NICE National Institute for Health and Care Excellence

Surveillance report 2017 – Psychosis and schizophrenia in adults: prevention and management (2014) NICE guideline CG178

Surveillance report

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Contents

Surveillance decision

We will not update the guideline on psychosis and schizophrenia in adults at this time.

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

Reason for the decision

Assessing the evidence

We found 234 studies through surveillance of this 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. 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 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 was not sufficient to impact the current recommendations.

Through consultation with topic experts, it was highlighted that with the introduction of new long acting injectable antipsychotics, it is no longer appropriate to only recommend that an initial small test dose of such medication is used. Some newer long acting injectables require stabilisation on the equivalent oral formulation prior to initiation, making the use of an additional small test dose unnecessary, according to their licence. Therefore,

it was concluded that an amendment would be made to recommendation 1.5.6.1 to remove 'initially use a small test dose as set out in the BNF or SPC' and replace this bullet point with 'prescribe according to the procedures set out in the BNF or SPC'.

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 antipsychotics with non-antipsychotics.

This evidence was considered to be insufficient to prompt 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 antipsychotics with non-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.

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 addressed in the guideline. It was also highlighted that a gap in the level of esteem between physical and mental health still exists, however, this is considered to be an implementation issue beyond the remit of the guideline. Physical health risk assessment tools for people with severe mental health conditions which consider deprivation and ethnicity were highlighted, however these tools have been considered during the 2017 surveillance review of NICE guideline CG181. Issues regarding bias in diagnosis with regard to culture, race and gender were raised, however this falls outside the remit of this guideline. No other equality issues were identified.

Overall decision

After considering all the evidence and views of topic experts and stakeholders, we decided that no update is necessary for this guideline.

See how we made the decision for further information.

Commentary on selected evidence

With advice from topic experts we selected 3 studies for further commentary.

Psychological therapy

We selected the systematic review and meta-analysis by Velthorst et al. (2015) for a full commentary due to the large number of primary studies included in the analysis and overall participant number. This area was chosen for full commentary following topic expert feedback which indicated that there is continuing uncertainty regarding the effects of cognitive behavioural therapy (CBT) for psychosis and that there have been reports suggesting that there may be little or no effect of CBT when evaluating certain outcomes. This study presents evidence which may contradict current recommendations on offering CBT for the treatment of negative symptoms, and therefore a consideration of the interventions in the primary evidence included and the methods used, will help ascertain the impact this study may have on the guideline.

What the guideline recommends

NICE's guideline on psychosis and schizophrenia in adults recommends that individual CBT should be offered to people at risk of developing schizophrenia or psychosis, during first and subsequent acute episodes and during the recovery period for people with persisting positive and negative symptoms. It is recommended that CBT is delivered on a one-to-one basis over at least 16 sessions. A treatment manual should be followed which aids people to establish links between their thoughts, feelings or actions and their symptoms and functioning as well as allowing a re-evaluation of their perceptions, beliefs or reasoning so that it relates to target symptoms. It is also recommended that at least 1 of the following components is included during CBT: monitoring your own thoughts, feelings or behaviours with respect to symptoms or symptom recurrence; promoting alternative ways of coping with target symptoms; reducing distress and improving functioning.

See recommendations 1.2.3.1, 1.3.4.1, 1.3.7.1, 1.4.2.1 and 1.5.4.1 in NICE guideline CG178 for full details.

Methods

This systematic review by Velthorst et al. (2015) includes 35 publications covering 30 randomised trials, in 2,312 people with schizophrenia. A random-effects meta-analysis was performed to provide an estimate of the effect size (calculated as Hedges' *g*) of the influence of CBT on negative symptom severity.

In order to meet the inclusion criteria for this review, primary studies must have evaluated CBT targeted at improving: psychotic symptomology; negative symptoms; social functioning; self-esteem or cannabis use, and included at least 1 behavioural and 1 cognitive technique as part of the primary intervention. All studies must also have reported a negative symptom score as an outcome. Scales used to report this outcome included the Scale for Assessment of Negative Symptoms (SANS), the Brief Psychiatric Rating Scale (BPRS), the Schizophrenia Change Scale (SCS) and the Positive and Negative Syndrome Scale (PANSS).

A number of effect modifiers were evaluated during analysis to account for differences across studies in the delivery of CBT, the participant characteristics and methodology used. Factors analysed included: the number of behavioural techniques included in an intervention; the number of CBT sessions attended; age; gender; illness duration; illness severity; study quality; primary outcome measure used and publication year.

Results

A total of 30 published randomised controlled trials were included in the systematic review (n=2,312). The population included people with chronic illness or recent-onset illness. Only 2 of the 30 studies reported on the effect on negative symptoms as a primary outcome, with 28 studies reporting this as a secondary outcome.

Primary and secondary outcome measures

When considering the effect of CBT from 28 studies which reported negative symptom severity as a secondary outcome, no statistically significant effect was found through a combined estimate for Hedges' *g* (0.093; 95% CI −0.028 to 0.214; p=0.130). There was also a high level of heterogeneity amongst the outcomes of these studies (χ^2=72.392; I^2=62.703). No statistically significant effect of CBT was found when considering the combined effect of the 2 studies which reported negative symptoms as a primary outcome (Hedges' *g*=0.157; 95% CI −0.010 to 0.409; p=0.225).

Short and long term effects

No statistically significant difference in negative symptom severity following treatment with CBT was found by stratifying studies by length of follow up. Measured at short term (3 to 6 months), an effect estimate for Hedges' *g* of 0.207 (95% CI −0.049 to 0.463, p=0.113) was reported, which decreased to −0.1 (95% CI −0.020 to 0.182, p=0.922) when long term outcomes were evaluated (9 to 12 months).

Potential effect modifiers

CBT which was given on an individual basis, compared to group CBT, was shown to be significantly more effective for reducing negative symptoms (Hedges' *g*=0.210, p=0.011 for individual CBT verses −0.174, p=0.204 for group CBT). The number of sessions provided, treatment type (CBT versus CBT 'plus'), study population or strictness of the control condition were not significantly associated with treatment effect.

Strengths and limitations

Strengths

All studies included in the systematic review were randomised controlled trials, which were independently assessed by 2 authors for study quality using a validated tool. The methodology used to identify relevant studies was appropriate, shown by the report of a clear search strategy which was used to identify relevant evidence from a variety of sources.

Thorough analysis has been performed to assess the differences in effect which may be concluded due to differences in study methodology, intervention delivery and participant characteristics across the included studies.

The population and outcomes evaluated are directly relevant to NICE guideline CG178, as all included participants were people with schizophrenia and the effect on symptoms is an important outcome for this guideline.

Limitations

The majority of studies included were not targeted at improving the presence of negative symptoms, although this was the outcome assessed during this meta-analysis. As such,

the overall population had a range of baseline negative symptom scores, which may have impacted the effect which could be identified following intervention. This may also have been impacted by the use of a range of different outcome measurement tools.

There was a high level of heterogeneity shown which could not be fully explained, including within the results for sensitivity analysis.

It was not possible to distinguish between the effect of antipsychotic medication and CBT in individual studies. Although CBT was the main intervention component in all studies included in the systematic review, an inability to ascertain which studies may have been influenced by changes in medication during the intervention is a limitation of this review.

Four of the 30 included studies are likely to include an intervention focusing on CBT to prevent substance misuse, which is not relevant to NICE guideline CG178. It cannot be determined in which sensitivity analyses this may have had a significant impact.

Impact on guideline

The current recommendations regarding CBT are specific, suggesting one-to-one interaction over 16 sessions. The evidence presented here suggests that CBT delivered individually is significantly more effective than CBT delivered within a group, which is consistent with the current recommendations. While the overall meta-analysis outcome suggests that CBT is not effective for the improvement of negative symptoms, a large range of methods for the delivery of CBT are used across the studies included. The topic expert view, that in some circumstances CBT may not be an effective treatment is supported by this. However, methods such as individual CBT, which were reported to be more effective than group CBT in this systematic review, are specifically recommended in this guideline. This, in combination with several important limitations to the study methodology, means that the evidence reported is not sufficient to suggest that the recommendations made in NICE guideline CG178 would be impacted.

Interventions for people whose illness has not responded adequately to treatment

We selected Samara et al. (2016) for a full commentary because it presents a network meta-analysis (NMA) which may contradict current recommendations for the use of clozapine for people with treatment resistant schizophrenia or psychosis. It was also

highlighted by topic experts that there may be issues regarding physical health risks associated with clozapine and therefore a commentary of this study's conclusions are warranted.

What the guideline recommends

Currently, NICE guideline CG178 recommends that people with illness which has not responded adequately to treatment of adequate doses of at least 2 other antipsychotic drugs (with at least 1 of these having been a non-clozapine second-generation antipsychotic), should be offered clozapine (recommendation 1.5.7.2).

Methods

This NMA considered 40 randomised controlled trials (n=5,172), evaluating drug treatment for adults with schizophrenia, schizophreniform disorder or schizoaffective disorder that has been resistant to treatment, as defined by the primary studies. To meet the inclusion criteria for the NMA, trials must also have: assessed the intervention as monotherapy; had a minimum duration of 3 weeks and included another antipsychotic or placebo treatment as a comparator.

Multiple relevant databases were searched, as well as reference searches of included studies being conducted, which were then screened and analysed by 2 independent reviewers. Studies which presented with a high risk of allocation or treatment concealment bias, as determined by the Cochrane Collaboration's risk of bias tool, were excluded, as were studies conducted in mainland China. There was also an attempt to alleviate missing data bias by contacting study authors.

The primary outcome measure was the change from baseline to end point as measured on the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), or any other validated scale which assesses schizophrenia symptoms. Effect sizes were calculated as Hedges' adjusted *g* standardised mean differences (SMD).

Results

Nine antipsychotics were considered as part of this study[1]. For improvement of the primary outcome – change in symptom severity in people with treatment resistant illness – the NMA indicated the following:

- Olanzapine was shown to be significantly more effective than quetiapine fumarate (SMD −0.29, 95% credible interval [CRI] −0.56 to −0.02), haloperidol (SMD −0.29, 95% CRI −0.44 to −0.13) and sertindole (SMD −0.46, 95% CRI −0.80 to −0.06).
- Clozapine was significantly more effective than haloperidol (SMD −0.22, 95% CRI −0.38 to −0.07) and sertindole (SMD −0.40, 95% CRI −0.74 to −0.04).
- Risperidone was significantly more effective than sertindole (SMD −0.32, 95% CRI −0.63 to −0.01).

All the other comparisons of antipsychotics made in the NMA did not show any significant difference in effect.

Strengths and limitations

Strengths

This NMA was conducted against an a priori study protocol, which included only blinded randomised controlled trials and excluded studies which showed high risk of bias. The methods used to conduct the NMA were robust, and included a range of relevant databases being searched and study selection and data extraction being performed by multiple study authors.

Inconsistencies throughout the network were identified, and analysed during sensitivity analysis, indicating robust methodology. The network was also entirely connected, without the need to expand the study protocol in order for connections to be made.

Limitations

The population included in this NMA is not specific to the population included in the current recommendations on inadequate response to treatment. This is due to the fact that NICE guideline CG178 defines treatment resistance as not responding adequately to treatment despite the sequential use of at least 2 different antipsychotics (with at least 1 of these being a non-clozapine second-generation antipsychotic). Treatment resistance was defined differently by many of the included studies. During a sensitivity analysis, only studies which defined treatment resistance as it is in NICE guideline CG178 were included, with only 11 comparisons remaining in the network. Results from this analysis indicated no statistically significant difference in mean change in overall symptoms between antipsychotics.

A number of the antipsychotics included in this NMA are not currently licenced for use in the UK (sertindole, ziprasidone and fluphenazine as an oral formulation).

The median trial length of included studies was 11 weeks, meaning long term outcomes cannot be reliably concluded.

There were high rates of attrition throughout the included studies, with the mean drop-out rate reported as 30.2%. There was also evidence of selective reporting in 45.0% of included studies.

Impact on guideline

While olanzapine, clozapine and risperidone were shown to be more effective than some other antipsychotics evaluated for treatment resistant schizophrenia, the results presented in this NMA do not clearly indicate a single antipsychotic to be most effective. As well as this, a number of limitations lessen the impact this study has on the guideline. Most notably, the overall population was not specific to that referred to in the relevant recommendations in NICE guideline CG178, and when this population was evaluated individually, no significant difference in antipsychotic efficacy was reported. In addition, a number of the antipsychotics included in the NMA are not currently available in the UK. Therefore, in combination with the evidence considered during guideline development, clozapine is likely to be the most effective treatment for the specific population described.

Promoting recovery and possible future care

We selected this network meta-analysis (NMA) (Zhao et al. 2016) for a full commentary because it provides an overview of the effects of a large range of antipsychotic treatments aimed at reducing relapse in people who are clinically stable, allowing a comparison of many treatment options for this specific population in a single study. Compared to other systematic reviews identified specifically for promotion of long term recovery, this is a relatively recent study with a large sample size.

What the guideline recommends

Currently there are no recommendations for treatment with a specific long term antipsychotic, although it is recommended that an antipsychotic should be offered to people at all stages of illness following a diagnosis of schizophrenia or psychosis. It is

recommended that the choice of antipsychotic should be made by the service user and healthcare professional together, taking into account a range of benefits and side effects which accompany individual treatment options. See recommendations 1.3.4.1, 1.3.5.1, 1.4.2.1 and 1.4.3.1 for details.

Methods

This NMA by Zhao et al. (2016) includes 56 trials with a total of 10,177 participants, evaluating 18 antipsychotics[2]. Literature was identified through searches of PubMed, PubMed/Medline and the Cochrane library, as well as through reference list searches. Studies were included if they were blinded randomised controlled trials evaluating the use of antipsychotic monotherapy for relapse prevention in people with clinically stable schizophrenia. Trials conducted in people with predominantly negative symptoms, known treatment resistance or acute illness were excluded.

The primary outcome reported was relapse as defined in each included study at its longest follow up. Definitions of relapse included clinically assessed or rating scale based exacerbation of psychotic symptoms, hospital admission and the need to change medication. Adverse effects such as weight gain were also reported as secondary outcomes.

Results

Results of the meta-analysis indicated that all antipsychotic treatments were significantly more effective than placebo at preventing relapse, with the exception of trifluoperazine, which did not achieve statistical significance. The NMA indicated that olanzapine was more effective at preventing relapse than chlorpromazine (odds ratio [OR]=0.35, 95% CI 0.14 to 0.88) and haloperidol (OR=0.50, 95% CI 0.30 to 0.82). Fluphenazine long acting injectable was also more effective than chlorpromazine (OR=0.31, 95% CI 0.11 to 0.88). Any other differences in efficacy between antipsychotics were minimal and non-significant.

Fifteen studies included the outcome of weight gain. It was found that olanzapine caused significantly more weight gain than amisulpride (OR=2.31, 95% CI 1.04 to 5.17) and haloperidol (OR=4.15, 95% CI 1.97 to 8.71). Quetiapine was shown to cause significantly less weight gain than olanzapine (OR=0.40, 95% CI 0.20 to 0.78), as was risperidone (OR=0.44, 95% CI 0.20 to 0.94), and ziprasidone (OR=0.13, 95% CI 0.06 to 0.27).

Strengths and limitations

Strengths

The systematic reviewing methodology of this NMA was thorough, as 2 reviewers selected the studies for inclusion, synthesised and analysed the evidence, and a validated tool was used to evaluate the potential risk of bias of each study.

Methodological strengths specific to NMA included that loop-specific tests were performed, for which 17 out of 21 loops showed no significant inconsistency. Furthermore, no significant inconsistency between direct and indirect evidence was identified within the entire network (p=0.14).

Limitations

Heterogeneity between studies was not specifically reported, and there are concerns that between study differences may have introduced bias. Only very limited sensitivity analysis was performed in order to account for differences in drug dosages across studies, meaning the assumption of transitivity is in doubt. It is also noted that relapse rates were measured differently across studies. Therefore, there is a potential for bias in favour of antipsychotics evaluated by studies which measured relapse using a more extreme outcome, such as hospitalisation, compared to decline on a symptom rating scale.

Some antipsychotics were better represented than others, with 44% of the agents being represented in only 2 to 3 trials. The smaller overall sample size that is likely to accompany fewer representative trials gives these antipsychotics a disadvantage for achieving statistical significance in a NMA.

The search approach conducted was limited, with backward citation searches of systematic reviews identified through PubMed forming the basis of the search, alongside a limited search of PubMed/Medline and the Cochrane library.

The exclusion of primary studies with a population who predominantly experience negative symptoms means that the population of this study does not wholly represent that included within NICE guideline CG178.

Impact on guideline

The evidence identified showed that across nearly all treatment options, antipsychotics are more effective than placebo at preventing relapse in clinically stable people with schizophrenia, consistent with the recommendations to offer antipsychotic medication as treatment. In the NMA, greater efficacy was shown for olanzapine and fluphenazine long acting injectable compared to a minimal number of other treatment options. However, full consideration of antipsychotic side effects such as weight gain – associated with olanzapine – and extrapyramidal effects – associated with typical antipsychotics such as fluphenazine – need to be considered before prescription. Other antipsychotics showed minor and non-significant differences in efficacy. It should also be considered that while it was reported that ziprasidone has less propensity to cause weight gain than olanzapine, this drug is not currently available in the UK. Overall, the evidence presented in this NMA does not convincingly place any antipsychotic above another after consideration of efficacy and side effects. This was also emphasised when the results of the meta-analysis were considered, which showed consistently overlapping confidence intervals, for all antipsychotics considered. Therefore, the current recommendations that choice of antipsychotic should be based on discussion between the service user and the healthcare professional, after consideration of benefits and side effects, are unlikely to be impacted by this evidence.

[1] chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone, sertindole and ziprasidone.

[2] amisulpride, aripiprazole, chlorpromazine, flupentixol decanoate (flupentixol LAI), fluphenazine decanoate (fluphenazine LAI), haloperidol, haloperidol decanoate (haloperidol LAI), olanzapine, paliperidone, paliperidone palmitate (paliperidone LAI), pipotiazine palmitate (pipotiazine LAI), quetiapine, risperidone, risperidone LAI, sulpiride, trifluoperazine, ziprasidone and zuclopenthixol decanoate (zuclopenthixol LAI).

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 3 years after the publication of NICE's guideline on psychosis and schizophrenia in adults (NICE guideline CG178) in 2014, following the 4-year surveillance process.

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.

Evidence

We found 223 studies in a search for systematic reviews and randomised controlled trials published between 1 November 2008 and 13 March 2017. We also included 6 relevant studies identified by members of the guideline committee who originally worked on this guideline. Five further studies were identified through post-publication communications.

From all sources, we considered 234 studies to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: summary of evidence from surveillance for details of all evidence considered and references.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline. Overall, 9 stakeholders commented. See appendix B for stakeholders' comments and our responses.

Five stakeholders agreed with the decision not to update the guideline, while 4 stakeholders disagreed with this decision. A number of issues were raised during consultation relevant to areas across the guideline.

Two stakeholders discussed the recommendations regarding the use of long acting injectable antipsychotics. It has been acknowledged that there have been a number of new long acting injectable formulations licenced since the last update of the pharmacological intervention section of this guideline, which have not specifically been considered. However, the body of evidence in this area is not likely to be sufficient to recommend a specific antipsychotic treatment over another. Therefore, it is considered that the current recommendation, which suggests considering the use of long acting injectable antipsychotics for the promotion of recovery in certain people, is unlikely to be impacted by this evidence.

One stakeholder raised that promising research has been conducted on an open-dialogue approach to treatment of psychosis and that new research is currently being conducted in this area. The limited evidence available for this intervention means that impact on the guideline at this time is unlikely. However, the ongoing trial highlighted will be monitored in order to consider the results at the next surveillance review, alongside other evidence in this area.

One stakeholder highlighted that consideration should be made to updating NICE guideline CG178 to include a recommendation on the risks associated with olanzapine and weight gain. Evidence was identified during the surveillance review that olanzapine causes weight gain, in support of this view. However, recommendations in NICE guideline CG178 describe that the choice of antipsychotic medication should be made between the service user and the healthcare professional together, and include a discussion of the side effects, including metabolic side effects. It is considered that this recommendation is sufficient to suggest that the metabolic side effects of olanzapine should be considered as part of the choice to prescribe it. Therefore, this evidence is not likely to have an impact on the current recommendations.

Two stakeholders commented on areas which are outside the current scope of the guideline. It was raised that a test for vitamin B12 deficiency should be included as part of the diagnosis procedure for schizophrenia. The remit provided to NICE for the development of CG178 specifically considers the prevention and management of psychosis and schizophrenia and therefore, the guideline does not consider diagnosis. It was also raised that the current recommendations do not cover any socio-cultural

interventions for the treatment of schizophrenia. However, no evidence in this area was identified and therefore it is not likely there would be an impact on the guideline at this time.

Three stakeholders commented on equality issues. It was raised that diagnosis can be biased with respect to gender, race and culture, however, diagnosis falls outside the remit for NICE guideline CG178. It was also raised that measuring cardiovascular disease risk should be performed using a tool which takes account of deprivation and ethnicity. Such a tool has been considered during the 2017 surveillance review of NICE guideline CG181 and therefore will not be included in this guideline. The gap in the parity of esteem regarding mental and physical health was highlighted, alongside the low uptake of services for people with schizophrenia and psychosis. It was suggested that NICE could strengthen recommendations for effective treatments focusing on medicines optimisation, and promote further shared and informed decision making to address this issue. NICE bases its recommendations on the best available evidence and the strength of the recommendations reflects the strength of this evidence. NICE views mental and physical health with equal importance, and issues with parity of esteem in this area are due to implementation of the guideline. No new evidence was identified during this surveillance review to prompt an update in this area, and the current recommendations on promoting shared decision making were supported. As well as this, other NICE guidelines have been published which focus on promoting these areas across both physical and mental health services, such as medicines optimisation, service user experience in adult mental health and patient experience in adult NHS services.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

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