Monitoring in chronic disease: a rational approach

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Clinical review

Conclusions

Clinical guidelines provide a useful reference for practising clinicians. However, they are often not long enough, or not easily approachable, and therefore underused. The sample case summaries presented here and the treatment flow chart in figure 1 provide a basis for the practical implementation of current guidelines and more recent clinical trial evidence.

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2 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary dis-
involved, monitoring is a surprisingly understudied area. We review the current literature (based on a Medline search using the terms “monitor*”, “therap*” or “treat*”; “limit*” or “threshold*”; “chronic” and a check of references of relevant papers found) on the clinical uses of monitoring, and develop some principles for good monitoring strategies.

Should we monitor at all?

Although intuitively monitoring should be beneficial, clinicians accept non-monitoring in many areas. Aspirin, for example, is used to prevent stroke without assessing platelet aggregation. Establishing benefit for patients is important, as it must be balanced against the downsides of monitoring, such as the inconvenience and costs, and the impact of false positive and false negative (monitoring) results that can lead to inappropriate or delayed actions. As with other interventions, this ideally requires a randomised controlled trial. The benefit should preferably be measured by outcomes that are relevant to patients rather than time spent in the target range (a surrogate marker). For example, in a trial of drug monitoring in epilepsy, monitored patients were more often within control limits than unmonitored patients (8% v 25%), but the proportion remaining free of seizures did not change (38% v 41%).

However, few monitoring practices have undergone such trials.

Monitoring is a complex intervention. It can have an impact through several means, including improvement of adherence, better selection of treatments based on individual response, better titration of treatment, and patients’ learning about non-treatment factors that alter the condition’s control. Because of this complexity, any trial should be preceded by developmental work to understand the optimal strategies.

Monitoring and adjustment may be controlled by clinicians or patients. For patients, monitoring may provide a signal for action or simply provide motivation to adhere to treatment. For example, in a recent study compared three modes of peak flow monitoring in childhood asthma: regular daily monitoring, measurement only when symptomatic, and monitoring only at times of symptoms. The study showed that peak flow monitoring is helpful but that the less intensive monitoring regimen is preferable.

The phases of monitoring

The objective and methods of monitoring change over the course of treatment. This course of monitoring can be usefully divided into the five phases listed in table 1.

Figure 1 shows a control chart for these stages. At (a) we first note the abnormal measurement and begin a quick series of measurements before treatment to confirm the abnormal result; (b) then, if appropriate, initiate treatment and monitor at short intervals to check response and achieve control; (c) but once control is achieved, the intervals may be longer (d), although this may be supplemented by patients’ self monitoring (small arrows) (e); but when one measurement is more than 3 standard deviations (SD) or two measurements are more than 2 standard deviations from target, we adjust therapy to re-establish control and shorten the re-check interval; and finally (f), if treatment becomes unnecessary, a period of monitoring after its cessation may be required. We now look at these phases in more detail.

Pretreatment monitoring

Monitoring before treatment should establish the need for treatment and then a baseline to judge the response to treatment or changes in the patient’s condition. Treatment should not start until sufficient measurements for a firm baseline have been obtained. This firm baseline confirms that the degree of abnormality is beyond the initiation threshold. Serial measurements often “normalise” before treatment for several reasons, such as training effects (for example, with a peak flow meter), accommodation to measurement (for example, with blood pressure measurement), and, perhaps most importantly, regression to the mean (the tendency of repeat tests to be closer to normal). For example, in the first biennial check in the Framingham study, the average blood pressure fell by 3.4 mm Hg systolic and 2.4 mm Hg diastolic. Among 99 Dutch patients with apparently raised blood pressure, re-measurement resulted in average reductions of 9 mm Hg systolic and 4 mm Hg diastolic. The same study showed that two measurements were sufficient to

The objectives for the five phases of monitoring

<table>
<thead>
<tr>
<th>Phase</th>
<th>Monitoring objectives</th>
<th>Optimal interval</th>
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<tbody>
<tr>
<td>Pretreatment</td>
<td>Check need for treatment</td>
<td>Short—based on variability within patients</td>
</tr>
<tr>
<td>Initial titration</td>
<td>Establish a baseline for determining response and change</td>
<td>Medium—based on pharmacokinetics (such as drug half life) and pharmacodynamics (physiological impact time (wash-in))</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Assess individual response to treatment</td>
<td>Long—based on rate of random and systematic “drift”</td>
</tr>
<tr>
<td>Re-establish control</td>
<td>Detect drift from control limits</td>
<td>Medium—as above</td>
</tr>
<tr>
<td>Cessation</td>
<td>Bring level back within control limits</td>
<td>Medium—as above</td>
</tr>
</tbody>
</table>

— based on pharmacokinetics (such as drug half life) and pharmacodynamics (physiological impact time (wash-in))
establish the need for treatment in patients who were well above the initiation threshold. For borderline patients, even four measurements resulted in substantial misclassification.

**Initial titration: response, control, and safety**

After establishing the baseline, we should set a target and start titration to achieve that target. However, achieving the target is just one of several objectives of the initial titration phase, which should include checking the individual’s response to treatment, detecting unacceptable adverse effects, and achieving the desired target range.

This initial monitoring checks adequate response to treatment—that is, whether it “works” as expected on the basis of clinical trials in other patients. Sometimes individual response to treatment can be predicted by other measurements, such as genetic testing (for example, the dose requirement on initiating warfarin treatment is strongly related to CYP2C9 gene variants). Sometimes it can be predicted by pharmacokinetic studies—for example, in initiating tricyclic antidepressants, short term measurement of the drug concentration can characterise individual metabolism and guide the long term dose used. However, personalising treatment usually requires some pragmatic trial and error. We can therefore think of this phase as an “n = 1” trial. Ideally, the estimate of effect will be based on both the measurements in that patient and the known effect from trials.

The initiation phase should also detect immediate or short term adverse effects. Measures of potential harm should hence be assessed and monitored. Almost half of the medicines in the electronic Medicines Compendium (www.medicines.org.uk) include a suggestion for some monitoring. Many drugs affect renal function, and regular monitoring of creatinine and electrolytes is widely recommended. A more specific example is treatment with clozapine, for which white cell counts are measured on a weekly basis for almost half of patients, even four measurements resulted in substantial misclassification.

Once the target is achieved, the objective of monitoring is to ensure that measurements stay within reasonable limits, called control limits. The control limits ensure that we detect real changes in the level of the target measure while minimising false positives resulting from variable measurements in the short term or errors in the technical measurement. The degree of short term variation can be estimated from population studies, subpopulations, or from the individual’s own measurements. Because extreme measurements are unlikely to be due to variability of short term measurements, they may justify action to re-establish control. One approach suggested by statistical control theory is to consider that a shift from control has occurred if a single measurement is outside an upper and lower control limit of 3 standard deviations, or if two or three successive measurements are more than 2 standard deviations from the target.

**Monitoring during treatment**

Figure 1 shows these two sets of action thresholds; one for action (SD 3) and one for re-measurement (SD 2), with action if the repeat result is also more than 2 standard deviations from target.

Monitoring during treatment can be less frequent than during the initiation phase. The interval depends on the probability of being outside the control limits, which in turn depends on both random drift and systematic changes (progression or regression of disease).

The measurements intervals may be shorter than the decision interval. For example, monitoring measurements of blood pressure might be done daily by patients, but the decision made at a monthly consultation with the doctor. This is illustrated in figure 1, where multiple measures (5b)—small arrows—occur between the decision points (3a)—large arrows. Ideally a graphical presentation, such as a control chart, should be used to aid recording and deciding treatment changes.

**Adjustment to re-establish control**

When a clear drift beyond the control limits occurs, we should re-establish control. As in the initiation phase, a shorter measurement interval is generally warranted until control is re-established.

We have already cited several examples (for example, monitoring digoxin therapy) in which audits have shown that clinical decisions taken as a result of monitoring are suboptimal—sometimes tending to the conservative. A New Zealand study of digoxin monitoring showed that 53% of ordered measurements were inappropriately timed and that 5% of the ordered measurements led to inappropriate dose adjustments. Patients too find this difficult: a survey of diabetes educators showed that correct adjustment of insulin dosage is the single hardest skill to teach. This may be because of the lack of a planned and explicit response to test results or because the tests are seldom considered in context—they usually arrive as a single value, without reference to past values or a clear and useful statement about the variability of measurements. The appropriate degree of adjustment may be helped by nomograms or computer algorithms.

**Cessation of treatment**

Most therapies are not lifelong. Monitoring should inform stopping decisions. Again, such decisions are...
usually based on a threshold level—either a negative outcome (such as an adverse effect on renal function or frequency of epileptic seizures exceeding a threshold), or a positive outcome (such as pain relief) that falls below a minimum threshold. However, the precise thresholds chosen and the monitoring interval depend on the phase of treatment. Cessation of treatment mirrors the first phases of pre-treatment and initiating treatment. A decision to stop based on current risks and control is made, treatment is withdrawn (perhaps in stages), and, after a “washout” period, the patient is rechecked to ensure that treatment does not need to be restarted.

Monitoring strategy

For all phases, several choices have to be made in devising a good monitoring strategy: whether to monitor at all, the choice of measurement(s), the choice of target range, the choice of measurement interval, and who should monitor.

Which measurement?

Monitoring the wrong target is obviously a fundamental error. Often various possible monitoring tests will be available, and there are advantages to choosing one main measurement (or a composite measure of several) to guide changes in management (fig 2). The criteria for the choice of measurement include the following.

- Is it a good predictor of clinically relevant outcomes? Monitoring measurements are surrogate markers for the patient relevant outcomes. "Can it detect changes in risk early? Risk predictors will vary in their responsiveness to the beneficial impact of treatment, with a good monitoring measurement providing an early indication of risk change." "Is the random variability acceptable or can it be made acceptable by repeated measurements?" "Is it sufficiently affordable, accessible, and acceptable to patients?"

Choosing the monitoring interval

The different phases require different monitoring intervals (table 1). The interval is shortest for the pretreatment phase, longest for the maintenance phase, and intermediate for the other three phases.

For the pretreatment phase, measurements need to be far enough apart to make allowance for the short term variability within and between days. For example, the multiple readings taken when monitoring blood pressure for 24 hours give an accurate picture over a full day but do not capture some patients’ considerable variability from day to day. For remeasurement during the treatment phases, we must know the time to therapeutic response (allowing for both pharmacokinetics and pharmacodynamics)—for example, the interval for statins is about six weeks2 and for angiotensin converting enzyme inhibitors for blood pressure about three weeks.4

Who should monitor?

Self monitoring by patients is becoming more common. Such monitoring may be for motivation—for example, by using pedometers to monitor physical activity or home blood glucose measurement for people with non-insulin dependent diabetes25; for providing a clinician with between visits measurements—for example, home blood pressure monitoring40, or home glucose monitoring; or for self adjustment of therapy—for example, peak flow rates to trigger actions in asthma patients26 or home blood glucose for insulin adjustments. As the examples show, monitoring of patients can be done for all three purposes.

Discussion

Although monitoring is common in clinical practice, the principles of monitoring have not been well conceptualised, which is in turn has led to suboptimal care. Chronic care could potentially be improved (and often at reduced costs) if for each chronic disease we determined whether and how monitoring was necessary, set explicit monitoring ranges and provided appropriate graphical representations that aided decision making, recognised the need for different optimal intervals for different phases, and understood better when and how to adjust treatment to avoid the increases in variability caused by overadjustment. Health professionals working in chronic care need to understand these principles better, and systems needs to be improved, including use of appropriate decision aids that have been shown to improve monitoring care.29

We thank Andrew Farmer, Jeffrey Aronson, and Tom Falco for detailed comments on various drafts, and Susan Jack who helped with initial searches and problem formulation.

Additional educational resources

For patients and clinicians

National electronic Library for Health (www.nell.nhs.uk)—contains UK relevant guidelines on monitoring for many areas. A search on “monitoring” and choosing “evidence” provides the evidence base for a number of monitoring topics

The BTS/SIGN British Guideline for Asthma (www.brit-thoracic.org.uk/sign/index.htm)—few long term conditions have appropriate monitoring charts, but asthma is one of the better served. A printable peak flow diary is downloadable from the websites of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (www.brit-thoracic.org.uk/sign/mainframe_download.html)

For researchers

Westgard QC (www.westgard.com)—a website for laboratory tests, which includes a database of within person variation for over 100 tests (see "Biologic Variation Database"), and the Westgard rules for detect readings beyond control limits
A patient's journey with myalgic encephalomyelitis
Bie Nio Ong, Daphne Evans, Andrew Bartlam

Myalgic encephalomyelitis (ME) presents patients and their general practitioners with the challenge of managing a life shaped by chronic debilitating illness, pain, and uncertainty. The notion that body limitations resulting from illness must be recognised is shown in monitoring aims to establish the response to treatment, detect the need to adjust treatment, and detect adverse effects.

Monitoring is not always necessary or beneficial and can lead to inappropriate changes.

Control charts help distinguish natural variability from true change and reduce unnecessary adjustment.

Monitoring for both benefit and harm is important, preferably with a single measurement.

The interval between measurements varies between phases and is shorter after changes in treatment.

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Competing interests: None declared.


6 Bie Nio Ong, Daphne Evans, Andrew Bartlam

A memorable patient: Home glucose monitoring, who started it?


10 Bland JM, Altman DG. Regression towards the mean. BMJ 2003;326:1336.

11 Brueren MM, Petri H, van Weel C, van Ree JW. How many measurements between phases and is shorter after changes in treatment.

is still some debate about the existence of the disease as a clinical category. Current guidance focuses on the symptoms of fatigue and malaise, cognitive impairment, and pain. The patient's account in this paper was collected as part of a research study on osteoarthritis of the knee. The patient, Daphne Evans, was interviewed by BNO, but the discussion centred on myalgic encephalomyelitis because she considered this condition of primary importance. Her doctor's account was added to her own account when the paper was drafted.

Diagnosing uncertain disease

Daphne's story illustrates the syndrome of myalgic encephalomyelitis as a chronic and fluctuating illness with a profusion of symptoms that affect many parts of...