NICE National Institute for Health and Care Excellence

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Surveillance report 2016 – Psychosis and schizophrenia in children and young people: recognition and management (2013) NICE guideline CG155

Surveillance report

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Contents

Surveillance decision

We will not update the guideline at this time.

Reason for the decision

We found 25 new studies through surveillance of this guideline.

This included new evidence on access to and the delivery of services and the experience of care, recognition and management of at risk mental states, psychological and psychosocial interventions, and pharmacological interventions that supports current recommendations. We asked topic experts whether this new evidence would affect current recommendations on psychosis and schizophrenia in children and young people. Generally, the topic experts thought that an update was not needed.

We did not find any new evidence related to cognition, employment and education.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

Other clinical areas

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to genetic basis of weight gain associated with antipsychotic medications. However, the preliminary nature of the evidence and paucity of further supporting evidence mean it is unlikely to impact the guideline at this time.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the new evidence and views of topic experts, we decided that an update is not necessary for this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 1 study for further commentary.

Pharmacological interventions

We selected the systematic review and network meta-analysis by Harvey et al. (2016) for a full commentary because this study provides data on the efficacy of antipsychotics for the treatment of early-onset schizophrenia. The results of this study have the potential to add to an otherwise limited evidence base as most studies on antipsychotics are conducted in an adult population.

What the guideline recommends

For the management of first episode psychosis, NICE guideline CG155 recommends oral antipsychotic medication in conjunction with psychological interventions following information and discussion of the benefits and side-effects of the available drugs. It also recommends baseline investigations and regular monitoring during treatment of physical, metabolic and cardiovascular effects.

Methods

The Harvey et al. (2016) systematic review and network meta-analysis investigated the effectiveness of antipsychotic medications for early-onset schizophrenia. The systematic review identified clinical trials, both randomised controlled trials and non-randomised trial designs, reporting symptoms using the Positive and Negative Syndrome Scale (PANSS) in children and adolescents with schizophrenia. Pharmacological interventions were compared with one another and each against placebo using a network meta-analysis. This analysis allowed the investigation of both direct and indirect comparisons between multiple interventions and placebo. A Bayesian approach was used to rank each antipsychotic with a probability for being the best treatment for each outcome.

Total PANSS scores provided the primary outcome measure which consisted of the mean change in score from baseline to 6 weeks. Secondary outcome measures consisted of:

- The mean change from baseline to 6 weeks in positive and negative subscale PANSS scores.
- The mean change from baseline to 6 weeks in patient weight.
- Odds of all-cause treatment discontinuation.

- Odds of treatment discontinuation because of adverse events.

The inclusion criteria for the systematic review consisted of studies with:

- Patients aged 18 years and below.
- Patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder.
- Conducted 2 or more arm trials in the disease area.
- Reported mean (and standard deviation or error) baseline and changes over time in PANSS symptom scores.
- Reported data between 6-week and 12-week endpoints.

Results

Systematic review

The systematic review identified a total of 11 studies meeting the inclusion criteria. Of these, 10 studies had a randomised design and 8 included a clear blinding method to reduce risk of bias.

A direct comparison of one type of antipsychotic with placebo was included in 6 of the studies. A further 4 studies compared multiple antipsychotics with each other and 1 study compared different doses of the same antipsychotic. In total, 8 different antipsychotics (paliperidone, ziprasidone, aripiprazole, quetiapine, risperidone, molindone, olanzapine and haloperidol) were identified within the treatment arms of the included studies.

Network meta-analysis

A total of 11 studies were included in the network meta-analysis with secondary outcomes reported less frequently as indicated below. For the one study comparing different doses of the same antipsychotic, the analysis reclassified the lower dose as a placebo arm. The one non-randomised study was also included within the final analysis as it was the only study with haloperidol in a treatment arm. Sensitivity analyses following removal of each of these two studies produced similar results to the final analysis.

From 11 studies, the primary outcome of change in total PANSS scores from baseline to 6 weeks compared to placebo indicated statistically significant improvements in symptoms with:

- Molindone (mean difference in total PANSS score [MD] = −13.51, 95% Credible Interval [CrI] = −24.12 to −1.45).
- Olanzapine (MD= −13.03, 95% CrI= −20.22 to −5.10).
- Risperidone (MD= −11.57, 95% CrI= −16.91 to −5.53).

The largest effect was found for haloperidol (MD= −15.55, 95% CrI= −35.37 to 4.11) however the result was not statistically significant. The remaining 4 antipsychotics also indicated statistically non-significant improvements in total PANSS score compared to placebo for aripiprazole (MD= −6.45, 95% CrI= −14.65 to 2.40), paliperidone (MD= −5.51, 95% CrI= −15.21 to 3.85), quetiapine (MD= −8.20, 95% CrI= −16.84 to 0.71) and ziprasidone (MD= −2.67, 95% CrI= −11.27 to 6.19).

Further analyses of pairwise treatment comparisons did not find any statistically significant differences in total PANSS scores between antipsychotics.

Using the Bayesian approach, haloperidol was ranked with the greatest probability (0.49) to be the best treatment for reducing total PANSS score, molindone (0.25) as the next, followed by the remaining antipsychotics all with a probability less than 0.13.

From 10 studies, the secondary outcome of change in positive PANSS scores from baseline to 6 weeks compared to placebo indicated statistically significant improvements in symptoms with:

- Haloperidol (mean difference in positive PANSS score [MD] = −8.48, 95% Credible Interval [CrI] = −15.60 to −1.28).
- Olanzapine (MD= −3.46, 95% CrI= −6.23 to −0.49).
- Risperidone (MD= −3.20, 95% CrI= −5.58 to −0.87).

The remaining 5 antipsychotics indicated statistically non-significant improvements in positive PANSS score compared to placebo for aripiprazole (MD= −2.22, 95% CrI= −5.73 to 1.42), molindone (MD= −3.44, 95% CrI= −7.64 to 0.91), paliperidone (MD= −1.66, 95% CrI= −5.60 to 2.29), quetiapine (MD= −2.45, 95% CrI= −6.11 to 1.26) and ziprasidone (MD= −1.32, 95% CrI= −4.95 to 2.46).

Further analyses of pairwise treatment comparisons did not find any statistically significant differences in positive PANSS scores between antipsychotics.

Using the Bayesian approach, haloperidol was ranked with the greatest probability (0.85) to be the best treatment for reducing positive PANSS score. Detailed statistical ranking probabilities for the remaining antipsychotics are not provided within the study.

From 10 studies, the secondary outcome of change in negative PANSS scores from baseline to 6 weeks compared to placebo indicated statistically non-significant improvements for all 8 antipsychotic treatments. Whilst the largest effects were found for haloperidol and molindone (both MD= −3.42), haloperidol had the largest amount of uncertainty (95% CrI= −11.55 to 4.65) of all the antipsychotics. Risperidone came closest to achieving statistical significance (MD= −2.87, 95% CrI= −5.32 to 0.08) and ziprasidone was closest to the line of no difference (MD= −0.38, 95% CrI= −4.51 to 3.92).

Further analyses of pairwise treatment comparisons did not find any statistically significant differences in negative PANSS scores between antipsychotics.

Using the Bayesian approach, haloperidol was ranked with the greatest probability (0.40) to be the best treatment for reducing negative PANSS score. Detailed statistical ranking probabilities for the remaining antipsychotics are not provided within the study.

From 10 studies, the secondary outcome of change in weight from baseline to 6 weeks compared to placebo indicated statistically significant weight gain with:

- Olanzapine (mean difference in weight [MD] = 3.96, 95% CrI= 2.43 to 5.44).
- Quetiapine (MD= 2.41, 95% CrI= 0.41 to 4.32).
- Risperidone (MD= 1.49, 95% CrI= 0.30 to 2.82).

Statistically non-significant weight gain compared to placebo was found for aripiprazole (MD= 0.90, 95% CrI= −0.97 to 2.74) and paliperidone (MD= 0.89, 95% CrI= −0.92 to 2.76).

Haloperidol (MD= −1.68, 95% CrI= −5.26 to 1.89), molindone (MD= −1.82, 95% CrI= −3.96 to 0.41) and ziprasidone (MD= −0.09, 95% CrI= −1.93 to 1.73) indicated statistically non-significant weight reduction compared to placebo.

Analyses of pairwise treatment comparisons found statistically significant weight reduction for ziprasidone (MD= −4.06, 95% CrI= −6.31 to −1.73), risperidone (MD= −2.47, 95% CrI= −3.80 to −1.12) and paliperidone (MD= −3.07, 95% CrI= −5.34 to −0.79) compared to olanzapine.

Further analyses of pairwise treatment comparisons found statistically significant weight gain was associated with:

- Risperidone (MD= 3.3, 95% CrI= 1.33 to 5.26), quetiapine (MD= 4.23, 95% CrI= 1.30 to 7.17) and olanzapine (MD= 5.79, 95% CrI= 3.82 to 7.76) compared with molindone.
- Quetiapine (MD= 4.05, 95% CrI= 0.13 to 8.12) and olanzapine (MD= 5.63, 95% CrI= 2.15 to 9.09) compared with haloperidol.
- Olanzapine (MD= 3.08, 95% CrI= 0.71 to 5.45) compared aripiprazole.

Using the Bayesian approach, haloperidol was ranked with the greatest probability (0.50) to be the best treatment for weight change, followed by molindone (0.45) and the remaining antipsychotics all with a probability less than 0.03.

The secondary outcome of all-cause discontinuation was reported in 7 studies and included 5 of the antipsychotics in the treatment arms with placebo. Risperidone indicated statistically significant reduced odds of discontinuation compared to placebo (Odds ratio [OR] = 0.48, 95% CrI= 0.25 to 0.84). Statistically non-significant reduced odds of discontinuation compared to placebo was found for haloperidol (OR= 0.19, 95% CrI= 0.01 to 2.42), olanzapine (OR= 0.50, 95% CrI= 0.22 to 1.24), quetiapine (OR= 0.43, 95% CrI= 0.18 to 1.06) and ziprasidone (OR= 0.58, 95% CrI= 0.26 to 1.32).

Further analyses of pairwise treatment comparisons did not find any statistically significant differences in odds of all-cause discontinuation between antipsychotics.

Using the Bayesian approach, haloperidol was ranked with the greatest probability (0.67) to be the best for continuing treatment, followed by quetiapine (0.16) and the remaining antipsychotics all with a probability less than 0.08.

The secondary outcome of discontinuation due to adverse events was reported in 9 studies and included 7 of the antipsychotics in the treatment arms with placebo. Statistically non-significant increased odds of discontinuation due to adverse events were found for all 7 antipsychotics compared with placebo. Due to the paucity of data in the included studies for this outcome, no further analyses were conducted or reported.

The results suggest that whilst all the antipsychotic treatments indicated improved symptom efficacy compared with placebo, no significant differences were found when compared with one another. Although haloperidol seems to be ranked with the greatest probability of being the most effective treatment, the variation in certainty across results should be noted. A considerable

amount of variation was also found for the effects of treatments on weight and rates of discontinuation.

Strengths and limitations

Strengths

The target population in the study is directly relevant to the population in NICE guideline CG155. The study clearly defines the population as children and adolescents under the age of 18 who experience early-onset schizophrenia. The results of this study add to an otherwise limited evidence base as most studies on antipsychotics are conducted in an adult population.

A methodological strength of the study is the inclusion of an extensive range of antipsychotic medication and placebo as comparators. NICE guideline CG155 recommends the use of oral antipsychotics however does not specify particular medications. The comparison of multiple first and second generation antipsychotics in this study offers data on their relative efficacy for this population. Also, the study adequately reported the network of evidence and the inclusion of treatment ranking probabilities to provide further useful information on efficacy.

The primary and secondary outcomes in the study are directly relevant to NICE guideline CG155. The outcomes are good indicators of the efficacy of the included antipsychotic medications and the PANSS scale being a commonly used measure of symptoms in this population. The reporting of weight changes associated with medications gives further strength and relevance to the study as this is one of the most concerning side-effects for this population.

Further methodological strengths consist of the use of an adequate search strategy to identify relevant studies and the use of an appropriate risk of bias tool to assess the quality of the included randomised controlled trials.

To give the network meta-analysis further strength, the study has adequately justified the inclusion of a non-randomised design. The network meta-analysis also accounted for the pooling of data from different doses and the reclassification of a low dose to placebo. Appropriate sensitivity analyses were conducted to test the effect on results when these were excluded.

Limitations

The network meta-analysis includes a number of limitations in its methodology. Although a risk of bias tool was used for RCTs, the study does not specify the tool used for the non-randomised study. Also, the quality assessment of several included studies identified bias from lack of blinding,

selective reporting, differences in baseline characteristics and failure to explain differences in drop-out rates.

Variations in baseline gender and mean age characteristics of the included studies indicated heterogeneity. However, a statistical test was not reported to confirm this or to account for the differences. These methodological limitations negatively impact upon the strength of the results and reduce the certainty of the treatment effects.

The authors also highlighted uncertainty in the treatment effects due to the limited number of included studies and small sample sizes. Further uncertainty in the network was created through the number of indirect comparisons and many comparisons being informed by single trials. The authors acknowledged that substantial responses for placebo have been previously reported. The effect of placebo alone was not investigated here which may reduce the reliability of the network meta-analysis results.

Impact on guideline

The results of the study fit with recommendations on choosing antipsychotic medications in NICE guideline CG155. The results support the recommendations highlighting the efficacy of antipsychotics compared to placebo. Further support is provided for recommendations to consider the choices of medications and to discuss the associated benefits and side-effects.

However, a limitation of the study is the relatively short end-point of 6 weeks to measure efficacy. Although NICE guideline CG155 recommends initially offering a trial of medication at optimum dose for 6 weeks, it is likely that antipsychotic treatment would be more long-term. Outcome data from longer follow-up would be more helpful to determine efficacy in this population.

Also, there are a number of the included studies which were already considered during the development of NICE guideline CG155 and informed the evidence base for the current recommendations. This reduces the amount of new evidence this study provides to impact on recommendations at this time.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of psychosis and schizophrenia in children and young people (2013) NICE guideline CG155.

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'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 9 new studies in a search for randomised controlled trials and systematic reviews published between 01 September 2014 and 13 June 2016.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 12 studies identified by the Evidence Update and 4 studies identified during the Addendum searches.

From all sources, 25 studies were considered 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 new evidence from surveillance and references for all new evidence considered.

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, 5 stakeholders responded and all agreed with the proposal to not update the guideline. See appendix B for stakeholders' comments and our responses.

Three stakeholders provided further comments on the proposal to not update the guideline. Comments highlighted a number of ongoing trials due to publish over the next 2–3 years. These have been noted already and will be considered at the next surveillance review following publication of results. One stakeholder highlighted the lack of guidance for the treatment of comorbid disorders in this population. However, no evidence was identified relating to comorbid disorders in this population therefore no impact on the guideline at this time. A further comment suggested coverage of Open Dialogue and Voice Dialogue treatments. These treatments have already been covered in the surveillance review following identification by a topic expert. However, no evidence was found relating to Open or Voice Dialogue treatments in this population therefore no impact on the guideline at this time.

We requested stakeholders to comment on the removal of 3 priority research recommendations. Stakeholders generally commented that more evidence is needed to answer the research questions. Relevant ongoing trials, which were not previously identified by the surveillance review, were highlighted by stakeholders. These trials will be considered at the next surveillance review when results publish. Having considered the views of topic experts and stakeholders, we propose to retain all the research recommendations in the NICE version of the guideline and the NICE research recommendations database.

Stakeholders were requested to comment on areas excluded from the scope of the guideline and any equalities issues. No comments on equalities issues were made by stakeholders during consultation. However, one stakeholder again raised the issue, as highlighted above, of a lack of guidance around managing comorbid disorders in children and young people.

Overall, we decided not to update the guideline.

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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