Switching antipsychotic medication to reduce sexual dysfunction in people with psychosis: the REMEDY RCT

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Declared competing interests of authors: Michael J Crawford is Director of the College Centre for Quality Improvement at the Royal College of Psychiatrists (London, UK) (from 2011 to present) and has been a member of the National Institute for Health Research (NIHR) Health Technology Assessment General Committee (2017–18). Elizabeth Hughes received personal fees for speaking at a Lundbeck (Copenhagen, Denmark)-sponsored event. Zoe Hoare has been a member of the NIHR Health Services and Delivery Research panel (2016–20). Carol Paton received personal fees as an advisory board member for Allergan Ltd (Marlow, UK). Sofia Pappa received personal fees as a speaker for Janssen Pharmaceutica (Beerse, Belgium), Sunovion (Marlborough, MA, USA) and Recordati (Milan, Italy). Thomas RE Barnes received personal fees as a speaker for Janssen and as an advisory board member for Lundbeck, Newron Pharmaceuticals (Milan, Italy) and Gedeon Richter (Budapest, Hungary).

Published September 2020
DOI: 10.3310/hta24440

Scientific summary

The REMEDY RCT

Health Technology Assessment 2020; Vol. 24: No. 44
DOI: 10.3310/hta24440

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Antipsychotic medication is an important part of the treatment of people with psychosis, but side effects are common. At least half of people who take antipsychotic medication for schizophrenia experience sexual dysfunction. People with psychosis who experience sexual side effects of antipsychotic medication have reduced quality of life and are less likely to adhere to medication, increasing the likelihood of relapse.

When sexual dysfunction is associated with use of antipsychotic medication, clinicians may consider switching to an antipsychotic drug that is considered less likely to cause sexual dysfunction. However, switching medication may increase the risk of relapse, and the new medication may have a greater liability for other side effects. To date, studies examining the impact of switching antipsychotic medication in an attempt to reduce sexual dysfunction associated with use of these medications have been too small to guide clinical practice.

The Randomised Evaluation of Management of sExual DYsfunction (REMEDY) trial was designed to generate high-quality evidence on the clinical effectiveness and cost-effectiveness of switching antipsychotic medication to reduce sexual dysfunction among people with psychosis.

Objectives

The main objective of the study was to examine if switching antipsychotic medication plus brief psychoeducation provides a clinically effective and cost-effective method for reducing sexual dysfunction in people with schizophrenia and related psychoses compared with brief psychoeducation and support alone. The study was designed to test if such a treatment intervention:

- leads to improved patient-rated sexual functioning over a 6-month period
- leads to changes in mental health, side effects of medication, health-related quality of life and service utilisation
- provides a cost-effective way to improve patient-rated sexual dysfunction and patient-reported quality of life.

Methods

Study design

A two-arm, parallel-group, double-blind, placebo-controlled randomised trial with an integrated economic evaluation and a parallel qualitative study.

Setting

Study participants were recruited from inpatient units and outpatient clinics in secondary care mental health services in England.

Target population

People aged $\geq$ 18 years who were in contact with mental health services, with a clinical diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis not otherwise specified, and who reported sexual dysfunction that was associated with the use of antipsychotic medication.

To take part in the study potential participants had to have significant sexual dysfunction indicated by a total score of ≥ 19 points on the Arizona Sexual Experience Scale or a score of ≥ 5 points on one of the scale items. We recruited only people for whom reducing the dose of their current antipsychotic was judged either ineffective or clinically inappropriate. We excluded potential participants if their sexual dysfunction was judged to be the result of an underlying physical health condition. We also excluded those who:

- were acutely psychotic, either currently or within the last 3 months
- were unable to speak sufficient English to complete the study assessments
- were currently prescribed clozapine
- reported that their current sexual problems started prior to their taking antipsychotic medication
- were taking part in another clinical trial.

Health technologies assessed

All participants taking part in the trial were offered enhanced standard care. This comprised usual care plus up to two sessions of brief psychoeducation and support to discuss their sexual health and functioning. In addition to this, those randomised to the switch arm of the trial were offered a change in their current antipsychotic medication to one considered to have a lower propensity to cause sexual dysfunction. A clinical decision was made to switch the patient to one of three antipsychotic medications (i.e. aripiprazole, quetiapine or olanzapine) based on their previous response to antipsychotic medication, the side effect profile of these medications, patient preference and potential interactions with other medications the patient was taking.

Internal pilot trial

Recruitment began at three Trusts as part of an internal pilot phase of the trial. The pilot trial was designed to assess the feasibility of recruiting and retaining study participants. The aim was to recruit 36 participants at three Trusts over a 6-month period. The stopping criteria were failing to recruit 80% of this sample and/or failing to follow up ≥ 75% of the sample at 3 months.

Measurement of costs and outcomes

Our primary outcome was the Arizona Sexual Experience Scale. Secondary outcomes were researcher-rated sexual functioning (using the Clinical Global Improvement for Sexual Functioning scale); mental health (using the Positive And Negative Syndrome Scale); side effects of medication and health-related quality of life (using the REcovering Quality Of Life questionnaire and the EuroQol-5 Dimensions); side effects of medication (using the Antipsychotic Non-Neurological Side Effects Rating Scale); and adherence to medication (using the Brief Adherence Rating Scale). Resource use and costs were assessed using a modified version of the Adult Service Use Schedule. This questionnaire collects detailed data on use of all hospital and community services, including medication. All measures were assessed at baseline and at 6 months. Sexual function and adverse effects were also assessed 3 months after randomisation. All assessments were conducted by researchers masked to the allocation status of the participants.

We also conducted qualitative interviews with clinicians and participants to examine factors that influenced whether or not people took part in the study.

Recruitment

Staff working in mental health services identified potential participants by asking them about sexual functioning during appointments and by sending letters to those who had indicated problems with sexual functioning in the past. We supplemented this approach by encouraging self-referral to the study through displaying posters and distributing flyers at outpatient clinics and day care services used by people with psychosis. We sought consent to contact the person's care co-ordinator and psychiatrist about their current treatment if a patient appeared to be eligible to take part in the study. We asked clinical staff to assess and treat possible underlying medical causes of sexual dysfunction and to consider reducing the patient's current dose of antipsychotic medication prior to referring them back to the study team. Researchers then met with potential participants to obtain written informed consent and complete a baseline assessment.

Randomisation

Study participants were allocated to treatment arms using remote web-based randomisation via a secure, fully automated web-based service. The system used a sequentially randomised dynamic adaptive algorithm to allocate participants in a 1 : 1 allocation ratio to either enhanced standard care plus a medication switch or enhanced standard care alone, while balancing for four stratification variables (i.e. age, gender, Trust and relationship status).

Sample size

The sample size was calculated on the basis of our primary hypothesis: for people receiving treatment for schizophrenia and related psychoses who have sexual dysfunction associated with use of antipsychotic medication, switching to an alternative antipsychotic in addition to brief psychosexual education and support improves sexual dysfunction (as rated using the Arizona Sexual Experience Scale), compared with brief psychosexual education and support alone. We calculated that 172 participants (86 participants randomised to 'switch' and 86 participants to 'no switch') would need to be randomised to have 90% power to detect a 3-point difference in total Arizona Sexual Experience Scale score (standard deviation 6.0 points) at 26 weeks using a 0.05 significance level. Allowing for a 20% loss to follow-up, we aimed to recruit 216 participants.

Data analysis

We planned for a main analysis using a generalised linear model fitted at 6 months and adjusted for baseline score, allocation arm and stratification variables (i.e. gender and Trust). Data were to be analysed on an intention-to-treat basis. Secondary outcomes would be assessed with an equivalent analysis model. Patterns of missing data were to be assessed and the sensitivity of treatment effect estimates to the missing data tested using multiple imputation strategies.

The primary cost-effectiveness analysis was to involve comparing incremental differences in total costs and incremental differences in mental health (assessed using the Arizona Sexual Experience Scale). In a secondary cost–utility analysis we planned to compare incremental differences in costs with differences in quality of life (measured using quality-adjusted life-years derived from the EuroQol-5 Dimensions).

Qualitative study

In parallel with the trial, we aimed to collect qualitative data from participants and clinicians to explore their experiences of the study and the interventions and if and how they thought that any changes to treatment could affect sexual functioning and quality of life. We planned to interview purposive samples of participants and clinicians after the 6-month follow-up interviews had been completed.

Results

Low recruitment led to an extension of the pilot phase of the trial, but recruitment remained low and the trial was stopped after a 12-month period. Ninety-eight patients were referred to the study between 1 July 2018 and 30 June 2019, of whom 61 provided verbal consent to meet a researcher. Of these patients, 46 (75%) declined to take part in the study. The two main reasons patients gave for not wanting to take part in the study were that (1) their problem was not important enough for them to feel that they needed to do something about it and (2) they were concerned about the impact of switching medication on their mental health.

Of the 15 patients who were screened, 10 were eligible to take part in the trial and were randomised (six patients to a switch of medication plus enhanced standard care and four patients to enhanced standard care alone).

The mean age of the study sample was 46 years (standard deviation 11.0 years) and eight were male. Seven participants received brief psychoeducation and support, and five of the six participants in the switch arm of the trial had a switch in their medication. In each instance the switch was to aripiprazole (three participants to oral aripiprazole and two participants to aripiprazole long-acting injection).

A total of eight (80%) participants completed 3 months' follow-up. Insufficient data were collected to be able to compare changes in study outcomes during the course of the trial. No participant reported being satisfied with their sex lives either at the start of the study or at follow-up. Only one participant, who was in the switch arm of the trial, was rated by the researcher as having improved sexual functioning at follow-up, but improvement was judged to be minimal. There was one serious adverse event in the switch arm of the trial: hospitalisation for a physical health condition that was unrelated to study procedures.

Implications for health care

We were unable to recruit sufficient numbers to the study to draw any conclusions about the benefits or harms associated with switching antipsychotic medication in an effort to manage sexual side effects of these medications.

Recommendations for future research

Consideration should be given to examining the clinical effectiveness and cost-effectiveness of adjuvant phosphodiesterase inhibitors for the treatment of sexual dysfunction associated with antipsychotic medication taken by people with psychosis.

Trial registration

This trial is registered as ISRCTN12307891.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 44. See the NIHR Journals Library website for further project information

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 16/95/01. The contractual start date was in May 2018. The draft report began editorial review in January 2020 and was accepted for publication in May 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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