Accidental awareness during anaesthesia, especially with pain and subsequent recall of the event, is a terrifying prospect. A high proportion of those who experience it are reported to go on to develop symptoms similar to post-traumatic stress disorder. The reported incidence of recall after general anaesthesia, as ascertained by later questioning using the Brice questionnaire, is high, ≏ 1–2 per 1000 cases (although the majority of these do not involve painful experiences, are very brief recollections, or both). Therefore, a monitor to help the anaesthetists identify those patients who are awake during surgery would be extremely useful.

The publication of Diagnostic Technologies Guidance from the National Institute for Clinical Excellence (NICE) on the role of EEG-based monitoring in reducing the risk of awareness during general anaesthesia, as ascertained by later questioning using the Brice questionnaire, is high, ≏ 1–2 per 1000 cases (although the majority of these do not involve painful experiences, are very brief recollections, or both). Therefore, a monitor to help the anaesthetists identify those patients who are awake during surgery would be extremely useful.

The available evidence on the impact of the technologies on reducing the likelihood of intraoperative awareness is limited. Overall, [EEG-base monitors are] not associated with a statistically significant reduction in intra-operative awareness in patients classified as at higher risk ...

What is the anaesthetist reader (or patient) to make of these contemporaneous and conflicting conclusions?

The bodies providing these two sources of advice had very different remits, which may explain the opposing conclusions. The Technology Assessment Report was a review (including a meta-analysis which incorporated results of a recent Cochrane review). The NICE guidance, on the other hand, is a consensus opinion which takes into account the findings of the Technology Report but also includes expert and individual views, perhaps importantly including that from companies which manufacture the devices under consideration. The broad aim of the NICE Diagnostics guidance programme is explicitly to promote rapid adoption of clinically innovative and cost-effective diagnostic technologies, based on their potential (not necessarily proven ability) to improve care (see: http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf).

On the ‘probability of unconsciousness’
In several places, the NICE guidance appropriately stresses that a monitor’s output reflects the probability of (un)consciousness in a given patient. It is repeatedly stated that a BIS (and also E-entropy) output reading of 40 (or 40–60)
indicates a ‘low’ probability of awareness. However, it is not specified what ‘low’ means. Also not explained is how the probability of awareness varies as the monitor reading increases: 40 may be a low probability, but how much higher is, say, 50 or 65? In other words, what is the shape of the relationship between monitor output and probability, if plotted graphically?

We already have answers to these questions, if they are posed in relation to expired volatile agent (end-tidal) concentrations. This is the basis of the concept of the MAC (minimum alveolar concentration), which is an ED50, the concentration at which 50% of patients move in response to a standard stimulus. The ED50 (or EDx; points when x%, 95%, 99% of patients do not move, etc.) has a constant value in arbitrary units, regardless of the agent used and the concept can be used for a variety of endpoints. For example in MAC, the endpoint is response to a standard incision, while in MAC-aware, the endpoint is response to verbal stimulus. In this way, MAC (or any EDx) ‘normalizes’ the population response across agents, and indicates the probability of no-response at any given dose, regardless of agent.12-15

Therefore, at 1 MAC (the ED50), there is always the same (50%) probability of no-response with halothane, isoflurane, or any other volatile anaesthetic. If a DOA monitor accurately reflected this fact, then its output should be the same at 1 MAC of any agent. Were the monitor to read, say, ~35 at 1 MAC sevoflurane but ~60 at 1 MAC halothane, it would not be a very useful monitor. Yet this is exactly what is reported with EEG-based monitoring.16 Thus, a BIS value of just below 60 (i.e. within the recommended target values for both BIS and E-entropy monitors) might in fact indicate an unacceptable risk of consciousness with some agents.17 NICE recommends that DOA monitoring should be considered when total i.v. anaesthesia with propofol is used, but the data of Glass and colleagues18 clearly demonstrate similarly disparate probabilities at equi-BIS values: at, say, a BIS value of 70, the probability of unconsciousness is ~50% for isoflurane but just ~15% for propofol.

The interpretation of existing clinical trial data

Both the NICE guidance and Technology Assessment Report use data from large clinical trials to inform their conclusions. The B-Aware trial reported two of 1225 cases of awareness when anaesthesia was guided using a BIS monitor (to achieve a BIS reading of 40–60) and 11 of 1238 without a BIS monitor (P=0.022).5 The attractive conclusions are that using the monitor has significantly reduced the occurrence of awareness and, furthermore, that maintaining the BIS in this range (i.e. <60) will prevent consciousness.

However, a monitor is not an intervention like a drug, whose efficacy can be measured as the simple incidence of beneficial outcome. Rather a monitor is a diagnostic tool, whose efficacy is usefully measured as the proportion of correct diagnoses it makes. The relevant data are therefore the numbers of cases of awareness in which the monitor indicated otherwise (i.e. the false negatives, FN) and the number of cases of appropriate anaesthesia in which the monitor indicated otherwise (the false positives, FP). These are then combined to yield quantities such as the sensitivity, specificity, and positive (and negative) predictive values of the diagnostic instrument. In the B-Aware trial, results were not presented in this way (and in the group of patients whose anaesthesia was not BIS-guided, the monitor was turned off, so no data were available). Nonetheless, the data can be re-arranged to show the relevant discriminatory capacity of the monitor (Supplementary Table S1). Examined in this manner, the monitor’s utility is far from encouraging, with the sensitivity and specificity of ~50% and the positive predictive value of just 0.2%.

In contrast to the B-Aware trial, the B-Unaware trial (with a similar study design) did not find a reduction in awareness with BIS monitoring.2 This time, BIS records were available for both groups. Again, re-arranging the data to explore diagnostic efficacy of the monitor does not suggest great utility (Supplementary Table S2), with the sensitivity 25%, specificity 45%, and positive predictive value of just 0.1%. A third trial (BAG-Recall) had limited information of this type (it also found no difference between BIS-guided anaesthesia and alternative groups), but the supplementary data appear to suggest the BIS remained <60 in 12 of 27 patients who experienced awareness.

NICE did not analyse the data in this way. In using the trial data in this manner, we have assumed (as did the trial investigators) that a BIS value of >60 is always indicative of awareness during anaesthesia, regardless of how brief this period is. It is in fact not known what exactly the BIS criteria are that suggest awareness (nor does NICE guidance help on this point). Is it the highest BIS in a certain time interval, or the average value, or a certain percentage increase over time, etc.? In other words, should an anaesthetist be concerned during an anaesthetic if the BIS value is 40 for many hours but jumps to 75 for just 10 s? Or much more concerned in a situation where the BIS value is steady at 61 for 30 min? Or are these situations equivalent? We also do not know if in these studies the anaesthetist (or anaesthetic agent) acted sufficiently promptly when the monitor indicated that the risk of awareness was high.19

To complicate matters, BIS appears to be ‘blind’ to several anaesthetic agents. Nitrous oxide is very well established to add to the effect of other volatile agents. Yet, the BIS value is unchanged (indeed, in one study, removing nitrous oxide caused BIS paradoxically to decline).20 21 Ketamine is popular with some anaesthetists, especially for emergency surgery,22 but does not influence (or can even paradoxically increase) BIS values.23 24

Problems in applying the NICE guidance into practice

Even those enthusiastic about EEG-based monitoring may find the NICE guidance vague and difficult to apply. NICE states that these monitors are ‘options’ in patients deemed
to be at ‘high risk’ of awareness during anaesthesia. Anaesthesiologists have long known that these monitors are options, so this is nothing new, but what they really need to know is how these monitors compare with other available options (other long-established options include end-tidal monitoring of anaesthetic vapour, or the isolated forearm technique). Indeed, a very recent, large (21,000 patients) trial has reported no difference in the incidence of accidental awareness during anaesthesia between a BIS-guided anaesthesia protocol vs one guided by end-tidal monitoring alone.25

NICE specifies patients at ‘high risk’ of accidental awareness during anaesthesia to be: patients with high opiate or high alcohol use, patients with airway problems, patients with previous experience of accidental awareness during anaesthesia, and those in whom neuromuscular blocking agents are used. Older patients and those with comorbidities are also judged at higher risk of accidental awareness during anaesthesia because their haemodynamic instability often results in a lower dose of anaesthetic administered. Although plausible, it is not known whether these groups are in fact at high risk, or what that relative magnitude of risk is. It is not clear what age group is to be regarded as ‘older’. Some readers may be surprised by the omission of obstetric and cardiac surgical patients from this explicit list as these groups are traditionally considered high risk.

The role of evidence

Perhaps the most intellectually troubling statements within the NICE guidance concern the role of evidence in decision-making. The scientific method involves rigorously adopting equipose to a hypothesis and constructing experiments that seek to disprove the initial prejudice. The well-established emphasis on evidence-based medicine means that practitioners are urged only to adopt those treatments or diagnostic tools which are supported by high levels of evidence.26 This seems inconsistent with NICE’s statement:

… the Committee considered that the current uncertainty in the evidence base does not justify a potentially long delay in the uptake of what is likely to be a beneficial technology.

At worst, this statement might be read as an abandonment of the need for evidence. As if to underline this, it is notable that the evidence for Narcotrend and Entropy monitors is reported by the Technology Report as almost absent, yet the guidance explicitly gives these monitors an equal strength of recommendations. If evidence is what really matters, then why regard these as equivalent? Some readers may be surprised at such reasoning from an organization created to promote the best clinical practice based on evidence. NICE is an influential organization and implementation of its guidance is one metric on which NHS Trusts are judged in terms of performance. NICE recommendations are also likely to influence research funders. NICE’s statement above may risk discouraging the much needed work to answer some of the questions quite correctly raised by the Technology Assessment Report. A statement more consistent with, and encouraging of, the scientific method might have been:

…the Committee considered that the current uncertainty in the evidence base does not justify further research into both the scientific basis and clinical utility of these devices so that we can better determine whether uptake of technology (that some believe beneficial) is appropriate.

While welcoming the interest of NICE in this technology, both the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland (see: http://www.rcoa.ac.uk/news-and-bulletin/rcoa-news-and-statements/nice-recommends-depth-of-anaesthesia-monitors) emphasized the overriding need for specific research (including the result of a current national audit on accidental awareness during anaesthesia)7 8 27 before the use of these monitors can be meaningfully incorporated into any clinical guidelines.

This is not the first time that NICE guidance will have proved to be controversial among anaesthetists: both the guidance on the use of ultrasound in central venous cannulation and oesophageal Doppler monitoring to guide fluid therapy have been strongly questioned.28–30 Among responses has been the suggestion that failure to heed the guidance should result in referral of the practitioner to the General Medical Council.31 There is also a common requirement for Trusts to confirm to commissioners that they are complying with NICE recommendations, or explain why they are not (see: http://www.institute.nhs.uk/commissioning/pct_portal/cquin.html). Clearly, NICE statements are taken very seriously by both readers and regulators.

Recent evidence indicates that EEG-based DOA monitors are only used by a very small fraction of anaesthetists, with one-third of hospitals having no such monitors and fewer than 2% of anaesthetists using such monitors routinely.7 8 For the current NICE guidance to be implemented would require a dramatic change in practice across the UK. The noticeable inconsistencies between the conclusions of the Technology Assessment and NICE guidance reports may not be sufficiently persuasive to achieve that change.

We are therefore left with a situation where current enthusiasts of EEG-based monitoring will likely use the NICE guidance to justify their decision to use EEG-based DOA monitoring, while those of the opposite view will use the Technology Report to justify not using it. Perhaps most importantly, this NICE guidance should not mislead patients, politicians, or planners into the erroneous belief that we currently understand the problem of awareness during anaesthesia, or that we have a monitor which reliably tells an anaesthetist whether the patient is anaesthetized. It is the probability of unconsciousness that matters and this we do not know from any of the available monitors.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.
Declarations of interest

J.J.P. is the Clinical Lead and T.M.C. is the Advisor to the Fifth National Audit Project on Accidental Awareness during General Anaesthesia, of the Royal College of Anaesthetists and Association of Anaesthetists of Great Britain and Ireland. The authors contributed to the Royal College’s feedback to the draft NICE Guidance, which included some of the points raised in this article. The views expressed are their own, and not that of the NAP5 Project or of the Royal College of Anaesthetists or of the Association of Anaesthetists of Great Britain and Ireland. Although much of the commentary above focuses on the bispectral index monitor, this is for no other reason than (as the NICE Guidance and Technology Report state) because most of the existing research concerns this monitor.

References

7. Pandit JJ, Cook TM, Jonker WR, O’Sullivan E. A national survey of anaesthetists (NAPS Baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the United Kingdom. Anaesthesia, in press