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Incidence of accidental awareness during general anaesthesia in obstetrics: a multi-centre, prospective cohort study

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Abstract:	General anaesthesia for obstetric surgery has distinct characteristics, which may contribute towards a higher risk of accidental awareness during general anaesthesia. The primary aim of this study was to investigate the incidence, experience and psychological implications of unintended conscious awareness during general anaesthesia in obstetric patients. From May 2017 to August 2018, 3115 consenting patients receiving general anaesthesia for obstetric surgery in 72 hospitals in England were recruited. Patients received three repetitions of standardised questioning over 30 days, with responses indicating memories during general anaesthesia verified using interviews and record interrogation. A total of 12 patients had certain/probable or possible awareness; an incidence of 1 in 256 (95%CI 1 in 149 – 1 in 500) for all obstetric surgery. The incidence was 1 in 212 (95%CI 1 in 122 – 1 in 417) for caesarean section surgery. Distressing experiences were reported by seven (58.3%) patients; paralysis by five (41.7%), paralysis with pain by two (16.7%) reported. Accidental awareness occurred during induction and emergence in nine (75%) patients. Factors associated with AAGA were high BMI (25-30 kg.m -2), low BMI (<18.5 kg.m -2), out-of-hours surgery and use of ketamine or thiopental for induction. Standardised psychological impact scores at 30 days were significantly higher in awareness patients (median (IQR [range]): 15 (2.75 – 52 [2 – 56]) than in patients without awareness: 3 (1 – 9 [0 – 64]; p = 0.010). Four patients had a provisional diagnosis of post-traumatic stress disorder. We conclude that direct postoperative questioning reveals high rates of accidental awareness during general anaesthesia for

	obstetric surgery, which has implications for anaesthetic practice, consent and follow-up.
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Additional Information:	
Question	**Response**
Was written informed consent obtained for the study (and not just for anaesthesia/surgery, etc.) from all participants (including where skills are assessed in manikin studies), as detailed in the Instructions for Authors?	Yes, I/we confirm all the above
Research Ethics Committee approval for the study has been obtained.	Yes, I/we confirm the above
Name of Research Ethics Committee as follow-up to "Research Ethics Committee approval for the study has been obtained."	London - Fulham Research Ethics Committee
Date approval granted as follow-up to "Research Ethics Committee approval for the study has been obtained."	20.1.17

Please confirm if any of the authors have competing interests data (e.g. personal, financial or academic). Please refer to the form at http://www.icmje.org/coi_disclosure.pdf for examples of potential competing interests (though we do not require you to complete that form).	The authors do not have any competing interests.
Is your manuscript a Clinical Trial?	Yes
Please confirm that your trial has been registered in a public trial registry by providing the name of the registry and the unique registration no./code. as follow-up to "Is your manuscript a Clinical Trial?"	ClinicalTrials.gov Identifier: NCT03100396

Cover letter - Re: ANAE.2020.01286 – Incidence of accidental awareness during general anaesthesia in obstetrics: a multi-centre, prospective cohort study

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Table 3 (the narrative descriptions) is too big to be published in the printed version. Can you supply a much-abbreviated version for publication and save the full table for an online supplementary version?

We were keen to have as much detail about the patient experience included in the primary paper, but appreciate the need for brevity in the printed version.

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Incidence of accidental awareness during general anaesthesia in obstetrics: a multi-centre, prospective cohort study

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Short title: Obstetric accidental awareness during general anaesthesia

Key words: Anaesthesia, general; Anaesthesia, obstetric; Accidental awareness during general anaesthesia; recall; post-traumatic stress disorder

Summary

General anaesthesia for obstetric surgery has distinct characteristics, which may contribute towards a higher risk of accidental awareness during general anaesthesia. The primary aim of this study was to investigate the incidence, experience and psychological implications of unintended conscious awareness during general anaesthesia in obstetric patients. From May 2017 to August 2018, 3115 consenting patients receiving general anaesthesia for obstetric surgery in 72 hospitals in England were recruited. Patients received three repetitions of standardised questioning over 30 days, with responses indicating memories during general anaesthesia verified using interviews and record interrogation. A total of 12 patients had certain/probable or possible awareness; an incidence of 1 in 256 (95%CI 1 in 149 – 1 in 500) for all obstetric surgery. The incidence was 1 in 212 (95%CI 1 in 122 – 1 in 417) for caesarean section surgery. Distressing experiences were reported by seven (58.3%) patients; paralysis by five (41.7%), paralysis with pain by two (16.7%) reported. Accidental awareness occurred during induction and emergence in nine (75%) patients. Factors associated with AAGA were high BMI (25-30 $kg.m^{-2}$), low BMI (<18.5 $kg.m^{-2}$), out-of-hours surgery and use of ketamine or thiopental for induction. Standardised psychological impact scores at 30 days were significantly higher in awareness patients (median (IQR [range]): 15 (2.75 – 52 [2 – 56]) than in patients without awareness: 3 (1 – 9 [0 – 64]; p = 0.010). Four patients had a provisional diagnosis of post-traumatic stress disorder. We conclude that direct postoperative questioning reveals high rates of accidental awareness during general anaesthesia for obstetric surgery, which has implications for anaesthetic practice, consent and follow-up.

Background

The incidence of accidental awareness during general anaesthesia (AAGA) may be influenced by patient characteristics, but also by the methods used to ascertain it. At one extreme, studies based on spontaneous reporting by patients find a very low incidence [1]. The largest study using this methodology – the 5th National Audit Project in the UK and Ireland (NAP5) – reported an average incidence of 1 in 19000, rising to 1 in 8000 when neuromuscular blocking (NMB) drugs are used [2]. In contrast, studies involving questioning patients directly about their memories of the intraoperative period (typically using a short series of questions termed the 'Brice' interview, which enquire about memories from immediately before, during and after general anaesthesia [3]) consistently report incidences of 1-2 per 1000 (averaging 1 in 600) [4-10]. Direct questioning tends to identify the highest incidence when the Brice questions are repeated three times over a month [9,11] (the 'thrice Brice' method).

The reasons for these differences in incidence are variously attributed. One interpretation is under-reporting, either because patients are distressed by AAGA and disinclined or not given the opportunity to make a report, or because patient reports are not considered credible or not escalated. Conversely, the Brice interview may not be sufficiently precise as to distinguish true AAGA from other memories and there is consensus that it is probably over-sensitive as a tool: its results require further consideration of the details of the case to establish whether a report represents AAGA or not [12].

One of the striking results of NAP5, was the relatively high incidence of AAGA in obstetric patients, at 1 in 1200, or 1 in 670 for caesarean section (CS) delivery. This latter estimate is notable for being very similar to the incidences cited using Brice interviews for non-obstetric surgery. For obstetric surgery, the incidence of AAGA detected by Brice interviews is between 1 in 110 and 1 in 152 but these estimates come from studies that are somewhat dated in terms of anaesthetic practice [13,14] and have not triangulated Brice responses against anaesthetic records and detailed patient reports in the way NAP5 did. Obstetric general anaesthesia for CS involves multiple risk factors for AAGA, including the nearly universal use of NMB drugs and rapid sequence induction, alongside a high incidence of difficult airway management and emergency or out of hours surgery [15]. It is unclear whether estimated differences in AAGA incidences between obstetric and non-obstetric surgery can be accounted for solely due to the combination of risk factors, or what the impact of detection methodology is [14], or whether other pregnancy-specific characteristics increase the risk further.

The aim of the Direct Reporting of Awareness in Maternity patients (DREAMY) study was to describe the epidemiology of AAGA and its consequences in adult patients undergoing obstetric surgery. The study aimed to describe the incidence (detected via direct questioning), nature of experiences, risk factors and psychological implications of AAGA. The specific hypothesis was that the incidence of AAGA detected with direct questioning would be higher in obstetric surgery compared with non-obstetric surgery, as was found with patient-initiated reporting in NAP5.

Methods

Research Ethics Committee (17/LO/0071) and Health Research Authority approvals were granted, alongside prospective registration of the trial aims (ClinicalTrials.gov Identifier: NCT03100396). Full details of the study protocol are available separately [16], and we provide salient details in brief below. Participants provided written informed consent for the study after their surgery.

Participants were aged 18 years or older, who underwent obstetric surgery under general anaesthesia in public healthcare sector hospitals in England. General anaesthesia was administered according to local institutional practice. Patients were excluded if the date of surgery was at <24 weeks gestation or ≥48 hours postpartum, or if surgery was for a non-obstetric indication during pregnancy. Only patients able to communicate in English were included.

A two-phase approach was initially used to assess whether AAGA had occurred. During the first phase, three repetitions of Brice screening interviews were conducted; the first within 24 hours following extubation, then between 24 and 48 hours, and at 30 days after surgery. During the second phase a verification semi-structured telephone interview was conducted by the study lead [PO] with all participants who indicated recall of events attributed to the period between ‘‘going to sleep” and ‘‘waking up”. This interview was conducted as soon as possible following patient reporting. Any specific description of events made in verification interviews, including the timing and nature of reported sensory perceptions, was investigated with clinical teams and case records to establish corroboration or refutation.

Patients reporting suspected intraoperative recall were followed up for 12 months, with further semi-structured telephone interviews and a self-report symptom measure for post-traumatic stress disorder (PTSD) administered at day 30, then at three, six, nine and 12 months – the PTSD Checklist for DSM-5 (PCL-5) [17]. In addition, patients were asked to report diagnoses and risk factors

associated with PTSD in the post-natal period, including postpartum depression [18]. A comparator sample of at least 300 patients with no intraoperative recall provided PCL-5 responses at day 30 only. All patients were offered best-practice supportive care in accordance with the NAP5 Anaesthesia Awareness Support Pack guidelines [19].

Researchers collected a detailed, standardised dataset from patients and their medical records, including characteristics of general anaesthesia and airway management, alongside workforce, timing and surgical parameters [16].

After all participants had completed the study, a panel of five authors [PO, SB, NL, JA, JP] reviewed all participant reports, interview transcripts and anaesthetic data. Assessors were blinded to hospital site and patient identifiers. Panel members collectively discussed each case, and their declared adjudication decisions were assessed using Fleiss's κ statistic to measure agreement. Detail, plausibility and consistency of reported experiences with the intra-operative process were considered. All cases were then reviewed a second time by the same group of assessors on a different date, to reach a final adjudication decision on each case, determined by majority. Reports were graded using the same schematic as for NAP5: as "certain/probable", "possible", "unlikely" or "none". Reports were classified accordingly to pre-declared structures, including sensory experience (the Michigan Awareness Classification Instrument), measure of psychological harm (a modified National Patient Safety Agency tool, revised for use in NAP5) and the phase of anaesthesia that AAGA was judged likely to have occurred during (i.e. induction, during maintenance of anaesthesia or emergence). Reports of dreaming during general anaesthesia, but with no evidence of AAGA, were graded according to whether specific memories of the dream content were present, and whether such content was pleasant, neutral or unpleasant.

The primary outcome was the proportion of obstetric patients reporting a composite of certain/probable and possible AAGA. This composite outcome reflects patient-centric reporting considerations and provides consistency with NAP5 [20].

A minimum sample size of 2015 patients was estimated, based an exact binomial test with power of 80% and alpha of 0.05 to detect an incidence of AAGA that was at least three times higher than a comparator baseline in non-obstetric surgical patients, taken as 0.15% [4,5,8,9,21]. Given expected imprecision in estimates for the binomial proportions with rare events, recruitment was planned to exceed this minimum estimate thereby improving confidence intervals for estimation of prevalence. The chi-square test, Fisher's exact test, an unpaired t-test, and an unpaired Mann–Whitney test were used for other comparisons between groups.

PTSD was evaluated using the PCL-5 instrument [17]. Any symptom rated as 'moderately' or higher was considered positive; patients were considered to have screened positive for PTSD if responses from a single follow up interval included at least: one 'positive' B (intrusion symptoms) item (questions 1-5), one C (avoidance symptoms) item (questions 6-7), two D (negative alterations of cognitions and mood) items (questions 8-14), two E (alterations in arousal and reactivity) items (questions 15-20).

Independent associations with AAGA and PTSD outcomes were explored using binary logistic regression and multiple imputation analyses. Suspected predictors of AAGA (age, urgency of surgery, ASA, body mass index (BMI) and timing of surgery) were entered into a stepwise regression model, alongside variables for anaesthetic characteristics (induction drugs, seniority of attending anaesthetist). PTSD associations were entered as self-declared maternal mental health conditions, which were defined as discrete binary variables (previous medical history of depression, anxiety disorder or PTSD). Ordinal variables were defined for neonate birth weight, and Likert scale responses on maternal perceptions of support from healthcare providers or family members. Pre-term neonates were defined as those born at <37 weeks gestation. The proportion of patients with missing data for any covariate included in the multivariable models ranged from 0% to 4.17%. Characteristics of the patients with full data were similar to those with missing data, hence a missing at random assumption was used to impute missing data. The regression model results are presented with the imputed data and as adjusted odds ratios.

Results

A total of 72 hospitals in England recruited patients to the study between May 2017 and August 2018. A total of 3115 patients provided written informed consent for inclusion following eligibility screening of 4969 patients (Figure 1). All 3115 patients completed at least one screening Brice interview and were included in the primary outcome analysis; 2937 (94.3%) completed two interviews and 1808 (58.0%) completed all three interviews. Table 1 shows the baseline characteristics of participants.

During at least one screening Brice interview, 266 (8.5%) patients reported memories they attributed to the period between "going to sleep" and "waking up" at the end of surgery (Figure 1 and Table 2). All these patients underwent further verification or interviews. The most commonly reported types of memories were of dreaming during anaesthesia, by 167 patients (62.8% of the 266); or hearing voices, by 96 patients (36.1%); or anxiety, by 31 patients (11.7%).

Verification of initial responses demonstrated the majority of memories, reported by 238 patients (89.4%), were evidently not AAGA events; instead representing memories of an unrelated dream (which may have occurred during or after general anaesthesia), planned awake extubation, misunderstanding of the Brice questions (e.g. reporting memories of the anaesthetist speaking during the initial process of induction of general anaesthesia) or reports that clearly did not represent intraoperative events (e.g. feeling initial application of cricoid pressure, or being unable to move lower limbs after a spinal neuraxial block but before general anaesthesia).

Of the remaining 28 (0.8%), patients with suspected AAGA, six patients were determined by the adjudicating panel as having unlikely AAGA; all these experiences consisted of reports that the patients considered to be intraoperative memories, but in which detail could not be established during verification interviews, or in which there was reasonable likelihood that the episode occurred outside the period of anaesthesia. A further four patients described an awareness experience during non-general anaesthetic circumstances: two experiences were associated with suspected total spinal anaesthesia, and two patients reported wakefulness during sedation whilst on the intensive care unit postoperatively. Finally, a further six patients described responses lacking detail in the Brice interviews that might represent AAGA, but further follow up was declined or verification of the Brice responses was not possible.

This left 12 patients whom the adjudication panel determined had certain/probable (seven) or possible (five) AAGA (Table 2); an estimated prevalence of 0.39% (95% CI 0.20 – 0.67) or 1 in 256

(95% CI 1 in 149 – 1 in 500). Grading of the AAGA events according to the Michigan Awareness Classification Instrument is provided in Table 3, alongside characteristics of the surgical and general anaesthesia procedures undertaken for each participant. This estimated prevalence of AAGA is significantly higher than reported in previous large cohort studies of AAGA in non-obstetric surgical patients (p = 0.010)[4,5] and is higher than following spontaneous reporting in obstetric by NAP5 (p = 0.001) [2].

In this cohort of 12 patients, AAGA was first detected on the initial screening interview at <24 hours postoperatively for 11 patients and at the second interview (24-48 hours postoperatively) for one patient. However, it was apparent during the verification interviews that this latter patient (ID 1), had recall of events following emergence but chose not to share these during her first Brice interview (abbreviated details of which are provided in Table 4; full details are in Supplementary materials Table S1). Of the 11 patients first detected at initial screening interview, two had already made a report of AAGA spontaneously to recovery nursing staff and a further five had spontaneously reported their experiences to relatives or partners. Thus, over half, seven of 12 (58.3%), in fact made a spontaneous report, and no additional patients were detected by repeating the Brice questionnaire. A total of nine patients completed 12 months of follow up; two patients withdrew from study follow up at 30 days following surgery, one withdrew at three months.

All patients with certain/probable or possible AAGA underwent CS (CS represented 2554 (81.9%) of all surgical procedures), and all received NMB drugs. The risk of AAGA after CS in our study is therefore 0.47% (95% CI 0.24 – 0.82) or 1 in 212 (95% CI 1 in 122 – 1 in 417). The degree of surgical urgency was Category 1 for only three (25.0%) patients, despite this category accounting for 52.0% of all CS surgery. One participant reported AAGA during an elective CS; the remainder were during Category 2 CS. Detailed analysis of baseline general anaesthesia characteristics and airway management techniques for the whole cohort are reported separately [15].

AAGA occurred during the dynamic phases of anaesthesia for nine (75%) patients; five at induction and four during emergence. Of the five patients reporting AAGA during induction a potentially insufficient hypnotic drug dose (<4.0mg.kg^{-1} thiopental or <2.0mg.kg^{-1} propofol respectively) was administered to two patients; one of which also involved management of an unpredicted difficult tracheal intubation. The remaining three patients reported tactile sensations that may have occurred due to anaesthetic or surgical manipulation before adequate anaesthetic depth was achieved.

Two patients experienced residual paralysis during emergence (16.7%); one of which occurred following administration of suxamethonium to a patient with previously undiagnosed abnormally reduced plasma cholinesterase function; the second being secondary to incompletely reversed neuromuscular blockade with rocuronium (neostigmine followed by sugammadex were administered sequentially during emergence). Neither patient received nerve stimulator monitoring before the AAGA event. The remaining two patients with emergence AAGA described less detailed accounts of events.

Two patients (16.7%) reported AAGA during the maintenance phase of anaesthesia. Both patients received suxamethonium as the NMB drug for tracheal intubation, but no further doses of NMB drug. One of these had low end-tidal anaesthetic agent concentrations (with no nitrous oxide) during the maintenance phase (estimated age-adjusted minimum alveolar median concentration of 0.7, high of 0.8 and low of 0.5); the other had a high BMI ($43 kg.m^{-2}$).

Conduct of anaesthesia differed in several respects between patients reporting AAGA and no AAGA (Figure 2). Propofol was under-represented in the AAGA group ($p = 0.045$), being used in only two patients (16.7%), compared with 1417 (45.5%) in the baseline group. Conversely, thiopental was used in nine patients (75.0%), compared with 1640 (52.9%) in the baseline group ($p = 0.121$). Opioid use during induction of GA was lower in the AAGA group, at four (33.3%) patients, but this was not significantly different ($p = 0.486$) when compared with the 1347 (43.4%) patients in the baseline group who received opioids. All AAGA patients received NMB drugs. Non-depolarising NMB use was similar in the AAGA group to the baseline, received by seven of 12 (58.3%), compared with 1620 of 3115 (52.0%) ($p = 0.661$). Five of the AAGA patients received suxamethonium, but no non-depolarising NMB drug (41.7%). Nerve stimulator use was influenced by the complications during emergence in the AAGA group, since monitoring was only applied after residual paralysis was clinically recognised (and AAGA had occurred) in two patients. Four of the remaining 12 AAGA patients (33.3%) received nerve stimulator monitoring, compared with use by 855 of all 3115 patients in the baseline cohort (27.4%). Use of nitrous oxide and sevoflurane was similar across the groups.

Ten patients with AAGA (83.3%) underwent surgery during the night shift (20:00 – 07:59); a far greater proportion compared with the non-AAGA cohort, in which only 1373 (44.4%) patients had surgery at night ($p = 0.007$). A total of five patients with AAGA (41.7%) had general anaesthesia after failed or inadequate neuraxial anaesthesia. This was not significantly different from the 861 (27.6%) in the non-AAGA group ($p = 0.278$). Processed electroencephalogram (pEEG) monitoring was low in

the baseline cohort, used on only 148 (4.7%) patients across only seven hospital sites. No AAGA patients received pEEG monitoring. There were no cases of AAGA attributed to wrong drug administration or syringe swap events. A consultant was the most senior anaesthetist present in theatre for only three (25.0%) of the AAGA patients (although one consultant attended only after the AAGA event had occurred), but this was not significantly different to the proportion in the baseline cohort of 1216 (39.0%; p = 0.32).

In the binary regression model, deviation from a healthy reference BMI of 18.5-25 $kg.m^{-2}$ was significantly associated with AAGA; specifically, BMI <18.5 (OR 18.1; 95% CI 1.0 – 318.9; p = 0.048) and BMI 25-30 (OR 10.8; 95% CI 1.23 – 93.8; p = 0.031). Although infrequently used as the primary induction drug overall, ketamine was over-represented in AAGA cases (OR 186; 95% CI 9.1 – 3824; p = 0.001). Thiopental use (OR 3.5; 95% CI 0.7 – 16.7) and start of general anaesthesia during a night shift (OR 3.3; 95% CI 0.61 – 18.2) were both significantly associated in univariate testing and had higher odds ratio of AAGA, but were not statistically significant (p = 0.122 and p = 0.163 respectively) in binary regression.

Table 4 provides abbreviated reports of each patient's experience of AAGA and a narrative description of individual psychological implications during the 12-month postoperative follow-up period (detailed reports for each patient are provided in Supplementary materials Table S1). Distressing AAGA experiences, in which fear, suffocation or a sense of impending death were reported, occurred in seven (58.3%) patients (Figure 3). Paralysis was reported by five (41.7%) patients, of whom two (16.7%) reported paralysis in conjunction with pain. A further two (16.7%) patients reported pain as the only feature of their AAGA experience. Four (33.3%) patients reported isolated auditory or tactile perceptions.

PCL-5 scores during postoperative follow up are provided in Figure 4 and 5. PCL-5 scores at 30 days postoperatively were significantly higher in the 12 certain/probable and possible AAGA patients (median (IQR [range]): 15 (2.75 – 52 [2 – 56]) than in the comparator cohort of 341 patients reporting no memories between "going to sleep" and "waking up" at the end of surgery: 3 (1 – 9 [0 – 64]; p = 0.010).

Four of the 12 AAGA patients (33.3%) met PCL-5 criteria for screening positive for PTSD (case IDs 1, 4, 6 and 12); all of whom were referred for psychological support or mental health team review. A fifth participant (case ID 3) was marginally below the criteria (having only one, rather than the required two, significant symptom scores in the intrusion cluster) but scored a maximum total of 36

points at 12 months following her surgery, above the threshold of 31-33 points indicative of probable PTSD.

AGAA was significantly associated with screening positive for PTSD (OR 32.4; 95% CI 1.6 – 662; p = 0.024); as was a diagnosis of postpartum depression (OR 25.4; 95% CI 2.4 – 274; p = 0.008). Other covariates in the regression model, including pre-term birth, history of depression, anxiety, PTSD and low birth weight, were not significant. Neither was self-perceived support from family or healthcare professionals, urgency of surgery or age. Four of the 341 (1.17%) patients in the non-AAGA comparator sample screened positive for PTSD, compared with four of the 12 patients (33.3%) in the AAGA group. The odds ratio of developing PTSD following AAGA, compared with non-AAGA controls was 42.1 (95% CI 8.9 – 199.1).

Of the 12 patients with certain/probable or possible AAGA, seven (58.3%) were graded ≥1 on NPSA scores, indicating at least mild anxiety about future anaesthesia or intrusive psychological symptoms. Five patients (41.7%) were graded as 2 or 3, indicating moderate to severe anxiety about future anaesthesia or related healthcare, with symptoms having some impact on daily living. Due to withdrawal from follow up, NPSA grades could not be allocated for two patients (16.7%) with possible AAGA.

Discussion

The main finding of the study is that the incidence of AAGA in obstetrics, using direct questioning, is almost three times higher than previously ascertained when relying on patient self-reports: 1 in 256 (95% CI 1 in 149 – 1 in 500) vs. 1 in 1200 (95% CI 1 in 714 – 1 in 2500) [2]. Both estimates are very much higher than the figure of 1 in 8000 reported for AAGA in the presence of NMB drugs for the general surgical population [2]. Almost two-thirds of the patients in our study described distressing experiences involving pain or paralysis during AAGA, and a third of patients with AAGA met screening criteria for PTSD during 12 months of postoperative follow-up. The odds ratio of developing post-natal PTSD after AAGA was very high, at 42, compared with non-AAGA controls.

Previously Paech et al. (also using the Brice interview and similar adjudication criteria, but without a detailed verification phase or any follow up) reported an even higher incidence of 1 in 152 after CS [14]. However, the use of thiopentone was very much higher in 2009 (83% in Paech's study vs. 52.9% in ours) and other changes in practice, perhaps informed by NAP5, may have reduced the incidence

of obstetric AAGA somewhat. Intriguingly, the use of depth of anaesthesia monitors in the Paech et al. study was high (32% vs. 4.7% in our study), and this perhaps reflects its limited utility in preventing AAGA [22]. This limitation may also be because the majority of AAGA cases arise in the dynamic phases of anaesthesia (induction and emergence) when the interpretation of depth of anaesthesia monitors can be difficult (or they are not used in these phases).

AAGA was a risk factor for PTSD, with AAGA patients having higher risk of developing PTSD and higher scores on the trauma symptomatology checklist. This finding extends previous research where nine of 16 (56.3%) people who had experienced AAGA met criteria for PTSD compared with zero of 10 non-AAGA controls [23]. These participants were recruited retrospectively and AAGA occurred a mean of 17.9 years before, so it is plausible that people with distressing AAGA experiences were over-represented. However, data from the B-Aware randomised trial by Leslie et al trial showed comparable risks with prospectively sampling [24]. AAGA cases were individually matched with non-AAGA controls. Five of seven AAGA cases (71%) met criteria for PTSD compared with three of 25 controls (12%). Our study confirms this serious risk of PTSD following AAGA in a prospective sample with a large control sample.

It is noteworthy that AAGA emerged as a strong additional risk because childbirth is itself a risk factor for PTSD [18]. Meta-analysis estimates that between 0.9 and 4.6% of women develop PTSD after childbirth [18]; our figure of 1.17% for the non-AAGA patients falls towards the lower end of this range, despite the additional complication of general anaesthesia and surgery occurring in our sample. Known predictors of PTSD such as low social support, infant complications, and history of mental health problems [18], were not significant covariates in our study, but there was an association between PTSD and post-natal depression [25,26].

This study confirms the high incidence of AAGA in obstetrics identified in NAP5 and which persists despite putative changes in practice. Some patient risk factors are immutable, such as the higher incidence of obesity and the difficult airway in obstetrics [15]. Some practices are constrained, such as the need to use NMBs. Other practice changes have occurred, which we reported on recently [15]. The use of opioids appears possibly at least a little protective for AAGA (Figure 2). It is plausible that opioids and prior neuraxial block attenuate pain responses, e.g. even ‘failed’ neuraxial technique might provide some partial analgesia and therefore serves to obtund the arousal effects of higher intensity surgical pain, which otherwise leads to AAGA. Opioids have traditionally been avoided in obstetric general anaesthesia due to concerns regarding neonatal respiratory depression, although this rationale is not supported by current evidence [27].

The over-representation of thiopentone in the AAGA cases is striking (Figure 2). Our data suggests the risk of AAGA is increased four-fold by thiopentone vs. propofol; and 26-fold with use of ketamine vs. propofol. It has recently been suggested that, based on EEG recordings, propofol induction maintains deeper anaesthesia than thiopental in pregnant women [28], so there may be a pharmacological basis to our observations. Regardless, it would now seem prudent to have a specific justification for the use of thiopentone or ketamine as induction agents in obstetrics, rather than consider these agents as default choices.

Our observation that night shift operations with predominantly trainee-led anaesthesia were a risk factor for AAGA presents a complex problem that requires careful consideration. Working pattern changes take time to implement and simply extending consultant hours or shifts may lead to other unintended consequences [29] or fail to improve outcomes.

We encountered two patients who reported 'AAGA' but in fact had endured the complication of a total spinal (they were not included as part of the AAGA cohort). This highlights the reality that apparently unconscious patients can be fully aware of surroundings (akin to neuromuscular blockade without anaesthesia). While the focus of attention in this emergency scenario should be on cardiorespiratory resuscitation, it is also essential to ensure hypnosis to avoid potential psychological sequelae. Current recommendations are that hypnotic drugs should be given only as soon as the clinical situation permits [30], but analysis of these patients' experiences suggests the two interventions – resuscitation and anaesthesia – should go hand in hand.

Other possibilities, apart from practice issues, should be considered for the markedly increased incidence of AAGA in obstetrics. One is that childbirth is a time of heightened attention to surrounding events, such that brief episodes of AAGA may be magnified in recall, much as are perhaps other details of the birthing experience [31]. These experiences in the general surgical population without the heightened attention, such as revealed using the isolated forearm technique [32], might be regarded as trivial (termed dysanaesthesia [33,34]; a brain state in which uncoupling of perception from sensation results in a neutral experience, leaving patients unconcerned with any awareness). In this regard, it is notable that in fact, the majority of our cases were also early self-reporters and that repeated Brice interviewing did not yield a higher estimated incidence. In other words, obstetric patients are more likely to make a report of AAGA, perhaps because of their heightened attention.

Another possibility is that the hormonal changes associated with pregnancy influence memory, recall or even sensitivity to general anaesthesia, such as to increase the likelihood of AAGA. Although

the minimum alveolar concentration (MAC) of volatile agents has been studied in animals and the first trimester of pregnancy in humans – and in both types of study shown in fact to be reduced as compared with non-pregnant females – it does not appear to have been studied in the third trimester. Uyema et al. report no effect of volatile anaesthetic sensitivity on electroencephalography in later stages of pregnancy, compared with non-pregnant matched controls undergoing general anaesthesia [35].

Our study clearly shows that simple administration of a Brice questionnaire alone is inadequate for accurate identification of AAGA, as it results in a misleadingly high incidence. The majority of 'positive Brice' responses were, in fact reports of dreaming or memories outside the period of anaesthesia, and not AAGA. Therefore, at best, the Brice questionnaire should be viewed as a preliminary screening tool, perhaps something which prompts recall in the patient's mind.

Yet given that the incidence we identified appears higher than many other obstetric GA complications [36], there is a case to suggest that Brice questioning (one administration) should become routine follow up after general anaesthesia in obstetrics.

Our data also have implications for seeking consent for general anaesthesia. The Montgomery ruling by the UK Supreme Court in 2015 concerned obstetric practice, and a complication that is arguably not greatly more frequent (1 in 136 [37]) than we now know from this study AAGA to be (1 in 254) [38]. Logically, it would seem incumbent upon anaesthetists to cite this risk of AAGA within the consent process for obstetric GA, as directed by the Supreme Court ruling.

Whilst some cases of AAGA may have been preventable by the practice changes discussed above, others occurred in the absence of obvious deficiency of general anaesthetic drug delivery. A previously undiagnosed suxamethonium apnoea episode triggered one patient's AAGA experience. Plasma pseudocholinesterase activity is known to fall rapidly during the first trimester and remain reduced for as long as into the immediate postpartum period [39]. This is of particular concern, given that nerve stimulator monitoring use was suboptimal in the baseline group [15].

It is important to acknowledge some methodological limitations to this study, some of which we have raised elsewhere [15,16], and many of which are common to all studies using the Brice interview. Administering this process involved two key steps – the patient interview followed by an adjudication process. The details of the latter can vary across studies [40], and therefore the rarity of AAGA events means that minor methodological inconsistencies within or between studies can influence the final result. We therefore employed the same adjudication structures as NAP5 and

introduced the kappa score, which at least confirmed consistency within our adjudication panel (Table 2).

Although 3115 patients completed the first Brice interview, only 1808 also completed the third; 42% were arguably 'lost to follow up' However, we used as our denominator the original 3115; i.e., our estimate of incidence is very conservative, and assumes that all these patients not followed up did not have AAGA memories. This is a safe assumption since we detected no new cases of AAGA with repeated Brice questioning. If even a small proportion of these lost-to-follow-up experienced AAGA, then our estimate of incidence would be very much higher than we report. Therefore, although we were disappointed not to follow up even more patients all the way to their third Brice interview, this does not affect our very striking result of a very high incidence of AAGA in obstetrics.

Conclusions

Action is needed to reduce the very high risk of AAGA in obstetrics that we report. National consensus guidelines would help ensure consistency of anaesthesia practice. With the incidence so high, and being associated with psychological harm in many patients, follow up and support for patients and staff is also necessary. The NAP5 psychological support pathway is a useful guide [19] but may need refinement for the obstetric setting. Attention should also focus on the process of seeking consent from a pregnant patient receiving general anaesthesia.

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Declaration of interest

JP was the clinical lead for the 5th National Audit Project (NAP5), is an elected Council member of the Royal College of Anaesthetists (RCOA) and Chair of the Safe Anaesthesia Liaison Group. DNL chairs the OAA Education subcommittee and is a senior editor for the International Journal of

Obstetric Anesthesia. RM holds senior and advisory positions in the Health Services Research Centre (RCOA) and NHS England. The views expressed are individual and not representative of those organisations. The authors declare that they have no other conflicts of interest.

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Tables

Characteristics	**All patients** (n = 3115)	**Patients reporting AAGA** (n = 12)
Patients		
Age; years	31.5 (6.1)	28.2 (5.7)
Weight; kg	70 (60.8 – 84 [38 – 188])	73.2 (64.0 – 78.2 [47 – 115])
BMI; $kg.m^{-2}$	26.3 (22.7 – 31.1 [14.4 – 80.4])	29.1 (25.7 – 30.4 [16.3 – 44.9])
BMI ≥30; n (%)	737 (23.7%)	4 (25%)
ASA PS ≥3; n (%)	504 (16.6%)	0
Parity		
1	1842 (59.1%)	7 (58.3%)
2	724 (23.2%)	3 (25%)
3	290 (9.3%)	2 (16.7%)
≥ 4	214 (6.9%)	0
Unknown	45 (1.4%)	0
Intraoperative		
Duration; minutes	60 (45 – 75 [6 – 390])	64.5 (58.5 – 75 [55 – 105])
Start time		
08:00 – 19:59	1732 (55.6%)	2 (16.7%)
20:00 – 07:59	1383 (44.4%)	10 (83.3%)
Surgical procedures		
CS	2554 (81.9%)	12 (100%)
EUA	214 (6.4%)	0
MROP	202 (5.3%)	0
Other	23 (4.1%)	0
Unknown	101 (3.2%)	0
Urgency of surgery		
Emergency / Category 1	1636 (52.5%)	3 (25.0%)
Urgent / Category 2	815 (26.1%)	8 (66.7%)
Expedited / Category 3	178 (5.7%)	0
Elective / Category 4	387 (12.4%)	1 (8.3%)
Unknown	101 (3.2%)	0
Estimated blood loss; n (%)		
<500ml	685 (22.0%)	4 (33.3%)
500-999ml	1192 (38.3%)	5 (41.7%)
1000 – 1999ml	740 (23.8%)	2 (16.7%)
≥2000ml	437 (14.0%)	1 (8.3%)
Unknown	61 (2.0%)	0
Experience of most senior attending anaesthetist; n (%)		
Consultant	1216 (39.0%)	3 (25.0%)
Staff grade or Associate Specialist	670 (21.5%)	2 (16.7%)
Higher/advanced trainee (ST5-7)	501 (16.1%)	3 (25.0%)
Intermediate trainee (ST3-4)	494 (15.9%)	4 (33.3%)
Junior trainee (CT1-2)	105 (3.4%)	0
Unknown	129 (4.1%)	0

Induction drug and dose; n (%), median (IQR [range]) $mg.kg^{-1}$		
Thiopental	1649 (52.9%) 6.3 (5.2 – 7.3 [1.3 – 14.6])	9 (75.0%) 6.4 (5.1 – 8 [3.9 – 10.6]
Propofol	1419 (45.5%) 2.8 (2.3 – 3.3 [0.4 – 6.9])	2 (16.7%) 1.7 & 2.0
Ketamine	28 (0.9%) 2.1 (1.7 – 3.2 [1.5 – 4])	1 (8.3%) 2.4

Table 1. Baseline patient and surgical characteristics for all patients and only patients reporting certain/probable AAGA. Values are mean (SD) or median (IQR [range]) or number (proportion). Weights were recorded at time of pregnancy booking appointment. ASA = American Society of Anesthesiologists' Physical Status score. CS = caesarean section; EUA = Exploration under anaesthesia; MROP = manual removal of placenta.

Adjudication panel outcome		**N**	**Prevalence (95% CI)**
AAGA	Total	12	1 in 256 (1 in 149 – 1 in 500)
	Certain/probable	7	1 in 455 (1 in 217 – 1 in 1111)
	Possible	5	1 in 625 (1 in 270 – 1 in 2000)
No AAGA	Unlikely	6	1 in 526 (1 in 238 – 1 in 1428)
	Awareness during non-GA circumstances	4	1 in 769 (1 in 303 – 1 in 3333)
	Awareness during total spinal anaesthesia	2	1 in 1666 (1 in 435 – 1 in 10,000)
	Awareness during postoperative sedation on intensive care unit	2	1 in 1666 (1 in 435 – 1 in 10,000)
	Dreaming	167	1 in 19 (95% CI 1 in 16 – 1 in 22)
	With content recall:	71*	1 in 44 (95% CI 1 in 35 – 1 in 56)
	Pleasant	20	28.2%
	Neutral	35	49.3%
	Unpleasant	8	11.2%
	Memories not during GA	71	N/A
Insufficient evidence	Unable to complete required verification assessment	6	N/A

Table 2. Adjudication outcomes of the likelihood of accidental awareness during general anaesthesia. A reported dream alone was not classified as awareness. *Eight patients reporting dreaming with content recall also described experiences consistent with AAGA; these patients were excluded from classification of dream emotional content.

ID	Adjudication outcome	Michigan Awareness Classification instrument	Phase of anaesthesia	Surgery	Induction drug; dose ($mg.kg^{-1}$) Opioid for induction NMB drug for tracheal intubation Add somewhere NMB moniitor	Maintenance drug Nitrous oxide for maintenance Minimum alveolar concentration (MAC); median [range] Additional NMB drug	NPSA	Summary of experience by the patient	κ
1	Certain/ probable	5D	Induction & maintenance	CS Cat 2	Thiopental (3.9) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 0.9 [0.7-1.0] No further NMB drug	3	A detailed recollection of the process of tracheal intubation and felt a painful initial surgical incision.	1.00
2	Certain/ probable	4D	Emergence	CS Cat 1	Thiopental (6.7) No opioid Suxamethonium	Sevoflurane + nitrous oxide MAC 0.9 [0.8 – 1.2] No further NMB drug	3	Residual paralysis during emergence. Confirmed suxamethonium apnoea.	1.00
3	Certain/ probable	5D	Maintenance	CS Cat 2	Thiopental (4.7) Alfentanil Suxamethonium	Sevoflurane + nitrous oxide MAC 1.4 [1.3 – 1.6] No further NMB drug	2	Felt surgical pain and hearing voices asking for surgical instruments.	1.00
4	Certain/ probable	4D	Emergence	CS Cat 2	Thiopental (10.6) Fentanyl Rocuronium	Sevoflurane + nitrous oxide MAC 1.1 [1 – 1.2] No further NMB drug	2	Residual paralysis during emergence, secondary to incomplete reversal of rocuronium.	1.00
5	Certain/ probable	2	Induction	CS Cat 1	Thiopental (8.0) No opioid	Sevoflurane + nitrous oxide	0	Painless sensation of the initial surgical incision.	1.00

					Suxamethonium	MAC 1.1 [1 – 1.2] Atracurium			
6	Certain/ probable	4	Induction	CS Cat 2	Propofol (1.7) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 1.1 [1.2 – 1.5] No further NMB drug	2	Felt unable to move and heard multiple voices; likely occurred during management of difficult airway.	1.00
7	Certain/ probable	4D	Induction	CS Cat 2	Thiopental (8.6) No opioid Suxamethonium	Isoflurane + nitrous oxide MAC 1.1 [0.9 – 1.2] Atracurium	1	Immediately after induction she experienced a dream-like sensation of falling into water, drowning and being unable to breath.	0.33
8	Possible	1	Other	CS Cat 4	Thiopental (5.9) No opioid Suxamethonium	Sevoflurane + nitrous oxide MAC 1.0 [0.8 – 1.2] Atracurium	0	Heard female voices holding a conversation, but unable to independently corroborate as occurring intraoperatively.	1.00
9	Possible	3D	Maintenance	CS Cat 2	Thiopental (5.1) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 0.8 [0.6 – 0.9] No further NMB drug	N/A	Reported possible pain sensation whilst expecting to be unconscious, but inconsistent details.	1.00
10	Possible	2	Emergence	CS Cat 1	Thiopental (6.4) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 1.0 [0.4 – 1.5] No further NMB drug	0	Possible dissociative anaesthesia; reporting sensation of being out of her body.	0.56
11	Possible	3D	Induction	CS Cat 2	Ketamine (2.4) Alfentanil Suxamethonium	Sevoflurane No nitrous oxide MAC 0.9 [0.7 – 1.0]	N/A	She felt a sting at the back of her throat shortly after induction. Possible dissociative anaesthesia; felt asleep but	0.56

						No further NMB drug		aware of what was happening, like in a dream.	
12	Possible	1	Emergence	CS Cat 2	Propofol (2.0) Fentanyl Rocuronium	Sevoflurane No nitrous oxide MAC 1.2 [1.1 – 1.3] No further NMB drug	1	Hearing voices at an unspecified time point after induction, with little other detail.	0.33

Table 3. Grading of accidental awareness during general anaesthesia events according to panel adjudication of likelihood and Michigan Awareness Classification Instrument. Class 1 indicates isolated auditory perceptions; class 2, tactile perceptions (e.g., perception of surgical manipulation or endotracheal tube); class 3, pain; class 4, paralysis (e.g., a feeling that one cannot move, speak, or breathe); and class 5, paralysis and pain. An additional designation of "D" is applied where the report described distress during the experience (e.g. fear, suffocation, sense of impending death, etc.). Surgical and anaesthetic of participant surgical, anaesthetic and accidental awareness are summarised. Modified National Patient Safety Agency (NPSA) classification, summarises the psychological impact on the patient as: 0 = No harm occurred. 1 = Resolved (or likely to resolve) with no or minimal professional intervention; no consequences for daily living, minimal or no continuing anxiety about future healthcare. 2 = Moderate anxiety about future anaesthesia or related healthcare; symptoms may have some impact on daily living; patient has sought or would likely benefit from professional intervention. 3 = Striking or long-term psychological effects that have required, or might benefit from, professional intervention or treatment; severe anxiety about future healthcare and/or impact on daily living; recurrent nightmares or adverse thoughts or ideations about events. 4 = Caused death. κ statistic indicates the measure of agreement of panel members on likelihood awareness classification, with a value of 1.0 representing unanimous agreement.

ID	Narrative description
1	**Patient:** 32 y/o; BMI 27 $kg.m^{-2}$. **Clinical scenario:** Failed epidural top-up for emergency CS. GA due to clinical urgency **Induction:** Thiopental 3.9$mg.kg^{-1}$ and Suxamethonium. **AAGA experience**: Detailed, unpleasant memories of uncontrollable muscle spasm, intubation and pain of first incision. **Follow-up:** Anxiety and panic attacks several weeks later. High PTSD scores for 12 months. Required antidepressant therapy and community mental health team input.
2	**Patient:** 30 y/o; BMI 28 $kg.m^{-2}$. **Clinical scenario:** GA for fetal cord prolapse **Induction:** Thiopental 6.7$mg.kg^{-1}$ and Suxamethonium. **AAGA experience**: Paralysis during emergence. Unable to breathe or move. Able to hear voices before being re-anaesthetised. **Follow-up:** Diagnosed with suxamethonium apnoea. PTSD scores initially low, rising at 6 months with anxiety symptoms. Patient required regular psychology consultations.
3	**Patient:** 24 y/o; BMI 43 $kg.m^{-2}$. **Clinical scenario:** GA for failed epidural top-up for emergency CS. **Induction:** Thiopental 4.7$mg.kg^{-1}$, 1mg alfentanil and Suxamethonium. **AAGA experience**: Detailed recall of voices and of sharp cutting pain across her abdomen. Unable to communicate. **Follow-up:** Low PTSD scores but required counselling after difficulty sleeping and nightmares of the experience.
4	**Patient:** 29 y/o; BMI 16 $kg.m^{-2}$. **Clinical scenario:** Intra-operative conversion to GA after inadequate neuraxial block. **Induction:** Thiopental 10.6$mg.kg^{-1}$, fentanyl 100mcg and rocuronium. **AAGA experience**: Recall of profound paralysis and throat obstruction at emergence. **Follow-up:** PTSD score high, reducing at 6 months.
5	**Patient:** 42 y/o; BMI 20 $kg.m^{-2}$. **Clinical scenario:** De novo GA due to clinical urgency. EBL >2L. **Induction:** Thiopental 8.0$mg.kg^{-1}$ and suxamethonium. **AAGA experience**: Painless sensation of a cut across the abdomen, unable to communicate. **Follow-up:** Very low PTSD scores
6	**Patient:** 27 y/o; BMI 45 $kg.m^{-2}$. **Clinical scenario:** GA following failed epidural top-up and unsuccessful spinal for emergency CS. **Induction:** Propofol 1.7$mg.kg^{-1}$ with suxamethonium. Difficult airway management with additional 100mg of propofol administered. **AAGA experience**: Recall of voices, but no distress or pain. **Follow-up:** High PTSD scores and subsequent mental health review. Diagnosed with postpartum depression
7	**Patient:** 29 y/o; BMI 25 $kg.m^{-2}$. **Clinical scenario:** GA following failed epidural top-up and unsuccessful spinal for emergency CS. **Induction:** Thiopental 8.6 $mg.kg^{-1}$ with suxamethonium.

	AAGA experience: Recall of a feeling of suffocation and inability to breathe together with a drowning sensation on induction. **Follow-up:** Low PTSD scores.
8	**Patient:** 31 y/o; BMI 30 $kg.m^{-2}$. **Clinical scenario:** Elective GA **Induction:** Thiopental 5.9$mg.kg^{-1}$ with suxamethonium. Two attempts at intubation. **AAGA experience**: Recall of female voices and specific conversations. **Follow-up:** Very low PTSD scores.
9	**Patient:** 19 y/o; BMI 29 $kg.m^{-2}$. **Clinical scenario:** Intra-operative conversion to GA after inadequate neuraxial block. **Induction:** Thiopental 5.1mg.kg-1 with suxamethonium. **AAGA experience**: Recall of pain in vagina and lower abdomen. Reported that she wasn't fully asleep. **Follow-up:** Patient withdrew from follow up
10	**Patient:** 29 y/o; BMI 27 $kg.m^{-2}$. **Clinical scenario:** De novo GA due to clinical urgency. **Induction:** Thiopental 6.4$mg.kg^{-1}$ with suxamethonium. **AAGA experience**: Describes a sensation of being out of her body, possible awareness during dissociative anaesthesia **Follow-up:** Patient withdrew from follow up.
11	**Patient:** 23 y/o; BMI 31 $kg.m^{-2}$. **Clinical scenario:** De novo GA due to clinical urgency. **Induction:** Ketamine 2.4$mg.kg^{-1}$, 1mg alfentanil and suxamethonium followed by 2mg midazolam after 15 minutes. **AAGA experience**: Describes a disturbing sensation of a sting at the back of the throat accompanied by what she describes as a 'déjà vu' experience. **Follow-up:** Patient withdrew from follow up.
12	**Patient:** 32 y/o; BMI 30 $kg.m^{-2}$. **Clinical scenario:** GA following failed epidural top-up **Induction:** Propofol 2.0mg.kg-1, fentanyl 50mcg and suxamethonium. **AAGA experience**: The patient recalled hearing voices and felt that she was partly awake during surgery **Follow-up:** High PTSD scores reducing over the course of 12 months.

Table 4. Abbreviated narrative reports of accidental awareness during general anaesthesia experiences and postoperative follow up psychological outcomes. Detailed reports of patient experiences and follow up are provided in Supplementary materials, Table S1. CS = caesarean section delivery.

Legends to figures

Figure 1. STROBE flowchart of participant recruitment and outcome adjudications. Outcomes are stratified as accidental awareness during general anaesthesia (AAGA) and "No AAGA", with "Unlikely AAGA" included in the latter category. A total of six patients had screening Brice interview responses indicating suspected awareness during general anaesthesia, however verification assessment was not able to be completed, hence insufficient evidence was available to adjudicate these reports using equivalent criteria to the remaining cases.

Figure 2. Comparison of the prevalence of characteristics in patients with certain/probable and possible accidental awareness during general anaesthesia (grey bars; n = 12) with baseline values for the whole cohort (dot and line; n = 3115). Thiopental use and general anaesthesia during the night shift (20:00-07:59) are over-represented in the accidental awareness group, whilst opioid use during induction of general anaesthesia is under-represented, for example. NMB drug = neuromuscular blocking drug. De novo GA indication general anaesthesia provided prior to the initial surgical incision (the remainder were conversions from neuraxial anaesthesia).

Figure 3. Hierarchical representation of Michigan Awareness Classifications for AAGA patients (n = 12), showing that immediate distress occurring exclusively in patients reporting pain and/or paralysis (affecting almost all patients reports those experiences). None of the four patients who reported auditory or tactile perceptions had distress.

Figure 4. PCL-5 scores at 30 days postoperatively for patients with certain/probable and possible accidental awareness during general anaesthesia (n = 12), compared with baseline (n = 341). Solid line = median; box = IQR; whisker = upper and lower adjacent values.

Figure 5. Psychological outcomes for each participant measured using PCL-5 scores. Each chart corresponds to a participant ID, with the Michigan Awareness Classification provided in parentheses ("D" designation is applied where the report described distress during the experience). The panels are arranged so that the higher Michigan classes are at the top, and the lower at the bottom. PCL-5 scores are grouped and labelled according to symptom clusters, as avoidance or intrusion symptoms etc. A PCL-5 score of between 31-33 is indicative of probable post-traumatic stress disorder.

Figure 1

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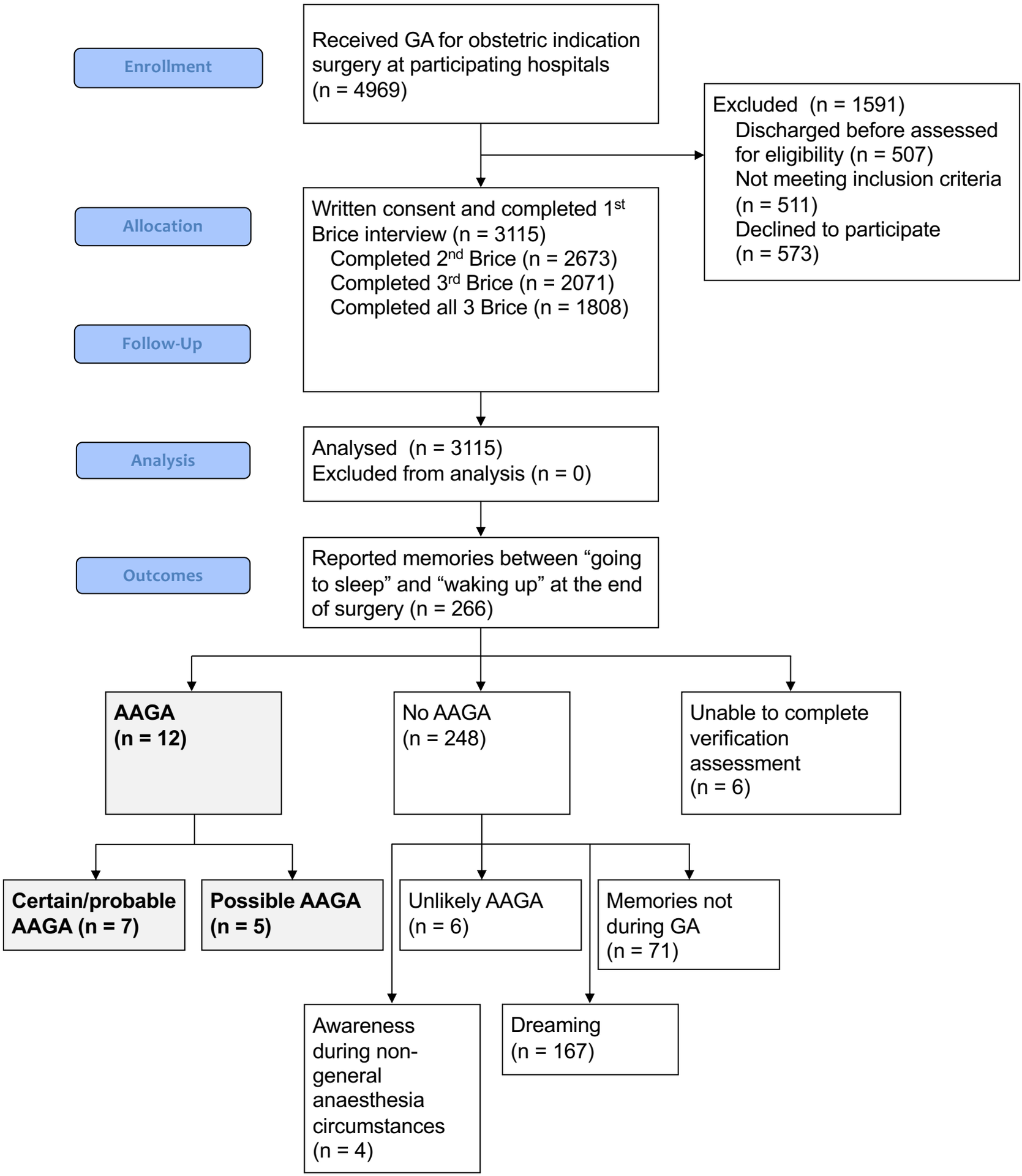

Figure 2

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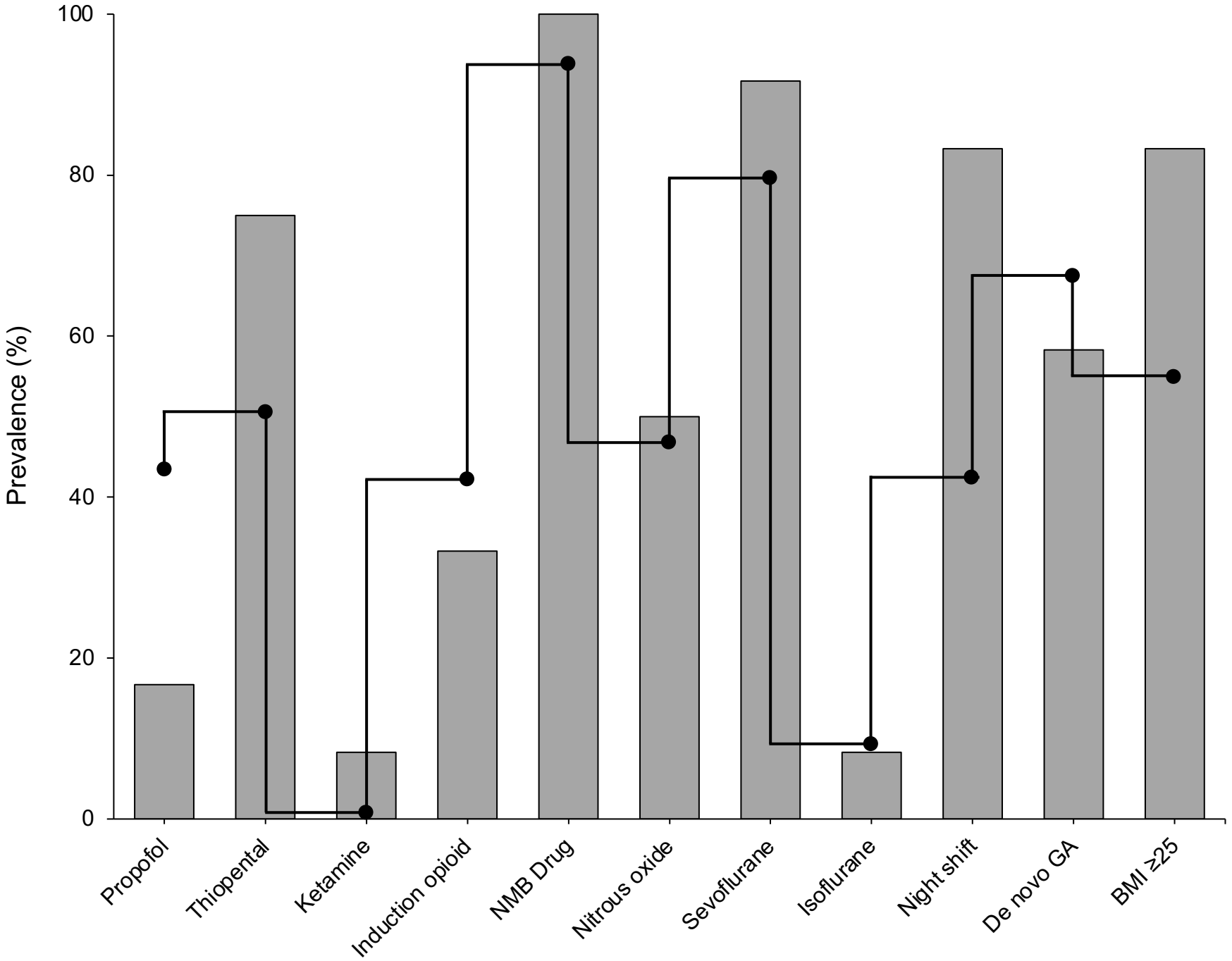

Figure 3

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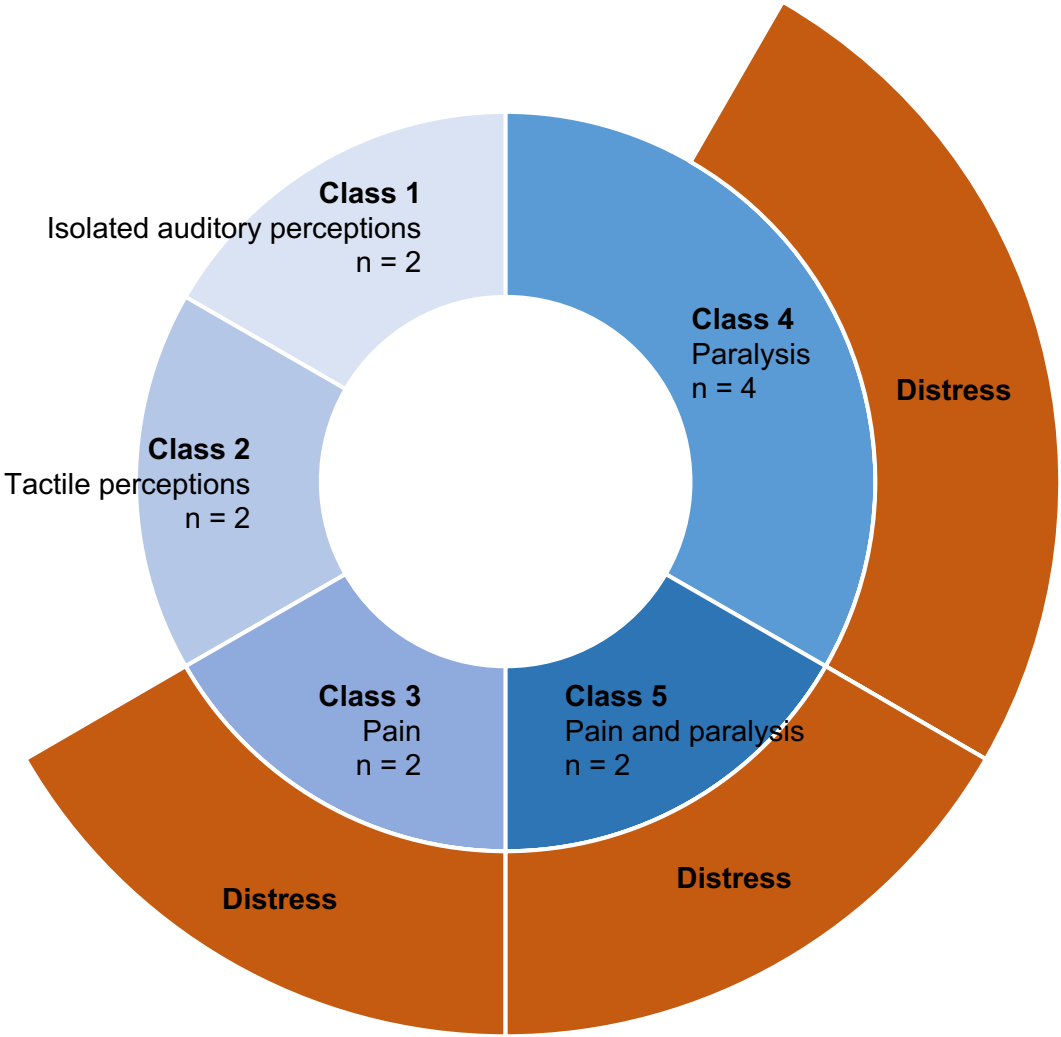

Figure 4

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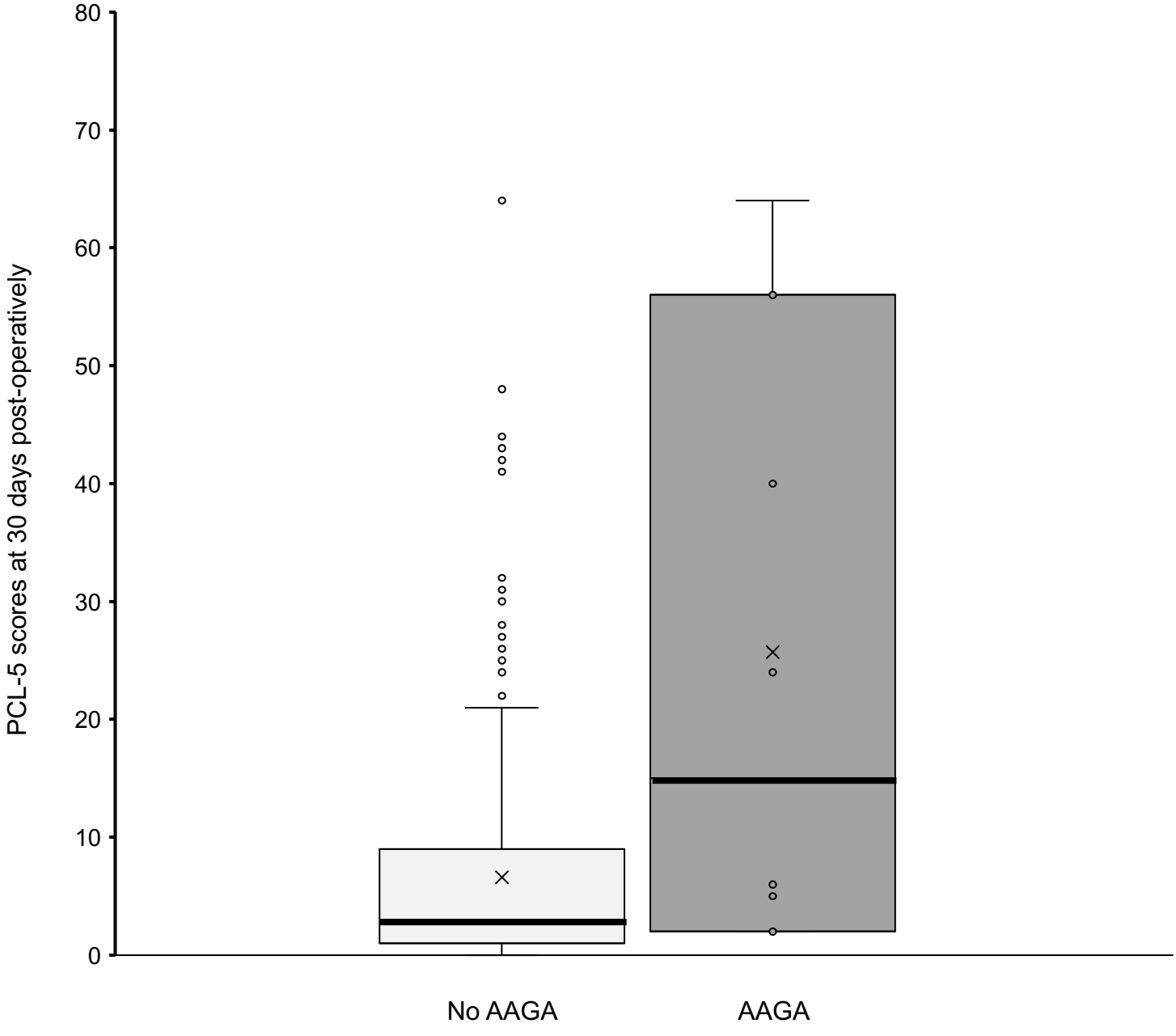
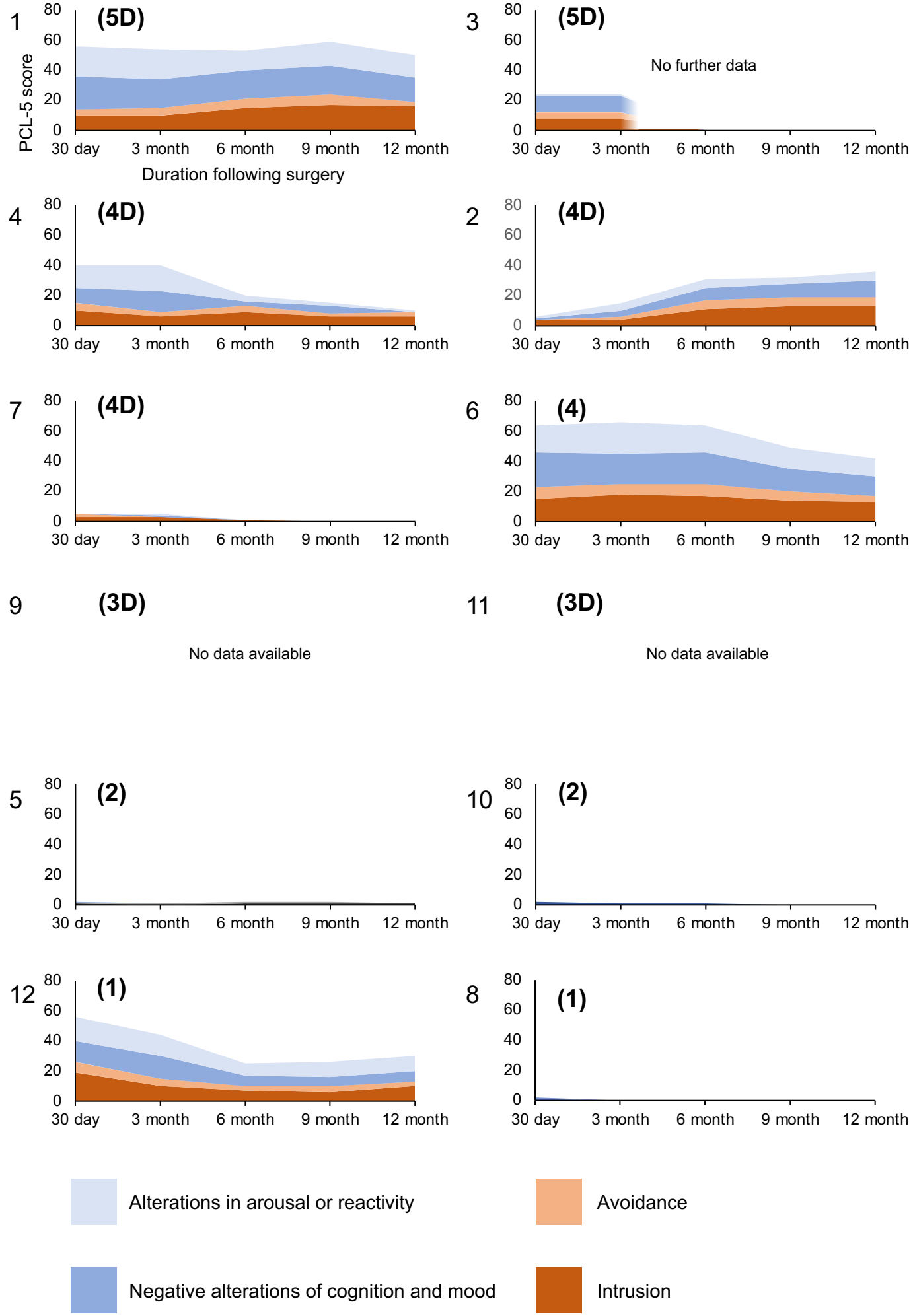


Figure 5



Supplementary materials

ID	Narrative description
1	32 year old woman with a BMI of 27 kg.m^2. The patient had never had a GA previously and had no significant medical history. Induction of anaesthesia began during the early morning (6am) for CS, with anaesthetic care provided by an intermediate trainee. An epidural bolus was administered, but there was inadequate sensory block on testing prior to the start of surgery. A de novo GA was chosen instead of spinal anaesthesia due to clinical urgency. Induction drugs provided were 300mg (3.9mg.kg^{-1}) thiopental and no opioids. She received suxamethonium for tracheal intubation. There was no airway management difficulty and surgery was otherwise uneventful. The patient had detailed unpleasant memories of intubation, including feeling her head and neck being involuntarily tilted backwards, uncontrollable muscle spasm (presumably following administration of suxamethonium) and sensation of a tube being passed into the back of her mouth then deep into her throat. She experienced sharp pain of the initial surgical incision and being unable to move or communicate. The episode seemed to her to last 5-10 minutes. The patient initially reported her experiences to her partner, who raised doubts about their credibility. As a consequence, she only reported the experience on her second Brice interview. Following her medical debrief the patient was referred for external counselling and follow up with her local maternity mental health team. Four weeks postpartum, she began to experience anxiety episodes and panic attacks. She had recurrent intrusive memories of her awareness experience triggered by non-threatening occurrences, including use of a throat spray leading to vivid recall of the intubation. Attendance within medical environments also led to physical avoidance symptoms. PTSD scores were high and remained relatively static throughout 12 months of follow up. She was prescribed an antidepressant and received community mental health team care. A local investigation concluded that inadvertent antibiotic administration during induction of anaesthesia was unlikely.
2	30 year old woman with a BMI of 28 kg.m^2. The patient had a history of previous GAs for ovarian cyst surgery with no reported complications. Emergency (Category 1) presentation for a CS in the evening (8pm) with an umbilical cord prolapse at 24 weeks gestation. Induction of GA was provided with 500mg (6.7mg.kg^{-1}) thiopental, no opioids and suxamethonium. A grade 2b direct laryngoscopy view was obtained, but tracheal intubation was not difficult. The neonate was delivered and taken to neonatal intensive care. The patient described residual paralysis during emergence. She recalled waking and not being able to breath or move, and hearing multiple voices using medical terminology. She did not feel any pain. She then remembers an abrupt loss of consciousness before waking again in the intensive care unit. A consultant anaesthetist was called after emergence, and use of a nerve stimulator only at this stage confirmed residual paralysis and a suspected diagnosis of suxamethonium apnoea; sevoflurane was re-administered. The patient was commenced on an intravenous propofol infusion (unclear if target controlled infusion mode or not) and transferred to the intensive care unit, where she was sedated for 15 hours, before being extubated uneventfully. Later serological testing confirmed an abnormal cholinesterase phenotype. The patients initially reported low PCL-5 scores, but these increased at 6 months, with mild anxiety symptoms and a recurrent sense of claustrophobia. She began regular psychologist consultations.
3	24 year old woman with a BMI 43 kg.m^2, history of fibromyalgia, bipolar disorder and a previous uneventful GA. A decision for CS was made overnight (12am) due to failure of labour progression and concerns regarding fetal distress. The patient had an existing epidural catheter but demonstrated persistent light touch sensation after the first epidural top up bolus, resolving after a second epidural dose. Surgery commenced but the patient felt pain during the initial surgical incision. Surgery was stopped immediately, and the anaesthesia converted to GA. Induction of GA was with 500mg (4.7 mg.kg^{-}1) thiopental, 1mg alfentanil and suxamethonium; intubation occurred with grade 1 laryngoscopy, anaesthesia lasted 80 minutes and surgery was otherwise uneventful. The patient had detailed chronological recall of initial loss of consciousness, later followed by hearing female voices asking for various surgical instruments. She felt a sharp, distressing, cutting pain across

	her abdomen, lasting approximately 10 mins, before she gradually lost consciousness again. She tried, but was unable, to open her eyes or communicate. The patient remembered these events immediately after waking but was initially unsure if the experience was normal. The patient had intrusive symptoms, difficulty sleeping and nightmares of the experience. After medical debriefing she was referred to counselling services. Her PCL-5 scores were otherwise generally low, and she withdrew from further follow up at 6 months.
4	29 year old woman with a BMI of 16 $kg.m^{2.}$ She reported a history of a previous uneventful GA. CS surgery took place overnight (2am), following conversion of failed regional anaesthesia to GA, due to breakthrough pain after the neonate was delivered. Induction was with 500mg (10.6 $mg.kg^{-}1$) thiopental and 100mcg fentanyl, with no airway difficulties. She received rocuronium as the NMDB for tracheal intubation. Both neostigmine and sugammadex were administered during emergence due to concern regarding inadequate reversal of neuromuscular blockade. No nerve stimulator was used. The patient had a background history of previous GAs for dental surgery and well controlled bipolar disorder, requiring no regular pharmacological therapy during pregnancy. The patient immediately and spontaneously reported recall of specific intra-operative events to recovery nursing staff. She remembered waking feeling profoundly paralysed, unable to breath, an obstruction in her throat and a sense that she was going to die. She felt the experience lasted only 1-2 minutes and later remembered being no longer paralysed, followed by a less distressing experience of the endotracheal tube being removed during emergence. She received multiple medical debrief consultations then later declined further offers of counselling. Her pre-term baby received ongoing paediatric input for possible development delay. Her PCL-5 scores were high, then reduced progressively from 6 months onwards. Of note she reported a previous history of parasomnias, including occasional nocturnal sleep paralysis.
5	42 year old woman with no prior medical history and BMI of 20 $kg.m^{2}$. She received a de novo GA (her first GA) for a Category 1 CS overnight (3am); induction with 450mg (8.0 $mg.kg^{-1}$) thiopental, no opioids and suxamethonium. There were no anaesthetic difficulties identified by the higher/advanced anaesthetic trainee, but there was extensive bleeding during surgery (EBL >2L) and a prolonged surgery time of 105 mins. The patient had memories, triggered by the first interview, of the induction phase of anaesthesia, during which she recalled feeling persistently drowsy but not unconscious. For a few seconds, occurring clearly before loss of consciousness, she recalled a painless sensation of being cut across her abdomen. She immediately tried to communicate, but was unable to do so, then couldn't feel anything else. She had no further recall and was not distressed. The patient had no adverse sequalae, did not require further psychological input after initial debriefing and had very low PCL-5 scores, despite risk factors for postpartum PTSD (including pre-term neonatal birth requiring neonatal intensive care unit admission). She had no fear regarding future anaesthesia.
6	27 year old woman with a high BMI (45 $kg.m^{2}$), history of depression and anxiety trait. No previous surgery or GA. Underwent a difficult anaesthetic for a Category 2 CS during the late evening (10pm) by an intermediate trainee. The initial epidural top-up failed to achieve an adequate sensory block, hence a spinal anaesthetic was attempted. The spinal anaesthetic was difficult, and the intrathecal space could not be identified. A GA was therefore administered with an induction dose of 200mg propofol (1.7 $mg.kg^{-1}$) and suxamethonium as the NMB drug. Unfortunately, airway management was challenging; the first attempt to intubate the tracheal was unsuccessful. Ventilation via bag-mask was inadequate, as were attempts to oxygenation via a second generation supraglottic airway device (Igel). A second attempt to intubate the trachea with a McGrath videolaryngoscope was subsequently successful. Pulse oxygen saturations fell to 30% at the lowest; there was no bradycardia or loss of cardiac output. The second intubation attempt was preceded by an additional dose of 100mg propofol, but no further NMB drug. After tracheal intubation and ventilation there was a rapid rise in oxygen saturations to 98%. The duration of airway management was reported as 3-4 minutes. There were no other intraoperative difficulties and surgical blood loss was minimal. The patient heard several voices speaking, but could remember any distinctive words or phrases spoken, nor could she identify or recognise the voices. She felt paralysed, but relaxed and calm. She

	didn't recall any pain or other physical sensations. She described the experience as dream-like, as though the voices were distant and a feeling of shadows or presence around her that she couldn't see. Although she initially denied pain or distress, she scored high on subsequent PCL-5 follow up and received mental health team review. She was diagnosed with postpartum depression for this pregnancy. She felt uneasy, but otherwise undeterred, at the prospect of future anaesthesia.
7	29 year old woman with no prior medical history and BMI of 25 $kg.m^2$. She underwent a GA at 6am with 500mg (8.6$mg.kg^{-1}$) thiopental, no opioids and suxamethonium; there were no anaesthetic or surgical complications. She had no prior surgical or GA history. The patient initially described her experience as being like an unpleasant dream, in which after administration of the induction drugs she felt immediately suffocated as she fell deeper into a pool of clear water. She reported being unable to breath, but described no sound, pain or other physical sensations. The experience was likened to drowning and lasted less than one minute. This experience was reported despite sufficient total induction dose of thiopental, although the exact timing and detail regarding sequence of NMB and induction drug were not clear. Despite the distressing experience, the patient had no adverse sequalae, did not require further psychological input after initial debriefing and had low PCL-5 scores. This description has time features and is consistent with descriptions of paralysis associated with suxamethonium.
8	31 year old woman, with a prior history of sexual assault as teenager, during which she was given a drug that reportedly rendered her temporarily immobile. She was subsequently diagnosed with PTSD. She had a history of multiple previous GAs, including her two previous LSCS, which had been conducted electively with GA due to maternal anxiety regarding lack of movement of her legs during spinal anaesthesia. She had a BMI of 30 $kg.m^2$. This LSCS was scheduled as elective, for the above reasons. Induction of GA commenced at 10am with consultant supervision. Thiopental 425mg (5.9$mg.kg^{-1}$) was administered, with no opioid and suxamethonium. The GA involved two intubation attempts: the first by a junior trainee and second by a consultant, during which the direct laryngoscopy view was grade 1. No further intravenous induction drug was administered. There were no other surgical or anaesthetic complications. The patient remembers hearing female voices only, including memories of specific conversations, which were not corroborated as having occurred intraoperatively. There was no indication that she felt paralysis, pain or any other physical sensation. Whilst surprised and confused by the experience, she denied any distress. She is convinced that what she remembers wasn't normal and that it did not align with her previous GA experiences, but was very accepting and didn't request any further support or intervention.
9	19 year old women with a BMI of 29 $kg.m^2$ and no prior medical history or previous GA. This patient had a poorly functioning epidural with unilateral block, with breakthrough contraction pain during labour. She was taken to theatre at 5am with failure to progress in labour for a category 2 CS. The epidural was topped up to provided regional anaesthesia and the neonate was safely delivered, despite a degree of surgical pain being experienced. This occurred at the insistence of the patient, who wanted to see her baby delivered whilst awake. General anaesthesia was then promptly provided, with a dose of 375mg thiopental (5.1 $mg.kg^{-1}$), no opioid and suxamethonium. The patient was fixated on pain experience during the whole labour and surgical process and found it difficult to focus on recall of specific elements during the operative phase. She however repeatedly referenced feeling as though she wasn't "fully asleep" and could still feel pain. She described two phases to her general anaesthesia; the first during induction, then a distinct second phase during which she thought everyone expected that she was asleep, but she was still conscious. She remembered feeling pain in her vagina and lower abdomen during this time - the same feeling pain as during the earlier, pre-GA, phase of surgery. The participant withdrew from subsequent follow up, hence no PCL-5 results were collected.
10	29 year old woman with a BMI of 27 $kg.m^2$ and no prior medical history or previous GA. Cat 1 de novo GA for clinical urgency at 12pm. 450mg (6.4 $mg.kg^{-1}$) thiopental was administered. She had no opioids and suxamethonium was used as the NMB drug for tracheal intubation.

	The patient lady gave slightly different accounts of reported intra-operative memories between interviews. All were described as being like dream-state, variably as though she were "flying in the sky" or that her "soul was out of her body". She was adjudicated to have awareness associated with possible dissociative anaesthesia.
11	23 year old woman with a raised BMI (31 $kg.m^2$), but no prior medical history (or previous GA) and received a de novo GA for clinical urgency overnight (at 1am). 200mg (2.4$mg.kg^{-1}$) ketamine,1mg alfentanil and suxamethonium were given by an associate specialist anaesthetist. The anaesthetist also provided 2mg of midazolam to the participant 15 minutes after induction of general anaesthesia. The patient provided an undetailed report but clearly described feeling a sting at the back of her throat. She considered the experience to be like "déjà vu", or as though events were happened to her in a dream state. She found the experience disturbing. The experience was considered to be possible awareness during dissociative anaesthesia. The participant withdrew from subsequent follow up, hence no PCL-5 scores were collected.
12	32 year old woman with a raised BMI (30 $kg.m^2$), no other medical history and no previous GAs. She underwent a conversion to GA for a failed regional epidural top up due to retained movement and sensation on her left side. Induction of GA occurred at 11pm, prior to surgical start and involved administration of propofol 200mg (2.0 $mg.kg^{-1}$), 50mcg fentanyl and rocuronium. There were no airway difficulties. Estimated blood loss during surgery was between 1-2L. The patient gave an account of possibly hearing voices at an unspecified time point after induction, with little other detail. She felt that she may have become partly awake during the surgery, but didn't remember any pain, any difficulty breathing or any further detail. She reported her experience immediately post-operatively to her husband, who was an anaesthetic registrar. The patient received detailed debrief from clinical team. She had high intrusion symptom cluster scoring on PCL-5, which reduced progressively throughout 12 months follow up. She had moderate anxiety about the prospect of future general anaesthesia.

Table S1. Full narrative reports of accidental awareness during general anaesthesia experiences and postoperative follow up psychological outcomes. CS = caesarean section delivery.