WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

Stopping medicines

When prescribing any medicine it is important to consider for how long treatment will be required, or even whether it is required at all – is it being given as part of a "prescribing cascade" to treat an iatrogenic illness? Most medicines do not need to be used lifelong and their risk-benefit profile should be frequently reassessed by both primary and specialist prescribers. There is much advice on when to initiate a medicine but there is less evidence to help support decisions to stop therapy.

There are many reasons why withdrawing a medicine might be beneficial, ranging from a serious adverse reaction to a lack of clinical response. A change in the circumstances of a patient or their disease state may make the risk-benefit profile unfavourable. New evidence and changing guidelines may also affect the desirability of using a medicine. In cases where the risks of treatment outweigh the benefits it would obviously be prudent to review the medicine in question.

Some therapies should not be stopped abruptly following long-term use. The number of medicines to which this applies is relatively limited; important examples are:

- Opiates
- Hypnotics and tranquilisers
- Antipsychotics
- Antidepressants
- Anticonvulsants
- Adrenal corticosteroids
- Centrally acting antihypertensives
- β-adrenoreceptor antagonists
- Alcohol.[1]

This bulletin highlights situations where drug therapy can potentially be discontinued safely and beneficially. It discusses medication review, some general circumstances where cessation of therapy is desirable, and provides advice on stopping some specific medicines. For more detailed information, see the WeMeReC e-notes on stopping medicines at www.wemerec.org/res_enotes.php.

Medication review

Medication review offers a simple way to proactively seek for unnecessary or inappropriate medicines being prescribed for a patient. Regular review is an indicator used in the general practice Quality and Outcomes Framework. There are many models and several levels of review. The "NO TEARS" process is a straightforward method that specifically looks at:

- **N**eed and indication
- **O**pen questions to gauge concordance
- **T**ests and monitoring
- **E**vidence and guidelines
- **A**dverse events
- **R**isks of treatment
- **S**implification of existing regimen.[2]

(See the WeMeReC bulletin on medication review at www.wemerec.org/bullet_avail_bulletins.htm.)

The simplification of an existing regimen is likely to result in improved adherence, although it is essential to take into account the patient's beliefs and preferences during the process. Table 1 shows an example of a model for shared decision-making where the advantages of an action are uncertain.

Table 1. Opportunities to discontinue treatment

Degree of uncertainty	**Reason for action** and examples
None/minimal (low stakes)	**To correct an error** - two versions of a single drug - history of allergy to drug **To simplify a regimen** - weekly not daily bisphosphonate **Irrational treatment** - a healthy patient on a multivitamin **Use 'prn' instead of regularly** - seasonal allergy but chronic therapy
Moderate (moderate stakes)	**Benefit has been achieved** - HRT for menopausal symptoms **Use a behavioural intervention** - benzodiazepines for insomnia **Benefit unlikely to be realised** - limited life expectancy; taking a statin
High (high stakes)	**Careful prioritisation necessary** - multiple symptomatic conditions - taking 15 or more medicines - cognitive problems

*Adapted from: Prioritizing and stopping prescription medicines.[3]

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Adverse drug reactions (ADRs)

The burden of ADRs on the NHS in England and Wales is significant; one study found that 6.5% of hospital admissions were precipitated by ADRs.[4]

Type A ADRs are "accentuated" reactions that can be expected from the normal pharmacological actions of a medicine. They account for about 75% of ADRs and have a high morbidity and a low mortality. It is not always necessary to discontinue the medicine (although it may be desirable) but a dose reduction may be required. A patient experiencing even relatively minor adverse effects may choose to discontinue a medicine, or at least reduce the regularity with which they take it.

Type B ADRs are "bizarre" reactions in that they cannot be predicted from the known pharmacology of a medicine. This type of reaction carries a higher risk of mortality than a type A reaction. There is no relationship between dose and incidence, although severity may be dose-related. The medicine should be stopped and not administered again.

The rate of ADRs in the **elderly** population is a major public health issue. Frail elderly patients are at increased risk because of significant age-related changes in drug handling and an increased likelihood of polypharmacy.[5] One study in the elderly population showed that almost half of all ADRs were caused by medicines that were contraindicated or unnecessary.[6] A recent expert review of the use of antipsychotics in dementia patients suggested that there is significant overuse of these medicines. It was estimated that, in the UK, about 180 000 patients a year with dementia are given antipsychotics with only around 36 000 of these patients deriving some benefit from treatment. This level of use equates to an additional 1620 cerebrovascular adverse events and 1800 deaths above the baseline for this population.[7]

Pregnancy and breastfeeding

Drug therapy in pregnancy leads to serious challenges for prescribers. To prevent potential harm to the foetus it would theoretically be ideal to discontinue all medication. However, this is often not possible and in some cases, where the condition being treated is likely to cause more harm than the medicine being used, it is not desirable. All women taking medicines for long-term conditions should be offered preconception counselling to decide on the most appropriate therapy. If a pregnancy is unplanned, therapeutic choices should be based on the best available evidence.

The decision to continue a medicine for a breastfeeding mother involves considering the benefits of breastfeeding itself, together with the risks and benefits of therapy. Few medicines are absolutely contraindicated in breastfeeding as most are present in breast milk in very small amounts.

Detailed guidance regarding medicines use in pregnancy and breastfeeding can be obtained via the Welsh Medicines Information Centre (see www.wmic.wales.nhs.uk).

Perioperative cessation

A significant proportion of patients take chronic medication prior to surgery. Where a medicine would produce deleterious effects during or following a procedure it may be necessary to stop that medicine temporarily. This kind of elective cessation is often poorly managed resulting in wasted appointments and patient dissatisfaction.

Whether a particular medicine will need to be discontinued depends not only upon its pharmacological actions but also on the procedure being undertaken. Some examples of medicines that may need to be withheld prior to surgery are potassium-sparing diuretics, anticoagulants, aspirin and other NSAIDs, oral contraceptives and HRT, lithium, and monoamine-oxidase inhibitors.[8]

Stopping specific medicines

Benzodiazepines

Benzodiazepines should only be used short-term and then only when the patient is suffering from unacceptable distress.[9] By definition, in the majority of cases, if a patient has been on long-term treatment, it is inappropriate.

In addition to other likely adverse effects, long-term benzodiazepine use can lead to tolerance (within weeks) and dependence (within weeks to months) and a significant proportion of patients will find it difficult to withdraw from their medication.[10] Elderly patients, whose treatment may have been started when they were fitter and more mobile, are more prone to the sedative effects and subsequent debilitating falls.[10,11,12]

The main problems with stopping are:

- Acute effects, especially anxiety.[10,13]
- A withdrawal syndrome that may occur up to three weeks after dose tapering. Symptoms may last for weeks or months and may lead to additional prescribing, which is discouraged.[13]
- Upon abrupt cessation: confusion, toxic psychosis, convulsions, or a condition similar to delirium tremens.[13]

How to discontinue benzodiazepines

The intervention recommended to facilitate withdrawal depends on patient circumstances, but generally a switch to a long-acting benzodiazepine (usually diazepam), gradual dose reduction, and psychological interventions are advised.[10,14]

There is no clear evidence to suggest the optimum rate of dose reduction, but it is proposed that the minimum time should be four weeks and the maximum time less than six months.[15] There is also an argument that the rate of taper should be determined by the patient and may take years.[10] Equivalence tables for conversion and withdrawal schedules are available from the "The Ashton Manual",[10] the British National Formulary,[13] and Clinical Knowledge Summaries,[14] but clinical judgement should always be exercised.

Some degree of psychological support can help patients withdraw from their medication more easily. Interacting with other people during group therapy may be beneficial and cognitive-behavioural therapy is effective when provided by trained and experienced therapists.[15,17] There is little evidence to support any recommendation for the use of adjunctive medication in the withdrawal process.[15,16,17] If the patient is depressed, however, pharmacological treatment for this underlying disorder can be helpful to assist withdrawal.[10, 15]

Antidepressants

Antidepressants should typically be reserved for patients with moderate to severe depression (defined using the DSM-IV criteria).[18,19] Patients should be counselled about taking their medicine as prescribed and the need to continue treatment for six months following recovery (12 months in the elderly).[13,18,19] Patients with a significant risk of relapse or recurrent depression should receive maintenance therapy for two years. Specific advice regarding the use of antidepressants in children and adolescents is available.[13]

It can take up to two weeks for an antidepressant to exert an effect and it should be continued with review every one to two weeks for at least four weeks to assess the full effect (six weeks in the elderly). If the response is partial, the length of treatment may need to be extended (e.g. for another two weeks) or the dose increased. Treatment should be stopped if there is no improvement after this period and another antidepressant considered.

A patient may also wish to change their therapy if an adverse effect that was initially tolerable becomes unacceptable in the long term, e.g. sexual dysfunction. In the case of a serious adverse event, e.g. hyponatraemia, treatment may need to be stopped immediately.

The main problems with stopping are:

- Relapse or recurrence of depression.
- Discontinuation symptoms.

Symptoms of withdrawal syndromes from antidepressants include gastrointestinal upset, flu-like symptoms, anxiety, sleep disturbance, dizziness, paraesthesia, shock-like sensations, and sometimes, hypomania and movement disorders. These can occur when stopping, missing doses or, occasionally, reducing the dose. They are usually mild, short-lasting, and manageable with reassurance and explanation, but they can be severe and interrupt normal functioning, especially if the medicine is stopped abruptly. They are more common with higher doses and longer courses and with agents with a short half-life, e.g. paroxetine and venlafaxine.

How to discontinue antidepressants

Doses should be tapered (although this is not necessary for fluoxetine 20mg). If stopping early in the course of treatment, doses may be gradually reduced over one or two weeks.[18,20] For patients who have been treated for at least eight weeks, the reducing schedule should be over about four weeks (or longer for drugs with a short half-life). When stopping maintenance therapy the dose may need to be gradually reduced over six months.

Symptoms can still occur with gradual cessation and the period of tapering can be extended if symptoms develop. In some cases the patient may want to consider whether a short, intense tapering period is preferable or less disruptive than a longer, less severe withdrawal.[21]

Antipsychotics

Antipsychotics are used for schizophrenia to relieve a variety of symptoms and to prevent relapse.[13] Generally, suitable therapy will be continued long-term. Antipsychotic medicines have also been used in the short-term to alleviate severe anxiety and to calm disturbed patients.[13]

Any use of antipsychotics in the elderly should be reviewed regularly as the risk of many adverse events associated with treatment is higher in older patients. There is also an increased risk of stroke and a small increased risk of death in elderly people with dementia treated with antipsychotics.

Such therapy should not be used for mild to moderate psychosis in the elderly, and is not recommended for dementia-related psychosis and/or behavioural disturbances.[13] (Risperidone▼ is indicated short-term for Alzheimer's dementia.)

An antipsychotic might be stopped due to an **inadequate response**. Initiation should be with lower doses that are titrated upwards and a trial of medication at optimum dosage should be carried out for four to six weeks. If necessary, a switch to another agent may be considered. Other than for short periods when switching, combined therapy should not be prescribed.[22]

Switching to another antipsychotic may also be considered in patients who experience **ADRs**. Some serious ADRs, however, warrant immediate discontinuation of therapy and careful monitoring:

- Tardive dyskinesia. This may be irreversible, but cessation at the earliest signs may halt full development.
- Prolongation of the QT interval (>500msec).[23]
- Neuroleptic malignant syndrome. This is very rare but life-threatening – stopping treatment is essential and urgent medical treatment is needed.
- Neutropenia or agranulocytosis (particularly with clozapine).[13]
- Myocarditis or cardiomyopathy (reported with clozapine).[13]

The main problems with stopping are:

- Relapse, which is often delayed after cessation.
- Discontinuation reactions if stopped abruptly.
- Long withdrawal periods (a month or longer) for depot preparations.

How to discontinue antipsychotics

Discontinuation should be gradual after long-term use (and in consultation with the specialist mental health team where applicable). Monitor for discontinuation effects, such as cholinergic rebound, and continue monitoring for relapse for two years. If switching to another agent, taper the dose slowly while the other agent is introduced (e.g. over three weeks). Record the rationale for continuing, changing, or stopping a medicine, and the effects of such changes.[22]

Conclusion

It is recognised that the decision not to prescribe or to discontinue a medicine is often difficult. Polypharmacy is often justifiable and may improve life expectancy and quality of life. About 20% of people over the age of 70 take five or more drugs,[24] but even where there is a seemingly clear indication, adding another medicine to existing therapy may not produce the expected benefit. One reason may be that many patients do not take their medicines as intended; this has been reported in as many as 50% of elderly patients.[25] Also, the overall benefit of a regimen may not equal the sum of that expected from the individual medicines.

Communication errors, especially at discharge and upon repeat prescribing, contribute significantly to inappropriate prescribing. Summaries of patient care provided by hospitals are frequently incomplete or inaccurate and some GP practices may not provide full patient information to hospitals.[26] It is hoped that this will improve with developing technology. However, alongside system review, it is beneficial to spend time engaging patients by involving them in decisions regarding their ongoing treatment.

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