

# Hypersexuality: fluoxetine

## Evidence summary

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[nice.org.uk/guidance/esuom46](https://www.nice.org.uk/guidance/esuom46)

## Key points from the evidence

The content of this evidence summary was up-to-date in July 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

No randomised controlled trials (RCTs) which evaluate the use of fluoxetine in the treatment of hypersexuality were found, nor any studies that compared fluoxetine with any of the hormonal treatments licensed to treat hypersexuality. Limited evidence from 3 small, short-term observational studies suggests that fluoxetine may improve some measurements of hypersexuality and sexual preoccupation in men who have either been convicted of a sexual offence or who have a [paraphilia](#) or a [non-paraphilic sexual addiction](#). However, these studies had a number of limitations which make it difficult to draw conclusions on the use of fluoxetine for this indication.

**Regulatory status:** off-label. This topic was prioritised because of the potential for variation in practice and because there is uncertainty about the balance of risks and benefits of fluoxetine for the treatment of hypersexuality.

Effectiveness	Safety
<ul style="list-style-type: none"><li>• An observational study in 64 men convicted of a sexual offence and treated with fluoxetine, cyproterone or both treatments found statistically significant improvements for the combined group for measures of hypersexuality, sexual compulsion and sexual preoccupation after 3 to 4 months' treatment.</li><li>• An observational study in 20 men with a paraphilic or non-paraphilic sexual addiction treated with fluoxetine found a statistically significant reduction in the total number of sexual activities per week from 10.6 at baseline to 3.6 after 12 weeks' treatment.</li><li>• A 12-week observational study in 58 men with a paraphilic disorder treated in a sexual behaviours clinic with 1 of 3 selective serotonin reuptake inhibitors (sertraline, fluoxetine or fluvoxamine) found a statistically significant reduction in severity of sexual fantasies from baseline to week 4 and from week 4 to week 8 but not from week 8 to week 12.</li></ul>	<ul style="list-style-type: none"><li>• The summary of product characteristics (<u>Prozac</u>) lists fatigue, nausea, diarrhoea, headache and insomnia as very common (1 in 10 or more) adverse reactions.</li><li>• The observational studies included in this evidence summary reported very limited safety data.</li></ul>

User factors	Resource implications
<ul style="list-style-type: none"> <li>Fluoxetine has a relatively long elimination half-life compared with other treatments and it can take up to 5 to 6 weeks after discontinuation to be completely eliminated from the body.</li> </ul>	<ul style="list-style-type: none"> <li>Fluoxetine 20 mg to 60 mg once a day costs from £14 to £289 for 12 months' treatment depending on the preparation chosen.</li> <li>Cyproterone acetate (<a href="#">Androcur</a>) costs approximately £376 for 12 months' treatment at a dose of 50 mg twice a day. Triptorelin (<a href="#">Salvacyl</a>) costs approximately £992 for 12 months' treatment at the licensed dose of 11.25 mg (1 vial) every 12 weeks.</li> </ul>

## Introduction and current guidance

Hypersexuality is unusual or excessive concern with or indulgence in sexual activity. Sometimes hypersexuality is associated with a medical condition, such as dementia, or is an adverse effect of drug treatment, for example in Parkinson's disease.

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders ([DSM-5](#)) notes that most people with atypical sexual interests such as hypersexuality do not have a mental health disorder. DSM-5 aims to differentiate between atypical human behaviour and behaviour that causes mental distress to a person or makes the person a serious threat to the psychological and physical well-being of other individuals. DSM-5 states that certain criteria should be met for people with atypical sexual interests to be diagnosed with a paraphilic disorder.

People with hypersexuality may be treated with medication to reduce libido. These medications broadly fit within 2 categories: hormonal medications that have a testosterone-suppressing effect and non-hormonal medications that affect libido through other mechanisms. Hormonal drug therapy includes anti-androgens (for example, cyproterone acetate) and gonadotropin-releasing hormone (GnRH) analogues (for example, triptorelin). Non-hormonal drug therapy includes antipsychotics (off-label use) and selective serotonin reuptake inhibitors (off-label use) [[Khan et al. 2015](#)].

[Full text of introduction and current guidance.](#)

## Product overview

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant ([summaries of product characteristics](#)). Fluoxetine is not licensed for the treatment of hypersexuality; therefore use for this indication is off-label.

[Full text of product overview.](#)

## Evidence review

- This evidence summary concentrates on the management of people with hypersexuality not associated with a medical condition including those in prison convicted of a sexual offence and people with a paraphilia or paraphilic disorder. No randomised controlled trials (RCTs) were found.
- This evidence summary is based on 3 [observational studies](#): 1 included 64 men who had been convicted of sexual offences ([Winder et al. 2014](#)), and the others included 20 men and 58 men respectively with a paraphilia (for example, paedophilia or sexual masochism) or non-paraphilic sexual addiction (for example, compulsive masturbation) [[Kafka and Prentky 1992](#) and [Greenberg et al. 1996](#)].
- [Winder et al. 2014](#) included 64 men convicted of a sexual offence (the majority of whom had committed sexual offences against children) who had been referred for treatment for hypersexuality: 36 received fluoxetine, 5 received cyproterone (after initial fluoxetine treatment was ineffective) and 7 received a combination of fluoxetine and cyproterone. Hypersexuality was measured by asking participants how many days in the previous week they had masturbated to orgasm. After 3 months' treatment, this was reduced from 3.67 days at baseline to 1.10 days in the fluoxetine group and from 3.97 days to 1.70 days in the cyproterone group. Sexual preoccupation was assessed by asking: 'how much time do you spend thinking about sex?' measured on a scale from 1 (low) to 7 (high). After 3 months' treatment there was a reduction from 4.71 at baseline to 2.00 in the fluoxetine group and from 5.60 to 2.80 in the cyproterone group. Sexual compulsivity was also assessed by asking relevant questions scored on a scale from 1 (not like me at all) to 4 (very much like me). The mean score reduced from 2.68 to 1.20 in the fluoxetine group and from 3.08 to 1.15 in the cyproterone group. For the combined group, there were statistically significant improvements from baseline in hypersexuality, sexual preoccupation and sexual compulsivity. The clinical significance of the findings however is unclear.

- In [Kafka and Prentky 1992](#) participants were self-referred by responding to a newspaper advertisement inviting people to participate in a study evaluating the treatment of sexual addictions and compulsions. The majority of the participants (19 out of 20) reported chronic depressive symptoms lasting more than 2 years. Fluoxetine was started at an initial dose of 20 mg daily and titrated to a mean dose of 39 mg daily, but there was no comparator arm of the study. Sexual behaviour was assessed using an unpublished and un-validated self-assessment tool. Total sexual outlet (defined as the total number of sexual activities in the measured week that either led to orgasm or would have done so had voluntary restraint not been utilised) was calculated using data obtained from the assessment tool. There was a statistically significant reduction in mean total sexual outlet from 10.6 at baseline to 3.6 at week 12 ( $p < 0.001$ ).
- [Greenberg et al. 1996](#) included 58 men treated in a sexual behaviours clinic with 1 of 3 SSRIs (sertraline [ $n=25$ ], fluoxetine [ $n=17$ ] or fluvoxamine [ $n=16$ ]). Outcomes included severity of sexual fantasies measured on a scale from 0 to 4. Results were presented for the whole group rather than for each individual SSRI, although it was reported that no differences were seen between them (no statistical analysis was provided). For the whole group, there were statistically significant decreases in the fantasy severity score from baseline to week 4 ( $p < 0.001$ ), from week 4 to week 8 ( $p < 0.05$ ) but not from week 8 to week 12 (no  $p$  value reported). The severity of fantasy score for the group was approximately 2 (moderate, frequent, disturbing, less able to stop) at baseline, approximately 1 (mild, occasional, not too disturbing, easily able to stop) at week 4 and approximately 0.75 at week 8.
- Fluoxetine has a well-documented adverse effect profile and the summaries of product characteristics (SPCs) contain a number of special warnings and precautions for use (for example: [Prozac](#)). From the studies discussed in this evidence summary, neither [Winder et al. 2014](#) nor [Kafka and Prentky 1992](#) reported any safety data. In [Greenberg et al. 1996](#) adverse effects were reported for all 3 SSRIs combined rather than individually, although it was reported that no differences were seen between them. Similar to those listed in the SPCs, the most common adverse effects reported included insomnia, delayed ejaculation, headaches, drowsiness, reduced sex drive, diarrhoea, nausea and blurred vision.
- Overall, the 3 small short-term observational studies included in this evidence summary provide very limited data on the use of fluoxetine to treat hypersexuality. None of the studies included a control group and none were randomised or blinded and so they are all subject to [bias](#) and [confounding](#) factors. All of the studies used self-reporting tools to assess sexual behaviour or sexual preoccupation and the validity of the results is unclear. Specialists who commented on this evidence summary highlighted that more objective measures of hypersexuality and sexual preoccupation may have been more appropriate for this group of people. The reliability of using self-reported data where there may be vested interests in

reporting positive responses to treatment in terms of progressing with sentencing for instance is unclear.

- All of the studies were in men (mean age around 40 years) and the majority of the participants (approximately 93%) had been convicted of a sexual offence or had a paraphilia. The studies provide no information on the use of fluoxetine to treat hypersexuality in the longer-term. [Kafka and Prentky 1992](#) assessed the effect of treatment on concomitant depressive symptoms; however the other 2 studies did not assess the effect of treatment on any concomitant mental health disorder.

[Full text of evidence review.](#)

### *Context and estimated impact for the NHS*

Cyproterone acetate ([Androcur](#)) is licensed for the control of libido in severe hypersexuality or sexual deviation in the adult male. Triptorelin ([Salvacyl](#)) is licensed for the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations. Cyproterone acetate (Androcur) costs approximately £376 for 12 months treatment at a dose of 50 mg twice a day. Triptorelin (Salvacyl) costs approximately £992 for 12 months treatment at the licensed dose of 11.25 mg (1 vial) every 12 weeks.

[Full text of context and estimated impact for the NHS.](#)

### *Information for the public*

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with hypersexuality who are thinking about trying fluoxetine.

### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Full evidence summary

### *Introduction and current guidance*

Hypersexuality is unusual or excessive concern with or indulgence in sexual activity. Sometimes hypersexuality is associated with a medical condition, such as dementia, or is an adverse effect of drug treatment, for example in Parkinson's disease.

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) notes that most people with atypical sexual interests such as hypersexuality do not have a mental health disorder. DSM-5 aims to differentiate between atypical human behaviour and behaviour that causes mental distress to a person or makes the person a serious threat to the psychological and physical well-being of other individuals.

People with atypical sexual interests need to fulfil the following criteria to be diagnosed with a paraphilic disorder according to DSM-5:

- feel personal distress about their interest, not merely distress resulting from society's disapproval; or
- have a sexual desire or behaviour that involves another person's psychological distress, injury, or death, or a desire for sexual behaviours involving unwilling persons or persons unable to give legal consent.

Sexual offending is a legal term which overlaps with, but is not necessarily the same as the clinical descriptions of disorders of sexual preference as described in the [ICD-10 Classification of Mental and Behavioural Disorders](#), or paraphilias as described in the DSM ([Khan et al. 2015](#)). A sex offence is defined as any violation of established legal or moral codes of sexual behaviour ([Adi et al. 2002](#)).

This evidence summary concentrates on the management of people with hypersexuality not associated with a medical condition including people in prison convicted of sexual offences or people with a paraphilia or paraphilic disorder.

People with hypersexuality may be treated with medication to reduce libido. These broadly fit within 2 categories: hormonal medications that have a testosterone-suppressing effect and non-hormonal medications that effect libido through other mechanisms.

Hormonal drug therapy includes anti-androgens (for example, cyproterone acetate) and gonadotropin-releasing hormone (GnRH) analogues (for example, triptorelin). Cyproterone acetate ([Androcur](#)) is licensed for the control of libido in severe hypersexuality or sexual deviation in adult men. Triptorelin ([Salvacyl](#)) is licensed for the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations.

Non-hormonal drug therapy includes antipsychotics (off-label use) and selective serotonin reuptake inhibitors (off-label use) ([Khan et al. 2015](#)).

## *Product overview*

### **Drug action**

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant (summary of product characteristics [SPC] for example: [Prozac](#)).

### **Regulatory status**

In adults, fluoxetine is licensed for the treatment of major depressive episodes and obsessive compulsive disorder. It is also licensed for use in the treatment of bulimia nervosa (as a complement to psychotherapy) for the reduction of binge-eating and purging activity (SPC: [Prozac](#)).

Fluoxetine is not licensed for the treatment of hypersexuality; therefore use for this indication is off-label.



In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using fluoxetine outside its authorised indications.

## Cost

According to the [Drug Tariff](#) (prices excluding VAT, June 2015):

- 30 fluoxetine 20 mg capsules cost £1.16
- 30 fluoxetine 60 mg capsules cost £20.17
- 28 fluoxetine 20 mg dispersible tablets cost £3.44
- 70 ml fluoxetine 20 mg/5 ml oral solution costs £3.69.

## Evidence review

This evidence summary is based on the [best available evidence](#) for using fluoxetine in the treatment of hypersexuality. No [randomised controlled trials](#) (RCTs) that evaluated the use of fluoxetine in the treatment of hypersexuality were found. In addition, a Cochrane review on pharmacological interventions for people who had committed sexual offences or were at risk of offending did not find any RCTs looking at the use of SSRIs ([Khan et al. 2015](#)).

This evidence summary is based on 3 [observational studies](#): 1 included 64 men who had been convicted of sexual offences ([Winder et al. 2014](#)), and the others included 20 men and 58 men respectively with a paraphilia (for example, paedophilia or sexual masochism) or non-paraphilic sexual addiction (for example, compulsive masturbation) [[Kafka and Prentky 1992](#) and [Greenberg et al. 1996](#)]. A Health Technology Assessment on the clinical effectiveness and cost-consequences of SSRIs for treating sex offenders has also been published ([Adi et al. 2002](#)), although this is not discussed in detail in this evidence summary. This review included 9 small (n=3 to n=58) observational studies and case series (including [Greenberg et al. 1996](#) and [Kafka and Prentky 1992](#)), most of which were not eligible for inclusion in this evidence summary, for example due to their small size or the SSRI used. The review concluded that there was a need for double-[blind](#) RCTs to provide evidence on the use of SSRIs for this indication.

A small randomised open-label study comparing 3 interventions (psychotherapy, drug treatment [including SSRIs and mood stabilisers] and psychotherapy and drug treatment combined) is currently being conducted in 135 people with compulsive sexual behaviours in Brazil ([NCT02300051](#)).

## Clinical effectiveness

### Winder et al. 2014

This observational study included 64 men convicted of sexual offences (average age 43 years) from a UK prison and who had been referred for medication to reduce hypersexuality, sexual compulsion or sexual preoccupation between 2010 and 2012. Criteria for referral for medication included evidence of 1 or more of: hyper-arousal, intrusive sexual fantasies or urges, subjective reports of experiencing urges that are difficult to control, sexual sadism or other dangerous paraphilia's such as necrophilia or highly repetitive paraphilic offending such as voyeurism or exhibitionism. Over 90% of the men had committed sexual offences against children with an average of 5 previous contact offences and 2 previous non-contact offences per offender. Approximately half (46%) of the group had an intelligence quotient (IQ) less than 80 (which is below the usual average IQ test score, for example the Wechsler Abbreviated scale of intelligence which was the scale used in the study).

Of the 64 men referred for treatment, 36 received fluoxetine, 5 received anti-androgen medication (cyproterone), 7 received a combination of fluoxetine and cyproterone, 1 received triptorelin and 15 did not receive any medication or were still under assessment for medication. It was reported that when fluoxetine did not appear to be working, cyproterone was prescribed. However it is unclear how 'did not appear to be working' was defined. Fluoxetine was usually started at a dose of 20 mg daily with an increase to 40–60 mg daily as necessary. Participation in the study was voluntary.

Participants in the study met with a psychiatrist on a regular basis to assess measures of sexual compulsivity, hypersexuality and sexual preoccupation. Data measures were reported at baseline, 1 month after participants started medication (except the sexual compulsivity score) and after 3 to 4 months' of treatment. Results were reported for the group treated with fluoxetine and the group treated with cyproterone. It was reported that participants taking cyproterone in addition to fluoxetine were included in the cyproterone group. Statistical analyses tested for associations between the outcome measures and time or medication group.

Sexual compulsivity was measured using a 10-item scale (validated in homosexual men with HIV who reported engaging in 'risky' sexual practices). Participants rated the extent to which they agreed with each statement in the scale for example, 'my sexual thoughts and behaviours are causing problems in my life' from 1 (not like me at all) to 4 (very much like me). The mean sexual compulsivity score for each item was reduced from 2.68 at baseline to 1.20 in the fluoxetine group after 3 months' treatment. In the cyproterone group it was reduced from 3.08 at baseline to 1.15

after 3 months' treatment. For the treatment groups combined, there was a statistically significant improvement after 3 months' treatment for the mean sexual compulsivity score ( $p=0.003$ ).

Hypersexuality was assessed by asking participants how many days in the last week they had masturbated to orgasm. After 3 months' treatment, there was a reduction from 3.67 days at baseline to 1.10 days in the fluoxetine group and from 3.97 days at baseline to 1.70 days in the cyproterone group. For the treatment groups combined, there was a statistically significant improvement after 3 months' treatment for the measurement of hypersexuality ( $p=0.001$ ). There was no statistically significant effect of medication type (fluoxetine or cyproterone) on the hypersexuality outcome (no  $p$  value provided).

To assess sexual preoccupation participants were asked 3 questions and asked to rate each question on a 7-point scale (it is unclear if the scale was validated). Questions 1 and 2 were rated from 1 (low) to 7 (high) and question 3 was rated from 1 (easy) to 7 (difficult):

- Question 1 'how much time do you spend thinking about sex?' After 3 months' treatment there was a reduction from 4.71 at baseline to 2.00 in the fluoxetine group and from 5.60 at baseline to 2.80 in the cyproterone group.
- Question 2 'what is the strength of your sexual urges and fantasies?' After 3 months' treatment there was a reduction from 5.23 at baseline to 2.16 in the fluoxetine group and from 5.99 at baseline to 3.30 in the cyproterone group.
- Question 3 'what is your ability to distract yourself from sexual thoughts?' After 3 months' treatment there was a reduction from 4.85 at baseline to 1.71 in the fluoxetine group and from 5.72 at baseline to 2.80 in the cyproterone group. For the treatment groups combined, there was a statistically significant improvement after 3 months' treatment for the 3 questions on sexual preoccupation ( $p=0.001$  for all outcomes). There was also a statistically significant effect of medication type (fluoxetine or cyproterone) on the outcome of each question ( $p=0.005$  for questions 1 and 3 and  $p=0.003$  for question 2). However, the clinical significance of this is unclear as reductions from baseline in the scores for these 3 questions were similar between the 2 groups and the cyproterone group was reported to include participants taking cyproterone alone or combined with fluoxetine.

#### Kafka and Prentky 1992

This 12-week US observational study included 20 men (10 with paraphilic and 10 with non-paraphilic sexual addictions; modal age 36 years) who were treated with fluoxetine. Participants were self-referred by responding to a newspaper advertisement inviting people to

participate in a study evaluating the treatment of sexual addictions and compulsions. Men reporting distress accompanied by social, psychological, or work impairment, unwanted medical risks, legal consequences or significant associated financial cost, were eligible for study inclusion. Nineteen of the men reported chronic depressive symptoms lasting more than 2 years.

After baseline assessment, fluoxetine was initiated at a dose of 20 mg daily with dose titration at 4-week intervals to a maximum of 60 mg daily if clinically indicated. The mean dose of fluoxetine at week 12 was 39 mg. Ten of the men in the study also received psychological therapies. Sexual behaviour was assessed at 4-week intervals using a self-assessment tool to document the incidence of sexual fantasies, urges and activities during a designated week. The self-assessment tool used in this study was previously unpublished and unvalidated. Total sexual outlet (defined as the total number of sexual activities in the measured week that either led to orgasm or would have done so had voluntary restraint not been utilised) was calculated using data obtained using the self-assessment tool.

Sixteen men completed the study. A statistically significant reduction in mean total sexual outlet was seen from 10.6 at baseline to 3.6 at week 12 ( $p < 0.001$ ).

#### Greenberg et al. 1996

This 12-week retrospective observational study, using data taken from medical charts and records, included 58 men (mean age 36 years) who were being treated for paraphilias (74% paedophilia) with 1 of 3 SSRIs (sertraline [ $n=25$ ], fluoxetine [ $n=17$ ] or fluvoxamine [ $n=16$ ]) at a sexual behaviours clinic in Canada between 1991 and 1995. Seventy-nine percent of the participants were also receiving some receiving some form of psychosocial intervention. It was reported that 31% of participants had a personality disorder, 28% had depression, 17% had alcohol dependence and 16% had adjustment disorders. Outcomes measured included severity of illness and global improvement (using a 7-point Clinical Global Impression Scale from 1 'very much improved' to 7 'very much worse') and frequency and severity of sexual fantasies. Severity of sexual fantasies was rated on a 5-point scale from 0 (no fantasies) to 4 (extreme, also constant, very disturbing, unable to stop).

Results were presented for the whole group together rather than for each individual SSRI. Between weeks 4 and 12, nearly 30% of the participants dropped out of the study and no further data was collected for them. Data until week 12 is available for 41 participants. For the global improvement scale there were statistically significant improvements from baseline to week 4 ( $p < 0.001$ ), from week 4 to week 8 ( $p < 0.001$ ) and from week 8 to week 12 ( $p < 0.05$ ). The global improvement scale score was approximately 4 (no change) at baseline, approximately 3 (minimally improved) at week 4 and approximately 2 (much improved) at week 12. There were statistically significant decreases in

the fantasy severity score from baseline to week 4 ( $p < 0.001$ ), from week 4 to week 8 ( $p < 0.05$ ) but not from week 8 to week 12 (no  $p$  value reported). The severity of fantasy score for the group was approximately 2 (moderate, frequent, disturbing, less able to stop) at baseline, approximately 1 (mild, occasional, not too disturbing, easily able to stop) at week 4 and approximately 0.75 at week 8. It was reported that there were no significant differences between the 3 SSRI groups for fantasy severity or global improvement scale scores but no statistical analysis is provided.

## Safety and tolerability

Neither [Winder et al. 2014](#) nor [Kafka and Prentky 1992](#) reported any safety data. In [Greenberg et al. 1996](#) adverse effects were reported for all 3 SSRIs (fluoxetine, sertraline and fluvoxamine) as a group rather than individually, although it was reported that no differences were seen between them. Forty percent of participants reported adverse effects at week 4, 30% at week 8 and 23% at week 12. The most common adverse effects included insomnia ( $n=8$ ), delayed ejaculation ( $n=8$ ), headaches ( $n=7$ ), drowsiness ( $n=6$ ), reduced sex drive ( $n=4$ ), diarrhoea ( $n=3$ ), nausea ( $n=3$ ) and blurred vision ( $n=2$ ). Seventeen people withdrew from the study, 3 because of adverse effects.

The summary of product characteristics (SPC) for fluoxetine (for example: [Prozac](#)) reports the following very common (1 in 10 or more) adverse reactions: fatigue, nausea, diarrhoea, headache and insomnia. Common (between 1 in 10 and 1 in 100) adverse reactions are reported to include: decreased appetite and weight loss, anxiety, nervousness, restlessness, sleep disorders and abnormal dreams, disturbances in attention, dizziness, lethargy, tremor, blurred vision, palpitations, vomiting, dry mouth, dyspepsia, flushing, rash and urticaria, arthralgia, frequent urination and chills.

Fluoxetine is contra-indicated in people taking monoamine oxidase inhibitors and has a number of special warnings and precautions for use, which are discussed in the SPC. See the [summaries of product characteristics](#) for licensed fluoxetine products for further information on contraindications, potential interactions and adverse effects of fluoxetine.

## Evidence strengths and limitations

No RCTs which evaluate the use of fluoxetine in the treatment of hypersexuality were found during literature searches conducted for the production of this evidence summary.

This evidence summary is based on 3 small observational studies (2 open label and 1 retrospective;  $n=64$ , 58 and 20 respectively) which provide limited information on the use of fluoxetine for hypersexuality. None of the studies included a control group and none were randomised or blinded, and are therefore subject to [bias](#) and [confounding](#). Observational studies are prone to confounding,

which limits the conclusions that can be drawn. Unlike in the setting of a randomised controlled trial, in 'real life', treatment plans are chosen, changed, or actively not chosen in the light of individual peoples' risk factors, preferences and tolerability or responses to other drugs. Thus observed differences in outcomes may be due to differences among the participants, not only the different treatments.

All of the studies were short-term (around 3 to 4 months) and, therefore, provide no evidence for using fluoxetine to treat hypersexuality in the longer term. All of the participants in the studies were male and had an average age of between 36 and 43 years. Because of this, they provide little information on the use of fluoxetine to treat hypersexuality in a younger or older population, and no information on use in women. The majority of men in the studies had committed a sexual offence or had a paraphilia (approximately 93% [132/142]). Only 10 participants in [Kafka and Prentky 1992](#) had a non-paraphilic sexual addiction (3 of whom dropped out of the study), providing little evidence for using fluoxetine to treat this group of people.

In [Winder et al. 2014](#) the average IQ of the population was lower than the average IQ of the general population, which may have influenced the relevance of the self-reported outcomes. The other 2 studies did not report IQ scores but participants in [Greenberg et al. 1996](#) had a mean duration in education of 12.2 years and in [Kafka and Prentky 1992](#) the modal participant had achieved a college or postgraduate degree. The majority of men in [Kafka and Prentky 1992](#) reported concomitant chronic depressive symptoms lasting more than 2 years. In [Greenberg et al. 1996](#), 31% of participants had a personality disorder, 28% had depression and 16% had adjustment disorders. [Winder et al. 2014](#) did not report on concomitant psychiatric illness. [Kafka and Prentky 1992](#) assessed the effect of treatment on concomitant depressive symptoms; however the other 2 studies did not assess the effect of treatment on any concomitant mental health disorder.

[Winder et al. 2014](#) included 64 men who had committed a sexual offence and were housed in a prison. Over 90% of the men had committed sexual offences against children with an average of 5 previous contact offences and 2 previous non-contact offences per offender. The results of the study may not be applicable to other populations with hypersexuality. Outcome measures were assessed by asking the participants questions relating to sexual compulsivity, hypersexuality and sexual preoccupation. The study authors highlight the use of self-reported data as a limitation of the study and raise the question of its validity and reliability. Specialists who commented on this evidence summary highlighted that more objective measures of hypersexuality and sexual preoccupation may have been more appropriate for this group of people. The reliability of using self-reported data where there may be vested interests in reporting positives responses to treatment in terms of progressing with sentencing is unclear. In addition, the average IQ of the population was less than 80, which is lower than the usual average IQ score; this may have also had

an impact on the validity of self-reported data. The sexual compulsivity scale used in this study had been validated in homosexual men who were HIV positive who had reported engaging in risky sexual practices, it is unclear if the scale is valid to use for the population included in this study.

The study was conducted over 12 weeks while the participants were still in prison and it provides no information on sexual re-offending rates such as re-convictions, self-reports or cautions. This study was a preliminary study and further data on correctional infractions is currently being collected. Participants in Winder et al. (2014) were treated with fluoxetine, cyproterone or a combination of the 2 treatments. Participants included in the cyproterone group for analysis had either been previously treated with fluoxetine or were currently taking fluoxetine in combination with cyproterone. The study comments that some participants stopped taking their medication but it provides no further information on this such as details on which medication they were taking or if outcomes from these participants were still included.

Kafka and Prentky 1992 included 20 men with a paraphilic or non-paraphilic sexual addiction. However, four men dropped out of the study and 12-week data is only provided for the 16 men who completed the study. Sexual behaviour was assessed using a self-assessment tool which documented the incidence of sexual fantasies, urges and activities during a designated week. This tool had not been previously validated and was unpublished.

Greenberg et al. 1996 was a retrospective observational study in 58 men with paraphilias treated with fluoxetine, sertraline or fluvoxamine. However, nearly 30% of the participants dropped out of the study and data until week 12 is only available for 41 participants. Outcomes were measured using a clinical global impression scale and a self-assessment scale to rate sexual fantasies. As with the other studies the use of self-reported data raises questions on its validity and reliability. In this study, the results are presented for the whole group together rather than for each individual SSRI and therefore it provides limited evidence on the use of fluoxetine. It was reported that there were no significant differences between the 3 SSRI groups for the outcomes but no statistical analysis is provided.

The clinical significance of the outcomes in all of these 3 studies is unclear. Assessment of outcomes used self-reported data or un-validated scales and no minimum clinically important differences are provided. Overall, these 3 studies provided very limited data on the use of fluoxetine to treat hypersexuality.

## Context and estimated impact for the NHS

### Cost effectiveness

Cyproterone acetate ([Androcur](#)) is licensed for the control of libido in severe hypersexuality or sexual deviation in adult men. Triptorelin ([Salvacyl](#)) is licensed for the reversible reduction of testosterone to castrate levels in order to decrease sexual drive in adult men with severe sexual deviations.

Drug <sup>a</sup>	Example dosage	Estimated cost for 12 months' treatment (excluding VAT)
Fluoxetine 20 mg capsules	20–60 mg once daily	£14.11 to £42.34 <sup>b</sup>
Fluoxetine 20 mg dispersible tablets	20–60 mg once daily	£44.84 to £134.53 <sup>b</sup>
Fluoxetine 60 mg capsules	60 mg once daily	£245.40 <sup>b</sup>
Fluoxetine 20 mg/5 ml oral solution	20–60 mg once daily	£96.20 to £289 <sup>b</sup>
Cyproterone acetate ( <a href="#">Androcur</a> ) <sup>b</sup>	50 mg twice daily	£381.30 <sup>c</sup>
Triptorelin ( <a href="#">Salvacyl</a> ) powder and solvent for suspension for intramuscular injection <sup>c</sup>	11.25 mg (1 vial) every 12 weeks	£992 <sup>c</sup>

<sup>a</sup> See [summaries of product characteristics](#) for details. The doses shown are example doses and may not represent the full range that can be used, and they do not imply therapeutic equivalence.

<sup>b</sup> Prices based on [Drug Tariff](#) June 2015 Prices are excluding VAT.

<sup>c</sup> Prices based on [MIMs](#) April 2015 Prices are excluding VAT.

### Current drug usage

No estimate of the current use of off-label fluoxetine for the treatment of people who have sexually offended or are at risk of offending in UK clinical practice was identified.



## *Information for the public*

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with hypersexuality who are thinking about trying fluoxetine.

## *Relevance to NICE guidance programmes*

This use of fluoxetine is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE guidance exists for the following licensed indications for fluoxetine:

- [Common mental health disorders: identification and pathways to care](#) (NICE guideline CG123)
- [Depression in adults: the treatment and management of depression in adults](#) (NICE guideline CG90)
- [Depression in adults with a chronic physical health problem](#) (NICE guideline CG91)
- [Depression in children and young people: identification and management in primary, community and secondary care](#) (NICE guideline CG28)
- [Obsessive compulsive disorder: core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder](#) (NICE guideline CG31)

## *References*

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### *Development of this evidence summary*

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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### **Declarations of interest**

No relevant interests declared.

### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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