National Institute for Health and Care Excellence

Surveillance programme

Surveillance proposal consultation document

Psychosis and schizophrenia in adults: prevention and management NICE guideline CG178 - 4-year surveillance review (2017)

Background information

Guideline issue date: February 2014

Surveillance proposal for consultation

We propose to not update the guideline on Psychosis and schizophrenia in adults at this time.

We also propose to remove the following NICE research recommendation from the NICE version of the guideline and the NICE research recommendations database:

- RR-03 - What are the short- and long-term benefits to physical health of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without major risks?

During surveillance editorial or factual corrections were identified. Details are included in appendix A: summary of evidence from surveillance.

Questions for consultation

- We have identified evidence which indicates that cognitive behavioural therapy (CBT) may not be effective for the treatment of negative symptoms of psychosis and schizophrenia. Does this concur with observations in clinical practice?

- How often are arts therapies offered to, and taken up, by people with psychosis and schizophrenia in the UK? What clinical observations can be made about the effectiveness of these treatments?
- In clinical practice, which pharmacological treatment options are generally given to people with schizophrenia or psychosis who are in remission?
- Currently, recommendation 1.3.5.1 recommends that the choice of antipsychotic should be made by the service user and healthcare professional together, through discussion of the benefits and a number of listed potential side effects. In practice, does this recommendation provide appropriate guidance, or would more specific guidance on the choice of drug in specific circumstances be welcomed?

Reason for the proposal

Assessing the evidence

We found 223 relevant studies in a search for RCTs and systematic reviews published between 01 November 2008 and 13 March 2017. We also included 2 relevant studies from a total of 80 which were identified by topic experts who originally worked on this guideline and 1 relevant study was identified through post-publication communications.

From all sources, we considered 226 studies to be relevant to the guideline.

This included evidence which supports the current recommendations on team and service-level interventions; carers' experience; prevention of psychosis; behavioural interventions to promote physical health and vocational rehabilitation.

There was a large volume of newly identified evidence, especially in the areas of psychological and pharmacological interventions. This evidence was mixed with some studies supporting current recommendations and other evidence being inconsistent with current recommendations in these areas. However, due to the large range of specific intervention types and outcomes reported, there was only a small volume of corroborating evidence in each area. Where there was evidence which reported on similar interventions, the outcomes

were often contradictory and/or from studies including small sample sizes. Overall, it is due to the lack of consistency across the volume of the evidence that the decision not to update the NICE guideline CG178 has been taken.

We asked topic experts whether this evidence would affect current recommendations. Generally, the topic experts agreed that the new evidence would not impact recommendations in these areas.

We found evidence on questions which were not covered during guideline development on the benefits and harms of non-antipsychotic pharmacological interventions; intermittent drug techniques; pharmacological interventions for the promotion of physical health; treatment with transcranial stimulation; the effect of changes to the environment; acupuncture as treatment and the effect of augmentation of non-antipsychotics with antipsychotics.

This evidence was considered to be insufficient to prompt the consideration of the addition of new recommendations in these areas at this time. This was in the main due to a small volume of evidence being identified in each area. Where larger volumes of evidence were identified, such as evidence for the augmentation of non-antipsychotics with antipsychotics, a lack of consistency in the specific interventions and outcomes reported resulted in little corroborating evidence being available.

We did not find any evidence related to access and engagement.

For any evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision as review of technology appraisals is outside the remit of the surveillance process. This included guidance on the use of electroconvulsive therapy.

Additionally, we identified relevant ongoing research that is expected to publish results in the next 1–5 years. The ongoing trials will be considered at the next surveillance review.

Research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. See the research recommendations section of appendix A for further information.

For this surveillance review we assessed 5 prioritised research recommendations. As no published trials or other evidence of current research activity was identified in the relevant area, we propose that 1 of the research recommendations (RR-03) should be removed from the NICE version of the guideline and the NICE research recommendations database.

Equalities

It was raised by topic experts that inequalities persist in the access and experience of services, however, it was recognised that these issues are already addressed in the guideline. No other equality issues were identified.

Overall proposed decision

After considering all the evidence and views of topic experts, we propose to not update this guideline.

We also propose to remove 1 NICE research recommendation from the NICE version of the guideline and the NICE research recommendations database.

Further information

See appendix A: summary of evidence from surveillance below for further information.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Appendix A: summary of evidence from surveillance

Summary of evidence from surveillance

Access and engagement

Preamble to the recommendations in this section of the guideline

The NICE guideline on service user experience in adult mental health (NICE clinical guidance 136) includes recommendations on communication relevant to this section.

Q – 01 **For all people from black and minority ethnic groups (particularly, African–Caribbean people) with psychosis, do services, such as ACT, CRHTTs and case management improve the number of people remaining in contact with services?**

Q – 02 **For all people from black and minority ethnic groups with psychosis, do specialist ethnic mental health services (culturally specific or culturally skilled) improve the number of people remaining in contact with services?**

Recommendations derived from these review questions

1.1.2.1 Healthcare professionals inexperienced in working with people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds should seek advice and supervision from healthcare professionals who are experienced in working transculturally.

1.1.2.2 Healthcare professionals working with people with psychosis or schizophrenia should ensure they are competent in:

- assessment skills for people from diverse ethnic and cultural backgrounds
- using explanatory models of illness for people from diverse ethnic and cultural backgrounds
- explaining the causes of psychosis or schizophrenia and treatment options
- addressing cultural and ethnic differences in treatment expectations and adherence
- addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the causes of abnormal mental states
- negotiating skills for working with families of people with psychosis or schizophrenia
- conflict management and conflict resolution.

1.1.2.3 Mental health services should work with local voluntary black, Asian and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to people from diverse ethnic and cultural backgrounds.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Teams and service-level interventions

Q – 03 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of intensive case management interventions compared to non-intensive case management or standard treatment?**

Q – 04 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of early intervention services compared to treatment as usual or another intervention?**

Q – 05 **Are early detection programmes effective in reducing duration of untreated psychosis and improving pathways to care for people with first episode psychosis?**

Q – 06 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of Crisis Interventions compared to treatment as usual or another intervention?**

Sub-questions:-

Crisis Resolution and Home Treatment teams (CRHTs)

Crisis Houses (also called Recovery Houses)

Q – 07 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of Community Mental Health Teams compared to treatment as usual or another intervention?**

Q – 08 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of acute day hospitals compared to treatment as usual or another intervention?**

Recommendations derived from these review questions

Care across all phases – service user experience

1.1.1.1 Use this guideline in conjunction with Service user experience in adult mental health (NICE clinical guidance 136) to improve the experience of care for people with psychosis or schizophrenia using mental health services, and:

- work in partnership with people with schizophrenia and their carers
- offer help, treatment and care in an atmosphere of hope and optimism
- take time to build supportive and empathic relationships as an essential part of care.

Care across all phases – comprehensive services provision

1.1.4.1 All teams providing services for people with psychosis or schizophrenia should offer a comprehensive range of interventions consistent with this guideline.

First episode psychosis – early intervention in psychosis services

1.3.1.1 Early intervention in psychosis services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person's age or the duration of untreated psychosis.

1.3.1.2 People presenting to early intervention in psychosis services should be assessed without delay. If the service cannot provide urgent intervention for people in a crisis, refer the person to a crisis resolution and home treatment team (with support from early intervention in

psychosis services). Referral may be from primary or secondary care (including other community services) or a self- or carer-referral.

1.3.1.3 Early intervention in psychosis services should aim to provide a full range of pharmacological, psychological, social, occupational and educational interventions for people with psychosis, consistent with this guideline.

1.3.1.4 Consider extending the availability of early intervention in psychosis services beyond 3 years if the person has not made a stable recovery from psychosis or schizophrenia.

First episode psychosis – primary care

1.3.2.1 Do not start antipsychotic medication for a first presentation of sustained psychotic symptoms in primary care unless it is done in consultation with a consultant psychiatrist.

First episode psychosis – assessment and care planning

1.3.3.1 Carry out a comprehensive multidisciplinary assessment of people with psychotic symptoms in secondary care. This should include assessment by a psychiatrist, a psychologist or a professional with expertise in the psychological treatment of people with psychosis or schizophrenia. The assessment should address the following domains:

- psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- physical health and wellbeing (including weight, smoking, nutrition, physical activity and sexual health)
- psychological and psychosocial, including social networks, relationships and history of trauma
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- social (accommodation, culture and ethnicity, leisure activities and recreation, and responsibilities for children or as a carer)
- occupational and educational (attendance at college, educational attainment, employment and activities of daily living)
- quality of life
- economic status.

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]**

1.3.3.4 Write a care plan in collaboration with the service user as soon as possible following assessment, based on a psychiatric and psychological formulation, and a full assessment of their physical health. Send a copy of the care plan to the primary healthcare professional who made the referral and the service user.

First episode psychosis – treatment options

1.3.4.3 If the person's symptoms and behaviour suggest an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in Bipolar disorder (NICE clinical guideline 38) or Depression (NICE clinical guideline 90).

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis – service-level interventions

1.4.1.1 Offer crisis resolution and home treatment teams as a first-line service to support people with psychosis or schizophrenia during an acute episode in the community if the severity of the episode, or the level of risk to self or others, exceeds the capacity of the early intervention in psychosis services or other community teams to effectively manage it.

1.4.1.2 Crisis resolution and home treatment teams should be the single point of entry to all other acute services in the community and in hospitals.

1.4.1.3 Consider acute community treatment within crisis resolution and home treatment teams before admission to an inpatient unit and as a means to enable timely discharge from inpatient units. Crisis houses or acute day facilities may be considered in addition to crisis resolution and home treatment teams depending on the person's preference and need.

1.4.1.4 If a person with psychosis or schizophrenia needs hospital care, think about the impact on the person, their carers and other family members, especially if the inpatient unit is a long way from where they live. If hospital admission is unavoidable, ensure that the setting is suitable for the person's age, gender and level of vulnerability, support their carers and follow the recommendations in Service user experience in adult mental health (NICE clinical guidance 136).

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis – early post-acute period

1.4.6.1 After each acute episode, encourage people with psychosis or schizophrenia to write an account of their illness in their notes.

Promoting recovery and possible future care – general principles

1.5.1.1 Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should:

- offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline
- be competent to provide all interventions offered
- place emphasis on engagement rather than risk management
- provide treatment and care in the least restrictive and stigmatising environment possible and in an atmosphere of hope and optimism in line with Service user experience in adult mental health (NICE clinical guidance 136).

1.5.1.2 Consider intensive case management for people with psychosis or schizophrenia who are likely to disengage from treatment or services.

Promoting recovery and possible future care – return to primary care

1.5.2.1 Offer people with psychosis or schizophrenia whose symptoms have responded effectively to treatment and remain stable the option to return to primary care for further management. If a service user wishes to do this, record this in their notes and coordinate transfer of responsibilities through the care programme approach.

Promoting recovery and possible future care – primary care

1.5.3.1 Develop and use practice case registers to monitor the physical and mental health of people with psychosis or schizophrenia in primary care.

1.5.3.6 When a person with an established diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances), primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan.

1.5.3.7 For a person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is:

- poor response to treatment
- non-adherence to medication
- intolerable side effects from medication
- comorbid substance misuse
- risk to self or others.

1.5.3.8 When re-referring people with psychosis or schizophrenia to mental health services, take account of service user and carer requests, especially for:

- review of the side effects of existing treatments

- psychological treatments or other interventions.

1.5.3.9 When a person with psychosis or schizophrenia is planning to move to the catchment area of a different NHS trust, a meeting should be arranged between the services involved and the service user to agree a transition plan before transfer. The person's current care plan should be sent to the new secondary care and primary care providers.

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

An RCT (Burns, 2013) (n=333) evaluated the rate of 12 month readmission to hospital after release under a community treatment order (CTO) compared to release under Section 17, where both groups receive equivalent clinical contact but more compulsory supervision under a CTO. At 12 months, the number of patients readmitted did not differ between the groups.

An RCT (Burns, 2015) (n=330) compared discharge from hospital under a CTO or under Section 17. No difference was identified between the groups in the number of patients' readmitted, total number of readmissions, duration of readmissions, time to first readmission or disengagement with the service after 36 months.

A multi-centre RCT (Chatterjee, 2014) (n=282) compared collaborative community-based care plus facility-based care and facility-based care alone. The addition of community-based care to facility-based care over 12 months was associated with a non-statistically significant decrease in Positive and Negative Syndrome Scale (PANSS) score but a statistically significant decrease on the Indian Disability Evaluation and Assessment Scale score. However, no difference was shown in the proportion of participants who had a reduction of more than 20% in overall symptoms.

An RCT (Owen, 2008) (n=291) evaluated the effectiveness of an enhanced strategy for implementing antipsychotic management recommendations of Veterans Affairs schizophrenia guidelines. The enhanced strategy involved a trained nurse prompting provider guideline adherence and patient compliance, for participants with acute exacerbation of schizophrenia. There was a mix of effectiveness with some medicine guideline recommendations showing increased implementation and others showing no difference.

A cluster RCT (Slade, 2015) randomised 27 community based mental health teams across 2 NHS trusts in England to a REFOCUS or usual treatment group. REFOCUS was a 1 year team level intervention targeting staff behaviour to increase focus on values, preferences, strengths and goals of patients with psychosis, and staff-patient relationships, through coaching and partnership. There was no significant difference in the Questionnaire about Processes of Recovery score after 1 year between the groups. Patients treated in the REFOCUS group incurred non-statistically significant lower adjusted costs than those in the control group.

An RCT (Albert, 2017) (n=400) compared the effects of five years of specialised early intervention (SEI) treatment for first episode schizophrenia with two years of SEI, plus 3 years of treatment as usual. SEI included modified assertive community treatment, family involvement and social skill training. The levels of negative symptoms did not differ between the groups, but 5 year SEI patients were more likely to stay in contact with specialised mental health services, had higher client satisfaction and had a stronger working alliance.

An RCT (Srihari, 2015) (n=120) including participants with first episode psychosis, evaluated a 'specialised treatment early in psychosis' programme in comparison to usual care, showing statistically significantly fewer hospitalisations and bed days for people in the intervention programme.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

No evidence of effect was found for the majority of interventions for which new evidence was identified. The use of community treatment orders, behavioural interventions aimed at staff

and specialised early intervention over a 5 year period, did not show significant evidence of effectiveness in critical outcomes. A single study indicated an effect of a collaborative community based care programme, however, this evidence is not deemed applicable to the UK setting as it was conducted in India. Evaluation of a 'specialised treatment early in psychosis' programme indicated a positive effect, however, this evidence supports the recommendation which currently suggests access to early intervention for psychosis without delay, which covers a broad range of interventions (1.3.1.1, 1.3.1.2 and 1.3.1.3). Overall, the new evidence identified is not likely to have an impact on the current recommendations.

New evidence is unlikely to change guideline recommendations.

Carers' experience

Q – 09 What factors improve or diminish the experience of health and social services for carers of people with severe mental illness?

Q – 10 What modification to health and social services improve the experience of using services for carers of adults with severe mental illness?

Recommendations derived from these review questions

1.1.5.1 Offer carers of people with psychosis or schizophrenia an assessment (provided by mental health services) of their own needs and discuss with them their strengths and views. Develop a care plan to address any identified needs, give a copy to the carer and their GP and ensure it is reviewed annually.

1.1.5.2 Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this.

1.1.5.3 Give carers written and verbal information in an accessible format about:

- diagnosis and management of psychosis and schizophrenia
- positive outcomes and recovery
- types of support for carers
- role of teams and services
- getting help in a crisis

When providing information, offer the carer support if necessary.

1.1.5.4 As early as possible negotiate with service users and carers about how information about the service user will be shared. When discussing rights to confidentiality, emphasise the importance of sharing information about risks and the need for carers to understand the service user's perspective. Foster a collaborative approach that supports both service users and carers, and respects their individual needs and interdependence.

1.1.5.5 Review regularly how information is shared, especially if there are communication and collaboration difficulties between the service user and carer.

1.1.5.6 Include carers in decision-making if the service user agrees.

1.1.5.7 Offer a carer-focused education and support programme, which may be part of a family intervention for psychosis and schizophrenia, as early as possible to all carers. The intervention should:

- be available as needed
- have a positive message about recovery.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A systematic review (Chen, 2016) including 9 studies (n=608) of non-pharmacological interventions for caregivers of patients with schizophrenia, identified a significant decrease in the care burden for those who received a non-pharmacological intervention, but no difference in family support, family functioning or satisfaction.

An RCT (Martín-Carrasco, 2016) (n=223) evaluated a psychoeducational intervention programme for carers of people with schizophrenia. There were mixed results, with a statistically significant decrease in caregiver burden reported by measurement on the Zarit Burden Interview scale, but no significant difference was reported in Involvement Evaluation Questionnaire scores.

Topic expert feedback

Topic expert feedback indicated that service user and carer experience is an important area as this population often report a need to improve experience, although the respondent was unaware of new evidence to add to current guidance.

The Collaborative Care Planning Project has developed insights into the value of the care programme approach for service users. The findings place emphasis on the co-production of care plans rather than following a bureaucratic process. Topic experts noted this strengthens the recommendations in the current guideline.

Impact statement

Evidence was identified evaluating non-pharmacological interventions for caregivers, which included support programmes. This evidence showed mixed results, including some outcomes which showed no difference following intervention. However caregiver burden was consistently shown to be decreased with intervention.

Recommendation 1.1.5.7 currently suggests offering carer-focused education and support programmes, which has been further supported by the new evidence identified in this area. The evidence identified during this surveillance review does not support a specific intervention, but the use of non-pharmacological interventions as a whole. Therefore, the current recommendations to offer education and support programmes are still supported and are unlikely to be impacted by the new evidence identified. NICE guideline CG178 also cross-refers to NICE guideline CG136 (recommendation 1.1.1.1) on service user experience in adult mental health, which provides further advice on care and support for carers of people using mental health services. The newly identified evidence supports these recommendations further, meaning an impact on the guideline is unlikely.

Co-production of care plans was highlighted as an important area for improving carer experience through topic expert feedback. Recommendations 1.1.5.4-1.1.5.6 emphasise encouraging collaboration and communication between service users and carers, which is supported by topic expert feedback regarding co-production of care plans.

Overall, the new evidence that has been identified in this area supports the recommendations and therefore no impact on the guideline is currently anticipated.

New evidence is unlikely to change guideline recommendations.

Preventing psychosis and schizophrenia: treatment of at risk mental states

Q – 11 For people who are at risk of developing psychosis and schizophrenia (at risk mental state), does the provision of pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes?

Recommendations derived from these review questions

Referral from primary care

1.2.1.1 If a person is distressed, has a decline in social functioning and has:

- transient or attenuated psychotic symptoms **or**
- other experiences or behaviour suggestive of possible psychosis **or**
- a first-degree relative with psychosis or schizophrenia

refer them for assessment without delay to a specialist mental health service or an early intervention in psychosis service because they may be at increased risk of developing psychosis.

Specialist assessment

1.2.2.1 A consultant psychiatrist or a trained specialist with experience in at-risk mental states should carry out the assessment.

Treatment options to prevent psychosis

1.2.3.1 If a person is considered to be at increased risk of developing psychosis (as described in recommendation 1.2.1.1):

- offer individual cognitive behavioural therapy (CBT) with or without family intervention (delivered as described in section 1.3.7) **and**
- offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse.

1.2.3.2 Do not offer antipsychotic medication:

- to people considered to be at increased risk of developing psychosis (as described in recommendation 1.2.1.1) **or**
- with the aim of decreasing the risk of or preventing psychosis.

Monitoring and follow-up

1.2.4.1 If, after treatment (as described in recommendation 1.2.3.1), the person continues to have symptoms, impaired functioning or is distressed, but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using a structured and validated assessment tool. Determine the frequency and duration of monitoring by the:

- severity and frequency of symptoms
- level of impairment and/or distress **and**
- degree of family disruption or concern.

1.2.4.2 If a person asks to be discharged from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's GP to continue monitoring changes in their mental state.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A cost effectiveness analysis (Ising, 2015) (n=196) evaluating CBT as an add-on treatment to routine care, to prevent first episode psychosis, showed a significantly higher proportion of averted psychoses with CBT. Although there was little difference in the QALY health gains for CBT than for usual care, the costs of CBT were lower than those of usual care. CBT showed a high probably of being more cost effective than usual care per prevented psychosis.

An RCT (McGorry, 2017) (n=304) evaluated treatment with a daily dose of omega-3 fatty acid plus cognitive behavioural case management (CBCM) in comparison to placebo plus CBCM, for people at ultrahigh risk of psychotic disorders. No significant difference was observed between transition into psychosis rates between groups.

Topic expert feedback

Topic experts highlighted a trial (McGorry, 2017) of Omega 3 fatty acid treatment which showed a trend level benefit in reducing transition to psychosis, which has been discussed in the surveillance summary section above. However, it was also indicated in topic expert feedback that larger trials have shown no benefit to Omega 3 treatment.

Feedback from topic experts indicated that attempts to improve personalised risk detection using a risk tool have been tested and show promise, however the feasibility and utility in routine care is not proven.

Additionally, the service delivery of early intervention in psychosis (and at risk mental state) has become a key policy objective since CG178 was published, and recently reinforced in '*Implementing the Five Year Forward View for Mental Health* (NHSE 2016).'

A single study was identified (Kantrowitz, 2015) which evaluated a treatment for people at high risk of transition into schizophrenia, which is not licensed for use in the UK.

Impact statement

The new evidence identified suggests that CBT as treatment for people at high risk of psychosis, has a higher probability of being cost effective, while no new evidence was identified regarding the health benefits of CBT. This evidence supports the current recommendations (1.2.3.1) which suggest CBT for people at increased risk of developing psychosis.

During development of CG178, evidence was considered regarding omega-3 fatty acids. The guideline committee concluded that evidence was insufficient to recommend the use of omega-3 for the prevention of psychosis. Further evidence identified through the surveillance review, shows no significant evidence of effect of omega-3 fatty acids. This corroborates the evidence that supported the conclusion drawn previously by the committee to not include a recommendation on this intervention, and therefore impact is unlikely.

Topic expert feedback indicates support for the current recommendations, which has also highlighted this as a key area of prioritisation in the mental health sector of the NHS.

Overall, the current recommendations are supported by cost effectiveness and effectiveness evidence, as well as topic expert feedback. Therefore, no impact is currently anticipated.

New evidence is unlikely to change guideline recommendation.

Interventions to promote physical health in adults

Q – 12 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote physical activity (all forms, with or without healthy eating)?**

Q – 13 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating?**

Q – 14 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of interventions for smoking cessation and reduction?**

Recommendations derived from these review questions

Care across all phases - physical health

1.1.3.1 People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider.

1.1.3.2 If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see Obesity [NICE clinical guideline 43], Lipid modification [NICE clinical guideline 67] and Preventing type 2 diabetes [NICE public health guidance 38]).

1.1.3.3 Offer people with psychosis or schizophrenia who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine.

1.1.3.4 Consider one of the following to help people stop smoking:

- nicotine replacement therapy (usually a combination of transdermal patches with a short-acting product such as an inhalator, gum, lozenges or spray) for people with psychosis or schizophrenia **or**
- bupropion[1] for people with a diagnosis of schizophrenia **or**
- varenicline for people with psychosis or schizophrenia.

  Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first 2–3 weeks.

1.1.3.5 For people in inpatient settings who do not want to stop smoking, offer nicotine replacement therapy to help them to reduce or temporarily stop smoking.

1.1.3.6 Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia. These should be audited in the annual team report.

1.1.3.7 Trusts should ensure compliance with quality standards on the monitoring and treatment of cardiovascular and metabolic disease in people with psychosis or schizophrenia through board-level performance indicators.

Promoting recovery and possible future care - monitoring physical health in primary care

1.5.3.2 GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia. Include all the checks recommended in 1.3.6.1 and refer to relevant NICE guidance on monitoring for cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist, and put in the secondary care notes.

1.5.3.3 Identify people with psychosis or schizophrenia who have high blood pressure, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity following relevant NICE guidance (see Lipid modification [NICE clinical guideline 67], Preventing type 2 diabetes [NICE public health guidance 38], Obesity [NICE clinical guideline 43], Hypertension [NICE clinical guideline 127], Prevention of cardiovascular disease [NICE public health guidance 25] and Physical activity [NICE public health guidance 44]).

1.5.3.4 Treat people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance (for example, see Lipid modification [NICE clinical guideline 67], Type 1 diabetes [NICE clinical guideline 15], Type 2 diabetes [NICE clinical guideline 66], Type 2 diabetes – newer agents [NICE clinical guideline 87]).

1.5.3.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 1.5.3.1–1.5.3.4.

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

An RCT (Cordes, 2014) (n=100) examining the effects of a weight management programme for people with schizophrenia who have gained weight on olanzapine found no significant difference in weight gain following the programme compared to usual care, although there was a significantly smaller increase in waist circumference, fasting glucose and 2 hour glucose level after glucose load.

1 RCT (Bhatia, 2016) (n=286) and 1 systematic review (Broderick, 2015) including 8 studies, evaluated yoga for people with schizophrenia, showing that yoga training was more effective than treatment as usual or alternative physical exercise training for improvement in cognition, mental state, social functioning, quality of life and withdrawal rates. Another systematic review (Cramer, 2013) including 5 studies contradicted this, finding no evidence that yoga was effective for altering mental state or social functioning, although indicated it was effective for improving quality of life.

1 RCT (Georgiev, 2012) (n=64) evaluated the effectiveness of progressive muscle relaxation compared to no treatment. With this intervention, a non-statistically significant difference in state anxiety and subjective wellbeing, and a statistically significant decrease in psychological stress was shown.

Topic expert feedback

Topic experts indicated that the recommendations for QRisk 2 as a CVD risk calculator in NICE guideline CG181 are based on observational studies of the general population. However a new study (Osborn, 2015) has developed a CVD risk calculator based on surveys of people with severe mental illness which may offer advantages over the QRisk 2 method that CG178 currently bases its recommendation (1.5.3.4) on.

The National Audit of Schizophrenia (2012), as well as a repeat audit published in 2014, continues to show poor physical health monitoring of people with schizophrenia.

Topic experts also noted that the NHS England national Commissioning for Quality and Innovation (CQUIN) guidance reinforces NICE guidelines and quality standards on physical health monitoring and promotion of healthy lifestyles. This initiative has incentivised Mental Health Trusts since 2014, to improve the management of cardiovascular and metabolic risk. The CQUIN applies to inpatient and community services; additionally from 2018 the CQUIN guidance will incentivise early intervention in psychosis services to reduce weight gain and smoking rates in people with a first episode of psychosis.

Impact statement

New evidence suggests that, across a range of outcomes, weight management programmes

result in some improved effects, specifically relating to waist circumference and fasting glucose. While yoga therapy is not specifically recommended by CG178, it is recommended that people with psychosis or schizophrenia should be offered a healthy eating and physical activity programme (1.1.3.1), which is broadly supported by the positive outcomes reported by this evidence.

Topic expert feedback suggests that there is new evidence indicating that monitoring cardiovascular health could be made more effective by utilising a risk calculator that is specifically for people with severe mental illness. Currently, CG178 recommends thorough monitoring of physical health according to appropriate NICE guidelines which are cross referenced (1.5.3.2). This includes the use of the QRisk 2 risk assessment tool as recommended in CG181 (1.1.8) and the use of this tool will be considered further through the surveillance review of CG181. The topic expert feedback does however broadly support the current recommendations, considering that recommendations specific to the population considered in CG178 are made alongside the cross-referral to CG181. It is therefore not anticipated that there will be any impact of this evidence on current recommendations.

Topic expert feedback indicates that physical health monitoring, which is recommended in CG178 (1.1.3.6), is being adhered to poorly. This evidence suggests issues with uptake and implementation, which is likely to be addressed in part by the 2018 CQUIN guidance. However, the issues regarding uptake do not affect the current recommendations made in CG178.

New evidence is unlikely to change guideline recommendations.

Peer-provided and self-management interventions

Q – 15 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of peer-provided interventions compared with treatment as usual or other intervention?**

Q – 16 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of self-management interventions compared with treatment as usual or other intervention?**

Recommendations derived from these review questions

Care across all phases – peer support and self-management

1.1.6.1 Consider peer support for people with psychosis or schizophrenia to help improve service user experience and quality of life. Peer support should be delivered by a trained peer support worker who has recovered from psychosis or schizophrenia and remains stable. Peer support workers should receive support from their whole team, and support and mentorship from experienced peer workers.

1.1.6.2 Consider a manualised self-management programme delivered face-to-face with service users, as part of the treatment and management of psychosis or schizophrenia.

1.1.6.3 Peer support and self-management programmes should include information and advice about:

- psychosis and schizophrenia
- effective use of medication
- identifying and managing symptoms
- accessing mental health and other support services
- coping with stress and other problems

- what to do in a crisis
- building a social support network
- preventing relapse and setting personal recovery goals.

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic expert feedback suggested that supportive therapy and befriending are unlikely to be superior to treatment as usual.

Impact statement

No new evidence was identified through systematic searches to support the topic expert view. As such, no impact on the guideline is anticipated.

New evidence is unlikely to change guideline recommendations.

Psychological therapy and psychosocial interventions

Q – 17 **For people with first-episode or early schizophrenia, what are the benefits and downsides of psychological/psychosocial interventions when compared with alternative management strategies at initiation of treatment?**

Q – 18 **For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of psychological/psychosocial interventions when compared with alternative management strategies?**

Q – 19 **For people with schizophrenia that is in remission, what are the benefits and downsides of psychological/psychosocial interventions when compared with alternative management strategies?**

Q – 20 **For people with schizophrenia who have an inadequate or no response to treatment, what are the benefits and downsides of psychological/ psychosocial interventions when compared with alternative management strategies?**

Q – 21 **For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of psychological management strategies for previous trauma compared with treatment as usual or another intervention?**

Recommendations derived from these review questions

First episode psychosis – assessment and care planning

1.3.3.2 Assess for post-traumatic stress disorder and other reactions to trauma because people with psychosis or schizophrenia are likely to have experienced previous adverse events or trauma associated with the development of the psychosis or as a result of the psychosis itself. For

people who show signs of post-traumatic stress, follow the recommendations in Post-traumatic stress disorder (NICE clinical guideline 26).

First episode psychosis – treatment options

1.3.4.1 For people with first episode psychosis offer:

- oral antipsychotic medication (see sections 1.3.5 and 1.3.6) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in section 1.3.7).

1.3.4.2 Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try psychological interventions alone:

- offer family intervention and CBT
- agree a time (1 month or less) to review treatment options, including introducing antipsychotic medication

continue to monitor symptoms, distress, impairment and level of functioning (including education, training and employment) regularly.

First episode psychosis – how to deliver psychological interventions

1.3.7.1 CBT should be delivered on a one-to-one basis over at least 16 planned sessions and:

- follow a treatment manual[2] so that:
  - people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning
  - the re-evaluation of people's perceptions, beliefs or reasoning relates to the target symptoms
- also include at least one of the following components:
  - people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms
  - promoting alternative ways of coping with the target symptom
  - reducing distress
  - improving functioning.

1.3.7.2 Family intervention should:

- include the person with psychosis or schizophrenia if practical
- be carried out for between 3 months and 1 year
- include at least 10 planned sessions
- take account of the whole family's preference for either single-family intervention or multi-family group intervention
- take account of the relationship between the main carer and the person with psychosis or schizophrenia

have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work.

First episode psychosis – monitoring and reviewing psychological interventions

1.3.8.1 When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including service user satisfaction and, if appropriate, carer satisfaction.

1.3.8.2 Healthcare teams working with people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review:

- access to and engagement with psychological interventions

decisions to offer psychological interventions and equality of access across different ethnic groups.

First episode psychosis – competencies for delivering psychological interventions

1.3.9.1 Healthcare professionals providing psychological interventions should:

- have an appropriate level of competence in delivering the intervention to people with psychosis or schizophrenia
- be regularly supervised during psychological therapy by a competent therapist and supervisor.

1.3.9.2 Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological therapy interventions recommended in this guideline.

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis – treatment options

1.4.2.1 For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:

- oral antipsychotic medication (see sections 1.3.5 and 1.3.6) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in section 1.3.7).

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis – psychological and psychosocial interventions

1.4.4.1 Offer CBT to all people with psychosis or schizophrenia (delivered as described in recommendation 1.3.7.1). This can be started either during the acute phase or later, including in inpatient settings.

1.4.4.2 Offer family intervention to all families of people with psychosis or schizophrenia who live with or are in close contact with the service user (delivered as described in recommendation 1.3.7.2). This can be started either during the acute phase or later, including in inpatient settings.

1.4.4.3 Consider offering arts therapies to all people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings.

1.4.4.4 Arts therapies should be provided by a Health and Care Professions Council registered arts therapist with previous experience of working with people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the service user. Aims of arts therapies should include:

- enabling people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others
- helping people to express themselves and to organise their experience into a satisfying aesthetic form
- helping people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to the person.

1.4.4.5 When psychological treatments, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption.

1.4.4.6 Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to people with psychosis or schizophrenia. However, take service user preferences into account, especially if other more efficacious psychological treatments, such as CBT, family intervention and arts therapies, are not available locally.

1.4.4.7 Do not offer adherence therapy (as a specific intervention) to people with psychosis or schizophrenia.

1.4.4.8 Do not routinely offer social skills training (as a specific intervention) to people with psychosis or schizophrenia.

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis – early post-acute period

1.4.6.2 Healthcare professionals may consider using psychoanalytic and psychodynamic principles to help them understand the experiences of people with psychosis or schizophrenia and their interpersonal relationships.

Promoting recovery and possible future care – psychological interventions

1.5.4.1 Offer CBT to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission. Deliver CBT as described in recommendation 1.3.7.1.

1.5.4.2 Offer family intervention to families of people with psychosis or schizophrenia who live with or are in close contact with the service user. Deliver family intervention as described in recommendation 1.3.7.2.

1.5.4.3 Family intervention may be particularly useful for families of people with psychosis or schizophrenia who have:

- recently relapsed or are at risk of relapse
- persisting symptoms.

1.5.4.4 Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms.

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

First or early episode psychosis or schizophrenia

An RCT (Guo, 2010) (n=1,268) evaluated a range of psychological interventions for people with early episodes of schizophrenia. A 12 month programme including psychoeducation, family intervention, skills training and CBT, combined with antipsychotic treatment, in comparison to usual antipsychotic treatment alone, showed statistically significantly lower relapse rates and lower withdrawal rates as well as significantly greater improvement in: insight; social functioning; activities of daily living; quality of life and employment rates.

An RCT (Stevens, 2013) (n=547) evaluated assertive specialised treatment for 2 years in comparison to standard care, for people with a first episode of psychosis, showing no differences in violent offending, or any offending over a 5 year follow up.

A systematic review (Revell, 2015) including 11 studies (n=615) evaluated cognitive remediation for treatment in early episode psychosis. Either no or borderline significant effect of cognitive remediation was shown for global cognition and 5 neurocognitive domains. There was however a significant positive effect on verbal and learning memory, functioning and symptoms. Effect was larger in trials with adjunctive psychiatric rehabilitation and small group interventions.

An RCT (Østergaard, 2014) (n=117) evaluated cognitive remediation for people with first episode psychosis, as part of early intervention services. Compared to early intervention services alone, cognitive remediation showed a significant improvement in positive symptoms, working memory and verbal learning domain, after 12 months. There was no difference in functional capacity.

An RCT (Drake, 2014) (n=61) evaluated cognitive remediation for people with recent first episode psychosis. Compared to time matched social contact, no differences in psychotic symptoms were found, however, it was shown that intervention was associated with shorter subsequent CBT length.

An RCT (Goldsmith, 2015) (n=308) evaluated supportive therapy over 6 weeks, in comparison to usual care, in people with an acute, early episode of schizophrenia. A statistically significant improvement in PANSS was shown, with good therapeutic alliance and higher session number attendance both associated with better outcomes.

Acute exacerbation or recurrence

3 RCTs were identified which evaluated adherence therapy for people with acute exacerbation of schizophrenia. 2 studies (Barkhof, 2013; Bormann, 2015) (n=114; n=70) showed that in comparison to health education or treatment as usual, 8 sessions of adherence therapy, including motivational interviewing, showed no difference in medication adherence, patient attitudes, hospitalisation rates across the whole population studied or medication side effects, at 26 week or 12 month follow up. In contradiction, a third study (n=349) (Hudson, 2008) compared adherence therapy to treatment as usual, finding a statistically significant difference in adherence after 6 months, favouring intervention.

An RCT (Goldsmith, 2015) (n=308) evaluated CBT in comparison to usual care for the treatment of an acute episode of psychosis, showing CBT to be statistically significantly associated with an improvement in PANSS score, also indicating an association between better outcomes with a good therapeutic alliance, and poor outcomes with poor therapeutic alliance.

An RCT (Lindenmayer, 2013) (n=59) evaluated computerised emotion perception for people with an exacerbation of schizophrenia. Cognitive remediation with an additional computerised emotion perception intervention was significantly more effective at improving emotion recognition and social cognition than cognitive remediation alone.

An RCT (Freeman, 2016) (n=30) evaluated CBT which utilised virtual reality to target delusions. In comparison to virtual reality exposure, a significant decrease in delusional conviction and real world distress was demonstrated with virtual reality CBT.

Promotion of recovery and ongoing care

2 RCTs evaluated adherence therapy for people with schizophrenia who require ongoing care during recovery. A telephone based programme over 4 months (Montes, 2011) (n=928) and a family supervision programme, after 1 year (Farooq, 2011) (n=110), both showed significant increases in medication adherence.

An RCT (Mausbach, 2008) (n=240) evaluated a skill building behavioural intervention for people with schizophrenia who require ongoing care, in comparison to a time-equivalent control, showing the intervention resulted in statistically significantly fewer uses of general and psychiatric emergency medical services, immediately post-intervention, but there was no difference in the long-term.

An RCT (Komatsu, 2013) (n=45) evaluated the effectiveness of an information technology aided relapse prevention programme, showing a statistically significantly reduced number of inpatient days and lower risk of rehospitalisation in those on the programme compared to those undertaking treatment as usual, as well as a significantly lower mental state score.

Unspecified stage of psychosis or schizophrenia

1 RCT and a systematic review evaluated adherence therapy for people with schizophrenia or psychosis. Both studies compared a form of adherence therapy to treatment as usual. An education, skills and alliance training programme (Mittal, 2009) (n=40) showed no difference in adherence. The systematic review (Chang, 2015) (n=125) reported mixed results, including 2 studies which found statistically significant improvements in drug attitude following adherence therapy and 1 study that showed no difference.

4 RCTs and 1 systematic review evaluated forms of arts therapy. Comparing group arts therapy to an activity group (Crawford, 2012) (n=417), both over 12 months, showed no difference in PANSS or Global Assessment of Functioning (GAF) scores. A comparison of 20 sessions of body psychotherapy, with 20 sessions of pilates classes (Priebe, 2016) (n=275) showed no differences in PANSS negative subscale score, but significant improvement in extrapyramidal movement disorder symptoms. Both dance (Ren, 2013) (n=45) and music therapy (Mössler, 2011) (8 studies; n=483) were compared to usual care and showed no differences in PANSS overall scores, but statistically significant improvement in negative symptoms. Dance therapy showed no difference in positive symptoms or quality of life and music therapy showed no differences for depression or anxiety. No difference in effectiveness was shown between participants with more or less severe negative symptoms at baseline or between those who did and did not express a preference for arts therapy (Leurent, 2014) (n=277).

A network meta-analysis (Steenhuis, 2015) including 10 studies, evaluated non-verbal therapy (including music, yoga, occupational

and exercise therapy) in comparison to treatment as usual, showing a statistically significant reduction in depressive symptoms in intervention groups overall, but occupational and exercise therapy were statistically significantly less effective than treatment as usual for depressive symptom reduction. Consistent with this evidence, an RCT (Cook, 2009) (n=44) found occupational therapy to have no difference in negative symptom severity or social functioning, compared to treatment as usual.

In comparison to standard care (7 studies (Birchwood, 2014, Freeman, 2015a; Freeman, 2015b; Gaag, 2011; Velthorst, 2015, SR; Jauhar, 2014, SR and Malik, 2009 (n=197; n=143; n=50; n=216; 34 studies; 35 studies; n=330)), CBT was associated with statistically significant improvements across 5 studies, with a decrease in: hallucination compliance (a decrease in the number of times a person complies with instructions given through a hallucination) in the long-term but not short-term; worry (measured on the Penn State Worry Questionnaire); delusions (measured on the Psychotic Symptom Rating Scales (PSYRATS)); positive, negative and overall symptoms; insomnia and relapse rates. CBT was also associated with an increase in the days of normal social functioning. Of these 7 studies, 1 systematic review (Velthorst, 2015) evaluated CBT adapted to negative symptoms, showing no difference in negative symptom alleviation.

A systematic review (Jones, 2012), including 31 studies, evaluated CBT in comparison to other psychosocial therapies, finding no difference in hospitalisation rates; withdrawal rates; global state, positive or negative measures; adverse event number; social functioning or quality of life. There was a significant improvement in affective symptoms shown, favouring CBT over other therapies. This is contradicted by an RCT (Li, 2015) (n=192) which shows CBT, in comparison to supportive therapy, has a significantly greater and more durable improvement in PANSS total and positive scores and an improvement in social functioning.

Cost effectiveness analysis of CBT was performed by 2 studies (Barton, 2009) (n=77) (Gaag, 2011) (n=216). Social recovery orientated CBT had a mean incremental QALY gain of 0.035 and cost per QALY of £18,844 but with a cost-effectiveness threshold of £20,000 per QALY, the probability of being cost-effective was 54.3%. Another study showed an ICER of £47 per day of normal functioning gained, with targeting of individuals who have not been hospitalised previously resulting in an ICER of £14 per day of normal functioning.

An RCT (Keefe, 2012) (n=53) evaluated cognitive remediation for people with schizophrenia. Comparing cognitive remediation – including auditory training – to a time matched computer game and healthy lifestyles intervention, showed a significant improvement in cognition scores in the short-term but not in the long-term.

2 RCTs evaluated cognitive therapy in comparison to treatment as usual. 1 study (Morrison, 2014) (n=74) evaluated cognitive therapy for people not taking antipsychotic drugs, showing a statistically significant decrease in PANSS score with intervention. The other (Grant, 2012) (n unreported) evaluated cognitive therapy compared to standard care showing statistically significant improvement in global functioning, reduction in avolition-apathy and reduction in positive symptoms over 18 months with intervention.

2 RCTs and a systematic review evaluated family intervention in comparison to treatment as usual. A family intervention programme including 12 months of psychoeducation (Mayoral, 2017) (n=88) was statistically significantly associated with a reduction in hospitalisation and symptom severity at end of treatment, but there was no difference in symptom severity 6 months following end of treatment. Family intervention involving a 9 month mutual support group programme (Chien, 2013 (n=135) showed a significant reduction in patient symptom severity and length of rehospitalisation up to 24 months post-intervention, and a significant improvement in family and patient functioning. Brief family intervention, in a systematic review of 4 studies (n=163) (Okpokoro, 2014) showed no difference in hospitalisation rates and relapses, but did show a statistically significant improvement in family member understanding.

A systematic review and an RCT evaluated psychoeducation in comparison to treatment as usual. Psychoeducation lasting 12 weeks (Hasan, 2016, n=121), including patients as well as their carers, showed a significantly lower relapse rate, greater reduction in symptom severity and improvement in

knowledge scores after 3 months. A systematic review including 6 studies evaluating psychoeducation which utilised information communication technology (Välimäki, 2012) (n=1,063), found no difference in global or mental state, knowledge, insight or compliance in the short-term but did show a significant improvement in compliance in the long-term.

An RCT (Liu, 2014) (n=24) evaluating horticultural therapy lasting 2 weeks, showed no difference in personal wellbeing index score but a decrease in depression, anxiety and stress when compared to standard care.

2 RCTs evaluated social skills training in comparison to usual care alone. Over 2 years, it was shown that social skills training was associated with a statistically significantly higher likelihood of social network improvement (Terzian, 2014) (n=357). When in combination with tai-chi (Kang, 2017) (n=244), social skills training showed a significant decrease in PANSS total and negative scores and a significantly lower risk of aggressive behaviour, after 1 year.

A systematic review, (Buckley, 2015) including 24 studies, (n=2,126) evaluated the efficacy of supportive therapy. In comparison to standard care, no differences in relapse rates, hospitalisation rates or general functioning were found. In comparison to psychological and social therapy, hospitalisation rates were shown to be statistically significantly higher, clinical improvement in mental state lower and patient satisfaction lower, under supportive therapy treatment. In comparison to CBT, no differences in relapse rates or symptom severity were found.

Previous trauma

An RCT (Berg, 2016) (n=155) evaluated trauma-focused treatment for post-traumatic stress disorder (PTSD) in people who have chronic schizophrenia, compared to a waiting list group. Intervention treatment was associated with lack of increase of hallucinations, dissociation or suicidality, and a significant decrease in paranoia. Intervention group participants were significantly less likely to be revictimised and had significantly fewer adverse events. More frequent symptom exacerbation was reported in control groups.

An RCT (Berg, 2015) (n=155) evaluated interventions for PTSD treatment in people with an acute exacerbation of schizophrenia. Participants undertaking prolonged exposure therapy or eye movement desensitisation and reprocessing therapy - in comparison to waiting list controls - were statistically significantly more likely to achieve loss of PTDS diagnosis. Both interventions showed no difference in serious adverse event rate, but only prolonged exposure therapy was associated with an increased likelihood of gaining full remission.

Topic expert feedback

Topic expert feedback suggested that there have been advances in the evidence base regarding CBT. It was highlighted that this evidence is mixed but may lead to a conclusion that CBT is ineffective. As well as this, it was highlighted that the implementation of brief psychological therapy in addition to CBT may provide economic benefits and improve outcomes. A number of topic experts raised that there is emerging evidence on the effectiveness of psychological intervention alone, in people who chose not to take antipsychotic medication, which has been included in the evidence summary above (Morrison, 2014). However it was also noted that a larger study would be needed to be confident in the conclusions.

A large pragmatic trial of arts therapy was highlighted and included in the above summary (Crawford, 2012), which does not support recommendation 1.4.4.3 for its use in the treatment of negative symptoms. It was topic expert opinion that arts therapy in general may not be appropriate as a recommendation, but that there does not seem to be evidence to change the recommendation for other arts therapies, such as music.

It was highlighted that there has been new evidence published regarding cognitive remediation (Revell, 2015), which has been summarised above. Topic expert opinion was that this new evidence could have an impact on the current recommendations as this was an intervention that was not previously recommended.

In regard to the research recommendation on trauma and psychosis, topic experts suggested that trial evidence was limited at the time of the CG178 guideline committee, but more recently, further evidence has been published. There have been 2 identified RCTs which focus on the treatment of PTSD in psychosis which are summarised above (Berg, 2015 and Berg, 2016). Topic experts suggested that specific guidance on the treatment of PTSD in those

with psychosis could benefit thousands of patients in England alone.

Impact statement

The current recommendations which suggest psychological therapy should be offered in combination with antipsychotic medication (1.3.4.1, 1.4.2.1 and section 1.5.4), was supported by new evidence identified through the surveillance review, which indicated improved outcomes with a combination of treatment approaches.

Assertive specialised treatment

Assertive specialised treatment is not currently recommended by CG178, and new evidence showed no effect of this intervention on offending rate, which was not a prioritised outcome during guideline development.

Assertive specialised treatment – summary of impact

It is not expected that new evidence identified would have an impact on the guideline.

Supportive therapy

New evidence evaluating supportive therapy was identified. Overall, new evidence identified suggested CBT is superior to supportive therapy, although there is also evidence suggesting there is no difference in efficacy between CBT and supportive therapy and evidence that supportive therapy is ineffective. However, 1 study indicated that supportive therapy is effective for people with first episode psychosis. Supportive therapy currently is not recommended (1.4.4.6) in CG178, due to a meta-analysis of 18 studies identified in 2014 indicating no improvement in outcomes with this treatment.

Supportive therapy – summary of impact

It is likely that the addition of the newly identified evidence regarding supportive therapy, in that is has mixed efficacy, would not have an impact on the outcome of the meta-analysis evaluated during guideline development, and therefore would be unlikely to have an impact.

Cognitive remediation

New evidence evaluating cognitive remediation did not show any long-term effects for improvement of cognition compared to other treatment, which was also highlighted by topic expert feedback. Some evidence suggesting a positive effect of cognitive remediation on verbal learning and memory and symptom severity was identified from a systematic review and a corroborating RCT, although little effect was shown across a variety of other outcomes such as global cognition and other neurocognitive domains. Evidence for the incorporation of a computerised emotion perception intervention into cognitive mediation therapy was identified, which is not an area currently covered by CG178. However, this evidence is derived from a single, small study. Topic expert feedback indicated that cognitive remediation is more likely to be effective than usual treatment once people are outside of the rehabilitation framework, however, primary evidence on this point has not been identified. The decision to not make recommendations on cognitive remediation during guideline development was based on a body of evidence with mixed efficacy, with a lack of UK studies showing an effect of this intervention.

Cognitive remediation – summary of impact

The studies identified during this surveillance review report mixed efficacy of cognitive remediation and it is anticipated that the addition of this evidence to the mixed evidence evaluated during guideline development would not be sufficient to impact the current recommendations.

CBT

A large amount of newly identified evidence, including cost-effectiveness evidence, considered CBT for treatment of people with schizophrenia across the range of stages. The majority of this evidence is considered to support the current recommendations, which suggest CBT is offered to people with schizophrenia or psychosis (1.3.4.1, 1.4.2.1, 1.4.4.1 and 1.5.4.1). Evidence of an intervention described only as ‘cognitive therapy’, was also supportive of current recommendations. There is however further evidence, from 2 systematic reviews including 35 and 20 studies, which indicates that CBT has no effect on a range of key outcomes, including hospitalisation rates, mental state (including positive and negative symptoms) and social functioning compared to other psychological interventions. 1 of these systematic reviews indicates that CBT is ineffective for the specific treatment of negative symptoms, as effect on symptom alleviation was small and heterogeneous amongst studies. The possibility that CBT is not effective was also highlighted as a point of consideration through topic expert feedback. This is contradictory to the evidence which forms the

basis for the current recommendation, which suggests CBT is offered to people with persistent negative symptoms (1.5.4.1). However, it was reported in one of the systematic reviews that the included studies had small sample sizes and only a limited number of studies reported on each relevant outcome. While there is evidence to support a possible lack of effect of CBT, there is also newly identified evidence suggesting the opposite, in support of the current recommendations.

Topic expert feedback also indicated there may be a positive effect of adding brief psychological treatment to CBT, which has not been considered previously. There was also limited evidence regarding the use of technology in CBT, however this specific area was only supported by 2 small studies which is unlikely to currently have an impact on recommendations.

CBT – summary of impact

Although evidence was identified which contradict the current recommendations, a significant amount of supporting evidence was also identified. Due to the lack of consistency, and the volume of studies both identified here and during guideline development which support the current recommendations, it is considered that the current recommendations will not be impacted by this evidence.

Relapse prevention programmes

A single small study was identified evaluating an information technology aided relapse prevention programme. No recommendations regarding this intervention are currently found in CG178.

Relapse prevention programmes – summary of impact

It is not anticipated that a single study evaluating relapse prevention programmes has any impact, especially considering the small participant number included in this trial.

Adherence therapy

Adherence therapy is currently not recommended by CG178 (1.4.4.7). This decision was based on a small body of evidence (5 RCTs) which showed limited and inconsistent efficacy. Mixed evidence has been identified during this surveillance review. In people with acute exacerbation, 2 smaller studies indicated no effect, while a larger study indicated improvement in outcomes. For studies which included people going through recovery, specialised methods of adherence therapy (a telephone based programme and a family supervision programme) were associated with outcome improvement. However, only 1 of these studies is applicable to the UK context.

Adherence therapy – summary of impact

It is suggested that if this evidence were to be considered alongside the evidence currently included in the guideline, it would be unlikely to impact the recommendations. This is due to the lack of consistency both in the outcomes reported and the efficacy of treatment and the limited number of large trials identified.

Arts therapy

Arts therapy is currently recommended as a form of treatment for people with subsequent acute episodes of schizophrenia or psychosis (1.4.4.3, 1.4.4.4 and 1.5.4.4), particularly for people with negative symptoms. The evidence identified here covers a range of types of arts therapy, which in the main, does not support the current recommendations. Evidence to suggest that group arts therapy is no more effective than other group sessions was identified (Crawford, 2012), however, the study reporting this outcome showed high attrition rates and potential bias regarding the recruitment of participants. Music, dance and horticultural therapy showed improvement in negative symptoms but not in other outcomes of interest. Topic expert feedback also highlighted that the treatment of negative symptoms through arts therapy may not be effective, but other arts therapies such as music therapy may be effective.

Arts therapy – summary of impact

Overall, while there is some evidence that art therapy may not be effective, a variety of different types of art therapy were evaluated, with a mix of efficacy reported. There are also concerns regarding the quality of the studies that contradict current recommendations following critical appraisal. Therefore, it is not anticipated that the evidence identified during this surveillance review would currently have an impact on the recommendations made in CG178.

Occupational therapy

Occupational therapy specifically for the treatment of negative symptoms in schizophrenia or psychosis was not considered during the development of CG178. Occupational therapy for treatment of negative

symptoms showed a negative or neutral effect in new evidence identified.

Occupational therapy – summary of impact

As there are currently no recommendations on occupational therapy to target symptoms of schizophrenia, and as the only evidence identified was from a branch of a network meta-analysis and a small trial, it is not anticipated that this will have an impact at this time.

Family intervention

New evidence was identified which evaluated family interventions, with somewhat mixed efficacy. The current recommendations, which suggest that family interventions are offered (1.2.3.1, 1.3.4.1, 1.3.4.2, 1.4.2.1, 1.4.4.2, 1.5.4.1 and 1.5.7.1) are based on 32 studies which showed robust and consistent evidence, some of which was in the UK setting. The newly identified evidence was not conducted in the UK, and the evidence which indicates there is no effect of family intervention, is based on a systematic review of a brief family intervention, which is not representative of the more intensive intervention recommended in CG178 (1.3.7.2).

Family intervention – summary of impact

It is not anticipated that the newly identified evidence has an impact on the guideline recommendations as it shows mixed efficacy and is not representative of the UK setting.

Psychoeducation

21 studies focusing on psychoeducation were considered during the development of CG178, showing no robust evidence of effectiveness. 2 additional studies have been identified in the surveillance review, of which 1 indicates no effect of psychoeducation. While the second study does indicate an improvement in outcomes, this is only assessed in the short term, and as a study that was conducted in Jordan, it is unlikely to reflect UK practice.

Psychoeducation – summary of impact

When added to the body of evidence reviewed during guideline development, the evidence on psychoeducation is unlikely to have any impact.

Skill building

A single study evaluating a skill building intervention was identified, showing no long term effect. Skill building is not currently recommended in CG178.

Skill building – summary of impact

It is not anticipated that a single study evaluating skill building as treatment for schizophrenia or psychosis has any impact, especially considering there are no current recommendations concerning this intervention.

Social skills training

New evidence was identified evaluating social skills training, which indicated a positive effect. However, as these are non-UK based studies, this evidence may not be directly applicable to UK practice. Currently social skills training is not recommended (1.4.4.8), a decision that was based on 23 trials which overall, showed no evidence of effect.

Social skills training – summary of impact

It is not anticipated that the 2 trials identified here would be sufficient to have an impact on the current recommendations, as when added to the overall body of evidence they are unlikely to have a large influence.

Treatment for trauma

Primary evidence evaluating the treatment of trauma in people with schizophrenia or psychosis was identified, and this was an area indicated by topic experts as having developed since CG178 was published, as well as being of high importance. The evidence evaluated suggests an improvement in symptom severity with trauma-focused treatment, prolonged exposure therapy or eye movement desensitisation and reprocessing therapy. This adds to the limited evidence which was available at the time of guideline development, which hindered the recommendation of treatment specifically for this indication. However, recommendation 1.3.3.2 suggests that recommendations in NICE guideline CG26 on Post-traumatic stress disorder are followed for people with psychosis or schizophrenia who show signs of post-traumatic stress. CG26 includes recommendations for the interventions identified by new evidence here.

Treatment for trauma – summary of impact

In the main, the evidence identified during the surveillance review indicates the effectiveness of interventions currently indirectly recommended by CG178, by cross-reference to other NICE guidance. Therefore, it is unlikely that the newly identified evidence would have any impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Pharmacological interventions

Q – 22 **For people with first-episode or early schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug at the initiation of treatment (when administered within the recommended dose range [BNF54])?**

Q – 23 **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 [BNF54])?**

Q – 24 **For people with schizophrenia that is in remission, what are the benefits and down sides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?**

Q – 25 **For people with schizophrenia whose illness has not responded adequately to treatment, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?**

Q – 26 **For people with schizophrenia with persistent negative symptoms, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?**

Q – 27 **For people with schizophrenia whose illness has not responded adequately to clozapine treatment, is augmentation of clozapine with another antipsychotic associated with an enhanced therapeutic response?**

Q – 28 **For people with schizophrenia that is in remission, is any depot or long-acting antipsychotic medication associated with improved relapse prevention over time?**

Q – 29 **For people with schizophrenia whose illness has not responded adequately to treatment and who have had long-term antipsychotic drug treatment, is there any evidence that patients have a preference for either depot/long-acting or oral preparations?**

Recommendations derived from these review questions

First episode psychosis

Choice of antipsychotic medication

1.3.5.1 The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

How to use antipsychotic medication

1.3.6.1 Before starting antipsychotic medication, undertake and record the following baseline investigations:

- weight (plotted on a chart)
- waist circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA_{1c}), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity.

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.

1.3.6.3 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following:

- Discuss and record the side effects that the person is most willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British national formulary (BNF) or SPC.
- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks.

1.3.6.4 Monitor and record the following regularly and systematically throughout treatment, but especially during titration:

- response to treatment, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart)
- waist circumference annually (plotted on a chart)
- pulse and blood pressure at 12 weeks, at 1 year and then annually
- fasting blood glucose, HbA_{1c} and blood lipid levels at 12 weeks, at 1 year and then annually

- adherence
- overall physical health.

1.3.6.5 The secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements.

1.3.6.7 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments.

1.3.6.8 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.3.6.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC.

1.3.6.9 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').

1.3.6.10 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).

1.3.6.11 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.

Subsequent acute episodes of psychosis or schizophrenia and referral in crisis

Pharmacological interventions

1.4.3.1 For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 1.3.5 and 1.3.6). Take into account the clinical response and side effects of the service user's current and previous medication.

Behaviour that challenges

1.4.5.1 Occasionally people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. The management of immediate risk should follow the relevant NICE guidelines (see recommendations 1.4.5.2 and 1.4.5.5).

1.4.5.2 Follow the recommendations in Violence (NICE clinical guideline 25) when facing imminent violence or when considering rapid tranquillisation.

1.4.5.3 After rapid tranquillisation, offer the person with psychosis or schizophrenia the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes.

1.4.5.4 Ensure that the person with psychosis or schizophrenia has the opportunity to write an account of their experience of rapid tranquillisation in their notes.

1.4.5.5 Follow the recommendations in Self-harm (NICE clinical guideline 16) when managing acts of self-harm in people with psychosis or schizophrenia.

Early post-acute period

1.4.6.3 Inform the service user that there is a high risk of relapse if they stop medication in the next 1–2 years.

1.4.6.4 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.

1.4.6.5 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.

Promoting recovery and possible future care

General principles

1.5.1.3 Review antipsychotic medication annually, including observed benefits and any side effects.

Pharmacological interventions

1.5.5.1 The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 1.3.5 and 1.3.6).

1.5.5.2 Do not use targeted, intermittent dosage maintenance strategies routinely. However, consider them for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity.

1.5.5.3 Consider offering depot /long-acting injectable antipsychotic medication to people with psychosis or schizophrenia:

- who would prefer such treatment after an acute episode
- where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

Using depot/long-acting injectable antipsychotic medication

1.5.6.1 When initiating depot/long-acting injectable antipsychotic medication:

- take into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics)
- take into account the same criteria recommended for the use of oral antipsychotic medication (see sections 1.3.5 and 1.3.6), particularly in relation to the risks and benefits of the drug regimen
- initially use a small test dose as set out in the BNF or SPC.

Interventions for people whose illness has not responded adequately to treatment

1.5.7.1 For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment:

- Review the diagnosis.
- Establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration.
- Review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families.
- Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.

1.5.7.2 Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic.

1.5.7.3 For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 1.5.7.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine.

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

First episode or early psychosis

A systematic review and meta-analysis (Crossley, 2010) of 15 RCTs (n=2,522) compared the use of atypical and typical

antipsychotics for first-line treatment of first-episode psychosis. No statistically significant differences between treatment with atypical and typical drugs were found for discontinuation rates or efficacy. Participants on atypical antipsychotics gained more weight than those on typical antipsychotics, whereas those on typical antipsychotics experienced more extrapyramidal side effects.

An RCT (Perez-Iglesias, 2008) including drug-naïve participants (n=164) compared weight gain induced by haloperidol, olanzapine and risperidone. Statistically significant differences in weight gain were identified at 3 months follow-up, with olanzapine causing the most and haloperidol causing the least. After 1 year, there was no statistically significant difference in weight gain.

A network meta-analysis (Zhu, 2017), including 13 studies (n=2669), evaluated 12 antipsychotics for their effect on the reduction of symptoms. Amisulpride, olanzapine, ziprasidone and risperidone were shown to be significantly more efficacious than haloperidol; amisulpride was also superior to quetiapine for overall symptom reduction and olanzapine was superior to haloperidol and risperidone for reduction of negative symptoms. When measuring all cause discontinuation, several atypical antipsychotics were superior to haloperidol.

An RCT (Möller, 2008) (n=289) compared haloperidol with risperidone for first episode schizophrenia. Extrapyramidal side-effects were significantly more prevalent in participants on haloperidol than risperidone, and the risperidone group had significantly fewer drop-outs and longer time to discontinuation than the haloperidol group.

Acute exacerbation

A systematic review and meta-analysis (Donnelly, 2013) included 19 studies, comparing varying doses of haloperidol for acute exacerbation of schizophrenia. The use of a standard lower dose (>3 to 7.5 mg/day) did not result in loss of efficacy versus standard higher dose (>7.5 to 15 mg/day). A standard lower dose also showed lower clinically significant extrapyramidal adverse effects than a higher dose.

6 RCTs (Ogasa, 2013; Nakamura, 2009; Loebel, 2013; Loebel, 2015; Durgam, 2015; Durgam, 2014) (n=149; 180; 365; 1525; 617; 732) were identified comparing an antipsychotics to placebo for treatment of acute exacerbations of psychosis or schizophrenia. These studies all indicated a significant decrease in PANSS score with antipsychotic treatment.

One of these antipsychotics evaluated was lurasidone, which was the subject of a NICE evidence summary, also indicating the drug's effectiveness for the treatment of schizophrenia in adults.

2 systematic reviews (Powney, 2012; Huf, 2016) including 32 and 6 studies (n unreported; 1,367) evaluated the effect of the use of haloperidol for psychosis induced aggression. Compared to placebo or aripiprazole, haloperidol was significantly more effective at achieving tranquilisation although dystonia was common. Compared to zuclopenthixol acetate, lorazepam or haloperidol plus promethazine, haloperidol was significantly less effective at achieving tranquilisation. Haloperidol plus promethazine was significantly more effective for avoidance of adverse events than haloperidol alone. Haloperidol plus promethazine compared to olanzapine or ziprasidone showed no significant difference in tranquilisation effect. Lorazepam compared to haloperidol plus promethazine was significantly less effective at achieving tranquilisation. Compared to midazolam, haloperidol plus promethazine was significantly less effective at achieving swift tranquilisation and there was no difference in the risk of adverse events.

A systematic review (Ahmed, 2010) including 1 study (n=30), compared the use of chlorpromazine to haloperidol for psychosis induced agitation or aggression, showing the number of required injections was the same in both groups and there was no significant difference in adverse effects.

8 studies (Buarski-Kirola, 2014; Downing, 2014; Durgam, 2014; Durgam, 2015; Egan, 2013; Garcia, 2009; Landbloom, 2017; Schmidt, 2012 (b)) were identified that evaluated a total of 7 drugs which are not licenced for any indication currently in the UK.

Promotion of recovery and ongoing care

An RCT (Deberdt, 2012) (n=133) evaluated olanzapine in comparison to quetiapine, for treatment of obese people with schizophrenia who were mentally stable. No significant difference in time to relapse was observed, but significantly more people remained on treatment in the olanzapine group. Significantly

more people in the olanzapine group also experienced an increase in BMI ≥ 1kg/m2.

A systematic review (Leucht, 2012) including 65 studies (n=6493), evaluated antipsychotics for relapse prevention compared to placebo. A significant reduction in relapse rates after 1 year was shown in those taking antipsychotics compared to placebo, as well as a reduction in hospital admission, an improved quality of life and fewer reports of aggressive acts. Antipsychotic treatment was however associated with weight gain, movement disorders and sedation.

An RCT (Peuskens, 2010) (n=197), evaluated quetiapine fumarate extended release tablets in comparison to placebo for people with schizophrenia in long-term symptomatic remission, showing a statistically significant improvement in relapse rates and mental state with treatment.

An RCT (Tandon, 2016) (n=285) evaluated lurasidone as maintenance treatment for schizophrenia in comparison to placebo. Lurasidone significantly delayed time to relapse compared to placebo over a 28 week period.

A network meta-analysis (Zhao, 2016) including 56 studies (n=10,177) compared the long-term effectiveness of a range of antipsychotic drugs with the aim of preventing relapse in people with schizophrenia. The meta-analysis found that olanzapine was significantly more effective than chlorpromazine; fluphenazine decanoate, haloperidol, haloperidol decanoate and trifluoperazine produced more extrapyramidal adverse effects than olanzapine or quetiapine and olanzapine was associated with more weight gain than other agents.

Unspecified stage of psychosis or schizophrenia

8 systematic reviews (Rattehalli, 2016; Mothi, 2013); Leucht, 2014 (b); Koch, 2014; Kumar, 2009; Iwata, 2015; Hartung, 2015 and Belgamwar, 2011) and 2 RCTs (Canuso, 2010 (b) and Shen, 2012) evaluated the efficacy of an antipsychotic versus placebo for the long-term treatment of schizophrenia. Of the studies that reported change in mental state, either by measurement in PANSS, Brief Psychiatric Rating Scale (BPRS) or by change in global mental state, 7 studies reported a significant improvement when treated with an antipsychotic. 8 studies reported relapse rates for participants taking antipsychotics versus those on placebo. 4 studies showed a significant decrease in relapse rates when taking antipsychotics, whereas 4 studies showed no significant difference. The number of withdrawals from studies comparing antipsychotics and placebo for treatment of schizophrenia was reported by 5 studies, with 3 studies reporting a significant increase of withdrawal rate on placebo compared to antipsychotic treatment and 2 studies reporting no significant difference in withdrawal rates. The rates of adverse events and side effects were also reported by the majority of studies. Additional outcomes reported to occur significantly more frequently in groups taking antipsychotics included weight gain, increased incidence of movement disorders, increased sedation and altered prolactin levels. No difference in cognitive function, incidence of movement disorders and general side effects was also reported in 4 studies.

2 systematic reviews (Komossa, 2010 (a) and Komossa, 2011), including 10 and 45 studies respectively (n= 1,549; 7,760), evaluated the efficacy of amisulpride in comparison to risperidone or olanzapine, showing no difference in withdrawal rates across the study arms, less weight gain on amisulpride and no difference in the number of extrapyramidal or cardiac side effects across groups.

A systematic review (Bhatachearjee, 2008), including 8 studies (n=3,122), evaluated aripiprazole in comparison to other antipsychotics, showing the number of withdrawals in groups treated with aripiprazole was lower. There were fewer extrapyramidal side effects and hyperprolactinaemia cases, but more dizziness and nausea on aripiprazole in general, compared to other antipsychotics. A cost-effectiveness analysis (Barnett, 2009) estimated a £37,261,293 saving over 10 years with aripiprazole treatment in avoided diabetes cases (23.4 cases per 1,000 treated patients) and a £7,506,770 saving over 10 years in avoided cardiovascular disease (3.7 events per 10,000 treated patients), in comparison to standard care.

A post-hoc analysis of two RCTs (Docherty, 2010) (n=1,294) compared aripiprazole with haloperidol. Aripiprazole showed significant improvement versus haloperidol on the prosocial subscale and on the modified prosocial subscale, over a 52 week period.

A systematic review (Khanna, 2014) including 29 studies (n= 2,132), evaluated aripiprazole compared to clozapine for people with

schizophrenia, showing no significant difference in efficacy, side effects or number of withdrawals but a statistically significantly better quality of life score in those on aripiprazole.

5 systematic reviews (Khanna, 2014; Kane, 2009; Komossa, 2010 (b); Krzystanek, 2011 and Mukundan, 2010) (n=29,132; 1,549; 794; 636) and an RCT (Newcomer, 2008) (n=546) evaluated aripiprazole in comparison to olanzapine. 4 studies evaluated psychiatric symptom severity, with 3 indicating a statistically significant decrease in PANSS score in people taking olanzapine, and 1 study showing no significant difference. 2 studies reported withdrawal rates, with 1 study reporting more withdrawals on aripiprazole and the other showing no difference. Increase in weight gain, blood glucose, cholesterol and triglyceride levels were reported for olanzapine, whereas decreased blood glucose levels were reported for aripiprazole.

A systematic review (Khanna, 2014) included 12 studies (n=991) which evaluated the efficacy of aripiprazole in comparison to quetiapine, showing no difference in symptom severity or withdrawal rates, but significantly better quality of life scores in people taking aripiprazole.

2 systematic reviews (Khanna, 2014 and Komossa, 2011) including 80 and 13 studies respectively (n=6,381; 2,599) that evaluated aripiprazole in comparison to risperidone, showing statistically significant improvement in mental state in those on aripiprazole, and no difference in withdrawal rates. Fewer side effects and lower cholesterol levels were reported in people taking aripiprazole.

A systematic review (Saha, 2016) included 14 studies evaluating the effect of chlorpromazine compared to olanzapine, showing no difference in BPRS score, withdrawal rates or relapse rates, more extrapyramidal side effects with chlorpromazine and a better quality of life score with olanzapine.

A systematic review (Saha, 2016) included 15 studies evaluating the efficacy of chlorpromazine in comparison to risperidone, showing no difference in BPRS score, withdrawal rates or side effects. However, quality of life scores were significantly higher in those on risperidone.

A systematic review (Saha, 2016) included 55 studies evaluating the efficacy of chlorpromazine in comparison to quetiapine, showing no difference in BPRS score or withdrawal rates. However, quality of life scores were significantly higher in those on quetiapine as extrapyramidal side effects were more common in those on chlorpromazine.

2 systematic reviews (Asenjo, 2010 and Komossa, 2010), including 27 and 50 studies, (n=3,099; 9,476) evaluated the efficacy of clozapine in comparison to olanzapine, showing no difference in psychiatric symptoms between the drugs. There were statistically significantly higher relapse rates in those on olanzapine but statistically significantly more withdrawals on clozapine.

A systematic review (Asenjo, 2010) including 27 studies (n=3,099), evaluated the efficacy of clozapine compared to quetiapine, finding no difference in psychiatric symptoms in people on either drug.

2 systematic reviews (Asenjo, 2010 and Komossa, 2011), including 27 and 13 studies (n=3,099; n=2,599) evaluated the efficacy of clozapine in comparison to risperidone, showing no difference in psychiatric symptoms between the drugs. However, more withdrawals and extrapyramidal side effects were found in those on risperidone. More weight gain and seizures were found in people taking clozapine.

A systematic review and cost-effectiveness analysis (Davies, 2008) compared clozapine treatment to atypical antipsychotics, finding clozapine to be more cost effective in over 50% of cases when treatment providers are willing to pay £30,000-£35,000 per QALY.

2 systematic reviews (Sampford, 2016 and Tardy, 2014 (b)), including 4 and 7 studies (n=202; 1567), evaluated fluphenazine treatment compared to other antipsychotics, both showing no difference in psychiatric symptoms or withdrawal rates between groups. Fluphenazine was however associated with increased incidences of movement disorders, akathisia and dystonia, loss of associated movement, rigor and tremor, but fewer incidences of dizziness, drowsiness, dry mouth, nausea and vomiting compared to other antipsychotics.

A systematic review (Tardy, 2014 (c)) including 17 studies (n=877) evaluated the efficacy of haloperidol in comparison to low potency antipsychotics, showing no difference in psychiatric symptoms or withdrawal rates between treatment groups. However, haloperidol was associated with fewer events of sedation, orthostasis and weight gain, but

more frequent occurrences of movement disorders.

A systematic review (Sivaraman, 2010) including 4 studies (n=192), compared the efficacy of levomepromazine and other antipsychotics, showing a statistically significant improvement in psychiatric symptoms as measured by PANSS and BPRS scores. No difference in withdrawal rates was found between the groups.

3 systematic reviews (Komossa, 2010; Komossa, 2011 and Krzystanek, 2011) including 50, 45 and 50 studies, (n=9,476; 7,760; 9,476) evaluated olanzapine in comparison to risperidone. These 3 studies all reported a statistically significant decrease in PANSS score in people taking olanzapine in comparison to people taking risperidone, and statistically significantly fewer withdrawals on olanzapine. Olanzapine groups showed increased weight and cholesterol gain, but fewer overall side effects and less prolactin increase.

4 systematic reviews (Komossa, 2010; Asmal, 2013; Mukundan, 2010 and Krzystanek, 2011), including 50, 11, 4 and 50 studies respectively (n=9,476; 1,486; 636; 9,476), evaluated olanzapine in comparison to quetiapine, showing that people on olanzapine had a statistically significantly greater decrease in PANSS score compared to people on quetiapine as well as statistically significantly lower relapse and withdrawal rates. Olanzapine showed statistically significantly greater weight gain and more overall side effects including movement disorders and glucose elevation, however quetiapine was associated with more QTc prolongation events.

1 systematic review (Bai, 2007) including 60 studies (n=6418) evaluated paliperidone in comparison to aripiprazole, showing that there were fewer withdrawals in people taking paliperidone.

2 systematic reviews (Bai, 2017 and Asmal, 2013) including 60 and 11 studies (n=6,418; 1,486), evaluated paliperidone in comparison to quetiapine, showing that paliperidone was more effective than quetiapine as measured on the PANSS, and resulted in statistically significantly fewer withdrawals. Fewer movement disorders, less prolactin increase but greater cholesterol increase was found in people taking quetiapine.

A systematic review (Mothi, 2013) including 26 studies evaluated pimozide in comparison to other antipsychotics, showing there was no difference in relapse rates or in side effect profiles in people in either treatment group.

2 systematic reviews (Asmal, 2013 and Komossa, 2011) including 50 and 45 studies (n=1,486; 7,760) evaluated quetiapine compared to risperidone, showing that risperidone is statistically significantly more effective than quetiapine as measured on the PANSS. There were fewer movement disorders and overall less prolactin increase in people taking quetiapine but cholesterol level and weight gain increases were larger.

A systematic review (Suttajit, 2013) including 42 studies, (n=7,217) evaluated quetiapine compared to typical antipsychotics, showing quetiapine to be more effective for the reduction of negative symptoms but there was no difference between treatment groups in other psychiatric symptoms. There were fewer withdrawals in quetiapine groups, and quetiapine caused statistically significantly fewer adverse effects than typical antipsychotics.

A systematic review (Tardy, 2014 (a)) including 7 studies (n=422) compared trifluoperazine with low potency antipsychotics, finding no difference in psychiatric symptoms or withdrawal rates, but an increase in the frequency of at least 1 movement disorder, incoordination and rigor in people who were taking trifluoperazine.

A systematic review (Kumar, 2009) including 18 studies (n=1,578) evaluating the effect of zuclopenthixol dihydrochloride, found a statistically significant decrease in the risk of being unchanged or worse in people taking zuclopenthixol dihydrochloride compared to other antipsychotics, but increased risk of side effects.

A systematic review (Cai, 2015) including 50 studies, evaluated paliperidone extended release tablets in comparison to other antipsychotics, showing a statistically significantly higher response rate in people taking paliperidone, as well as statistically significantly fewer withdrawals, and fewer adverse events.

An RCT (Canuso, 2010 (a)) (n=316) evaluated different doses of paliperidone palmitate for relapse prevention. There was an indication that a higher dose (12 mg/d) was more

effective for improving outcomes than a lower dose (6 mg/d), with the former showing a statistically significant improvement in PANSS score but the later showing a non-statistically significant improvement.

18 studies (Adams, 2014; Alvarez, 2012; Asenjo, 2010; Asmal, 2013; Bai, 2017; Chattopadhyay, 2016; Fenton, 2009; Haig, 2016; Khanna, 2014; Kishi, 2013 (c); Komossa, 2010; Komossa, 2009; Komossa, 2011; Krzystanek, 2011; Leucht, 2014 (a); Matar, 2013 Schoemaker, 2010 and Subramanian, 2010) were identified that evaluated a total of 14 drugs which are not licenced for any indication in the UK at this time.

Inadequate response to treatment

A network meta-analysis (Samara, 2016) including 40 studies, evaluated antipsychotics for treatment resistant schizophrenia. For reducing overall symptoms of schizophrenia, olanzapine was statistically significantly more effective than quetiapine and haloperidol; clozapine was statistically significantly more effective than haloperidol.

A systematic review (Essali, 2009) including 52 studies (n=4,746), evaluated the efficacy of clozapine in comparison to typical antipsychotics, showing there were statistically significantly more clinical improvements measured on the BPRS in people taking clozapine, as well as significantly fewer relapses. While there were fewer motor adverse effects on clozapine, there was a greater number of blood problems, drowsiness and hypersalivation.

2 studies (Sacchetti, 2009 and Miyaoka, 2015) were identified which evaluated 2 drugs which are not currently licenced for any indication in the UK.

Augmentation of clozapine treatment with another antipsychotic

An RCT (Weiner, 2010) (n=69) evaluated augmentation of clozapine with risperidone, showing no difference in BRPS positive or total symptom score in intention to treat analysis, but improvement in completer only analysis. A positive effect was seen in the treatment of negative symptoms.

A systematic review (Srisurapanont, 2015) including 4 studies (n= 347), evaluated clozapine augmentation with aripiprazole. Compared to placebo, withdrawal rates were no different, and there were non-statistically significant improvements on overall psychotic, positive and negative symptom scores. Aripiprazole showed no change in fasting plasma glucose, triglyceride or high-density lipoprotein levels but showed statistically significant decreases in weight change and LDL-cholesterol, as well as an association with agitation.

Augmentation of clozapine treatment with another non-antipsychotic medication

A systematic review (Tiihonen, 2009) including 5 studies (n=161), evaluated lamotrigine augmentation with clozapine treatment, showing lamotrigine treatment to be statistically significantly more effective than placebo for improving total symptoms of psychosis and PANSS score.

Depot/long acting injections for promotion of recovery and on-going care

6 systematic reviews (Leucht, 2012 (b); Leucht, 2011; Lafeuille, 2014; Kishimoto, 2013; Maayan, 2015 and Sampson, 2016) including 65, 10, 58, 25; 73 and 12 studies (n= 6,493; 1700; 23,516; 5940; 4870; 5723), evaluated the efficacy of antipsychotic long acting injections in comparison to oral medication. 4 studies indicated a statistically significant reduction in relapse rate in people on long acting injectable medication in comparison to those on oral medication; there were also fewer withdrawals in groups given long acting injectables. However 1 study indicated that nervous system disorders were more common on long acting injectable treatment and 2 studies indicated that there was no difference between long acting injectables and oral medication in terms of mental state or relapse rates. The efficacy of long acting injectables over oral medication is supported by another RCT (Alphs, 2015) (n=444), which showed once monthly paliperidone palmitate long-acting injectable antipsychotic to be significantly more effective at delaying time to relapse than oral antipsychotics.

This evidence is contradicted by 3 systematic reviews (Ciudad, 2013; Oya, 2015; Dinesh, 2009) including 2, 4 and an unreported number of studies respectively (n=252; 1,860; unreported) which compare long acting injectable antipsychotics to oral antipsychotics. No difference in mental state, relapse rates or withdrawal rates were shown when comparing olanzapine long acting injections to oral olanzapine, aripiprazole long acting injections to oral aripiprazole or pipotiazine palmitate to oral antipsychotics. This supports a published

NICE evidence summary on aripiprazole long acting injection which indicates non-inferiority of long acting injectable aripiprazole in comparison to oral aripiprazole.

4 systematic reviews (Nussbaum, 2012; Maayan, 2015, Oya, 2016 and Sampson, 2016), including 5, 73, 7 and 12 studies (n=2,215; 4,870; 206; 5,723) and 5 RCTs (Silwa, 2011; Fu, 2015; Bossie, 2011; Lauriello, 2008; Kane, 2012) (n=216; 334; 652; unreported; 403) evaluated the effect of long acting injectable antipsychotic medication. Fluphenazine decanoate, olanzapine, risperidone, paliperidone palmitate and aripiprazole, all in long acting injectable forms, were compared to placebo, with fluphenazine decanoate, paliperidone palmitate and aripiprazole being associated with a statistically significant decrease in relapse rates for people in remission. Olanzapine, paliperidone palmitate and aripiprazole showed a statistically significant improvement in mental state, whilst fluphenazine decanoate showed no difference. Aripiprazole was also associated with more incidences of insomnia, tremor and headache. Risperidone was associated with fewer adverse events than placebo, while paliperidone palmitate was associated with fewer reports of agitation, aggression or use of anxiolytic medication but a significant rise in prolactin levels and weight increase. Paliperidone palmitate treatment was also associated with headaches, nasopharyngitis, tremor, akathisia and sedation.

An RCT (McEvoy, 2014) (n=311) evaluated long acting injectable paliperidone palmitate in comparison to long acting injectable haloperidol decanoate, finding no difference in the rates of hospitalisation between the groups. Haloperidol decanoate was statistically significantly associated with larger increases in akathisia whereas paliperidone palmitate was statistically significantly associated with more weight gain and more incidences of prolactin level increase.

A systematic review (Dinesh, 2009 (study number unreported) evaluated pipotiazine palmitate in comparison to other long-acting antipsychotics, showing no differences in relapse rates or mental state.

2 systematic reviews (Sampson, 2016; Nussbaum, 2012) including 12 and 5 studies (n=5,723; 2,215) and an RCT (Pandina, 2011) (n=1,220) evaluated risperidone long acting injectable treatment in comparison to paliperidone palmitate long acting injectable treatment. No difference in PANSS score was shown between groups, but risperidone treatment was associated with more extrapyramidal side effects. No statistically significant difference was shown in weight gain, prolactin or glucose related adverse events or deaths, although 5 people within a paliperidone palmitate group died compared to 1 death in the risperidone group. People on paliperidone palmitate treatment were less likely to require anticholinergic medication.

7 studies (Purgato, 2012; Nasser, 2016; Meltzer, 2015; Maayan, 2015; Bisol, 2008; Kishi, 2014 (a) and Abhjinhan, 2009) were identified which evaluated a total of 6 long acting antipsychotics which are not currently licensed for use in the UK for any indication.

Depot/long acting injections for acute exacerbations

An RCT (Fleischhaker, 2012) (n=749) evaluated risperidone long acting antipsychotic in comparison to paliperidone palmitate long acting antipsychotic in people with acute exacerbation of schizophrenia, finding no statistically significant difference in PANSS score between groups.

An RCT evaluating aripiprazole long acting injection, in comparison to placebo in people with recent acute exacerbation of schizophrenia, indicated a decrease in PANSS score over 12 weeks of treatment.

Depot treatment preference for unresponsive treatment

No evidence was identified specifically for depot/long acting injectable treatment for people who have not responded to treatment.

Depot/long acting injection treatment preference for people with acute exacerbation or early psychosis

An RCT (Kane, 2014) (n=340) including people with acute exacerbation of schizophrenia, evaluated treatment with aripiprazole long acting injection in comparison to placebo. Aripiprazole treatment was associated with weight gain and akathisia, but also associated with a significant improvement in mental state, measured by the PANSS and the Clinical Global Impression scale.

An RCT (Lauriello, 2008) (n unreported) evaluated olanzapine long acting injectable treatment in comparison to placebo for the treatment of acute exacerbation of schizophrenia. A statistically significant

improvement in PANSS score and weight gain was shown in people taking olanzapine.

Topic expert feedback

Topic experts suggested that this area of the guideline would benefit from being updated. This is due in part to a vulnerability to olanzapine-induced weight gain. Topic experts suggested that olanzapine appears to cause relatively more weight gain than other antipsychotics, with the exception of clozapine. It was also highlighted that treatment naïve individuals are a group that are most likely to reflect the true obesogenic impact of antipsychotics. Furthermore, topic experts felt there are potential issues regarding the safety of clozapine and physical health risks.

It was also suggested that there has been progress in the area of long-term antipsychotic treatment compared to discontinuation, and that this could benefit from a review.

Topic experts also highlighted that there are new depots available which have not been considered in the guideline, and that this may have impact on recommendations suggesting that an initial small test dose is administered before starting treatment. However, feedback indicated that there is unlikely to be strong enough evidence to change the recommendation on choice of drug through shared decision making.

However, the topic experts suggested that the cost of drugs and services are likely to have changed which may have an impact on recommendations.

Impact statement

First episode or early psychosis

New evidence was identified which evaluated pharmacological treatment for first or early episodes of schizophrenia or psychosis. Overall, the new body of evidence suggests that there is no difference in efficacy between typical and atypical antipsychotics in this specific population. This supports the evidence which was the basis for the current recommendation (1.3.5.1), which suggests that antipsychotic medication choice should be made by the service user and healthcare professional together. Further evidence was identified which compared a number of antipsychotics, finding little difference between atypical antipsychotics for symptom reduction, varying side effects amongst different treatments, and a lack of superiority of treatment with haloperidol. However, this evidence comes from studies with low participant numbers and deemed as low quality by the study authors, and therefore is unlikely to have an impact on the current recommendations for a collaborative approach to medication choice.

Evidence was identified suggesting differences in side effect prevalence between antipsychotics, specifically weight gain on olanzapine, which was also shown in studies which included populations in other stages of illness. As well as this, topic experts highlighted that there was an association between olanzapine and weight gain. Evidence relating to olanzapine related weight gain is covered by the current recommendations which specify that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account side effects such as weight gain (1.3.5.1). Specifically for the treatment of first episode psychosis, evidence on the association between olanzapine and weight gain does not show any long term effects. Evidence identified evaluating other side effects in this specific population, is limited to one study comparing 2 drugs.

First episode or early psychosis - summary of impact

The combination of limited topic expert feedback in this area, mixed evidence across a range of antipsychotic treatments and a single study which demonstrates any long term effects in people taking a specific antipsychotic, indicates that there is unlikely to be any impact of new evidence on the current recommendations.

Acute exacerbations

New evidence was identified which compared antipsychotic treatment to placebo for acute exacerbations of schizophrenia or psychosis. This supports the current recommendation (1.4.3.1) suggesting that people with acute exacerbations of psychosis or schizophrenia should be offered antipsychotic medication or have a review of existing medication. Evidence was identified which suggested that a lower dose of an antipsychotic did not result in loss of efficacy. This supports the current recommendation (1.3.6.3) that the lower dose range of antipsychotics should be used during the initiation of treatment.

Evidence was identified regarding rapid tranquilisation. Currently, recommendations on

regarding tranquilisation (1.4.5.2) refer to other NICE guidance on violence (NG10). The evidence identified therefore is unlikely to have an impact on CG178 directly, but may have an impact on NG10. This will be recorded and reviewed at the next surveillance review of NG10.

Acute exacerbation – summary of impact

The evidence identified supports current recommendations, and therefore it is not anticipated that there would be an impact at this time.

Promotion of recovery and ongoing care

In the main, the evidence which was identified for pharmacological treatment for the promotion of recovery and ongoing care, supports the current recommendations that during continuing treatment and care in early intervention services or community based teams, pharmacological interventions should be offered (1.5.1.1). This is because the evidence in this area comparing antipsychotics to placebo, showed that use of antipsychotics was associated with reduced relapse rates. While there was evidence that antipsychotics are associated with more side effect prevalence, this is a factor that was previously considered during guideline development when the decision to recommend antipsychotics was made. This evidence is therefore unlikely to have an impact on the current recommendations to offer pharmacological interventions for this population. Evidence that antipsychotics are associated with side effects, as well as mixed evidence on the efficacy of individual antipsychotics, indicates that there is no impact of the newly identified evidence on the current recommendations, which suggest that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account side effects (1.5.5.1 in reference to 1.3.5.1).

Topic expert feedback did suggest that there may be a benefit to discontinuing antipsychotic medication for some people. However, only limited primary evidence was identified in this area, which is not anticipated to have an impact on the guideline, especially considering the number of studies identified which indicate that antipsychotics are more effective than placebo for preventing relapse.

Promotion of recovery and ongoing care – summary of impact

The evidence in this area indicates that the use of antipsychotic medication for the promotion of recovery and in ongoing care is effective for the prevention of relapse. This is complementary to the current recommendations and therefore there is unlikely to be any impact of newly identified evidence in this area.

Unspecified stage of psychosis or schizophrenia

The majority of new evidence identified showed that antipsychotic medication is effective for the treatment of schizophrenia and psychosis in comparison to placebo treatment. There was also some evidence which did not show an effect in a variety of outcomes, although no studies reported superiority of placebo treatment over antipsychotics. This supports the current recommendations to offer antipsychotic medication to people with schizophrenia and psychosis, which does not alter depending on the stage of illness (recommendations 1.3.4.1, 1.4.2.1 and 1.5.1.1).

A large body of evidence was identified which compared antipsychotics to each other for people with schizophrenia or psychosis. However, there was only a limited amount of evidence for each individual comparison made, especially when also trying to compare similar outcomes across studies. Where there were similar comparisons made across different studies, results were inconsistent. Topic expert feedback did not suggest a specific drug which could be more advantageous over another in practice, consistent with the lack of evidence showing efficacy in a single direction identified during this surveillance review.

There was consistency however in olanzapine treatment outcomes, which indicated there was an association with increased weight gain. However, interventions to promote physical health, including weight management, are included in CG178 (1.1.3.1, 1.1.3.2, 1.1.3.6, and 1.5.3.1-1.5.3.5). As well as this, current recommendations suggest that the choice of antipsychotic should be made by the service user and healthcare professional together, with consideration of side effects including weight gain (1.3.5.1, 1.4.2.1, 1.4.3.1, 1.5.5.1).

Unspecified stage of psychosis or schizophrenia – summary of impact

Due to the number of drugs compared, the number of outcomes reported and the lack of consistency across most studies, it cannot be

concluded from the identified evidence that a particular drug is more or less effective than any other. If added to the body of evidence evaluated during the development of CG178, it is unlikely that there would be any impact on the current recommendations which suggest that service users and healthcare professionals should make antipsychotic choices together, including consideration of any benefits and side effects (1.3.5.1, 1.4.3.1 and 1.5.5.1).

Inadequate response to treatment

The evidence identified for treatment of schizophrenia that has shown an inadequate response to treatment is limited. However, a systematic review was identified which indicated superiority of clozapine treatment compared to typical antipsychotics, which support the current recommendation to offer clozapine (1.5.7.2). A network meta-analysis compared a variety of antipsychotics for this specific population, indicating clozapine or olanzapine were the most effective antipsychotics of those evaluated. No comparison of olanzapine and clozapine was reported, and therefore it cannot be concluded whether one of these drugs is more effective than the other. Topic expert feedback highlighted that there may be safety issues regarding clozapine use. However, no evidence has been identified regarding these issues and feedback in this area was limited.

Inadequate response to treatment – summary of impact

Overall, the evidence identified here is supportive of the current recommendations and despite safety concerns, no evidence has been identified to substantiate this. Therefore it is not anticipated that there would be any impact at this time.

Augmentation of clozapine

The evidence identified regarding augmentation of clozapine with another antipsychotics, indicated there was no difference in symptom severity with risperidone augmentation, however this is based on a study with a small sample size. Aripiprazole augmentation to clozapine also showed no difference in effect compared to placebo, as reported by a systematic review of 4 studies. This evidence goes someway to contradict current recommendations (1.5.7.3), which suggests offering augmentation of clozapine with other antipsychotics to people with schizophrenia whose illness has not responded adequately to clozapine treatment. However, the evidence identified during this surveillance review is limited to 2 studies of different drugs, and it is not clear if populations relevant to the specific population described in this recommendation (1.5.7.3) has been evaluated by these studies.

Augmentation of clozapine – summary of impact

Overall, the limited amount of evidence identified is not anticipated to have an impact on the current recommendations, which are specific to a particular population not necessarily included in the evidence identified during this surveillance review.

Long acting injectable antipsychotics

Overall, the body of evidence that has been newly identified indicates that long acting injectable antipsychotics are effective for treatment of schizophrenia or psychosis in comparison to placebo. This supports the current recommendation which suggests offering this treatment to people who would prefer it after an acute episode or where non-adherence is likely (1.5.5.3). However, evidence comparing either long acting injectables to oral antipsychotics or to other long acting injectables is contradictory across studies, indicating varying efficacy of each type of preparation. This evidence helps support the recommendation suggesting that service user preferences, organisational procedure, and the side effects and the benefits of each drug should be considered before the choice of medication is made (as opposed to a recommendation for a specific drug). Currently, long acting injectable antipsychotic treatment is recommended only for people with schizophrenia who are in recovery (1.5.5.3). In this surveillance review, evidence has been identified which indicates an improvement in symptom severity in people with acute exacerbation of symptoms who have been treated with long acting antipsychotic injections. However, there was no evidence identified comparing long acting injectables to oral antipsychotic medication, and so it cannot be determined if this evidence would have any effect on the current recommendations to offer oral antipsychotic medication for an acute episode (1.4.2.1).

While there was topic expert feedback that suggested newer, second generation long acting injectable antipsychotics would not require an initial test dose currently

recommended (1.5.6.1), no primary evidence to support this was identified. Further topic expert opinion also suggested that shared decision making is likely to still be the best approach to choosing long acting injectables.

Long acting injectables – summary of impact

New evidence identified is unlikely to have an impact on the current recommendations as there is no consistent evidence indicating that a particular drug over another is more advantageous, and there is mixed evidence regarding the efficacy of long acting injectables over oral antipsychotics.

New evidence is unlikely to change guideline recommendations.

NQ – 01 For people with schizophrenia or psychosis, what are the benefits and harms of non-antipsychotic pharmacological intervention alone?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

A systematic review (Dold, 2012) including 14 studies evaluated the efficacy of benzodiazepine compared to antipsychotics, for people with schizophrenia or psychosis not responding adequately to monotherapy, showing no difference in psychiatric symptoms but an increased likelihood of desired sedation on benzodiazepine. When comparing benzodiazepine treatment to placebo, no difference in psychiatric symptoms between groups was shown.

A systematic review (Leucht, 2014 (b)) including 10 studies (n=283) evaluated the efficacy of carbamazepine compared to antipsychotics, showing no difference in psychiatric symptoms between groups.

An RCT (Wonodi, 2011) (n=20) evaluated the efficacy of dipyridamole in comparison to olanzapine, showing no significant difference in BRPS scores in people on either treatment.

A systematic review (Leucht, 2015) including 22 studies (n=763) evaluated treatment with lithium compared to treatment with antipsychotics, showing that statistically significantly more people on lithium withdrew from the study.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence identified comparing non-antipsychotic drugs to antipsychotic drugs or to placebo treatment did not show any difference in effect of symptom severity. It is unlikely that the evidence identified in relation to this question would have impact on the current recommendation to offer antipsychotics (1.3.4.1), as there is a large body of evidence showing a positive effect of antipsychotic medication which was considered during the development of CG178.

New evidence is unlikely to impact on the guideline.

NQ – 02 What are the benefits and harms of different drug techniques, including suspension of antipsychotic medication, in people with schizophrenia or psychosis?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

A systematic review (Sampson, 2013) including 17 studies evaluated the effects of different intermittent drug techniques compared with maintenance treatment, showing a statistically significant increase in relapse rates in people receiving any intermittent drug treatment in the long term, however, intermittent treatment was shown to be more effective than placebo.

An RCT (Wunderink, 2013) (n=103) evaluated the effectiveness of a dose reduction/discontinuation treatment for 18 months minimum, in comparison to maintenance treatment in people with remitted first-episode psychosis. After 7 years of follow-up, a statistically significant increase in recovery rate was shown in the dose reduction/discontinuation treatment group.

An RCT (Chen, 2010) (n=178) evaluated antipsychotic discontinuation in people with first episode psychosis who had received at least 1 year of antipsychotic treatment, compared to quetiapine maintenance treatment. Rates of relapse were statistically significantly greater in the discontinuation group.

Topic expert feedback

Topic expert feedback indicated that there may be value in some patients (particularly those with first episode psychosis), undergoing medication discontinuation. Evidence regarding this was highlighted (Wunderink, 2013) and included in the evidence summary above.

Impact statement

The majority of new evidence identified supports the current recommendations which advise to not use targeted, intermittent dosage maintenance strategies unless the user is unwilling to accept a continuous maintenance regimen or there is another contraindication to maintenance therapy (1.5.5.2). There is some inconsistency in the newly identified evidence, including a suggestion from topic expert feedback that discontinuation could benefit some patients. Despite this inconsistency, in the main, the newly identified evidence supports the current recommendations, especially as the current recommendations suggest considering intermittent dosage strategies in some cases. Therefore it is unlikely that new evidence would have an impact on CG178.

New evidence is unlikely to impact on the guideline.

Vocational rehabilitation

Q – 30 For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of vocational rehabilitation interventions compared with treatment as usual or another interventions?

Recommendations derived from these review questions

First episode psychosis – assessment and care planning

1.3.3.5 For people who are unable to attend mainstream education, training or work, facilitate alternative educational or occupational activities according to their individual needs and capacity to engage with such activities, with an ultimate goal of returning to mainstream education, training or employment.

Promoting recovery and possible future care – employment, education and occupational activities

1.5.8.1 Offer supported employment programmes to people with psychosis or schizophrenia who wish to find or return to work. Consider other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment.

1.5.8.2 Mental health services should work in partnership with local stakeholders, including those representing black, Asian and minority ethnic groups, to enable people with mental health problems, including psychosis or schizophrenia, to stay in work or education and to access new employment (including self-employment), volunteering and educational opportunities.

1.5.8.3 Routinely record the daytime activities of people with psychosis or schizophrenia in their care plans, including occupational outcomes.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

An RCT (Craig, 2014) (n=134) including outcomes from participants with early psychosis, evaluated the effect of a motivational interviewing intervention directed at clinical staff to address ambivalence about employment. Both groups of participants received individual support for return to work, but significantly more participants in intervention groups achieved employment at 12 months.

An RCT (Smith, 2015) (n=32) evaluated the use of virtual reality job interview training. Those in the intervention group were significantly more likely to receive a job offer over a 6 month period and more training was associated with fewer weeks until receiving an offer.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

New evidence was identified which adds further intervention strategies for the promotion of vocational rehabilitation to the current body of evidence. Of the two new interventions for which evidence has been identified, one in particular - virtual reality job training - is based on a single study of small sample size which is unlikely to provide sufficient evidence of effect for the purposes of updating this guideline.

The second intervention identified - motivational interviewing for clinicians – identifies a team level intervention that targets vocational rehabilitation. This evidence is complementary to the current recommendation (1.5.8.1) which encourages employees to offer supported employment programmes, although it does add an additional form of intervention not currently evaluated.

There was no topic expert feedback relevant to this section of the guideline, and this, in

conjunction with evaluation of the small body of evidence identified through the systematic search, leads to the conclusion that there is currently no likely impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered in the guideline

NQ – 03 For people with schizophrenia or psychosis, what are the benefits and harms of electroconvulsive therapy?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

An RCT was identified (Phutane, 2013) that evaluated electrode placement in electroconvulsive therapy (ECT). However, ECT for treatment of schizophrenia is covered by the published technology appraisal 'Guidance on the use of electroconvulsive therapy'.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence identified which relates to this question is covered by a technology appraisal.

New evidence is unlikely to impact on the guideline.

NQ – 04 For people with schizophrenia or psychosis, what are the benefits and harms of pharmacological treatment for the promotion of physical health, especially for areas affected by the use of antipsychotic medication?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

A systematic review (Mizuno, 2014) including 40 studies evaluated medication to counteract antipsychotic induced metabolic adversities. A statistically significant difference in body weight was found when comparing metformin treatment to placebo.

2 RCTs (Carrizo, 2009; Jarskog, 2013) (n=116; 116) evaluated the effect on metabolic profile of antidiabetic metformin in people with schizophrenia who are on antipsychotics. A statistically significant improvement in metabolic control was demonstrated in those on metformin compared to placebo.

An RCT (Dickerson, 2014) (n=65) evaluated the effect of probiotic compounds on bowel function and schizophrenia symptom severity. There were no differences in mental symptoms shown, but people in the probiotic group were statistically significantly less likely to develop severe bowel difficulty.

An RCT (Modabbernia, 2014) (n=36) including people with first episode schizophrenia evaluated the effect of melatonin for the prevention of olanzapine-induced metabolic side-effects. Melatonin was associated with significantly less weight gain, less increase in waist circumference and less increase in triglyceride concentration. Changes in other metabolic measures were not significantly different from placebo. A statistically significant improvement in mental state score was demonstrated in the melatonin group.

A systematic review (Schmidt, 2012 (a)) including 4 studies, evaluated pharmacological treatment for sexual dysfunction in males. Treatment with sildenafil (n=32) was effective for improved sexual function as was switching from risperidone to olanzapine (n=54); no evidence of effectiveness of selegiline (n=10) or switching from risperidone to quetiapine (n=36) on improving sexual function was found.

An RCT (Tek, 2014) was identified which evaluated a drug not currently licensed for any indication in the UK.

Topic expert feedback

Topic experts indicated that the British Association for Psychopharmacology guidelines include some recommendations about the use of adjunctive metformin as a way to reduce antipsychotic-induced weight gain.

Impact statement

A systematic review and an RCT showed positive effects in physical health outcomes in people treated with metformin who were on antipsychotic medication. Other non-antipsychotic medication was also shown to have effects on physical health, including positive outcomes for weight, insomnia and sexual dysfunction. Topic expert feedback specifically highlighted the potential for metformin to mitigate antipsychotic weight gain. Recommendation 1.1.3.2 refers to NICE public health guideline 38, which provides recommendations for people who are at high risk of type 2 diabetes. PH38 recommends the use of metformin in combination with lifestyle change, therefore, it is considered that the current recommendations, which refer to PH38 are not impacted by the new evidence identified. Other studies identified in the area of non-antipsychotic pharmacological treatment do not report consistently on the same intervention and are all small studies. Therefore, it is not anticipated that new evidence will have an impact on the guideline.

New evidence is unlikely to change guideline recommendations.

NQ – 05 For people with schizophrenia or psychosis, what are the benefits and harms of transcranial stimulation?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

3 RCTs and 2 systematic reviews evaluated the effect of transcranial stimulation for the treatment of schizophrenia. With transcranial direct-current simulation (Brunelin, 2012; Orlov, 2017) (n=30; 49), a statistically significant improvement in the occurrence of auditory verbal hallucinations, positive and negative symptoms and working memory was observed. Temporoparietal transcranial magnetic stimulation (TMS) was compared to sham in 1 systematic review (41 studies, n=1,473) (Dougall, 2015), showing a statistically significant improvement in global mental state and positive symptoms, but a statistically significant increase in the number of headaches. When compared to treatment as usual, there was no difference found for improvement in global state. A second systematic review (Zhang, 2013) including 17 studies (n=398) identified temporoparietal TMS as being significantly effective for treatment of hallucinations, but no significant differences for positive or negative symptoms were shown. Prefrontal theta burst stimulation TMS compared to sham TMS showed a significant decrease of score on the PANSS. Prefrontal TMS showed no differences compared to sham, apart from significantly more headaches. Wobrock, 2015 (n=157) also evaluated prefrontal TMS compared to sham and showed no statistically significant difference in improvement of negative symptoms, depression or cognitive function but a small, statistically significant improvement in positive symptoms was shown.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence evaluating a range of types of TMS were identified, indicating a mixed efficacy depending on the specific type. Temporoparietal TMS showed positive effects in some outcomes, but not in others and also showed a mix of efficacy amongst studies. Overall, there is limited evidence reporting on the same intervention and outcomes across studies, indicating that there is unlikely to be an impact on CG178 at this time.

New evidence is unlikely to impact on the guideline.

NQ – 06 What changes to the environment of people with schizophrenia or psychosis can be made to improve symptoms?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

A systematic review (Chamberlain, 2013) including 1 study (n=52) compared nidotherapy (a therapeutic method aiming to modify the environment) with standard care or no treatment for people with schizophrenia. There was no significant difference found in social functioning, or medium term engagement with non-inpatient services although a significant improvement in engagement was found in the short term.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Limited evidence from a single study did not show an effect of environmental changes for the treatment of schizophrenia. It is unlikely that this new evidence would have an impact on current recommendations, which do not consider environmental changes for treatment.

New evidence is unlikely to impact on the guideline.

NQ – 07 What are the benefits and harms of acupuncture as a treatment for schizophrenia or psychosis?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

2 systematic reviews (Lee, 2009; Shen, 2014) including 13 and 30 studies and an RCT (Jing, 2009) (n=60) evaluated the effectiveness of acupuncture as a treatment for schizophrenia. In comparison to antipsychotic medication alone, addition of acupuncture to antipsychotic medication had a significant improvement on decreasing the number of people who were 'not improved', reducing the number of days in hospital, reducing adverse effects, increasing response rate and decreasing relapse; incidences of extrapyramidal symptoms were also significantly lower. Acupuncture alone compared to antipsychotic drugs showed mixed results across studies with reports of no difference in the number of people who were 'not improved' but significantly better response rate with acupuncture. Compared to sham plus drug therapy, participants receiving electroacupuncture plus drug therapy showed improved mental state scores, including positive symptom and hallucination scores and significantly greater response rates.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Evidence from 3 studies indicates that acupuncture is an effective treatment alongside antipsychotic medication for the treatment of schizophrenia or psychosis. However, the majority of the RCTs identified and studies included in the systematic reviews are not applicable to UK practice as they were performed in China. As there are currently no recommendations in CG178 in this area, and there was no topic expert feedback highlighting this issue, it is not anticipated that there would be an impact of this evidence at this time.

New evidence is unlikely to impact on the guideline.

NQ – 08 For people with schizophrenia or psychosis, does the augmentation of antipsychotic drugs with other pharmacological or dietary supplement interventions improve outcomes?

This review question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision

This review question should not be added.

4-year surveillance summary

Dietary supplements

An RCT (Bentsen, 2013) (n=99) evaluated the efficacy of adding omega-3 fatty acids and/or vitamins E+C to antipsychotic treatment in people with schizophrenia or psychosis. This showed that, in people with low baseline levels of polyunsaturated fatty acids, the addition of omega-3 or vitamins E+C to antipsychotic medication was associated with an increase in psychotic symptoms. However, in combination, omega-3 and vitamins E+C both added to antipsychotics had no effect on psychotic symptoms. In contradiction to this, another RCT (Pawełczyk, 2016) (n=71) evaluated omega-3 fatty acid treatment over 6 months as add-on treatment to usual care in people with first episode psychosis, and found a significant difference in total PANSS score change, in the number of people with a 50% improvement in symptom severity, in general psychopathology and in depressive symptoms, favouring omega-3 fatty acids.

A systematic review (Magalhães, 2016) including 22 studies evaluated the effect of antioxidants as adjunction treatment to standard antipsychotics. A statistically significant improvement in PANSS and BPRS scores was shown, but no difference in withdrawal rates or general functioning was shown.

Adjunctive medication to usual care for treatment of persistent symptoms

2 RCTs (Kulkarni, 2015; Kulkarni, 2017) (n=183; 56) evaluated drugs that target oestrogen - raloxifene hydrochloride and transdermal estradiol – as adjunctive treatment to antipsychotics in females with persistent schizophrenic symptoms, showing a reduction in the total PANSS score relative to placebo with both drugs. Raloxifene hydrochloride also showed an increased probability of a clinical response, but no significant difference in PANSS positive score, mood, cognition, reproductive hormone levels or adverse events.

An RCT (Dickerson, 2009) (n=59) evaluated allopurinol, adjunctive to other pharmacotherapy, for people with persistent schizophrenic symptoms, showing an improvement in the number of people with a significant decrease in symptoms compared to placebo.

An RCT (Joffe, 2009) (n=39) and a systematic review (Vidal, 2015; including 5 studies) evaluated the efficacy of adjunctive mirtazapine in people with insufficient antipsychotic response, showing mirtazapine to be statistically significantly more effective than add-on placebo at improving PANSS total, positive and negative scores.

Adjunctive psychoactive medication to usual care for treatment across stages of illness

A positive effect was shown for treatment of schizophrenia or psychosis with additional psychoactive drugs, in conjunction with usual care, across a number of studies. 2 systematic reviews (Singh, 2012 and Zheng, 2016), including 2 and 12 studies, and evaluated the effect of acetylcholinesterase inhibitors in conjunction with antipsychotics for schizophrenia treatment, both showing a statistically significant improvement in mental

state, cognition and tolerability compared to adjunctive placebo.

A systematic review (Correll, 2016) including 8 studies, evaluated topiramate augmentation with antipsychotic treatment, showing treatment to be significantly more effective than placebo for decreasing overall psychopathology. There was also a statistically significant decrease in positive and negative symptom scores, as well as significant decrease in weight and body mass index with treatment. Topiramate was similar to control with respect to withdrawal rates and adverse events, but associated with higher incidence of paresthesia. A systematic review (Okuyama, 2016) including 12 studies supports this evidence for efficacy of topiramate augmentation with antipsychotics.

An RCT (Meltzer, 2012) (n=423) evaluated the addition of pimavanserin to treatment with risperidone in people with a recent exacerbation of psychosis. For people on low dose risperidone (2 mg), add-on pimavanserin compared to add-on placebo, showed a statistically significant improvement in PANSS total score. However, no difference in PANSS scores were found when comparing people on high dose risperidone (6 mg) with add-on placebo, compared to low dose risperidone with add-on pimavanserin. The percentage of people with >20% improvement at day 15 on risperidone plus add-on pimavanserin was statistically significantly higher than those on high or low dose risperidone plus add-on placebo.

A systematic review (Kishi, 2013 (b)), including 7 studies, evaluated adjunctive fluvoxamine to antipsychotic treatment, showing a statistically significant positive effect for add-on therapy on overall and negative symptoms, with no effect on the other symptoms investigated. Fluvoxamine was more effective for negative symptoms in those taking first generation antipsychotics.

Mixed efficacy was shown for a variety of psychoactive drugs which were used in treatment as add on therapy to usual care in people with schizophrenia or psychosis. Evaluation of modafinil and armodafinil showed a significant reduction in negative psychopathology symptoms, but not in positive symptoms or absolute advantage (Andrade, 2015; systematic review including 8 studies). A systematic review including 8 studies, evaluating adjunctive carbamazepine (Leucht, 2014 (b)), showed no difference in acceptability or mental state as measured by BPRS, but a statistically significant improvement in global state and the number of people experiencing movement disorders. Buspirone as adjunctive treatment to usual care in schizophrenia, showed more improvement in psychopathology than placebo add on treatment, but a non-statistically significant difference in positive and negative symptoms and withdrawal rates was indicated (Kishi, 2013 (d)). A systematic review (Galling, 2016) including 67 studies (n=4,861) compared antipsychotic co-treatment with monotherapy. No difference in tolerability was shown, but incidence of more than 1 adverse event was lower with co-treatment. Adjunctive D2-antagonists to other medication lead to significantly less nausea, insomnia but higher prolactin levels. Conversely, adjunctive D2-agonists lead to significantly lower electrocardiogram abnormalities, constipation, hypersalivation, prolactin and total and LDL-cholesterol. Another systematic review (Correll, 2009) included 19 studies and showed antipsychotic co-treatment with other medication to be significantly more effective at reducing treatment inefficacy and withdrawal rates.

Augmentation of usual care with valproate, noradrenaline reuptake inhibitors, benzodiazepines, citalopram or lithium showed no significant evidence of effect for improvement of mental state, or in other non-critical outcomes reported, across 6 studies (Wang, 2016; Kishi, 2013 (e); Gillies, 2013; Dold, 2013; Barnes, 2016 and Leucht, 2015).

Adjunctive non-psychoactive medication to usual care for treatment across stages of illness

4 systematic reviews (Sommer, 2014; Nitta, 2013; Garner, 2016 and Oya, 2016) (number of included studies=26; 8; 6 and 7) and 3 RCTs (Laan, 2010; Berk, 2008; Chaundhry, 2012) (n=unreported; 180; 144), evaluated augmentation of non-psychoactive pharmacological agents to antipsychotics for the treatment of psychosis or schizophrenia. 2 studies showed N-acetyl cysteine treatment adjunctive to usual care was associated with improvement in symptom severity compared to treatment alone. Evaluation of aspirin as an additional therapy to usual care, indicated an improvement in total and positive symptom PANSS scores but not on other PANSS

subscale scores, with effect significantly larger in those with a more altered immune function. 2 studies evaluated augmentation of usual care with non-steroidal anti-inflammatory drugs (NSAIDs) finding no significant effect compared to when placebo was added to usual care. No significant effect of adding antiglucocorticoid or minocycline treatment to usual care was shown in 1 study including people at an unspecified stage of illness; however, in a study including people specifically with early episode psychosis, minocycline had a statistically significant effect on decreasing PANSS scores. Compared to placebo, the addition of oxytocin to usual care was shown to be significantly more effective at decreasing PANSS general and negative score but there was no difference in total or positive symptom scores.

An RCT (Noroozian, 2013) was identified evaluating a drug which is not currently licensed for any indication in the UK.

Topic expert feedback

Topic expert feedback suggested that trials on oxytocin for social deficits in schizophrenia require NICE recommendations as this is a key area where deficits in treatment exist.

Impact statement

A large body of evidence was identified which evaluated the use of an additional medication or dietary supplement to treatment as usual; however, it was not possible to identify the particular population, in terms of stage of illness, in the majority of studies. While there is a significant volume of evidence in this area, most studies report different specific interventions. This means there is little corroborating evidence of effect across studies for particular interventions. Where similar interventions have been reported across studies, the result is not always consistent, for example, for treatment with omega-3. It is also unclear what the clinical relevance many of these interventions may be. A range of outcomes were reported across studies, the majority of which included some critical outcomes such as mental state, but there were also a number of outcomes reported which do not appear to be clinically relevant. Overall, while there is some supporting evidence for the addition of this area to CG178, there is little consistency in the studies identified and a lack of confidence that the interventions and outcomes reported are clinically relevant. Therefore, it is not anticipated that at this time, the evidence identified is likely to have impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Editorial and factual corrections identified during surveillance

During surveillance, editorial or factual corrections were identified.

- CG178 recommendation 1.5.3.4 cross refers to CG66 and CG87, which have both been replaced by NG28 since publication. CG178 will need an editorial correction to reflect this.
- CG178 recommendation 1.4.5.2 cross refers to CG25 which has been replaced by NG10 since publication. CG178 will need an editorial correction to reflect this.
- CG178 recommendations 1.1.3.2 and 1.5.3.3 cross refer to CG43 which has been partially replaced by NG7 since publication, affecting the recommendations relevant to this cross referral. CG178 will need an editorial correction to reflect this.
- CG178 recommendation 1.3.4.3 cross refers to CG38 which has been replaced by CG185 since publication. CG178 will need an editorial correction to reflect this.
- CG178 recommendations 1.1.3.2, 1.5.3.3 and 1.5.3.4 cross refer to CG67 which has been replaced by CG181 since publication. CG178 will need an editorial correction to reflect this.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 What is the clinical and cost effectiveness of peer support interventions in people with psychosis and schizophrenia?

Ongoing research relevant to the research recommendation was found.

Surveillance decision

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 02 What is the clinical and cost effectiveness of psychological intervention alone, compared with treatment as usual, in people with psychosis or schizophrenia who choose not to take antipsychotic medication?

No new evidence was identified which evaluated psychological intervention alone, although there is a large body of recent evidence around the effectiveness of psychological therapies generally.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

RR – 03 What are the short- and long-term benefits to physical health of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without major risks?

No new evidence evaluating the effects on physical health with different drug techniques were identified. Although evidence (NQ2) was identified on the effect on mental health, including in those with first episode psychosis, physical health was not an outcome reported.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 04 How can the benefits of early intervention in psychosis services be maintained once service users are discharged after 3 years?

Evidence was identified evaluating the effect of extended early intervention services, over a period of 5 years. However, there was no positive effect in critical outcomes reported (Albert, 2017).

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

RR – 05 What is the benefit of a CBT-based trauma reprocessing intervention on PTSD symptoms in people with psychosis and schizophrenia?

No new evidence was identified evaluating the effect of trauma reprocessing interventions using CBT specifically, but evidence was identified which evaluated the effect of psychological trauma reprocessing interventions, which showed a positive effect. However, evidence was insufficient to propose an update of this area.

Surveillance decision

The research recommendation will be retained because there is evidence of research activity in this area.

Other research recommendations

The following research recommendations were not deemed as priority areas for research by the guideline committee.

RR – 01 What are the benefits for service users and carers for family intervention combined with a carer-focused intervention compared with family intervention alone?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 For people with schizophrenia, RCTs of psychological and psychosocial interventions should be adequately powered to assess clinical and cost effectiveness in specific ethnic groups (or alternatively in ethnically diverse samples).

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 An adequately powered RCT should be conducted to investigate the clinical and cost effectiveness of CBT that has been culturally adapted for African–Caribbean people with schizophrenia where they are refusing or intolerant of medication.

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 Studies of ethnically specific and specialist services and new service designs should be appropriately powered to assess effectiveness. Studies should include sufficient numbers of specific ethnic groups and be evaluated using an agreed high quality evaluation framework (Moffat et al., 2009).

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 05 **For people with schizophrenia from black and minority ethnic groups living in the UK, does staff training in cultural competence at an individual level and at an organisational level (delivered as a learning and training process embedded in routine clinical care and service provision) improve the service user's experience of care and chance of recovery, and reduce staff burnout?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 06 **An adequately powered proof of principle study should be conducted to investigate the feasibility of comparing language skills development for those with English as a second language against using interpreters.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 **A study should be conducted to investigate engagement and loss to follow-up, prospective outcomes and care pathways, and the factors that hinder engagement. For example, ethnic, religious, language or racial identity matching may be important. This is not the same as ethnic matching, but matching on ability to work with diverse identities.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 08 **A study should be conducted to investigate the use of pre-identification services, including assessment, diagnosis and early engagement, across racial and ethnic groups.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 09 **An adequately powered RCT should be conducted to investigate the clinical and cost effectiveness of arts therapies compared with an active control (for example, sham music therapy) in people with schizophrenia.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 10 **An adequately powered RCT should be conducted to investigate the most appropriate duration and number of sessions for arts therapies in people with schizophrenia.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 11 **An adequately powered RCT should be conducted to investigate the most appropriate duration and number of sessions for CBT in people with schizophrenia.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 12 **An adequately powered RCT should be conducted to investigate CBT delivered by highly trained therapists and mental health professionals compared with brief training of therapists in people with schizophrenia.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 13 **Research is needed to identify the competencies required to deliver effective CBT to people with schizophrenia.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 14 **An adequately powered RCT with longer-term follow-up should be conducted to investigate the clinical and cost effectiveness of cognitive remediation compared with an appropriate control in people with schizophrenia.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although evidence was identified investigating the clinical effectiveness of cognitive remediation, these studies were considered to be unlikely to be adequately powered.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 15 **For people with schizophrenia from black and minority ethnic groups living in the UK, does ethnically adapted family intervention for schizophrenia (adapted in consultation with black and minority ethnic groups to better suit different cultural and ethnic needs) enable more people in black and minority ethnic groups to engage with this therapy, and show concomitant reductions in patient relapse rates and carer distress?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 16 **Research is needed to identify the competencies required to deliver effective family intervention to people with schizophrenia and their carers.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 17 **A pilot RCT should be conducted to assess the efficacy of contemporary forms of psychodynamic therapy when compared with standard care and other active psychological and psychosocial interventions.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 18 **More long-term, head-to-head RCTs of the efficacy and safety/tolerability and patient acceptability of the available antipsychotic drugs are required, in individuals in their first episode of schizophrenia, testing the risk- benefit of dosage at the lower end of the recommended dosage range.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 19 Large-scale, observational, survey-based studies, including qualitative components, of the experience of drug treatments for available antipsychotics should be undertaken. Studies should include data on service user satisfaction, side effects, preferences, provision of information and quality of life.

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Evidence regarding service user satisfaction, side effects and quality of life in people on different drug treatments was identified, however, these were quantitative, RCTs as opposed to qualitative observational studies.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 20 Quantitative and qualitative research is required to investigate the utility, acceptability and safety of available drugs for urgent sedation/control of acute behavioural disturbance (including benzodiazepines and antipsychotics), systematically manipulating dosage and frequency of drug administration.

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 21 Further work is required on the nature and severity of antipsychotic drug discontinuation phenomena, including the re-emergence of psychotic symptoms, and their relationship to different antipsychotic withdrawal strategies.

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 22 Direct comparisons between available oral antipsychotics are needed to establish their respective risk/long-term benefit, including effects upon relapse rates and persistent symptoms, and cost effectiveness. Trials should pay particular attention to the long-term benefits and risks of the drugs, including systematic assessment of side effects: metabolic effects

(including weight gain), EPS (including tardive dyskinesia), sexual dysfunction, lethargy and quality of life.

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although new evidence was identified, the available evidence was not considered to show consistent efficacy of any particular oral antipsychotic, and therefore is not considered to be sufficient to trigger an update of this area.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 23 Further RCT-based, long-term studies are needed to establish the clinical and cost effectiveness of available depot/long-acting injectable antipsychotic preparations to establish their relative safety, efficacy in terms of relapse prevention, side-effect profile and impact upon quality of life.

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although new evidence was identified, the available evidence was not considered to show consistent efficacy of any particular long acting injectable antipsychotic, and therefore is not considered to be sufficient to trigger an update of this area.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 24 Further RCT-based, long-term studies are needed to establish the clinical and cost effectiveness of augmenting antipsychotic monotherapy with an antidepressant to treat persistent negative symptoms.

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although new evidence was identified, it was limited and therefore not considered sufficient to trigger an update in this area.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 25 Controlled studies are required to test the efficacy and safety of combining antipsychotics to treat schizophrenia that has proved to be poorly responsive to adequate trials of antipsychotic monotherapy.

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although new evidence was identified, it was limited and therefore not considered sufficient to trigger an update in this area.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 26 **A randomised placebo-controlled trial should be conducted to investigate the efficacy and post effectiveness of augmentation of clozapine monotherapy with an appropriate second antipsychotic where a refractory schizophrenic illness has shown only a partial response to clozapine.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Although new evidence was identified, it was limited and therefore not considered sufficient to trigger an update in this area.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 27 **A randomised placebo-controlled trial should be conducted to investigate the efficacy and cost effectiveness of augmentation of antipsychotic monotherapy with lithium where a schizophrenic illness has shown only a partial response. The response in illness with and without affective symptoms should be addressed.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 28 **A randomised placebo-controlled trial should be conducted to investigate the efficacy and cost effectiveness of augmentation of antipsychotic monotherapy with sodium valproate where a schizophrenic illness has shown only a partial response. The response of illness in relation to behavioural disturbance, specifically persistent aggression, should be specifically addressed to determine if this is independent of effect on potentially confounding variables, such as positive symptoms, sedation, or akathisia.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 29 **Further controlled studies are required to test the claims that clozapine is particularly effective in reducing hostility and violence, and the inconsistent evidence for a reduction in suicide rates in people with schizophrenia.**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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