# Monitoring drug therapy

Andrew W Hitchings

**Abstract**

It is important to monitor drug therapy because the effects of a particular drug regimen can vary significantly between individuals. Wherever possible, therapeutic effect should be monitored using a clinical endpoint (i.e. a measure that directly reflects how the patient feels, functions or survives). In practice, it is often not feasible to use a clinical endpoint to guide therapy, particularly for preventive treatments. The next best option is to use a surrogate endpoint: a measure that changes so as to predict whether the clinical endpoint will be achieved. For a few drugs, neither a clinical nor a surrogate endpoint is available. In these instances, if the drug has a narrow therapeutic index and there is a predictable relationship between its concentration and its effects, it may be appropriate to measure its concentration in the blood. This article discusses approaches to monitoring drug therapy using clinical and surrogate endpoints, and plasma concentration monitoring. Specific guidance is provided for plasma concentration monitoring of digoxin, gentamicin, vancomycin, phenytoin, lithium and theophylline.

**Keywords** Biomarkers; clinical markers; drug monitoring; drug therapy; surrogate endpoints

## Key points

- Drug therapy should be monitored due to the potential for inter-individual variability in drug response
- Wherever possible, drug therapy should be monitored using a clinical endpoint — a characteristic or variable that reflects how a patient feels, functions or survives
- When it is not possible to use a clinical endpoint to guide therapy, a surrogate endpoint can be used — a characteristic or variable that changes in such a way as to predict whether the clinical endpoint will be achieved
- Measurement of plasma concentrations is indicated for only a few drugs — those in which effects of the drug are difficult to measure, the relationship between plasma concentration and clinical effects is predictable or the therapeutic index is narrow
- When measuring the plasma concentration of a drug, usually take the sample at steady state (at least five half-lives after starting the dosage regimen), and always record the time of the sample in relation to the last dose

## What is monitoring?

When we prescribe a medicine, we do so in the expectation that its benefits will outweigh its risks. Subsequently, some assessment is invariably required to confirm whether our judgement holds true for that individual. We can simply ask the patient to return if their symptoms do not improve or if they experience adverse effects. Alternatively, we can objectively assess the drug's effects. Occasionally, we measure the concentration of the drug in the blood. These are all forms of monitoring. This article will focus on monitoring the beneficial effects of drug therapy, but prescribers should also be aware of the importance of monitoring as a means of detecting early signs of adverse drug effects.

## Why monitor drug therapy?

The relationship between a prescribed dosage regimen and its resultant clinical effects is complex. It can be influenced by the patient's concordance with the treatment plan (affecting the amount of drug entering the body), the manner in which the drug is handled within the body (pharmacokinetic variability) and the effect the drug has on that individual (pharmacodynamic variability). Together, these sources of variability create uncertainty over how a particular patient will respond to a particular treatment regimen. This can be resolved only by monitoring the effects of therapy in that individual.

## How can drug therapy be monitored?

### Monitoring using clinical and surrogate endpoints

In general, monitoring parameters are most likely to be informative if they are closely related to the clinical outcome that the treatment is intended to produce (Figure 1). Indeed, wherever possible, it is best to monitor the clinical endpoint itself. A *clinical endpoint* can be defined as a 'characteristic or variable that reflects how a patient feels, functions, or survives'.[1] For example, when a benzodiazepine is administered to allow an interventional procedure to be performed, the clinical endpoint — sedation — is usually readily apparent. The drug dosage can be titrated to achieve the required level of sedation.

Often, however, measuring the effect of the drug on the clinical endpoint is impractical or cannot readily be used to guide therapy. This could be because the clinical endpoint is an event that cannot be detected until it is inevitable or irreversible, as is typically the case in preventive therapy (e.g. anticoagulation to reduce the risk of stroke in atrial fibrillation). Alternatively, it can be because the clinical endpoint is a delayed event, which cannot be measured until after treatment has finished. For example, the clinical endpoint in the treatment of pneumonia — cure of the infection, most reliably confirmed by the resolution of symptoms and radiographic consolidation — may not be measurable until weeks after the treatment course has ended. In these situations, we should seek to attempt to identify a suitable *surrogate*

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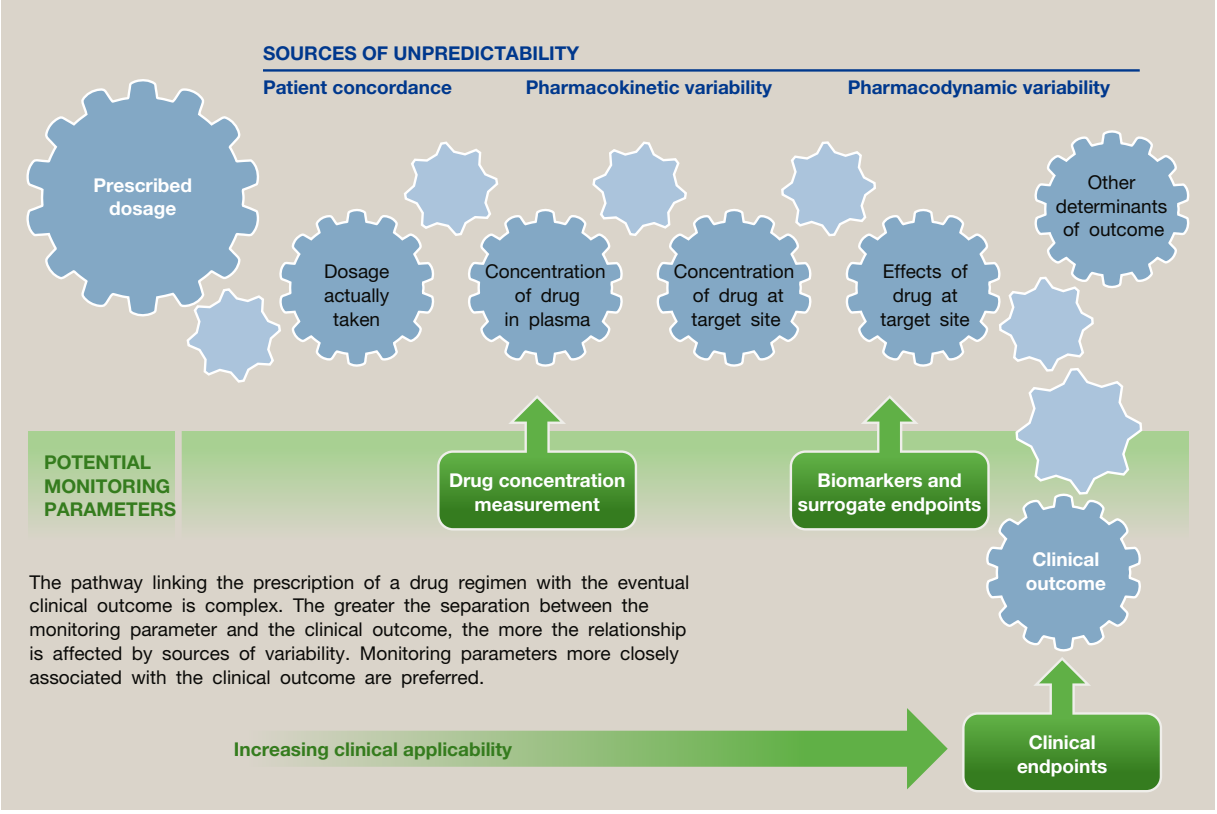



**Figure 1**

*endpoint*. A surrogate endpoint is a clinical variable, such as a blood test or examination finding, that does not itself affect the way the patient feels, functions or survives, but which changes in such a way as to predict whether the clinical endpoint will be achieved. Surrogate endpoints may be:

- **Directly related to the clinical endpoint** as an intermediate step in the causal pathway: for example, blood pressure (surrogate endpoint) is directly related to the risk of heart attack or stroke (clinical endpoint).
- **Indirectly related to the clinical endpoint**, not as part of the causal pathway but changing in parallel to it: for example, correction of an abnormal body temperature (surrogate endpoint) can provide an indication of the likelihood of curing an infection (clinical endpoint).

Any biological characteristic that is *objectively measured* as a marker of physiological, pathological or therapeutic pathways (e.g. white cell count) can be termed a *biomarker*.[1] When used to measure the effect of treatment, the biomarker is acting as a surrogate endpoint. Thus, from a semantic perspective, biomarkers and surrogate endpoints can be considered related but not synonymous terms (Figure 2).

### Monitoring using drug concentration measurements

A variety of factors can complicate the interpretation of plasma drug concentration, as illustrated in Figure 3, such that this is generally considered the monitoring parameter of 'last resort'. Criteria have been proposed to help identify drugs for which plasma concentration measurement is likely to be worthwhile.[2]

1. **The clinical and pharmacodynamic effects of the drug are difficult to monitor** – i.e. it is not feasible to measure the clinical endpoint directly, and no suitable surrogate endpoint exists. For example, it would clearly be inappropriate to measure the plasma concentration of a glucose-lowering agent, given that a suitable surrogate endpoint – blood glucose concentration – is readily available.
2. **The relationship between plasma concentration and clinical effects is predictable** – we should know the range of plasma concentrations at which there is a high probability of beneficial effects and a low risk of toxicity (the target range). For example, there is a good correlation between the plasma concentration of phenytoin and its clinical effects, with a well-defined target range. This, combined with its narrow therapeutic index (see below), makes a compelling case for monitoring plasma phenytoin concentration to guide dosage adjustment. For other antiepileptic drugs, regular plasma concentration monitoring is generally not necessary in routine practice.
3. **The therapeutic index is 'narrow'** – i.e. the ratio between the lowest concentration associated with toxicity, and the lowest concentration associated with benefit, is low. This

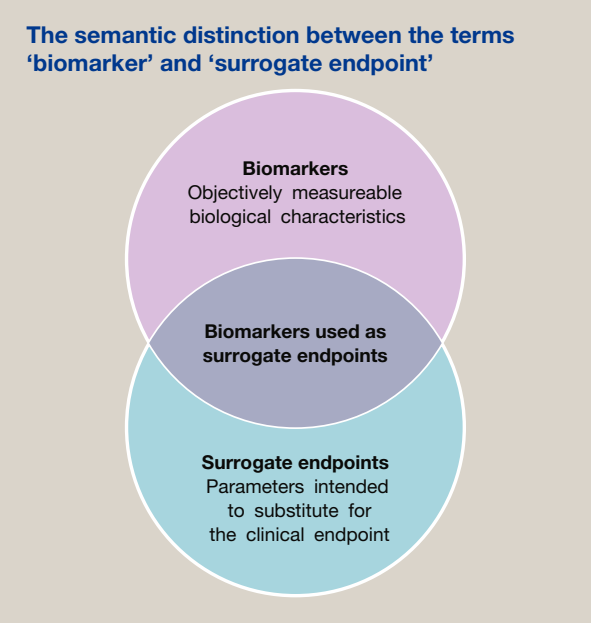



**Figure 2**

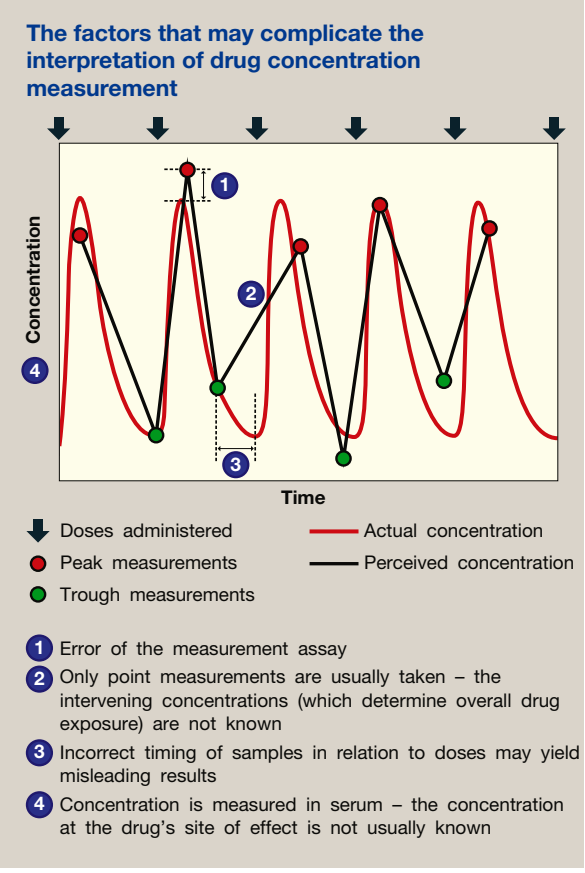



**Figure 3**

means that the concentration range over which the drug is both safe and effective is narrow: there is little 'safety margin' before toxicity supervenes. This is the case for drugs such as phenytoin, lithium and gentamicin. By contrast, drugs with a broad therapeutic index (e.g. penicillins) are both safe and effective over a relatively wide concentration range. At usual dosages, therefore, the risk that the concentration will stray outside this range is much lower, making measurement unnecessary.

For drugs not fulfilling these criteria, routine measurement of plasma concentration is generally unhelpful. However, there may be exceptions. For example, whereas there is limited evidence that routine monitoring of carbamazepine concentration improves seizure control in populations, there may be a case for measuring its concentration in selected individuals. If one suspects that a suboptimal clinical response is due to non-adherence, for example, finding a very low or undetectable plasma carbamazepine concentration can be informative. Likewise, in a patient established on an effective treatment regimen, a change in circumstances that could alter the relationship between dosage and plasma concentration (e.g. use of an alternative preparation with different bioavailability) might present a reason to measure plasma concentrations to guide dosage adjustment.

## The practicalities of drug concentration measurement

Current recommendations with respect to drugs commonly subject to plasma concentration measurements are summarized in Table 1.

### When is measurement of drug concentration indicated?

Sampling may be indicated in the following circumstances:[3]

- There is (or, in the case of a preventive therapy, may be) inadequate clinical response, which might be attributable to subtherapeutic concentration or incomplete adherence.
- It is difficult to determine clinically whether an adverse event is due to drug toxicity or features of the underlying condition (e.g. renal impairment occurring in a patient with sepsis may be a manifestation either of the disease or of aminoglycoside toxicity).
- There is a change in circumstances that can alter the plasma drug concentration. For example, if a patient taking lithium requires antihypertensive therapy with a thiazide diuretic or angiotensin-converting enzyme inhibitor, one should be alert to the risk of a drug–drug interaction leading to lithium accumulation. Monitoring the lithium concentration is essential in this context. Similarly, clearance of gentamicin depends on renal function; in situations where this is fluctuating, more frequent plasma concentration monitoring may be required.

### When should samples be taken?

**Timing in relation to doses:** the concentration of drug rises and falls during the dosage interval. The interpretation of measurements made during the initial absorption and distribution phases will be complex and usually uninformative. It is therefore generally best to take samples during the elimination phase, such

**Drugs commonly subject to plasma concentration monitoring**

| Drug | Half-life[a] | When to sample | Target concentration | Notes |
|---|---|---|---|---|
| Digoxin | 40 hours | Steady state will be attained approximately 1 week after starting or changing a dosage regimen. Samples should be taken at least 6 hours after a dose | Efficacy is best determined with a clinical or surrogate endpoint (e.g. heart rate). The risk of toxicity increases progressively at concentrations >1.5 microgram/litre (1.92 nmol/litre), and becomes likely at concentrations >3.0 microgram/litre (3.84 nmol/litre) | The BNF does not recommend routine monitoring of serum digoxin concentrations, although it suggests it may be useful to confirm a clinical impression of toxicity or non-adherence. Toxicity can occur even when the concentration is below the 'toxic threshold', particularly with hypokalaemia |
| Gentamicin | 2 hours | Consult local guidelines. Often, pre-dose (trough) concentrations are measured | Consult local guidelines. Typically, in once-daily dosing, trough concentrations <1 microgram/litre are targeted | Serum concentration measurement is essential in parenteral aminoglycoside therapy. There are no nationally accepted monitoring guidelines for once-daily dosing; local protocols should be consulted |
| Lithium | 18—36 hours (varies between formulations) | Weekly after initiation and dosage changes until concentrations are stable, then every 3 months. Samples should be taken 12 hours after the dose | 0.4—1 mmol/litre | The BNF recommends that lithium should not be prescribed unless facilities for monitoring serum lithium concentrations are available |
| Phenytoin | Varies as a function of plasma concentration (average 22 hours, range 7—42 hours) | Acute: 1 hour after an intravenous loading dose to aid the determination of maintenance dose or need to reload<br>Chronic: trough concentrations are preferable | 10—20 mg/litre (40—80 micromol/litre) | The BNF recommends monitoring serum phenytoin concentration to guide dosage adjustment. There is a good relationship between plasma concentration and clinical effects<br>In the presence of hypoalbuminaemia, the free (unbound) phenytoin concentration should ideally be measured. If this is facility is not available, a correction can be applied to allow the total concentration to be assessed against the usual target range. A formula proposed for the correction of serum phenytoin concentrations in the elderly, critically ill and head-injured patients is:[4]<br>$C_{adj} = C_{obs} \div [(0.025 \times C_{alb} + 0.1)]$ |

**Table 1** (*continued*)

| Drug | Half-life[a] | When to sample | Target concentration | Notes |
|---|---|---|---|---|
| | | | | Where:<br>$C_{adj}$ = adjusted phenytoin concentration (mg/litre)<br>$C_{obs}$ = observed phenytoin concentration (mg/litre)<br>$C_{alb}$ = serum albumin concentration (g/litre) |
| Theophylline (and aminophylline) | 3–9 hours | At least 5 days after starting treatment or dosage changes. Samples should be taken 4–6 hours after the dose | 10–20 mg/litre (55–110 micromol/litre) | Monitoring plasma theophylline concentrations is recommended, although it is noted that some patients can achieve sufficient bronchodilation at concentrations below the target range; likewise, adverse effects can occur within the target range |
| Vancomycin | 6 hours | A pre-dose (trough) concentration should be taken after 3–4 doses have been administered | 10–15 mg/litre (15–20 mg/litre for severe infections or less sensitive organisms) | The BNF recommends that plasma concentration monitoring is required |

BNF, British National Formulary.
[a] Typical elimination half-lives in adults. Depending on the drug, the half-life may be altered in renal or hepatic impairment, at extremes of age and by the effect of concomitant drugs. See the BNF or the drugs' summaries of product characteristics for details (available at www.medicines.org.uk).

**Table 1**

as at the end of the dosage interval (a 'trough' or 'pre-dose' concentration). Whatever time is selected, it is essential that it is accurately recorded with the measurement request, otherwise interpretation will be impossible.

**Timing in relation to the start of the treatment regimen:** following the introduction of a medicine, the amount of drug in the body will accumulate. At some point, provided the situation remains stable, a state of equilibrium will be reached at which the amount of drug administered in a given period is equal to the amount of drug eliminated during that period. This is termed *steady state*. The time taken to reach steady state depends on the *half-life* ($t_{½}$) of the drug. A good rule of thumb is that steady state will be achieved five half-lives after the introduction of the drug or any change to the dosage regimen.

For example, the antibiotic vancomycin has a half-life of approximately 6 hours. After starting treatment, it will take approximately 30 hours (5 × 6 hours) for steady state to be achieved (Figure 4a). Only at this point can the plasma concentration associated with that dosage regimen be reliably assessed. Likewise, if the dosage is changed, it will take another 30 hours before a new steady state is reached.

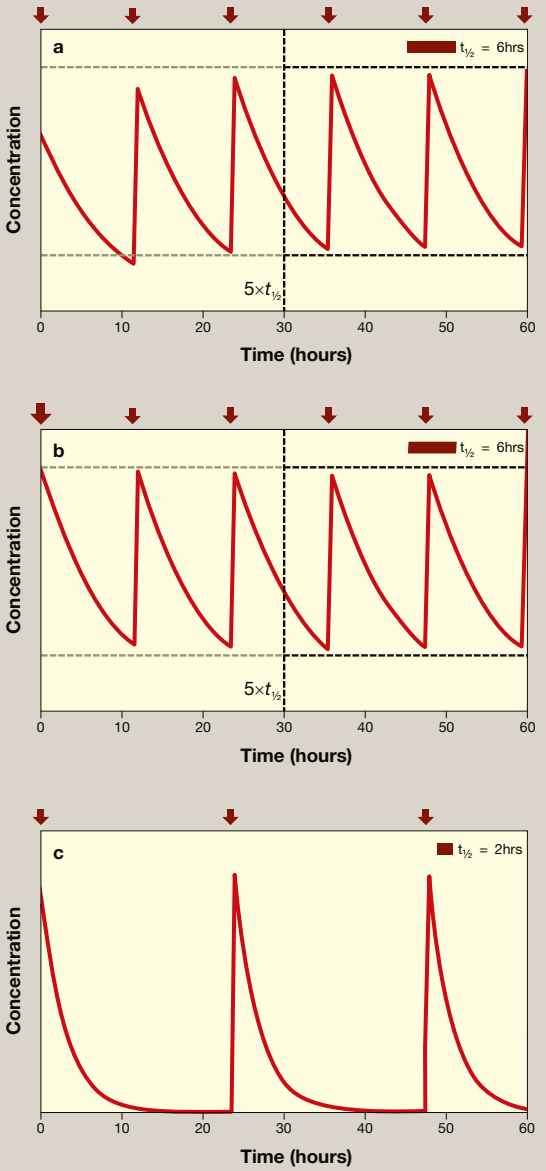
There are, however, circumstances in which it can be useful to measure concentrations before steady state is reached:[3]

- Concentrations approximating steady state can be achieved sooner if a *loading dose* has been given (Figure 4b).
- After starting a drug with a *narrow therapeutic index and a long half-life*, it may be appropriate to measure its concentration before steady state is achieved, as an early indicator of whether the steady-state concentration is likely to exceed the target range. This can provide an opportunity to adjust the dosage before toxicity occurs.
- If drug concentration is being measured *to aid the diagnosis of toxicity*, it can be measured irrespective of whether steady state has been achieved.

The concept of steady state is meaningful only if doses are administered sufficiently frequently that the previous dose has not been completely cleared before the next dose is given. If the dosage interval is substantially longer than the half-life of the drug (typically $\geq 5 \times t_{½}$), the regimen may be better visualized as recurring single doses. For example, in a patient with normal renal function, gentamicin has a half-life of approximately 2 hours. For most indications, gentamicin is administered once daily. In this scenario, there is no meaningful accumulation between doses, and the pre-dose (trough) concentration should be negligible (Figure 4c). By measuring the trough gentamicin concentration, one can identify those patients in whom gentamicin clearance is reduced (invariably due to impaired renal function), and who might therefore be exposed to accumulating gentamicin concentrations if the dose and/or dosage interval is not adjusted.

## How do the results guide treatment?

**Interpreting the target range:** the target range is derived from population studies. Natural inter-individual variation dictates that there will be people who do not derive therapeutic benefit




(**a**) A drug, such as vancomycin, with a half-life of 6 hours, administered intravenously every 12 hours (doses are indicated by arrows). Steady-state, indicated by the dashed lines, is attained approximately 5 half-lives (5×6=30 hours) after the regimen started. (**b**) The same drug, this time administered with a loading dose (large arrow). Steady-state concentrations are approximated earlier by virtue of the loading dose. (**c**) A drug, such as gentamicin, with a half-life of 2 hours, administered 24-hourly. As the dosage interval is substantially longer than the half-life, no appreciable accumulation occurs, such that the concept of steady state is not meaningful.

**Figure 4**

within the population target range, and others who experience toxicity below the population toxicity range. Moreover, the range may need to be interpreted in light of other variables. For example, phenytoin is heavily protein-bound, but only the unbound drug exerts an effect. If the measured concentration includes both the unbound and protein-bound fractions (i.e. it is a 'total' concentration), then, in the presence of hypoalbuminaemia, a low total concentration could be associated with a therapeutic or toxic concentration of unbound drug.[4] It is therefore more informative to measure the unbound fraction specifically, but if this facility is unavailable, a mathematical correction can be applied to allow the total concentration to be assessed against the standard target range (Table 1).

**The concept of diminishing returns:** as discussed in 'Pharmacodynamics for the prescriber' (pp 401–406 of this issue), dose–response curves classically take a sigmoidal form. Dosage increases within the log-linear portion of the curve might reasonably be expected to lead to a discernible increase in response. However, as the concentration rises further, the curve plateaus. Increases in dosage now produce progressively less incremental change in therapeutic effect. By contrast, there may be a marked increase in the risk of toxicity.

**Frequency and magnitude of dosage adjustments:** the appropriate frequency of measurements depends to a great extent on the stability of the patient's condition. During times of stability, excessively frequent monitoring can simply reveal fluctuations that are an inherent part of clinical measurement (due to both biological and analytical variability). This can encourage prescribers to make changes that are not warranted.[5] Likewise, excessive changes in dosage can lead to what has been described as the 'ping-pong' phenomenon.[5] The combined effects of overzealous changes in dosage, too early a remeasurement of the monitoring variable, and natural fluctuations, can lead to a series of treatment changes that generate increasing instability. It is generally advisable to make only small changes at a time, remeasuring only once a new steady state has been attained. ◆

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# Transient loss of consciousness

Peter O'Callaghan


## Abstract

Transient loss of consciousness (T-LOC) is usually caused by cardiovascular (syncope), neurological (seizure) and psychological (non-epileptic attack disorder) conditions. Suspected cardiovascular causes should be further defined as reflex/blood pressure regulatory or cardiac/heart rhythm disorders. Identifying select individuals at high risk of sudden death from a large cohort of patients with more benign causes of T-LOC is a major challenge. The key to assessing a patient with T-LOC lies in a detailed history. Risk stratification into patients at high and low risk of future cardiac arrest should be an integral part of the initial assessment of every T-LOC patient. Risk stratification is easily performed by considering the presence or absence of structural heart disease and family history of sudden unexplained death below 40 years of age, and by systematic analysis of a 12-lead electrocardiograph. Patients with high-risk features whose T-LOC is thought to be cardiovascular in origin should be referred to a heart rhythm specialist for urgent assessment. In these cases, T-LOC is an opportunity to intervene with highly effective therapies before a cardiac arrest occurs.


**Keywords** Arrhythmia; cardiac arrest; cardiomyopathy; channelopathy; electrocardiogram; implantable cardioverter defibrillator; inherited cardiac conditions; sudden cardiac death; syncope; transient loss of consciousness

## Key points

- Transient loss of consciousness (T-LOC) can be caused by cardiovascular (syncope), neurological (seizure) or psychological (non-epileptic attack disorder) causes
- Risk stratification into those at high risk and low risk of future cardiac arrest is easy based on history and 12-lead ECG analysis, and should be a standard component of the initial assessment of every patient with T-LOC
- The challenge is to identify a minority of high-risk individuals from the larger number of patients with benign causes of T-LOC
- T-LOC in high-risk patients should be considered an opportunity to intervene and, if appropriate, offer effective treatments to prevent future death from cardiac arrest
- Patients with T-LOC at low risk of sudden death in whom a diagnosis has not been established can at least be reassured that their condition is benign and not life-threatening

## Introduction

Transient loss of consciousness (T-LOC) is defined as abrupt complete loss of consciousness that is transient, self-limiting and not caused by head trauma. T-LOC is a subset of a much larger cohort of patients presenting acutely with collapse of unknown cause. Defined in this manner, the causes of T-LOC are limited to cardiovascular (syncope), primary neurological (seizure/epilepsy) and psychogenic (non-epileptic attack disorder) causes. Syncope is T-LOC caused by cerebral hypoperfusion. It is characterized by both loss of consciousness and loss of postural tone. T-LOC is highly prevalent, affecting up to 50% of the general population at some stage. Its importance lies in the clinical challenge associated with diagnosis and the fact that a proportion of T-LOC patients are at high risk of sudden death, which is usually both predictable and preventable.

Approximately 12% of all natural deaths result from out-of-hospital cardiac arrest.[1] A significant minority of these patients will have experienced syncope before cardiac arrest. A challenge for clinicians is to identify the high-risk individual from the large number of patients with benign causes of T-LOC, and to intervene effectively to prevent future sudden death. This article summarizes the clinical features associated with different types of syncope and emphasizes that risk stratification should become an integral part of clinical assessment.

## Clinical assessment

The clinician's first task is to confirm that the patient has had an episode of T-LOC and to exclude other conditions, such as metabolic disorders, intoxications, falls and coma, which can present to an emergency department or rapid-access T-LOC clinic. The key to assessing the patient is taking a detailed, methodical history (Table 1).

Features in the history are used to differentiate events that are primarily cardiovascular (syncope) from those that are primarily neurological (seizure). Cardiovascular events are generally preceded by prodromal symptoms (dizziness, lightheadedness, tunnel vision) culminating in loss of consciousness, during which eyewitnesses notice the patient to be pale and either motionless or exhibiting coarse asymmetrical jerking movements (myoclonic jerks secondary to cerebral hypoxia). The patient becomes oriented soon after regaining consciousness. Neurological events are characterized by either a lack of prodrome or a stereotypical aura culminating in loss of consciousness, during which the patient has tonic—clonic movements of all four limbs. Patients remain confused for a longer period after regaining consciousness than is the case after a cardiovascular event.

If the history suggests a cardiovascular cause of loss of consciousness (syncope), further questioning is needed to differentiate reflex/blood pressure regulatory problems from cardiac/heart rhythm disorders. Reflex forms of syncope frequently have an identifiable trigger (e.g. prolonged standing) and autonomic-mediated prodromal features (nausea caused by vagal activation, sweating from sympathetic activation), and result in post-

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### History-taking when assessing a patient with transient loss of consciousness (T-LOC)

A detailed history focussing on prodromal features, an eyewitness account of the event itself and features during recovery can be used to differentiate cardiovascular from primary neurological causes of T-LOC. Cardiovascular causes can be divided into blood pressure regulatory problems (reflex syncope, postural hypotension) and cardiac/heart rhythm causes (mechanical obstruction, bradycardia, tachycardia). Postural hypotension, not covered in this table, occurs while standing, is frequently associated with symptoms of presyncope on assuming an upright posture and is best diagnosed at the time of presentation by recording a >20 mmHg drop in systolic blood pressure between lying and standing, or by recording a systolic blood pressure <90 mmHg

| | Reflex | Cardiac | Seizure |
|---|---|---|---|
| Trigger | Common (e.g. standing) | Rare | Rare |
| Prodrome | Common | Uncommon or brief | Aura |
| Autonomic activation | Yes (nausea, sweating) | No | No or rare |
| Onset | Gradual | Sudden | Sudden |
| Colour | Pale | Pale | Normal, red, blue or pale |
| Convulsive jerks | None or brief | None or brief | Common/prolonged |
| Incontinence | Uncommon | Uncommon | Common |
| Tongue-biting | Uncommon | Uncommon | Common (lateral tongue) |
| Duration | Brief | Variable | Variable |
| Post-event confusion | Rare | Rare | Common |
| Post-event fatigue | Common | Rare | Common |

**Table 1**

event fatigue that can last many hours. Indeed, in patients with a convincing history of syncope, nausea as a symptom gives the clinician great reassurance that the pathophysiological mechanism is benign rather than life-threatening. In contrast, cardiac/heart rhythm causes of syncope have no identifiable trigger, a brief or often absent prodrome and little evidence of autonomic activation, and individuals recover quickly with no post-event confusion or fatigue.

## Risk stratification

Establishing a clinical diagnosis in some patients with T-LOC can be difficult. In contrast, stratifying all patients with T-LOC into those at low risk and high risk of sudden death is easy and should become a standard part of the initial assessment of every T-LOC patient. To stratify risk, assess whether the patient has a personal history of structural heart disease or a family history of an inherited cardiac condition, and consider relevant 12-lead electrocardiograph (ECG) abnormalities.

### Structural heart disease

Patients with a history of myocardial infarction or congestive heart failure and unexplained syncope are at high risk of future cardiac arrest. A new diagnosis of heart failure can be considered in patients with exertional dyspnoea who have noticed a reduction in their exercise capacity in recent months. Less common forms of significant structural heart disease can usually be suspected by eliciting abnormal physical signs. These include a displaced apex beat (dilated cardiomyopathy), a thrusting apex beat (hypertrophy) or a systolic murmur caused by left ventricular outflow tract obstruction (aortic stenosis, hypertrophic cardiomyopathy). In contrast, patients with excellent exercise capacity are unlikely to have significant structural heart disease.

The most common cause of structural heart disease in developed societies is atherosclerotic coronary artery disease. Over many years, this results in coronary artery occlusion and myocardial infarction. Infarction permanently scars the ventricle, and the risk of a cardiac arrest and sudden death from ventricular tachycardia (VT) and ventricular fibrillation (VF) is directly proportional to the amount of ventricular scarring. This relationship is now so well established that consideration is given to use of an implantable cardioverterdefibrillator (ICD) in all patients with heart failure and an ejection fraction less than 35%. Sudden cardiac death due to pulseless VT or VF accounts for 12% of all natural deaths and 50% of all cardiovascular deaths.[1] Some patients are fortunate that scar-related VT is self-terminating, resulting in syncope rather than out-of-hospital cardiac arrest. This life-threatening event should be recognized by the medical community as an opportunity to intervene and prevent a future death from cardiac arrest. Untreated syncope secondary to VT in patients with significant structural heart disease is associated with 20–30% fatality within 2 years.[2] UK national guidelines recommend that patients with unexplained syncope and significant structural heart disease should be considered to have a life-threatening event until proved otherwise.

### Family history of sudden death below 40 years of age

Inherited cardiac conditions that predispose to sudden arrhythmic death include cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, familial dilated cardiomyopathy) and channelopathies (congenital long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, short QT syndrome). These are inherited in an autosomal manner with variable phenotype penetrance.

A family history should be obtained tactfully in a way that does not cause anxiety in patients with undiagnosed T-LOC, most of whom have a benign aetiology. I usually enquire about the age and health of each parent and sibling, and the cause of any premature deaths. For completeness, I discreetly ask about any tragedies such as drownings or single-vehicle road traffic accidents in the more extended family. Patients with unexplained

T-LOC and a family history of sudden death below 40 years old should be assessed as a matter of urgency by a cardiologist specializing in heart rhythm disorders. Absence of a family history does not exclude an inherited arrhythmic condition. In fact, up to 25% of cases can be caused by new sporadic mutations.[3] Neurologists should constantly be alert to the possibility that patients with conditions such as congenital long QT syndrome can be referred to their clinics, and should be prepared to pick up relatively easily the more obvious cases with ECG abnormalities.

### Relevant 12-lead ECG abnormalities

ECG analysis using an approach that seeks proactively to diagnose or rule out specific conditions results in a greater diagnostic yield than simply inspecting the ECG (Figures 1 and 2).[4] In patients aged 40 years and over, the emphasis should be on excluding acquired cardiac conditions, such as ventricular scarring or significant conduction system disease. The former predisposes to syncopal VT, the latter to intermittent complete heart block. In patients aged under 40 years, the emphasis should be on excluding congenital conditions, cardiomyopathies and channelopathies. Urgent referral of patients suspected of having one of these conditions is important as they can, and frequently do, culminate in sudden death (e.g. pulseless VT/VF, asystole), which can be prevented by, for example, accessory pathway ablation, β-adrenoceptor blockade or ICD implantation.

## Diagnostic challenges

However detailed the clinical history and however experienced the clinician, there is always a significant minority of patients in

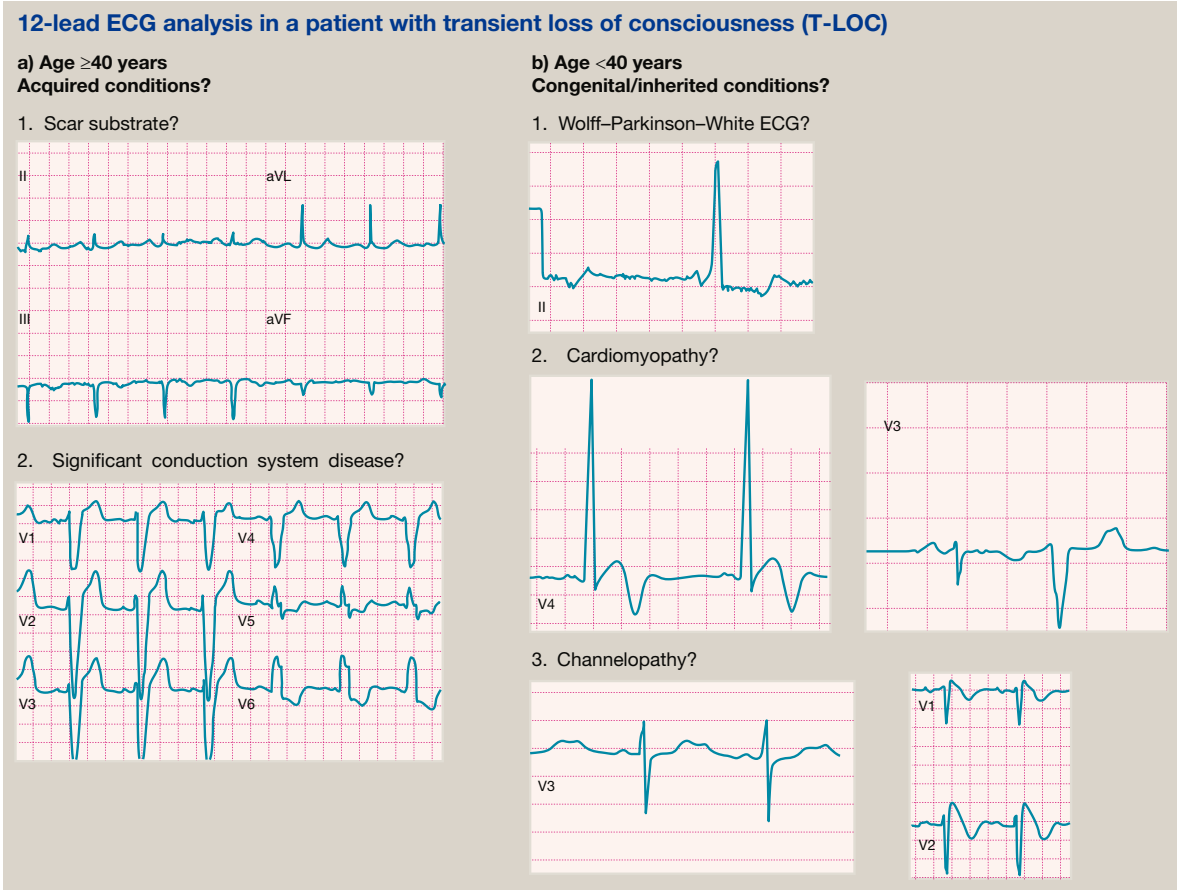


**Figure 1** Conditions to consider when assessing the 12-lead ECG in a patient with T-LOC. (**a**) In patients aged ≥40 years, acquired conditions should be ruled out. (**a1**) The most common cause of ventricular scarring is previous myocardial infarction, which usually results in pathological Q waves (Q waves in leads III and AVF in a patient with previous inferior myocardial infarction). (**a2**) Significant conduction system disease predisposing to intermittent complete heart block may be obvious on the ECG (complete left bundle branch block). (**b**) In patients with T-LOC who are <40 years old, congenital and inherited conditions should be ruled out. (**b1**) An accessory pathway bypassing the usual atrioventricular delay in Wolff–Parkinson–White syndrome results in a short PR interval and an initial slurring of the QRS complex (δ wave). (**b2**) Cardiomyopathies such as hypertrophic cardiomyopathy (left) can result in tall R waves and significant ST/T wave changes over the left ventricular leads (V4 shown). Arrhythmogenic cardiomyopathy (right) results in right ventricular abnormalities such as T wave inversion in V3, which is normal in children but suggestive of right ventricular pathology in >16-year-olds. (**b3**) Channelopathies such as congenital long QT syndrome (left) can result in QT prolongation with abnormal T wave morphology (notched V3 T wave with QT = 560 ms). Brugada syndrome (right) results in a right bundle branch block-type appearance with persistent ST elevation over the right ventricular leads (V1 and V2 shown).

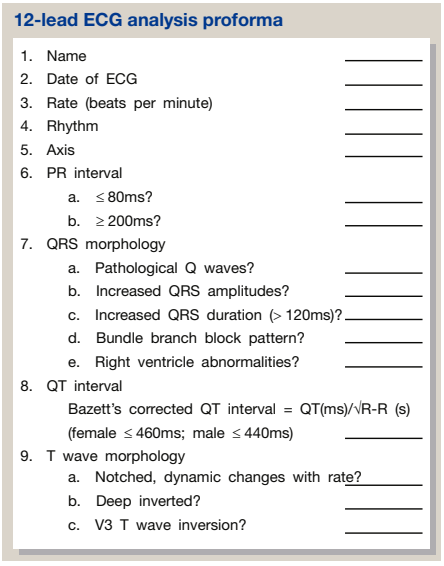


**Figure 2** Proforma for 12-lead ECG analysis. This proforma developed in collaboration between cardiology and neurology departments can be used systematically to analyse the ECG in clinic. Reproduced from Marsh E, O'Callaghan P, Smith P. The humble ECG. *Pract Neurol* 2008; **8**: 46–59 with permission from BMJ Publishing Group Ltd. ms, milliseconds.

whom an initial clinical diagnosis cannot be reached. Attention should then turn to risk stratification. Patients at low risk of sudden death (i.e. those with unexplained T-LOC, a structurally normal heart, no family history of premature sudden death and a normal 12-lead ECG) can at least be reassured that, whatever the aetiology, they are unlikely to die suddenly from their condition.

Patients at high risk of sudden death (i.e. those with unexplained T-LOC and structural heart disease or a family history of premature sudden death or a significant ECG abnormality) should be referred for urgent assessment to a heart rhythm specialist.

## Further investigation and management

Patients with recurrences thought to be cardiovascular in origin can be further investigated. Low-risk patients can undergo non-invasive monitoring (24-hour tape if recurrences occur more than once per week; 1–2-week event monitor if occurring more than once a month), tilt-table testing or insertion of an injectable loop recorder. This is now routinely performed in a minor procedures room. Patients with reflex/blood pressure regulatory problems can be educated and given advice regarding fluid and electrolyte intake, avoidance of identified triggers, etc. In contrast, high-risk patients should be referred for urgent assessment by a heart rhythm specialist to consider further tests, such as a diagnostic electrophysiological study (to look for inducible tachycardias, especially scar-related VT), an ajmaline test (using a sodium channel blocker capable of unmasking the Brugada ECG) or QT assessment using a 24-hour tape and exercise stress testing. In high-risk patients, a single episode should be sufficient to trigger urgent referral and investigation. Some of these conditions are characterized by a small number of arrhythmic events with a high lethality index. In these cases, T-LOC is best understood as a near-death event and an opportunity to intervene and alter the natural history of the condition.

Few conditions in medicine can be as effectively treated in 2016 as life-threatening arrhythmic conditions. ICDs offer 99.9% protection against death from VF.[5] Syncope should be considered an opportunity for the physician to detect heart rhythm disorders and ensure the patient is afforded protection from future cardiac arrest. Failure to stratify risk by simply assessing the patient for evidence of structural heart disease, family history of premature sudden death and a relevant ECG abnormality is a missed opportunity that can result in the patient becoming one of approximately 100,000 sudden deaths that occur in the UK annually. ◆

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# What do we need to do to sustain compassionate medical care?

Raymond J Chadwick
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**Abstract**

The term 'compassion' is widely used, but what it requires is rarely analysed. It has been defined as understanding another's suffering, combined with a commitment to doing something to relieve this. It involves an emotional component – a personal reaction to the plight of another – and sensitivity to the personal meaning a condition may hold for the individual. An emotional response to tragic circumstance is by nature spontaneous. But compassion also requires deliberate responses – respect, courtesy and attentive listening.

The human brain is hard-wired with the capacity to share the experience of others, including their emotions. So the potential for empathy and compassion is innate. However, this can be limited by repeated exposure to suffering, when the neural networks involved become downregulated. In addition, an organizational culture geared to performance targets with diminishing resources can lead to exhaustion and burnout. This results in reduced capacity to attend to the needs of patients.

The traditional solutions of education and further research may not be sufficient. A framework is proposed for doctors to contribute to compassionate medical care, taking account of organizational factors. The key elements are awareness, self-care, attentive listening to patients, collaboration and support for colleagues.

**Keywords** Compassion; empathy

## Key points

- Responsibility for providing compassionate care is both individual and collective
- For the individual doctor, compassion involves not only an emotional response to suffering, but also a commitment to treating all patients with respect, courtesy and kindness
- Sustaining compassionate care – in the face of organizational and other barriers – requires a moral and ethical commitment to upholding the values of the medical profession

## What is compassion?

Compassion is now freely invoked in specifications of healthcare. It is clearly desirable and apparently the solution to many ills. It commonly enters public awareness as a deficiency – lack of compassion was a salient theme in the Francis Report on failings in the UK Mid-Staffordshire Trust, and specific training in compassionate care figures in the report's recommendations.

There is an assumption that we all know what compassion involves, but its meaning is rarely analysed. Attempts to define it indicate more than a single dimension – for example 'recognising and understanding another's concerns, distress, pain or suffering, coupled with … taking action to ameliorate them'.[1]

It is characterized by an emotional response to suffering, which requires the ability to enter imaginatively into another's situation, and a commitment to doing something about it. But there is also a rational element, including an evaluation of the seriousness of the condition. We may feel compassion for a life-changing disease or injury; in the case of a cut finger, sympathy is often more appropriate. But a note of caution. We should be sensitive to the personal meaning a condition holds for the individual – which may not be obvious. One of us recalls treating a patient with a cold sore on her lip, who was emotionally distressed. She was a flautist and feared the swelling and discomfort would mar her performance at an important concert.

To the extent that compassion involves an emotional response, it is by nature spontaneous – it cannot be mandated. If it is to be part of the doctor's daily work (and within the ambit of duty), compassion needs to consist of more than a personal emotional reaction. Doctors have to deal with a wide range of conditions varying in clinical severity – and also in emotional valence. What they all require is respect, attentive listening, simple courtesy and kindness.

## Where does responsibility lie?

Individual doctors are of course responsible for the way in which they treat their patients. It is easy to assume that the matter ends there, but a powerful case can also be made for collective responsibility resting with the organization. From this perspective, there needs to be a balance of responsibilities between the individual and the system as a whole.[2] This matters in terms of both accountability – how and from whom to learn about individual and systems errors – and responsibility – where and with whom to locate the focus for getting things *right*. Where a lack of compassion is identified as underlying a significant failure in healthcare, as recently in the Francis Report, this needs to be seen as both an individual and a collective responsibility.[1]

Compassionate medical care is dependent not only on the individual clinician, but also on his or her team and the organizational context within which he or she practises. All are responsible and all must be engaged if compassionate care is to be sustained.

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## What does the science tell us?

What do we know so far about the nature of compassion? First, advances in neuroscience have demonstrated that the human brain has neural networks that are hard-wired with the ability to share the experiences of others, including their emotions and sensations.[3] At least two neural networks are involved: one activated during empathy for pain, and another activated by compassion.[4] So the human capacity for empathy and compassion is innate.

However, the practice of medicine brings exposure to a high level of distress and fear, associated with disease and mortality, combined with inevitable uncertainty around clinical decision-making. These conditions are to some degree anxiety-provoking for most clinicians (whether or not openly acknowledged) and can lead to feelings of being overwhelmed that require some form of defence or coping strategy. Most such defences involve some separation or distancing from emotional responses. The parallel evidence from the field of neuroscience indicates that the neural networks responsible for empathizing with the pain of others become 'downregulated' after repetitive exposure to observing others' pain.

## What happens in clinical practice?

In addition to the inherent stress of the work, it is increasingly common for clinicians to experience pressure to achieve service efficiencies by meeting performance targets even when resources (finance, staffing) are reduced. Along with nursing and other healthcare colleagues, they are faced with the challenge of doing more with less. In this context, it is all too easy for the organizational culture to shift and emphasize the attainment of targets and the maintenance of marginal returns as the priority — perhaps to the detriment of the service's core purpose.

As a result, clinicians are likely to experience a loss of professional autonomy, in that they are no longer able to practise freely as they judge best. In emotional terms, the effects of this include a heightened state of anxiety, feelings of anger and what can only be described as moral distress. The result of these states is increasingly one of burnout — emotional exhaustion, cynicism and a low sense of accomplishment. This inevitably serves to distract from a proper focus on the needs and concerns of individual patients and their families, and has been associated with medical errors.

## Traditional solutions may not be the answer

There are consequently obstacles to the expression of compassionate care at all service levels — individual clinicians, their teams and the wider organization. One solution to this might be to provide more education. And, to a degree, there are grounds for believing that education can help, at least in the right circumstances. Human beings are born with the capacity for compassion — but can still learn to deepen their potential to provide compassionate care.[1] Sensitive teaching about communication skills and attentive listening will result in patients who are more satisfied with their care and *may* also lead to improved outcomes.[5]

But there is little lasting value unless compassion also has reality within the culture of the organization. Where this is not the case, we might be better served by asking how we can at least mitigate the organizational factors that suppress the innate compassion of healthcare professionals.

A further solution might be to recommend more research. And, again, there is reason to hope that gathering additional data would be useful — provided that certain conditions were satisfied. It would be helpful to know more about the impact of care experienced as compassionate on patient well-being, and to understand whether and how this mediates the outcome of treatment. But it matters crucially how any such findings are *applied*. In their book *Intelligent Kindness* (see Further reading), Ballatt and Campling make an important point:

> Research of this kind can only be helpful — with the proviso … that the learning would be at risk of being applied in a

### Actions required to sustain compassionate care

| Action | Descriptor |
|---|---|
| Awareness | A high degree of awareness — both of one's emotions, thoughts and reactions, and of the impact of the organizational and educational context in which care is provided |
| Self-care | A conscious approach to self-care — taking account of emotional as well as physical needs, and seeking opportunities for support and emotional expression — through mentoring, supervision, peer discussion and other opportunities for reflection |
| Attentive listening | Commitment to giving priority to the needs of patients and their families, through attentive listening beneath the surface for their concerns, and by remaining open to new perceptions and experience |
| Collaboration | Commitment to working collaboratively with colleagues, patients and families to change systems of education and care delivery that create barriers to compassion |
| Support for colleagues | Continual attention to the needs of students, trainees and colleagues — fellow doctors and staff from other disciplines — noticing when they are under pressure, acknowledging this and where possible and appropriate offering support |
| Commitment | Maintaining a moral and ethical commitment to upholding the values of the medical profession, and to acting with and advocating for compassion despite existing barriers |

**Table 1**

'technological' manner that misses the point, or indeed works against promoting kindness.

## How to enact compassion in healthcare

In this complex situation, where individual and collective responsibilities are interdependent, what should be the priorities for the medical trainee and their teachers? The suggestions in Table 1 are offered, not in order of importance, as a guide that takes realistic account of the challenges of providing compassionate care.

In a given set of circumstances, it is only ever possible for any of us to do our best. However, we have a responsibility to consider what this best might be. We have multiple responsibilities — to patients, to colleagues, to the wider organization — and in addition to ourselves to resist burnout and sustain our own well-being so that we can care for others. In this way, whatever the context, it is always possible to contribute to the capacity for compassion in medical care. ◆

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