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Who is taking their tablets?

The efficacy and safety of a drug cannot be assessed unless it is being taken as instructed. This applies equally to the prescription of a drug to an individual patient and in the assessment of new drugs in clinical trials. The ways of determining the degree of compliance—the extent to which the patient adheres to instructions—can be divided into indirect and direct methods.¹

Indirect methods of assessment include outcome, detection of physiological markers, the physician's impression, structured interviews, prescription filling, pill count, and medication monitors. The outcome of an effective regimen of treatment or prevention might seem at first sight to be a reasonable measure of compliance, and there are some reports of a relation between non-compliance and failure. For example, streptococcal infection can be shown to be a risk for non-compliant patients with rheumatic fever prescribed oral penicillin,² and uncontrolled epilepsy is a risk for patients prescribed phenytoin.³ This method takes no account of the effects of other aspects of medical care not mediated by compliance.

Sometimes a physiological marker is available—for example, when the reduction in exercise-induced tachycardia produced by a beta-blocking drug can distinguish compliant and non-compliant patients. Many doctors believe that they can make that distinction on the basis of their clinical impression, but studies of compliance among patients with peptic ulcer and their consumption of antacids⁴ and of patients' return for follow-up and their adherence to treatment⁵ suggest that this confidence is unwarranted. A study of oral antibiotics given to children with rheumatic fever for prophylaxis against streptococcal infection⁶ suggested that a structured interview might be more successful in identifying non-compliant patients. Examination of the adherence of patients with tuberculosis to their drug regimen, however,⁷ showed that while 24 out of 25 patients claimed at interview to take their oral medication regularly only 18 gave positive results in urine tests for the drugs.

Some aspects of compliance can be measured by assessing the presentation of prescriptions to the pharmacist. One recent paper⁸ concluded that up to 20% of patients fail to cash their prescriptions within one month of issue. The pill count—checking the amount of medication remaining in the patient's bottle—is a useful practical method of testing compliance

provided that its limitations are recognised. In a classic study of different groups of patients in a general practice,⁹ Porter found that tablet counts allowed compliance to be tested without the patients being aware that they were under close observation. In a two-year follow-up of 105 patients with peptic ulcer who were treated with liquid antacid to which sodium bromide was added as a tracer 10 consistently returned more empty bottles than was justified on the basis of the bromide concentration in their blood, and it was evident that for these patients the bottle counts were completely misleading.¹⁰ A study of children to whom 10-day courses of penicillin were prescribed¹¹ showed that on the basis of pill counts 18% would have been considered compliant, whereas from tests for the antibiotic in urine only 8% of the children were actually taking the drug. Data on the validity of pill counts suggest that compliance may be overestimated when the medication prescribed could be used by members of the family as well as by the patient.

Pill counts can be performed directly—for example, in the "discrepancy count" a known number of tablets are issued, and the patient is asked to bring back the box at the next attendance and the remaining tablets are counted in front of the patient. This lacks subtlety and might cause the patient to dispose of unused tablets. Better is the "discrepancy estimate," in which a fixed and critical number of tablets are issued to the patient and at determined times the patient is seen again.⁹ The estimate hangs on the patient's reply to the challenge "Do you need any tablets or have you enough until I see you next time?" This technique is flexible, and by adjusting the number of tablets and the interval between consultations, most treatment schedules can be allowed for. Above all it ensures that patients are not aware that they are under close observation.

Medication monitors are devices which allow the withdrawal of a dose from its container to be recorded and timed. In a study¹² of compliance using a monitor among outpatients with tuberculosis it was found that 38 out of 122 supposedly reliable patients took less than 70% of their medication for one or more months. It cannot safely be assumed, however, that the tablets withdrawn from the monitor were actually ingested. A device for recording the removal of pilocarpine eye drops¹³ showed that an education programme was effective in improving compliance.

Compliance may be measured more directly by examining

some fluid or tissue from the patient for the drug or a marker. This approach has several problems, including the sensitivity and specificity of the method of detection and the interpretation of the results. Sampling of blood has been used to detect carbon monoxide in smokers¹⁴ and propranolol in hypertensive patients receiving dialysis.¹⁵ The study of smokers showed that up to 40% of those who stated that they had reformed had not, while 53% of the patients prescribed propranolol were non-compliant.

Urine sampling can be used to assess adherence to an antibiotic regimen.¹⁶ When it is impossible to detect either the medication or any metabolite directly, a detectable label may be added to the medication. The requirements of an effective label include non-toxicity, stability in urine, rapid non-cumulative excretion, availability of a sensitive and specific detection method, and inability of the patient to detect it.⁹ Among markers which have been used are riboflavin, sodium bromide, phenol red, and quinine. One problem with the measurement of drug, metabolite, or marker in blood or urine is the variation due to pharmacokinetic differences between patients, and differences in drug recovery may not be due solely to differences in compliance. Furthermore, the presence of the drug or marker indicates compliance only at the time of sampling and may mislead. By combining a marker with tablet counts⁹ compliance rates in a general practice among a group of patients with depression, acute infections, and in pregnancy were examined with confidence and without detracting from the doctor-patient relationship.

Some drugs can be recovered from faeces, and this method was used in a study of compliance with iron treatment in pregnant women, which showed that 32% of them were not taking their tablets.¹⁷ The detection of drugs in urine can be simplified when a specific stick test is available.¹⁸ Breath testing has been used to detect carbon monoxide in a trial of the effect of nicotine chewing gum in abstinence from cigarettes in smokers¹⁹ and to detect carbon disulphide,²⁰ a metabolite of disulfiram, in alcoholics.

All these methods give a record of ingestion at the time of sampling, but recent ingenious advances may allow a more longitudinal survey to be performed, particularly of abstinence from alcohol and drugs of abuse. Several drugs are secreted into sweat in concentrations proportional to that in blood. Absorbent pads were used²¹ to collect sweat at a steady rate over eight days in a study to test for alcohol use over a period of time. Hair sampling²² can provide useful information on heroin and cocaine used over the preceding two years. The drugs are not easily removed by washing, and the time course of drug use can be reconstructed by testing hair segments at different distances from the root.

A possible unwanted effect of all methods of detecting non-compliance is the destruction of the doctor-patient relationship. In clinical practice, when treatment fails and non-compliance seems a possibility, questions should be asked in a way that does not imply criticism and allows the patient to answer truthfully without humiliation. Better to ask "Were you able to take the tablets?" than "Did you take the tablets?" In routine clinical practice the consequences of failing to detect non-compliance may be serious or bizarre. If doctors faced with a patient who does not respond merely increase the dose of the drug the gap may widen between what the patient actually does and what the doctor thinks the patient is doing. In clinical studies to test the efficacy of drugs a reasonable approach is to test compliance with treatment by a combination of tablet counting and blood or urine testing in the run-in or tolerability phase. Those patients who take treatment con-

sistently can then be entered in the study, and overall adherence to treatment again assessed with tablet counts and blood or urine testing through the study proper.

No method of assessing compliance is completely effective. In particular, patients who take a single or a few doses immediately before assessment and discard the remainder are especially difficult to detect even when a combination of methods is used. All patients, whether from routine clinical practice or in studies, should be encouraged to bring back their medication at each visit. Though the corollary does not necessarily hold true, one single fact remains a beacon: if the tablets are in the bottle then they are not in the patient.

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