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Cite this as: *BMJ* 2022;378:o1454
http://dx.doi.org/10.1136/bmj.o1454
Published: 08 July 2022

GUIDELINES

Medicines associated with dependence or withdrawal symptoms: summary of NICE guideline

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What you need to know

- Ensure decisions to start a medicine associated with dependence or withdrawal symptoms are based on a shared decision between the healthcare professional and person following an informed discussion of the risks and benefits of the medicine, documented in a management plan
- Such medicines should not be stopped abruptly unless there are exceptional medical circumstances
- Ensure plans for withdrawal are tailored according to the medicine and the individual's circumstances and that there is flexibility to review and adapt these as required

Medicines associated with dependence and withdrawal symptoms can provide lasting symptom management with few adverse effects for some people. But they do not work for everyone and can have negative consequences that outweigh their benefits. Even when people are not getting clinical benefit, these medicines often continue to be prescribed for various reasons, including concerns about the risk of unpleasant withdrawal symptoms or fear of worsening of the underlying condition.

This article summarises the most recent recommendations from the National Institute for Health and Care Excellence (NICE) guideline on medicines associated with dependence or withdrawal symptoms.[1] It follows on from Public Health England's *Prescribed medicines review*[2] describing how these medicines are prescribed in England. It aims to address the gap in guidelines and focuses on minimising the risk of dependence and managing withdrawal for the following drug classes: opioids, benzodiazepines, gabapentinoids, "Z drugs," and antidepressants.

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Making decisions about prescribing and taking a dependence-forming medicine or antidepressant

The guideline assumes that all treatment options have been appropriately discussed and starts from the point that pharmacological treatment is being considered. Decision making about medicines associated with dependence and withdrawal (see box 1 for definitions) can be difficult for both the person considering or already taking these medicines and healthcare professionals. Special consideration needs to be given to people who find it difficult to communicate their symptoms, such as people with learning disabilities or dementia, including a full assessment to ensure that they do not have other unmet needs and prescribing is the most appropriate option. A collaborative, trusting, and supportive relationship between the person and the healthcare professional is necessary to facilitate shared decision making and enable effective outcomes as described in the NICE guideline on patient experience in adult NHS services.[3]

Box 1: Dependence, addiction, and withdrawal

The terms dependence and addiction are often used interchangeably and people with a dependence on prescribed medicines may be reluctant to seek help from their healthcare professionals because of a perceived stigma of dependence, which they may associate with illicit drug use or alcohol misuse.

However, dependence describes the need for increasing doses to maintain clinical effect and the appearance of withdrawal symptoms on sudden stopping or dose reduction. This is an expected effect of many medicines and differs from addiction, which has the additional features of craving and continued use despite harm as well as behaviours associated with attempts to procure additional medicines supply. Antidepressants, are historically not classified as dependence forming, but they cause withdrawal symptoms when they are stopped.

- When making decisions about prescribing medicines, determine whether there are any factors that might increase the person's risk of developing problems associated with dependence, but do not withhold the medicine solely on the basis of one of these factors. Explain and discuss the risk with the person. Factors that might increase risk include:
  - A comorbid mental health diagnosis
  - A history of drug or alcohol misuse
  - Not having a clear, defined diagnosis to support the prescription
  - Taking an opioid together with a benzodiazepine.

  [*Based on high to very low quality evidence from retrospective cohort studies*]

- Consider delaying prescribing if the person needs more time to think about their options or the prescriber needs to consult with other members of the healthcare team. If prescribing is delayed, ensure that a follow-up appointment is arranged. [*Based on the experience and opinion of the Guideline Committee*]
- If a prescriber thinks that a medicine is not in the person's best interests but a shared decision about starting or continuing a medicine cannot be reached with the person, the prescriber should follow the advice on "Handling patient requests for medicines you don't think will benefit them" in the General Medical Council guidance *Good practice in prescribing and managing medicines and devices*.[4] The prescriber should:
  - Not prescribe a medicine if they believe it is not in the person's best interests
  - Explain the reasons for their decision to the person
  - Document all discussions carefully and give a copy to the person
  - Offer the person a second opinion.

  [*Based on the experience and opinion of the Guideline Committee*]

Starting a dependence-forming medicine or antidepressant

The guideline recommends factors to be considered, discussed, and documented in a management plan during the decision making process. This should be updated throughout a person's care.

Information and support

- Before starting treatment with an opioid, benzodiazepine, gabapentinoid, or Z drug, explain and discuss with the person:
  - That dependence is an expected effect of these medicines and is not a reason in itself to avoid the medicine
  - The potential for developing problems associated with dependence
  - The symptoms that suggest the development of problems associated with dependence and, if appropriate, the importance of making family members, carers, or other people close to them aware of these symptoms.

  [*Based on qualitative evidence with high confidence in the findings*]
- Before starting treatment with an antidepressant or gabapentinoid, explain and discuss with the person:
  - That any beneficial effect of the medicine may occur slowly, and they might experience side effects before noticing any benefit
  - That many side effects are likely to ease over time.

  [*Based on evidence from qualitative studies with high confidence in the findings and the experience and opinion of the Guideline Committee*]

Prescribing strategies

- Take steps to reduce the risk of developing problems associated with dependence; for example, starting at a low dose and consider avoiding modified-release opioids. Explain the importance of these steps to the person. [*Based on moderate to very low quality evidence from three RCTs, moderate to low quality evidence from one prospective cohort study, and the experience and opinion of the Guideline Committee*]
- Discuss with the person the range of doses likely to be safe and effective. Start with a low dose and agree frequent, regular reviews to ensure that timely adjustments can be made to test effectiveness, safety, and acceptability and to find the lowest effective dose. Once an effective dose has been established, avoid automatically increasing the dose if the response is not sustained. [*Based on the experience an opinion of the Guideline Committee*]

Reviewing a dependence-forming medicine or antidepressant

Use of dependence-forming medicines or antidepressants should be regularly reviewed, with the frequency tailored to the medicine and the individual circumstances. These reviews may need to be more frequent during dose adjustment.

Withdrawing a dependence-forming medicine or antidepressant

Discussions about withdrawal can be difficult, particularly due to anxiety about stopping. Principles of shared decision making should be followed while also acknowledging that the opinions of the person and healthcare professional may differ and being sensitive to the use of terminology that may seem to apportion blame to the person or be perceived adversely. Information should be provided to support the decision and the process, which may include sources of peer support.

- Discuss withdrawing an opioid, benzodiazepine, gabapentinoid, Z drug, or antidepressant with the person if:
  - It is no longer benefiting the person
  - Problems associated with dependence have developed
  - The condition for which the medicine was prescribed has resolved
  - The harms of the medicine outweigh the benefits
  - The person wants to stop taking the medicine.

  [*Based on the experience and opinion of the Guideline Committee*]
- Do not stop a medicine abruptly (complete cessation with immediate effect) unless there are exceptional medical circumstances, such as the occurrence of serious side effects (for example, upper gastrointestinal bleeding from an antidepressant, respiratory depression from an opioid, or severe ataxia from a gabapentinoid). In these circumstances, consider:
  - Scheduling more frequent reviews
  - Short term use of medicines to treat the physical symptoms of withdrawal (for example, abdominal cramps and diarrhoea during withdrawal of an opioid).

  [*Based on moderate to very low quality evidence from five RCTs, and the experience and opinion of the Guideline Committee*]
- When planning withdrawal from an opioid, benzodiazepine, gabapentinoid, Z drug, or antidepressant, take into account:
  - The urgency of the withdrawal, for example, gradual withdrawal of a medicine that is no longer effective or necessary, or more rapid withdrawal of a medicine that is causing significant harm (the speed of rapid withdrawal

depends on the type of medicine and the person's circumstances)

- Whether the initial goal should be complete withdrawal or, for people who find complete withdrawal too difficult, whether dose reduction with ongoing review is a more realistic initial aim
- Which medicine to reduce first, if the person will be withdrawing from more than one medicine
- Factors that might increase the person's risk of problems during withdrawal, including:
  - Long duration of medicine use
  - High dose of medicine
  - History of withdrawal symptoms
  - History of problems associated with dependence
  - Taking an antidepressant with a short half-life
- Any concurrent medicines and how these might affect the person's response to withdrawal
- Factors that might influence the timing of the start of the dose reduction, such as the person's circumstances and available support.

[*Based on the experience and opinion of the Guideline Committee*]

Information and support for people withdrawing from a medicine

- Discuss withdrawal symptoms with the person and tell them about the support that is available. When discussing withdrawal symptoms, explain that:
  - Withdrawal can be difficult and may take several months
  - Support will be available throughout the withdrawal process
  - Withdrawal symptoms do not affect everyone, and it is not possible to predict who will be affected
  - Withdrawal symptoms vary widely in type and severity, can affect both physical and mental health, may occur at any time during withdrawal or be delayed in onset, and can change over time or persist over a prolonged period
  - There are options for managing withdrawal symptoms (see the sections on identifying and managing withdrawal symptoms and on interventions to support withdrawal)
  - Some people may experience withdrawal symptoms that can be difficult to distinguish from a re-emergence of their original symptoms or a new disorder, and it is important to discuss these with a healthcare professional if they occur (see recommendation in section on identifying and managing withdrawal symptoms).

  [*Based on evidence from five qualitative studies with moderate confidence in the findings and the experience and opinion of the Guideline Committee*]

Dose reduction

Flexibility according to the individual's circumstances and medicine being used is key to successfully reducing or stopping a medicine. The recommendations therefore provide guidance to guide the general principles of safe dose reduction that can be tailored to the individual and allow for adaptations during the process.

- When agreeing a dose reduction schedule with the person:
  - Explain the risk of abrupt discontinuation and that the rate of safe withdrawal varies between people and can vary over time for the same person
  - Balance the risk of adverse events from continued exposure to the medicine with minimising the risk of withdrawal symptoms by slow dose reduction and withdrawal
  - Ensure that the planned rate of reduction is acceptable to the person
  - Explain that, although withdrawal symptoms are to be expected, the reduction schedule can be modified to allow intolerable withdrawal symptoms to improve before making the next reduction
  - Consider giving the person additional control over the process of dose reduction (for example, by issuing their usual daily dose in a form that allows them to reduce the amount in small decrements at a pace of their choosing, rather than issuing successive prescriptions for reduced daily doses)
  - Agree regular intervals for reviewing and adjusting the reduction schedule as needed
  - Ensure the person knows who to contact if problems occur.

  [*Based on the experience and opinion of the Guideline Committee*]
- If the person is withdrawing from an opioid, benzodiazepine, Z drug, or antidepressant, suggest a slow, stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed. [*Based on moderate to very low quality evidence from five RCTs and the experience and opinion of the Guideline Committee*]
- If the person is withdrawing from a gabapentinoid, reduce the dose by a fixed amount at each decrement, unless clinical risk is such that rapid withdrawal is needed. [*Based on the experience and opinion of the Guideline Committee*]

Identifying and managing withdrawal symptoms

- Be aware that it can be difficult to distinguish between the re-emergence of underlying conditions and the emergence of withdrawal symptoms. The following may indicate withdrawal symptoms rather than symptoms of an underlying condition:
  - Rapid or early onset of symptoms after a dose reduction or cessation of the medicine
  - Symptoms of the underlying illness that the person reports as qualitatively different or more intense than before
  - New symptoms that the person has not experienced before.

  [*Based on the experience and opinion of the Guideline Committee*]
- If distressing symptoms occur or worsen after a dose reduction:
  - Determine whether they are withdrawal symptoms or a re-emergence of symptoms that were relieved by the medicine

- If the symptoms are new, think about delaying the next dose reduction, trying a smaller dose reduction, or reverting to the previous dose.

  [*Based on the experience and opinion of the Guideline Committee*]

Supporting withdrawal

Although there are some established interventions for management of withdrawal from illicit substances, the evidence for interventions for withdrawal from prescribed medicines is much more limited. Recommendations highlight areas where benefit has been observed, and practices which are not useful for prescribed medicines withdrawal.

- Do not treat withdrawal symptoms with another medicine that is associated with dependence or withdrawal symptoms. [*Based on the experience and opinion of the Guideline Committee*]
- Consider group cognitive behavioural therapy (CBT) when withdrawing from a benzodiazepine. Discuss the timing of referral for CBT with the person. [*Based on moderate to very low quality evidence from three RCTs and health economic analysis*]
- If dose reduction has been unsuccessful (for example, because of intolerable withdrawal symptoms or a change in the person's physical, mental, or social circumstances) and the current prescription needs to be continued:
  - Aim to stop any further escalation in dose
  - Make a plan to attempt dose reduction again at a later date
  - Clearly record the advice given to the person about the potential harms of continuing the medicine, and the reasons for continuing without a reduction, in the management plan.

  [*Based on the experience and opinion of the Guideline Committee*]

Implementation

Longer consultations or additional follow-up may be needed to allow for full discussion of treatment options when starting or reviewing these medicines. However, enabling these effective conversations could reduce unnecessary prescribing, have large health benefits for the person, and have economic benefits for the healthcare service. Visual summaries of some of the key points to include in these discussions have been produced to accompany the guideline: https://www.nice.org.uk/guidance/ng215/resources.

Provision of services specifically for withdrawal from prescription medicines is limited. There are some local centres that have established good practice, but they are not widely available. Additional resources may be needed to support people withdrawing from medicines, but this should enable more successful withdrawal and improvements in quality of life.

Guidelines into practice

- Do you discuss potential problems associated with withdrawal when first prescribing a dependence-forming medicine?
- What systems are in place to regularly review patients who are prescribed dependence-forming medications?

How patients were involved in the creation of this article

Committee members involved in this guideline included lay members who contributed to the formulation of the recommendations. One of them is an author on this guideline summary.

Further information on the guidance

This guidance was developed by the National Guideline Centre in accordance with NICE guideline methodology (www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf). A guideline committee (GC) was established by the National Guideline Centre, which incorporated healthcare and allied healthcare professionals (one consultant in complex pain, two general practitioners (one based in Her Majesty's Prison Service), one advanced pharmacist practitioner, one consultant rheumatologist, one nurse specialist, two consultant psychiatrists (one an addiction psychiatrist and one consultant clinical psychologist in substance misuse), and two lay members.

The GC identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The GC agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods.

The scope and the draft of the guideline went through a rigorous reviewing process in which stakeholder organisations were invited to comment; the GC took all comments into consideration when producing the final version of the guideline.

NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.

The guideline is available on the NICE website. Information for the public from this guideline is also available at: www.nice.org.uk/guidance/ng215/informationforpublic.

Contributors: All authors contributed to the development of the guideline and to the planning, drafting, and revision of this summary, approved the final version, and take responsibility for its accuracy. SC acts as guarantor. The corresponding authors attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: SC was an employee of the National Guideline Centre at the time of developing this guideline, which was commissioned and funded by NICE to develop clinical guidelines. SC is now an employee of NICE.

Competing interests: We declared the following interests based on NICE's policy on conflicts of interests (https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf): SC has no declared interests. The guideline authors' full statements can be viewed at the Register of interests (www.nice.org.uk/guidance/ng215/documents/register-of-interests).

The members of the Guideline Committee were (shown alphabetically, excluding authors of this summary): Mark Buitendach, Emma Davies, Benjamin Ellis, Emily Finch, Jens Foell, Andre Geel, Parashar Ramanuj, Caroline Watson, and Colin Wilkinson.

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2 Public Health England. Prescribed medicines review: report. 2019. www.gov.uk/government/publications/prescribed-medicines-review-report.
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