National Institute for Health and Care Excellence

Final

Rehabilitation in adults with complex psychosis and related severe mental health conditions

[H] Principles to guide adjustments to standard treatment

NICE guideline NG181

Evidence review

August 2020

Final

This evidence review was developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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Principles to guide adjustments to standard treatment

Review question: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Introduction

This review question aims to identify the principles to guide adjustments to standard treatments in the management of underlying psychosis in people using rehabilitation services. To identify these principles, this review investigated the effectiveness of interventions for treatment of refractory psychosis resistant to standard treatment in people with complex psychosis and related severe mental health conditions. For people with treatment resistant psychosis, clozapine is generally considered as the first line of treatment. However, some people fail to respond to clozapine, and hence this review particularly focussed on clozapine augmentation. The review also looked at adaptations to non-pharmacological interventions like psychosocial interventions and modifications of cognitive behavioural therapy and family interventions for treatment of treatment resistant psychosis. The findings of the review will inform recommendations to guide adjustments to standard treatment in this population.

The title of the guideline changed to “Rehabilitation for adults with complex psychosis” during development. The previous title of the guideline has been retained in the evidence reviews for consistency with the wording used in the review protocols.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (aged 18 years and older) with complex psychosis and related severe mental health conditions with refractory psychosis resistant to standard treatment

Intervention	• Pharmacological interventions:
	  ○ For example: clozapine augmentation interventions
	• Non-pharmacological interventions:
	  ○ Adaptation of psychosocial interventions
	  ○ Modifications of cognitive behavioural therapy
	  ○ Modifications of family interventions

Comparison	• Standard treatment
Outcomes	**Critical** • Psychosis symptoms • Relapse/readmission rates **Important**

	• Quality of life • Adverse events • Mortality

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

3 systematic reviews were identified for this review (Bartoli 2019, Polese 2019 and Siskind 2018). The included studies are summarised in Table 2.

1 systematic review compared augmentation strategies for clozapine refractory schizophrenia with standard treatment (Siskind 2018), 1 compared psychotherapy in treatment resistant schizophrenia with clozapine monotherapy ± placebo (Polese 2019), and 1 compared adjunctive second generation antipsychotics for specific symptom domains of clozapine resistant schizophrenia (Bartoli 2019). See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Bartoli 2019 Systematic review Italy, Belgium and UK	N=726 Treatment resistant schizophrenia (partial and non-responders)	Clozapine augmentation intervention with second generation antipsychotics	Clozapine and placebo	• Psychotic symptoms: ○ Total symptoms ○ Negative symptoms ○ Positive symptoms • Adverse events
Polese 2019 Systematic review Italy and US	N=843 Clozapine resistant schizophrenia and non-affective psychosis (only data from the meta-analysis comparing individual CBT and	Individual CBT	Clozapine monotherapy ± placebo	• Psychotic symptoms: ○ Total symptoms ○ Negative symptoms ○ Positive symptoms • Adverse events

Study	Population	Intervention	Comparison	Outcomes
	treatment as usual was included)			
Siskind 2018 Systematic review Australia	N=2223 Clozapine resistant schizophrenia	Clozapine augmentation interventions (pharmacological and non-pharmacological agents like antipsychotics, antidepressants, mood stabilisers, glutamergic agents, other agents and electroconvulsive therapy)	Clozapine plus placebo or other augmentation agent	• Psychotic symptoms: ○ Total symptoms ○ Negative symptoms ○ Positive symptoms • Adverse events

CBT: cognitive behavioural therapy; UK: United Kingdom; US: United States

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of studies included in the economic evidence review

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. The unit costs of the relevant pharmacological treatments for this evidence review are displayed below and the considerations for resource impact is included in the cost effectiveness and resource use section of the committee discussion.

Unit Costs

Table 3: Unit Costs for Clozapine augmentation

Drug[a]	Unit Cost	Source
Amisulpride 200mg, 60 tablets	£14.10	NHS Drug Tariff Part VIIIA (November 2019)
Amisulpride 400mg, 60 tablets	£42.08	NHS Drug Tariff Part VIIIA (November 2019)
Aripiprazole 10mg, 28 tablets	£1.51	NHS Drug Tariff Part VIIIA (November 2019)
Aripiprazole 15mg, 28 tablets	£1.82	NHS Drug Tariff Part VIIIA (November 2019)
Aripiprazole 30mg, 28 tablets	£13.43	NHS Drug Tariff Part VIIIA (November 2019)
Pimozide 4mg,100 tablets	£40.31	NHS Drug Tariff Part VIIIA (November 2019)
Risperidone 3mg, 28 tablets	£43.50	NHS Drug Tariff Part VIIIA (November 2019)
Risperidone 4mg, 28 tablets	£50.29	NHS Drug Tariff Part VIIIA (November 2019)

(a) No drug tariffs available for Sertindole and Ziprasidone

Evidence statements

Clinical evidence statements

Comparison 1. Antipsychotic augmentation versus Clozapine monotherapy ± placebo

Critical outcomes

Psychosis Symptoms: Psychosis Positive symptoms

Very low quality evidence from 2 RCTs (N=245) showed that there was a clinically important decrease in psychosis positive symptoms in those receiving aripiprazole augmentation therapy (5-15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16-24 weeks' follow-up.

Low quality evidence from 4 RCTs (N=201) showed that there was no clinically important difference in psychosis positive symptoms in those receiving risperidone augmentation therapy (3-6 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=50) showed that there was no clinically important difference in psychosis positive symptoms in those receiving sertindole augmentation therapy (16 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically important difference in psychosis positive symptoms in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Low quality evidence from 1 RCT (N=53) showed that there was no clinically important difference in psychosis positive symptoms in those receiving pimozide augmentation therapy (6.48 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Psychosis Symptoms: Psychosis Negative symptoms

Low quality evidence from 1 RCT (N=53) showed that there was no clinically important difference in psychosis negative symptoms in those receiving amisulpiride augmentation therapy (400 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Low quality evidence from 2 RCTs (N=245) showed that there was no clinically important difference in psychosis negative symptoms in those receiving aripiprazole augmentation therapy (5-15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16-24 weeks' follow-up.

Low quality evidence from 4 RCTs (N=201) showed that there was no clinically important difference in psychosis negative symptoms in those receiving risperidone augmentation therapy (3-6 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=50) showed that there was no clinically important difference in psychosis negative symptoms in those receiving sertindole augmentation therapy (16 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Low quality evidence from 1 RCT (N=40) showed that there was a clinically important decrease in psychosis negative symptoms in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Low quality evidence from 1 RCT (N=53) showed that there was no clinically important difference in psychosis negative symptoms in those receiving pimozide augmentation therapy (6.48 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Psychosis Symptoms: Psychosis Total symptoms

Low quality evidence from 1 RCT (N=53) showed that there was no clinically important difference in psychosis total symptoms in those receiving amisulpiride augmentation therapy (400 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Low quality evidence from 1 RCT (N=40) showed that there was a clinically important decrease in psychosis total symptoms in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 24 weeks' follow-up.

Low quality evidence from 3 RCTs (N=161) showed that there was no clinically important difference in psychosis total symptoms in those receiving risperidone augmentation therapy (3-4 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-16 weeks' follow-up.

Low quality evidence from 1 RCT (N=50) showed that there was no clinically important difference in psychosis total symptoms in those receiving sertindole

augmentation therapy (16 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Low quality evidence from 1 RCT (N=40) showed that there was a clinically important decrease in psychosis total symptoms in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=53) showed that there was no clinically important difference in psychosis total symptoms in those receiving pimozide augmentation therapy (6.48 mg/day) compared to those receiving clozapine monotherapy ± placebo at 12 weeks' follow-up.

Relapse/Readmission rate

No evidence was identified to inform this outcome.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Adverse events

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically significant difference in restlessness in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 24 weeks' follow-up.

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically significant difference in insomnia in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy/Placebo at 24 weeks' follow-up.

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically significant difference in nausea in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 24 weeks' follow-up.

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically significant difference in constipation in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 24 weeks' follow-up.

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically significant difference in hypersalivation in those receiving aripiprazole augmentation therapy (15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 24 weeks' follow-up

Low quality evidence from 1 RCT (N=205) showed that there was a higher decrease in body weight in those receiving aripiprazole augmentation therapy (5-15 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in gastrointestinal symptoms in those receiving ziprasidone

augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in headache in those receiving ziprasidone (80 mg/day) augmentation therapy compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in dizziness in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in constipation in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in nausea in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in blurred vision in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=31) showed that there was no clinically significant difference in the duration of QTc interval in those receiving ziprasidone augmentation therapy (80 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Mortality

No evidence was identified to inform this outcome.

Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo

Critical outcomes

Psychosis Symptoms: Psychosis Positive symptoms

Very low quality evidence from 1 RCT (N=40) showed that there was no clinically important difference in psychosis positive symptoms in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 2 RCTs (N=39) showed that there was no clinically important difference in psychosis positive symptoms in those receiving mirtazapine augmentation therapy (30 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-8 weeks' follow-up.

Psychosis Symptoms: Psychosis Negative symptoms

Low quality evidence from 1 RCT (N=40) showed that there was a clinically important decrease in psychosis negative symptoms in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 2 RCTs (N=39) showed that there was no clinically important difference in psychosis negative symptoms in those receiving mirtazapine augmentation therapy (30 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-8 weeks' follow-up.

Psychosis Symptoms: Psychosis Total symptoms

Low quality evidence from 1 RCT (N=40) showed that there was a clinically important decrease in psychosis total symptoms in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 2 RCTs (N=39) showed that there was no clinically important difference in psychosis total symptoms in those receiving mirtazapine augmentation therapy (30 mg/day) compared to those receiving clozapine monotherapy ± placebo at 6-8 weeks' follow-up.

Relapse/Readmission rate

No evidence was identified to inform this outcome.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Adverse events

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in gastrointestinal symptoms in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in headache in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up.

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in blurred vision in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in constipation in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in insomnia in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up

Very low quality evidence from 1 RCT (N=33) showed that there was no clinically significant difference in nausea in those receiving duloxetine augmentation therapy (60 mg/day) compared to those receiving clozapine monotherapy ± placebo at 16 weeks' follow-up

Mortality

No evidence was identified to inform this outcome.

Comparison 3. Mood stabiliser augmentation versus Clozapine monotherapy ± placebo

Critical outcomes

Psychosis Symptoms: Psychosis Positive symptoms

Low quality evidence from 1 RCT (N=60) showed that there was a clinically important decrease in psychosis positive symptoms in those receiving topiramate augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Very low quality evidence from 1 RCTs (N=51) showed that there was no clinically important difference in psychosis positive symptoms in those receiving lamotrignine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Negative symptoms

Low quality evidence from 1 RCT (N=60) showed that there was a clinically important decrease in psychosis negative symptoms in those receiving topiramate augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Very low quality evidence from 2 RCTs (N=51) showed that there was no clinically important difference in psychosis negative symptoms in those receiving lamotrignine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Total symptoms

Low quality evidence from 1 RCT (N=60) showed that there was no clinically important difference in psychosis total symptoms in those receiving topiramate augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Very low quality evidence from 2 RCTs (N=51) showed that there was no clinically important difference in psychosis total symptoms in those receiving lamotrignine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Relapse/Readmission rate

No evidence was identified to inform this outcome.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Adverse events

No evidence was identified to inform this outcome.

Mortality

No evidence was identified to inform this outcome.

Comparison 4. Glutamergic augmentation versus Clozapine monotherapy ± placebo

Critical outcomes

Psychosis Symptoms: Psychosis Positive symptoms

Low quality evidence from 3 RCTs (N=134) showed that there was no clinically important difference in psychosis positive symptoms in those receiving memantine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Low quality evidence from 3 RCTs (N=58) showed that there was no clinically important difference in psychosis positive symptoms in those receiving glycine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Negative symptoms

Low quality evidence from 3 RCTs (N=134) showed that there was a clinically important decrease in psychosis negative symptoms in those receiving memantine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Very low quality evidence from 3 RCTs (N=58) showed that there was no clinically important difference in psychosis negative symptoms in those receiving glycine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Total symptoms

Very low quality evidence from 3 RCTs (N=134) showed that there was no clinically important difference in psychosis total symptoms in those receiving memantine

augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Low quality evidence from 3 RCTs (N=58) showed that there was no clinically important difference in psychosis total symptoms in those receiving glycine augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Relapse/Readmission rate

No evidence was identified to inform this outcome.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Adverse events

No evidence was identified to inform this outcome.

Mortality

No evidence was identified to inform this outcome.

Comparison 5. Other agent augmentation versus Clozapine monotherapy ± placebo

Critical outcomes

Psychosis Symptoms: Psychosis Positive symptoms

Low quality evidence from 1 RCT (N=50) showed that there was no clinically important difference in psychosis positive symptoms in those receiving minocycline augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Negative symptoms

Low quality evidence from 1 RCT (N=50) showed that there was a clinically important decrease in psychosis negative symptoms in those receiving minocycline augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Psychosis Symptoms: Psychosis Total symptoms

Low quality evidence from 1 RCT (N=50) showed that there was no clinically important difference in psychosis total symptoms in those receiving minocycline

augmentation therapy compared to those receiving clozapine monotherapy ± placebo.

Relapse/Readmission rate

No evidence was identified to inform this outcome.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Adverse events

Low quality evidence from 1 RCT (N=52) showed that clinically significantly lesser number of people experienced constipation in those receiving minocycline augmentation therapy compared to those receiving clozapine monotherapy ± placebo at 10 weeks' follow-up.

Low quality evidence from 1 RCT (N=52) showed that clinically significant increase in HDL cholesterol among those receiving minocycline augmentation therapy compared to those receiving clozapine monotherapy ± placebo at 10 weeks' follow-up.

Mortality

No evidence was identified to inform this outcome.

Comparison 6. Individual cognitive behavioural therapy (CBT) versus treatment as usual (TAU)

Critical outcomes

Psychosis Symptoms: PANSS Positive symptoms (Follow-up: 6 to 8 months)

Moderate quality evidence from 4 RCTs (N=800) showed that there was a clinically important decrease in psychosis symptoms assessed with the PANSS positive symptoms scale in those receiving individual cognitive behavioural therapy compared to those receiving treatment as usual.

Psychosis Symptoms: PANSS Negative symptoms (Follow-up: 6 to 8 months)

Moderate quality evidence from 4 RCTs (N=800) showed that there was no clinically important difference in psychosis symptoms assessed with the PANSS negative symptoms scale in those receiving individual cognitive behavioural therapy compared to those receiving treatment as usual.

Psychosis Symptoms: PANSS Total symptoms (Follow-up: 6 to 8 months)

Moderate quality evidence from 5 RCTs (N=843) showed that there was no clinically important difference in psychosis symptoms assessed with the PANSS total symptoms scale in those receiving individual cognitive behavioural therapy compared to those receiving treatment as usual.

Important outcomes

Quality of life

No evidence was identified to inform this outcome.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to investigate the effectiveness of interventions for treatment of refractory psychosis resistant to standard treatment in people with complex psychosis and related severe mental health conditions. For this reason, the committee included psychosis symptoms as a critical outcome for this review. Relapse/readmission rate was included as a critical outcome, given its implications for people and resources. Improvement in quality of life is one of the objectives of mental health treatments so it was included as an important outcome. To offer a balance of benefits and harms, adverse events was included as an important outcome. Considering the seriousness of the outcome, mortality was included as an important outcome.

The quality of the evidence

The evidence for outcome psychosis symptoms ranged from very low to moderate using GRADE. The evidence was downgraded mainly for imprecision, but also due to indirectness as it was unclear whether the population in the included studies received rehabilitation services. Some evidence was also downgraded for indirectness arising from inclusion of some studies included in the systematic review from countries that were not on our review protocol list of included countries. The evidence for outcome adverse events ranged from very low to low; the main reason for downgrading evidence being imprecision and indirectness of population. No evidence was identified for the outcomes relapse/readmission rate, quality of life and mortality.

There was a lack of evidence about adaptations of psychosocial interventions and modifications of family interventions for people with refractory psychosis resistant to standard treatment.

Benefits and harms

To address the question of what adjustments should be made to standard treatments for people using rehabilitation services, the committee focussed the population in this review to people with refractory psychosis resistant to standard treatment, as this is representative of people using rehabilitation services. The committee wanted to make readers aware that standard treatments for psychosis are described in other guidance on psychosis and schizophrenia (NICE guideline CG178) and bipolar disorder (NICE guideline CG185), and made this their first recommendation for the section.

The evidence in this review indicated that each of the treatment options had related benefits and harms, and for this reason and reasons of good practice, the committee agreed that there should be a discussion of treatment options with the person, and they referred to the recommendations on shared decision-making in NICE's guideline on patient experience in adult NHS services.

The committee were also aware that comorbidities, including other mental illnesses, and autism spectrum disorder, can affect outcomes in people with complex psychosis, and so recommended treating these comorbidities in line with the relevant NICE guidance.

Psychological therapies

The committee reviewed the evidence on adjustments to standard treatments for underlying psychosis for people using rehabilitation services. There was some evidence from randomised controlled trials showing that for people with treatment-resistant psychosis, CBT decreased psychosis symptoms (positive) compared with pharmacological therapy alone. Based on this evidence and their experience, the committee recommended that the standard treatment of CBT with family intervention for psychosis be continued in this treatment-resistant population. They also referred to the NICE guideline CG178 for delivery, monitoring and implementation of this intervention.

The committee agreed from their experience, that some people may not be able to engage in CBT. They discussed the importance of additional psychological interventions in such people, based on their knowledge and experience. Given the lack of evidence for such additional psychological interventions, the committee made a weak recommendation on the types of interventions that might be able to help people in rehabilitation services. While considering such interventions, the committee emphasised the importance of psychological assessment, formulation and consideration to individual preferences to identify the most appropriate therapeutic intervention for an individual. The types of interventions the committee considered were those that focus importance of learned behaviours and how context influences behaviours, mindfulness approaches, and approaches with focus on wider systems such as families or ward environments. The committee also acknowledged the importance of psychologically informed approaches such as motivational interviewing, positive behaviour support, behavioural activation, trauma informed care and simple techniques for supporting people experiencing troubling thoughts and feelings. Despite the lack of evidence from trials, the committee considered it important that staff are trained in such interventions to deliver them in rehabilitation settings.

Pharmacological treatments

Evidence from randomised controlled trials indicated that in people with schizophrenia refractory to clozapine, psychosis symptoms (positive and total) decreased in those receiving clozapine augmentation with antipsychotic (aripiprazole), psychosis symptoms (negative and total) decreased in those receiving antipsychotic (ziprasidone) augmentation, psychosis symptoms (negative and total) decreased in those receiving antidepressant (duloxetine) augmentation; psychosis symptoms (positive and negative) decreased in those receiving mood stabilizer (topiramate) augmentation, and psychosis symptoms (negative) decreased in those receiving memantine (glutamergic agent) and minocycline (other agent) augmentation with clozapine compared with people receiving clozapine alone. The committee noted that the evidence was limited by small sample sizes. The committee also discussed that evidence on adverse events following these medications was

also very sparse. The committee acknowledged that recruiting people with complex psychosis to trials is a challenge, and also that therapeutic options are limited, current prescribing for this population is inconsistent, and they emphasised that there was a need for recommendations about augmentation with these agents.

While making the recommendations, the committee recommended classes of drugs (e.g. antipsychotics, antidepressants, mood stabilisers), alone or in combination, rather than specifying individual drugs. They considered that the evidence did not compare effectiveness of individual augmentation agents against each other, but rather looked at the effectiveness of augmentation therapies against standard care (clozapine monotherapy or clozapine with placebo). The committee recognised that augmentation compared to standard therapy was effective in reducing psychosis symptoms, but one drug could not be recommended over the other based on the evidence. However, the committee gave an example of aripiprazole while recommending augmentation with antipsychotics. They noted that amisulpiride is more commonly prescribed than aripiprazole, but the evidence did not show a change in psychosis symptoms following amisulpiride, while there was some evidence regarding the effectiveness of aripiprazole in reducing total psychosis symptoms. Given the safety profiles of these drugs, and their potential interactions when combined, the committee recommended seeking advice from a psychiatrist specialising in treatment resistance and/or a specialist mental health pharmacist if needed.

The committee discussed dosing and combinations of treatments. They were aware that in clinical practice, for this difficult-to-treat condition, doses above those recommended in the BNF or SPC are sometimes used, as well as combinations of treatments. Although no direct evidence was found assessing doses of treatment, and limited information on combinations, the committee were aware of the safety concerns of high doses and interactions. They therefore recommended cautions when using high doses or combinations, including discussion and agreement on treatment with the person and people involved in the person's care; a limited therapeutic trial, returning to conventional dosages or monotherapy after 3 months, unless the higher doses or combined therapy is effective and benefits clearly outweigh the risks; targeting specific signs and symptoms (for example some drugs might be more effective in reducing positive symptoms and others in negative symptoms); and taking into account side effects and proactively monitoring for side effects.

The committee agreed that in psychosis refractory to standard treatment, there may be need to maximise the doses using BNF and therapeutic plasma levels. However, the committee agreed that if such treatments are not ineffective, they should be stopped or doses reduced. The committee considered it important to be aware that changes to medication should be made slowly. For people who have been on medications for many years, in the committee's experience, changes to multiple medications or changes made too quickly can lead to relapse in psychosis.

The committee agreed it was important to measure drug levels regularly to assess adherence and guide dosing; however, there was a lack of evidence to guide frequency of measurement. For monitoring lithium, the committee recommended following the guidance for using lithium in NICE guideline Bipolar disorder [CG 185]. For clozapine and mood stabilising antiepileptic medication, the committee recommended annual measurement, based on their knowledge and experience.

The committee also agreed it was important to monitor effects after receiving specific medications; however, again there was no evidence in the review to guide frequency of monitoring. The committee agreed that some antipsychotics increase prolactin,

increasing the risk of hyperprolactinaemia. However, there was some disagreement on whether prolactin should be measured just before treatment initiation of a drug that raises prolactin (as is common practice, and in the NICE guideline Psychosis and schizophrenia in adults [CG 178]), if a person is symptomatic for hyperprolactinaemia, or at regular intervals. The consensus view was that if a person is taking a drug that increases prolactin, to consider monitoring prolactin annually and more regularly if symptomatic. For monitoring thyroid function, renal function and calcium levels in people taking lithium, the committee recommended following the guidance for using lithium in NICE guideline Bipolar disorder [CG 185]

The committee also highlighted the importance of ECG monitoring. The committee were aware that antipsychotic medications may cause cardiac abnormalities, for example, lengthened QT interval on electrocardiography. Although the committee were conscious that the guidance in the NICE guideline Psychosis and schizophrenia in adults [CG 178] and NICE guideline Bipolar disorder [CG 185] recommends ECGs at the initiation of starting antipsychotic medications (based on consensus opinion), they recommended considering annual ECGs, and more frequent than annual ECGs for people with complex antipsychotic regimens, including doses above BNF levels. The committee agreed that most people in rehabilitation services will have been on medications long term, or combinations of medications that may alter cardiac rhythm, or both. There was also evidence that this population have a higher prevalence of cardiovascular disease and members of the committee had specific experience of unexpected cardiac complications identified with ECGs in this group of people. The committee noted it was common practice to perform ECGs if exceeding BNF limits for antipsychotics.

The committee also considered it important to make a recommendation about clinicians being aware about the use non-prescription drugs in this population and ensure that substance misuse interactions with medicines are important considerations when planning medications.

The committee were aware, based on their experience, that some people using rehabilitation services may need to initiate or re-initiate treatment with clozapine. Many of these people are currently admitted to hospital as clozapine requires strict monitoring; however, it is possible to provide clozapine in the community through an extended-hours service while ensuring the requisite monitoring. The committee agreed that clozapine availability in the community would prevent unnecessary hospital admissions and is an important part of a successful rehabilitation service.

The committee recommended following the NICE guideline on managing medicines in care homes, given that many people using rehabilitation services will be living in supported accommodation.

The committee noted that although there was some evidence on psychosis symptoms and adverse drug events, there was lack of evidence on relapse/readmission rates, quality of life, which could aid a person's ability to live in the community. The committee also noted that studies assessing either psychological or pharmacological interventions in a rehabilitation setting could provide useful information for guiding adjustments. The committee therefore made a research recommendation to address the evidence gap in this area.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the evidence for CBT for people who are treatment resistant and noted that the evidence was congruent with CG178. However, the committee also took the view that people in this patient group can present with symptoms and behaviours that are difficult to treat through conventional CBT. Where there are already psychology staff (or staff with a similar role), then psychological assessment and formulation to identify the most appropriate alternative intervention is already current practice. Specifically, the committee recommended the use of other psychological interventions such as; those that focus on learned behaviours and mindfulness-based approaches. A weak 'consider' recommendation was made in light of the lack of evidence, though the committee's opinion was that not providing these kinds of interventions can result in service users being less well understood and supported by staff teams, and potentially more likely to be hospitalised.

Regarding the recommendation to consider training all rehabilitation staff in low-intensity psychological interventions, the committee believed that such interventions, including motivational interviewing, positive behaviour support and behavioural action are already current practice as many staff in rehabilitation services will already have had some experience as part of their training. Moreover, the committee believed that where such expertise isn't common practice that it is relatively inexpensive to train staff in brief interventions such as motivational interviewing, and once learnt, can be incorporated into routine practice at little extra cost to services.

For people with schizophrenia refractory to clozapine, augmentation therapy was acknowledged as more effective than clozapine alone. Current practice is variable owing to a lack of available data, though the committee noted that amisulpride is commonly prescribed in addition to clozapine. Whilst this is standard first line practice, other pharmacological augmentation strategies are considered, including using aripiprazole.

The committee refrained from recommending one drug over another as first line treatment, and believed that both amisulpride and aripiprazole could be used as first line treatment. This recommendation may therefore entail an increase in the use of aripiprazole, though the committee suggested that there would not be a resource impact as monitoring would be similar as it is for amisulpride. In addition, the unit costs, based on the NHS Drug Tarff 2019, are lower for aripiprazole compared with amisulpride.

Regarding monitoring of drug levels, and monitoring physical effects of treatments, the recommendations largely reflect current practice. The recommendation to consider an annual ECG reflects current guidance, though the committee also acknowledged that this may be required more regularly if the person is taking medicines above BNF limits. This may have a small resource impact, though the allowance for increased monitoring is stated in the Royal College of Psychiatrists Consensus statement on high-dose antipsychotic medication (CR190)

Although clozapine in the community is not currently available in all areas, most areas do already have a team in place providing an extended-hours service for people with mental illness, for example a crisis resolution home treatment team. Enabling initiation and re-initiation of clozapine in the community would likely require additional resources for those teams providing out of hours services. However, the committee agreed that initiation of clozapine in the community could reduce inpatient admissions and allow people to stay in a less supported setting, both of which are cost saving.

Other considerations

The committee were aware that treatment decision making, standard treatments for psychosis, management of co-existing autism spectrum disorder and managing medicines in care homes have been covered in other NICE guidance, and therefore directed readers to the relevant sections in these guidelines, which will be relevant to people using rehabilitation services. The committee were also aware of NICE guidance on electroconvulsive therapy and agreed it was appropriate to cross-refer to this.

References

Bartoli et al., 2019

Bartoli, F., Crocamo, C., Di Brita, C., Esposito, G., Tabacchi, T. I., Verrengia, E., Clerici, M., Carra, G., Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis, Journal of psychiatric research, 108, 24-33, 2019

Polese et al., 2019

Polese, D., Fornaro, M., Palermo, M., De Luca, V., de Bartolomeis, A., Treatment-Resistant to Antipsychotics: A Resistance to Everything? Psychotherapy in Treatment-Resistant Schizophrenia and Nonaffective Psychosis: A 25-Year Systematic Review and Exploratory Meta-Analysis, Frontiers in psychiatry Frontiers Research Foundation, 10, 210, 2019

Siskind et al., 2018

Siskind, D. J., Lee, M., Ravindran, A., Zhang, Q., Ma, E., Motamarri, B., Kisely, S., Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis, Australian and New Zealand journal of psychiatry, 52, 751-767, 2018

Appendices

Appendix A – Review protocols

Review protocol for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Table 4: Review protocol for principles to guide adjustments to standard treatment

Field (based on PRISMA-P)	Content
Review question	What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?
Type of review question	Intervention review
Objective of the review	To study the effectiveness of modifications to standard treatments which may help to identify the principles to guide adjustments to standard treatments for the management of underlying psychosis in people using rehabilitation services. Although the question in the scope included only pharmacological interventions, the review studied the effectiveness of modifications to non-pharmacological interventions such as cognitive behavioural therapy as well, considering the important role of these interventions in the management of refractory psychosis.
Eligibility criteria – population	Adults (aged 18 years and older) with complex psychosis and related severe mental health conditions with refractory psychosis resistant to standard treatment. Studies with mixed populations should include at least 66% with complex psychosis and related severe mental health conditions.

Eligibility criteria – intervention(s)	Augmenting treatments
	• Pharmacological interventions:
	  ○ For example, clozapine augmentation interventions
	• Non-pharmacological interventions:
	  ○ Adaptation of psychosocial interventions
	  ○ Modifications of cognitive behavioural therapy
	  ○ Modifications of Family interventions

Field (based on PRISMA-P)	Content
Eligibility criteria – comparator(s)/control	• Standard treatment
Outcomes and prioritisation	**Critical** • Psychosis symptoms. For example, ○ Total psychosis symptom scores (Positive and Negative Symptom Scale [PANSS]) (Kay et al., 1987) ○ Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) ○ Negative symptoms (Scale for the Assessment of Negative Symptoms [SANS] (Andreasen and Olsen, 1982) ○ PANSS negative symptom subscale) and positive symptoms (Scale for the Assessment of Positive Symptoms [SAPS] (Andreasen and Olsen, 1982) ○ PSYRATS/AH/Delusions (Haddock 1999) ○ KGV(M) symptom severity scale (Krawiecka et al, 1977) • Relapse/readmission rates **Important** • Quality of life, for example: ○ Manchester Short Assessment of Quality of Life (MANSA) • Adverse events • Mortality
Eligibility criteria – study design	RCTs. If no RCTs are available for any of the interventions, comparative observational studies will be considered.
Other inclusion exclusion criteria	Date limit: 2000 The date limit of 2000 was set for this review as Clozapine was reintroduced in the UK in 1990s and studies reporting clozapine augmentation interventions are likely to be published 2000 onwards. Country limit: UK, USA, Australasia, Europe, Canada. The GC limited to these countries because of similar healthcare settings to the UK.
Proposed sensitivity/sub-group analysis, or meta-regression	Confounders that will be used to explore heterogeneity: • Duration of long term follow-up • Observational studies should adjust for the following: • Age

Field (based on PRISMA-P)	Content
	• Measure of clinical severity • Gender
Selection process – duplicate screening/selection/analysis	A random sample of the references identified in the search will be sifted by a second reviewer. This sample size of this pilot round will be 10% of the total, (with a minimum of 100 studies). All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.
Data management (software)	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations. RevMan will be used to generate plots and for any meta-analysis. 'GRADEpro' will be used to assess the quality of evidence for each outcome
Information sources – databases and dates	Sources to be searched: Embase, Medline, PsycINFO, Cochrane library (CDSR and CENTRAL), DARE and HTA (via CRD) Limits (e.g. date, study design): Human studies /English language Date limit: 2000
Identify if an update	Not an update
Author contacts	For details please see https://www.nice.org.uk/guidance/indevelopment/gid-ng10092
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014.

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Gillian Baird in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods see supplementary document C.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not applicable

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PANSS: Positive and Negative Syndrome Scale; PSYRAT: psychotic symptom rating scale; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: 3.1 What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Databases: Embase/Medline/PsycInfo

Date searched: 10/05/2019

#	Searches
1	exp psychosis/ use emczd
2	Psychotic disorders/ use ppez
3	exp psychosis/ use psyh
4	(psychos?s or psychotic).tw.
5	exp schizophrenia/ use emczd
6	exp schizophrenia/ or exp "schizophrenia spectrum and other psychotic disorders"/ use ppez
7	(exp schizophrenia/ or "fragmentation (schizophrenia)"/) use psyh
8	schizoaffective psychosis/ use emczd
9	schizoaffective disorder/ use psyh
10	(schizophren* or schizoaffective*).tw.
11	exp bipolar disorder/ use emczd
12	exp "Bipolar and Related Disorders"/ use ppez
13	exp bipolar disorder/ use psyh
14	((bipolar or bipolar type) adj2 (disorder* or disease or spectrum)).tw.
15	Depressive psychosis/ use emczd
16	Delusional disorder/ use emczd
17	delusions/ use psyh
18	(delusion* adj3 (disorder* or disease)).tw.
19	mental disease/ use emczd
20	mental disorders/ use ppez
21	mental disorders/ use psyh
22	(psychiatric adj2 (illness* or disease* or disorder* or disabilit* or problem*)).tw.
23	((severe or serious) adj3 (mental adj2 (illness* or disease* or disorder* or disabilit* or problem*))).tw.
24	(complex adj2 (mental adj2 (illness* or disease* or disorder* or disabilit* or problem*))).tw.
25	or/1-24
26	exp Treatment resistant disorders/ use psyh
27	depressive disorder, treatment-resistant/ use ppez
28	(refractory* or resistan* or recurren*).tw.
29	(nonrespon* or non-respon* or "non respon*" or "not respon*" or "no respon*" or "partial respon*" or "partially respon*" or unrespon* or "insufficient* respon*").tw.
30	("failed to respond" or "failed to improve" or "failure to respon*" or "failure to improve" or "failed medication*" or "antidepressant fail*" or "treatment fail*").tw.
31	(inadequate* and respon*).tw.
32	or/26-31
33	drug augmentation/ use psyh
34	drug synergism/ use ppez
35	drug potentiation/ use emczd
36	(augment* or potentiat*).tw.
37	((drug* or medication* or treatment* or therap*) adj3 (synergy or synergism)).tw.
38	((modify or modification* or alter* or adapt* or adjust* or re-adjust* or readjust*) adj4 (psychosocial or psychological or psychotherap*)).tw.

#	Searches
39	((modify or modification* or alter* or adapt* or adjust* or re-adjust* or readjust*) adj4 (family adj3 (therap* or intervention*))).tw.
40	((modify or modification* or alter* or adapt* or adjust* or re-adjust* or readjust*) adj4 ((behavio?r* adj2 therap*) or CBT or DBT)).tw.
41	or/33-40
42	25 and 32 and 41
43	limit 42 to (yr="1990 - current" and english language)
44	remove duplicates from 43
45	Letter/ use ppez
46	letter.pt. or letter/ use emczd
47	note.pt.
48	editorial.pt.
49	Editorial/ use ppez
50	News/ use ppez
51	news media/ use psyh
52	exp Historical Article/ use ppez
53	Anecdotes as Topic/ use ppez
54	Comment/ use ppez
55	Case Report/ use ppez
56	case report/ or case study/ use emczd
57	Case report/ use psyh
58	(letter or comment*).ti.
59	or/45-58
60	randomized controlled trial/ use ppez
61	randomized controlled trial/ use emczd
62	random*.ti,ab.
63	cohort studies/ use ppez
64	cohort analysis/ use emczd
65	cohort analysis/ use psyh
66	case-control studies/ use ppez
67	case control study/ use emczd
68	or/60-67
69	59 not 68
70	animals/ not humans/ use ppez
71	animal/ not human/ use emczd
72	nonhuman/ use emczd
73	"primates (nonhuman)"/
74	exp Animals, Laboratory/ use ppez
75	exp Animal Experimentation/ use ppez
76	exp Animal Experiment/ use emczd
77	exp Experimental Animal/ use emczd
78	animal research/ use psyh
79	exp Models, Animal/ use ppez
80	animal model/ use emczd
81	animal models/ use psyh
82	exp Rodentia/ use ppez
83	exp Rodent/ use emczd
84	rodents/ use psyh
85	(rat or rats or mouse or mice).ti.
86	or/69-85
87	44 not 86

Database: Cochrane Library

Date searched: 10/05/2019

#	Searches
1	MeSH descriptor: [Psychotic Disorders] explode all trees
2	(psychos?s or psychotic):ti,ab,kw
3	MeSH descriptor: [Schizophrenia] explode all trees
4	(schizophren* or schizoaffective*):ti,ab,kw
5	MeSH descriptor: [Bipolar Disorder] explode all trees
6	(((bipolar or bipolar type) near/2 (disorder* or disease or spectrum))):ti,ab,kw
7	MeSH descriptor: [Delusions] this term only
8	((delusion* near/3 (disorder* or disease))):ti,ab,kw
9	MeSH descriptor: [Mental Disorders] this term only
10	((psychiatric near/2 (illness* or disease* or disorder* or disabilit* or problem*))):ti,ab,kw
11	(((severe or serious) near/3 (mental adj2 (illness* or disease* or disorder* or disabilit* or problem*)))):ti,ab,kw
12	((complex near/2 (mental adj2 (illness* or disease* or disorder* or disabilit* or problem*)))):ti,ab,kw
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	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
15	(refractory* or resistan* or recurren*):ti,ab,kw
16	(nonrespon* or non-respon* or "non respon*" or "not respon*" or "no respon*" or "partial respon*" or "partially respon*" or unrespon* or "insufficient* respon*"):ti,ab,kw
17	("failed to respond" or "failed to improve" or "failure to respon*" or "failure to improve" or "failed medication*" or "antidepressant fail*" or "treatment fail*"):ti,ab,kw
18	(inadequate* and respon*):ti,ab,kw
19	(#14 or #15 or #16 or #17 or #18)
20	MeSH descriptor: [Drug Synergism] this term only
21	(augment* or potentiat*):ti,ab,kw
22	((drug* or medication*) near/3 (synergy or synergism)):ti,ab,kw
23	((modify or modification* or alter* or adapt* or adjust* or re*adjust*) near/4 (psychosocial or psychological or psychotherap*)):ti,ab,kw
24	((modify or modification* or alter* or adapt* or adjust* or re*adjust*) near/4 (family near/3 (therap* or intervention*))):ti,ab,kw
25	((modify or modification* or alter* or adapt* or adjust* or re*adjust*) near/4 ((behavio*r* near/2 therap*) or CBT or DBT)):ti,ab,kw
26	(#20 OR #21 OR #22 OR #23 OR #24 OR #25)
27	(#13 AND #19 AND #26) with Cochrane Library publication date Between Jan 1990 and May 2019

Database: CRD

Date searched: 10/05/2019

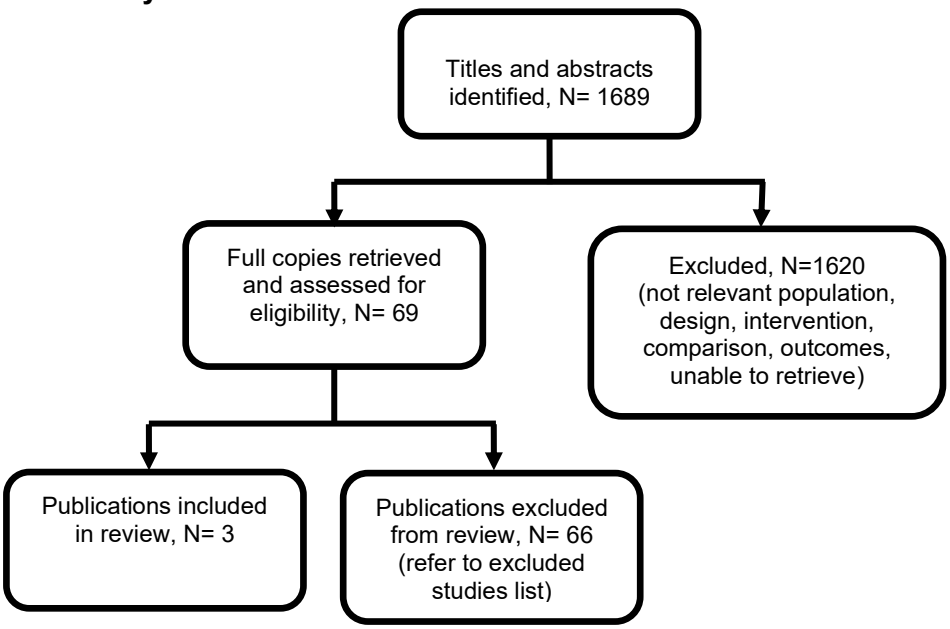
#	Searches
1	MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES IN DARE,HTA
2	(psychos*s or psychotic) IN DARE, HTA
3	MeSH DESCRIPTOR Schizophrenia EXPLODE ALL TREES IN DARE,HTA
4	(schizophren* or schizoaffective*) IN DARE, HTA
5	MeSH DESCRIPTOR Bipolar Disorder EXPLODE ALL TREES IN DARE,HTA
6	(((bipolar or bipolar type) NEAR2 (disorder* or disease or spectrum))) IN DARE, HTA
7	MeSH DESCRIPTOR Delusions IN DARE,HTA
8	(delusion* NEAR3 (disorder* or disease)) IN DARE, HTA
9	MeSH DESCRIPTOR Mental Disorders IN DARE,HTA
10	(psychiatric NEAR2 (illness* or disease* or disorder* or disabilit* or problem*)) IN DARE, HTA
11	((severe or serious) NEAR3 (mental NEAR2 (illness* or disease* or disorder* or disabilit* or problem*))) IN DARE, HTA

#	Searches
12	(complex NEAR2 (mental NEAR2 (illness* or disease* or disorder* or disabilit* or problem*))) IN DARE, HTA
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	MeSH DESCRIPTOR Rehabilitation IN DARE,HTA
15	MeSH DESCRIPTOR Rehabilitation, Vocational IN DARE,HTA
16	MeSH DESCRIPTOR Residential Facilities IN DARE,HTA
17	MeSH DESCRIPTOR Assisted Living Facilities IN DARE,HTA
18	MeSH DESCRIPTOR Halfway Houses IN DARE,HTA
19	(resident* NEAR (care or centre or center)) IN DARE, HTA
20	((inpatient or in-patient or long-stay) NEAR3 (psychiatric or mental health)) IN DARE, HTA
21	((Support*) NEAR (hous* or accommodat* or living)) IN DARE, HTA
22	(halfway house* or assist* living) IN DARE, HTA
23	(rehabilitation or rehabilitative or rehabilitate) IN DARE, HTA
24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#13 AND #24

Appendix C – Clinical evidence study selection

Clinical study selection for: 3.1 What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: 3.1 What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Table 5: Clinical evidence tables

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Bartoli, F., Crocamo, C., Di Brita, C., Esposito, G., Tabacchi, T. I., Verrengia, E., Clerici, M., Carra, G., Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis, Journal of psychiatric research, 108, 24-33, 2019 **Ref Id** 1013844 **Country/ies where the study was carried out** Italy, Belgium and UK	**Sample size** N=726 (Data from only 2 additional studies was extracted from this systematic review, i.e. Josiassen 2005, Muscatello 2014a). Other included studies overlapped with Siskind 2018. **Characteristics** Treatment resistant schizophrenia **Inclusion criteria** Double-blind, randomized, placebo-controlled trials (RCTs) studying the efficacy	**Interventions** Clozapine augmentation intervention with second generation antipsychotics	**Results** The primary outcome was efficacy of adjunctive SGAs as measured by change in (i) positive, (ii) negative, (iii) depressive symptoms. Standard instruments measuring psychotic and depressive symptoms of schizophrenia were used: the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS); the Scale for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS); the Calgary	**Limitations** ROBIS checklist summary Concerns regarding specification of study eligibility criteria. LOW CONCERN Concerns regarding methods used to identify and/or select studies. LOW CONCERN Concerns regarding

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Systematic review **Aim of the study** To evaluate the efficacy of adjunctive SGAs in individuals with clozapine-resistant schizophrenia **Study dates** Studies published from 1997 to 2017. **Source of funding** No external funding	of adjunctive SGAs in individuals with clozapine-resistant schizophrenia with data on treatment effects for at least one domain among positive, negative and depressive symptoms **Exclusion criteria** Case reports/case series, open and uncontrolled trials and trials without a placebo arm		Depression Scale for Schizophrenia (CDSS); the Hamilton Depression Rating Scale (HDRS); and the Montgomery Asberg Depression Rating Scale (MADRS). The secondary outcome was the tolerability, measured by the difference in any-cause discontinuation rates between subjects on adjunctive SGAs and placebo	methods used to collect data and appraise studies. LOW CONCERN Concerns regarding methods used to synthesize results. LOW CONCERN Risk of bias: Low Risk of bias for individual outcomes is based on the critical appraisal reported in the review **Other information** NA
Full citation Polese, D., Fornaro, M., Palermo, M., De Luca, V., de Bartolomeis,	**Sample size** N=843 (only data from the meta-analysis comparing	**Interventions**	**Results** Follow up 6-9 months; Only patients who had been stable	**Limitations** ROBIS checklist summary

Study details	Participants	Interventions	Outcomes and Results	Comments
A., Treatment-Resistant to Antipsychotics: A Resistance to Everything? Psychotherapy in Treatment-Resistant Schizophrenia and Nonaffective Psychosis: A 25-Year Systematic Review and Exploratory Meta-Analysis, Frontiers in psychiatry Frontiers Research Foundation, 10, 210, 2019 **Ref Id** 1014838 **Country/ies where the study was carried out** International **Study type** Systematic Review **Aim of the study** To evaluate the effectiveness of psychotherapy interventions in treatment resistant psychosis patients of the last 25 years **Study dates**	individual CBT and treatment as usual was included) **Characteristics** Clozapine resistant schizophrenia and non-affective psychosis **Inclusion criteria** 1. Uniform control group (patients treated with clozapine monotherapy ± placebo therapy) (TAU) 2. Measurement of outcome with validated scale 3. Randomized controlled trials 4. Individual CBT intervention 5. Evaluation, pre- and post treatment, with the same type of scale 6. Follow-up to 6 or 9 months **Exclusion criteria**	Individual CBT (The meta-analysis only included individual CBT intervention)	on medication for a defined period (from 8 weeks to 6 months) were included in the studies.	Concerns regarding specification of study eligibility criteria. LOW CONCERN Concerns regarding methods used to identify and/or select studies. LOW CONCERN Concerns regarding methods used to collect data and appraise studies. LOW CONCERN Concerns regarding methods used to synthesize results. LOW CONCERN Risk of bias: Low

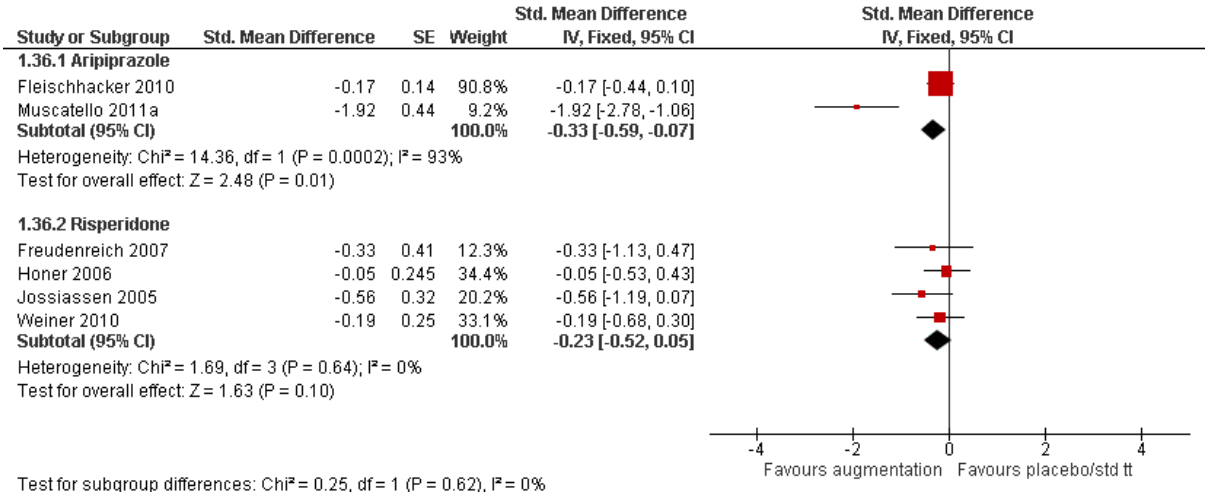
Study details	Participants	Interventions	Outcomes and Results	Comments
Studies published between January 1, 1993, to August 1, 2018 were included **Source of funding** The open access publication of the review was supported by a grant of the Department of Neuroscience, Reproductive Science and Odontostomatology of the University of Naples "Federico II" to the Section of Psychiatry	Studies reporting pharmacological augmentation interventions			Risk of bias for individual outcomes is based on the critical appraisal reported in the review **Other information** NA
Full citation Siskind, D. J., Lee, M., Ravindran, A., Zhang, Q., Ma, E., Motamarri, B., Kisely, S., Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis, Australian and New Zealand journal of psychiatry, 52, 751-767, 2018 **Ref Id** 1015041	**Sample size** 46 studies including 2223 subjects (Data from only 15 studies satisfying the inclusion criteria were included) Included studies (Muscatello 2011a, **Characteristics** Clozapine refractory schizophrenia	**Interventions** Clozapine augmentation interventions (pharmacological and non-pharmacological agents like antipsychotics, antidepressants, mood stabilisers, glutamergic agents, other agents and electroconvulsive therapy) Aripiprazole augmentation:	**Results** The primary outcome was total psychotic symptoms, with secondary outcomes being positive and negative symptom subscales and adverse drug reactions Psychosis symptoms Total: Muscatello 2011a Freudenreich 2007 Honer 2006 Weiner 2010 Barnes 2017 Nielson 2012	**Limitations** ROBIS checklist summary Concerns regarding specification of study eligibility criteria. LOW CONCERN Concerns regarding methods used to identify and/or select

Study details	Participants	Interventions	Outcomes and Results	Comments
Country/ies where the study was carried out International (Studies from UK, Europe, US, Canada and Australia) **Study type** Systematic review **Aim of the study** To evaluate the effectiveness of augmentation interventions for clozapine refractory schizophrenia **Study dates** Databases were searched from start to October 2017 **Source of funding** No funding support	**Inclusion criteria** RCTs reporting on clozapine augmentation strategies **Exclusion criteria** Narrative and systematic reviews, posters, conference abstracts, case reports and letters to editors	Muscatello 2011 a (24 weeks follow-up): 15 mg/day of aripiprazole + clozapine (mean dose 310.7±73.1 mg/day) versus placebo+clozapine (mean dose 341.2±77.5 mg/day) Risperidone augmentation: Freudenreich 2007 (6 weeks follow-up): 4 mg/day risperidone + clozapine versus placebo + clozapine Honer 2006 (8 weeks follow-up): 3 mg/day risperidone + clozapine versus placebo + clozapine	Freidman 2011 Adverse drug reactions: Freudenreich 2007: Adverse Neurological events: SARS score (Simpson–Angus Rating Scale; change from baseline at 6 weeks' follow-up) Drug induced akathisia: BARS score (Barnes Akathisia Rating Scale; change from baseline at 6 weeks' follow-up) Drug induced abnormal movements: AIMS score (Abnormal Involuntary Movement Scale; change from baseline at 6 weeks follow-up)	studies. LOW CONCERN Concerns regarding methods used to collect data and appraise studies. LOW CONCERN Concerns regarding methods used to synthesize results. LOW CONCERN Risk of bias: Low Risk of bias for individual outcomes is based on the critical appraisal reported in the review **Other information** NA

Appendix E – Forest plots

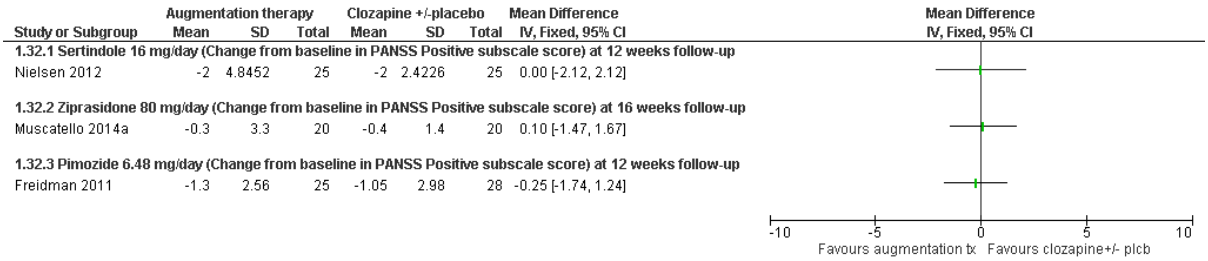
Forest plots for review question: 3.1 What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Figure 2: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Positive symptoms



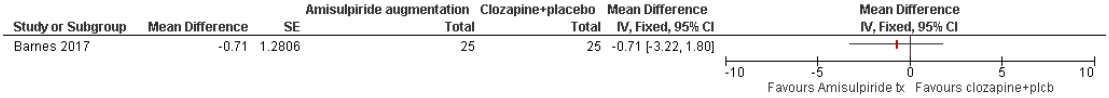
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 3: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Positive symptoms



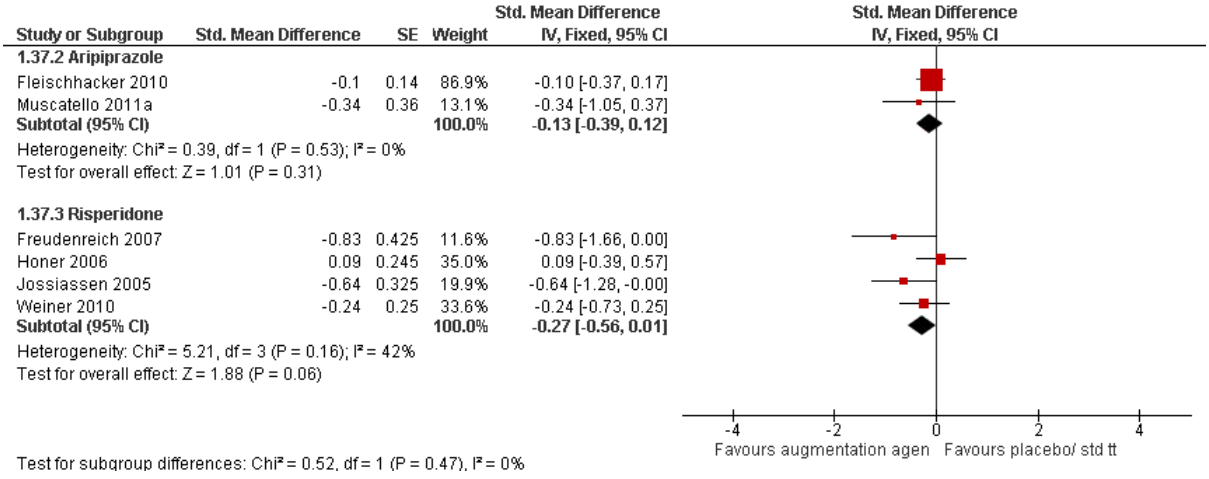
CI: confidence interval; IV: inverse variance; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation

Figure 4: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Amisulpride. Psychosis Negative symptoms: PANSS



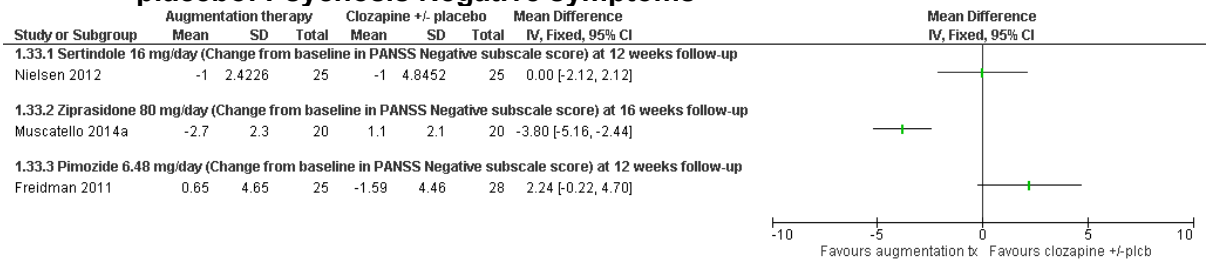
CI: confidence interval; IV: inverse variance; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation

Figure 5: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Negative symptoms



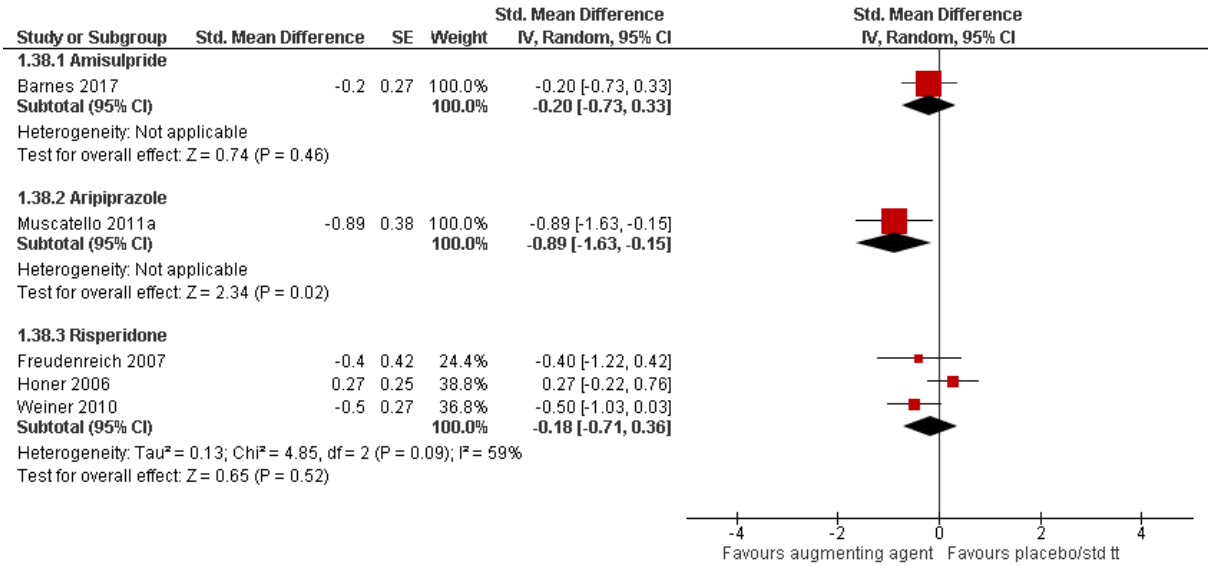
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 6: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Negative symptoms



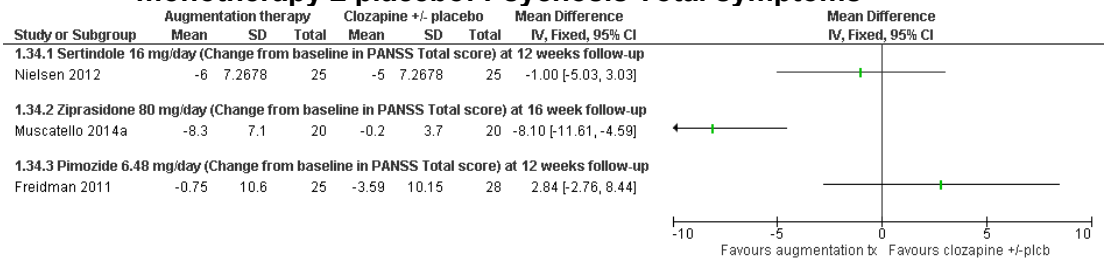
CI: confidence interval; IV: inverse variance; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation

Figure 7: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Total symptoms



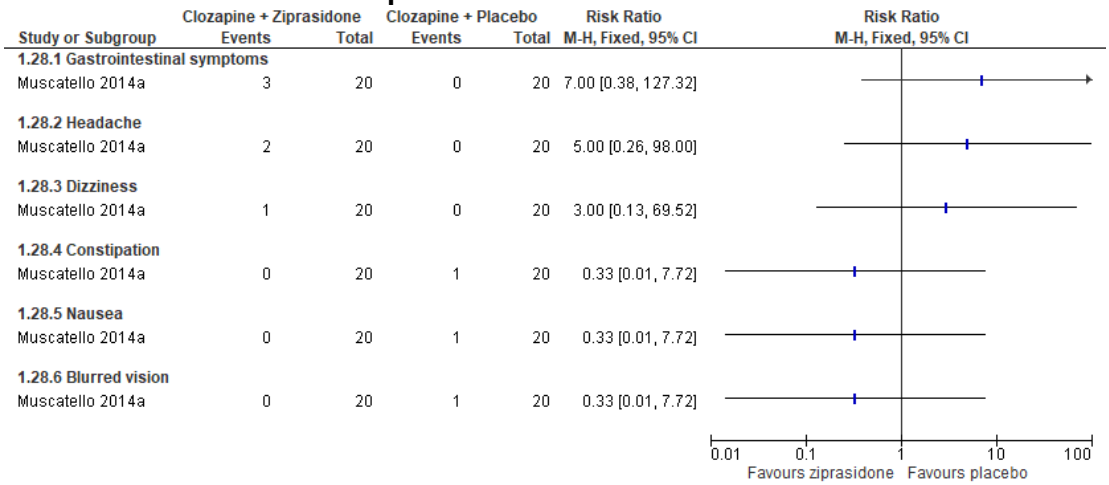
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 8: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Psychosis Total symptoms



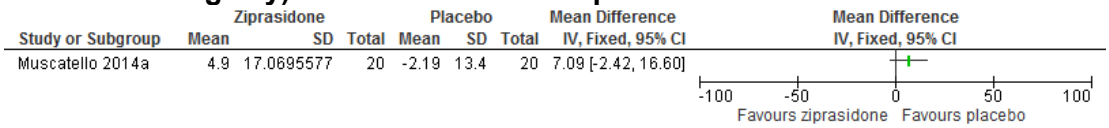
CI: confidence interval; IV: inverse variance; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation

Figure 9: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Adverse events (Ziprasidone 80 mg/day) at 16 weeks follow-up



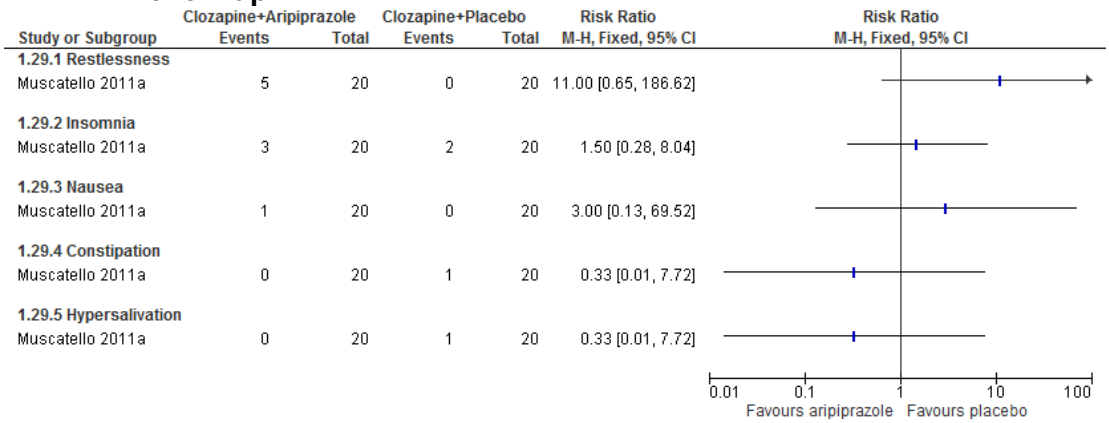
CI: confidence interval

Figure 10: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Adverse events: QTc interval (Ziprasidone 80 mg/day): at 16 weeks follow-up



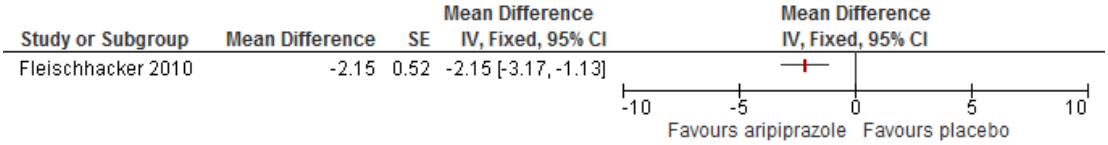
CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 11: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Adverse events (Aripiprazole) at 24 weeks follow-up



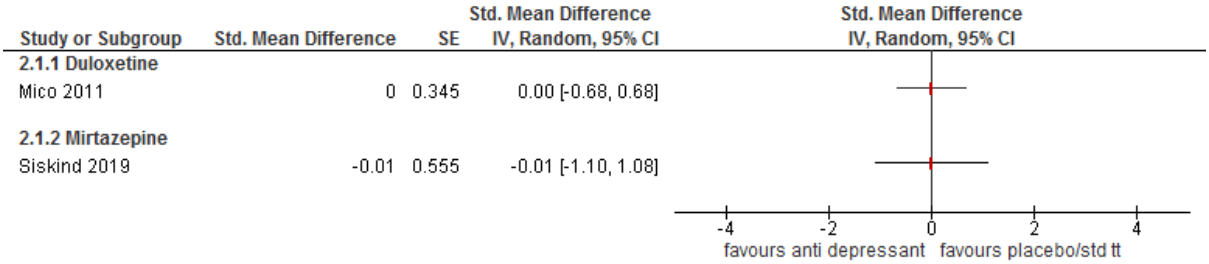
CI: confidence interval; IV: inverse variance

Figure 12: Comparison 1. Antipsychotic augmentation versus clozapine monotherapy ± placebo: Adverse events: decrease in body weight (Aripiprazole) at 16 weeks follow-up



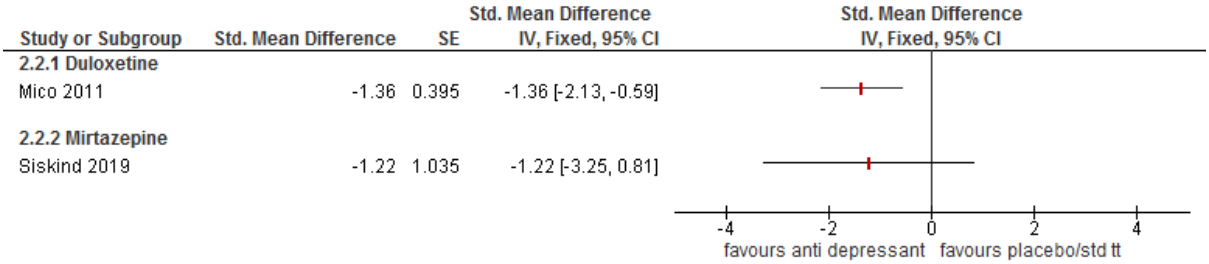
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 13: Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo: Psychosis Positive symptoms



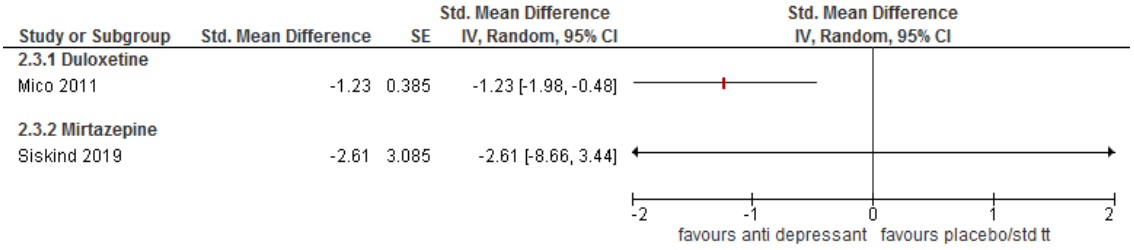
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 14: Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo: Psychosis Negative symptoms



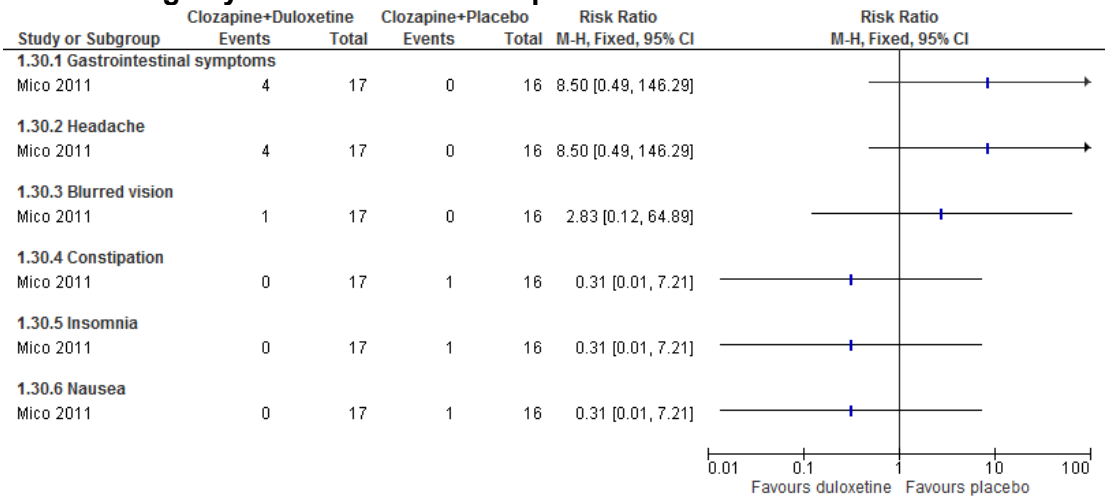
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 15: Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo: Psychosis Total symptoms



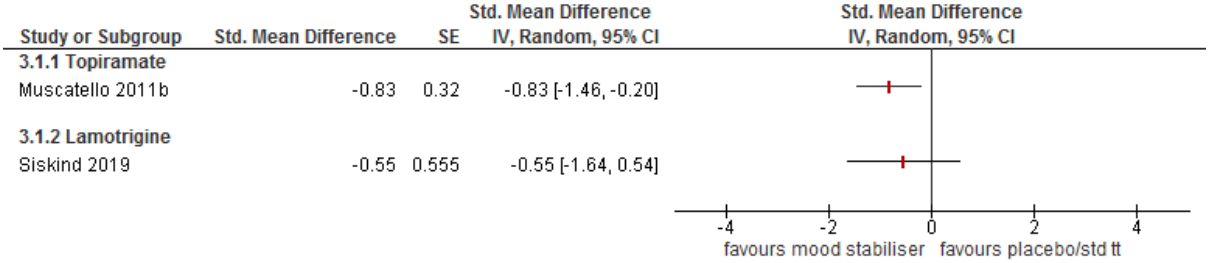
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 16: Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo: Adverse events following Duloxetine 60 mg/day at 16 weeks follow-up



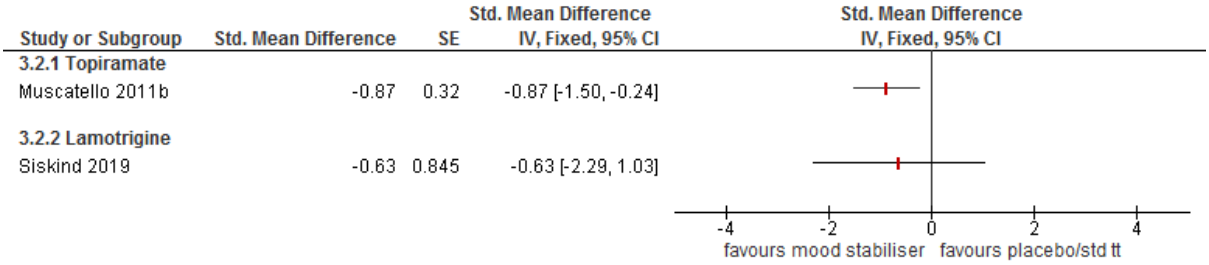
CI: confidence interval

Figure 17: Comparison 3. Mood stabiliser augmentation versus Clozapine monotherapy ± placebo: Psychosis Positive symptoms



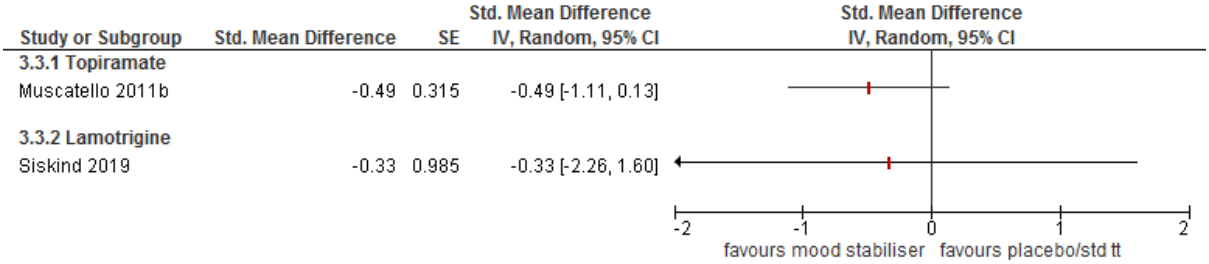
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 18: Comparison 3. Mood stabiliser augmentation versus Clozapine monotherapy ± placebo: Psychosis Negative symptoms



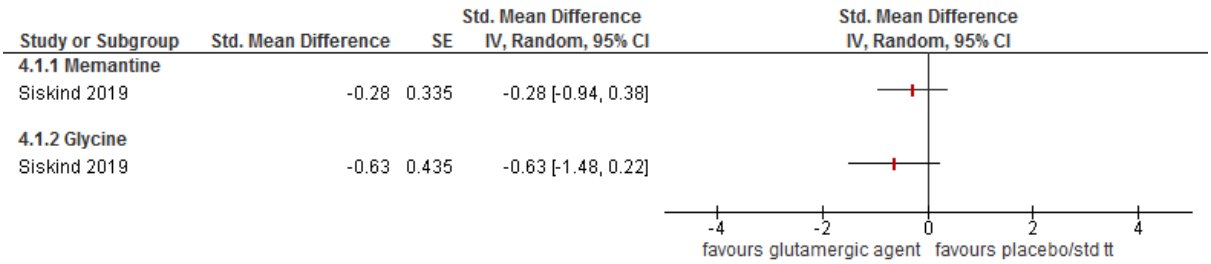
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 19: Comparison 3. Mood stabiliser augmentation versus Clozapine monotherapy ± placebo: Psychosis Total symptoms



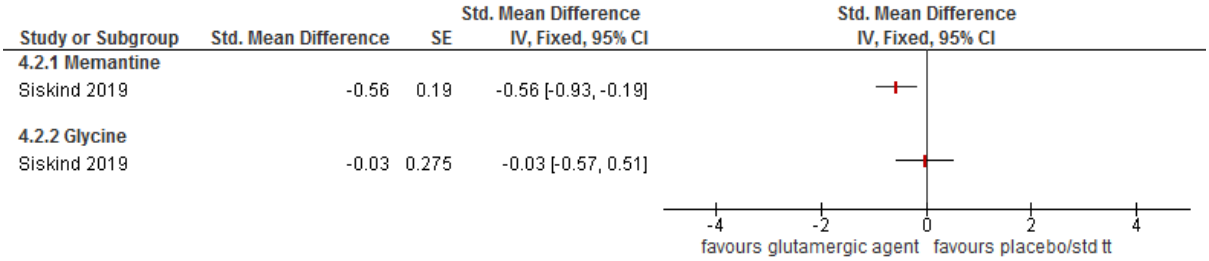
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 20: Comparison 4. Glutamergic augmentation versus Clozapine monotherapy ± placebo: Psychosis Positive symptoms



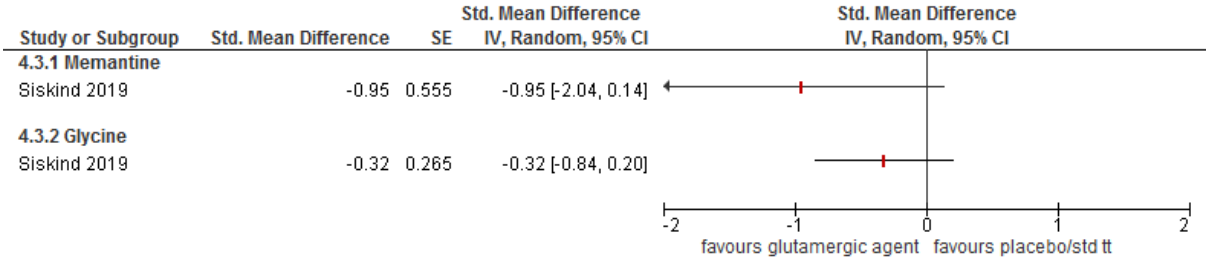
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 21: Comparison 4. Glutamergic augmentation versus Clozapine monotherapy ± placebo: Psychosis Negative symptoms



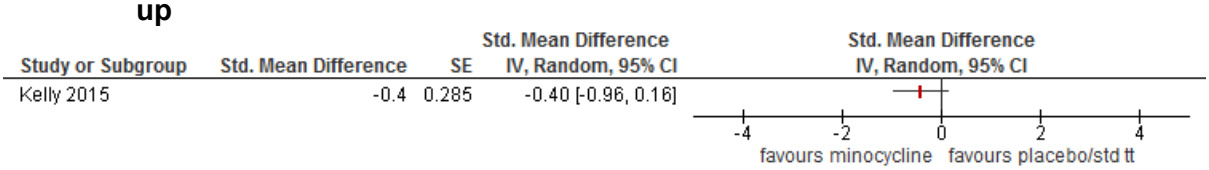
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 22: Comparison 4. Glutamergic augmentation versus Clozapine monotherapy ± placebo: Psychosis Total symptoms



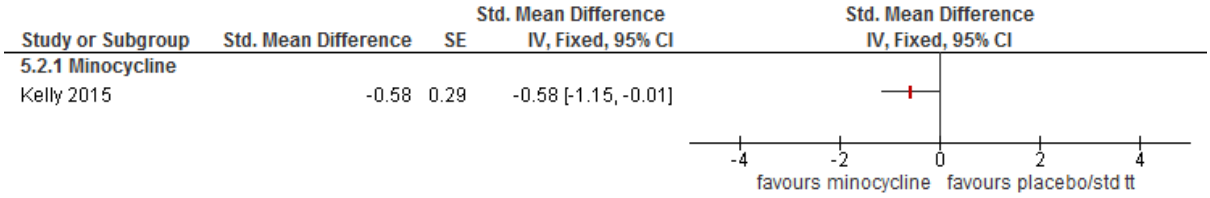
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 23: Comparison 5. Other agent (minocycline) augmentation versus Clozapine monotherapy ± placebo: Psychosis Positive symptoms at 10 weeks follow-up



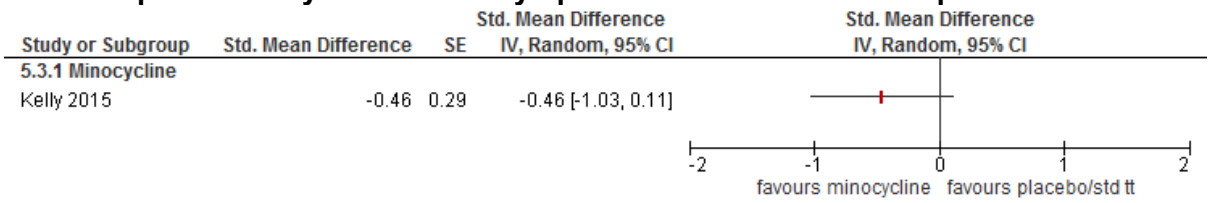
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 24: Comparison 5. Other agent (minocycline) augmentation versus Clozapine monotherapy ± placebo: Psychosis Negative symptoms at 10 weeks follow-up



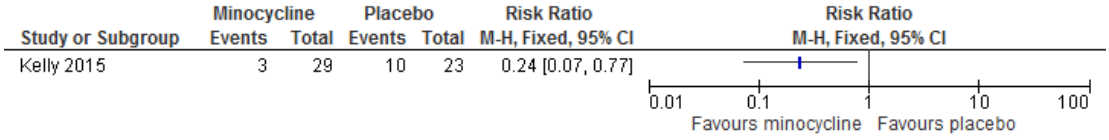
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 25: Comparison 5. Other agent augmentation versus Clozapine monotherapy ± placebo: Psychosis Total symptoms at 10 weeks follow-up



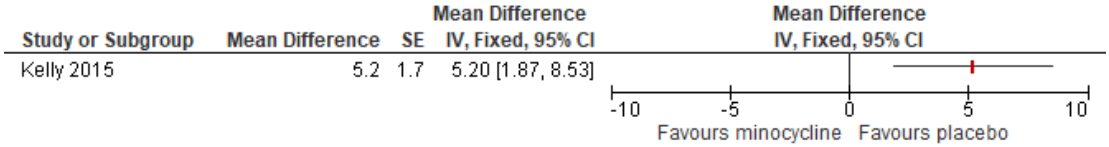
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 26: Comparison 5. Other agent augmentation versus Clozapine monotherapy ± placebo: Adverse events: Minocycline (constipation) at 10 weeks follow-up



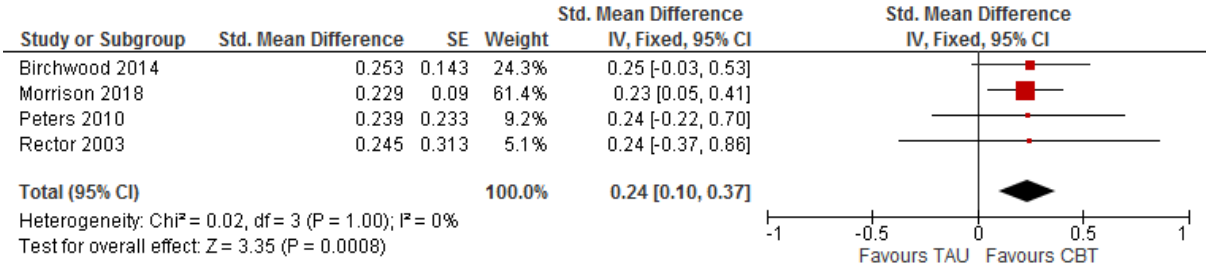
CI: confidence interval

Figure 27: Comparison 5. Other agent augmentation versus Clozapine monotherapy ± placebo: Adverse events: Minocycline (increase in HDL) at 10 weeks follow-up



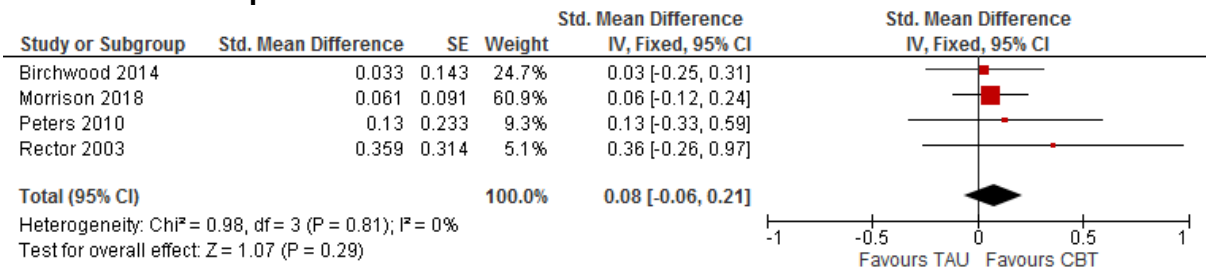
CI: confidence interval; HDL: high density lipoprotein; IV: inverse variance; SE: standard error

Figure 28: Comparison 6. Individual cognitive behavioural therapy (CBT) versus treatment as usual (TAU): Psychosis Positive symptoms at 6-8 months follow-up



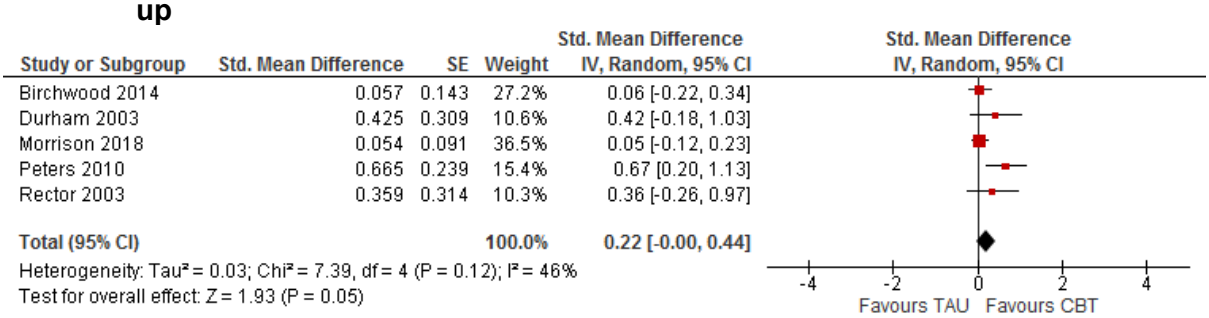
CI: confidence interval; IV: inverse variance; SE: standard error

Figure 29: Comparison 6. Individual cognitive behavioural therapy (CBT) versus treatment as usual (TAU): Psychosis Negative symptoms at 6-8 months follow-up



CI: confidence interval; IV: inverse variance; SE: standard error

Figure 30: Comparison 6. Individual cognitive behavioural therapy (CBT) versus treatment as usual (TAU): Psychosis Total symptoms at 6-8 months follow-up



CI: confidence interval; IV: inverse variance; SE: standard error

Appendix F – GRADE tables

GRADE tables for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Table 6: Clinical evidence profile for Comparison 1. Antipsychotic augmentation versus Clozapine monotherapy ± placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation	Clozapine monotherapy ± placebo	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Positive – Aripiprazole 5-15 mg/day at 16-24 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	120	125	-	SMD 0.33 lower (0.59 lower to 0.07 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Positive – Risperidone 3-6 mg/day at 6-16 weeks follow-up (Various scales; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	98	103	-	SMD 0.23 lower (0.52 lower to 0.05 higher)	LOW	CRITICAL
Psychosis symptoms - Positive – Sertindole 16 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	25	25	-	MD 0.00 (2.12 lower to 2.12 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Positive - Ziprasidone 80 mg/day at 16 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	20	-	MD 0.10 higher (1.47lower to 0.66 1.67)	VERY LOW	CRITICAL
Psychosis symptoms - Positive – Pimozide 6.48 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation	Clozapine monotherapy ± placebo	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	25	28	-	MD 0.25 lower (0.63 lower to 0.45 higher)	LOW	CRITICAL
Psychosis symptoms - Negative - Amisulpiride 400-800 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	25	28	-	MD 0.71 lower (3.22 lower to 1.80 higher)	LOW	CRITICAL
Psychosis symptoms - Negative – Aripiprazole 5-15 mg/day at 16-24 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	120	125	-	SMD 0.13 lower (0.39 lower to 0.12 higher)	LOW	CRITICAL
Psychosis symptoms - Negative – Risperidone 3-6 mg/day at 6-16 weeks follow-up (Various scales; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	98	103	-	SMD 0.27 lower (0.56 lower to 0.01 higher)	LOW	CRITICAL
Psychosis symptoms - Negative - Sertindole 16 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	25	25	-	MD 0.00 (2.12 lower to 2.12 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Negative - Ziprasidone 80 mg/day at 16 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	20	20	-	MD 3.80 lower (5.16 to 2.44 lower)	LOW	CRITICAL
Psychosis symptoms - Negative – Pimozide 6.48 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	25	28	-	MD 2.24 higher (0.22 lower to 4.70 higher)	LOW	CRITICAL
Psychosis symptoms - Total - Amisulpiride 400-800 mg/day at 12 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation	Clozapine monotherapy ± placebo	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	25	28	-	SMD 0.2 lower (0.73 lower to 0.33 higher)[4]	LOW	CRITICAL
Psychosis symptoms - Total - Aripiprazole 15 mg/day at 24 weeks follow-up (PANSS total score; range 30 to 120; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	20	20	-	SMD 0.89 lower (1.63 to 0.15 lower)[4]	LOW	CRITICAL
Psychosis symptoms - Total – Risperidone 3-4 mg/day at 6-16 weeks follow-up (Various scales; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	78	83	-	SMD 0.18 lower (0.71 lower to 0.36 higher)	LOW	CRITICAL
Psychosis symptoms - Total - Sertindole 16 mg/day at 12 weeks follow-up (PANSS total score; range 30 to 120; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	25	25	-	MD 1.00 lower (5.03 lower to 3.03 higher)	LOW	CRITICAL
Psychosis symptoms - Total – Ziprasidone (PANSS total score; range 30 to 120; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	20	20	-	MD 8.10 lower (11.61 lower to4.59 lower)	LOW	CRITICAL
Psychosis symptoms - Total – Pimozide 6.48 mg/day at 12 weeks follow-up (PANSS total score; range 30 to 120; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	25	28	-	MD 2.84 higher (2.76 lower to 8.44 higher)	VERY LOW	CRITICAL
Adverse events: Restlessness – Aripiprazole 15 mg/day at 24 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	5/20 (25%)	0/20 (0%)	RR 11 (0.65 to 186.62)	-	VERY LOW	IMPORTANT
Adverse events: Insomnia – Aripiprazole 15 mg/day at 24 weeks follow-up (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation	Clozapine monotherapy ± placebo	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/20 (15%)	2/20 (10%)	RR 1.5 (0.28 to 8.04)	50 more per 1000 (from 72 fewer to 704 more)	VERY LOW	IMPORTANT
Adverse events: Nausea– Aripiprazole 15 mg/day at 24 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/20 (5%)	0/20 (0%)	RR 3 (0.13 to 69.52)	-	VERY LOW	IMPORTANT
Adverse events: Constipation– Aripiprazole 15 mg/day at 24 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/20 (5%)	0/20 (0%)	RR 0.33 (0.01 to 7.72)	-	VERY LOW	IMPORTANT
Adverse events: Hypersalivation– Aripiprazole 15 mg/day at 24 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/20 (5%)	0/20 (0%)	RR 0.33 (0.01 to 7.72)	-	VERY LOW	IMPORTANT
Adverse events: Decrease in body weight– Aripiprazole 5-15 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	100	105	MD -2.15(-3.17 to -1.13)	-	LOW	IMPORTANT
Adverse events: Gastrointestinal symptoms - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/20 (15%)	0/20 (0%)	RR 7.0(0.38 to 127.32)	-	VERY LOW	IMPORTANT
Adverse events: Headache - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2/20 (10%)	0/20 (0%)	RR 5.0(0.26 to 98.0)	-	VERY LOW	IMPORTANT
Adverse events: Dizziness - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmentation	Clozapine monotherapy ± placebo	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/20 (5%)	0/20 (0%)	RR 3.0(0.13 to 69.52)	-	VERY LOW	IMPORTANT
Adverse events: Constipation - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/20 (0%)	1/20 (5%)	RR 0.33(0.01 to 7.72)	-	VERY LOW	IMPORTANT
Adverse events: Nausea- Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/20 (0%)	1/20 (5%)	RR 0.33(0.01 to 7.72)	-	VERY LOW	IMPORTANT
Adverse events: Blurred vision - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/20 (0%)	1/20 (5%)	RR 0.33(0.01 to 7.72)	-	VERY LOW	IMPORTANT
Adverse events: QTc interval - Ziprasidone 80 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	20	-	MD 7.09 higher (2.42 lower to 16.6 higher)	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; PANSS: Positive and Negative Syndrome Scale; RR: risk ratio; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services
2 Downgraded 2 levels for very serious imprecision as 95% CI of effect crosses both default MID thresholds
3 Downgraded 1 level for serious imprecision as 95% CI of effect crosses 1 default MID threshold
4 SMD used for single trial because systematic review did not report MD

Table 7: Clinical evidence profile for Comparison 2. Antidepressant augmentation versus Clozapine monotherapy ± placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant augmentation	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Positive – Duloxetine 60 mg/day at 16 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	20	-	SMD 0 higher (0.68 lower to 0.68 higher)[4]	VERY LOW	CRITICAL
Psychosis symptoms - Positive – Mirtazepine 30 mg/day at 6-8 weeks follow-up (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	19	-	SMD 0.01 lower (1.1 lower to 1.08 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Negative - Duloxetine 60 mg/day at 16 weeks follow-up (PANSS; range 7 to 49; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	20	20	-	SMD 1.36 lower (2.13 to 0.59 lower)[4]	LOW	CRITICAL
Psychosis symptoms - Negative – Mirtazepine 30 mg/day at 6-8 weeks follow-up (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	19	-	SMD 1.22 lower (3.25 lower to 0.81 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Total - Duloxetine 60 mg/day at 16 weeks follow-up (PANSS total score; range 30 to 120; Better indicated by lower values)												
1	randomised trials	no seriou	no serious inconsistency	serious[1]	serious[3]	none	20	20	-	SMD 1.23 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant augmentation	Control	Relative (95% CI)	Absolute		
		s risk of bias								(1.98 to 0.48 lower)[4]		
Psychosis symptoms - Total – Mirtazepine 30 mg/day at 6-8 weeks follow-up (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	20	19	-	SMD 2.61 lower (8.66 lower to 3.44 higher)	VERY LOW	CRITICAL
Adverse events – Gastrointestinal symptoms : Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	4/17 (23.5%)	0/16 (0%)	RR 8.5 (0.49 to 146.29)	-	VERY LOW	IMPORTANT
Adverse events – Headache: Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	4/17 (23.5%)	0/16 (0%)	RR 8.5 (0.49 to 146.29)	-	VERY LOW	IMPORTANT
Adverse events – Blurred vision: Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/17 (5.9%)	0/16 (0%)	RR 2.83 (0.12 to 64.89)	-	VERY LOW	IMPORTANT
Adverse events – Constipation: Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/17 (0%)	1/16 (6.3%)	RR 0.31 (0.01 to 7.21)	43 fewer per 1000 (from 62 fewer to 388 more)	VERY LOW	IMPORTANT
Adverse events – Insomnia: Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressant augmentation	Control	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/17 (0%)	1/16 (6.3%)	RR 0.31 (0.01 to 7.21)	43 fewer per 1000 (from 62 fewer to 388 more)	VERY LOW	IMPORTANT
Adverse events – Nausea: Duloxetine 60 mg/day at 16 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	0/17 (0%)	1/16 (6.3%)	RR 0.31 (0.01 to 7.21)	43 fewer per 1000 (from 62 fewer to 388 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio; PANSS: Positive and Negative Syndrome Scale; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services
2 Downgraded 2 levels for very serious imprecision as 95% CI of effect crosses both default MID thresholds
3 Downgraded 1 level for serious imprecision as 95% CI of effect crosses default MID thresholds

4 SMD used for single trial because systematic review did not report MD

Table 8: Clinical evidence profile for Comparison 3. Mood stabiliser augmentation versus Clozapine monotherapy ± placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mood stabiliser augmentation	Control	Relative (95% CI)	Absolute		
Psychosis symptoms - Positive – Topiramate* (Better indicated by lower values)												
1	randomised trials	no serious	no serious inconsistency	serious[1]	serious[2]	none	30	30	-	SMD 0.83	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mood stabiliser augmentation	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								lower (1.46 to 0.2 lower) [3]		
Psychosis symptoms - Positive – Lamotrigine* (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[5]	none	26	25	-	SMD 0.55 lower (1.64 lower to 0.54 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Negative – Topiramate* (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	30	30	-	SMD 0.87 lower (1.5 to 0.24 lower) [3]	LOW	CRITICAL
Psychosis symptoms - Negative – Lamotrigine* (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[5]	none	26	25	-	SMD 0.63 lower (2.29 lower to 1.03 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Total – Topiramate* (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	30	30	-	SMD 0.49 lower (1.11 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mood stabiliser augmentation	Control	Relative (95% CI)	Absolute	Quality	Importance
										0.13 higher) [3]		
Psychosis symptoms - Total – Lamotrigine* (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[5]	none	26	25	-	SMD 0.33 lower (2.26 lower to 1.6 higher) [3]	VERY LOW	CRITICAL

**Data on dose and follow-up duration unavailable in the systematic review*
CI: confidence interval; RR: risk ratio; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services
2 Downgraded 1 level for serious imprecision as 95% CI of effect crosses default MID thresholds
3 SMD used for single trial because systematic review did not report MD
4 Downgraded by 1 level due to serious indirectness of population as it is unclear whether the population received rehabilitation services and due to inclusion of some studies from countries outside protocol eligibility criteria
5 Downgraded 2 levels for very serious imprecision as 95% CI of effect crosses both default MID thresholds

Table 9: Clinical evidence profile for Comparison 4. Glutamergic augmentation versus Clozapine monotherapy ± placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glutamergic agents	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Positive – Memantine* (Better indicated by lower values)												
3	randomised trials	no serious	no serious inconsistency	serious[1]	serious[2]	none	NR	NR	-	SMD 0.28	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glutamergic agents	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								lower (0.94 lower to 0.38 higher)		
Psychosis symptoms - Positive – Glycine* (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	NR	NR	-	SMD 0.63 lower (1.48 lower to 0.22 higher)	LOW	CRITICAL
Psychosis symptoms - Negative – Memantine* (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	NR	NR	-	SMD 0.56 lower (0.93 to 0.19 lower)	LOW	CRITICAL
Psychosis symptoms - Negative – Glycine* (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3]	none	NR	NR	-	SMD 0.03 lower (0.57 lower to 0.51 higher)	VERY LOW	CRITICAL
Psychosis symptoms - Total – Memantine* (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3]	none	NR	NR	-	SMD 0.95 lower (2.04 lower to 0.14 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glutamergic agents	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Total – Glycine* (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	NR	NR	-	SMD 0.32 lower (0.84 lower to 0.2 higher)	LOW	CRITICAL

**Data on dose, follow-up duration and participants in each group unavailable in the systematic review*
CI: confidence interval; NR: not reported; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services and due to inclusion of some studies from countries outside protocol eligibility criteria
2 Downgraded 1 level for serious imprecision as 95% CI of effect crosses 1 default MID threshold
3 Downgraded 2 levels for very serious imprecision as 95% CI of effect crosses both default MID thresholds

Table 10: Clinical evidence profile for Comparison 5. Other agent augmentation versus Clozapine monotherapy ± placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other agents	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Positive - Minocycline at 10 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	29	23	-	SMD 0.40 lower (0.96 to 0.16 higher)[3]	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other agents	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Negative - Minocycline at 10 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	29	23	-	SMD 0.58 lower (1.15 to 0.01 lower)[3]	LOW	CRITICAL
Psychosis symptoms - Total - Minocycline at 10 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	29	23	-	SMD 0.46 lower (1.03 lower to 0.11 higher)[3]	LOW	CRITICAL
Adverse events – Constipation: Minocycline at 10 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	3/29 (10.3%)	10/23 (43.5%)	RR 0.24 (0.07 to 0.77)	330 fewer per 1000 (from 100 fewer to 404 fewer)	LOW	CRITICAL
Adverse events – Increase in HDL cholesterol: Minocycline at 10 weeks follow-up (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	29	23	-	MD 5.2 (1.87 to 8.53)	LOW	CRITICAL

CI: confidence interval; HDL: high density lipoprotein; MD: mean difference; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services
2 Downgraded 1 level for serious imprecision as 95% CI of effect crosses 1 default MID threshold
3 SMD used for single trial because systematic review did not report MD

Table 11: Clinical evidence profile for Comparison 6. Individual cognitive behavioural therapy (CBT) versus treatment as usual (TAU)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	Control	Relative (95% CI)	Absolute	Quality	Importance
Psychosis symptoms - Positive - CBT (Better indicated by higher values) at 6-8 months follow-up												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	-	-	-	SMD 0.237 higher (0.097 to 0.376 higher)	MODERATE	CRITICAL
Psychosis symptoms - Negative - CBT (Better indicated by higher values) at 6-8 months follow-up												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	-	-		SMD 0.075 higher (0.063 lower to 0.214 higher)	MODERATE	CRITICAL
Psychosis symptoms - Total – CBT(Better indicated by higher values) at 6-8 months follow-up												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none		-	-	SMD 0.220 higher (0.04 lower to 0.443 higher)	MODERATE	CRITICAL

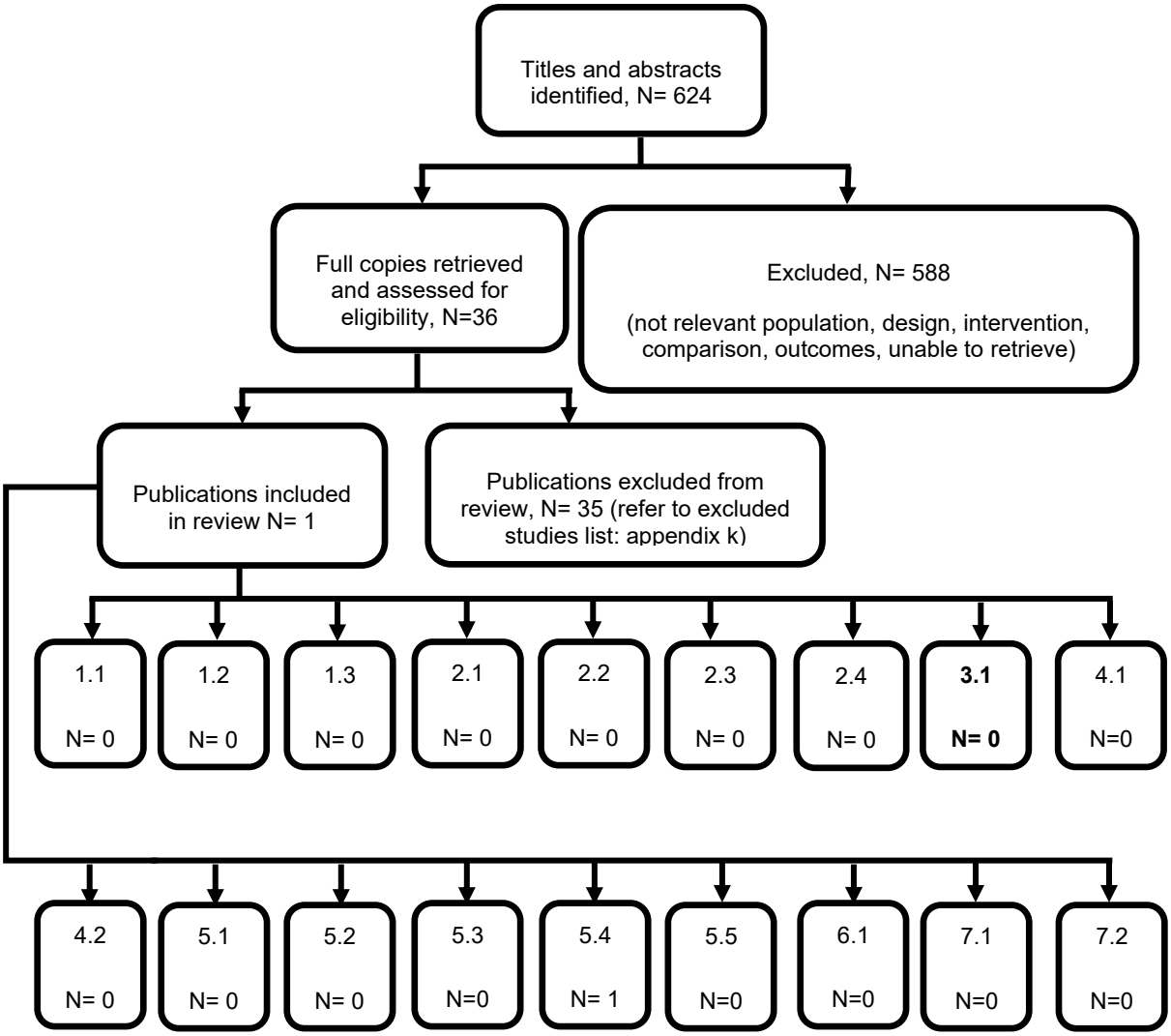
CI: confidence interval; SMD: standardised mean difference
1 Downgraded by 1 level for serious indirectness as it is unclear whether the population received rehabilitation services

Appendix G – Economic evidence study selection

Economic evidence study selection for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

A global health economic literature search was undertaken, covering all review questions in this guideline. However, as shown in Figure 31, no evidence was identified which was applicable for this review question.

Figure 31: Health economic study selection flow chart



Appendix H – Economic evidence tables

Economic evidence tables for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

No evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Clinical studies

Table 12: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Akhondzadeh, S., Mackinejad, K., Ahmadi-Abhari, S. A., Alem, Z. M., Does the addition of lamotrigine to risperidone improve psychotic symptoms and cognitive impairments in chronic schizophrenia?, Therapy, 2, 399-406, 2005	The study does not include a clozapine augmentation intervention
Ashton, A. K., Aripiprazole augmentation of clozapine: in refractory schizophrenia, Psychiatry, 2, 18-9, 2005	Letter to editor
Assion, H. J., Reinbold, H., Lemanski, S., Basilowski, M., Juckel, G., Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to clozapine. A randomized, double-blind, placebo-controlled trial, Pharmacopsychiatry, 41, 24-28, 2008	The data from this trial is not sufficient to extract mean differences as standard deviation of change of scores is not reported
Barbui, C., Accordini, S., Nosè, M., Stroup, S., Purgato, M., Girlanda, F., Esposito, E., Veronese, A., Tansella, M., Cipriani, A., Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia in routine clinical care: a randomized, controlled trial, Journal of Clinical Psychopharmacology, 31, 266-273, 2011	Not a comparison with standard care
Barbui, Corrado, Signoretti, Alessandra, Mule, Serena, Boso, Marianna, Cipriani, Andrea, Does the addition of a second antipsychotic drug improve clozapine treatment?, Schizophrenia Bulletin, 35, 458-468, 2009	Old systematic review without additional relevant papers
Barnes, T. R. E., Leeson, V. C., Paton, C., Marston, L., Davies, L., Whittaker, W., Osborn, D., Kumar, R., Keown, P., Zafar, R., Iqbal, K., Singh, V., Fridrich, P., Fitzgerald, Z., Bagalkote, H., Haddad, P. M., Husni, M., Amos, T., Amisulpride augmentation in clozapine-unresponsive schizophrenia (AMICUS): A double-blind, placebo-controlled, randomised trial of clinical effectiveness and cost-effectiveness, Health Technology Assessment, 21, i-53, 2017	Data from this trial is included in the Siskind 2018 Systematic review.
Barnes, T. R. E., Leeson, V., Paton, C., Marston, L., Osborn, D. P., Kumar, R., Keown, P., Zafar, R., Iqbal, K., Singh, V., et al.,, Amisulpride augmentation of clozapine for treatment-refractory schizophrenia: a double-blind, placebo-controlled trial, Therapeutic advances in psychopharmacology, 8, 185-197, 2018	Data from this trial is included in the Siskind 2018 Systematic review
Barnes, T., Leeson, V., Paton, C., Marston, L., Osborn, D., Kumar, R., Keown, P., Zafar, R., Iqbal, K., Singh, V., et al.,, Amisulpride augmentation of clozapine for treatment-refractory schizophrenia: the amicus study, Schizophrenia Bulletin, 43, S165-, 2017	Data from this trial is included in the Siskind 2018 Systematic review
Benedetti, A., Di Paolo, A., Lastella, M., Casamassima, F., Candiracci, C., Litta, A., Ciofi, L., Danesi, R., Lattanzi, L., Del Tacca, M., Cassano, G. B., Augmentation of clozapine with aripiprazole in	Not a randomised controlled trial

severe psychotic bipolar and schizoaffective disorders: A pilot study, Clinical Practice and Epidemiology in Mental Health, 6, 30-35, 2010	
Chang, J. S., Ahn, Y. M., Park, H. J., Lee, K. Y., Kim, S. H., Kang, U. G., Kim, Y. S., Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: An 8-week, randomized, double-blind, placebo-controlled trial, Journal of Clinical Psychiatry, 69, 720-731, 2008	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Chang, Jae Seung, Lee, Nam Young, Ahn, Yong Min, Kim, Yong Sik, The sustained effects of aripiprazole-augmented clozapine treatment on the psychotic systems and metabolic profiles of patients with refractory schizophrenia, Journal of Clinical Psychopharmacology, 32, 282-284, 2012	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Cipriani, A., Accordini, S., Nose, M., Purgato, M., Girlanda, F., Tansella, M., Barbui, C., Aripiprazole versus haloperidol in combination with clozapine for treatment-resistant schizophrenia: A 12-month, randomized, naturalistic trial, Journal of Clinical Psychopharmacology, 33, 533-537, 2013	Not a comparison with standard treatment
Dardennes, R. M., Al, A. N. N., Rouillon, F., Successful augmentation of clozapine-resistant treatment of schizophrenia with clonidine, Progress in neuro-psychopharmacology & biological psychiatry, 34, 724-725, 2010	Case report
Euctr, D. K., Augmenting clozapine with sertindole - A double-blinded randomized placebo study (SERCLOZ) - SERCLOZ, Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2006-002682-40-dk, 2006	The data from this trial is included in the Siskind 2018 systematic review
Freudenreich, O., Henderson, D. C., Walsh, J. P., Culhane, M. A., Goff, D. C., Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial, Schizophrenia Research, 92, 90-94, 2007	The data from this trial is included in the Siskind 2018 systematic review
Friedman, J. I., Lindenmayer, J. P., Alcantara, F., Bowler, S., Parak, M., White, L., Iskander, A., Parrella, M., Adler, D. N., Tsopelas, N. D., Tsai, W. Y., Novakovick, V., Harvey, P. D., Davis, K. L., Pimozide augmentation of clozapine inpatients with schizophrenia and schizoaffective disorder unresponsive to clozapine monotherapy, Neuropsychopharmacology, 36, 1289-1295, 2011	The data from this trial is included in the Siskind 2018 systematic review
Friedman, Joseph I., Lindenmayer, Jean-Pierre, Alcantara, Frances, Bowler, Stephanie, Parak, Mohan, White, Leonard, Iskander, Adel, Parrella, Michael, Adler, David N., Tsopelas, Nicholas D., Tsai, Wei-Yann, Novakovick, Vladan, Harvey, Philip D., Davis, Kenneth L., "Pimozide augmentation of clozapine inpatients with schizophrenia and schizoaffective disorder unresponsive to clozapine monotherapy": Corrigendum, Neuropsychopharmacology, 36, 1317, 2011	The data from this trial is included in the Siskind 2018 systematic review
Genç, Y., Taner, E., Candansayar, S., Comparison of clozapine-amisulpride and clozapine-quetiapine combinations for patients with schizophrenia who are partially responsive to clozapine: a single-blind randomized study, Advances in therapy, 24, 1-13, 2007	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Ginsberg, David L., Lamotrigine effective for treatment-resistant schizophrenia, Primary Psychiatry, 11, 20-24, 2004	This article is not original research but discusses findings of the Tiihonen 2003 study

Gitlin, M., Treatment-resistant bipolar disorder, Molecular Psychiatry, 11, 227-240, 2006	Not a systematic review
Glick, I. D., Bosch, J., Casey, D. E., A double-blind randomized trial of mood stabilizer augmentation using lamotrigine and valproate for patients with schizophrenia who are stabilized and partially responsive, Journal of Clinical Psychopharmacology, 29, 267-271, 2009	Not a clozapine augmentation intervention
Goff, D. C., Keefe, R., Citrome, L., Davy, K., Krystal, J. H., Large, C., Thompson, T. R., Volavka, J., Webster, E. L., Lamotrigine as add-on therapy in schizophrenia: Results of 2 placebo-controlled trials, Journal of Clinical Psychopharmacology, 27, 582-589, 2007	Not a clozapine augmentation intervention
Heresco-Levy, U., Ermilov, M., Lichtenberg, P., Bar, G., Javitt, D. C., High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia, Biological Psychiatry, 55, 165-171, 2004	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Heresco-Levy, U., Javitt, D. C., Ebstein, R., Vass, A., Lichtenberg, P., Bar, G., Catinari, S., Ermilov, M., D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia, Biological Psychiatry, 57, 577-585, 2005	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Honer, W. G., Thornton, A. E., Chen, E. Y., Chan, R. C., Wong, J. O., Bergmann, A., Falkai, P., Pomarol-Clotet, E., McKenna, P. J., Stip, E., et al.,, Clozapine alone versus clozapine and risperidone with refractory schizophrenia, New England journal of medicine, 354, 472-482, 2006	The data from this trial is included in the Siskind 2018 systematic review
Houston, J. P., Gatz, J. L., Degenhardt, E. K., Jamal, H. H., Symptoms predicting remission after divalproex augmentation with olanzapine in partially nonresponsive patients experiencing mixed bipolar I episode: a post-hoc analysis of a randomized controlled study, BMC Research Notes, 3, 276, 2010	Not relevant outcomes
Jenner, J. A., Nienhuis, F. J., Wiersma, D., van de Willige, G., Hallucination focused integrative treatment: a randomized controlled trial, Schizophrenia Bulletin, 30, 133-145, 2004	Not a clozapine augmentation intervention
Joffe, G., Terevnikov, V., Joffe, M., Stenberg, J. H., Burkin, M., Tiihonen, J., Add-on mirtazapine enhances antipsychotic effect of first generation antipsychotics in schizophrenia: A double-blind, randomized, placebo-controlled trial, Schizophrenia Research, 108, 245-251, 2009	Not a clozapine augmentation intervention for people with treatment resistant schizophrenia
Jones, S., Castle, D. J., Management of treatment resistant schizophrenia, South African Psychiatry Review, 9, 17-23, 2006	Not a systematic review
Josiassen, R. C., Joseph, A., Kohegyi, E., Stokes, S., Dadvand, M., Paing, W. W., Shaughnessy, R. A., Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial, American Journal of Psychiatry, 162, 130-136, 2005	The data from this trial is included in the Bartoli 2019 systematic review
Kontaxakis, V. P., Ferentinos, P. P., Havaki-Kontaxaki, B. J., Roukas, D. K., Randomized controlled augmentation trials in clozapine-resistant schizophrenic patients: a critical review, European Psychiatry, 20, 409-415, 2005	Older systematic review with no additional relevant studies
Kotler, M., Strous, R. D., Reznik, I., Shwartz, S., Weizman, A., Spivak, B., Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: evidence	Not a clozapine augmentation intervention

for improvement of mood symptomatology, International Clinical Psychopharmacology, 19, 23-26, 2004	
Kreinin, A., Novitski, D., Weizman, A., Amisulpride treatment of clozapine-induced hypersalivation in schizophrenia patients: a randomized, double-blind, placebo-controlled cross-over study, International Clinical Psychopharmacology, 21, 99-103, 2006	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Lally, J., Tully, J., Maccabe, J. H., Clozapine augmentation for treatment-resistant schizoaffective disorder, Cochrane Database of Systematic Reviews, 2016 (3) (no pagination), 2016	Systematic review protocol
Leucht, S., McGrath, J., White, P., Kissling, W., Carbamazepine augmentation for schizophrenia: How good is the evidence?, Journal of Clinical Psychiatry, 63, 218-224, 2002	This systematic review only includes studies conducted before the date inclusion criteria (2000).
Lin, C. H., Chang, Y. C., Huang, Y. J., Chen, P. W., Yang, H. T., Lane, H. Y., Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, Added to Clozapine for the Treatment of Schizophrenia: a Randomized, Double-Blind, Placebo-Controlled Trial, Biological Psychiatry, 84, 422-432, 2018	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Mao, Y. M., Zhang, M. D., Augmentation with antidepressants in schizophrenia treatment: Benefit or risk, Neuropsychiatric Disease and Treatment, 11, 701-713, 2015	Not a systematic review
Mico, U., Bruno, A., Pandolfo, G., Maria Romeo, V., Mallamace, D., D'Arrigo, C., Spina, E., Zoccali, R. A., Muscatello, M. R. A., Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: A randomized, placebo-controlled trial, International Clinical Psychopharmacology, 26, 303-310, 2011	The data from this trial is included in the Siskind 2018 systematic review
Miyamoto, S., Jarskog, L. F., Fleischhacker, W. W., Schizophrenia: When clozapine fails, Current Opinion in Psychiatry, 28, 243-248, 2015	Not a systematic review
Morrison, A. P., Pyle, M., Gumley, A., Schwannauer, M., Turkington, D., MacLennan, G., Norrie, J., Hudson, J., Bowe, S. E., French, P., et al.,, Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomised controlled trial, The Lancet. Psychiatry, 5, 633-643, 2018	Data from this trial is included in the Polese 2019 systematic review
Muscatello, M. R. A., Bruno, A., Pandolfo, G., Mico, U., Scimeca, G., Di Nardo, F., Santoro, V., Spina, E., Zoccali, R. A., Effect of aripiprazole augmentation of clozapine in schizophrenia: A double-blind, placebo-controlled study, Schizophrenia Research, 127, 93-99, 2011	The data from this trial is included in the Siskind 2018 systematic review
Muscatello, M. R., Bruno, A., De Fazio, P., Segura-Garcia, C., Pandolfo, G., Zoccali, R., Augmentation strategies in partial responder and/or treatment-resistant schizophrenia patients treated with clozapine, Expert Opinion on Pharmacotherapy, 15, 2329-2345, 2014	Older systematic review with no additional relevant papers
Muscatello, M. R., Pandolfo, G., Micò, U., Lamberti Castronuovo, E., Abenavoli, E., Scimeca, G., Spina, E., Zoccali, R., Bruno, A., Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study, Journal of Clinical Psychopharmacology, 34, 129-133, 2014	Included in Bartoli 2019 systematic review
Muscatello, M., Bruno, A., Pandolfo, G., Mico, U., Bellinghieri, P. M., Scimeca, G., Cacciola, M., Campolo, D., Settineri, S., Zoccali, R., Topiramate augmentation of clozapine in schizophrenia: A double-	The data from this trial is included in the Siskind 2018 systematic review

blind, placebo-controlled study, Journal of Psychopharmacology, 25, 667-674, 2011	
Paton, C., Whittington, C., Barnes, T. R., Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis, Journal of Clinical Psychopharmacology, 27, 198-204, 2007	Old systematic review with no additional relevant studies
Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Orbach, G., Morgan, C., Psychological treatments in schizophrenia - I: meta-analysis of family intervention and cognitive behaviour therapy, Psychological Medicine, 32, 763-782, 2002	Data from this trial is included in Polese 2019 systematic review
Porcelli, S., Balzarro, B., Serretti, A., Clozapine resistance: augmentation strategies, European Neuropsychopharmacology, 22, 165-182, 2012	Older systematic review with no additional relevant studies
Ranasinghe, Iyoni, Sin, Jacqueline, A systematic review of evidence-based treatment for individuals with treatment-resistant schizophrenia and a suboptimal response to clozapine monotherapy, Psychosis: Psychological, Social and Integrative Approaches, 6, 253-265, 2014	Older systematic review with no additional relevant papers
Remington, G., Augmenting clozapine response in treatment-resistant schizophrenia, Therapy-resistant schizophrenia, Â, 129-151, 2010	Not a systematic review
Remington, G., Kapur, S., Foussias, G., Agid, O., Mann, S., Borlido, C., Richards, S., Javaid, N., Tetrabenazine augmentation in treatment-resistant schizophrenia: a 12-week, double-blind, placebo-controlled trial, Journal of Clinical Psychopharmacology, 32, 95-99, 2012	Not a clozapine augmentation intervention (only 73% subjects on clozapine)
Shafti, S. S., Adjunctive depot antipsychotic in treatment-Resistant schizophrenia, Current Psychopharmacology, 5, 20-27, 2016	Study excluded as conducted in a country outside the country limit of the protocol, due to differences in healthcare settings.
Shafti, Saeed Shoja, Augmentation of aripiprazole by flupenthixol decanoate in poorly responsive schizophrenia: A randomized clinical study, Psychiatry and Clinical Psychopharmacology, 27, 241-248, 2017	The study does not include a clozapine augmentation intervention
Sommer, I. E., Begemann, M. J. H., Temmerman, A., Leucht, S., Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: A quantitative literature review, Schizophrenia Bulletin, 38, 1003-1011, 2012	Old systematic review with no additional relevant studies
Srisurapanont, M., Suttajit, S., Maneeton, N., Maneeton, B., Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials, Journal of psychiatric research, 62, 38-47, 2015	Old systematic review with no additional relevant studies
Taylor, Christine G., Flynn, Sean W., Altman, Siemion, Ehmann, Tom, MacEwan, G., Honer, William G., An open trial of risperidone augmentation of partial response to clozapine, Schizophrenia Research, 48, 156-158, 2001	Letter to editor with insufficient details for quality assessment of the study
Taylor, D. M., Smith, L., Augmentation of clozapine with a second antipsychotic: a meta-analysis of randomized, placebo-controlled studies, Acta Psychiatrica Scandinavica, 119, 419-425, 2009	Old systematic review with no additional relevant studies
Tiihonen, J., Hallikainen, T., Ryynänen, O. P., Repo-Tiihonen, E., Kotilainen, I., Eronen, M., Toivonen, P., Wahlbeck, K., Putkonen, A.,	Conference abstract

Lamotrigine in clozapine-resistant schizophrenia: a randomized placebo-controlled cross-over trial, European neuropsychopharmacology; 15th international congress of the european college of neuropsychopharmacology, october 5-9, barcelona, spain, 12, S262, 2002	
Tiihonen, J., Wahlbeck, K., Kiviniemi, V., The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis, Schizophrenia Research, 109, 10-14, 2009	Old systematic review with no additional relevant studies
Tiihonen, Jari, Halonen, Pirjo, Wahlbeck, Kristian, Repo-Tiihonen, Eila, Hyvarinen, Soile, Eronen, Markku, Putkonen, Hanna, Takala, Pirjo, Mehtonen, Olli-Pekka, Puck, Martin, Oksanen, Jorma, Koskelainen, Pasi, Joffe, Grigori, Aer, Juhani, Hallikainen, Tero, Ryynanen, Olli-Pekka, Tupala, Erkki, Topiramate Add-On in Treatment-Resistant Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial, The Journal of Clinical Psychiatry, 66, 1012-1015, 2005	Not a clozapine augmentation intervention
Veerman, S. R., Schulte, P. F., Smith, J. D., de Haan, L., Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study, Psychological Medicine, 46, 1909-1921, 2016	Data from this trial is included in the Siskind 2018 Systematic review
Wagner, E., Lohrs, L., Siskind, D., Honer, W. G., Falkai, P., Hasan, A., Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance, Journal of Psychopharmacology, 33, 423-435, 2019	Does not include quantitative data for pooling of results
Wang, G., Zheng, W., Li, X. B., Wang, S. B., Cai, D. B., Yang, X. H., Ungvari, G. S., Xiang, Y. T., Correll, C. U., ECT augmentation of clozapine for clozapine-resistant schizophrenia: A meta-analysis of randomized controlled trials, Journal of psychiatric research, 105, 23-32, 2018	Not a relevant intervention
Weiser, M., The effect of estrogen in treatment resistant schizophrenia: results from a randomized controlled trial, Neuropsychopharmacology, 43, S76-, 2017	Conference abstract
Ziegenbein, M., Sieberer, M., Kuenzel, H. E., Kropp, S., Augmentation of Clozapine with amisulpride in patients with treatment-resistant schizophrenia an open clinical study, German Journal of Psychiatry, 9, 17-22, 2006	Not a randomised controlled trial
Ziegenbein, M., Wittmann, G., Kropp, S., Aripiprazole augmentation of clozapine in treatment-resistant schizophrenia: a clinical observation, Clinical Drug Investigation, 26, 117-124, 2006	Not a randomised controlled trial
Zink, M., Kuwilsky, A., Krumm, B., Dressing, H., Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: A randomised controlled clinical trial, Journal of Psychopharmacology, 23, 305-314, 2009	Data from this trial is included in the Siskind 2018 Systematic review

Economic studies

A global economic literature search was undertaken for this guideline, covering all 18 review questions. The table below is a list of excluded studies across the entire guideline and studies listed were not necessarily identified for this review question.

Table 13: Excluded studies from the economic component of the review

Study	Reason for Exclusion
Aitchison, K J, Kerwin, R W, Cost-effectiveness of clozapine: a UK clinic-based study (Structured abstract), British Journal of PsychiatryBr J Psychiatry, 171, 125-130, 1997	Available as abstract only.
Barnes, T. R., Leeson, V. C., Paton, C., Costelloe, C., Simon, J., Kiss, N., Osborn, D., Killaspy, H., Craig, T. K., Lewis, S., Keown, P., Ismail, S., Crawford, M., Baldwin, D., Lewis, G., Geddes, J., Kumar, M., Pathak, R., Taylor, S., Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS): a double-blind, placebo-controlled, randomised clinical trial, Health Technology Assessment (Winchester, England)Health Technol Assess, 20, 1-46, 2016	Does not match any review questions considered in the guideline.
Barton, Gr, Hodgekins, J, Mugford, M, Jones, Pb, Croudace, T, Fowler, D, Cognitive behaviour therapy for improving social recovery in psychosis: cost-effectiveness analysis (Structured abstract), Schizophrenia ResearchSchizophr Res, 112, 158-163, 2009	Available as abstract only.
Becker, T., Kilian, R., Psychiatric services for people with severe mental illness across western Europe: what can be generalized from current knowledge about differences in provision, costs and outcomes of mental health care?, Acta Psychiatrica Scandinavica, SupplementumActa Psychiatr Scand Suppl, 9-16, 2006	Not an economic evaluation.
Beecham, J, Knapp, M, McGilloway, S, Kavanagh, S, Fenyo, A, Donnelly, M, Mays, N, Leaving hospital II: the cost-effectiveness of community care for former long-stay psychiatric hospital patients (Structured abstract), Journal of Mental HealthJ Ment Health, 5, 379-94, 1996	Available as abstract only.
Beecham, J., Knapp, M., Fenyo, A., Costs, needs, and outcomes, Schizophrenia BulletinSchizophr Bull, 17, 427-39, 1991	Costing analysis prior to year 2000
Burns, T., Raftery, J., Cost of schizophrenia in a randomized trial of home-based treatment, Schizophrenia BulletinSchizophr Bull, 17, 407-10, 1991	Not an economic evaluation. Date is prior to 2000
Bush, P. W., Drake, R. E., Xie, H., McHugo, G. J., Haslett, W. R., The long-term impact of employment on mental health service use and costs for persons with severe mental illness, Psychiatric ServicesPsychiatr Serv, 60, 1024-31, 2009	A United States costing analysis. Outcomes which relate to the Welfare system differs in substantial ways to a UK context.

Study	Reason for Exclusion
Chalamat, M., Mihalopoulos, C., Carter, R., Vos, T., Assessing cost-effectiveness in mental health: vocational rehabilitation for schizophrenia and related conditions, Australian & New Zealand Journal of PsychiatryAust N Z J Psychiatry, 39, 693-700, 2005	Australian cost-benefit analysis - welfare system differs from UK context.
Chan, S., Mackenzie, A., Jacobs, P., Cost-effectiveness analysis of case management versus a routine community care organization for patients with chronic schizophrenia, Archives of Psychiatric NursingArch Psychiatr Nurs, 14, 98-104, 2000	Study conducted in Hong Kong. A costing analysis.
Clark, R. E., Teague, G. B., Ricketts, S. K., Bush, P. W., Xie, H., McGuire, T. G., Drake, R. E., McHugo, G. J., Keller, A. M., Zubkoff, M., Cost-effectiveness of assertive community treatment versus standard case management for persons with co-occurring severe mental illness and substance use disorders, Health Services ResearchHealth Serv Res, 33, 1285-308, 1998	Not cost-utility analysis. Cost-effectiveness analysis but does not consider UK setting. Date of study is prior to year 2000.
Crawford, M. J., Killaspy, H., Barnes, T. R., Barrett, B., Byford, S., Clayton, K., Dinsmore, J., Floyd, S., Hoadley, A., Johnson, T., Kalaitzaki, E., King, M., Leurent, B., Maratos, A., O'Neill, F. A., Osborn, D., Patterson, S., Soteriou, T., Tyrer, P., Waller, D., Matisse project team, Group art therapy as an adjunctive treatment for people with schizophrenia: a randomised controlled trial (MATISSE), Health Technology Assessment (Winchester, England)Health Technol Assess, 16, iii-iv, 1-76, 2012	Study not an economic evaluation.
Dauwalder, J. P., Ciompi, L., Cost-effectiveness over 10 years. A study of community-based social psychiatric care in the 1980s, Social Psychiatry & Psychiatric EpidemiologySoc Psychiatry Psychiatr Epidemiol, 30, 171-84, 1995	Practice has changed somewhat since 1980s - not a cost effectiveness study.
Garrido, G., Penades, R., Barrios, M., Aragay, N., Ramos, I., Valles, V., Faixa, C., Vendrell, J. M., Computer-assisted cognitive remediation therapy in schizophrenia: Durability of the effects and cost-utility analysis, Psychiatry ResearchPsychiatry Res, 254, 198-204, 2017	Cost effectiveness study, but population of interest is not focussed on rehabilitation for people with complex psychosis.
Hallam, A., Beecham, J., Knapp, M., Fenyo, A., The costs of accommodation and care. Community provision for former long-stay psychiatric hospital patients, European Archives of Psychiatry & Clinical	Economic evaluation predates 2000. Organisation and provision of care may have changed by some degree.

Study	Reason for Exclusion
NeuroscienceEur Arch Psychiatry Clin Neurosci, 243, 304-10, 1994	
Hu, T. W., Jerrell, J., Cost-effectiveness of alternative approaches in treating severely mentally ill in California, Schizophrenia BulletinSchizophr Bull, 17, 461-8, 1991	A United States costing analysis. Outcomes which relate to the Welfare system differs in substantial ways to a UK context.
Jaeger, J., Berns, S., Douglas, E., Creech, B., Glick, B., Kane, J., Community-based vocational rehabilitation: effectiveness and cost impact of a proposed program model.[Erratum appears in Aust N Z J Psychiatry. 2006 Jun-Jul;40(6-7):611], Australian & New Zealand Journal of PsychiatryAust N Z J Psychiatry, 40, 452-61, 2006	Study is a New Zealand based costing analysis of limited applicability to the UK.
Jonsson, D., Walinder, J., Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia, Acta Psychiatrica ScandinavicaActa Psychiatr Scand, 92, 199-201, 1995	Costing analysis which predates year 2000.
Knapp, M, Patel, A, Curran, C, Latimer, E, Catty, J, Becker, T, Drake, Re, Fioritti, A, Kilian, R, Lauber, C, Rossler, W, Tomov, T, Busschbach, J, Comas-Herrera, A, White, S, Wiersma, D, Burns, T, Supported employment: cost-effectiveness across six European sites (Structured abstract), World Psychiatry, 12, 60-68, 2013	Available as abstract only.
Lazar, S. G., The cost-effectiveness of psychotherapy for the major psychiatric diagnoses, Psychodynamic psychiatry, 42, 2014	Review of clinical and cost studies on psychotherapy. Studies cited do not match population for relevant review question.
Leff, J, Sharpley, M, Chisholm, D, Bell, R, Gamble, C, Training community psychiatric nurses in schizophrenia family work: a study of clinical and economic outcomes for patients and relatives (Structured abstract), Journal of Mental HealthJ Ment Health, 10, 189-197, 2001	Structured abstract. Not a cost effectiveness study.
Liffick, E., Mehdiyoun, N. F., Vohs, J. L., Francis, M. M., Breier, A., Utilization and Cost of Health Care Services During the First Episode of Psychosis, Psychiatric ServicesPsychiatr Serv, 68, 131-136, 2017	A United States costing analysis. Outcomes which relate to the Welfare system differs in substantial ways to a UK context.
Mihalopoulos, C., Harris, M., Henry, L., Harrigan, S., McGorry, P., Is early intervention in psychosis cost-effective over the long term?, Schizophrenia BulletinSchizophr Bull, 35, 909-18, 2009	Not a cost utility analysis. Australian costing analysis.
Perlis, R H, Ganz, D A, Avorn, J, Schneeweiss, S, Glynn, R J, Smoller, J W, Wang, P S, Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model (Structured	Structured abstract. Does not match any review question considered in this guideline.

Study	Reason for Exclusion
abstract), Journal of Clinical Psychopharmacology, 25, 427-434, 2005	
Quinlivan, R., Hough, R., Crowell, A., Beach, C., Hofstetter, R., Kenworthy, K., Service utilization and costs of care for severely mentally ill clients in an intensive case management program, Psychiatric ServicesPsychiatr Serv, 46, 365-71, 1995	A United States costing analysis. Outcomes which relate to the Welfare system differs in substantial ways to a UK context.
Roine, E., Roine, R. P., Rasanen, P., Vuori, I., Sintonen, H., Saarto, T., Cost-effectiveness of interventions based on physical exercise in the treatment of various diseases: a systematic literature review, International Journal of Technology Assessment in Health CareInt J Technol Assess Health Care, 25, 427-54, 2009	Literature review on cost effectiveness studies based on physical exercise for various diseases and population groups - none of which are for complex psychosis.
Rosenheck, R A, Evaluating the cost-effectiveness of reduced tardive dyskinesia with second-generation antipsychotics (Structured abstract), British Journal of PsychiatryBr J Psychiatry, 191, 238-245, 2007	Structured abstract. Does not match any review question considered in this guideline.
Rund, B. R., Moe, L., Sollien, T., Fjell, A., Borchgrevink, T., Hallert, M., Naess, P. O., The Psychosis Project: outcome and cost-effectiveness of a psychoeducational treatment programme for schizophrenic adolescents, Acta Psychiatrica ScandinavicaActa Psychiatr Scand, 89, 211-8, 1994	Not an economic evaluation. Cost effectiveness discussed in narrative only, with a few short sentences.
Sacristan, J A, Gomez, J C, Salvador-Carulla, L, Cost effectiveness analysis of olanzapine versus haloperidol in the treatment of schizophrenia in Spain (Structured abstract), Actas Luso-espanolas de Neurologia, Psiquiatria y Ciencias Afines, 25, 225-234, 1997	Available as abstract only.
Torres-Carbajo, A, Olivares, J M, Merino, H, Vazquez, H, Diaz, A, Cruz, E, Efficacy and effectiveness of an exercise program as community support for schizophrenic patients (Structured abstract), American Journal of Recreation Therapy, 4, 41-47, 2005	Available as abstract only
Wang, P S, Ganz, D A, Benner, J S, Glynn, R J, Avorn, J, Should clozapine continue to be restricted to third-line status for schizophrenia: a decision-analytic model (Structured abstract), Journal of Mental Health Policy and Economics, 7, 77-85, 2004	Available as abstract only.
Yang, Y K, Tarn, Y H, Wang, T Y, Liu, C Y, Laio, Y C, Chou, Y H, Lee, S M, Chen, C, Pharmacoeconomic evaluation of schizophrenia in Taiwan: model comparison	Taiwan is not an OECD country.

Study	Reason for Exclusion
of long-acting risperidone versus olanzapine versus depot haloperidol based on estimated costs (Structured abstract), Psychiatry and Clinical Neurosciences, 59, 385-394, 2005	
Zhu, B., Ascher-Svanum, H., Faries, D. E., Peng, X., Salkever, D., Slade, E. P., Costs of treating patients with schizophrenia who have illness-related crisis events, BMC Psychiatry, 8, 2008	USA costing analysis. The structure of the US health system means that costs do not translate well into a UK context.

Appendix L – Research recommendations

Research recommendations for review question 3.1: What principles should guide adjustments to standard treatments in the management of the underlying psychosis in people using rehabilitation services?

Research question

What tailored interventions (pharmaceutical and psychological) specific to rehabilitation are effective at equipping people with complex psychosis with the ability to live in the community?

Why this is important

Tailored interventions for people using rehabilitation services could help people with complex psychosis live in the community; however, the review did not find evidence on relapse, readmission rates or quality of life, which the committee considered to be proxy outcomes for people's ability to live in the community. The evidence identified on psychosis symptoms and adverse effects was also not specific to people using rehabilitation services.

Table 14: Research recommendation rationale

Research question	What tailored interventions (pharmaceutical and psychological) specific to rehabilitation are effective at equipping people with complex psychosis with the ability to live in the community?
Why is this needed	
Importance to 'patients' or the population	Improvements in people's relapse, readmission and quality of life could enable them to live in the community.
Relevance to NICE guidance	Ability to provide guidance on effective tailored interventions for people in rehabilitation services.
Relevance to the NHS	Increase community living.
National priorities	Improve well-being.
Current evidence base	Current evidence base does not all assess all relevant outcomes, and is not specific to rehabilitation settings.
Equality	All patients in rehabilitation services.
Feasibility	Recruiting people to trials with psychosis refractory to treatment is difficult.
Other comments	None.

SMI: severe mental illness

Table 15: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (aged 18 years and older) with complex psychosis with refractory psychosis resistant to standard treatment, using a rehabilitation service
Intervention	Tailored pharmaceutical or pharmacological interventions
Comparator	Treatment as usual or other tailored interventions

Criterion	Explanation
Outcomes	Critical Outcomes • Readmission/Relapse • Quality of life
Study design	Randomised controlled trial
Timeframe	1-3 years
Additional information	None.

1 Appendix M – Evidence behind the reference recommendations

2 Supporting evidence and rationale/impact for adopted & adapted recommendations for review question 3.1: What principles 3 should guide adjustments to standard treatments in the management of the underlying psychosis in people using 4 rehabilitation services?

Recommendation	Original recommendation	Supporting evidence	Committee's discussion – rationale and impact
Monitor drug levels to check adherence and guide dosing: • at least annually and as needed for clozapine and mood stabilising antiepileptic medicines • every 3 to 6 months for people established on lithium, following guidance on using lithium in the NICE guideline on bipolar disorder. Monitor thyroid function, renal function and calcium levels at least every 6 months for people established on lithium, following guidance on using lithium in the NICE guideline on bipolar disorder.	CG 185 NICE guideline on Bipolar disorder: assessment and management Recommendations: 1.10.19 to 1.10.24 1.10.19 Measure the person's plasma lithium level every 3 months for the first year. 1.10.20 After the first year, measure plasma lithium levels every 6 months, or every 3 months for people in any of the following groups: •older people •people taking drugs that interact with lithium •people who are at risk of impaired renal or thyroid function, raised calcium levels or other complications •people who have poor symptom control •people with poor adherence •people whose last plasma lithium level was 0.8 mmol per litre or higher. 1.10.21 Measure the person's weight or BMI and arrange tests for urea and electrolytes including calcium, estimated glomerular filtration rate (eGFR)	Required laboratory testing was determined by the GDG expert opinion. It was agreed that at initiation of all drugs a number of tests should be undertaken, including electrocardiogram (ECG), assessment of renal function (creatinine, blood urea and electrolytes), glucose, lipid profile and thyroid function tests. The costs of these tests were not included in the analysis because they were common to all arms of the model. In addition to these tests, the GDG expressed the opinion that liver function should be tested at initiation of all drugs except lithium; for lithium, three tests of plasma lithium concentration were required to determine optimal dose.	The committee agreed with the existing guidance about the monitoring of drug levels, thyroid and calcium levels in NICE guidelines. They adapted the wording to align with the population in the current guideline. The CG185 guidance recommends plasma lithium levels every 3 months in the first year and every 3 or 6 months thereafter depending on whether they have one of the risk factors listed in the recommendation. The committee also considered it important to do 6 monthly assessment of thyroid function, renal function and calcium in the population receiving rehabilitation.

Recommendation	Original recommendation	Supporting evidence	Committee's discussion – rationale and impact
	and thyroid function every 6 months, and more often if there is evidence of impaired renal or thyroid function, raised calcium levels or an increase in mood symptoms that might be related to impaired thyroid function. 1.10.22 Monitor lithium dose and plasma lithium levels more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests, and assess the rate of deterioration of renal function. For further information, see NICE's guidance on chronic kidney disease and acute kidney injury. 1.10.23 When discussing whether to continue lithium, take into account clinical efficacy, other risk factors for renal impairment and cardiovascular disease, and degree of renal impairment; if needed seek advice from a renal specialist and a clinician with expertise in managing bipolar disorder. 1.10.24 Monitor the person at every appointment for symptoms of neurotoxicity, including paraesthesia, ataxia, tremor and cognitive impairment, which can occur at therapeutic levels of lithium.		
Consider monitoring prolactin levels annually if the person is taking a medicine that raises prolactin, and more regularly if they have symptoms.	CG 178 NICE guideline on Psychosis and schizophrenia in adults: prevention and management 1.3.6.1 Before starting antipsychotic medication, undertake and record the following baseline investigations:	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared	The existing guidance recommends baseline investigation of prolactin levels before starting antipsychotic medication. The committee adapted the recommendation for the population receiving rehabilitation and considered it

Recommendation	Original recommendation	Supporting evidence	Committee's discussion – rationale and impact
	•weight (plotted on a chart) •waist circumference •pulse and blood pressure •fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels •assessment of any movement disorders •assessment of nutritional status, diet and level of physical activity.	with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10 of Psychosis and Schizophrenia in Adults (NCCMH, 2014).	important that prolactin levels not only be measured at the baseline, but monitored annually if the person is receiving a medication that raises prolactin, and if symptomatic, more regularly.
Consider annual ECGs for everyone with complex psychosis and related severe mental health conditions in rehabilitation services, and more regularly if they are taking medicines, combinations of medicines, or medicines above BNF or SPC limits that may alter cardiac rhythm (for example, causing prolonged QT interval).	CG 178 NICE guideline on Psychosis and schizophrenia in adults: prevention and management 1.3.6.2 Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if: •specified in the summary of product characteristics (SPC) • a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure) •there is a personal history of cardiovascular disease or •the service user is being admitted as an inpatient. [2009]	Review question: For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])? Evidence base: Based on expert opinion of the GDG after reviewing the evidence for pharmacological interventions. See Chapter 10	The committee agreed with the existing guidance regarding offering an ECG before starting antipsychotic medication. Adapting the recommendation for the population receiving rehabilitation, the committee deemed it crucial to consider annual ECGs, and consider offering ECGs more regularly if the person is taking medication above prescribed BNF or SPC limits that may alter cardiac rhythm.

Recommendation	Original recommendation	Supporting evidence	Committee's discussion – rationale and impact
		of Psychosis and Schizophrenia in Adults (NCCMH, 2014) Antipsychotic medication may cause… cardiac abnormalities (for example, lengthened QT interval on electrocardiography) (American Diabetes Association et al., 2004; Expert Group, 2004; Holt et al., 2005; Koro et al., 2002; Lieberman et al., 2005; Lindenmayer et al., 2003; Nasrallah, 2003; Nasrallah, 2008; Saari et al., 2004; Thakore, 2005).	
Routinely monitor for and treat other coexisting mental health conditions, including depression, obsessive compulsive disorder, anxiety, substance misuse and risk of suicide (for guidance on these conditions see NICE's web page on mental health and behavioural conditions).	CG 178 NICE guideline on Psychosis and schizophrenia in adults: prevention and management 1.3.3.3 Routinely monitor for other coexisting conditions, including depression, anxiety and substance misuse particularly in the early phases of treatment. [2009; amended 2014]	The GDG for the 2014 guideline reconsidered the 2002 and 2009 guidelines in the area of primary care and the primary and secondary care interface. It was agreed that although there is no robust evidence to guide recommendations in this area, the GDG for the 2014 guideline concurred with its predecessors that consensus-based recommendations	The committee agreed with the existing guidance about the monitoring of other coexisting mental health conditions in the NICE guideline on psychosis and schizophrenia in adults. The committee adapted the recommendation for the population receiving rehabilitation and also added that such conditions should be monitored and treated. The committee reworded the recommendation to align with the population of this guideline.

Recommendation	Original recommendation	Supporting evidence	Committee's discussion – rationale and impact
		should be developed to help guide primary and secondary care health and social care professionals in these areas.	

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