Clinical pharmacology

Why don't patients use medication as prescribed?

What does the term 'adherence' mean?

Adherence describes all aspects of how well or how poorly a patient follows a prescribed drug-dosing regimen or medical advice. Adherence is synonymous with the old term 'compliance', but is preferred as it is more patient centred (compliance implies following orders). Adherence to therapy remains a challenge regardless of the patient's age, illness and social background. Health care providers initiate therapeutic regimens on the assumption that patients will take all their pills at the right time. Adherence is better with acute than chronic medication and tends to wane over time in cases of chronic disease. Even in the ideal circumstances of a randomised clinical trial, adherence to chronic medication is seldom more than 80%.

Patterns of non-adherence

Three major patterns of non-adherence are recognised: non-acceptance (the patient never actually starts treatment), incomplete execution (extra or missed doses, including 'drug holidays'), and early discontinuation (early cessation of dosing that is not resumed). Adherence is not limited to the number of doses taken every day, but also includes taking the dose at the right time or dosing interval. The most commonly observed deviations are missed or delayed doses. Taking drug holidays – the sudden cessation and resumption of dosing – is a potentially hazardous adherence behaviour. Restarting medications such as anti-arrhythmics (e.g. encainide or flecainide) or peripheral vasodilators without re-titration has resulted in lethal pro-arrhythmia or hypotension, respectively.

The consequences of poor adherence range from personal disability (treatment failure, e.g. ineffective pain control) to a worldwide threat (e.g. emergence of multidrug-resistant tuberculosis), depending on the illness, pattern of non-adherence and acceptable limits of the dosing interval (the degree of 'forgiveness' in the dosing regimen).

Table I. Common barriers to adherence to treatment for chronic conditions

Patient characteristics
- Adolescence
- Forgetfulness
- Running out of pills
    - Missed clinic appointments
    - Travelling
    - Poor access to pharmacy
- Other priorities (including financial commitments)
- Lack of information
    - Lack of belief in benefit of treatment
    - Lack of insight into the illness
    - Not counselled in home language
- Psychological problems
    - Active depression
    - Substance abuse
    - Cognitive impairment
    - Lack of self-efficacy (the belief that a patient can execute a behaviour required to produce a certain outcome successfully)

Treatment/disease characteristics
- Treatment of asymptomatic diseases
- Side-effects of medication
- Complexity of treatment (e.g. dosing frequency, number of pills, food restrictions)
- Treatment regimen incompatible with patient's lifestyle/routine

Prescriber characteristics
- Poor knowledge of drug costs/medical-aid coverage
- Low level of job dissatisfaction
- Prescribing complex regimen
- Prescribing a regimen incompatible with the patient's lifestyle
- Poor therapeutic relationship

Health care system
- Missed appointments
- High health care costs (costs of drugs, co-payments, or both)
- Inability of patient to access the pharmacy
- Switching to a different formulary

Why are patients non-adherent?

Adherence is a complex human behaviour and is influenced by the patient's personal and social characteristics. Health care facilities and prescribers can be barriers to adherence. Some common barriers to adherence are listed in Table I. Note that socio-economic status (except homelessness) and level of education are not barriers to adherence.

In his book, *Improving Medication Adherence – How to Talk With Patients About Their Medication,* Shawn Shea suggests three considerations in the decision to take medication:

1. feeling that there is something wrong

2. feeling motivated to try to get help through the use of medication

3. believing that the advantages of taking the medication will, in the long run, outweigh the disadvantages.

In addition, he suggests that there are three different beliefs that determine if a patient will start or stay on a medication:

1. efficacy of the medication

2. cost of the medication

3. psychological meaning of the medication.

If the health care worker does not address the above issues, then it is unlikely that the patient will adhere to the prescribed treatment.

How can adherence be measured?

A major problem in assessing adherence, both for individual patient care and research, is that a gold standard for measuring adherence has not been

Table II. Advantages and disadvantages of direct and indirect adherence methods

Method	Advantages	Disadvantages
Self-report **Caregiver report** (questioning patients directly, and completing questionnaires)	Inexpensive Allows discussion of reasons for low adherence	Considerably overestimates adherence
Clinical outcome (measuring drug effect, e.g. HbA$_{1c}$ in diabetics, lipid profiles for patients on statins, viral loads for patients on HAART)	Inexpensive Allows discussion of reasons for low adherence	Confounded by factors other than non-adherence
Pharmacy refill (rates of refilling prescriptions)	Suitable for individual patients as well as programmes	Moderately overestimates adherence (more sensitive than pill counts)
Pill count (counting the number of pills remaining in the patient's medication bottles or vials)	Inexpensive Useful to detect misconceptions about dosing, especially early on in therapy	Patients rapidly learn to provide the correct number of pills (discarding unused doses/not returning unused medication) Time consuming Moderately overestimates adherence
Therapeutic drug monitoring (measuring drug and metabolite concentrations in blood or urine)	Direct measure Detection/prevention of drug toxicity, especially in populations at risk (e.g. elderly, children, pregnancy, renal or liver impairment)	Expensive Subject to 'white coat' adherence and may reflect only that the last dose was taken Confounded by other causes of low concentrations May overestimate adherence
Electronic medication monitoring (electronic monitor that records the date and time of opening pill bottles, actuating canisters, etc.)	Provides data on timing and patterns of missed doses	Expensive Unable to detect if patient takes wrong dose, or takes multiple doses out of container at the same time (e.g. taking morning and evening doses out simultaneously and putting the evening dose into a small pill box) May underestimate adherence

identified. Direct and indirect methods are used to monitor adherence, each with advantages and disadvantages (Table II).

Directly observed therapy and measurement of drug concentrations (e.g. therapeutic drug monitoring) are considered direct methods of measuring adherence, but are expensive and provider intensive. Directly observed therapy has been promoted by national tuberculosis programmes, but recent studies indicate that more patient-centered approaches are more successful than traditional clinic-based directly observed therapy. 'White coat' adherence, the phenomenon whereby patients increase adherence a few days before or after a consultation, is common. If the patient is taking a drug that is suitable for therapeutic drug monitoring, white coat adherence can result in drug concentrations being in the therapeutic range, thus masking poor adherence. This is especially likely if the drug has a short half-life.

Methods to monitor adherence include self-report (asking patients about adherence or using questionnaires/medication diaries),

caregiver/peer reports, assessing clinical response (e.g. correlating an outcome measure to adherence), pill counts, pharmacy refill rates, and electronic medication monitors (electronic monitors that record the date and time of opening pill bottles or actuating canisters).

How can adherence be improved?

One of the problems in addressing poor adherence is that it can be difficult to distinguish different types of adherence behaviour. For example, 50% adherence can mean either a patient who follows the dosing instructions meticulously but stops completely halfway into treatment because of intolerable side-effects, or a patient who only takes half the number of pills every day to try to save money. The interventions required to improve adherence will be completely different in these two examples.

Several adherence interventions and combinations of interventions have been studied. The type of intervention will depend on the barrier(s) to adherence. Informational interventions aim to increase

the provision and retention of treatment-related information (e.g. structured individual or group counselling or education by physicians, health educators, and/or pharmacists). The most common and effective behavioural interventions are simplifying dose regimens, specialised packaging, and cognitive behaviour therapy. Informational and behavioural interventions are often combined.

Interventions that are simple and easy to implement in practice are:

- Always make a point of checking patients' adherence. Doctors often overestimate patients' reported medication use. Patients like to please health care providers, and will report what they expect the health care provider would like to hear.

- Asking patients in a reassuring and non-judgemental manner if it has been difficult for them to take all their medications, and asking what you can do to help them not to miss doses.

- Asking patients about side-effects; this can also often unmask poor adherence.

- It is important to make the patient feel part of the therapeutic decision-making process.

- Always follow-up adherence inter-ventions and reassess the patient's commitment/interest in the treatment plan.

What is the take-home message?

Patients' adherence to a prescribed regimen or medical advice is a complex behaviour. A patient's engagement with his/her illness, the prescribed drug regimen, the health care providers and health care facilities can all act as barriers to acceptable levels of adherence. Heatlh care providers usually overestimate patients' reported medication use. Monitor for

poor adherence in asymptomatic diseases and when patients fail therapy despite an optimal dosing regimen.

C. Everett Koop, former Surgeon General of the USA, is accredited with the following excellent advice: 'Drug's don't work in patients who don't take them'.

Recommended reading

Diiorio C, McCarty F, Depadilla L, *et al.* Adherence to antiretroviral medication regimens: A test of a psychosocial model. *AIDS Behaviour* 3 November 2007 (Epub ahead of print).

Osterberg L, Blaschke, T. Adherence to medication. *N Engl J Med* 2005; 353: 487 - 497.

Shea SC. *Improving Medication Adherence: How to Talk With Patients About Their Medications.* Philadelphia: Lippincott Williams & Wilkins, 2006.

Simoni JM, Montgomery A, Martin E, New M, Demas AD, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. *Pediatrics* 2007; 119(6): e1371 – e1383. (Epub 28 May 2007, Review.)

Urquhart J, Vrijens B. Introduction to pharmionics: the vagaries in ambulatory patients' adherence to prescribed drug dosing regimens, and some of their clinical and economic consequences. In: Mann RD, Andrews EB, eds. *Pharmacovigilance.* Chichester: John Wiley & Sons Ltd, 2007: 603 - 618.

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Single Suture

Bare below the elbows

In a widely criticised move, a new dress code is about to be introduced in British hospitals that includes not wearing a wrist watch. The new dress code is part of efforts to prevent the spread of infection in hospitals. But in a letter to the *British Medical Journal*, James Henderson and Sarah McCracken say that lack of a wristwatch leads to clinical errors and consistently late arrival on ward rounds. They assessed the ability of 20 health care staff to carry out clinical observations, such as respiratory rate and pulse, without the use of the second hand or LCD display available on a wristwatch. Participants instead used clocks in the wards, which were often difficult to see. They found that all participants took longer than 1 minute to make their observations and all would have failed an OSCE. The brief trial showed that the range of observations was so wide that it would be difficult to distinguish normal from abnormal without the use of a second hand or display. There is apparently little evidence to suggest that wrist watches carry infection, so the authors cannot see the point behind the ban. Perhaps frequent handwashing would be a better idea?

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