COMPARATIVE EFFECTIVENESS OF ACUTE PHASE INTERVENTIONS DURING FIRST EPISODE PSYCHOSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

PROTOCOL

Version 3.2 (February 2017)

Charlotte Cliffe, 1 Franco De Crescenzo, 2 Cinzia Del Giovane, 3 Daniel Maughan, 4 Belinda Lennox, 4, 5 Andrea Cipriani 5

1 Kings College London, London, UK - charlotte.cliffe@kcl.ac.uk (C Cliffe)

2 Institute of Psychiatry and Clinical Psychology, Catholic University of the Sacred Heart, Rome, Italy – decrescenzo.franco@gmail.com (F De Crescenzo)

3 Cochrane Italy, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy and Institute of Social and Preventative Medicine (ISPM), University of Bern, Switzerland- cinzia.delgiovane@unimore.it (C Del Giovane)

4 Oxford health NHS foundation trust, Oxfordshire, UK- Daniel.Maughan@oxfordhealth.nhs.uk (D Maughan)

5 Department of Psychiatry, University of Oxford, Oxford, UK – belinda.lennox@psych.ox.ac.uk (B Lennox), andrea.cipriani@psych.ox.ac.uk (A Cipriani)

Corresponding Author:

Andrea Cipriani, MD PhD
Department of Psychiatry
Warneford Hospital
OX3 7JX, Oxford
UK
Tel: +44 (0)1865 618228 or 618202
Email: andrea.cipriani@psych.ox.ac.uk
Introduction

A first episode of psychosis (FEP) affects about 1 in 200 of the population during the course of a year. 80% of those affected are between 16 years to 30 years old and the average age of onset is 22. Psychosis is characterised by symptoms such as hallucinations, delusions, thought disorder and altered perceptions. Psychosis is primarily associated with a diagnosis of Schizophrenia but may also result in Schizoaffective Disorder, Bipolar Disorder, Delusional Disorder or Major Depressive Disorder with psychotic features or remain as a Brief Psychotic Disorder or diagnosed as Unspecified Psychosis. About 25% of those who are diagnosed with Schizophrenia will make a full recovery and have no further episodes of psychosis. The global burden in terms of cost for Schizophrenia is estimated between 1.5-3% of total national health care expenditures in developed countries.

Current treatment guidelines recommend Early Intervention Services (EIS) for all patients presenting with a first episode of psychosis to provide intensive treatment for up to three years. Treatments provided by EIS include both pharmacological and psychological interventions. Randomised controlled trials (RCTs) have investigated whether the EIS model of care is effective, as well as specific therapies such as individual placement support and family therapy improve outcomes during the acute phase of FEP, there is conflicting evidence as to the efficacy of these interventions. Pharmacological interventions, including both atypical and typical antipsychotics, such as haloperidol, quetiapine, olanzapine, ziprasidone, risperidone and clozapine have also be assessed using RCTs among FEP patients, however it is unclear if one is more superior. There is some suggestion clozapine causes a reduction in symptoms during the first year and that olanzapine has a greater tolerability. Studies have demonstrated a shorter duration of untreated psychosis is
associated with better outcomes in the long term, based on symptom remission and functional outcomes.\textsuperscript{16,17} Therefore determining which treatments, whether pharmacological or psychological, improve symptoms during the acute phase of FEP is important. Although current guidelines recommend EIS in those with FEP, the purpose of this study is to determine which elements of the care within the service provide the most effective treatment.

The interventions may vary from single pharmacological treatments to complex interventions such as EIS. EIS includes both intense psychological and pharmacological intervention specific for treating first episode psychosis. In comparison standard community care teams, may also include a variety of psychological and pharmacological interventions, however, not specifically aimed at treating first episode psychosis. Therefore, there may be a number of components within each intervention, adding to the complexity of this study. It is also possible to hypothesize that there are common ingredients throughout the treatment interventions that share the same components and if this is the case, we will attempt to group these components together. The objective of this review is to provide an up-to-date review on the comparative efficacy and acceptability of different psychological and pharmacological interventions (either as monotherapy or add-on therapy) in the treatment of the acute phase of FEP.

A network meta-analysis (NMA) allows us to compare these interventions directly against one another in the treatment of the acute phase of FEP. To overcome the limitations of the available comparisons and to allows us to compare these interventions against one another also indirectly.\textsuperscript{18} In NMA, the information available from within-trial direct comparisons of interventions A and B is combined with indirect comparisons of A and B derived from trials that compare either of the two interventions with a common comparator C (either a third psychological intervention or a control condition).\textsuperscript{19} NMA has previously been
used to investigate the effectiveness of pharmacological treatments for depression\textsuperscript{20} and mania,\textsuperscript{21} and in the evaluation of psychological interventions for depression\textsuperscript{22} and PTSD.\textsuperscript{23}

\textbf{Methods}

\textbf{Types of studies}

\textit{Inclusion criteria}

Only RCTs, including cluster design, comparing interventions against either a control comparison, such as treatment as usual, or a comparison treatment, conducted during the acute phase of a first episode psychosis. For an intervention to qualify it has to be implemented for an individual or family member. Both single and double-blinded trials will be included. We will only include trials reported as full text articles (we will not include studies reported as abstract only).

\textit{Exclusion criteria}

Quasi-randomized controlled trials, in which treatment assignment is decided through methods such as alternate days of the week, will be excluded. Medical or psychiatric comorbidity will not be an exclusion criterion.

\textbf{Types of participants}

\textit{Inclusion criteria}

Participants aged 18 or older, within the acute phase of a first episode of psychosis with an onset of less than 3 years. The acute phase includes participants who currently exhibit
symptoms that match the criteria for Schizophrenia spectrum diagnoses\(^8\) according to standardised criteria such as the Diagnostic and Statistical manual of mental disorders: DSM III, DSM III-R, DSM IV, DSM IV-TR, DSM 5,\(^{24,25,26}\) ICD 10,\(^{27}\) or Melbourne Criteria.\(^{28}\). Some studies may include some patients aged less than 18, these will only be included if the mean age of the patient population is greater than 18. Studies conducted in both inpatient and outpatient settings will be included.

**Exclusion criteria**

We will exclude studies recruiting children or adolescents (i.e. less than 18 years old). Studies with participants who have a diagnosis of organic psychosis or head injury will also be excluded. Long term, relapse prevention studies will be excluded.

**Types of interventions**

The aim is to include all interventions aimed at treating the acute phase of first episode psychosis. Interventions may include: EIS, community care teams, counselling sessions, family therapies, individual placement support, adherence coping therapy and home based care. Pharmacological treatments may include antipsychotics (for example olanzapine, quetiapine, risperidone, clozapine and ziprasidone) or other drugs, such as modafinil and ethyl-eicosapentaenoic acid. The interventions vary considerably from the number of components to the timings of treatment administration (for example home visits daily or once a week) and the members within the teams providing the treatments.

We will obtain further information about the components in both the early intervention and control teams from the authors, where not available. The synthesis comparator set consists of all the interventions listed above, their combinations and placebo (if the search strategy will retrieve other eligible interventions, we will include them in the network).
We assume that any patient that meets all inclusion criteria is likely, in principle, to be randomised to any of the interventions in the synthesis comparator set.

**Grouping of interventions**

If possible the services and interventions will be grouped together based on expert advice and they will independently group together the treatments within the services. Initially, we will group interventions with common ingredients, in other words, which share common methods, assumptions or structure (see Introduction). In order not to be biased by the retrieved evidence, we will merge – if possible - the interventions “a priori” through after discussing with experts (who will independently find an agreement about grouping) a consensus process within the review group will be relied on before selecting the final list of references to be included in the review and before carrying out the statistical analyses.

**Types of outcome measures**

*Primary Outcomes*

1. Reduction of psychotic symptoms during the acute phase treatment of a first episode psychosis according to a standardised scale, such as Positive and negative symptom scale (PANSS)$^{20}$ or Brief Psychiatric Rating Scale (BPRS)$^{30}$ or any other standardised scale at time points: 6 weeks, 3 months and 1 year.

2. All-cause dropouts.

*Secondary Outcomes*

1. Symptoms of depression measured using a standardised scale, such as the Calgary Depression Scale$^{31}$ or Hamilton Depression Rating Scale$^{32}$ or any other standardised scale.
2. Assessment of social and occupational functioning based on a measurement scale such as the Social and Occupational Functioning Assessment Scale (SOFAS) tool, status of employment, global assessment of functioning, the quality of life assessment tool\textsuperscript{13} or any other standardised scale.

3. Adverse events such as weight gain, metabolic features, QT prolongation and extrapyramidal symptoms or any other adverse outcomes reported.

4. Dropouts due to adverse events.

\textit{Search methods for identification of studies}

\textit{1. Electronic searches}

Searches for published studies will be undertaken in the following electronic bibliographic databases: CENTRAL, MEDLINE, CINAH and Web of Science. The search will be performed in each database using the MeSH terms, text word or subject headings relevant to that database and included in the following terms: [(psychosis OR early psychosis OR first episode psychosis) AND (early intervention service OR community care team OR counselling session OR family therapy OR individual placement support OR adherence coping therapy OR home based care OR pharmacological treatment)]. No language restriction will be applied (see Appendix for full details on the search strategy).

\textit{Searching other resources}

\textit{Research registers}

We will search ClinicalTrials.gov and the World Health Organization's trials portal (ICTRP) to identify unpublished or ongoing studies.

\textit{Grey literature}
We will conduct complementary searches of the following drug approval agencies for additional published and unpublished data: The European Medicines Agency (EU), the Food and Drug Administration (US), the Medicines and Healthcare products Regulatory Agency (UK), the Medicines Evaluation Board (Netherlands), the Medical Products Agency (Sweden), the Pharmaceuticals and Medical Devices Agency (Japan), and the Therapeutic Goods Administration (Australia).

Reference lists

We will check the reference lists of all included studies, relevant papers and previous systematic reviews for identification of additional studies that may be missed by the electronic database searches. We will undertake a cited reference search of the included studies in the Web of Science.

Personal communication

Subject experts will be contacted to check that all relevant studies, either published or unpublished, have been considered for inclusion.

Data collection and analysis

Selection of studies

Three review authors will examine the abstracts of all publications obtained through the search strategy. Full articles of all the studies identified by either of the review authors will then be obtained and inspected by the same review authors to identify trials meeting the following criteria: (i) randomised controlled trial; (ii) participants with FEP diagnosed by operationalised criteria; (iii) diagnosis within 3 years before entering the trial; (iv) phase specific intervention (i.e. acute treatment). Conflicts of opinion regarding eligibility of a study will be discussed with a fourth review author (AC), having retrieved the full paper and
consulted the authors if necessary, until consensus is reached. Methodological experts will be consulted if necessary.

**Data extraction and management**

*Outcome data*

We will extract from each included study the total score on any standardised scale (with the corresponding standard deviation), the duration of the intervention, the number of participants, the dropout rates, the number of patients that responded and the interventions being compared. A data extraction form will be designed to ensure consistency of collection and appraisal for each study.

*Data on potential effect modifiers*

We will extract from each included study data on the following study, intervention and population characteristics that may act as effect modifiers:

1. Year of publication
2. Baseline severity
3. Number of previous treatments (treatment naïve patients will be defined as those who had received less than 12 weeks’ treatment prior to the trial and then underwent a washout phase)
4. Blinding (outcome assessors)

At least two review authors (CC, FDC or DM) will independently extract data from each study independently. Degree of agreement between the independent raters will be reported in terms of kappa coefficients and percentage agreements for main outcomes, study and population characteristics and risk of bias items. Any disagreement will be resolved through discussion and in consultation with the principal investigators (AC, BL). Where necessary, the authors of the studies will be contacted for further information. Information relating to
study population, sample size, interventions, comparators, potential biases in the conduct of the trial, and outcomes will be abstracted from the original reports into specially designed paper forms, and then entered into a spreadsheet.

**Assessment of risk of bias in included studies**

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool, as a model.34

The following 6 domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of outcome assessors (performance bias): was knowledge of the allocated treatment adequately prevented during assessment?
4. Incomplete outcome data for the primary outcomes: were incomplete outcome data adequately addressed?
5. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?
6. Sponsorship (or intellectual) bias.

A description of what was reported to have happened in each study will be provided, and a judgment on the risk of bias will be made for each domain, based on the following three categories:

- High risk of bias
- Low risk of bias
- Unclear risk of bias.

The independent review authors will assess the risk of bias in selected studies. Degree of agreement between the two independent raters will be reported. Any disagreement will be
resolved through discussion and in consultation with the principal investigators (AC, BL).

Where necessary, the authors of the studies will be contacted for further information.

**Measures of treatment effect**

Continuous outcomes: Where different measures are used to assess the same outcome, data will be pooled with standardized mean difference (SMD) Hedges’s adjusted $g_{34}$.

Dichotomous outcomes will be analysed by calculating the odds ratio (OR).

**Dealing with missing data**

Missing dichotomous outcome data will be managed according to the intention to treat (ITT) principle, and it will be assumed that patients in the full analysis set who dropped out after randomization had a negative outcome. Missing continuous outcome data will either be analysed on an endpoint basis, including only participants with a final assessment, or analysed using last observation carried forward (LOCF) to the final assessment, if LOCF data were reported by the trial authors. When p-values, t-values, confidence intervals or standard errors are reported in articles, SD will be calculated from their values. Where SDs are missing, attempts will be made to obtain these data through contacting trial authors. Where SDs are not available from trial authors and the vast majority of actual SDs are available and only a minority of SDs are unavailable or unobtainable, a method used for imputing SDs will be used. We will check that the original standard deviations are properly distributed, so that the imputed standard deviation represents the average. Where this method is employed, data will be interpreted with caution, taking account of the degree of heterogeneity observed. A sensitivity analysis will also be undertaken to examine the effect of the decision to use imputed data.
**Assessment of clinical and methodological heterogeneity within treatment comparisons**

The studies synthesized in each pairwise comparison should be similar enough in terms of patient characteristics, setting, outcome definitions etc. in order to obtain interpretable and useful results. To evaluate the presence of clinical and methodological heterogeneity we will generate descriptive statistics for trial and study population characteristics across all eligible trials. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics.

**Assessment of transitivity across treatment comparisons**

The assumption of transitivity (i.e. one can compare indirectly treatments B and C via treatment A) underlies NMA and needs careful evaluation. In case that transitivity is not plausible in a network of trials, the indirect and mixed treatment effect estimates are not valid. To infer about the assumption of transitivity:

1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether interventions are administered the same way in studies comparing active treatments to usual care (or no treatment) and in those comparing active treatments to other active treatments.

2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons (see ‘Data extraction and management’ for the list of potential effect modifiers). If the distributions are balanced across comparisons we will conclude against evidence of intransitivity.

**Data synthesis**

**Methods for direct treatment comparisons**
Initially, we will perform standard pairwise meta-analyses using a random effects model in STATA for every treatment comparison with at least two studies.

Methods for indirect and mixed comparisons

We will also perform NMA to synthesise the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will use the methodology of multivariate meta-analysis where the different treatment comparisons are treated as different outcomes. This approach is described in detail in White et al. For this analysis we will use STATA (network and mvmeta packages). Results from the NMA will be presented as summary relative effect sizes (SMD or OR) for each possible pair of treatments. We will also estimate the ranking probabilities for all interventions of being at each possible rank. Then, we will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA can also be expressed as a percentage interpreted as the percentage of efficacy/safety of a treatment that would be ranked first without uncertainty. We will present jointly the relative ranking of treatments for efficacy and acceptability. Such outputs will be created in STATA (network graphs package).

Assessment of statistical heterogeneity

Assumptions when estimating heterogeneity

In standard pairwise meta-analyses we will estimate a different heterogeneity variance for each pairwise comparisons. In NMA we will assume a common estimate for the heterogeneity variance across the different comparisons.

Measures for heterogeneity
We will assess statistically the presence of heterogeneity within each pairwise comparison using the I-squared statistic and its 95% confidence interval that measures the percentage of variability that cannot be attributed to random error.

The assessment for the presence of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ($\tau^2$) estimated from the NMA models. The magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner and Rhodes for dichotomous and continuous outcomes respectively. We will also estimate a total I-squared value for heterogeneity in the network as described elsewhere. We will also obtain the predictive intervals of the relative effects to assess how much each comparison is affected by the heterogeneity regarding the additional uncertainty anticipated in a future study.

**Assessment of statistical inconsistency**

NMA assumes that there is consistency in the network (i.e. direct and indirect evidence are in agreement). However, the assumption of consistency can be violated either in the entire network or in certain parts (i.e. loops of evidence). We will evaluate the presence of inconsistency using the following approaches:

**Local tests**

To evaluate the presence of inconsistency locally we will use the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer about the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the network graphs package in STATA.
Global tests

To check the assumption of consistency in the entire network simultaneously we will use the ‘design-by-treatment’ model as described by Higgins and colleagues.\textsuperscript{56} This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer about the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in STATA using the network package.\textsuperscript{43} Inconsistency and heterogeneity are inter-weaved; to distinguish between these two sources of variability we will employ the I-squared for inconsistency that measures the percentage of variability that cannot be attributed to random error or heterogeneity (within comparison variability).\textsuperscript{50}

Investigation of heterogeneity and inconsistency

If we find important heterogeneity or/and inconsistency, we will explore the possible sources. If sufficient studies are available, we will perform meta-regression or subgroup analyses by using the following effect modifiers as possible sources of inconsistency and or heterogeneity: (i) year of publication; (ii) study precision; (iii) baseline severity; (iv) blinding.

GRADE quality assessment of the comparisons in the network

The quality of the evidence contributing to the network will be assessed using the GRADE framework for the primary outcomes.\textsuperscript{57} This assesses five characteristics within the studies: indirectness, imprecision, inconsistency, study limitations and publication bias. According to the GRADE framework each network estimate starts high and can be downgraded according to its fulfilment of each of these domains.
Sensitivity analysis

In order to examine if the obtained results are preserved when we limit the included studies to those with lower risk of bias, we will examine the following variable:

1. Imputation – Trials where standard deviations have been imputed will be excluded.
2. Comorbidity - Trials with participants with medical or psychiatric comorbidity will be excluded
References


43. White IR. Network meta-analysis. 2015 The STATA Journal (in press)


Appendix. Full search strategy

1. CENTRAL (via onlinelibrary.wiley.com)
   #1 psychoses 478
   #2 psychosis:TI,AB,KY 2951
   #3 (early psychosis):TI,AB,KY 107
   #4 (first episode psychosis):TI,AB,KY 287
   #5 (early intervention service):TI,AB,KY 28
   #6 (early intervention services):TI,AB,KY 41
   #7 (community care team ):TI,AB,KY 3
   #8 (community care ):TI,AB,KY 769
   #9 (counselling session ):TI,AB,KY48
   #10 counselling :TI,AB,KY 2190
   #11 (family therapy ):TI,AB,KY 1098
   #12 (individual placement support ):TI,AB,KY 4
   #13 (individual placement ):TI,AB,KY 100
   #14 (adherence coping ):TI,AB,KY 4
   #15 (coping therapy):TI,AB,KY 8
   #16 (home based care ):TI,AB,KY 54
   #17 (home based ):TI,AB,KY 2632
   #18 (pharmacological treatment):TI,AB,KY 1346
   #19 #1 OR #2 OR #3 OR #4 3264
   #20 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 8007
   #21 #19 AND #20 190

2. MEDLINE (via PubMed)
   1. "Early Intervention (Education)"[Mesh]
   2. "Community Health Services"[Mesh]
   3. "Community Mental Health Services"[Mesh]
   4. "Counseling"[Mesh]
   5. "Psychotherapy"[Mesh]
   6. "Family Therapy"[Mesh]
   7. "Home Care Services, Hospital-Based"[Mesh]
8. "Drug Therapy"[Mesh]
9. “early intervention service”[tiab]
10. “community care team”[tiab]
11. “individual placement support”[tiab]
12. “adherence coping therapy”[tiab]
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. "Psychotic Disorders"[Mesh]
15. Schizophrenia[Mesh]
16. psychosis[tiab]
17. “early psychosis”[tiab]
18. “first episode psychosis”[tiab])
19. “Randomized Controlled Trial”[Publication Type]
20. 14 OR #15 OR #16 OR #17 OR #18
21. #13 AND #19 AND #20

3. CINAHL (via EBSCO HOST)
1. (MM "Community Mental Health Services+")
2. (MM "Early Intervention+")
3. (MM "Counseling")
4. (MM "Psychotherapy+") OR (MH "Psychotherapy, Brief") OR (MH "Psychotherapy, Psychodynamic") OR (MH "Psychotherapy, Group") OR (MH "Cognitive Therapy") OR (MH "Validation Therapy")
5. (MH "Family Therapy") OR (MH "Family Therapy (Iowa NIC)")
6. (MM "Community Mental Health Services+")
7. (MM "Drug Therapy")
8. (MM "Support, Psychosocial")
9. (“early intervention” OR “community care team” OR “individual placement support” OR “adherence coping therapy”) 
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. MH "Clinical Trials+")
12. PT Clinical trial
13. TI clinic* N1 trial* or AB clinic* N1 trial*
14. TI ( singl* or doubl* or trebl* or tripl* ) and TI ( blind* or mask* )
15. AB ( singl* or doubl* or trebl* or tripl* ) and AB ( blind* or mask* )
16. TI randomi?ed control* trial* or AB randomi?ed control* trial*
17. MH "Random Assignment"
18. TI random* allocat* or AB random* allocat*
19. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20. (MM "Psychotic Disorders+)")
21. ("Schizophrenia" OR psychosis OR “early psychosis” OR “first episode psychosis”)
22. #20 OR #21
23. #10 AND #19 AND 22

4. Web of Science (via THOMSON REUTERS)
1. "Early Intervention" OR "Community Health Services" OR "Community Mental Health Services" OR "Counseling" OR "Psychotherapy" OR "Family Therapy" OR "Home Care Services, Hospital-Based" OR "Drug Therapy" OR “early intervention service” OR “community care team” OR “individual placement support” OR “adherence coping therapy”)
2. ("Psychotic Disorders" OR "Schizophrenia" OR psychosis OR “early psychosis” OR “first episode psychosis”)
3. TS= clinical trial* OR TS= research design OR TS= comparative stud* OR TS= evaluation stud* OR TS= controlled trial* OR TS= prospective stud* OR TS= random* OR TS= placebo* OR TS= (single blind*) OR TS= (double blind*)
4. #1 AND #2 AND #3