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

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

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# Abstract

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

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**Background:** Sexual dysfunction is common among people who are prescribed antipsychotic medication for psychosis. Sexual dysfunction can impair quality of life and reduce treatment adherence. Switching antipsychotic medication may help, but the clinical effectiveness and cost-effectiveness of this approach is unclear.

**Objective:** To examine whether or not switching antipsychotic medication provides a clinically effective and cost-effective method to reduce sexual dysfunction in people with psychosis.

**Design:** A two-arm, researcher-blind, pilot randomised trial with a parallel qualitative study and an internal pilot phase. Study participants were randomised to enhanced standard care plus a switch of antipsychotic medication or enhanced standard care alone in a 1 : 1 ratio. Randomisation was via an independent and remote web-based service using dynamic adaptive allocation, stratified by age, gender, Trust and relationship status.

**Setting:** NHS secondary care mental health services in England.

**Participants:** Potential participants had to be aged  $\geq 18$  years, have schizophrenia or related psychoses and experience sexual dysfunction associated with the use of antipsychotic medication. We recruited only people for whom reduction in medication dosage was ineffective or inappropriate. We excluded those who were acutely unwell, had had a change in antipsychotic medication in the last 6 weeks, were currently prescribed clozapine or whose sexual dysfunction was believed to be due to a coexisting physical or mental disorder.

**Interventions:** Switching to an equivalent dose of one of three antipsychotic medications that are considered to have a relatively low propensity for sexual side effects (i.e. quetiapine, aripiprazole or olanzapine). All participants were offered brief psychoeducation and support to discuss their sexual health and functioning.

**Main outcome measures:** The primary outcome was patient-reported sexual dysfunction, measured using the Arizona Sexual Experience Scale. Secondary outcomes were researcher-rated sexual functioning, mental health, side effects of medication, health-related quality of life and service utilisation. Outcomes were assessed 3 and 6 months after randomisation. Qualitative data were collected from a purposive sample of patients and clinicians to explore barriers to recruitment.

**Sample size:** Allowing for a 20% loss to follow-up, we needed to recruit 216 participants to have 90% power to detect a 3-point difference in total Arizona Sexual Experience Scale score (standard deviation 6.0 points) using a 0.05 significance level.

**Results:** The internal pilot was discontinued after 12 months because of low recruitment. Ninety-eight patients were referred to the study between 1 July 2018 and 30 June 2019, of whom 10 were randomised. Eight (80%) participants were followed up 3 months later. Barriers to referral and recruitment included staff apprehensions about discussing side effects, reluctance among patients to switch medication and reticence of both staff and patients to talk about sex.

**Limitations:** Insufficient numbers of participants were recruited to examine the study hypotheses.

**Conclusions:** It may not be possible to conduct a successful randomised trial of switching antipsychotic medication for sexual functioning in people with psychosis in the NHS at this time.

**Future work:** Research examining the acceptability and effectiveness of adjuvant phosphodiesterase inhibitors should be considered.

**Trial registration:** Current Controlled Trials 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.

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## List of abbreviations

ANNSERS	Antipsychotic Non-Neurological Side Effects Rating Scale	Natsal-3	National Survey of Sexual Attitudes and Lifestyles
ASEX	Arizona Sexual Experience Scale	PANSS	Positive And Negative Syndrome Scale
BARS	Brief Adherence Rating Scale	REMEDY	Randomised Evaluation of Management of sExual DYsfunction
CDSS	Calgary Depression Scale for Schizophrenia	ReQoL	Recovering Quality of Life
CGI	Clinical Global Impression	SD	standard deviation
EQ-5D	EuroQol-5 Dimensions		
GP	general practitioner		



## Plain English summary

Antipsychotic medications can improve the mental health of people with psychosis but may also cause side effects. These include sexual side effects, such as reduced desire for sex or less pleasure from having sex. One way to try to tackle this problem is to switch the medicine people take to one that is thought less likely to cause these problems. However, it is unclear if this helps, and switching medication could potentially harm mental health or cause new side effects.

We conducted a study to compare the effect of switching with not switching the medication of people with psychosis experiencing sexual side effects. We collected information about sexual functioning, mental health, quality of life and use of services at the start of the study and 6 months later. We also interviewed nurses, doctors and patients to get their views about the study.

We recruited 10 patients over a 12-month period and conducted interviews with 51 clinicians and four patients.

Many clinicians said that they found it difficult to talk to their patients about sex. Some thought that these problems occurred rarely and that other side effects mattered more to patients. Many patients were concerned about switching their medication, especially when it had improved their mental health. Others felt that these side effects were not very important, and some were not prepared to take part in a trial that could delay a change being made to their medication.

We did not collect enough information to be able to find out if switching medication helps people who experience sexual side effects of antipsychotic drugs.

It is important that clinicians ask about sexual side effects of antipsychotic medication and that further efforts are made to find ways to help patients who experience them.



# 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  $\geq 19$  points on the Arizona Sexual Experience Scale or a score of  $\geq 5$  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  $\geq 75\%$  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**

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# Chapter 1 Introduction

Schizophrenia is a severe mental health condition that affects almost 250,000 people in Britain. The illness usually starts in early adult life and can have a major impact on a person's quality of life and social functioning.<sup>1,2</sup> Antipsychotic medication can improve the mental health of most people with the condition, but it can have a range of side effects that can impair a person's quality of life. Over recent years, interventions have been developed that counteract some of the adverse effects (e.g. weight gain and changes in blood glucose) of antipsychotic medications.<sup>3,4</sup> By contrast, sexual dysfunction is a common side effect of antipsychotic medication, and there is no clear evidence to guide clinicians and patients seeking to manage this side effect.<sup>5</sup>

## Impact of sexual dysfunction associated with antipsychotic medication

At least half of people who take antipsychotic medication for schizophrenia experience sexual dysfunction.<sup>6-8</sup> The mechanisms through which antipsychotic drugs cause sexual dysfunction are varied.<sup>9,10</sup> Many antipsychotic drugs block dopamine receptors. This can lead to increased levels of prolactin, which reduces sex drive.<sup>11</sup> Some antipsychotic drugs have sedative effects, which may also reduce libido. Others have direct effects on blood flow to reproductive organs and can impair sexual functioning. Changes in blood lipids and glucose metabolism associated with antipsychotic medications may also lead to peripheral vascular disease and associated impairments to sexual functioning over the longer term.<sup>12</sup>

Sexual dysfunction can have a negative impact on a person's well-being and quality of life.<sup>13-15</sup> In a study of 139 men with schizophrenia in North America, those with sexual dysfunction reported lower overall quality of life than those with no sexual dysfunction.<sup>16</sup> Among those with sexual partners, people experiencing sexual dysfunction reported having poorer-quality relationships and being less likely to discuss their illness with their partner.<sup>16</sup>

Sexual dysfunction can also affect adherence to antipsychotic medication. Surveys of people with psychosis indicate that sexual dysfunction is a common reason for stopping antipsychotic medication, which increases the likelihood of relapse and readmission to hospital.<sup>17,18</sup> Many patients find it difficult to talk to their mental health team about sexual dysfunction. For example, in one survey 80% of women who had experienced sexual dysfunction associated with use of antipsychotic medication had not discussed this with their mental health nurse or psychiatrist.<sup>17</sup> This means that people may stop their medication without seeking advice about how to manage these important problems.

## Assessment of sexual dysfunction among people taking antipsychotic medication

Although sexual side effects of antipsychotic drugs are those that people with psychosis are most troubled by,<sup>18</sup> there is evidence that clinicians find it difficult to discuss them.<sup>19</sup> Data from audits of prescribing practice show that sexual side effects of antipsychotic drugs are those least likely to be recorded in a patient's clinical records.<sup>20</sup> It is unclear why mental health professionals have paid less attention to sexual side effects of antipsychotic medications than to other adverse effects. It is possible that some find it difficult to talk to patients about sexual side effects or are not aware how common they are. By contrast, most people using mental health services consider their sexual health and functioning to be important for their quality of life<sup>16</sup> and expect mental health professionals to enquire about sexual matters.<sup>21</sup>

## Management of sexual dysfunction associated with antipsychotic medication

When sexual dysfunction is associated with the use of antipsychotic medication, clinicians may try reducing the dose of medication they prescribe.<sup>9</sup> This can be an effective strategy when it is possible to do this without having a negative impact on the person's mental health.<sup>22</sup>

When reducing the dose of medication is not possible, an alternative approach is to switch to an antipsychotic that is associated with a lower incidence of sexual dysfunction. Open-label studies of switching a person's antipsychotic medication to aripiprazole<sup>23</sup> or quetiapine<sup>24</sup> have demonstrated beneficial effects. However, to the best of our knowledge, only two small randomised trials have compared the effects of switching medication with no switch for the management of sexual dysfunction associated with antipsychotic medication. Kinon *et al.*<sup>25</sup> randomised 54 men and women who were taking antipsychotic medication for schizophrenia and who had sexual dysfunction to either a switch to olanzapine or continuation of their current drug regimen. The study<sup>25</sup> noted improved self-reported sexual functioning among those switched to olanzapine at 4 months. Byerly *et al.*<sup>26</sup> compared switching from risperidone to quetiapine with maintenance risperidone on sexual functioning of 42 men and women with schizophrenia. Participants were followed up for only 6 weeks. No statistically significant differences were found, but a non-statistically significant trend towards improved sexual functioning was seen in those who switched to quetiapine. Neither study was sufficiently powered to assess harms associated with switching antipsychotic drugs.

Switching a person's antipsychotic medication may increase the risk of relapse,<sup>27,28</sup> and different side effects associated with the medication may lead to poorer health outcomes or reduced quality of life.<sup>3</sup> A Cochrane review<sup>29</sup> of the management of sexual dysfunction associated with antipsychotic medication among people with schizophrenia concluded that switching to another drug may provide an effective way to manage sexual side effects. An update<sup>5</sup> of this review in 2018 found no new trials that tested the effects of switching medication.

### The REMEDY trial

Switching medication may provide an effective strategy for improving sexual functioning and quality of life for people with schizophrenia who experience sexual dysfunction associated with use of antipsychotic medication. However, uncertainty about how effective this strategy is, together with concerns about increased risk of relapse and emergence of new side effects, means that clinicians and patients do not know whether or not this is an effective approach to help people who experience these problems.

The Randomised Evaluation of Management of sExual DYsfunction (REMEDY) trial was designed to address this uncertainty. The main aim of the study was to test whether or not switching a person's antipsychotic medication to one considered to have a relatively low propensity for sexual side effects plus brief psychoeducation and support improved patient-reported sexual dysfunction compared with brief psychoeducation and support alone.

### Trial objectives

- To examine whether or not switching medication is a clinically effective and cost-effective strategy for improving sexual functioning among people with psychosis who experience sexual dysfunction associated with the antipsychotic medication they are prescribed.
- To examine whether or not switching antipsychotic medication leads to changes in mental health, side effects of medication, health-related quality of life or service utilisation for people with psychosis who report sexual side effects.
- To examine barriers to recruitment when conducting a trial of an intervention to reduce sexual dysfunction among people with psychosis.

# Chapter 2 Methods

## Design

The study was a multicentre, two-arm, parallel-group, researcher-blind randomised controlled trial with an internal pilot and a parallel qualitative study.

## Study setting

The study setting was secondary care NHS community mental health services in England. We planned to recruit participants from all those in contact with community mental health services in five Trusts in the north and north-east of England and west and north-west of London.

## Participants

To be eligible to take part in the study, potential participants had to be aged  $\geq 18$  years, have a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychosis not otherwise specified, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,<sup>30</sup> and have sexual dysfunction associated with their use of antipsychotic medication, for which reducing the dose they were taking was either not effective or not appropriate.

Potential participants were excluded if:

- they were acutely psychotic or had been acutely psychotic
- their clinical team judged that they had an underlying physical health condition that was responsible for their sexual dysfunction
- their current sexual problems began prior to their starting antipsychotic medication
- they were already taking part in another clinical trial
- they were unable to speak sufficient English to complete the baseline assessment
- they were currently prescribed clozapine (a medication used when people have not responded to other antipsychotic medications).

## Interventions

All study participants were offered enhanced standard care comprising treatment as usual plus brief psychoeducation and support to discuss their sexual health and functioning. The content of these sessions was based on that published by NHS Choices.<sup>31</sup> Brief psychoeducation and support included written information on specific psychosexual issues and psychoeducation, and signposting to the NHS Choices website and their primary care team should participants want additional help. Those delivering the brief psychoeducation and support were asked to keep a record of the time taken to deliver it and the content of the session. All those who took part in the study continued to have access to mental health services. No restrictions were placed on the use of other treatments.

## Treatment in the switch arm of the trial

In addition to enhanced standard care, those in the switch arm of the trial were offered a switch from their current antipsychotic medication to an equivalent dose of another antipsychotic medication that

is considered to have a lower propensity to cause sexual dysfunction. Evidence from observational and experimental studies suggest that improvements in sexual dysfunction associated with antipsychotic medication may result from swapping to aripiprazole,<sup>23,32</sup> quetiapine<sup>24,26</sup> or olanzapine.<sup>25</sup> A meta-analysis<sup>33</sup> of the occurrence of sexual dysfunction among people taking antipsychotic medication found that two of these drugs (i.e. aripiprazole and quetiapine) were among those least likely to be associated with sexual side effects and that these three medications (i.e. aripiprazole, quetiapine and olanzapine) were the least likely to be associated with arousal dysfunction.

We asked clinicians to use their clinical judgement to select which medication to switch to, based on the known side effect profiles of these medications, patient preference, previous response to antipsychotic medication and potential interactions with other drugs the patient may be taking.<sup>34</sup> For patients who were being prescribed long-acting injectable antipsychotic preparations, clinicians could decide to switch the participant's medication to oral aripiprazole, quetiapine or olanzapine, or aripiprazole long-acting injection. This was because quetiapine is not available as a long-acting injection and participating Trusts had not approved the use of olanzapine long-acting injection in community settings during the recruitment phase of the trial.

Prescribers overseeing any switch in medication were asked to gradually discontinue the participant's current antipsychotic while at the same time gradually introducing the new antipsychotic medication (i.e. cross-tapering) to reach an equivalent dose. The equivalent was based on the Prescribing Observatory for Mental Health-UK's *Antipsychotic Dosage Ready Reckoner – Version 6.1*.<sup>35</sup> We asked prescribers to aim to complete this cross-tapered switch of antipsychotic medication over a 4-week period (Table 1).

## Assessments

### Assessment of eligibility and covariates

A summary of all data collected from study participants is presented in Table 2. In addition to collecting basic demographic data on age, sex, ethnicity, marital/relationship status, socioeconomic status and education level, we assessed eligibility using the Arizona Sexual Experience Scale (ASEX) and a question on the onset of sexual dysfunction. We collected additional information on the participant's sex life using questions from the National Survey of Sexual Attitudes and Lifestyles (Natsal-3).<sup>37</sup>

The ASEX is a five-item self-report measure of sexual dysfunction that is widely used, sensitive to change and takes < 5 minutes to complete.<sup>26,38</sup> To take part in the study, potential participants had to have a total ASEX score of  $\geq 19$  points or a score of  $\geq 5$  points on one of item of the ASEX. Potential participants were then asked when their sexual problems started. Only those who stated that their problem began after they started medication for their mental health condition were judged eligible to take part in the study. Those who were ineligible were thanked for their time, informed of the reason(s) why they were ineligible and offered a leaflet containing information about sexual dysfunction and sources of help.

TABLE 1 Recommendation for switching pre-study antipsychotic

Week	Recommended dose of pre-study antipsychotic medication	Recommended dose of switch medication
1	80% of pre-study dose	British National Formulary-recommended starting dose for the switch drug <sup>36</sup>
2	60% of pre-study dose	Adjust based on clinical judgement
3	40% of pre-study dose	Adjust based on clinical judgement
4	20% of pre-study dose	Adjust based on clinical judgement
5	Nil	Equivalent dose of switch medication

TABLE 2 Study assessment schedule

Assessment	Time point			
	Post-consent screening	Baseline	3-month follow-up	6-month follow-up
Demographic information	X			
Participant contact details	X		X	
Sexual functioning (ASEX)	X		X	X
Sexual behaviour (Natsal-3)	X			X
Question on onset of sexual dysfunction	X			
Alcohol and drug use (ASSIST)		X		
BARS		X		X
Service use (AD-SUS)		X		X
Depression (CDSS)		X		X
CGI for Sexual Functioning scale				X
Symptoms of schizophrenia (PANSS)		X		X
Side effects of antipsychotic drugs (ANNSERS)		X		X
Health-related quality of life (EQ-5D-5L)		X		X
Recovery and well-being (ReQoL)		X		X

AD-SUS, Adult Service Use Schedule; ANNSERS, Antipsychotic Non-Neurological Side Effects Rating Scale; ASEX, Arizona Sexual Experience Scale; ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; BARS, Brief Adherence Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; Natsal-3, National Survey of Sexual Attitudes and Lifestyles; PANSS, Positive And Negative Syndrome Scale; ReQoL, Recovering Quality of Life.

In keeping with recommended practice we used computerised-assisted direct interview for obtaining information about sexual functioning during study visits.<sup>39</sup> Participants used the Bristol Online Survey tool to complete the ASEX and to answer additional questions on sexual behaviour [URL: [www.onlinesurveys.ac.uk/](http://www.onlinesurveys.ac.uk/) (accessed 11 June 2020)].

### Primary outcome

The primary outcome was patient-reported sexual dysfunction, measured at 6 months using the ASEX. The ASEX is the most widely used measure of sexual dysfunction in this field.<sup>40</sup> It also provides a reliable assessment of sexual dysfunction among people with psychosis.<sup>41,42</sup>

### Secondary outcomes

- Total score on the ASEX at 3 months.
- Researcher-rated sexual functioning at 6 months, using the Clinical Global Impression (CGI) for Sexual Functioning.<sup>43</sup>
- Mental health, using the total score on the Positive And Negative Syndrome Scale (PANSS).<sup>44</sup> This is a 30-item rating scale that is accompanied by a structured interview. It has been widely used to examine changes in symptoms in people with schizophrenia and related psychoses.
- Side effects of medication, using the Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS). The ANNSERS covers a range of negative subjective experiences as well the cardiovascular, gastrointestinal and metabolic side effects of antipsychotic medication.<sup>45</sup>
- Medication adherence at baseline and 6 months, using the Brief Adherence Rating Scale (BARS).<sup>46</sup>
- Resource use data collected at baseline and 6 months, assessed using the Adult Service Use Schedule. The Adult Service Use Schedule is an instrument designed on the basis of previous studies in adult mental health populations.<sup>47</sup>
- Health-related quality of life, assessed using the EuroQol-5 Dimensions (EQ-5D)<sup>48</sup> and the Recovering Quality of Life (ReQoL) questionnaire<sup>49</sup> at 3 and 6 months.

## Blinding

All researchers who assessed study participants were masked to allocation status. Participants and clinical staff were aware of which arm of the trial people had been allocated to. To help maintain blinding researchers were not based with unblinded clinical team members. Prior to follow-up interviews participants were asked not to reveal the arm they have been allocated to. If any researcher became inadvertently unmasked, we arranged for another researcher to collect all further data.

## Study logistics

The flow of participants through the study is presented in *Figure 1*.

### Recruitment

We contacted clinical teams and asked them to identify potential participants. Researchers and other members of the study team, including people with lived experience of poor mental health, gave presentations at team meetings to explain the study rationale and inclusion criteria. Following feedback that staff wanted advice about how to raise the topic of sexual dysfunction with their patients, we distributed a short script by e-mail and circulated a link to a video illustrating how people could be asked about sexual side effects of their medication. We also used a broad range of methods to communicate directly with people with psychosis to let them know about the study. We asked clinicians to seek verbal consent from people they believed met our inclusion criteria, so that they could be approached by a member of the research team.

We also used a range of direct marketing strategies, including displaying posters in clinics, day care and residential services; giving presentations to patients attending NHS, social care and voluntary sector groups; and writing to people who had reported sexual dysfunction in the past. Approved study posters asked potential participants either to speak to their psychiatrist/mental health team about the possibility of their taking part in the study or to contact a member of the REMEDY research team. We also worked with clinical teams to identify people who had already undergone screening for side effects of medication and helped them send letters to patients who had indicated that they had experienced sexual side effects. Prior to meeting potential participants, researchers liaised with clinicians to check whether or not the person's sexual dysfunction could be the result of a physical health condition and whether or not they felt that they needed to have a trial of a reduction in the dose of their medication prior to taking part in the study.

If potential participants appeared to meet study inclusion criteria, arrangements were made for them to receive a copy of a patient information sheet and meet with a researcher to obtain written informed consent and complete a screening assessment. Researchers encouraged potential participants to spend as much time as they wanted asking questions about the study and considering if they wished to take part. In all instances potential participants were given at least 24 hours before deciding whether or not to take part in the study. Those who declined to take part were asked if they would be willing to take part in a short interview to establish their reasons for deciding not to take part. This interview took up to 10 minutes. Researchers took contemporaneous hand-written notes, which were subsequently transcribed. If potential participants declined to take part in an interview we asked them to provide a brief comment on their reason for deciding not to take part in the study.

### Screening and baseline assessment

If written informed consent was given and documented, the referring clinician completed a document to confirm their medical opinion of the participant's eligibility and a researcher then completed the post-consent screening assessment (see *Table 1*). Potential participants were screened using the ASEX and asked about the onset of their sexual dysfunction in relation to the antipsychotic medication they were prescribed. If the participant fulfilled all the eligibility criteria then the baseline assessment was

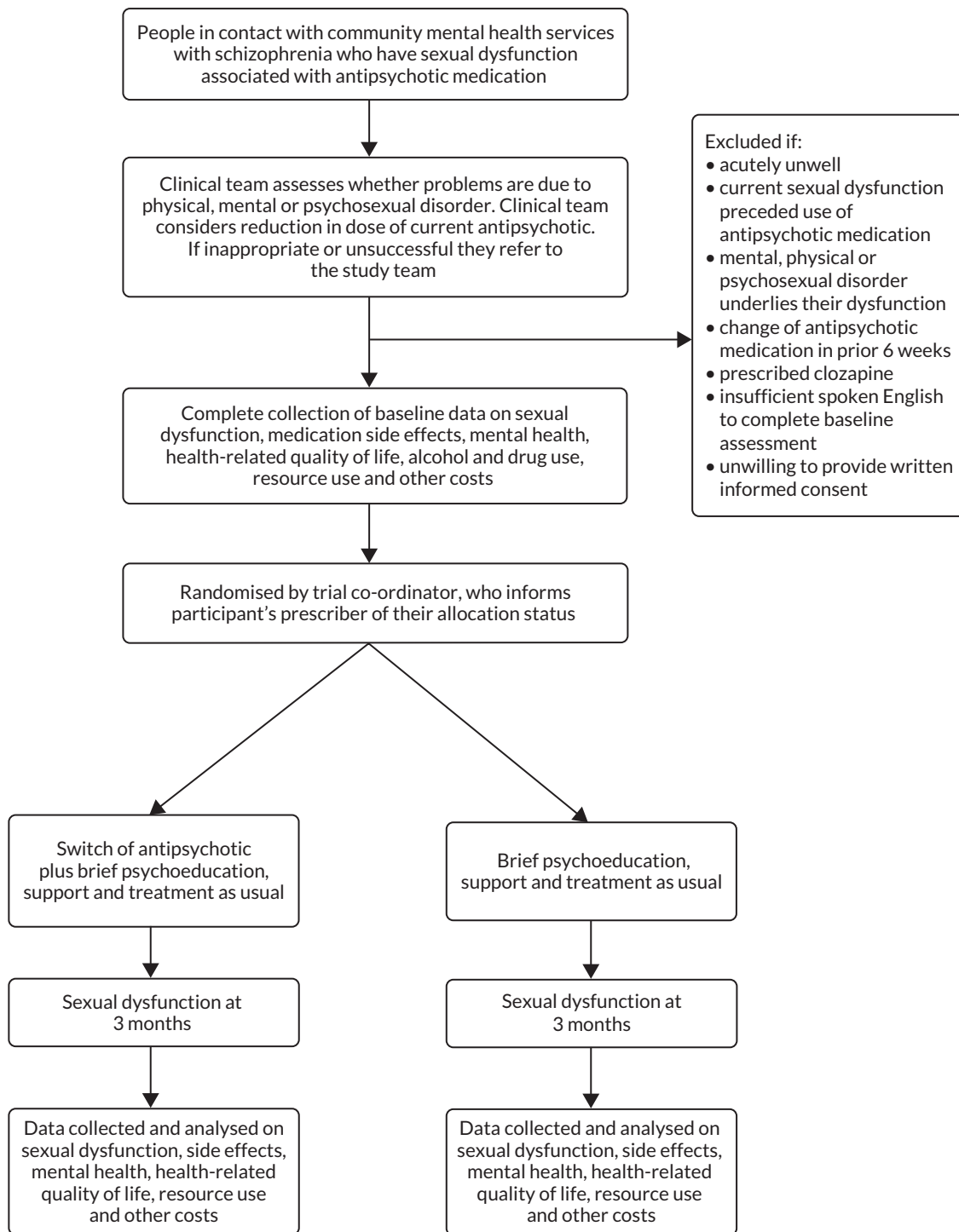


FIGURE 1 Study flow chart.

also completed and he/she was randomised into the trial. Following randomisation, the participant's general practitioner (GP) and consultant were informed of their enrolment into the trial.

### Assignment of interventions

Study participants were randomly allocated to study interventions using a remote web-based system developed and maintained by the North Wales Organisation for Randomised Trials in Health.<sup>50</sup> The system uses a sequentially randomised, dynamic and adaptive algorithm which randomises participants in a 1 : 1 allocation ratio to either enhanced standard care plus a medication switch or enhanced



standard care alone, while balancing for stratification variables. Stratification was by age (i.e. < 40 or ≥ 40 years), gender (i.e. male or female), Trust and relationship status (i.e. steady relationship or no steady relationship). For each participant randomised, the likelihood of their allocation to each treatment arm was recalculated based on the participants already recruited and allocated. This recalculation was done at the overall allocation level, within stratification variables and within strata. By undertaking this recalculation the algorithm ensured that balance was maintained within acceptable limits of the assigned allocation ratio while also maintaining unpredictability.

Following randomisation a member of the trial co-ordination team contacted the doctor or nurse who had agreed to oversee the delivery of study interventions. This clinician then made arrangements to offer the participant the brief psychoeducation and support and, for those in the switch arm of the trial, a switch in their medication.

### **Follow-up**

Participants received subsequent assessments 3 and 6 months after randomisation. The timing and content of all assessments are summarised in *Table 1*. Participants were asked to complete the ASEX 3 months after randomisation, either in person using the touch-screen computer or over the telephone (in which case the researcher completed a paper version of the questionnaire).

### **Data management**

All quantitative data were entered onto a secure web-based database. Access was restricted by encrypting the files. Audio-recordings of interviews with patient and staff were stored at local Trusts on encrypted files. Recordings were professionally transcribed verbatim and quality checked for accuracy. Once the transcriptions were verified, the recordings were deleted. Hand-written notes were taken during interviews with patients who declined to participate in the trial. These notes were then typed up, the files encrypted and the hand-written notes destroyed.

### **Sample size**

We based the sample size calculation on our primary hypothesis: for people who experience sexual dysfunction associated with use of antipsychotic medication, switching to alternative medication that is considered to have a lower propensity to cause these side effects will result in improved self-reported sexual functioning (as rated using the ASEX).

In their randomised trial of switching antipsychotics among 42 people with sexual dysfunction associated with use of antipsychotic medication, Byerly *et al.*<sup>26</sup> reported a mean ASEX score of 19.5 points at 6-weeks follow-up and a standard deviation (SD) of 5.7 points.

We based the sample size calculation on having 90% power to detect a 3-point difference in the ASEX score between study arms. Three points on this scale equates to a clear improvement in one of the five domains in the ASEX or marginal improvement in three areas. In addition, it is at the lower end of the range of differences (2.0–5.6 points) seen in previous small-scale studies of switching antipsychotic medication that have used ASEX.<sup>26,51</sup> Feedback from our service user advisory group was that a change of this magnitude would represent an important change in sexual functioning.

Using these data we calculated that a total sample of 172 participants (86 participants in the switch arm and 86 participants in the control arm) would be needed to have 90% power to detect a 3-point difference in total ASEX score (SD 6.0 points) at 26 weeks, using a 0.05 significance level. To allow for a 20% loss to follow-up we aimed to recruit 216 participants.



## Statistical analyses

We were not able to analyse differences in outcomes between study arms because of the very small sample size and limited number of follow-up data collected. Instead, we report details of participant flow, recruitment figures, demographic data, outcome measure descriptive statistics and details of safety events in *Chapter 3*. No inferences should be made from these data regarding differences between treatment arms, and summary statistics should be treated with caution because of low samples, especially when split by randomised allocation arm.

## Health economics analysis

Data on the use of health and social services were collected using a modified version of the Adult Service Use Schedule, which has been used extensively in research in similar populations.<sup>52,53</sup> Prior to recruitment starting during the set-up phase of the trial, the questionnaire was modified based on a literature review and in collaboration with clinical and service user members of the research team to ensure that it included all relevant services. Use of services was collected in interview using patient recall, which we considered to be sufficient for the 6-month follow-up.

For each service use item a relevant and suitable unit cost was identified, and these costs are listed in *Table 3*. All unit costs were for the financial year 2017/18. Costs for NHS hospital contacts were extracted from NHS reference costs,<sup>56</sup> community health and social care costs were taken from the *Unit Costs of Health and Social Care 2018*<sup>54</sup> and the cost of antipsychotic medication was estimated using costs per dose per item.<sup>36</sup>

Health-related quality-of-life data were collected using the EuroQol-5 Dimensions, five-level version,<sup>57</sup> and the ReQoL.<sup>58</sup> The EQ-5D is the measure preferred by the National Institute for Health and Care Excellence,<sup>59</sup> although there are concerns about its lack of sensitivity in people with psychotic symptoms.<sup>60</sup> To mitigate these concerns, we included the ReQoL,<sup>49</sup> which is a self-report outcome measure for use in people experiencing poor mental health.

The final sample size was too small to conduct the planned economic analysis. Instead, we conducted descriptive statistics on service use data, cost data at 6-month follow-up by randomised arm and quality-of-life data at baseline and 6-month follow-up. No inferences should be made from these data regarding the size and direction of differences in service use and costs, and summary statistics should be considered in the context of very small sample sizes.

## Parallel qualitative study

We originally set out to conduct a parallel process evaluation in keeping with Medical Research Council guidelines.<sup>61</sup> However, as the study progressed and we realised how challenging it was to recruit study participants, we changed the focus of the qualitative component of the study to explore these barriers.

TABLE 3 Unit costs and sources used in economic evaluation

Service	Unit cost (£)	Source
GP (per contact)	31.30	<i>Unit Costs of Health and Social Care 2018</i> <sup>54</sup>
Practice nurse (per contact)	9.30	<i>Unit Costs of Health and Social Care 2018</i> <sup>54</sup>
Key worker/community psychiatric nurse (per contact)	37.00	<i>Unit Costs of Health and Social Care 2018</i> <sup>54</sup>
Drug/alcohol support worker/advice worker (per contact)	31.00	<i>Unit Costs of Health and Social Care 2018</i> <sup>54</sup>
Social worker (per contact)	61.00	<i>Unit Costs of Health and Social Care 2018</i> <sup>54</sup>
NHS Direct (per telephone call)	19.00	<i>Evaluation of NHS 111</i> <sup>55</sup>

We aimed to interview as many as possible of the potential participants who were eligible to take part in the study but who declined to do so. We also interviewed a purposive sample of NHS staff to ensure that the views of people with a range of different backgrounds and seniority were captured. We developed semistructured interview schedules in consultation with the service user panel. Interview schedules were designed to explore patient views about reasons for not taking part in the study, and staff views about factors that promoted and hindered their referring people to the study team. Interviews lasted for up to 1 hour. Face-to-face interviews with staff were recorded, professionally transcribed and quality checked prior to data analysis. Researcher notes taken during interviews with patients were immediately typed up and stored securely following interviews.

Data were analysed using thematic analysis.<sup>62</sup> The researcher (LT) used an interpretative approach for analysing the data and developed themes concerning contextual factors, mechanisms and associations that may be inherent in the interviewee's descriptions but not overtly stated.

The results of an interim analysis of data from the first 14 interviews (11 interviews with staff and three interviews with patients) were presented to members of the Trial Management Committee in June 2019. Following this, changes were made to the content of the interview guides, to take account of feedback from the group, as well as the emerging themes. These revised guides were then used for the remaining interviews with patients and staff. In the final data collection and analysis phase, themes were subjected to critical scrutiny, revision and refinement as well as restructuring of the thematic hierarchy where more prominent themes were generated.

### Service user involvement

Patients identified this topic as a research priority through their membership of the James Lind Alliance Schizophrenia Priority Setting Partnership. This group, which included patient and carer representatives, rated the question 'How can sexual dysfunction due to antipsychotic drug therapy be managed?' as one of their top 10 research priorities.<sup>63</sup>

Patients helped us to develop plans for this study through taking part in a survey and a focus group. Nine people attended the focus group. Members expressed enthusiasm for the topic and said that it was often neglected by mental health services. Members felt that the primary outcome should be patient-rated sexual functioning, which should be assessed over months rather than weeks. They asked us to also include assessments of people's mental health and side effects of medication. They told us that everyone who agreed to take part in the study should be offered some support for their difficulties.

A co-applicant with lived experience of using mental health services (CG) contributed to the development of the study through attending regular Trial Management Group meetings. After the study had started, we set up a service user panel, which met on three occasions during the first 18 months of the trial. Members of the panel helped us design a leaflet for patients and a study poster and made suggestions for community-based groups among which the study could be publicised. Panel members also helped generate a list of topics to be covered in qualitative interviews with patients and staff.

Later in the study another member of the group (SJ) joined researchers in publicising the study and meeting clinical teams to help raise the profile of the trial and encourage clinicians to refer people to the study. At the final meeting of the group, members commented on the quantitative and qualitative results of the study, helped revise a draft version of the lay summary and made suggestions for future research in this field.

## Ethics approval and governance

The trial was approved by the West Midlands – Solihull Research Ethics Committee (reference 18/WM/0076). In accordance with the current revision of the Declaration of Helsinki (amended October 2000,<sup>64</sup> with additional footnotes added 2002 and 2004), a participant had the right to stop trial treatment and to withdraw from the trial at any time for any reason, without prejudice to his or her future treatment. The investigator could also withdraw a participant from trial treatment at any time in the interests of the participant's health and well-being or for administrative reasons. Trial follow-ups continued after treatment was withdrawn unless the participant withdrew consent.

All potential participants were provided with written and verbal information about the study before being asked to provide written informed consent to take part. All participants were offered a £10 voucher at 3 months and a £20 voucher following completion of the follow-up interview at 6 months. Participants were also reimbursed for any travel expenses.

Study progress was overseen by a Trial Steering Committee and a Data Monitoring and Ethics Committee.

## Changes to trial design

- During the preparatory phase of the trial we encountered problems when trying to use software for generating an Operational Criteria Checklist for Psychotic Illness and Affective Illness diagnosis from data in case records. We therefore dropped plans to confirm the clinical diagnosis assigned to the patient by the referring team.
- Following a request from the Trial Steering Committee we sent a reminder to all doctors overseeing medication of participants in the switch arm of the trial. The doctors were advised about the importance of monitoring body weight, blood glucose, blood pressure and blood lipids in the period following any change in medication.
- In the initial phase of recruitment it became clear that some patients who would otherwise be eligible to take part in the study had been psychotic within the 3 months prior to being asked about taking part in the study. We therefore changed this criterion from 'acutely psychotic within the last 3 months' to 'judged by the clinical team to be sufficiently stable to take part in the study'.
- We obtained ethics and other approvals to contact all patients who were sent a letter about the study by telephone. We attempted to contact potential participants 7–14 days after sending them a letter to check that they had received it and to ask if they were interested in finding out more about the study.
- Because it became apparent that we were struggling to recruit study participants, we changed the focus of the qualitative component of the study from a formal process evaluation to a qualitative exploration of barriers to recruitment.
- We originally planned to recruit patients from three Trusts in England during the pilot phase of the trial; however, we extended this to four Trusts in the final 3 months of the recruitment phase of the study.
- Two study participants were due to have both a 3- and a 6-month follow-up assessment when the decision was made to stop the study. We obtained approvals to complete all 6-month assessments with these participants at the 3-month visit to reduce the time and cost of a longer study.



## Chapter 3 Results

Six participants were recruited during the first 6 months of the pilot phase of the trial. A decision was made to increase the pilot phase for a further 6 months, during which time an additional four patients were recruited. A decision was made to stop recruitment at this time. Between 1 July 2018 and 30 June 2019, 98 patients were referred to the study, of whom 61 (62%) met a researcher to assess eligibility. Of these 98 referrals, 85 (87%) were from staff and 13 (13%) were self-referrals. Five self-referred participants contacted the team after seeing a study poster or leaflet. Eight (2%) patients were among the 341 patients who were sent a letter about the study. None of the five self-referred participants who responded to a poster or leaflet had a diagnosis of psychosis, and none of the eight patients who responded to a letter agreed to take part in the trial after finding out more about it.

### Participant flow

Table 4 and Figure 2 detail patient flow through the study. Among the 61 patients who met with a researcher, 15 (25%) consented to be screened and 46 (75%) did not. Among the 46 patients who declined to be screened, 28 (61%) provided a brief comment about their reasons for not wanting to take part in the trial. Of these, 10 (36%) patients stated that their sexual dysfunction was not important enough to need to do something about it, 11 (39%) patients said that they were worried about the possibility of having to switch their medication, three (11%) patients wanted their medication to be changed and were worried about being randomised to the control arm of the trial. The three remaining patients declined to take part, one because of work commitments, one because they did not want to be asked 'intrusive questions' and one patient stated that they had started taking Viagra® (Pfizer Inc., New York, NY, USA) and told us that this had improved their sexual functioning.

Of the 15 patients who consented to be screened, 11 (73%) were eligible and four (27%) were ineligible. Of the four patients who were ineligible, one did not have psychosis and should not have been screened. No screening data for this patient have been included in the remainder of this report.

TABLE 4 Participants who were approached, screened, eligible, recruited or withdrew

Patient recruitment	Total	Trust			
		1	2	3	4
Number of patients identified and referred	98	56	28	10	4
Number of patients not approached for consent	37	18	13	5	1
Number of patients approached for consent	61	38	15	5	3
Number of patients who did not consent	46	28	12	4	2
Number of patients who did consent	15	10	3	1	1
Number of patients screened (of those who consented)	15	10	3	1	1
Number eligible (of those screened)	11	7	3	0	1
Number ineligible (of those screened)	4	3	0	1	0
Number of participants recruited (of those eligible)	10	6	3	0	1
Number of patients not recruited (of those eligible)	1	1	0	0	0
Number of participants withdrawn before the 3-month follow-up	2	2	0	0	0
Number of participants withdrawn before the 6-month follow-up	0	0	0	0	0

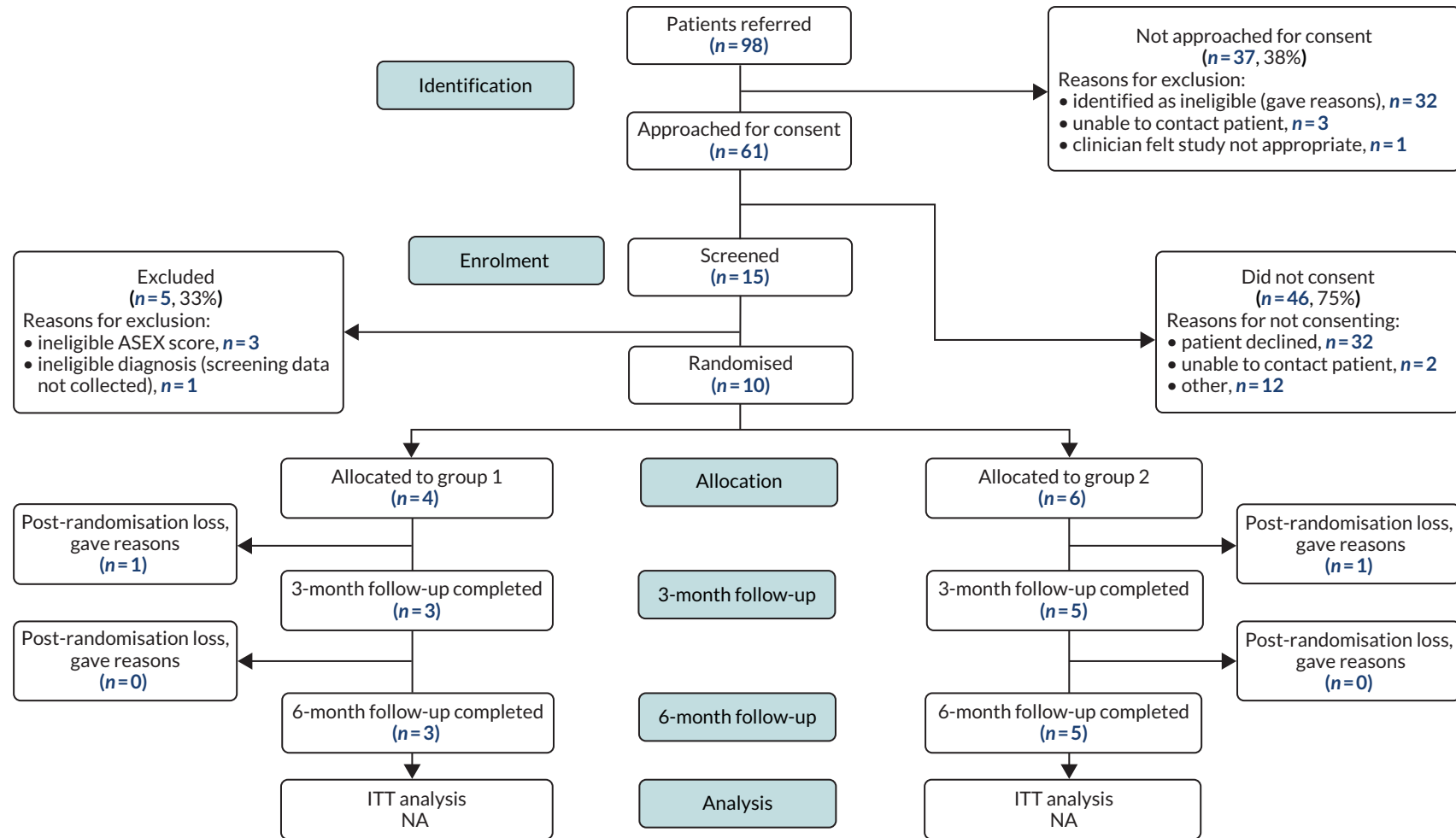


FIGURE 2 Diagram of participant flow: guided by Consolidated Standards of Reporting Trials (CONSORT) guidelines. ITT, intention to treat; NA, not applicable.

Of the 11 eligible patients, 10 (91%) were recruited and randomised into the study and one (9%) withdrew consent prior to baseline assessment and randomisation. Of the 10 patients randomised, four were allocated to enhanced standard care and six were randomised to enhanced standard care plus switch of medication (see *Figure 2*). Following randomisation, a further two patients withdrew from the study (one from the control arm and one from the switch arm).

A breakdown detailing the reasons for non-approach, non-consent, ineligibility, non-recruitment and post-randomisation loss is given in *Figure 2*. The most common reason for a researcher not approaching a patient was that they were found to be ineligible ( $n = 32$ , 86%). The main reasons for ineligibility prior to consent were not having a primary diagnosis of schizophrenia or related psychoses ( $n = 11$ , 34%), being prescribed clozapine ( $n = 7$ , 22%) or not having a suitable switch medication ( $n = 4$ , 13%). Three (9%) patients were excluded because they were being prescribed aripiprazole long-acting injection, three (9%) patients were judged by the clinical team to be insufficiently stable to take part in the study, two (6%) patients had an underlying physical health condition responsible for their dysfunction and one (3%) patient had not had a trial of dose reduction to see if this improved their sexual functioning.

The main reason for non-consent was the participant declining ( $n = 32$ , 70%). Following consent one participant was found not to have a primary diagnosis of psychosis and three patients did not meet the threshold score on the ASEX for sexual dysfunction.

## Descriptive statistics

Patient and demographic details of the 14 study participants are detailed in *Table 5*. For patients who were randomised ( $n = 10$ ) the data are split into randomised allocation arm. As indicated in *Participant flow*, 15 patients were screened; however, data for one patient, who should not have been screened,

TABLE 5 Screening and demographic data

Variable	Overall screened ( $N = 14$ ), $n$ (%)	Randomisation status, $n$ (%)		Randomised arm, $n$ (%)	
		Not randomised ( $N = 4$ )	Randomised ( $N = 10$ )	Control ( $N = 4$ )	Switch ( $N = 6$ )
Gender					
Male	11 (79)	3 (75)	8 (80)	2 (50)	6 (100)
Female	3 (21)	1 (25)	2 (20)	2 (50)	0 (0)
Trust					
1	9 (64)	3 (75)	6 (60)	2 (50)	4 (67)
2	3 (21)	0 (0)	3 (30)	2 (50)	1 (17)
3	1 (7)	1 (25)	0 (0)	0 (0)	0 (0)
4	1 (7)	0 (0)	1 (10)	0 (0)	1 (17)
Marital status					
Single	11 (79)	4 (100)	7 (70)	2 (50)	5 (83)
Married and living with partner	1 (7)	0 (0)	1 (10)	0 (0)	1 (17)
Divorced	2 (14)	0 (0)	2 (20)	2 (50)	0 (0)

continued

## RESULTS

TABLE 5 Screening and demographic data (continued)

Variable	Overall screened (N = 14), n (%)	Randomisation status, n (%)		Randomised arm, n (%)	
		Not randomised (N = 4)	Randomised (N = 10)	Control (N = 4)	Switch (N = 6)
Relationship status					
Living with a partner	2 (14)	0 (0)	2 (20)	1 (25)	1 (17)
Steady relationship, not cohabiting	1 (7)	1 (25)	0 (0)	0 (0)	0 (0)
No steady relationship, previously cohabiting	3 (21)	1 (25)	2 (20)	2 (50)	0 (0)
No steady relationship, never cohabited	7 (50)	2 (50)	5 (50)	1 (25)	4 (67)
Missing	1 (7)	0 (0)	1 (10)	0 (0)	1 (17)
Sexuality					
Heterosexual/straight	12 (86)	3 (75)	9 (90)	3 (75)	6 (100)
Gay/lesbian	1 (7)	0 (0)	1 (10)	1 (25)	0 (0)
Bisexual	1 (7)	1 (25)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity					
White	6 (43)	1 (25)	5 (50)	2 (50)	3 (50)
Mixed	1 (7)	1 (25)	0 (0)	0 (0)	0 (0)
Asian (British Asian or other)	3 (21)	1 (25)	2 (20)	1 (25)	1 (17)
Black (black British or other)	4 (29)	1 (25)	3 (30)	1 (25)	2 (33)
Age (years) <sup>a</sup>					
< 40			2 (20)	1 (25)	1 (17)
≥ 40			8 (80)	3 (75)	5 (83)
Medical conditions <sup>b</sup>					
Hypertension (high blood pressure)	3	1	2	0	2
Diabetes (high blood sugar)	3	0	3	0	3
Chronic lung disease	2	1	1	0	1
Epilepsy	2	1	1	0	1
None of the above	1	1	0	0	0

a Collected for randomisation data and therefore not available for screened sample.

b Percentages not given for medical conditions because patients may be in more than one category.

were not entered into the database, and therefore data on 14 screened patients are presented. Of these patients, four were not randomised (three were ineligible and one withdrew from the study) and 10 were randomised.

Data from the Alcohol, Smoking and Substance Involvement Screening Test revealed that six participants smoked tobacco (three in the control arm and three in the switch arm) and eight participants consumed



alcohol (three in the control arm and five in the switch arm). No participant was currently using any other substance but five had a lifetime history of cannabis use, three had a lifetime history of amphetamines use, three a lifetime history of hallucinogenic drugs use, two a lifetime history of cocaine use and two had a lifetime history of opiates use.

The mean ASEX score for the 14 participants who were screened was 20.6 points (SD 4.97 points). Among the four participants who were not randomised, the mean score was 17.0 points (SD 6.88 points) and among the 10 participants who were randomised the mean score was 22.0 points (SD 3.46 points).

Table 6 describes the status of the patients screened according to whether or not they were eligible and, if eligible, whether or not they were randomised and, if randomised, whether or not they completed baseline data collection, and 3- (the primary outcome only) and 6-month follow-up data collection. Complete baseline data were collected for all 10 randomised participants, complete 3-month follow-up

TABLE 6 Status of patients screened in relation to eligibility, randomisation and follow-up data collection

Screening status	Reason for ineligibility	Randomised	Study arm	Time point			Status
				Baseline	3-month follow-up (primary outcome)	6-month follow-up	
Eligible		Yes	Switch	Yes	Yes	Yes (primary outcome only)	Completed
Ineligible	ASEX	No					
Eligible		Yes	Control	Yes	No	No	Withdrew
Eligible		Yes	Control	Yes	Yes	Yes	Completed
Eligible		No (withdrawn before randomisation)					
Ineligible	Diagnosis	No (screened when should not have been)					
Ineligible	ASEX	No					
Eligible		Yes	Switch	Yes	Yes	Yes	Completed
Eligible		Yes	Switch	Yes	Yes	Yes	Completed
Eligible		Yes	Switch	Yes	No	No	Withdrew
Eligible		Yes	Switch	Yes	Yes	Yes	Completed
Eligible		Yes	Control	Yes	Yes	Yes	Completed
Eligible		Yes	Control	Yes	Yes	Yes <sup>a</sup> (secondary outcomes only)	Completed
Ineligible	ASEX	No					
Eligible		Yes	Switch	Yes	Yes	Yes <sup>a</sup> (secondary outcomes only)	Completed

<sup>a</sup> Six-month data were collected at the 3-month time point.

data were collected for eight participants and complete 6-month follow-up data were collected for seven participants.

Six-month follow-up data could not be collected for the two participants randomised in the final months of the study (see footnote a in *Table 6*) but instead 6-month secondary outcome data were collected at the 3-month follow-up time point. Therefore, ASEX score was available for all 10 participants at baseline, for eight participants at 3 months and for six participants at 6 months (two participants did not reach the point when their 6-month interview was due because the study closed earlier than originally planned).

## Uptake of allocated treatments

Antipsychotic medication was switched for five out of the six participants in the switch arm of the trial (three to oral aripiprazole and two to aripiprazole long-acting injection) and one six participant withdrew from the study before a switch could be initiated. None of those in the control arm of the trial had a change in their antipsychotic medication during the follow-up period.

Nine study participants were offered brief psychoeducation and support and one six participant withdrew from the study before they could be offered it. Seven (78%) of these nine participants attended a session. Sessions lasted between 30 and 60 minutes (mean duration of 45 minutes). The main problems discussed at sessions were lack or loss of desire for sex ( $n = 4$ ), erectile dysfunction ( $n = 3$ ) and orgasmic dysfunction ( $n = 2$ ). All participants who attended a session were told about the prevalence and possible causes of sexual dysfunction and given information about the NHS Choices website and other sources of help. All seven participants were offered the possibility of a follow-up session. One participant accepted this offer.

### Primary outcome

*Table 7* contains the summary statistics of the ASEX scores (primary outcome) at baseline, and at 3- and 6-month follow-ups, presented overall and split by randomisation allocation arm. The ASEX data presented are the total scores calculated by summing the five items. The mean and median scores for the ASEX measure have little variation between time points and arms; however, the summary statistics should be treated with caution because small numbers represent the samples (especially when split by arm).

*Table 8* contains the summary statistics of the continuous secondary outcomes [i.e. BARS, PANSS, Calgary Depression Scale for Schizophrenia (CDSS) and ANNSERS]. The total scores for each and, if applicable, the total subscale scores are presented. As with the ASEX data, the summary statistics represent very small samples and should be interpreted as such. The BARS data presented in *Table 8* relate to the adherence percentage (the third item of the measure), which is calculated by dividing the proportion of doses taken by the patient in the past month by the total number of prescribed antipsychotic medication doses over the same period. The PANSS, CDSS and ANNSERS data are summary scores calculated from the individual measure items. The completion rates of the measures are high (relative to expected  $n$ ) for all measures, with 100% completion at baseline for PANSS, CDSS and ANNSERS, and just one missing case at the 6-month follow-up for all. The BARS completion rates are a little lower, with 7 out of 10 participants completing at baseline and five out of eight participants completing at follow-up.

*Table 9* contains the frequencies of the categorical outcomes for CGI at 6-month follow-up and the Natsal-3 questionnaire at baseline and 6-month follow-up and *Table 10* reports the Natsal-3 count data summary statistics. No participant reported being satisfied with their sex lives either at the start of the study or at follow-up. Only one participant, in the switch arm of the trial, was rated by the researcher as having improved sexual functioning on the CGI at follow-up, but the improvement was judged to be minimal.

TABLE 7 Summary statistics of the study primary outcome measure

Outcome	Allocation	Time point											
		Baseline, N = 10 (control, n = 4; switch, n = 6)				3-month follow-up, N = 8 (control, n = 3; switch, n = 5)			6-month follow-up, N = 8 (control, n = 3; switch, n = 5)				
		n	Mean score (points) (SD)	Observed score (points) range	Median score (points) (IQR 25%, 75%)	n	Mean score (points) (SD)	Observed score (points) range	Median score (points) (IQR 25%, 75%)	n	Mean score (points) (SD)	Observed score (points) range	Median score (points) (IQR 25%, 75%)
ASEX	Overall	10	22.0 (3.46)	18.0–30.0	21.0 (19.75, 24.0)	8	21.3 (5.12)	13.0–28.0	20.5 (17.5, 26.0)	6	22.2 (4.49)	17.0–29.0	22.0 (17.75, 26.0)
	Control	4	21.8 (2.06)	20.0–24.0	21.5 (20.0, 23.75)	3	23.0 (4.36)	20.0–28.0	21.0 (20.0, –)	2	22.0 (1.41)	21.0–23.0	22.0 (21.0, –)
	Switch	6	22.2 (4.36)	18.0–30.0	21.0 (18.75, 25.5)	5	20.2 (5.72)	13.0–26.0	19.0 (15.0, 26.0)	4	22.3 (5.34)	17.0–29.0	21.5 (17.25, 28.0)

–, quartile not calculated because of small sample; IQR, interquartile range.

TABLE 8 Summary statistics of continuous secondary outcomes

Outcome	Randomised arm	Time point							
		Baseline, N = 10 (control, n = 4; switch, n = 6)				6-month follow-up, N = 8 (control, n = 3; switch, n = 5)			
		n	Mean (SD)	Observed range	Median (IQR 25%, 75%)	n	Mean (SD)	Observed range	Median (IQR 25%, 75%)
BARS	Overall	7	96.6 (6.27)	83 to 100	100 (95.0, 100)	5	98.0 (4.47)	90 to 100	100 (95.0, 100)
	Control	3	99.3 (1.16)	98 to 100	100 (98.0, -)	3	100.0 (0.00)	100 to 100	100 (100, 100)
	Switch	4	94.5 (8.02)	83 to 100	97.5 (86.0, 100)	2	95.0 (7.07)	90 to 100	95.0 (90.0, -)
PANSS: total	Overall	10	59.6 (13.83)	41.0 to 83.0	59.5 (46.0, 70.0)	7	55.9 (9.32)	44.0 to 69.0	55.0 (49.0, 67.0)
	Control	4	61.25 (18.23)	41.0 to 83.0	60.5 (44.0, 79.25)	3	55.3 (11.50)	56.3 (9.22)	55.0 (44.0, -)
	Switch	6	58.5 (11.90)	43.0 to 73.0	59.5 (46.0, 70.0)	4	56.3 (9.22)	49.0 to 69.0	53.5 (49.25, 66.0)
PANSS: index	Overall	10	4.1 (8.16)	-7.0 to 15.0	5.5 (-5.0, 11.0)	7	1.14 (6.47)	-8.0 to 11.0	0.00 (-3.0, 8.0)
	Control	4	8.5 (9.26)	-5.0 to 15.0	12.0 (-1.25, 14.75)	3	3.67 (10.21)	-8.0 to 11.0	8.0 (-8.0, -)
	Switch	6	1.17 (6.52)	-7.0 to 9.0	1.5 (-5.5, 7.5)	4	-0.75 (1.71)	-3.0 to 1.0	-0.5 (-2.5, 0.75)
PAN: positive subscale	Overall	10	16.2 (6.78)	8.0 to 28.0	15.0 (10.75, 22.0)	7	13.9 (4.14)	8.0 to 18.0	14.0 (9.0, 18.0)
	Control	4	19.5 (8.96)	8.0 to 28.0	21.0 (10.25, 27.25)	3	14.7 (5.77)	8.0 to 18.0	18.0 (8.0, -)
	Switch	6	14.0 (4.47)	10.0 to 21.0	12.0 (10.75, 18.75)	4	13.3 (3.30)	9.0 to 17.0	13.5 (10.0, 16.25)
PANS: negative subscale	Overall	10	12.1 (3.76)	7.0 to 18.0	11.5 (10.0, 14.25)	7	12.7 (3.68)	7.0 to 18.0	12.0 (10.0, 16.0)
	Control	4	11.0 (2.83)	7.0 to 13.0	12.0 (8.0, 13.0)	3	11.0 (4.58)	7.0 to 16.0	10.0 (7.0, -)
	Switch	6	12.8 (4.36)	7.0 to 18.0	11.5 (10.0, 18.0)	4	14.0 (2.83)	12.0 to 18.0	13.0 (12.0, 17.0)
PANSS: general psychopathy subscale	Overall	10	31.3 (7.07)	20.0 to 42.0	30.5 (25.75, 38.5)	7	29.3 (6.21)	20.0 to 39.0	29.0 (24.0, 34.0)
	Control	4	30.8 (9.07)	20.0 to 42.0	30.5 (22.25, 39.5)	3	29.7 (9.50)	20.0 to 39.0	30.0 (20.0, -)
	Switch	6	31.7 (6.35)	25.0 to 40.0	30.5 (25.75, 38.5)	4	29.0 (4.08)	24.0 to 34.0	29.0 (25.25, 32.75)
CDSS: total	Overall	10	6.8 (4.42)	1.0 to 15.0	6.0 (3.5, 10.25)	7	5.7 (4.50)	0.0 to 12.0	5.0 (1.0, 10.0)
	Control	4	5.0 (3.46)	2.0 to 10.0	4.0 (2.5, 8.5)	3	5.7 (6.03)	0.0 to 12.0	5.0 (0.0, -)
	Switch	6	8.0 (4.86)	1.0 to 15.0	8.0 (4.0, 12.0)	4	5.8 (4.03)	1.0 to 10.0	6.0 (1.75, 9.5)
CDSS: mild	Overall	10	2.1 (1.20)	1.0 to 5.0	2.0 (1.0, 2.25)	7	1.9 (1.07)	0.0 to 3.0	2.0 (1.0, 3.0)
	Control	4	2.0 (0.00)	2.0 to 2.0	2.0 (2.0, 2.0)	3	1.7 (1.53)	0.0 to 3.0	2.0 (0.0, -)
	Switch	6	2.2 (1.60)	1.0 to 5.0	1.5 (1.0, 3.5)	4	2.0 (0.82)	1.0 to 3.0	2.0 (1.25, 2.75)

Outcome	Randomised arm	Time point							
		Baseline, N = 10 (control, n = 4; switch, n = 6)				6-month follow-up, N = 8 (control, n = 3; switch, n = 5)			
		n	Mean (SD)	Observed range	Median (IQR 25%, 75%)	n	Mean (SD)	Observed range	Median (IQR 25%, 75%)
CDSS: moderate	Overall	10	2.6 (2.32)	0.0 to 8.0	2.0 (1.5, 4.0)	7	1.7 (2.43)	0.0 to 6.0	0.0 (0.0, 4.0)
	Control	4	1.5 (1.00)	0.0 to 2.0	2.0 (0.5, 2.0)	3	0.0 (0.00)	0.0 to 0.0	0.0 (0.0, 0.0)
	Switch	6	3.3 (2.73)	0.0 to 8.0	3.0 (1.5, 5.0)	4	3.0 (2.58)	0.0 to 6.0	3.0 (0.5, 5.5)
CDSS: severe	Overall	10	2.1 (2.85)	0.0 to 6.0	0.0 (0.0, 6.0)	7	2.1 (3.34)	0.0 to 9.0	0.0 (0.0, 3.0)
	Control	4	1.5 (3.00)	0.0 to 6.0	0.0 (0.0, 4.5)	3	4.0 (4.58)	0.0 to 9.0	3.0 (0.0, -)
	Switch	6	2.5 (2.95)	0.0 to 6.0	1.5 (0.0, 6.0)	4	0.8 (1.50)	0.0 to 3.0	0.0 (0.0, 2.25)
ANNSERS: total	Overall	10	22.9 (11.28)	6.0 to 40.0	21.5 (15.0, 32.25)	7	14.4 (10.60)	5.0 to 36.0	10.0 (7.0, 18.0)
	Control	4	18.0 (15.38)	6.0 to 40.0	13.0 (6.75, 34.25)	3	10.0 (5.57)	5.0 to 16.0	9.0 (5.0, -)
	Switch	6	26.2 (7.41)	17.0 to 36.0	27.0 (18.5, 32.25)	4	17.8 (13.02)	7.0 to 36.0	14.0 (7.75, 31.5)
ANNSERS: present	Overall	10	14.9 (7.52)	3.0 to 31.0	14.5 (10.5, 19.0)	7	11.14 (5.96)	5.0 to 19.0	7.0 (7.0, 18.0)
	Control	4	12.0 (7.39)	3.0 to 19.0	13.0 (4.5, 18.5)	3	9.0 (5.29)	5.0 to 15.0	7.0 (5.0, -)
	Switch	6	16.8 (7.60)	11.0 to 31.0	14.5 (11.0, 22.0)	4	12.8 (6.65)	7.0 to 19.0	12.5 (7.0, 18.75)
ANNSERS: mild	Overall	10	3.7 (4.00)	0.0 to 12.0	2.5 (0.75, 6.0)	7	4.9 (0.90)	3.0 to 6.0	5.0 (5.0, 5.0)
	Control	4	3.3 (1.71)	1.0 to 5.0	3.5 (1.5, 4.75)	3	4.3 (1.16)	3.0 to 5.0	5.0 (3.0, -)
	Switch	6	4.0 (5.18)	0.0 to 12.0	1.5 (0.0, 9.75)	4	5.3 (0.50)	5.0 to 6.0	5.0 (5.0, 5.75)
ANNSERS: moderate	Overall	10	10.7 (7.63)	1.0 to 24.0	9.0 (5.5, 17.5)	7	7.1 (7.73)	0.0 to 22.0	4.0 (2.0, 12.0)
	Control	4	9.3 (9.29)	1.0 to 22.0	7.0 (1.75, 19.0)	3	4.67 (3.06)	2.0 to 8.0	4.0 (2.0, -)
	Switch	6	11.7 (7.09)	6.0 to 24.0	9.0 (6.0, 18.0)	4	9.0 (10.13)	0.0 to 22.0	7.0 (0.50, 19.5)
ANNSERS: severe	Overall	10	8.2 (8.03)	0.0 to 24.0	7.5 (0.75, 12.75)	7	2.43 (3.51)	0.0 to 9.0	0.0 (0.0, 5.0)
	Control	4	4.8 (6.95)	0.0 to 15.0	2.0 (0.25, 12.0)	3	1.0 (1.73)	0.0 to 3.0	0.0 (0.0, -)
	Switch	6	10.5 (8.43)	0.0 to 24.0	12.0 (2.25, 15.0)	4	3.5 (4.36)	0.0 to 9.0	2.5 (0.0, 8.0)

-, quartile not calculated because of small sample; IQR, interquartile range.

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TABLE 9 Frequencies of categorical secondary outcomes

Stratification variable	Time point, n (%)					
	Baseline			6-month follow-up		
	Overall (N = 10)	Randomised arm		Overall (N = 8)	Randomised arm	
		Control (N = 4)	Switch (N = 6)		Control (N = 3)	Switch (N = 5)
CGI: clinical judgement rating						
Not assessed				0 (0)	0 (0)	0 (0)
Very much improved				0 (0)	0 (0)	0 (0)
Much improved				0 (0)	0 (0)	0 (0)
Minimally improved				1 (12.5)	0 (0)	1 (20)
No change				5 (62.5)	3 (100)	2 (40)
Minimally worse				1 (12.5)	0 (0)	1 (20)
Much worse				0 (0)	0 (0)	0 (0)
Very much worse				0 (0)	0 (0)	0 (0)
Missing (data not completed)				1 (12.5)	0 (0)	1 (20)
Natsal-3 question 1: I feel satisfied with my sex life						
Agree strongly	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Agree	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neither agree nor disagree	1 (10)	1 (25)	0 (0)	1 (12.5)	0 (0)	1 (20)
Disagree	3 (30)	1 (25)	2 (33)	3 (37.5)	1 (33)	2 (40)
Disagree strongly	6 (60)	2 (50)	4 (67)	4 (50)	2 (67)	2 (40)
Natsal-3 question 2: I feel distressed or worried about my sex life						
Agree strongly	5 (50)	2 (50)	3 (50)	3 (37.5)	1 (33)	2 (40)
Agree	2 (20)	0 (0)	2 (33)	1 (12.5)	2 (67)	1 (20)
Neither agree nor disagree	2 (20)	1 (25)	1 (17)	3 (37.5)	0 (0)	1 (20)
Disagree	1 (10)	1 (25)	0 (0)	1 (12.5)	0 (0)	1 (20)
Disagree strongly	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Natsal-3 question 3: I have avoided sex because of sexual difficulties, either my own or those of my partner						
Agree strongly	2 (20)	1 (25)	1 (17)	3 (37.5)	1 (33)	2 (40)
Agree	4 (40)	1 (25)	3 (50)	0 (0)	0 (0)	0 (0)
Neither agree nor disagree	3 (30)	2 (50)	1 (17)	3 (37.5)	2 (67)	1 (20)
Disagree	1 (10)	0 (0)	1 (17)	1 (12.5)	0 (0)	1 (20)
Disagree strongly	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (20)
Natsal-3 question 4: sought help regarding your sex life from a friend, family members, GP, doctor or nurse in the last 6 months?						
No	5 (50)	3 (75)	2 (33)	5 (62.5)	2 (67)	3 (60)
Yes	5 (50)	1 (25)	4 (67)	3 (37.5)	1 (33)	2 (40)
Natsal-3 question 5: thinking of the way things are for you these days, which one would you really prefer?						
To have sex much more often than I do now	6 (60)	2 (50)	4 (67)	3 (37.5)	1 (33)	2 (40)
To have sex a bit more often	3 (30)	2 (50)	1 (17)	4 (50)	2 (67)	2 (40)
It is about right as it is	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (10)
To have sex a little less often	1 (10)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)

TABLE 9 Frequencies of categorical secondary outcomes (continued)

Stratification variable	Time point, n (%)					
	Baseline			6-month follow-up		
	Overall (N = 10)	Randomised arm		Overall (N = 8)	Randomised arm	
		Control (N = 4)	Switch (N = 6)		Control (N = 3)	Switch (N = 5)
Natsal-3 question 6: thinking about your sex life in the last 6 months, how many people have you had sexual intercourse with?						
None	5 (50)	2 (50)	3 (50)	5 (62.5)	2 (67)	3 (60)
One	4 (40)	1 (25)	3 (50)	3 (37.5)	1 (33)	2 (40)
Two	1 (10)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)
Three	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Four	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Five	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Six	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Six or more	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TABLE 10 Summary statistics of Natsal-3 count questions

Natsal-3 continuous measure	Time point					
	Baseline			6-month follow-up		
	Overall (n = 10)	Randomised arm		Overall (n = 8)	Randomised arm	
		Control (n = 4)	Switch (n = 6)		Control (n = 3)	Switch (n = 4)
Question 7: in the last month, how many times have you had sexual intercourse?						
Mean (SD)	0.9 (1.52)	0.5 (1.00)	1.2 (1.84)	0.9 (1.45)	0.3 (0.58)	1.2 (1.79)
Observed range	0.0–4.0	0.0–2.0	0.0–4.0	0.0–4.0	0.0–1.0	0.0–4.0
Median (IQR 25%, 75%)	0.0 (0.0, 2.25)	0.0 (0.0, 1.5)	0.0 (0.0, 3.25)	0.0 (0.0, 1.75)	0.0 (0.0, –)	0.0 (0.0, 3.0)
Question 8: thinking about your sex life in the last month, how many times have you masturbated? <sup>a</sup>						
Mean (SD)	19.6 (36.7)	32.0 (58.7)	11.3 (12.5)	57.3 (138.79)	136.7 (228.1)	9.6 (11.44)
Observed range	0.0–120.0	1.0–120.0	0.0–31.0	0.0–400.0	2.0–400.0	0.0–28.0
Median (IQR 25%, 75%)	5.0 (0.75, 22.75)	3.5 (1.0, 91.5)	8.5 (0.0, 22.75)	9.0 (0.5, 23.5)	8.0 (2.0, –)	10.0 (0.0, 19.0)

–, quartile not calculated because of small sample; IQR, interquartile range.

<sup>a</sup> Count data presented for Natsal-3 question 8 should be treated with caution as large observations in some patients are skewing the sample.

## Side effects of medication

Table 11 provides the frequencies that patients scored 'absent', 'mild', 'moderate' or 'severe' to side effects at baseline and at 6-month follow-up using ANNSERS. The most common side effects reported at baseline were lethargy/lassitude, daytime sleepiness or difficulty waking, loss of energy or drive, problems with memory, problems with concentration and dry mouth.

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Headache		
Absent	6 (60)	6 (75.0)
Mild	2 (20)	0 (0.0)
Moderate	2 (20)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Lethargy/lassitude		
Absent	3 (30)	3 (37.5)
Mild	1 (10)	3 (37.5)
Moderate	3 (30)	1 (12.5)
Severe	3 (30)	0 (0.0)
Missing	0 (0)	1 (12.5)
Disturbed sleep		
Absent	3 (30)	2 (25.0)
Mild	2 (20)	2 (25.0)
Moderate	2 (20)	3 (37.5)
Severe	3 (30)	0 (0.0)
Missing	0 (0)	1 (13.0)
Daytime sleepiness		
Absent	3 (30)	4 (50.0)
Mild	2 (20)	1 (12.5)
Moderate	2 (20)	0 (0.0)
Severe	3 (30)	2 (25.0)
Missing	0 (0)	1 (12.5)
Loss of energy/drive		
Absent	3 (30)	5 (62.5)
Mild	1 (10)	1 (12.5)
Moderate	4 (40)	1 (12.5)
Severe	2 (20)	0 (0.0)
Missing	0 (0)	1 (12.5)
Problems with memory		
Absent	3 (30)	2 (25.0)
Mild	2 (20)	1 (12.5)
Moderate	3 (30)	3 (37.5)
Severe	2 (20)	1 (12.5)
Missing	0 (0)	1 (12.5)



TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Impaired concentration		
Absent	4 (40)	6 (75.0)
Mild	2 (20)	0 (0.0)
Moderate	3 (30)	0 (0.0)
Severe	1 (10)	1 (12.5)
Missing	0 (0)	1 (12.5)
Dysphoria		
Absent	5 (50)	5 (62.5)
Mild	0 (0)	2 (25.0)
Moderate	4 (40)	0 (0.0)
Severe	1 (10)	0 (0.0)
Missing	0 (0)	1 (12.5)
Emotional numbing		
Absent	6 (60)	4 (50.0)
Mild	3 (30)	3 (37.5)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Tachycardia		
Absent	8 (80)	4 (50.0)
Mild	0 (0)	2 (25.0)
Moderate	2 (20)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Postural hypotension		
Absent	8 (80)	5 (62.5)
Mild	1 (10)	1 (12.5)
Moderate	1 (10)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Hypertension		
Absent	9 (90)	6 (75.0)
Mild	0 (0)	1 (12.5)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)

continued

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
ECG abnormality		
Absent	9 (90)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Peripheral oedema		
Absent	6 (60)	4 (50.0)
Mild	1 (10)	2 (25.0)
Moderate	0 (0)	1 (12.5)
Severe	3 (30)	0 (0.0)
Missing	0 (0)	1 (12.5)
Breathlessness		
Absent	8 (80)	6 (75.0)
Mild	1 (10)	0 (0.0)
Moderate	0 (0)	1 (12.5)
Severe	1 (10)	0 (0.0)
Missing	0 (0)	1 (12.5)
Nausea/vomiting		
Absent	6 (60)	6 (75.0)
Mild	1 (10)	0 (0.0)
Moderate	3 (30)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Constipation		
Absent	8 (80)	7 (87.5)
Mild	1 (10)	0 (0.0)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Diarrhoea		
Absent	4 (40)	5 (62.5)
Mild	1 (10)	1 (12.5)
Moderate	3 (30)	0 (0.0)
Severe	2 (20)	1 (12.5)
Missing	0 (0)	1 (12.5)

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Weight gain		
Absent	9 (90)	5 (62.5)
Mild	1 (10)	2 (25.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Weight loss		
Absent	6 (60)	4 (50.0)
Mild	2 (20)	1 (12.5)
Moderate	1 (10)	1 (12.5)
Severe	1 (10)	1 (12.5)
Missing	0 (0)	1 (12.5)
Gynaecomastia		
Absent	10 (100)	6 (75.0)
Mild	0 (0)	1 (12.5)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Galactorrhoea		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Onset/worsening of diabetes		
Absent	9 (90)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	1 (10)	0 (0.0)
Missing	0 (0)	1 (12.5)
Dyslipidaemia		
Absent	8 (80)	7 (87.5)
Mild	1 (10)	0 (0.0)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)

continued

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Blurred vision		
Absent	8 (80)	6 (75.0)
Mild	0 (0)	0 (0.0)
Moderate	2 (20)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Dry mouth		
Absent	3 (30)	4 (50.0)
Mild	3 (30)	1 (12.5)
Moderate	2 (20)	2 (25.0)
Severe	2 (20)	0 (0.0)
Missing	0 (0)	1 (12.5)
Hypersalivation		
Absent	8 (80)	7 (87.5)
Mild	2 (20)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Sweating		
Absent	5 (50)	5 (62.5)
Mild	2 (20)	1 (12.5)
Moderate	3 (30)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Fever		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Nocturnal enuresis		
Absent	8 (80)	6 (75.0)
Mild	0 (0)	0 (0.0)
Moderate	1 (10)	1 (12.5)
Severe	1 (10)	0 (0.0)
Missing	0 (0)	1 (12.5)

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Difficulty passing urine		
Absent	6 (60)	7 (87.5)
Mild	2 (20)	0 (0.0)
Moderate	2 (20)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Change in menstruation (females only)		
Absent	1 (50)	2 (100.0)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	1 (50)	0 (0.0)
Missing	0 (0)	0 (0.0)
Confusion		
Absent	8 (80)	5 (62.5)
Mild	1 (10)	2 (25.0)
Moderate	1 (10)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Fits		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Neuroleptic malignant syndrome		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Hepatic dysfunction		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)

continued

TABLE 11 Frequencies of side effects reported using the ANNSERS outcome measure (continued)

Side effect	Time point, n (%)	
	Baseline (N = 10)	6-month follow-up (N = 8)
Skin rash		
Absent	9 (90)	4 (50.0)
Mild	1 (10)	2 (25.0)
Moderate	0 (0)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Blood dyscrasias		
Absent	10 (100)	7 (87.5)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	0 (0.0)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Facial oedema		
Absent	10 (100)	6 (75.0)
Mild	0 (0)	0 (0.0)
Moderate	0 (0)	1 (12.5)
Severe	0 (0)	0 (0.0)
Missing	0 (0)	1 (12.5)
Other side effects		
Absent	6 (60)	4 (50.0)
Mild	2 (20)	1 (12.5)
Moderate	1 (10)	1 (12.5)
Severe	1 (10)	1 (12.5)
Missing	0 (0)	1 (12.5)
ECG, electrocardiography.		

## Safety data, protocol compliance and withdrawals

Tables 12 and 13 contain data on the number of adverse events, protocol deviations and withdrawals noted in the study. There was one adverse event and one serious adverse event, both in the switch arm of the trial. Neither were thought to be related to study procedures. The serious adverse event was for hospitalisation for an unrelated physical health condition. Three withdrawals occurred, one before randomisation and two after, one of which was because of the serious adverse event. The other two withdrawals were due to patients withdrawing consent. One protocol deviation was noted, which occurred when a patient was screened who did not meet eligibility criteria because they did not have schizophrenia or a related psychosis.

TABLE 12 Count of adverse events and protocol deviations

Event	Allocation arm (n)		Total (n)
	Control	Switch	
Adverse event	0	1	1
Serious adverse event	0	1	1
Protocol deviation	NA	NA	1
Withdrawal (prior to randomisation)	NA	NA	1
Withdrawal (after to randomisation)	1	1	2

NA, not applicable.

TABLE 13 Details of adverse events

Adverse event	Arm	Trust	Serious	Severity	Relationship with trial	Adverse reaction	Expectedness	Outcome
1	2	1	Yes	Severe	Unrelated	No	Unexpected	Worsened
2	2	2	No	Moderate	Unlikely	No	Expected	Persisting

## Economic evaluation

Service use data were collected at follow-up for eight participants (four participants in the control arm and four participants in the switch arm of the trial). All resources used by study participants over the follow-up are summarised in *Table 14* and the costs of these services are provided in *Table 15*.

TABLE 14 Use of services and percentage using the service at least once over the 6-month follow-up period, by allocation arm

Service	Allocation arm			
	Control (n = 4)		Switch (n = 4)	
	Mean (SD)	%	Mean (SD)	%
Brief psychoeducation and support sessions (number)	1.25 (0.50)	100	0.60 (0.55)	60
Inpatient (nights)	45.00 (90.00)	25	0.00 (0.00)	0
Outpatient (appointments)	1.50 (1.29)	75	1.00 (1.41)	50
A&E (attendances)	0.00 (0.00)	0	0.25 (0.50)	25
GP (contacts)	1.50 (1.73)	50	1.00 (1.41)	50
Practice nurse (contacts)	0.25 (0.50)	25	1.50 (3.00)	25
Key worker (contacts)	3.50 (3.11)	75	4.25 (2.63)	100
Psychiatrist (contacts)	0.50 (1.00)	25	0.75 (0.50)	75
Social worker (contacts)	0.00 (0.00)	0	1.25 (2.50)	25
NHS Direct (contacts)	0.25 (0.50)	25	0.25 (0.50)	25

A&E, accident and emergency.

## RESULTS

TABLE 15 Cost over 6-month follow-up period, by allocation arm

Cost	Allocation arm, mean (SD) (£)	
	Control (n = 4)	Switch (n = 4)
Advice sessions	102.19 (78.27)	54.50 (44.50)
Hospital services	18,660.00 (36,987.00)	165.00 (194.04)
Community services	233.22 (249.39)	418.62 (359.01)
Medication	162.19 (320.76)	270.23 (299.14)
Total	19,157.60 (317,171.33)	908.35 (691.91)

The substantial difference in total costs over the 6-month follow-up period between randomised arms is the result of one participant, in the control arm, being an inpatient throughout this period. Mean scores on measures of health-related quality of life at baseline and follow-up are presented in Table 16.

TABLE 16 Health-related quality of life at baseline and 6-month follow-up

Outcome	Allocation arm	Time point			
		Baseline		6-month follow-up	
		n	Mean (SD)	n	Mean (SD)
EQ-5D utility score	Control	6	0.788 (0.180)	5	0.848 (0.290)
	Switch	4	0.653 (0.162)	3	0.853 (0.114)
ReQoL	Control	6	48.82 (15.93)	5	46.67 (17.95)
	Switch	4	40.67 (14.61)	3	47.50 (11.00)



## Chapter 4 Qualitative findings

Fifty-one members of staff and four patients took part in a qualitative interview. Characteristics of staff and patient participants are presented in *Tables 17* and *18*. All four patients who were interviewed were eligible to take part in the study but declined to do so.

TABLE 17 Characteristics of staff who took part in a qualitative interview

Identification number	Gender	Ethnicity	Professional background	Job title	Time (years) spent working in mental health
1ST001	Female	White (other)	Doctor	Consultant psychiatrist	10–15
1ST002			Doctor	Psychiatrist	10–15
1ST003			Doctor	Psychiatrist	> 15
1ST004	Male		Doctor	Psychiatrist	10–15
1ST005	Male		Doctor	Psychiatrist	5–10
1ST006			Doctor	Psychiatrist	10–15
1ST007	Female		Mental health nurse	Mental health nurse	< 5
1ST008	Female		Mental health nurse	Community psychiatric nurse	10–15
1ST009	Female		Mental health nurse	Mental health nurse	< 5
1ST010	Female	British Asian	Mental health nurse	Mental health nurse	< 5
1ST011	Male	White (other)	Doctor	Consultant psychiatrist	< 5
1ST012	Male	Asian (other)	Mental health nurse	Mental health nurse	> 15
1ST013	Male	Other Chinese	Doctor	Specialist registrar	< 5
1ST014	Female	White (other)	Doctor	Psychiatrist	> 15
1ST015	Male	White (other)	Doctor	Consultant psychiatry	> 15
1ST016	Male	White British	Social worker	Care co-ordinator/social worker	> 15
1ST017	Male	Black African	Mental health nurse	Mental health nurse	> 15
1ST018	Female	Mixed	Mental health nurse	Mental health nurse	> 15
1ST019	Female	White (other)	Doctor	Psychiatrist	> 15
1ST020	Male	Asian (other)	Doctor	Consultant psychiatrist	> 15
1ST021	Male	British Asian	Mental health nurse	Mental health nurse	> 15
1ST022	Female	White British	Mental health nurse	Mental health nurse	< 5
1ST023	Male	Black African	Mental health nurse	Nurse manager	> 15
1ST024	Female	White (other)	Social worker	Social worker	> 15
1ST025	Male	White British	Mental health nurse	Staff nurse	5–10
1ST026	Female	White British	Pharmacist	Pharmacist	> 15
1ST027	Female	Black British	Mental health nurse	Senior staff nurse	10–15
1ST028	Female	White (other)	Doctor	Consultant psychiatrist	> 15

continued

## QUALITATIVE FINDINGS

TABLE 17 Characteristics of staff who took part in a qualitative interview (continued)

Identification number	Gender	Ethnicity	Professional background	Job title	Time (years) spent working in mental health
1ST029	Female	British Asian	Pharmacy technician	Pharmacy technician	10–15
1ST030	Female	White (other)	Doctor	Psychiatrist	< 5
1ST031	Female	White British	Peer support worker	Peer support co-ordinator	< 5
1ST032	Female	Black African	Pharmacist	Pharmacist	10–15
1ST033	Female	White British	Peer support worker	Peer worker	5–10
1ST034	Female	White British	Peer support worker	Peer support worker	< 5
2ST001	Female	White British	Doctor	Specialty registrar	< 5
2ST002	Female	White (other)	Doctor	Consultant psychiatrist	> 15
2ST003	Male		Doctor	Specialty doctor	< 5
2ST004	Male	British Asian	Doctor	Consultant psychiatrist	> 15
2ST005	Male		Nurse	Senior nurse practitioner	
2ST006	Male		Nurse	Community psychiatric nurse	
2ST007	Female	Sudanese	Doctor	Specialty doctor	
3ST001	Male	White British	Doctor	Consultant psychiatrist	> 15
3ST002	Female	Black African	Doctor	Consultant psychiatrist	10–15
3ST003	Female	White British	Doctor	Consultant psychiatrist	> 15
3ST004	Female	African	Doctor	Consultant psychiatrist	> 15
3ST005	Male	White, non-British	Doctor	Consultant psychiatrist	10–15
3ST006	Male	British Asian	Doctor	Psychiatry	5–10
3ST007	Male	White British	Nurse	Senior care co-ordinator	10–15
3ST008	Male	Indian	Doctor	Consultant psychiatrist	> 15
3ST009	Female	White British	Doctor	Consultant psychiatrist	> 15
3ST010	Female	White British	Mental health nurse	Team manager	> 15

TABLE 18 Characteristics of patients who took part in a qualitative interview

Identification number	Age (years)	Gender	Ethnicity
1PT001		Male	
1PT002		Female	White British
1PT003	40–50	Male	Black (other)
2PT001	30–40	Male	White British

## Emerging themes from interviews with patients

The small number of qualitative interviews we conducted with patients means that we are unable to report fully developed themes. Instead, we present emerging themes. Potential participants who decided not to take part in the study did so having weighed up concerns about their sexual functioning with concerns about their current mental health and loss of control about their treatment if they took part in the trial. Because all the qualitative patient interviews were with those who declined to take part, these emerging themes are from a biased sample and reflect barriers to taking part and not the thoughts of all patients prescribed antipsychotic medication who experience sexual side effects. Three main themes emerged and these are discussed below.

### *Previous adverse experiences when medication was switched*

Patients reported that previous negative experiences with changes to their medication put them off taking part in the study. Patients were worried about the side effects of any new medication they were prescribed (e.g. weight gain). Patients also reported concerns about jeopardising their mental health. One patient was concerned that a switch in their medication could lead to them having a mental health crisis and one patient stated that they would be 'unhappy' on any new medication.

### *Not a priority*

Patients reported that sexual dysfunction was important to them; however, they had to weigh this up against what might happen if their medication was switched. Two of the four patients said that sexual dysfunction was not a 'pressing issue': one patient was not in a sexual relationship and the other patient did not feel that their sexual problems affected their relationship.

### *Lack of control/choice*

Patients reported concerns about being randomised to one of the two treatment arms of the study. They were concerned that randomisation limited their choice about what treatment they would be given and would reduce the control they had over this. Making a switch in medication was significant event. Patients stated that they wanted as much control over their treatment as they could have, so it made sense for them not to restrict this by taking part in the study.

## Staff perspectives: barriers to talking about sexual functioning and the study

Staff highlighted the complex nature of sexual dysfunction among people with psychosis and discussed a range of reasons why it was difficult to refer people to the trial. Many reported that they had not referred anyone to the study despite being aware that recruitment was taking place. Barriers included reluctance to discuss sex in general as well as specific factors concerning sexual dysfunction among people with psychosis and involving people with psychosis in clinical trials. Eight main themes emerged and these are discussed below.

### *Not a common problem*

Staff views about the prevalence of sexual dysfunction among people with psychosis differed greatly. Some believed that it was a frequent occurrence and others believed that it was rare. Clinicians who said that they often or routinely asked patients about sexual dysfunction were more likely to consider it a frequent occurrence. Clinicians who thought it was common for people with psychosis to experience sexual side effects of antipsychotic medication felt that it was under-reported:

*I think it's very difficult to ascertain, actually. I think it's a much bigger problem than it appears.*

1ST033

### Timing

Clinicians said that it was difficult to find the right time to talk to patients about sexual dysfunction. Much of the contact they had with patients was when they were acutely unwell. Clinicians reported that the priority at that stage was trying to help stabilise a person's mental state. They reported a 'trade-off' between concerns about side effects and concerns about mental health, in which side effects were unlikely to be discussed until mental health had improved:

*It's just not the time or place, you really want to get the person well, regardless of whatever side effects.*

1ST004

However, when asked about what happened when patients were more stable, some staff stated that they still had to weigh up having this conversation with the possibility of relapse if the medication needed to be changed or the dose reduced. Staff said that it may be necessary for a patient to be stable over a longer period of time to be able to tolerate a switch in medication. Some reported that patients tended to 'ride on the side of caution' in relation to switching medication:

*[Patients will say] 'No, I don't want to change my medication, I'm stable on it' and you can understand that ... Really they've been quite unwell in the past and, they've become stable ...*

3ST010

### A 'taboo' issue

Although staff reported being able to discuss a range of other side effects with their patients, most reported discomfort and some reported 'ignoring' issues around sexual functioning when meeting their patients. Staff said that it was not part of their professional culture or 'routine practice' to ask such questions.

Moreover, many staff reported that these feelings of discomfort or embarrassment were mutual, and they thought that patients also experienced difficulties in discussing these 'sensitive', 'personal' and 'taboo' subjects:

*... I think it's a two-way thing. The patients tend to be finicky about reporting it because it can be quite personal and we sometimes feel finicky in asking it because it can be quite personal. So both things don't help. It becomes a hidden thing, that's something you don't talk about.*

1ST004

*... so you see it's a big taboo for our patients to come [to] us and talk about it. That's my experience on it.*

1ST017

When conversations with patients about sexual functioning did take place, staff reported that they may need to cover a range of sensitive subjects, including masturbation, sexual intercourse with partners and risky behaviours resulting from sexual disinhibition. Staff reported that they avoided such conversations to avoid upsetting or unsettling patients:

*... many patients suffer in silence due to embarrassment or not hav[ing] any opportunity to discuss this.*

1ST034

*... personal embarrassment, or subconsciously or deliberately ignoring [sexual dysfunction], I think I'm guilty of [that] ...*

3ST007

Staff said that it was 'safer' to discuss other side effects of medication (e.g. weight gain) or psychological factors (e.g. low self-esteem) that could be linked to sexual dysfunction.

Social and demographic factors, such as the patients' gender, age, ethnicity and relationship status, affected the likelihood of discussions about sexual functioning. Staff reported that it was easier to discuss the topic with younger males, particularly those who were sexually active, and others said that they avoided taking about these issues with female patients altogether. Several staff said that it was easier to talk to men about erectile dysfunction than it was to talk to women about loss of libido. Male members of staff were particularly concerned about speaking to female patients about sexual matters:

*It's something I discuss more with men than women, maybe for women with a male care co-ordinator it's more difficult to bring up.*

1ST016

A few staff questioned the relevance of sexual functioning for older adults; however, others acknowledged that an active sex life was part of general well-being at any age:

*I've noticed that a lot of our ladies who are older are very reluctant to talk about it. They don't want to talk about their sexuality let alone their sexual functioning.*

1ST031

*It doesn't seem to be something that older service users, by that I mean 50 plus, find easy to talk about, maybe that's because younger people are more sexually active.*

1ST016

In addition, most staff said that they avoided raising the topic of sex with those from cultural/religious backgrounds that are perceived to be more 'traditional' or conservative, such as Asian, Middle Eastern and/or Muslim and Jewish, and particularly females from those cultures. Staff were of the view that discussion of the topic might be considered 'taboo' or shameful in these cultures.

### **'Reactive' stance**

Staff appeared to adopt a passive rather than an active role in relation to their patients' sexual functioning. They often said that they relied on patients raising the subject themselves and took a 'reactive' stance. Some clinicians felt that it was up to the patient to flag pertinent side effects:

*Sexual side effects I don't usually discuss – I am more reactive.*

3ST005

*To me, [what is of] importance is what the patient tells me.*

2ST003

*I don't really feel like it's appropriate as it's such a personal and sensitive issue. I'd discuss healthy eating and sleep and topics like that but I wouldn't just bring up someone's sexual functioning without them discussing it first.*

1ST016

However, some staff acknowledged disconnect between what they 'should' ideally be doing and what actually took place in practice. Although staff often said that they waited for patients to raise any problems they had with sexual side effects of medication, they acknowledged that patients rarely raised these issues themselves. Other staff reported that if a patient did not raise the issue of sexual dysfunction then they concluded that the patient was not affected by these problems.

### **Distinguishing different causes of sexual dysfunction**

Another primary concern for clinicians in identifying potential participants was their ability to investigate and eliminate other underlying causes of sexual dysfunction. Clinicians raised concerns that other factors, such as co-prescribed medication, diabetes, obesity (which can have an impact

on self-image and self-esteem) and depression, made it difficult to identify people who experienced sexual side effects of antipsychotic drugs. Staff stated that untangling the varied and multifactorial potential causes of sexual dysfunction was a difficult undertaking. It sometimes involved periods of trial and error, which added another layer of complexity to the process of identifying patients for the study:

*Some sexual issues, it can be related to . . . [issues] of a psychological nature, because the illness might impact their self-confidence . . . self-esteem or can be of organic cause. So if it's an organic cause you're trying to establish the possible factors or co-factors that might be the reason for their sexual dysfunction.*

1ST015

*It seems for some people that the antipsychotic medications that they are on are clearly linked to their sexual dysfunction but for others who may have so many side effects including potentially developing diabetes/obesity that may contribute to sexual dysfunction too as well as personal issues and juggling mental health symptoms sometimes it's difficult to pin down what exactly is causing the dysfunction in some. Some service users are on antidepressants and antipsychotics so both could be contributing . . .*

1ST016

### **Keeping the study 'in mind'**

Many staff reported finding it difficult to keep the study in mind. They described being in a position of 'spinning multiple plates', suggesting that it was often necessary to 'fight fires' and focus their efforts on priorities. For example, some staff reported that working in crisis care settings meant that there was not enough time to explore side effects and the focus had to be on stabilising mental state:

*I don't know if I'm a bit skewed by being in the home treatment team, seeing people who are acutely psychotic. And almost giving them minimal reason not to take treatment because we might be the ones just starting it or getting them to restart treatment when they've had a serious relapse . . .*

1ST003

Staff often described how pressures on mental health services meant that they struggled to remember the study or make time to discuss it with their patients. A few participants discussed working in teams that were understaffed and had high levels of staff turnover, which had an impact on their ability to keep the study in mind:

*That's purely maybe because there's a lack of time, not enough manpower to review side effects for patients.*

1ST029

Some staff felt that they did not know enough about the study and wanted more contact with the research team to remind them about the study protocol and eligibility criteria. These staff said that it would have been helpful to have more frequent contact with researchers, more guidance on recruitment procedures and more reminders about the study. Other staff felt that the study was well advertised and said that they had received a prompt response to any queries that they had raised:

*The researchers have done their best to be present; however . . . more presence would have been much more important. So that we have in mind that we need to tackle these questions because as I said not many professionals go in depth with regard to sexual life.*

1ST030

### ***Fear of unwanted consequences***

Some staff were concerned about potential consequences of having conversations with their patients about sexual functioning. A few suggested that raising the topic could have a negative impact on their efforts to maintain trust and rapport with patients, especially for patients with psychotic symptoms:

*[Patients could become] agitated, angry and argumentative and might create unpleasant situations and then you have to avoid it.*

2ST007

Some staff expressed concern about complaints from patients who had psychotic symptoms and questioned whether or not it was appropriate to discuss sex with these patients.

Clinicians also raised concerns about speaking about sex to patients who had a history of sexual abuse. Staff were worried that such discussions could trigger painful memories and emotions related to these experiences. Staff feared that raising the study with such patients could negatively affect their relationship with them, with some staff stating that they had avoided talking to patients about the study as a result.

Other staff reported reluctance to speak to patients about the study because it could lead patients to stop taking their medication, leading to relapse. These concerns were most pronounced in the case of patients who had been treatment resistant, because staff had often spent a lot of time and energy identifying a drug regime that was effective in reducing psychotic symptoms in these patients.

### ***'Risky' patients***

Staff were particularly cautious about discussing the study with patients who were currently sexually disinhibited or had been so in the past:

*The only moment when I'm cautious is if the person is unwell or sexually disinhibited.*

1ST028

There were concerns that improving the sexual functioning of such patients could even be 'detrimental' because increased risk-taking behaviours could place sexually disinhibited patients in dangerous situations. Staff reported that discussion of sexual functioning with risky patients would require extra precautions, such as the presence of a chaperone:

*We need to be cautious depending on every case . . . Everybody is, as I said, different. We've got different patients, and we need to be cautious . . . on what kind of, part of the life we are going to improve.*

1ST030

Other staff expressed concern about raising the topic of sexual functioning or the study with patients who had deviant sexually fantasies (e.g. paedophilia) or with women who had thoughts around harming children.

## **Staff perspectives: facilitators of discussions about sexual functioning and the study**

### ***Raising the topic indirectly***

Staff reported that it was easier to discuss sexual functioning in the context of other subjects that were less taboo. For example, exploring self-esteem linked to weight gain and difficulties establishing romantic relationships could open up channels for conversations about sex and sexual dysfunction:

*It's a big issue; however it's difficult to record. So in my career hardly ever do I get patients say[ing] they suffer from sexual dysfunction directly. You can get the information indirectly that it's making them not have energy, making them unmotivated, making them not have a relationship.*

1ST017



Clinicians reported that including questions about sexual functioning as part of a battery of questions that patients were asked to complete during medication reviews could be helpful:

*... sometimes it's difficult to bring it up in general conversation so if you have a form that they can then fill in then you can see whether they've ticked it or not and bring it up that way.*

1ST018

### **Quality of the therapeutic relationship**

Many staff reported that it was necessary to establish trust and rapport with patients prior to discussing these types of side effects. This was often difficult in circumstances when patients were acutely unwell and required crisis intervention because of the short-term nature of the work. In contrast, a few inpatient staff suggested that it was easier to discuss with patients who were well known to them on the wards:

*Someone's likelihood to speak to you and have an open conversation about their sexual functioning will also very much depend on the relationship that the staff member has with the individual. Although we work as a team, as an MDT [multidisciplinary team], often cases particularly with females clients and patients build up rapport in particular with one individual ... all patients will have one nurse that's their favourite to go to talk to.*

1ST031

### **Other staff perspectives**

During the course of the interviews some staff made suggestions for future studies of sexual dysfunction among people with psychosis. Suggestions included staff training and studies examining add-on medications. Staff suggested that pharmacists, because they focus on side effects of medication, may find it easier to ask patients about these side effects. Others highlighted the importance of staff training and guidance to help facilitate discussions about sexual dysfunction.

Clinicians reported that it would be easier to start discussions about sexual dysfunction if they knew that switching medication provided an effective approach to helping people who experience these problems.

Some staff said that they already offered additional medication, such as sildenafil citrate (Viagra), and asked if this could be a topic for a future study. They suggested that offering additional medication could avoid some of the concerns they and their patients had about switching their antipsychotic medication:

*When we have tried medications ... with less side effects and these medications haven't worked because [we] haven't been able to control the psychic symptoms then we know we probably need something else, and the Viagra and other drugs maybe would be an alternative.*

1ST028



## Chapter 5 Discussion

Recruitment to this trial was very challenging. Over the course of an extended 12-month pilot trial we recruited only 10 participants. This led to the early termination of the study, and we were unable to collect sufficient data to test study hypotheses. We explored reasons why recruitment was so difficult in qualitative interviews with 51 members of staff and four patients who declined to take part in the study. Themes derived from these interviews highlighted the discomfort and embarrassment that many staff and patients felt when talking about sex. Staff also had concerns about talking to patients about side effects of antipsychotic medication and patients were uncomfortable about the idea of switching medication, especially if they felt that the one they were already taking had helped them achieve better mental health.

Staff reported finding it difficult to talk to people with psychosis about side effects of medication when patients were acutely unwell. They told us that the priority at this point was to help the patient achieve better mental health. However, staff said that, even when patients had achieved better mental health, they found it difficult to talk about sexual functioning because they were concerned how patients would experience this. Some believed that attempts to discuss sexual functioning could damage their relationship with a patient. Staff reported finding it especially difficult to talk to people of the opposite sex, to older adults and to people with religious beliefs that they felt made them less open to discussing sex. Staff were also worried about raising the topic with people who had a history of sexual abuse, people with paranoid thoughts and people with a history of sexual disinhibition or paraphilia. Most staff therefore waited for patients to raise the topic of sexual functioning themselves, although many recognised that patients were unlikely to do this. This meant that problems with sexual functioning often went undetected. Some staff preferred to avoid the topic of sexual dysfunction altogether. One consultant psychiatrist advised 'none of my patients have these problems'.

Staff beliefs that patients can find it difficult to talk about sexual dysfunction were supported by (1) the poor response we had to direct marketing of the study and (2) the high proportion of people who were eligible to take part in the study but who declined to do so. Of 341 patients who were identified as potential candidates for the study, only eight responded to a letter from their clinical team with information about the study. None of these eight patients agreed to take part in the trial after they were provided with additional information about it. Despite the fact that as many as half of people with psychosis reported experiencing sexual dysfunction associated with use of antipsychotic medication,<sup>7</sup> only five people contacted the study team having seen one of the many posters and leaflets that were distributed at clinics, day services and community support services for people with psychosis. None of these patients had schizophrenia or a related psychosis and were therefore ineligible to take part in the study.

Data from four qualitative interviews with patients and brief comments from 28 others who declined to take part suggest that, although sexual dysfunction is important, it is a problem that people often feel they can live with. Many of those interviewed were concerned about the impact that switching medication could have on their mental health or were worried about new side effects they might experience with the drug they were switched to. Others did not like the lack of control they would have about whether or not their medication was switched. A minority of patients wanted to have a change in their medication in an effort to improve their sexual functioning and were not prepared to take part in a study in which there might not be a change. These data highlight the barriers to recruiting to a study of the management of sexual dysfunction among people with psychosis, especially one that involves randomising people to a switch in their current medication.

## Strengths and weaknesses

To the best of our knowledge, the REMEDY trial is the first trial in the UK to test the impact of an intervention aimed at reducing sexual dysfunction associated with use of antipsychotic medication. We used a broad range of strategies to publicise the study. We encouraged staff to refer potential participants to the trial by presenting it at local and regional meetings. Researchers attended clinical meetings to remind staff about the study and encouraged the use of screening tools for assessing sexual and other side effects of antipsychotic medication. A person with lived experience joined some of these meetings and talked to staff about the importance of sexual functioning for people with psychosis. We also used a broad range of methods to communicate directly with people with psychosis to let them know about the study.

The main limitation of the study was the small sample size, which meant that we were unable to test differences in study outcomes between those who were and were not offered a switch in medication. We do not know how successful we would have been had we tried to recruit participants at other services. After 9 months of failing to recruit to target at three Trusts we decided to open recruitment up in a fourth Trust that had expressed particular interest in the study. Part of the rationale for this was to check whether or not the difficulties we had recruiting study participants were specific to the places where we initially tried to recruit from. This fourth Trust had a track record of successfully recruiting to other clinical trials involving people with psychosis, and feedback from local clinicians was that they could recruit patients to the REMEDY trial. Although one participant was recruited over a 3-month period, the slow rate of recruitment at this fourth Trust and the findings from our qualitative interviews with staff suggest that the barriers to recruitment we experienced were ones that are likely to exist across secondary care mental health services in England.

Another limitation was the small number of qualitative interviews we completed with patients. It is inherently challenging to recruit people to take part in an in-depth interview when they had already indicated that they do not want to take part in a study. We attempted to overcome this limitation by gathering brief comments from all potential participants, including those who did not want to take part in an in-depth interview. We were able to collect brief comments from 28 patients who may have been eligible but declined to be interviewed. These comments supported the views of staff, that is, patients may not consider problems with sexual functioning to be a sufficiently important to risk the potential for negative effects of a switch in their medication. Others patients were anxious about not having a change in their treatment when they did want something to be done to try to improve their sexual functioning.

## Comparison with previous literature

A recent systematic review<sup>5</sup> of interventions for managing sexual dysfunction associated with antipsychotic medication identified six RCTs. The authors concluded that there was insufficient evidence to make recommendations for clinical practice based on the results of these trials. This was, in part, because previous studies have been small and underpowered. The six trials had between 10 and 50 participants, and the authors speculated that it 'may be difficult to recruit participants with antipsychotic-related sexual dysfunction' to clinical trials.<sup>5</sup> The results of the REMEDY trial provides further support for this suggestion and, to the best of our knowledge, for the first time, provide a rich source of data about possible reasons for this.

One of the main reasons for poor recruitment was that clinical staff found it difficult to ask patients about sexual functioning. A number of surveys have reported that clinical staff believe that sexual functioning is an important component of health and well-being, but they are reluctant to raise the subject with their patients. For instance, a survey of 100 mental health nurses in Sweden found that two-thirds believed that they had a responsibility to talk to patients about sexual concerns, but only

20% did so in practice.<sup>65</sup> Similar surveys in the UK also report that mental health nurses believe that it is important to discuss sexual functioning with patients.<sup>66</sup> By contrast, retrospective audits of clinical records find that patients are unlikely to be asked about sexual functioning unless they raise it themselves.<sup>19,20</sup> In-depth interviews with 14 mental health nursing staff members in the UK found that staff avoided talking to patients about sex because they did not think it is an important priority or believed that others were better placed to have these discussions.<sup>67</sup>

When staff were able to talk to patients about sexual side effects of antipsychotic medication and identify potential participants, many patients were reluctant or unwilling to take part because of concerns about a possible switch in their medication. Very little research has examined the personal experiences of people prescribed antipsychotic medication. Research that has been conducted suggests that patient experiences are complex and that problems with side effects are a major concern.<sup>68-70</sup> Patients who feel settled on their medication may be fearful about the consequences of a change.<sup>71</sup> Such concerns are well founded given evidence that switching antipsychotic medication may increase the risk of relapse<sup>27,28</sup> or cause new side effects.<sup>3</sup>

## Implications for future research

Although the costs and benefits of switching antipsychotic medication to help people with psychosis who experience sexual dysfunction associated with the use of these medications remain unclear, we are not able to recommend future studies of using this approach in the NHS because of the substantial problems we had with recruitment. Indeed, any trials of interventions to manage sexual dysfunction among people with psychosis are likely to be challenging unless there are changes within mental health services and in society at large to make it easier for staff and patients to talk about sex and sexual functioning.

Patient and staff concerns about switching antipsychotic medication were an important barrier to recruitment in this trial. Patients may be more willing to consider taking part in studies examining the use of adjunctive medication. Although adjunctive antipsychotic medications (e.g. aripiprazole) may lead to reductions in prolactin, which have the potential to improve sexual functioning,<sup>72</sup> concerns about co-prescribing different antipsychotic drugs<sup>73</sup> may limit the willingness of patients and staff to support such a study. There is evidence from a small randomised trial<sup>74</sup> that phosphodiesterase inhibitors can improve sexual function among married men with schizophrenia who experience sexual dysfunction associated with antipsychotic medication. There is also evidence that phosphodiesterase inhibitors can improve sexual dysfunction among women in the general population.<sup>75</sup> If it were possible to overcome barriers to assessing sexual dysfunction among people with psychosis then consideration could be given to testing the acceptability, clinical effectiveness and cost-effectiveness of phosphodiesterase inhibitors.



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## Data-sharing statement

Anonymised data can be obtained from the corresponding author.

## Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.





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