NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of psychosis and schizophrenia in children and young people: recognition and management (NICE guideline CG155)

Surveillance report

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Surveillance decision

We will not update the NICE guideline on psychosis and schizophrenia in children and young people in relation to depot and long-acting antipsychotic injections.

Reason for the exceptional review

This exceptional review was triggered by an NHS commissioned independent investigation into the care and treatment of Mr N, a mental health service user who killed 'L' on 16 August 2016. In brief: the investigation describes the events leading up to the killing of 'L' by 'N' who, at the time of the homicide, was 17 years old and had been prescribed risperidone long-acting injection while detained under the Mental Health Act in a secure unit after being diagnosed with first-episode psychosis. 'N' was initially given oral risperidone and was started on long-acting injectable risperidone following concerns about adherence. 'N' was discharged from acute services 6 weeks prior to his eighteenth birthday. As local early intervention in psychosis (EIP) services did not accept people less than 18 years old, 'N' was discharged into the care of a local CAMHS service until eligible for EIP services. A lack of coordination and discharge planning between services resulted in 'N' missing doses of his long-acting injectable risperidone. In concert with several other factors detailed in the investigation report, this contributed to 'N's' mental health deteriorating and the subsequent homicide.

This investigation recommends: 'NHS England and NHS Improvement should work with NICE to consider including in existing guidance information about the prescribing of injectable anti-psychotics for the treatment of psychosis in under 18s.' (National recommendation 1). This exceptional review addresses this recommendation by assessing whether NICE's guideline on psychosis and schizophrenia in children and young people should be updated to include recommendations about depot and long-acting antipsychotic injections.

Licensing of depot and long-acting antipsychotic injections

At the time of publication of this surveillance review no depot or long-acting antipsychotic injections are licensed in the UK for use in children and young people aged less than 18

years.

Reasons for the decision

The circumstances that resulted in barriers to 'Mr N' accessing depot antipsychotic injections could have been avoided by more robust transition planning. The independent investigation into the care and treatment of 'Mr N', notes that if recommendations in NICE's guideline on transition from children's to adults' services for young people using health or social care services had been used to inform the care of 'Mr N', better consideration would have been given to transition arrangements including access to depot antipsychotics. Additionally, NICE have also produced recommendations on medicines-related communication systems when patients move from one care setting to another in the guideline on medicines optimisation. Therefore, the issues raised by the independent investigation about transition planning are already addressed by existing NICE recommendations.

As part of this exceptional review, we checked whether there was robust evidence on which to base recommendations on in NICE's guideline on psychosis and schizophrenia in children and young people about the use of depot and long-acting antipsychotic injections. We identified a small volume of low quality studies which report very limited data for non-inferiority of paliperidone palmitate injections compared with oral olanzapine. We also identified very limited data for superiority for long-acting risperidone and long-acting paliperidone palmitate injections over oral antipsychotics for some outcomes. No evidence about the impact on adherence of depot and long-acting antipsychotic injections versus oral antipsychotics was identified. A narrative systematic review we identified concludes more randomised controlled trial (RCT) evidence is needed for their use in children and young people (see information considered in this exceptional surveillance review). New evidence is not robust or sufficient to update the guideline with recommendations about depot and long-acting antipsychotic injections.

Methods

The exceptional surveillance process consisted of:

- Literature searches to identify relevant evidence about the use of long-acting depot antipsychotic injections in children and young people.
- Considering the new information that triggered the exceptional review.

- Considering relevant information from previous surveillance reviews of the guideline in 2022.
- Considering the evidence used to develop the NICE guideline on psychosis and schizophrenia in children and young people in 2013 and the NICE guideline on psychosis and schizophrenia in adults in 2014.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- The comments and opinions of a NICE consultant clinical adviser and NICE medicines adviser.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

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

Search and selection strategy

We searched for new evidence related to the use of depot and long-acting antipsychotic injections in children and young people with schizophrenia.

We found 2 studies in a search for RCTs and systematic reviews published between 1 June 2016 and 31 October 2022.

We checked the full-text of studies for the average age of participants. Studies from populations of children and young people (less than 18 years) were prioritised for inclusion. Where this was not possible, studies that included people under and over 18 years, but with a mean age of under 25 are used, as per the guideline review protocols (pages 163 and 219 of the full guideline).

Information considered in this exceptional surveillance review

New evidence for the use of depot and long-acting antipsychotic injections in children and young people

Two studies were identified: 1 narrative systematic review (meta-analysis was not possible due to study heterogeneity) and 1 RCT. The study abstracts from PubMed are linked to below. A short commentary assessing the impact of each study on the NICE guideline on psychosis and schizophrenia in children and young people follows each abstract.

Study 1

Systematic review of efficacy, tolerability, and acceptance of long-lasting antipsychotics in children and adolescents

Objectives: While long-lasting antipsychotics (LLA) were specifically developed to address the problem of adherence in patients with chronic psychiatric disorders, their role in paediatric populations is not clear.

Methods: To document the efficacy, tolerance, and acceptance of LLAs in children and adolescents, a literature search was conducted using several databases for published studies (PubMed, PsycINFO) from January 1965 to December 2020. Twenty-two studies were identified (16 case reports/series, 3 open-label studies, 2 controlled studies, and 1 retrospective analysis of national database).

Results: Demographic features were widely heterogeneous across studies (total n=480, 58% male, mean age=15.0±1.8). Case reports/series presented positive therapeutic outcomes in noncompliant youths with severe mental illness. Three open-label one-arm studies supported the clinical efficacy of risperidone long-acting injection in patients previously stabilised with oral risperidone. One study showed lower clinical symptoms and higher functioning at 12 months in youths treated for an acute psychotic episode with paliperidone palmitate compared to oral risperidone. The types and rates of side effects of LLA were comparable to those observed for oral antipsychotics. Two studies suggested better metabolic and neurological tolerance of LLA compared to an oral form. Preliminary evidence supported a satisfactory level of treatment satisfaction in patients treated with LLA and their families, while concerns were raised regarding practical administration in

outpatient services. However, the average quality of the evidence based on the RoB2 tool was low.

Conclusions: The level of evidence was low for the efficacy of LLA in paediatric populations and very low for the tolerance and acceptance. It concerned mostly the effect of risperidone long-acting injection in adolescents with psychotic disorders. Randomised maintenance clinical trials using noninferiority analysis would be more appropriate for further research.

Assessment of impact on the NICE guideline on psychosis and schizophrenia in children and young people: This study provides some low quality evidence for the efficacy and tolerability of long-acting risperidone injection and long-acting paliperidone palmitate injection in adolescents. It also provides some evidence that long-acting antipsychotic injections may be superior to oral antipsychotics for some efficacy and tolerance outcomes. It is noteworthy that despite reports of treatment satisfaction, evidence was also identified from patients and their families about issues with the administration of injections in 'outpatient' settings. This is not strong nor sufficient enough evidence to warrant an update to include recommendations about depot and long-acting antipsychotic injections in the NICE guideline. As the study authors note, further evidence from RCTs is needed.

Study 2

A randomised, 13-week study assessing the efficacy and metabolic effects of paliperidone palmitate injection and olanzapine in first-episode schizophrenia patients

Background: This study was conducted to evaluate the efficacy and metabolic effects of paliperidone palmitate (PP) injections against oral olanzapine in first-episode schizophrenia (FES) patients.

Methods: Eligible patients were randomised to receive PP or olanzapine. Efficacy assessments and weight-related parameters were assessed at baseline, weeks 1, 5, 9, and endpoint or at early withdrawal. Lipid, glucose, insulin and prolactin were evaluated at baseline and endpoint or at early withdrawal.

Results: The Positive And Negative Syndrome Scale (PANSS) scores declined significantly after treatment in both groups. Significant increases in weight-related parameters from baseline to endpoint were shown in both groups. Although there was no significant

difference in PANSS scores and weight-related parameters between the 2 groups through the whole 13-week study. The increased level of triglyceride and HOMA-IR at endpoint from baseline in the olanzapine group was higher than the PP group. There was a stronger elevation of prolactin level in the PP group.

Conclusions: In summary, PP and olanzapine showed similar improvement in the treatment of FES patients. This study also reinforced the necessity for regular monitoring of metabolic parameters in schizophrenia patients prescribed atypical antipsychotics.

Assessment of impact on the NICE guideline on psychosis and schizophrenia in children and young people: This RCT investigated the effectiveness of PP with young people (n=51) with a mean age of 21.5 (+/- 5.6) years. It reports non-inferiority of PP compared with oral olanzapine (5 mg daily for week 1 with dosage varied based on efficacy and tolerability thereafter) at 13 weeks' follow-up. PP was administered on day 1 at 234 mg (equivalent to 150 mg paliperidone) and day 8 at 156 mg (equivalent to 100 mg paliperidone, both via deltoid injection) then every 4 weeks by deltoid or gluteal injections according to patient preference, and variable dosage on days 36 and 64 based on efficacy and tolerance. Although this demonstrates non-inferiority for PP for both efficacy and adverse effects, the full-text does not report data about comparable adherence, a commonly cited benefit of depot antipsychotics. Nor does it report how many people aged less than 18 years are included in the study. Furthermore this a small RCT conducted in China making the relevance of its results to an NHS setting questionable. This is not sufficiently robust evidence on which to update the NICE guideline with recommendations about depot and long-acting antipsychotic injections.

Information considered in previous surveillance of this guideline

This issue was not raised during 2022 surveillance of the NICE guideline and no evidence relevant to the use of depot and long-acting antipsychotic injections was identified.

Information considered when developing the guideline

No evidence about the use of depot and long-acting antipsychotic injections with children and young people was identified during guideline development.

Other relevant NICE guidance

Recommendation 1.5.5.3 in NICE's guideline on psychosis and schizophrenia in adults, states to consider offering depot/long-acting injectable antipsychotic medication to people with psychosis or schizophrenia based on patient preference or where adherence is a concern. This recommendation is based on 2 RCTs and a meta-review of 5 Cochrane reviews including only participants older than 18 years.

NICE's guideline on transition from children's to adults' services for young people using health or social care services is referenced by the independent enquiry triggering this review, which notes that the guideline should have informed 'Mr N's' discharge from the Wells Unit, as he was 6 weeks short of his eighteenth birthday. It makes particular reference to recommendation 1.2.3, which states that the point of transfer should not be based on a rigid age threshold and take place at a time of relative stability for the young person.

Although not referenced by the independent enquiry, NICE has produced 6 recommendations about medicines-related communication systems when patients move from one care setting to another in the guideline on medicines optimisation, that are relevant to the case.

Equalities

See appendix A for details.

Overall decision

We will not update the NICE guideline on psychosis and schizophrenia in children and young people in relation to depot and long-acting antipsychotic injections.

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