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Attenuated Psychotic Symptom Interventions in Youth at Risk of Psychosis: A Systematic Review and Meta-Analysis

Daniel J Devoe, MSc¹, Megan Farris, MSc¹, Parker Townes, BSc¹, and Jean Addington, PhD¹

¹Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Alberta, Canada

Abstract

Aim—Attenuated psychotic symptoms, APS) have been the primary emphasis in youth at clinical high risk, CHR) for psychosis for assessing symptomology and determining subsequent transition to a psychotic disorder. Previous reviews primarily focused on the efficacy of cognitive behavioral therapy, CBT) on APS, however a comprehensive assessment of other interventions to date is lacking. Therefore, we conducted a systematic review and meta-analysis of all intervention studies examining APS in CHR youth.

Method—The authors searched Embase, CINAHL, PsycINFO, Medline, and EBM from inception to May 2017. Studies were selected if they included any intervention that reported follow-up APS in youth at CHR. Interventions were evaluated and stratified by time using both pairwise and network meta-analyses, NMA). Due to the differences in APS scales, effect sizes were calculated as Hedges *g* and reported as the standardized mean difference, SMD).

Results—Forty-one studies met our inclusion criteria. In pairwise meta-analyses, CBT was associated with a significant reduction in APS compared to controls at 18 to 24-month follow-up, SMD, −0.22; 95% CI, −0.43 to −0.01; $I^2=0\%$; $P=0.04$, 3 studies, $N=356$). In the NMA, integrated psychological therapy, CBT, supportive therapy, family therapy, needs based interventions, omega-3, risperidone plus CBT, and olanzapine were not significantly more effective at reducing APS at 6- and 12-months relative to any other intervention.

Conclusions—CBT was more effective at reducing APS at long-term follow-up compared to controls. No interventions were significantly more effective at reducing APS compared to all other interventions in the NMA.

1. Introduction

Attenuated psychotic symptoms, APS) have been the primary emphasis in youth at clinical high risk, CHR) of psychosis in terms of assessing current symptomology and determining criteria for being at CHR and subsequent transition to full-blown psychosis, Paolo Fusar-Poli et al., 2013; P. Fusar-Poli & Van Os, 2013; McGlashan, Walsh, & Woods, 2010). APS are often assessed by measures such as the Comprehensive Assessment of At-Risk Mental State, CAARMS), Alison R. Yung et al., 2005) or the Structured Interview of Psychosis-Risk

Syndromes, SIPS), McGlashan et al., 2010). APS typically include unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication. Both severity of APS and unusual thought content, disorganized communication, and suspiciousness have been shown to be predictive of transition to psychosis, Jean Addington et al., 2017; Barbara A. Cornblatt et al., 2015; Paolo Fusar-Poli et al., 2013), thus examining the impact of interventions on APS may help inform clinical guidelines and future trials. Interestingly, most treatment studies in CHR samples have focused primarily on diminishing transition rates to a psychotic disorder with the mean reduction of APS usually as a secondary aim.

To date, only two traditional pairwise meta-analyses have examined the effects of interventions on APS in CHR youth. Both reviews primarily focused on the efficacy of cognitive behavioral therapies, CBT) and found that CBT had a small effect on the reduction of APS at 12-months, P. Hutton & Taylor, 2014; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013). However, since then, treatment studies in CHR samples have significantly increased and encompass novel interventions such as cognitive remediation therapy, CRT), glycine, D-serine, and omega-3. Our review, therefore, includes not only CBT studies but all interventions and explores their impact on APS as a primary outcome, using both traditional pairwise meta-analyses and a network analysis. Executing a network meta-analysis, NMA) allows for indirect comparisons between intervention arms in randomized controlled trials that have not previously been compared, e.g. CBT to family therapy to antipsychotics) and that use common comparators, e.g. supportive therapy or placebo). By including new interventions, more studies, and incorporating both direct and indirect evidence, the evidence base for APS interventions in CHR youth will be expanded.

2. Method

Protocol

We conducted this systematic review and meta-analysis according to a protocol established a priori, PROSPERO [International Prospective Register of Systematic Reviews] number: CRD42017067291) and reported in accordance with PRISMA and MOOSE guidelines, B. Hutton, Salanti, Caldwell, & et al., 2015; Liberati et al., 2009; Moher et al., 2015; Stroup, Berlin, Morton, & et al., 2000). PRISMA checklists are provided for both the pairwise and the NMA in Supplementary Material 1, B. Hutton, Salanti, Caldwell, Chaimani, et al., 2015; Moher, Liberati, Tetzlaff, & Altman, 2009).

Objective

The primary objective of this systematic review and meta-analysis was to summarize and analyze the impact of all interventions on APS in youth at CHR of psychosis.

Data Sources and Search Strategy

The authors conducted database searches in PsycINFO, Medline, Embase, CINAHL, and EBM from inception to May 2017. All search details are shown in Supplementary Material 2. Each reviewer, PT and MF) autonomously completed title and abstract screening, and the full-text of any study considered appropriate according to the selection criteria was retrieved

for a comprehensive review. In addition, a Scopus, (<https://www.scopus.com>) search was conducted using the key words “psychosis risk” and “treatment” and both the Clinicaltrials.gov registry and The International Clinical Trials Registry Platform, (<http://apps.who.int/clinicaltrialssearch/>) were searched using the terms “psychosis” and “risk”. Lastly, reference lists of included full-text articles were hand-searched for relevant citations.

Study Selection

Two reviewers, PT and MF) independently assessed the full-text of each relevant study for inclusion. Studies that met the following eligibility criteria were selected: 1) studies including participants at risk of psychosis meeting criteria for at-risk mental state, ARMS), attenuated psychosis symptom syndrome, APSS), or schizotypy; 2) studies including non-randomized observational studies and RCTs; 3) studies reporting follow-up attenuated psychotic symptom scores using either the Scale for the Assessment of Positive Symptoms, SAPS), Andreasen, 1984), Brief Psychiatric Rating Scale, BPRS), Overall & Gorham, 1962), the Positive and Negative Syndrome Scale, PANSS), Kay, Fiszbein, & Opfer, 1987), the Scale of Prodromal Symptoms, SOPS), Miller et al., 2003), or the Comprehensive Assessment of At-Risk Mental States, CAARMS), Alison R Yung et al., 2005), and, 4) studies reporting a mean age between 12–30. Studies were not excluded based on languages. Case reports, review articles, editorials, and studies that did not employ an intervention were excluded. Differences were resolved by a third co-author, DD or JA).

Data Extraction

Two co-authors extracted all data in duplicate, PT and MF) and a third, DD) verified it. Extracted data included study characteristics, author, publication year, country, study design, CHR sample size, and attenuated psychotic symptom scales), patient characteristics, mean $\pm$ *SD* age, number of/percent male), and treatment characteristics, intervention, control, duration, endpoint). The following clinical outcome data were extracted from RCTs: 1) mean $\pm$ *SD* APS at follow-up, 2) mean $\pm$ *SD* APS changes from baseline scores to follow-up scores, 3) sample size per treatment group. If articles only provided standard error or confidence intervals, a standard deviation was obtained using the Cochrane Handbook methods, J.P.T. Higgins & Green, 2011). We obtained additional data by contacting corresponding authors, obtaining follow-up or review articles, and extracting data from graphs using GraphClick software in duplicate, Boyle, Samaha, Rodewald, & Hoffmann, 2013).

For randomized studies risk of bias was evaluated using the Cochrane Collaboration’s tool for assessing risk of bias, J.P.T. Higgins & Green, 2011). For non-randomized studies, the Risk-Of-Bias In Non-randomized Studies of Interventions, ROBINS-I) was utilized to appraise quality of evidence, Sterne et al., 2016). In the NMA, the Grading of Recommendations Assessment, Development and Evaluation, GRADE) approach was used to evaluate the quality of evidence associated with the results in the NMA at each time point, Puhan et al., 2014).

Data Synthesis and Analysis

Due to the differences in scales used to assess APS the principal summary measures used across the majority of meta-analyses, i.e. pairwise and network meta-analyses) were effect sizes calculated as Hedges g . Hedges g was reported as the standardized mean difference, SMD) of APS scores at follow-up, Julian P. T. Higgins, Green, & Scholten, 2008). However, in pairwise analysis if APS were rated on the same scale the pooled mean difference, MD) was reported instead of the SMD. D-serine and glycine, herein: NMDAR modulators) are both amino acids that serve as neuromodulators that act as coagonist on the NMDAR with glutamate, Javitt & Zukin, 1991; Scott W. Woods et al., 2013), therefore we combined both treatments in the pairwise and the NMA. Enhanced care, treatment as usual, community care, monitoring, and needs focused interventions were coalesced as needs based interventions in meta-analyses due to similarities in design. Due to expected differences between studies due to study design, dose, CHR criteria, and the idiosyncratic treatment strategies, all results were combined using random-effects models. Only RCTs were included in both pairwise and NMA. The kappa statistic was used to determine inter-rater reliability for title and abstract screening. All SMDs, effect sizes) with a $P < .05$ were considered significant and as a typical guide SMDs of 0.2 represented a small effect, 0.5 a medium effect, and 0.8 a large effect, Cohen, 1988).

For the primary analysis, direct treatment effects on APS from interventions were combined using a pairwise random-effects model by DerSimonian and Laird, DerSimonian & Laird, 1986). APS was stratified by available time points, e.g. 6-months, 12-months, 18-months). Thus, the likelihood of a reduction in APS in CHR youth who received a similar intervention was compared to a control intervention. Direct treatment comparisons and risk of bias were analyzed using Review Manager 5, Collaboration, 2011). Statistical heterogeneity was calculated using the I^2 statistic with an $I^2 \leq 50\%$ indicating substantial heterogeneity and an $I^2 > 75\%$ indicating considerable heterogeneity with a $P < .05$ considered significant.

For the secondary analysis, treatment effects between intervention arms in RCTs were evaluated using a random-effects multivariate NMA assuming consistency and a common heterogeneity across all comparisons in the network using the generic inverse-variance method, Caldwell, Ades, & Higgins, 2005; Dias, Sutton, Ades, & Welton, 2013). We opted for a random effects multivariate network meta-analysis as described by White, White, 2011) and Higgins, J. Higgins et al., 2012) because it can handle more than two arms in one RCT, I. R. White, J. K. Barrett, D. Jackson, & J. Higgins, 2012) and properly accounts for correlations between effect sizes from multi-arms in RCTs. Arms in RCTs that were observational in nature, e.g., monitoring) was excluded from the NMA and studies including additional participants other than CHR were excluded from the NMA, e.g., schizotypy). The formulae for Hedges' g detailed by White and Thomas 2005, White & Thomas, 2005) was used to calculate the SMD for the NMA, which is considered an unbiased estimator and involves corrections for small numbers of degrees of freedom. APS was stratified by available time points, i.e., 6-months and 12-months). Transitivity is an important assumption in a network meta-analysis, which assumes that comparisons in the network model are consistent, Cipriani, Higgins, Geddes, & Salanti, 2013; Jansen & Naci, 2013; Salanti, 2012). Therefore, both a global test for inconsistency, I. R. White, J. K. Barrett, D. Jackson, & J. P.

Higgins, 2012) and inconsistency plots assuming loop-specific heterogeneity were produced to determine if inconsistency existed in the NMA, Chaimani, Higgins, Mavridis, Spyridonos, & Salanti, 2013; Dias, Welton, et al., 2013; Song, Altman, Glenny, & Deeks, 2003; Veroniki, Vasiliadis, Higgins, & Salanti, 2013). In addition, baseline characteristics, age, CHR criteria, percent male) that might modify the treatment effect were restricted using an a priori inclusion criteria to prevent inconsistencies from being introduced into the model. Surface under the cumulative ranking curve, SUCRA) plots were inspected to establish the most effective interventions compared to a better hypothetical treatment, the quicker the curve advances to one, the more probable it will be more effective, Chaimani et al., 2013; Salanti, 2012). Network comparison-adjusted funnel plots, Chaimani et al., 2013) were used to evaluate publication bias by arrangement of interventions as active treatment vs controls. Data in the network meta-analysis were analyzed using Stata, version 13.1, StataCorp LP). The graphical toolset in Stata called “networkplot” was utilized to generate graphical illustrations of the network evidence, Chaimani et al., 2013).

3. Results

Search Yield

The search produced 3,164 citations after duplicates; 2,995 citations were excluded after reviewing title and abstract. Study eligibility agreement between reviewers for abstract and title screening was high, $\kappa=0.86$). A total of 170 articles were retrieved for full-text review. Of these, 41 primary studies were eligible for inclusion in our systematic review, 17 were included in pairwise meta-analyses and 13 were included in the NMA. See Figure 1 for reasons for exclusion.

Study and Participant Characteristics

Characteristics of the 41 studies included in the systematic review are outlined in Table 1. Of the 41 studies, 19 studies were conducted in North America, 11 in Europe, four in Australia, six in Asia, and one multi-national study. Twenty-four studies measured APS with the SOPS, PANSS, $N=11$), SAPS, $N=3$), BPRS, $N=4$), and the CAARMS, $N=4$). The number of CHR participants ranged from 6 to 304, for a total of 3,146 CHR participants. The mean age was 19.6 years, $SD=2.98$) and 1,680, 53.4%) were male, range=28–75%).

Features of Treatment Interventions and Controls

The mean treatment duration was 30.0 weeks, range=4–104 wks.). Interventions included: cognitive remediation therapy, $N=6$), Choi et al., 2016; Hooker et al., 2014; Loewy et al., 2016; Piskulic, Barbato, & Addington, 2012; Rauchensteiner et al., 2011; Urben, Pihet, Jaugey, Halfon, & Holzer, 2012), family-based treatments, $N=5$), Grano et al., 2016; Landa et al., 2016; McFarlane et al., 2015; Miklowitz Dj, 2014; O'Brien et al., 2007), CBT, $N=6$), J. Addington et al.; Kim et al., 2011; Morrison Ap, 2004; Morrison et al., 2012; Stain et al., 2016; van der Gaag et al., 2012), aripiprazole, $N=3$), Kobayashi et al., 2009; Liu et al., 2013; S. W. Woods et al., 2007), NMDAR modulators, $N=3$), Kantrowitz et al., 2016; S. W. Woods et al.), omega-3, $N=3$), Amminger et al.; Cadenhead et al., 2017; Patrick D. McGorry et al., 2017), integrated psychological intervention, $N=3$), Albert et al., 2016; Nordentoft et al., 2006; Wessels et al., 2015), risperidone plus CBT, $N=2$), McGorry Pd, 2013; P. D. McGorry

et al., 2002), amisulpride, $N=1$), Ruhrmann et al., 2007), olanzapine, $N=1$), McGlashan Th, 2006), low-dose lithium, $N=1$), Berger et al., 2012), ziprasidone, $N=1$), S. Woods et al., 2017), perospirone, $N=1$), Tsujino et al., 2013), second generation anti-psychotics, $N=1$), Cornblatt et al., 2007), antipsychotics not specified, $N=3$) (Morita et al., 2014; Shim et al., 2008; Walker et al., 2009), and heart rate variability biofeedback training, $N=1$), McAusland & Addington, 2016). The control conditions varied as well; placebo, $N=8$), computer games, $N=4$), needs based interventions, $N=12$), supportive therapy, $N=3$), and enhanced care, $N=1$). Thirteen studies did not use a control group.

Risk-of-Bias Assessment

Quality assessment of RCTs, $N=23$) is reported in Figure 2. All RCTs had a low risk of bias for random sequence generation, $N=23$). RCTs had low risk of bias for allocation concealment, 56%) and selective reporting, 75%). Studies had a higher risk of bias for attrition bias, $N=9$) and other biases such as pharmaceutical funding, $N=6$). Blinding of participants and personnel had the highest risk of bias, $N=10$). Quality assessment of observational studies using ROBINS-I and the quality of the NMA using GRADE are reported in Supplementary Material 3.

Network Pattern and Network Plot

The network formed complex star-shaped network plots at both 6 and 12-months due to having many competing interventions. In addition, the network plots had some sparse connections, e.g., integrated psychological therapy and family therapy). Placebo and needs based interventions were the most common comparators, Figure 3).

Consistency and Publication Bias

Visual inspection of the comparison-adjusted funnel plots at 6- and 12-month follow-up for symmetry demonstrated the absence of small study effects with most observations falling on the null line, Supplementary Material 4). Global tests of inconsistency and inconsistency plots found no statistically significant evidence of inconsistency in the NMA, Supplementary Material 4).

Primary and Secondary Outcomes of Meta-analyses

Psychosocial Interventions—In the pairwise analyses, CBT interventions were not associated with a significant reduction in APS compared to controls at 6 and 12 months, SMD, -0.08 ; 95% CI, -0.26 to 0.10 ; $I^2=0\%$; $P=0.37$, 5 studies, $N=499$ vs SMD, -0.15 ; 95% CI, -0.33 to 0.02 ; $I^2=0\%$; $P=0.09$, 6 studies, $N=500$; Supplementary Material 5). However, CBT was associated with a significant reduction in APS compared to controls at 18 to 24-month follow-up, SMD, -0.22 ; 95% CI, -0.43 to -0.01 ; $I^2=0\%$; $P=0.04$, 3 studies, $N=356$). In the 6 and 12-month NMA, CBT interventions were not significantly more effective at reducing APS compared to any other intervention, Figure 4). At 12-months, SUCRA plots of the absolute effects and rank test among the 7 treatments indicated that CBT ranked higher than the other 6 treatments but this is in the context of no statistically supported efficacy compared to other interventions, see Supplementary Material 4).

In the NMA family therapy was not significantly more effective at reducing APS compared to all other interventions at 6-months. At 6-months, SUCRA plots of the absolute effects and rank test among the 6 treatments indicated that family therapy ranked higher than the other 5 treatments but this is in the context of no statistically supported efficacy compared to other interventions, see Supplementary Material 4). In the NMA, IPT was not significantly more effective at reducing APS compared to any other intervention at 12-months.

Antipsychotics—In the pairwise analyses, risperidone plus CBT interventions were not associated with a significant reduction in APS at 6 or 12-month follow-up, MD, 0.39; 95% CI, -0.93 to 1.71; $I^2=46\%$; $P=0.56$, 2 studies, N=146 vs MD, 0.19; 95% CI, -0.92 to 1.31; $I^2=0\%$; $P=0.73$, 2 studies, N=110; Supplementary Material 5). In the 6-month and 12-month NMA, risperidone plus CBT interventions were not significantly more effective at reducing APS compared to any other intervention. Amisulpride and ziprasidone could not be analyzed in pairwise analyses or the NMA. Olanzapine could only be analyzed in the 12-month NMA and was not significantly more effective at reducing APS compared to any other intervention.

NMDAR modulators—In the pairwise analyses, NMDAR modulator interventions were not associated with a significant reduction in APS compared to placebo, MD, -1.19; 95% CI, -4.19 to 1.80; $I^2=0\%$; $P=0.43$, 2 studies, N=43; Supplementary Material 5). No NMDAR modulator studies were evaluated in the NMA due to having no comparable time-point, e.g., 6- or 12-months).

Omega-3—In the pairwise analyses, omega-3 interventions were not associated with a significant reduction in APS at 3-, 6-, or 12-month follow-up compared to placebo, SMD, -0.23; 95% CI, -0.60 to 0.14; $I^2=26\%$; $P=0.23$, 2 studies, N=153 vs SMD, -0.34; 95% CI, -0.97 to 0.29; $I^2=87\%$; $P=0.30$, 3 studies, N=389 vs SMD, -0.31; 95% CI, -0.87 to 0.26; $I^2=81\%$, $P=0.30$, 3 studies, N=347; Supplementary Material 5). In the 6- and 12-month NMA, omega-3 was not significantly more effective at reducing APS compared to any other intervention.

Cognitive remediation therapy—In the pairwise analyses, CRT interventions were not associated with a significant reduction in APS compared to computer games, MD, 1.60; 95% CI, -0.11 to 3.30; $I^2=0\%$; $P=0.07$, 3 studies, N=170; Supplementary Material 5). No CRT studies were not assessed in the NMA because it was not connected to any treatment in the network.

Integrated Treatment in Schizotypy—In the pairwise analyses, integrated treatments were not associated with a significant reduction in APS compared to standard care at long-term follow-up, 2–3.5 years) in studies that targeted schizotypy participants only, MD, -0.29; 95% CI, -0.72 to 0.14; $I^2=0\%$; $P=0.18$, 2 studies, N=116; Supplementary Material 5). Schizotypy studies were not assessed in the NMA because it would violate the transitivity assumption.

4. Discussion

In summary, this systematic review compared the effects of CBT, family therapy, integrated psychological therapy, risperidone plus CBT, olanzapine, omega-3, and NMDAR modulators on reducing APS in CHR populations using both pairwise and network meta-analyses. First, pairwise meta-analyses revealed that CBT was associated with a significant reduction in APS compared to control treatments 18 to 24-month follow-up, based on $n=356$), with a trend towards significance at 12-month follow-up, based on $n=500$). Risperidone plus CBT, NMDAR modulators, omega-3, and integrated treatments were not significantly better than controls in pairwise analyses.

In the NMA there were no significant results at both 6- and 12-months with all confidence intervals crossing the null line. However, there were some trends and effect sizes that may be of interest. First, there was a trend favoring family therapy over the majority of interventions at both 6-month follow-up and a trend favoring CBT at 12-months, compared to most other treatments.

CBT demonstrated a statistically significant benefit over controls at reducing APS at 18–24 month follow-up. This is contrary to a previous meta-analysis which reported that CBT reduced APS at 12 months but not at 6 months or long-term follow-up, P. Hutton & Taylor, 2014). However, in the current review we did find a trend towards a significant reduction in APS at 12 months. This discrepancy in significance between reviews may be due to the presence of two additional CBT studies; one which demonstrated no impact on APS compared to controls, Stain et al., 2016), and the other which demonstrated at long term follow-up a large effect at reducing APS, Morrison et al., 2012). Regardless, both this and the previous reviews demonstrated similar effect sizes for CBT. Finally, there was a trend favoring CBT relative to other treatments at reducing APS in the 12-month NMA, albeit it was not significant.

Next, there was a trend favoring family therapy relative to other treatments at reducing APS in the NMA at 6-months, albeit it was not significant. Unfortunately, there was only one RCT examining family therapy in CHR youth and thus, the results of the NMA should be interpreted with caution until larger RCTs investigating the impact of family therapy in CHR samples emerge. However, three observational studies in CHR samples have examined the impact of family therapy on APS in CHR samples all of which have found favorable results for family therapy, Landa et al., 2016; McFarlane et al., 2015; O'Brien et al., 2007). In addition, family interventions in patients with schizophrenia have a well-established effectiveness at reducing positive symptoms and are recommended by several international clinical guidelines, Caqueo-Urizar, Rus-Calafell, Urzúa, Escudero, & Gutiérrez-Maldonado, 2015). A recent meta-analysis in early psychosis samples demonstrated that family interventions significantly decreased both relapse and readmission rates, Bird et al., 2010).

Strengths and limitations

This review included 41 interventions with more than 3,100 CHR youth. We searched multiple electronic databases, hand searched references to identify interventions, reviewed studies and extracted data in duplicate, published our protocol a priori, and followed

PRISMA and MOOSE guidelines. Thus, making this review the most comprehensive systematic review and largest meta-analysis of APS interventions in CHR to date. However, our study has important limitations to consider.

First, there is a lack of high-quality studies that examine interventions in CHR and the impact these interventions have on APS. Almost half of the RCTs failed to blind assessors from their respective treatment groups. Indeed, a lack of blinding of outcome assessments may have introduced important biases such as detection biases and performance biases which may have inflated the effect on APS in RCTs that failed to blind assessors, Julian P T Higgins et al., 2011).

Second, we pooled a variety of APS scales using the SMD which may have important implications when interpreting the current results. The majority of studies employed the SOPS scale for measuring APS which includes unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication. However, the PANSS was the second most commonly reported measure of APS which includes two additional positive symptoms, i.e., excitement and hostility) and was developed to measure psychotic symptoms in patients with schizophrenia. Interestingly, although a consensus for negative symptoms exists no consensus has emerged for positive symptoms in schizophrenia, Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Thus, future considerations should be given to the strengths and weaknesses of available instruments for measuring APS and a collective agreement of what constitutes APS in CHR should be explored by CHR researchers.

Third, there was only one closed loop of evidence at both 6- and 12-month thus inconsistency can only statistically be examined between the nodes in these loops. A global test for inconsistency at 6- and 12-month revealed no significant evidence of inconsistency. Other contributions of inconsistency were further examined using GRADE.

Fourth, another issue that arises from this NMA is that consistency of the indirect evidence cannot be adequately checked against direct evidence, especially given the limited amount of trials included in this NMA. Even though we found nothing statistically significant in terms of inconsistency in this NMA these results should be interpreted with great caution because there is a limited amount of data. Moreover, this NMA formed a complex star-shaped network and had many sparse connections, which elucidates the lack of direct evidence available in CHR studies. Indeed, the emergence of more trials in the future may change the results of this NMA entirely.

Fifth, in this NMA several estimates have been based on little data and without direct evidence. Moreover, there were many large confidence intervals as can be seen in the NMA forest plots and thus the results may be based more on interference than on the actual impact of any particular intervention. Due to this lack of precision the results should be interpreted cautiously. In addition, a lack of direct comparisons in a star-shaped network coupled with a limited amount trials could have inflated the chances of a type 2 error, which in this case may have led to the false-negative conclusion that a particular type of intervention had no effect. Indeed, as more trials emerge a single new trial could ultimately alter all of the results

and conclusions made in this NMA. Thus, one should interpret the results of the NMA with great caution.

Sixth, risperidone plus CBT and omega-3 pairwise meta-analyses exhibited significant amounts of heterogeneity, but in meta-analyses of very few studies the I^2 statistic may not be accurate, von Hippel, 2015).

Directions for future research

The findings of the current systematic review and meta-analysis may inform several areas for future research. First, further RCTs are needed to explore the effect of family therapy. Such investigations may want to consider age of the young person, impact of expressed emotion, O'Brien et al., 2006), and implementation, Caqueo-Úrizar et al., 2015). Moreover, future studies should investigate what specific components of family therapy are more effective at reducing APS, e.g. family involvement, stress management, communication training) compared to a treatment that is matched in time and clinician exposure. Finally, future CBT trials may need to consider optimal dose of treatment, and timing of intervention.

Conclusions

In conclusion, CBT was more effective at reducing APS at long-term follow-up compared to controls in pairwise analyses. No interventions were significantly more effective at reducing APS compared to all other interventions in the NMA. Family therapy although promising, require more clinical trials to determine a more precise and generalizable effect in CHR youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
PRISMA flow diagram of systematic search and included studies.

Figure 2.

Figure 3.

Figure 4.

Table 1

Details of Included Studies, N=41)

Author, Year	Country	Study Design	Intervent on	Control	Treatment Duration (weeks)	Included Analysis	CHR Patients		Baseline Positive M±SD	Change score End of treatment – baseline	Positive Symptom	Positive Symptom Measure
Cognitive Behavioral Therapy												
Addington, 2011	Canada	RCT	CBT	Supportive therapy	24	PW, NMA	51	CBT: 20.8±4.5 Supportive: 21.1±3.7	CBT: 10.8±4.1 Supportive: 12.3±5.0	CBT: -4.4 Supportive: -4.7	Both groups improved	SOPS
Ising, 2016	Netherlands	RCT	CBT + TAU	TAU	24	PW, NMA	196	CBT: 22.7±5.6 TAU: 22.6±5.4	CBT: 10.2±3.0 TAU: 10.3±2.6	CBT: -6.1 TAU: -5.4	Both groups improved	CAARMS
Kim, 2011	Korea	Open label	CBT	None	10	NA	22	19.4±4.4	11.4±3.0	-4.7	Significantly improved	PANSS, SOPS
Morrison, 2004	United Kingdom	RCT	CBT	TAU	26	PW, NMA	58	22±4.5	CBT: 15.6±3.5 TAU: 13.8±2.7	CBT: -5.1 TAU: -2.9	CBT improved significantly compared to TAU	PANSS
Morrison, 2012	United Kingdom	RCT	CBT + monitoring	Monitoring	24	PW, NMA	288	20.7±4.3	CBT: 38.7±6.8 Monitoring: 38.2±17.8	CBT: -20.8 Monitoring: -19.5	Both groups improved	CAARMS
Stam, 2016	Australia, New Zealand	RCT	CBT + TAU	TAU	24	PW, NMA	57	CBT: 16.2±2.7 TAU: 16.5±3.2	CBT: 10.2±4.5 TAU: 9.5±3.5	CBT: -6.5 TAU: -7.8	Both groups improved	CAARMS
Family-based Therapy												
Gruno, 2016 [†]	Finland	Naturalistic	FCTM	TAU	52	NA	56	FCTM: 15.5±1.6 TAU: 16.3±0.8	RCTM: 0.02±0.9 TAU: -0.2±0.8	RCTM: 0.6 TAU: 0	No change	SOPS-psychoicism factor score
Landa, 2016	USA	Open label	Group and family-based CBT	None	15	NA	6	19.5±1.5	7.7±5.1	-6.2	Significantly improved	CAARMS, PANSS
McFarlane, 2015	USA	RDD [†]	FACIT	None	104	NA	205	16.4±3.3	15.5±NR	-5.9	Significantly improved	SOPS
Miklowitz, 2014	USA + Canada	RCT	FFT	Enhanced care	24	NMA	129	17.4±4.1	FFT: 12.4±1.4 Enhanced care: 11.7±1.3	FFT: -4.6 Enhanced care: -1.9	FFT improved significantly compared to enhanced care	SOPS
O'Brien, 2007	USA	Open label	PMFG	None	36	NA	16	15.7±NR	13.6±NR	-4.7	Significantly improved	SOPS
Omega-3												
Amminger, 2010	Austria	RCT	Omega-3 PUFA: 1.2 g/day	Placebo	12	PW, NMA	81	Omega: 16.8±2.4 Placebo: 16.0±1.7	Omega: 15±3.4 Placebo: 14.2±3.1	Omega: -4.4 Placebo: -1.5	Omega group improved compared to placebo	PANSS
Cadenhead, 2017 [†]	USA, Canada	RCT	Omega-3:740 mg EPA, 400 mg DHA/day	Placebo	52	PW, NMA	127	18.8±NR	Omega: 12.58±3.4 Placebo: 12.38±4.19	Omega: -5.19 Placebo: -5.77	Both groups slightly improved	SOPS
McGorry, 2017 [†]	Multi-national	RCT	Omega-3 w-3 PUFA: 1.4 g/day + CBCM	Placebo + CBCM	24	PW, NMA	304	19.1±4.6	Omega: 7.7±NR Placebo: 7.9±NR	Omega: -2.3 Placebo: -2.4	Omega improved significantly compared to placebo	BPRS
Cognitive Remediation												
Choi, 2016 [†]	USA	RCT	CRT	Active control	8	PW	62	18.4±3.7	CRT: 14.9±3.8 Control: 13.3±4.3	CRT: 0.2 Control: 1.7	No difference between groups	SOPS
Hooker, 2014	USA	Open label	CRT	Computer games	8	NA	14	21.9±4.2	14.3±4.8	-4.8	Symptoms improved	SOPS
Loewy, 2016	USA	RCT	CRT	Computer games	8	PW	83	CRT: 17.8±3.1 Control: 18.7±4.6	CRT: 10.5±3.4 Control: 9.4±4.4	CRT: -1.8 Control: -2.7	Both groups improved	SOPS
Piskulic, 2015 [†]	Canada	RCT	CRT	Computer games	12	PW	32	CRT: 19.7±5.7 Games: 17.5±5.5	CRT: 10.1±4.7 Games: 8.6±4.8	CRT: -1.8 Games: -3.1	Both groups improved	SOPS
Rauchensteiner, 2011	Germany	Open label	CRT	None	4	NA	10	27.2±5.3	10.9±10.3	-6.6	No change	PANSS
Urban, 2012	Switzerland	RCT	CRT	Computer games	8	NA	12	CRT: 15.4±1.3 Games: 15.7±1.4	CRT: 14.1±6.2 Games: 13.7±5.9	CRT: -0.4 Games: -1.3	No difference	PANSS
Integrated Psychological Therapies												
Albert, 2016	Denmark	RCT	IPT	TAU	104	PW	83	26.6±4.4	IPT: 1.0±0.8 TAU: 1.0±0.8	IPT: 0.1 TAU: 0.1	Both groups slightly improved	SAPS

Author, Year	Country	Study Design	Control	Intervent on	Treatment Duration (weeks)	Included in Analysis	CHR Patients			Baseline Positive MELD	Change score (End of treatment – baseline)	Positive Symptom	Positive Symptom Measure
							N	Age M±SD	Male N, %				
Nordenfloth, 2006	Denmark	RCT	TAU	IPT	104	PW	79	24.9±4.9	53, 67)	IPT: 0.9±1.0 TAU: 1.0±1.0	IPT: –0.3 TAU: –0.1	IPT group improved compared to TAU	SAPS
Wosch, 2015		RCT											
	Germany	RCT	Supportive therapy	IPT	52	NMA	128	IPT: 25.2±5.4 Supportive: 26.8±6.2	81, 63)	IPT: 9.2±2.3 Supportive: 8.8±2.0	IPT: –1.2 Supportive: –1.2	Both groups significantly improved	PANSS
N-methyl-D-aspartate-receptor (NMDAR) modulators													
Knutrowitz, 2016	USA	RCT	Placebo	D-serine: 60 mg/kg	16	PW	35	D-serine: 19±3.5 Placebo: 19±3.5	23, 65)	D-serine: 9.4±4.6 Placebo: 11.0±4.0	D-serine: –1.9 Placebo: –2.9	Both groups improved	SOPS
Woods, 2013 [‡]	USA	Open label	None	Glycine: 0.8 g/kg/day	8	NA	10	17.3±3.3	7, 70)	11.3±3.3	–5.7	Significantly improved	SOPS
Woods, 2013	USA	RCTd	Placebo	Glycine: 0.8 g/kg/day	12	PW	8	Glycine: 15.3±0.5 Placebo: 16.5±2.4	6, 75)	Glycine: 14.8±2.2 Placebo: 13.0±2.8	Glycine: –2.3 Placebo: –2.0	Glycine improved compared to placebo	SOPS
Antipsychotics													
Aripiprazole													
Kobayashi, 2009	Japan	Open label	None	Aripiprazole: 7.1–10.7 mg/day	8	NA	36	23.4±5.6	15, 42)	14.8±4.1	–6.8	Significantly improved	SOPS
Liu, 2013	Taiwan	Open label	None	Aripiprazole: 3.8–15 mg/day	4	NA	11	21.3±3.5	6, 55)	13.3±2.1	–3.5	Significantly improved	PANSS
Woods, 2007	USA	Open label	None	Aripiprazole: 5–30mg/day	8	NA	15	17.1±5.5	8, 53)	13.6±3.7	–10.0	Significantly improved	SOPS
Risperidone + CBT													
McGorry, 2002	Australia	RCT	NBI	Risperidone: 1–2 mg/day + CBT	24	PW, NMA	59	20±4.0	34, 58)	Risperidone: 4.7±2.7 NBI: 4.6±2.6	Risperidone: –1.6 NBI: –1.0	Both groups improved	BPRS
McGorry, 2013	Australia	RCT	Supportive therapy + placebo or monitoring	Risperidone 0.5–2 mg/day + CBT or CBT + placebo	52	PW, NMA	193	18.1±3.0	81, 42)	Risperidone + CBT: 6.6±2.3 CBT + placebo: 6.6±3.5 Supportive: 5.8±2.2 Monitoring: 5.0±3.4	Risperidone + CBT: –4.0 CBT + placebo: –4.1 Supportive: –3.5 Monitoring: –3.5	All groups improved	BPRS
Other Anti-psychotics													
Comblant, 2007	USA	Naturalistic	Anti-depressants: varied	Second generation anti-psychotics: varied	24	NA	48	Treatment: 16.3±2.6 TAU: 15.7±1.9	29, 60)	Anti-psychotics: 8.5±NR Anti-depressants: 10.5±NR	NR	Both groups improved	SOPS
McGlashan, 2006	USA + Canada	RCT	Placebo	Olanzapine: 5–15 mg/day	52	NMA	60	Olanzapine: 18.2±5.5 Placebo: 17.2±4.0	39, 65)	Olanzapine: 10.7±5.7 Placebo: 9.6±4.3	Olanzapine: –3.5 Placebo: 0.31	No difference between groups	SOPS, PANSS
Morita, 2014	Japan	Naturalistic	None	Supportive therapy and/or psychotropic medication.	52	NA	46	23.5±6.6	13, 28)	18.9±4.8	0.7	No change	SOPS
Ruhmann, 2007	Germany	RCT	NFI	Amisulpride mean dose 118.7 mg/day + NFI	12	NA	124	25.6±6.3	70, 57)	Amisulpride: 13.3±3.8 NFI: 12.8±4.0	Amisulpride: –2.6 NFI: –1.0	Amisulpride + NFI improved compared to NFI	PANSS
Shim, 2008	Korea	Open label	None	Anti-psychotics varied	varied	NA	27	21.5±4.8	16, 59)	8.8±6.5	–2.0	Significantly improved	PANSS, SAPS
Tajima, 2013	Japan	Open Label	None	Perospirone: 4.0–10.2 mg/day	26	NA	11	26.7±6.5	4, 36)	15.0±2.1	–8.8	Significantly improved	SOPS
Walker, 2009	Canada, USA	Naturalistic	No medication	Anti-depressant/anti-psychotic treatments varied	NR	NA	191	18.6±4.7	107, 56)	Anti-psychotics at baseline and follow-up: 14.4±5.0 Anti-psychotics at baseline and follow-up: 14.4±5.0	–7.7	Anti-psychotic groups improved compared to no anti-psychotic use groups	SOPS
Woods, 2017 [‡]	USA	RCT	Placebo	Ziprasidone: 20–160 mg/day	52	NA	50	22.3±NR	32, 64)	Ziprasidone: 13.8±3.8 Placebo: 11.4±3.5	Ziprasidone: –9.0 Placebo: –4.9	Ziprasidone improved compared to placebo	SOPS
Mood Stabilizers													
Berger, 2012	Australia	Open Label	Monitoring	Low-dose lithium: 450 mg/day	52	NA	103	Lithium: 20.1±3.4 Monitoring: 17.8±2.6	45, 32)	Lithium: 6.5±2.0 Monitoring: 5.8±3.0	Lithium: –3.0 Monitoring: –2.7	Both groups improved	BPRS
Other interventions													
McAusland, 2016	Canada	Open label	None	HRV biofeedback training	4	NA	20	16.7±2.3	6, 30)	8.6±3.8	–1.5	Significantly improved	SOPS

Abbreviations: APS= Attenuated psychosis syndrome; ARMS= At-risk mental state; BPRS= Brief psychiatric rating scale; CAPE= Community assessment of psychiatric experiences; CAARMS= Comprehensive assessment of at-risk mental states; CBCM= Cognitive-behavioral case management; CBT= cognitive behavioral therapy; COPS= Criteria for prodromal symptoms; CRT= cognitive remediation therapy; DHA= docosahexaenoic acid; DSM-IV= Diagnostic and statistical manual for mental disorders 4th edition; EPA= eicosapentaenoic acid; FACT= Family-aided assertive community treatment; FCTM= Family- and community-oriented integrative treatment model; FFT= Family focused therapy; HRV= Heart rate variability; ICD= International IPT= Integrated psychological therapy; NFI= Needs focused

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intervention; NR= not reported; PANSS= Positive and negative syndrome scale; PMFG= Psychoeducational multi-family group; PUFA= polyunsaturated fatty acid; RDD= Regression discontinuity design; RCT= Randomized controlled trial; SAPS= Scale for the assessment of positive symptoms; SOPS= Scale of *prodromal symptoms*; SSRIs= Selective serotonin reuptake inhibitors; TAU= treatment as usual; USA= United States of America

⁷Positive symptom data obtained from corresponding authors

[‡]Multinational trial: Australia, Switzerland, Germany, Denmark, Hong Kong, Austria, and Singapore

[§]Article was translated from German to English using the Google Translator Kit

[¶]Risk-based Allocation Design