NICE National Institute for Health and Care Excellence

2019 exceptional surveillance of psychosis and schizophrenia in adults: prevention and management (NICE guideline CG178)

Surveillance report

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Surveillance decision

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

Reasons for the decision

Assessing the evidence

The purpose of this exceptional review was to examine any impact on NICE's guideline on psychosis and schizophrenia using evidence from 2 trials (Morrison et al. 2018 and Holt et al. 2018) and information from a Coroner's report.

The FOCUS trial

Methods

The focusing on clozapine unresponsive symptoms (FOCUS) trial (Morrison et al. 2018) was a parallel-group, randomised, outcome-blinded evaluation trial assessing the clinical effectiveness of cognitive behavioural therapy (CBT) versus treatment-as-usual (TAU) for people with clozapine-resistant schizophrenia (CRS).

Participants were recruited from 5 secondary care mental health services in the UK. To be included, participants must have been aged 16 years or over and given a diagnosis on the schizophrenia spectrum from ICD-10 or met criteria for an Early Intervention in Psychosis (EIP) service. They must also have had an inadequate response to a trial of clozapine treatment at a dose of ≥400 mg for 12 weeks or more. This included those who received augmented treatment for 12 weeks or more with a second antipsychotic and did not experience remission of psychotic symptoms. Also included were participants who in the previous 2 years had discontinued clozapine due to side effects, lack of efficacy or identified problems with blood levels. Further inclusion criteria required participants to score at least 58 on the Positive and Negative Syndrome Scale (PANSS).

Participants were excluded if the potential cause of psychotic experiences could be attributed to a primary diagnosis of substance or alcohol dependence. Also excluded were those with a diagnosis of developmental disability or organic impairment and those who

did not speak English. Additionally those who had received CBT in line with the NICE guideline during the previous 12 months were excluded.

Baseline clinical assessments consisting of the PANSS interview and the secondary outcome self-report measures were conducted prior to randomisation and at follow-up intervals of 9 and 21 months. The main outcome assessed was the change in total PANSS score from baseline to 21 months to determine the severity of psychiatric symptoms. The PANSS scale consists of 30 items designed to assess positive, negative, depression-anxiety, agitation-excitement, and disorganisation symptoms.

Secondary outcomes were also measured at baseline, 9 and 21 months and consisted of:

- Hallucinations and delusions measured by the Psychotic Symptoms Rating Scales (PSYRATS) semi-structured interview.
- Recovery measured by the Questionnaire about the Process of Recovery (QPR).
- Social and occupational function using the Personal and Social Performance (PSP) scale.
- Depression measured with the Calgary Depression Scale for Schizophrenia (CDSS).
- Anxiety measured using the Anxious Thoughts Inventory (AnTI).
- Substance use measured using the Alcohol Use Disorders Identification Test (AUDIT) and the Drug Abuse Screening Test (DAST).
- The Clinical Global Impression (CGI) was used by the researcher to rate the participant's current difficulties and to rate changes in presentation since baseline.
- Health outcomes were measured using the EuroQol-5 Dimensions (EQ-5D) questionnaire.

A web-based system was used to randomise individuals in blocks of random size and stratified by site. Investigators and assessors were blind to treatment allocation and measures were taken to mask the researchers from accidently breaking the blinding.

The trial intervention consisted of ≤30 hours of CBT delivered over 9 months in weekly individual sessions. A treatment manual was developed to be in line with CBT as delivered within NHS services. The TAU group were allocated a keyworker and all patients in both groups received regular outpatient follow-up from a secondary mental health service.

Results

The results were derived from an intention-to-treat analysis with descriptive statistics, statistical significance levels and confidence intervals (CI), 95% CI reported.

A total of 487 participants were randomised with 242 in the CBT group and 245 in the TAU group. Baseline characteristics of participants were found to be similar in both groups.

The results of the FOCUS study have been described in detail in an NIHR signal. In summary, the new evidence suggests that, in the long-term, CBT does not significantly improve symptoms in people with schizophrenia whose illness has not responded adequately to pharmacological treatment.

For the primary outcome 425 participants had at least 1 follow-up measurement and were included in the analysis. Total PANSS score was lower in the CBT group at 9 months (−2.40, 95% CI −4.79 to −0.02, p=0.049). Although it was also lower in the CBT group at 21 months (−0.89, 95% CI −3.32 to 1.55, p=0.48) this difference was not statistically significant.

Analysis of secondary outcomes at 9 months found in favour of the CBT group for the following:

- PANSS positive score (–1.56 [mean difference in scores], 95% CI –2.53 to –0.59, p=0.002).
- PANSS emotional distress score (–1.08, 95% CI –2.02 to –0.13, p=0.025).
- PSYRATS score for auditory hallucinations (−2.56, 95% CI −4.87 to −0.26, p=0.029).
- PSYRATS score for physical voices (−0.58, 95% CI −1.11 to −0.04, p=0.034).

Analysis of secondary outcomes at 21 months found in favour of the CBT group for the following:

- PSYRATS unusual beliefs: emotional (–0.53, 95% CI –1.05 to –0.00, p=0.049).
- CGI (–0.33, 95% CI –0.54 to –0.11, p=0.013).

All other secondary outcomes were not significantly different at the 9- or 21-month follow-up period between groups.

Guideline development

Recommendation 1.5.7.3 in NICE's guideline currently recommends CBT for people with schizophrenia whose illness has not responded adequately to pharmacological treatment. For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider reviewing engagement with and use of psychological treatments and ensure that these have been offered according to the guideline. The guideline development group noted that there was evidence to suggest that CBT was effective at reducing symptoms and would likely be cost-effective. However, no direct evidence was identified for a population with CRS.

Previous surveillance

Although evidence on CBT was identified, the 2017 surveillance review did not identify any new evidence for a clozapine-resistant population.

Views of topic experts

In this exceptional review we engaged with topic experts who were either members of the guideline committee involved in the development of the NICE guideline or were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received feedback from 6 topic experts all of which felt the results of the FOCUS study would not impact on recommendations in the NICE guideline. The main reason for this view was because the guideline recommendations for CBT treatment are not specific to people whose symptoms have failed to respond to clozapine treatment, limiting the applicability of the study to the guideline.

Impact

The FOCUS study was conducted in a group of people with long-standing schizophrenia and continued symptoms despite the use of clozapine. Strengths of the trial are that it is a UK-based study with interventions that are available in the NHS. The study authors noted a number of limitations which may impact on the accuracy of the results. They highlighted that the duration of CBT may be insufficient for CRS and that no corrections were made for multiple comparisons.

The finding that there are significant improvements in PANSS score at the end of CBT treatment is in line with recommendation 1.5.7.1 to offer CBT for people with schizophrenia

whose illness has not responded adequately to pharmacological treatment, and this is recommended for people with clozapine-resistance (see recommendation 1.5.7.3). CBT is just one of several options for addressing inadequate response to treatment in people with schizophrenia and so the finding that there may not be a long-term improvement in symptoms once CBT has finished, does not necessarily indicate that the recommendations should be considered for update.

There is evidence that CBT is generally effective for a population with schizophrenia and that there are, at the very least, short-term benefits for a clozapine-resistant population. This would indicate that the recommendations are unlikely to be impacted by the results of the FOCUS trial.

Finally, NICE is developing a guideline on rehabilitation in adults with complex psychosis and related severe mental health conditions. This guideline is aiming to cover the delivery of optimised treatments for people with complex psychosis to help recovery and prevent relapse and may cover some of the issues raised by the FOCUS trial.

The STEPWISE trial

Methods

The structured lifestyle education to support weight loss for people with schizophrenia, schizoaffective disorder and first episode psychosis (STEPWISE) trial (Holt et al. 2018) was a parallel-group, randomised, analyst-blinded trial. The objective was to develop and evaluate group lifestyle sessions for people with first episode psychosis or schizophrenia.

Participants were recruited from community mental health teams across 10 NHS mental health trusts in England. To be eligible for the study, participants were required to be aged 18 or over, have a diagnosis of schizophrenia or schizoaffective disorder or first episode psychosis, treated with an antipsychotic, able to give written informed consent, able and willing to participate in a group intervention, able to speak and read English, and have a BMI of $\geq$25 kg/m^2 or were concerned about their weight. The BMI value was reduced to $\geq$23 kg/m^2 for participants from a South Asian or Chinese background.

Participants were excluded from the trial if they had: a physical illness that either reduced their life expectancy or affected metabolic measures, a mental illness that reduced their ability to participate in the trial, a current pregnancy, a condition associated with significant weight gain, a diagnosis of psychotic depression or mania, a learning disability,

significant alcohol or substance misuse, or were already participating in a weight management programme.

A web-based system was used to generate lists in permuted blocks of random sizes. This was done in a central location to ensure allocation blinding from the study team. In a 1:1 ratio, participants were allocated to either the TAU only group or the TAU plus intervention group. The study team performing outcome measurements were blinded to the allocation.

The STEPWISE education programme intervention consisted of a foundation course of 4 weekly 2.5-hour group sessions followed by individual support contacts until the end of the 12-month follow-up period. The support contacts consisted of 10-minute personalised discussions with each participant every 2 weeks. Participants in the intervention group also attended 2.5-hour booster group sessions at 4, 7 and 10 months after randomisation. The main components of the STEPWISE intervention consisted of providing the participants with skills in problem-solving around dietary and physical activity choices. The aim of these skills was to promote schizophrenia symptom relapse-prevention and weight improvement in participants.

The TAU consisted of providing participants with written leaflets containing advice on the risk of weight gain and lifestyle advice on diet, physical activity, smoking and alcohol use. All participants were provided TAU prior to randomisation.

The primary outcome measure was weight change at 12 months. Secondary outcome measures were: BMI, waist circumference, physical activity, adapted Dietary Instrument for Nutrition Education questionnaire, blood pressure, fasting glucose, lipid profile, glycated haemoglobin, health state utility (EuroQol-5 Dimensions five-level version [EQ-5D-5L]), Short Form questionnaire-36 items (SF-36), Brief Illness Perception Questionnaire ([B-IPQ] weight), Brief Psychiatric Rating Scale, health and social care resource use (Client Service Receipt Inventory), Patient Health Questionnaire 9-item depression scale, and adverse events. All measures were taken at baseline along with a medical and psychiatric history, fasting blood sample, and measures of vital signs. For analysis, the secondary outcomes were measured at the 3-month and 12-month follow-up periods.

Health outcomes were measured using EQ-5D-5L and the SF-36 in order to derive quality-adjusted life-years (QALYs). The threshold set by NICE of £20,000-per-QALY-gained was used to determine cost-effectiveness.

Results

A total of 412 participants were included in the intention-to-treat analysis with 207 in the intervention and 205 in the control groups.

For the primary outcome of weight change, the difference between groups was not statistically significant at 3 months. Participants in the intervention group showed a mean reduction of 0.2 kg and those in the control group showed a mean increase of 0.4 kg (−0.55 kg difference between groups, 95% CI –1.44 to 0.35 kg, p=0.230).

The difference between groups was not statistically significant at the primary comparison time of 12 months either. Participants in the intervention group showed a mean reduction of 0.47 kg and those in the control group showed a mean reduction of 0.51 kg (0.04 kg difference between groups, 95% CI –1.59 to 1.67 kg, p=0.964).

At 12 months the mean weight loss for each group was below the 4.5 kg defined threshold for minimally clinically important difference.

Participation in the intervention group did not significantly change any of the secondary outcomes compared to TAU.

The health economic analysis found an incremental cost-effectiveness ratio (ICER) from the healthcare perspective to be £246,921 per QALY gained and the ICER from the societal perspective to be £367,543 per QALY gained.

Guideline development

Recommendation 1.1.3.1 in NICE's guideline currently recommends that 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. The guideline development group noted that there was evidence to suggest that behavioural interventions to promote physical activity and healthy eating are effective in reducing body weight/BMI in the short-term (6 months). No longer-term data was available at the time of guideline development.

Previous surveillance

Some evidence was identified in the 2017 surveillance review that broadly supported the

recommendation to offer a physical activity programme to people with psychosis or schizophrenia.

Views of topic experts

The majority of topic experts that provided feedback on this study (4 out of 5) felt that STEPWISE was unlikely to impact on the current recommendation to offer people with psychosis or schizophrenia a combined healthy eating and physical activity programme as the current guidance does not specify the type or structure of lifestyle interventions. It was noted that the recent Management of physical health conditions in adults with severe mental disorders (WHO Guidelines, published in November 2018) also include recommendations very similar to the NICE guideline on healthy eating and physical activity for people who were overweight or obese, and do not specify how the intervention should be delivered.

Impact

The STEPWISE study results are relevant to recommendation 1.1.3.1 in NICE's guideline and it is a UK-based study. The study aimed to recruit people with schizophrenia and first episode psychosis, as weight gain is most noticeable following the onset of the condition and commencement of antipsychotic medication. However, the study was unable to recruit many people with first episode psychosis, and those that were recruited had been on treatment for several months or longer meaning that the researchers were unable to test whether the intervention was effective at the time of most rapid weight gain (in particular, the first 3 months following antipsychotic initiation).

The overall finding that the STEPWISE lifestyle education intervention is not clinically effective or cost-effective does not necessarily contradict recommendation 1.1.3.1 in the NICE guideline. This recommendation advises that people with psychosis or schizophrenia should be offered a combined healthy eating and physical activity programme by their mental healthcare provider to improve their physical health but is not specific about what that intervention should comprise. Although the specific STEPWISE intervention was not clinically effective it doesn't necessarily refute the benefits of healthy eating or physical activity programmes generally.

The STEPWISE intervention was based on a lifestyle programme aimed at people with diabetes. Although STEPWISE had been adapted for people with schizophrenia or psychosis, it remains unclear whether the adaptations were adequate enough to be

relevant for this population. The study authors recognised that further changes may be required to create a lifestyle programme suitable for people with schizophrenia or psychosis. They concluded that the lifestyle programmes that are effective in other populations may not be effective for schizophrenia.

However, the recommendations in the NICE guideline do not specify the type or structure of lifestyle interventions. This decision would be the responsibility of individual services to develop and provide based on their local service and patient population needs. Recommendation 1.1.3.1 was originally developed as a way to challenge the problems of weight gain, lack of physical activity and high rates of physical comorbidities often associated with schizophrenia and psychosis. Although there was a paucity of evidence at the time of developing the recommendations on physical health, it was seen as important to reduce weight and improve the quality of life for people with schizophrenia.

While the STEPWISE trial suggests that this specific lifestyle intervention is not effective, it does not indicate the effectiveness of general lifestyle interventions for this population. For this main reason, the current recommendations in the NICE guideline are unlikely to be impacted.

The Coroner's report

Background

NICE received details of a Coroner's investigation which included a report on preventing further deaths. This report highlighted concerns regarding an individual whose death was determined to have been caused by clozapine toxicity, pneumonia, and treatment resistant schizophrenia. The Coroner concluded that action should be taken at a national level to develop policy that requires 6 monthly or yearly monitoring of blood plasma in people prescribed clozapine.

Current practice

The Coroner's report implies that the blood levels of clozapine should be monitored as well as blood counts. In order to be prescribed clozapine, the patient, prescriber and supplying pharmacist must be registered with the appropriate Patient Monitoring Service.

The summary of product characteristics (SPC) for clozapine and processes outlined in the British National Formulary (BNF) contain extensive and detailed advice around the

monitoring of specific parameters during clozapine administration, in particular strict guidance on monitoring white blood cell counts and absolute neutrophil count to minimise the risk of agranulocytosis and advice on monitoring of other parameters including electrocardiogram, blood pressure, weight, plasma lipids and plasma glucose. There is no specific advice about monitoring blood levels of clozapine.

The Medicines and Healthcare products Regulatory Agency (MHRA) have also issued the following drug safety advice on clozapine:

- Antipsychotics: risk of venous thromboembolic events
- Atypical (second-generation) antipsychotics: reminder to monitor and manage weight, glucose, and lipid levels
- Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus
- Smoking and smoking cessation: clinically significant interactions with commonly used medicines

When considering plasma monitoring of clozapine, the advice on smoking and smoking cessation and its effect on concentrations of clozapine should be viewed as relevant as the dose may need to be adjusted. The SPC also contains advice on interactions that can influence blood levels of clozapine.

As for all medicines, the MHRA will closely monitor the safety of clozapine and take actions as necessary to amend regulatory documents and inform healthcare professionals (and NICE through established routes) of any identified safety issues.

Views of topic experts

Feedback was sought from topic experts about whether blood level monitoring for clozapine is conducted routinely in clinical practice. It was noted that some prescribers may carry out blood level monitoring but it may not always be done routinely. There was a view that blood levels may not be an entirely reliable predictor of effectiveness and toxicity due to variability in how clozapine can be metabolised. Additionally, changes in patient circumstances, such as smoking cessation, can impact on how clozapine is metabolised and put patients at risk of toxicity if drug levels are not adjusted. Topic experts indicated that, for these reasons, clinician judgement is key in when and if to monitor blood levels of clozapine.

Impact

NICE's guideline includes recommendations in section 1.5.7 to offer clozapine for people with schizophrenia who have not responded to treatment with at least 2 different antipsychotic drugs. The guideline also includes recommendations to monitor fasting blood glucose, glycosylated haemoglobin, blood lipid profile, and prolactin levels before starting any antipsychotic medication. The recommendations also advise that these blood measures should be routinely and systematically monitored throughout treatment, specifically at 12 weeks then annually. However, these recommendations may not give an indication of toxicity associated with the use of clozapine.

It is recognised that the current recommendations in the NICE guideline on monitoring may not account for adverse effects and risks of toxicity associated with the use of clozapine, however this is specified in detail in the BNF and the SPC. The SPC also contains advice on interactions that can influence blood levels of clozapine and the MHRA have produced a drug safety update on smoking and smoking cessation and its effect on concentrations of clozapine. In order to be prescribed clozapine, the patient, prescriber and supplying pharmacist must be registered with the appropriate Patient Monitoring Service. There is an expectation for prescribers to follow national medicine guidance as well as the SPC for all medicines.

For these reasons, it is recommended not to update the NICE guideline but instead make the Department of Health and Social Care and the MHRA aware of the issue raised in the Coroner's report to consider whether any action is needed to amend regulatory documents.

Overview of 2019 surveillance methods

Exceptionally, significant new evidence may mean an update of a guideline is agreed before the next scheduled check of the need for an update. The evidence might be a single piece of evidence, an accumulation of evidence or other published NICE guidance.

Evidence

This exceptional review provides an overview of 2 studies and a Coroner's report published since the end of the search period for the previous surveillance review (March 2017). The results of this new evidence was considered in detail to determine if there is an impact on guideline recommendations.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Because this was an exceptional surveillance review we did not consult on the decision.

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.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we decided that no update is necessary.

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