In the main findings from the 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia (AAGA), presented in this issue of the British Journal of Anaesthesia, Pandit and colleagues\(^1\) report the overall incidence of AAGA in the UK to be 1:19,600. The denominator is the estimated 2,766,600 general anaesthetics administered in the UK during the 12 month catchment period, and the numerator the 141 patient self-reports of AAGA adjudicated to be certain, probable, or possible. Other estimates of incidence are provided, reflecting more stringent or relaxed definitions and evidentiary criteria for AAGA—but it is the value of 1:19,600 that the authors most emphasize, and that is likely to be the headline result as NAP5 is quoted in both the medical and non-medical press.

K. O. Pryor* and H. C. Hemmings Jr
Department of Anesthesiology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA

* Corresponding author. E-mail: kap9009@med.cornell.edu
This finding is so vastly different from the incidence reported in multiple level 1 randomized controlled trials (RCTs) that it cannot be interpreted without critically addressing the discrepancy. Over the past decade, five large RCTs have addressed the efficacy of the bispectral index (BIS®) monitor in the prevention of AAGA, and in the process have provided an assessment of incidence that extends the findings from earlier prospective cohort studies. The B-Aware trial evaluated patients at high risk for AAGA, randomized to either BIS®-directed management or routine care, and found an overall incidence of 1:190. The B-Unaware and BAG-RECALL trials similarly evaluated high-risk patients, randomized to either BIS®-directed or anaesthetic concentration management, and reported overall incidence of AAGA to be 1:485 and 1:635, respectively. Zhang and colleagues reported an overall incidence of 1:275 in an unselected population, reporting an overall incidence of 1:190. The B-Unaware trials similarly evaluated high-risk patients, randomized to either BIS®-directed or anaesthetic concentration management, and reported overall incidence of AAGA to be 1:485 and 1:635, respectively. Zhang and colleagues reported an overall incidence of 1:275 in an unselected population, reporting an overall incidence of 1:190. The B-Aware and Zhang and colleagues’ reports were detected by quality control based on self-report during the post-anaesthesia visit, and instead are offered only at subsequent assessment points.

Conversely, success of goal-directed vigilance protocols evaluated by the RCTs likely skewed results towards an underestimate of incidence relative to an unselected population. Notably, NAP5 reports the incidence of AAGA to be 1:8600 in cardiothoracic surgery, a subpopulation that commonly possesses one or more criteria conferring increased risk. This is more than double the incidence observed in the broader unselected cohort, but nonetheless remains at least an order of magnitude lower than that reported in the RCTs.

The NAP5 cohort—which was unselected and subject to routine care without any intervention protocol—is not perfectly equivalent to any of these RCTs. The B-Aware, B-Unaware, and BAG-RECALL trials all selected patients at elevated risk for AAGA, which likely skewed results towards an overestimate of incidence relative to an unselected population. Notably, NAP5 reports the incidence of AAGA to be 1:8600 in cardiothoracic surgery, a subpopulation that commonly possesses one or more criteria conferring increased risk. This is more than double the incidence observed in the broader unselected cohort, but nonetheless remains at least an order of magnitude lower than that reported in the RCTs.

Conversely, success of goal-directed vigilance protocols evaluated by the RCTs likely skewed results towards an underestimate of incidence relative to a population for which no protocol was in place. The B-Aware and Zhang and colleagues trials both reported >75% reduction in AAGA with BIS®-directed management compared with routine care, while the B-Unaware, BAG-RECALL, and Michigan Awareness Control Study converged to demonstrate that anaesthetic concentration-based protocols and BIS®-based protocols were equally effective. NAP5 reports that depth of anaesthesia monitors such as the BIS® are used in only 2.8% of general anaesthetics in the UK, and so it is unlikely that goal-directed management based on these devices has a substantial influence on the incidence of AAGA. It is certainly possible that UK anaesthetists have altered practice in response to a decade of high-profile RCTs and commentaries, and have become more vigilant in maintaining anaesthetic concentrations. But it would seem unlikely that routine care has evolved to become so attentive that its efficacy is far superior to that of the rigorously controlled research protocols on which it is based.

The extent of these and other counteracting influences cannot be known with precision. But even allowing for the most generous and congruous estimates for the effects of cohort and practice differences on the incidence of AAGA, we believe the discrepancy between NAP5 and the level 1 RCTs conducted over the last decade to be at least an order of magnitude. This level of difference cannot be reconciled: the studies must be assessing different outcomes.

Whether a memory is detected depends significantly on how you test for it. The defining characteristic of NAP5 may not be its impressive sample size, but the methodology that it used to assess for AAGA. The RCTs discussed above, and a plurality of other prospective cohort studies, have utilized a detection paradigm termed the Brice protocol, in which patients are directly questioned about perioperative memory on three discrete occasions. The Brice protocol is weighted towards sensitivity: it provides contextual cues and prompts, focusing attention and decision-making on the question of interest, and facilitating conscious access to memory traces that might be weak or fragmented. This sensitivity might incur a cost in specificity, as cues have the potential to integrate false information into a memory, especially when it is weak and contextually difficult to discriminate from the cue. In contrast, NAP5 assessed AAGA through uncued patient self-reporting. This methodology is weighted towards specificity, but its sensitivity could be substantially compromised. It is a fundamental of neuropsychology that memories are less accessible to spontaneous recall than they are to cued recognition. But further, the NAP5 methodology then required a sequence of complex behavioural decisions by both the patient and anaesthetist, which could not be standardized, and which constitute unknowable variables.

Reports from the anaesthesia literature corroborate these concerns. Mashour and colleagues reported that only one-fifth of the AAGA cases identified by the Brice protocol in the Michigan Awareness Control Study were detected by quality assurance methods that rely on patient self-report or non-standardized cues provided during the post-anaesthesia visit. Mashour and colleagues earlier described a retrospective audit based on self-report during the post-anaesthesia visit, in which the incidence of AAGA was again one-fifth of what was identified at the same institution during the Michigan Awareness Control Study. Moerman and colleagues demonstrated over 20 yr ago that only one-third of patients with definite episodes of AAGA report the event to their anaesthetist, even when the event is highly negative. And several trials have shown that reports of AAGA, even when detected through the Brice protocol, might not emerge during the initial post-anaesthesia interview, and instead are offered only at subsequent assessment points.

Paradoxically, the apparent strength of NAP5 is also its Achilles heel. It is logistically impossible to use the Brice protocol to assess AAGA in a study of this ambitious scale. The results of NAP5 speak more to the difficulty of detecting AAGA in routine practice than they do to its absolute incidence.

The real strength that NAP5 derives from its sample size is its ability to provide an abundance of data on relative risk factors...
for AAGA. This is not without caution, as the self-report detection methodology used by NAP5 allows for a significant effect of reporting bias. Notably, we suspect that the reported incidence of 1:60 000 in paediatric patients—which in distinct contrast to prior cohort studies—is far lower than the adult population—in part reflects that this group is less likely to self-report AAGA than adult patients. But for many of the risk factors identified by NAP5, the effect size is sufficiently large to withstand even a substantial confound. Most emphatically, NAP5 reports the incidence of AAGA when neuromuscular blocking drugs are used to be more than 15 times that observed when they are not: neuromuscular block was associated with 131 of the 141 certain, probable, or possible AAGA events—but was used in only 46% of the denominator anaesthetics. We caution that the decision to use neuromuscular blocking drugs, based on surgical or patient requirements, will covary with other factors that modify risk, and it is unfortunate that NAP5 does not offer any multivariate analysis to discriminate the independence of effects. In the case of neuromuscular blocking drugs, we wonder whether the stronger independent effect might in fact be the benefit conferred by the use of a minimally stimulating supra-glottic airway device, which has been previously described.

NAP5 corroborates existing reports that the risk of AAGA is elevated in Caesarean section, cardiothoracic surgery, total i.v. anaesthesia, rapid sequence induction, and obese patients. But it also offers a number of relatively novel, if not definitive, insights. The authors note, for example, the overrepresentation of AAGA events that cannot be adequately explained, family or personal history of AAGA, and apparent heterogeneity in the distribution of risk across the volatile anaesthetics—and go on to suggest that a subset of patients possesses a genetic predisposition, an idea also recently addressed by Aranake and colleagues in a secondary analysis of the B-Unaware, BAG-RECALL, and Michigan Awareness Control Studies. NAP5 also reports a significantly disproportionate risk of AAGA associated with the use of thiopental, perhaps providing a clinical correlate for controlled neuropsychopharmacology studies demonstrating that thiopental has weak amnestic potency.

In NAP5, Pandit and colleagues have undertaken a project of truly remarkable scope. It is precisely because the study will generate such impact that we believe its flaws and limitations must be articulated and understood, but that does not remove our respect for its authors. NAP5 is by far the largest cohort study of AAGA ever undertaken, and in addition to the main findings, will likely generate substantial opportunity for secondary analyses. But we repeat our caution that NAP5 must not be read to indicate that the incidence of AAGA is less in the UK than it is in other nations, or that the incidence has decreased precipitously over the last decade. NAP5 demonstrates that the large-scale study of AAGA is extraordinarily difficult and highly methodologically nuanced. The greatest contribution of NAP5 may not be the story of the AAGA cases that were detected, but the uncomfortable knowledge that in routine practice, the vast majority of occurrences are never revealed.

Authors’ contributions

Declaration of interest
H.C.H. has served as a consultant for Cadence, CSL Behring, Sky-Pharma, and Becton-Dickinson, and has received research support from the US National Institutes of Health and Cadence. H.C.H. is an editor of the BJA and an editor of Anesthesiology. K.O.P. has nothing to declare.

Funding
Departmental funding only. No extramural funding.

References
10 Schiller D, Phelps EA. Does reconsolidation occur in humans? Front Behav Neuosci 2011; 5: 24
In the manuscript arising from the joint RCA and AAGBI 5th National Audit Project (NAP5) in this issue,1 Cook and colleagues consider the patient’s experience, human factors and medicolegal issues of awareness during anaesthesia. Their findings and conclusions are interesting for several reasons, and in this editorial, we will add our observations based on medicolegal experience of the phenomenon of accidental awareness.

Of note, the authors report an incidence of awareness that is considerably lower than previously reported.2 This may reflect the tendency of the Brice and colleagues’ interview2 to elicit episodes of awareness that were not captured by the NAP5 methodology; these uncaptured episodes are likely to be less severe and less impactful than those that came to light during the NAP5 window.

The incidence of awareness demonstrated in the NAP5 results is also interesting in its very clear indication that neuromuscular block hugely increases (by a factor of around 17) the chance of a self-reported, clinically relevant episode of awareness. Indeed, the increase in risk induced by the use of neuromuscular blocking agents appears greater than previously reported,4 and this may, again, represent a bias in the NAP5 methodology; these uncaptured episodes are more minor, and are elicited only via interview or are reported late. Of note, the absolute risk of awareness in paralysed patients is still lower than has been reported in studies using the Brice and colleagues’ interview; the likely reasons have been discussed above.

The great increase in the risk of awareness when neuromuscular block is used serves to emphasize that patients are traumatized not only by pain during awareness, but also by feelings of panic and helplessness, and that the reduction in the dose of anaesthetic required to prevent movement is not linked to any reduction in the dose required to prevent awareness. It is also apparent that non-painful awareness of paralysis can have long-term sequelae, including post-traumatic stress disorder, phobias, and depression. We are prompted to wonder whether our patients should be informed explicitly of the risk of awareness when we plan to use neuromuscular block. Of course, this might make for a rather uncomfortable preoperative visit, but we recommend including such information in a preoperative information leaflet and that anaesthetists should be prepared to discuss this subject openly at the patient’s request.

It is of note that the NAP5 results included many reports of awareness during sedation. To many anaesthetists, this might seem bizarre—surely, the provision of sedation does not include the guarantee of a lack of awareness, so why would patients complain? However, this may reflect a mismatch between patients’ and anaesthetists’ expectations; it is thus our obligation to be sure that patients are clear as to what they should expect from sedation—including the likely recall of some parts of their procedure, albeit usually non-painful.

The number of patients receiving sedation who reported paralysis is, again, surprising. However, it emphasizes that the formation of recallable memories is complex and difficult to predict. The inaccurate recollection of paralysis may help explain some criminal cases in which assault (usually sexual) has been reported during sedation, accompanied by a feeling of paralysis which rendered the patients unable to reject or verbally object to the alleged advances of their assailant.5 It may also reflect an issue with patients’ expectations, and clear explanation of the possibility of recall during sedation may reduce the risk of patients panicking while lightly sedated, and reporting imagined/perceived inability to move.

---

17 Pryor KO, Reinsel RA, Mehta M, Li Y, Wixted JT, Veselis RA. Visual P2–N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. Anesthesiology 2010; 113: 313–26
18 Veselis RA, Feshchenko VA, Reinsel RA, Dnistrian AM, Beattie B, Akhurst TJ. Thiopental and propofol affect different regions of the brain at similar pharmacologic effects. Anesth Analg 2004; 99: 399–408, table of contents