and - 18.3 with 80 mg per day ($p < 0.001$ vs. placebo; effect size = 0.48). A 2-year open-label follow-up (Correll et al.2020b) reports a discontinuation rate of 42.4%, 10.7% due to adverse events with headache (24.0%) the most common. It reports minimal weight gain at 52-weeks and 104-weeks of + 3.3 kg and + 4.9 kg, respectively compared to an expected weight gain of + 3.4 kg and + 5.7 kg, respectively; estimated from sex- and age-matched US Center for Disease Control normative data.

A systematic review (15) (54 studies about antipsychotics, n=67,764) of psychotropic medication in children and adolescents (age: less than 18 years) investigated adverse events for each drug. The study ranked antipsychotics by safety based on the number of adverse events significantly worse than placebo or no treatment relative to the number of adverse events covered by the literature. Lurasidone was ranked highest with 1/33 reported adverse event (nausea/vomiting) and olanzapine lowest with 13/25.

See impact statement for rationale for monitoring the evidence base in this area.

Intelligence gathering

Lurasidone received a licence extension in September 2020 for the treatment of schizophrenia in people aged 13 years and over. We asked topic experts if they thought this had affected practice. Five responded, 1 thought that it had impacted, the other responders indicated they did not have sufficient information to fully answer this question. One respondent commented lurasidone's licensing has widened the choice of antipsychotic options available but recommendations about it would need to take account of its relative efficacy. The same topic expert also thought CG155 recommendations should be updated to include more effectiveness information about named antipsychotics.

Impact statement

New evidence was identified for the effectiveness of lurasidone compared with placebo; that it is not associated with significant weight gain; and may be associated with less adverse events than other antipsychotics. Evidence for its head-to-head efficacy against other antipsychotics is limited to a network meta-analysis that contains only one RCT about lurasidone. This reports it is superior to fluphenazine for reducing symptoms and of comparable efficacy and tolerability to most of the other antipsychotics investigated, except clozapine, which was reported as having the best efficacy overall of the antipsychotics investigated.

CG155-1.3.14 recommends antipsychotic choice should be a shared decision that considers benefits and side-effects and 1.3.18 says this should be an explicit time limited therapeutic trial. This is based on 22 RCTs in children and 81 RCTs in adults experiencing FEP or acute episodes and an assessment of whether side-effects in children would be greater than those in adults. The committee concluded minimal differences between antipsychotics for FEP and subsequent acute episodes. They noted weight gain was the most reported adverse event, particularly in children.

New evidence supports the committee's conclusions and does not suggest CG155-1.3.14 should be changed to recommend specific antipsychotics. The recently licensed lurasidone has not been considered during development or during any previous surveillance timepoint. Whilst the evidence for lurasidone is promising, particularly its benign association with weight gain, it is limited in volume. We will therefore monitor the evidence base for any emerging evidence for lurasidone's relative effectiveness.

New evidence is unlikely to change guideline recommendations.

Treatment options– psychological and psychosocial interventions

Previous surveillance

Evidence identified by the 2015 evidence update was assessed as being consistent with recommendations in this section. Evidence identified by the 2016 surveillance review was assessed as being consistent with recommendations in this section. Topic experts highlighted the then ongoing IFCBT and COMPARE trials (see pp.14-15). Publications from both trials were identified during this surveillance review and were excluded because they reported only feasibility or baseline results.

2021 surveillance summary

Studies that impact recommendations

None identified.

Studies that do not impact recommendations

CBT

One RCT (16) reports that social recovery therapy (a type of CBT) for children and adults with FEP (n=155, age range 16-35 years) increased time spent in structured social activity. An individual participant data meta-analysis (17) (14 studies, n=898 children, young people, and adults with a diagnosis of schizophrenia, age range 15-70 years (mean: 33.9 years) reports CBTp was superior to other psychological interventions for reducing psychotic symptoms (PANSS score). These studies support CG155-1.3.11 to offer CBTp for FEP.

Arts therapies

One RCT (18) (n=275 adults, age range: 31.5 to 52.9 years) with schizophrenia reports group body psychotherapy (a form of arts therapy) reduces negative symptoms but not significantly compared with Pilates. It should be noted this trial did not include children less than 18 years old. This supports CG155-1.4.6 which recommends to consider arts therapies but does not specify a particular therapy reflecting their diversity and mixed evidence.

Social skills training

A systematic review (19) (27 RCTs, n=1437 adults with a diagnosis of schizophrenia) compared social skills training (SST) with treatment as usual/wating list control for negative symptoms reported superiority for SST with a small effects size. The new evidence is derived from non-UK RCTs, several of which have already been assessed during development of CG155, and it supports CG155-1.4.10 which accommodates the use of SST but not routinely.

Studies of various psychological therapies

One Cochrane Review (20) (7 RCTs, n=317) of children and adolescents (age range: 13-17 years) with psychosis investigated various psychological therapies and reports largely equivocal results. This supports CG155 which does not make currently make recommendations about the therapies investigated.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

Two Cochrane Reviews (21,22) were identified that report equivocal results for the superiority of CBT compared to care as usual and other psychosocial therapies.

One Cochrane Review (21) compared CBT plus standard care with standard care alone (standard care includes but is not limited to antipsychotics) in children, young people, and adults with schizophrenia (60 RCTs, n=5992 (n=801 with FEP), age range: 16 to 78 years) for several outcomes. It reports no difference for relapse prevention (RR 0.78, 95% CI 0.61 to 1.00; participants = 1538; studies = 13, low-quality evidence) or mental state change (RR 0.81, 95% CI 0.65 to 1.02; participants = 501; studies = 5). The authors assessed included studies as low or very low quality and conclude: 'The quality of evidence available is poor...we...cannot make firm conclusions until more high quality data are available.'

A second Cochrane Review (22) (36 RCTs, n=3542, age range 18 to 65 years) compared CBT plus standard care with other psychosocial interventions plus standard care. It reports no

difference between interventions for relapse (RR 1.05, 95% CI 0.85 to 1.29; participants = 375; studies = 5, low-quality evidence); rehospitalisation RR 0.96, 95% CI 0.82 to 1.14; participants = 943; studies = 8, low-quality evidence); and long-term mental state (RR 0.82, 95% CI 0.67 to 1.01; participants = 249; studies = 4, low-quality evidence). The authors conclude: 'Good quality research is needed before firm conclusions can be made' about CBT. It should be noted none of the data in this review is from children less than 18 years old.

See impact statement for rationale for monitoring the evidence base in this area.

Intelligence gathering

One topic expert commented there are significant inequalities around deprivation, and stigma about recognising mental health problems in some ethnicities and cultures that may lead to delays in engaging with talking therapies. Another commented that the use of individual CBTp with or without family therapy has become the subject of some debate with mixed evidence for its effectiveness and provided several references outlined above. They also highlighted new evidence for briefer CBTp (i.e., less than the 16 sessions recommended by CG155-1.3.29) and that individual CBT may not be superior to group CBT.

Impact statement

Addition of CBT to standard care

New evidence from 2 Cochrane Reviews suggests evidence for the addition of CBT to standard care is not superior to standard care alone or to the addition of other psychotherapies for relapse prevention or hospital readmission. The authors of both reviews note that the included evidence is of poor or very poor quality and further good quality research is needed to draw firm conclusions. It should be noted one Cochrane Review's conclusion of no superiority of CBT plus standard care compared with standard care alone for relapse reduction is based on a meta-analysis where the confidence interval touches but does not cross the line of no-effect. The authors note that additional studies will improve precision and the point estimate suggests CBT offers something additional to standard care although its cost-effectiveness is uncertain.

CG155-1.3.11 recommends an oral antipsychotic medication in conjunction with CBT. It acknowledges that people may want to try CBT alone but advises that CBT is more effective with antipsychotic medication and that CBT monotherapy should be time limited. By making this recommendation the guideline development committee explicitly acknowledge the equivocal nature of the evidence around CBT as an adjunct and the importance of patient choice. Although new evidence about adding CBT to standard care remains equivocal it does suggest some benefit and is therefore judged to support recommendations. We will monitor the evidence base about the effectiveness of adding CBT (and other psychological therapies) to standard care.

CBT duration and modality

New evidence from an individual participant meta-analysis reports CBTp is superior to other psychological therapies, a conclusion based largely on data from individual CBTp modalities. The meta-analysis included RCTs with treatment durations ranging from 4 to 52 weeks and reports patients receiving more sessions reported significantly lower total psychotic symptoms than patients who received less sessions. This evidence is largely consistent with recommendations to offer individual CBT for 16 or more sessions.

Equality of access to therapies

Topic experts noted that some subgroups may not engage with talking therapies. The guideline equality impact assessment (EIA) acknowledges this and notes: 'The scope identified that children, young people and adults with schizophrenia from black and minority ethnic (BAME) backgrounds tend to present late to services. They are more frequently subject to compulsion and have less access to psychological therapies than their white counterparts.' Recommendations 1.1.18 to 1.1.23 encourage services to work collaboratively with BAME and other minority groups, and to ensure culturally appropriate psychosocial interventions. Additionally, CG155-1.1.18 recommends being respectful and sensitive to children's socioeconomic status.

We identified the ECLIPSE Study 9 and will assess its impact on recommendations when it publishes in 2022.

New evidence is unlikely to change guideline recommendations.

1.8 Interventions for children and young people whose illness has not responded adequately to treatment

We identified the ongoing CLEAR: (CLozapine in EARly psychosis) trial a multi-centre RCT of Clozapine for Young People with Treatment Resistant Psychosis in Real World Settings. We will monitor its progress and assess its impact on CG155-1.8.9 on publication.

Research recommendation 6 – weight management interventions for children and young people being treated with antipsychotics.

One study (23) discussed below which reports the results of the IMPACT trial was identified which addresses CG155 research recommendation 6: 'What is the most effective management strategy for preventing the development of excessive weight gain and metabolic syndrome associated with the use of antipsychotic medication in children and young people?'

We carried out systematic searches to check for RCTs or systematic reviews investigating weight management interventions for children and young people being treated with antipsychotics and identified 2 additional studies which are summarised below.

Surveillance proposal

New evidence is unlikely to impact recommendations. We will monitor the evidence base for weight management interventions for people receiving antipsychotics and consider the need for recommendations across all NICE guidelines as a whole that currently recommend antipsychotics.

Previous surveillance

No evidence was identified during the 2015 evidence update or 2016 surveillance review for weight management interventions.

2021 surveillance summary

Studies that impact recommendations

None identified

Studies that do not impact recommendations

Behavioural

One RCT (24) (n=203, age range: 13-17 years) reports no difference in BMI between single and multiple weight counselling sessions for adolescents receiving clozapine for schizophrenia or bipolar I disorder. CG155 does not make recommendations about weight management counselling but it is accommodated by 1.5.3 in obesity: identification, assessment and management (NICE guideline CG189).

Pharmacological

One RCT (25) (n=61) reports betahistine is no better than placebo for its effect on weight gain in adults and adolescents (age not given in abstract) although a clozapine-receiving sub-group (n=26) did have significant reductions. Betahistine is not licensed for this indication and this small experimental investigation does not suggest new recommendations need to be made.

Studies that do not impact but indicate a need to monitor the evidence base for emerging evidence

An RCT (23) (n=127) compared the effects of metformin, switching antipsychotics (to aripiprazole or if already exposed to that drug, perphenazine or molindone) or continuing baseline antipsychotics on the BMI of children and adolescents (age range: 8-19 years) who had gained weight following antipsychotic treatment for schizophrenia spectrum disorder, bipolar spectrum disorder or psychotic depression. All participants received healthy lifestyle education. It reports that at 24-weeks BMI z-score decreased significantly in the metformin (-0.09±0.03, p=0.002) and switch groups (-0.11±0.04, p=0.003), and increased non-significantly in the control group (+0.04±0.03). Metformin and 'switching' were each superior to the control group (p=0.002), with effect sizes of 0.68 and 0.81 respectively, but did not

differ significantly from each other. Psychiatric symptoms improved in all groups and did not significantly differ

See impact statement for rationale for monitoring the evidence base in this area.

Intelligence gathering

We identified guidelines from the Royal Australian and New Zealand College of Psychiatrists for the management of schizophrenia and related disorders (2016) covering adults and children that recommends metformin. This is based on a single placebo-controlled trial in adults (age range: 20-65 years) that reports adjunctive metformin prevented weight gain and reduced BMI. Metformin is not licensed for managing weight gain or for prevention of diabetes in children. Obesity: identification, assessment and management (NICE guideline CG189) makes no recommendations about metformin for children but recommendation 1.8.6 recommends orlistat for children aged 12 years and older if physical or severe psychological comorbidities are present. Recommendation 1.8.4 advises drug treatment for children less than 12 years old is not recommended.

Impact statement

New evidence from one study suggests metformin and 'switching' antipsychotics are superior to advice about weight management. This study was conducted in a population of US children of whom less than 10% had schizophrenia spectrum disorder and therefore its direct relevance to CG155's population is questionable. The study potentially impacts CG155-1.3.4 which accommodates giving weight management advice but supports CG155-1.3.18 which accommodates 'switching'. However, as CG155-1.3.18 does not specify named antipsychotics, the new evidence for switching only applies to those antipsychotics used in the study. Further, whilst the study reports positive outcomes for metformin it also reports a significant association with gastrointestinal side-effects although drop-out in the metformin arm was minimal (4/46).

The 2018 surveillance review of CG189 identified evidence that metformin reduces BMI and bodyweight in obese children but assessed it as unlikely to impact on CG189, due to metformin's licensing status and evidence quality. New evidence identified by this surveillance of CG155 adds to this, but due to uncertainty about its relevance to CG155's population it is not enough alone to make a recommendation about metformin.

In addition to CG155 NICE guidelines on bipolar disorder (CG185), psychosis and schizophrenia in adults (CG178), and antisocial behaviour and conduct disorders in children and young people (CG158) also make recommendations about antipsychotics. None of these currently contain specific recommendations about interventions to minimise weight gain associated with their use beyond cross-referral to other NICE guidelines and monitoring indicators of weight gain and cardiovascular risk. We will therefore monitor for new evidence about weight management in people receiving antipsychotics and consider the need for recommendations across these guidelines as a whole.

New evidence is unlikely to change recommendations.

References

1. Zheng Y, Xu T, Zhu Y, Li C, Wang J, Livingstone S, et al. Cognitive Behavioral Therapy for Prodromal Stage of Psychosis-Outcomes for Transition, Functioning, Distress, and Quality of Life: A Systematic Review and Meta-analysis. Schizophr Bull. 2021;

2. Mei C, M van der G, Nelson B, Smit F, HP Y, Berger M, et al. Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. Clin Psychol Rev. 2021;86:102005.

3. McGorry, PD, Nelson B, Markulev C, HP Y, MR S, Mossaheb N, et al. Effect of omega-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders: The NEURAPRO Randomized Clinical Trial. JAMA psychiatry. 2017;74(1):19–27.

4. Nelson B, GP A, HP Y, Markulev C, Lavoie S, MR S, et al. NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders-medium-term follow-up and clinical course. NPJ Schizophr. 2018;4(1):11.

5. Puntis S, Minichino A, De Crescenzo F, Harrison R, Cipriani A, Lennox B. Specialised early intervention teams for recent-onset psychosis. Cochrane Database Syst Rev [Internet]. 2020;(11). Available from: http://dx.doi.org/10.1002/14651858.CD013288.pub2

6. Puntis S, Minichino A, De Crescenzo F, Harrison R, Cipriani A, Lennox B. Specialised early intervention teams (extended time) for recent-onset psychosis. Cochrane Database Syst Rev [Internet]. 2020;(11). Available from: http://dx.doi.org/10.1002/14651858.CD013287.pub2

7. Davies C, Cipriani A, JPA I, Radua J, Stahl D, Provenzani U, et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. World Psychiatry. 2018;17(2):196–209.

8. Pagsberg AK, Jeppesen P, DG K, KG J, Ruda D, Stentebjerg-Olesen M, et al. Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. The lancet Psychiatry. 2017;4(8):605–18.

9. Jensen KG, CU C, Ruda D, DG K, Stentebjerg-Olesen M, Fagerlund B, et al. Pretreatment Cardiometabolic Status in Youth With Early-Onset Psychosis: Baseline Results From the TEA Trial. J Clin Psychiatry. 2017;78(8):e1035–46.

10. Jensen KG, Gartner S, CU C, Ruda D, DG K, Stentebjerg-Olesen M, et al. Change and dispersion of QT interval during treatment with quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: results from the TEA trial. Psychopharmacology (Berl). 2018;235(3):681–93.

11. Jensen KG, CU C, Ruda D, DG K, MS D, Fagerlund B, et al. Cardiometabolic Adverse

Effects and Its Predictors in Children and Adolescents With First-Episode Psychosis During Treatment With Quetiapine-Extended Release Versus Aripiprazole: 12-Week Results From the Tolerance and Effect of Antipsychotics in Children and Adolescents With Psychosis (TEA) Trial. J Am Acad Child Adolesc Psychiatry. 2019;58(11):1062–78.

12. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol. 2018;28(6):659–74.

13. Goldman R, Loebel A, Cucchiaro J, Deng L, RL F. Efficacy and Safety of Lurasidone in Adolescents with Schizophrenia: A 6-Week, Randomized Placebo-Controlled Study. J Child Adolesc Psychopharmacol. 2017;27(6):516–25.

14. Correll CU, RL F, Tocco M, Pikalov A, Deng L, Goldman R. Safety and effectiveness of lurasidone in adolescents with schizophrenia: results of a 2-year, open-label extension study. CNS Spectr. 2020;1–11.

15. Solmi M, Fornaro M, EG O, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020;19(2):214–32.

16. Fowler D, Hodgekins J, French P, Marshall M, Freemantle N, McCrone P, et al. Social recovery therapy in combination with early intervention services for enhancement of social recovery in patients with first-episode psychosis (SUPEREDEN3): a single-blind, randomised controlled trial. The lancet Psychiatry. 2018;5(1):41–50.

17. Turner DT, Reijnders M, M van der G, Karyotaki E, LR V, Moritz S, et al. Efficacy and Moderators of Cognitive Behavioural Therapy for Psychosis Versus Other Psychological Interventions: An Individual-Participant Data Meta-Analysis. Front psychiatry. 2020;11:402.

18. Priebe S, Savill M, Wykes T, RP B, Reininghaus U, Lauber C, et al. Effectiveness of group body psychotherapy for negative symptoms of schizophrenia: multicentre randomised controlled trial. Br J Psychiatry. 2016;209(1):54–61.

19. Turner DT, McGlanaghy E, Cuijpers P, M van der G, Karyotaki E, MacBeth A. A Meta-Analysis of Social Skills Training and Related Interventions for Psychosis. Schizophr Bull. 44(3):475–91.

20. Datta SS, Daruvala R, Kumar A. Psychological interventions for psychosis in adolescents. Cochrane Database Syst Rev [Internet]. 2020;(7). Available from: http://dx.doi.org/10.1002/14651858.CD009533.pub2

21. Jones C, Hacker D, Xia J, Meaden A, Irving CB, Zhao S, et al. Cognitive behavioural therapy plus standard care versus standard care for people with schizophrenia.

Cochrane Database Syst Rev [Internet]. 2018;(12). Available from: http://dx.doi.org/10.1002/14651858.CD007964.pub2

22. Jones C, Hacker D, Meaden A, Cormac I, CB I, Xia J, et al. Cognitive behavioural therapy plus standard care versus standard care plus other psychosocial treatments for people with schizophrenia. Cochrane database Syst Rev. 11:CD008712. Available from: https://doi.org/10.1002/14651858.CD008712.pub3

23. Correll CU, Sikich L, Reeves G, Johnson J, Keeton C, Spanos M, et al. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. World Psychiatry. 2020;19(1):69–80.

24. Detke HC, DelBello MP, Landry J, Hoffmann VP, Heinloth A, Dittmann RW. A 52-Week Study of Olanzapine with a Randomized Behavioral Weight Counseling Intervention in Adolescents with Schizophrenia or Bipolar I Disorder. J Child Adolesc Psychopharmacology 2016;26(10):922–34.

25. Smith RC, Maayan L, Wu R, Youssef M, Jing Z, Sershen H, et al. Betahistine effects on weight-related measures in patients treated with antipsychotic medications: a double-blind placebo-controlled study. Psychopharmacology 2018;235(12):3545–58.