Purpose of review
There are several commercially available electroencephalogram-derived devices for monitoring anaesthesia depth. This article reviews all published studies describing their use in children; first assessing studies of performance in measuring anaesthesia depth in observational, physiological studies and then describing relevant outcome studies. There is also a brief discussion of why they might be useful, what physiological problems may arise and what the reader should be wary of in the methodology of these studies. The subject is approached from a clinical perspective.

Recent findings
There are several physiological studies suggesting that for older children the bispectral index, entropy, Narcotrend index, cerebral state index and A-line ARX index all change with induction of anaesthesia, and have reasonable correlations with doses of anaesthetic agent. There is consistent evidence that the performances are substantially poorer in infants. Some of these devices have been demonstrated to reduce anaesthesia drug consumption and hasten recovery in older children.

Summary
The bispectral index is the most widely studied, but at this stage there is no evidence to suggest any one device is substantially superior to any other. There may be a role emerging for their use in older children, but their use in infants cannot be supported.

Keywords
anaesthesia, anaesthesia depth, awareness, electroencephalogram, paediatrics

Introduction
In 2004 this journal published a review of bispectral index (BIS) monitoring in paediatric anaesthesia [1]. Since that review there have been a large number of publications investigating anaesthesia depth monitors. A small but increasing number of these have focused on children. The breadth of the topic has also widened as more devices have entered the market and as new areas of possible use have been explored (Table 1). Many of the published studies are designed to validate the indices, while only a few studies have assessed their utility or impact on important outcomes.

In this review I shall provide an update from the recent published literature. The review will be limited to electroencephalogram (EEG)-derived devices. There are other ways to assess anaesthetic depth [12], but the EEG has been the focus of the overwhelming majority of research and publications in recent years. The review will approach the topic from a clinical perspective.

Validation studies – do they work in children?
The question is more complex than it seems. First, what do we mean by ‘working’? What do we aim to achieve with these monitors? Simply put, an anaesthetic depth monitor ‘works’ if it monitors anaesthetic depth, but what exactly do we mean by ‘anaesthetic depth’ in children? [13]. As anaesthesia depth is a poorly defined and abstract concept, there are several ways that these monitors are ‘validated’ and no method of validation can claim to be perfect. These monitors (or indices) are usually validated by examining measures of association between the index and either steady-state anaesthetic concentration, or some clinical level of arousal. The measures of association may be correlation coefficients or the prediction coefficient ($P_k$) described by Smith (see Davidson [13]). The $P_k$ value gives the probability that two points on an ordinal scale are correctly ordered. In other words, a $P_k$ value of 1.0 means the monitor predicts the ranked levels
of outcome with 100% accuracy; a value of 0.5 means the monitor is no better than chance. Receiver operating characteristic curves may also be generated to summarize the specificity and sensitivity of an index to predict a dichotomous and clinically relevant state. Using these measures, there have been many studies that have examined the performance of these indices in adults. BIS, state entropy/response entropy and the Narcotrend index have been the most closely examined. In general, no particular index has been shown to be substantially superior in these studies.

If they ‘work’ in adults can we assume they work in children? These devices have all been derived from adult EEG data. In adults the difference between the EEG when awake and the EEG when anaesthetized is obvious (hence the large number of devices on the market). The EEG in awake children is well described and steadily changes with maturation, but our knowledge of the EEG during anaesthesia in children is scant and at this stage too limited to make any assumptions about extrapolating adult data to children. Therefore they ought to be assessed specifically in children.

### Bispectral index

Early studies indicated a fair correlation between BIS and sevoflurane concentration – most obviously in older children [14–16]. Another early study found a moderate correlation between BIS and responsiveness in children aged 3–13 years [17]. Two early studies by Brosius and Bannister [18,19] also demonstrated that in adolescents and younger children the BIS was lower in 5% sevoflurane compared to 0.5% sevoflurane, and that it rose during emergence. Interestingly, the BIS values at 5% sevoflurane were higher in the younger age group. More recently in a study involving 33 children aged 1–17 years undergoing a standard nonstimulating procedure, BIS steadily rose as sevolurane concentration fell in a way qualitatively similar to that described in adults [20]. Recent studies have also found good correlations between BIS and predicted propofol concentration [21,22].

Rodriguez et al. [23] determined the correlation between BIS and a scale of clinical signs of anaesthesia (CSA) in a group of 87 children aged 4 months to 14 years having a standard sevolurane anaesthetic. The CSA scale was determined by breathing pattern, pupillary reflex and size, and eye movement. BIS correlated with the CSA scale during induction and emergence, but there was considerable overlap of BIS values between different levels of CSA. BIS was a very poor predictor of response to incision. At emergence, the sensitivity of BIS to detect consciousness was between 81 and 71%, and the positive predictive value of BIS to predict consciousness was between 53 and 65%. The authors also described the effects of caudal blockade, age and midazolam premedication on awakening and preinduction BIS. These results were difficult to interpret given the multiple nonlinear comparisons and other confounding influences.

In contrast to Rodriguez et al. [23], several other recent papers have demonstrated an influence of neuraxial blockade on the BIS. The BIS falls with caudal block during general anaesthesia (in older children, but not in infants) [24,25] and falls during spinal anaesthesia in infants [26].

### Spectral entropy

In a pilot study, Davidson et al. [27] recorded spectral entropy and BIS in 23 children aged 1 month to 12 years having isoflurane and nitrous oxide. Values were noted during anaesthesia and pre/postawakening. Both BIS and response entropy/state entropy were low during anaesthesia and rose on awakening. There was a significant difference between values postawake and during anaesthesia for all age groups and monitors. There was no difference found between preawake and postawake for any index in infants less than 1 year old.

In a later study the same group also compared BIS and spectral entropy in 54 children having cardiac catheterization under sevolurane anaesthesia [28]. Children were divided into four age groups (0–1, 1–2, 2–4 and 4–12 years), and state entropy/response entropy and BIS recorded at

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### Table 1 What devices are available?

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Index</th>
<th>EEG parameters used</th>
<th>Publications in paediatric anaesthesia</th>
<th>References to describe function</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS</td>
<td>Bispectral index</td>
<td>Power–frequency ratio, bispectral analysis, burst suppression</td>
<td>+++</td>
<td>[2,3]</td>
</tr>
<tr>
<td>M-Entropy</td>
<td>State entropy and response</td>
<td>Degree of disorder in the EEG</td>
<td>+++</td>
<td>[4,5]</td>
</tr>
<tr>
<td>Narcotrend</td>
<td>Narcotrend index</td>
<td>Pattern recognition in the EEG</td>
<td>+++</td>
<td>[6,7]</td>
</tr>
<tr>
<td>AEP/2</td>
<td>AAI-1.6</td>
<td>Mid-latency auditory evoked</td>
<td>+</td>
<td>[8]</td>
</tr>
<tr>
<td>Cerebral State Monitor</td>
<td>Cerebral state index</td>
<td>Spectral analysis using fuzzy logic</td>
<td>–</td>
<td>[9]</td>
</tr>
<tr>
<td>PSA4000 or SEDline</td>
<td>Patient state index</td>
<td>Power, frequency, phase, coherence between different regions</td>
<td>–</td>
<td>[10]</td>
</tr>
<tr>
<td>SNAP II</td>
<td>SNAP II index</td>
<td>Both low and very high EEG frequencies</td>
<td>–</td>
<td>[11]</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram.
steady-state sevoflurane concentrations of 1.5, 2 and 2.5%, and prewakening. The BIS and entropy fell as sevoflurane concentration rose, with the relationships between sevoflurane and response entropy/state entropy or BIS being weakest in the 0–1 age group. There was no substantial difference in performance between BIS and response entropy or state entropy. For all indices the prewakening values were significantly lower in the 0–1-year-olds.

Klockars et al. [29] recently studied spectral entropy and BIS in 20 infants aged 1–12 months and 40 children aged 1–15 years. The children all received sevoflurane anaesthesia, and had BIS, response entropy, and modified Observer’s Assessment of Alertness/Sedation Scale scored on multiple occasions. There was large overlap between modified Observer’s Assessment of Alertness/Sedation Scale scores during emergence in both age groups (most in infants) and for all indices. On induction there was less overlap. The $P_k$ values across modified Observer’s Assessment of Alertness/Sedation Scale scores were similar in infants, but higher in children. $P_k$ values were also higher at induction compared to emergence. For all comparisons the $P_k$ values were similar when spectral entropy and BIS were compared. There was a reasonable correlation between sevoflurane concentration and spectral entropy and BIS for older children, but less clear correlation between sevoflurane and indices in infants.

**NarcoTrend index**

There are several recent studies evaluating the NarcoTrend as a measure of anaesthetic depth in children. Initially Weber et al. [30] studied 20 children aged 5 months to 6 years having sevoflurane anaesthesia. The $P_k$ values differentiating awake and anaesthesia was 1.0. There was also a significant negative correlation between sevoflurane concentration and the NarcoTrend index. In a further study, Weber et al. [31] enrolled 30 children and adults for ophthalmic surgery investigating the relationship between nonsteady-state desflurane and the NarcoTrend index. They found a correlation between desflurane and the NarcoTrend index in all age groups, and a $P_k$ of 1.0 differentiating awake and loss of consciousness. Similarly, in a third study, Weber et al. [32] enrolled 30 children aged 1–11 years and examined the NarcoTrend index and sevoflurane concentration. Results showed a strong correlation between NarcoTrend index and sevoflurane concentration, and $P_k$ values were 1.0 for awake versus loss of consciousness and 0.95 for anaesthetized versus return of consciousness.

Wallenborn et al. [33] compared BIS and the NarcoTrend index in 45 children aged 0–5 years divided into three age groups (0–6, 7–18 and 19–60 months). The $P_k$ for awake and anaesthetized was 1.0 in all age groups and for each index. During awakening at the end of surgery BIS performed a little better than the NarcoTrend index. For the same sevoflurane concentration, they found children aged 7–18 months had higher BIS values compared to older children, and in the 0–6 month age group awakening occurred at lower concentrations of sevoflurane and lower BIS values.

**A-line ARX index**

The A-line ARX index (AAI) generated from the A-line monitor extracts the mid-latency auditory evoked potentials with an autoregressive model. Weber et al. [34] studied 20 children undergoing ophthalmic surgery aged less than 7 years. The anaesthesia included midazolam/ketamine premedication, sevoflurane then remifentanil anaesthesia, with measures at awake, eye closure and laryngeal mask airway insertion. On induction the AAI fell, but overlapped between awake and anaesthetized measures. The $P_k$ for awake-eye close was 0.77 and awake-laryngeal mask airway insertion was 0.99. Addition of remifentanil made no difference to AAI. The AAI was also evaluated by Disma et al. [35] (see below). This version of the AAI has now been superseded by the AAI-1.6. The earlier AAI using only mid-latency auditory evoked potentials was found to be unable to differentiate deep levels of anaesthesia. Therefore the AAI-1.6 was developed, which incorporated passive EEG measures at deeper levels of anaesthesia.

The AAI-1.6 was evaluated in a pilot study by Ironfield and Davidson [36]. In this study the AAI-1.6 was compared to BIS in infants and older children under steady-state conditions of sevoflurane 1.5, 2 and 2.5%. The AAI-1.6 was a poor predictor of anaesthesia concentration in both age groups, although small numbers limited the applicability of the findings.

**Cerebral state index**

There has been a limited evaluation of the cerebral state index (CSI) in children. In an abstract by Bergonzi et al. [37], 10 children aged 4–14 years CSI and BIS were compared. Similar performances were observed. Disma et al. [35] compared the CIS to the AAI in 20 children aged from 8 months to 7 years. Both CSI and AAI decreased with induction and rose with emergence. There was also a strong correlation between CSI and sedation scores and AAI and sedation scores.

**Electroencephalogram and age**

In children older than 6 months, Lerman et al. [38] found no evidence for a change in minimum alveolar concentration (MAC) with age. In contrast, several studies have demonstrated that the BIS and spectral entropy at 1 MAC of sevoflurane (or desflurane) steadily falls from late infancy [28,33,39–41]. The reason for this finding is...
unclear. It may represent a fundamental difference in how anaesthetic agents affect the EEG during anaesthesia in children or it may represent an age-related change in relative potencies (arousal and antinociception). Either way this phenomenon has great significance for anaesthesia depth monitoring in children. Several studies mentioned in this review have reported some raw EEG parameters alongside the indices generated by the devices, but there are few good studies examining the confounding effect of age on the relationship between anaesthesia and the EEG [42].

What about infants?

While there is some evidence that the depth monitors ‘work’ in older children (at least as well as they work in adults), the findings in infants are very different. One early study found preawakening BIS values were lower in infants compared to older children [15]. In another early study, researchers found that BIS levels remained very low even when sevoflurane concentrations were titrated to very low values [43]. More recently, Kawaraguchi et al. [44] also reported lower BIS values in younger infants. Other recent studies have all confirmed low BIS values in infants prior to awakening [28,29,33], and poor correlations between anaesthetic concentration and index [28,29]. There is thus good evidence to suggest that all devices examined so far have substantially different performances in infants and that if they are used at all, they should be used very cautiously in this age group.

Why would I need one for paediatric anaesthesia?

In adult anaesthesia BIS has been shown to reduce awareness in high risk patients [45], and for BIS, the Narcotrend index, entropy and AAI several studies in adults have demonstrated reduced amount of anaesthetic drug used, reduced postoperative vomiting and shortened recovery. Often the margins of improvement are small, however, and some studies have found no evidence for improvement in these outcomes [46]. It is suggested, but not proven, that they may improve safety for procedural sedation. The practice of anaesthesia differs in children, and there are arguments for and against the need for depth monitors in children. The total quantity of drug used may be less and hence savings with decreased usage will be less. As children are discharged into their parents’ care there is a question of the need for street fitness, and indeed it is plausible that if rapid awakening is accompanied with delirium then it would result in increased levels and costs of nursing care in postanaesthesia care units. On the other hand, the pharmacology of anaesthetics changes with age. It is plausible that depth monitors could enhance accurate drug delivery, particularly for propofol infusion. Awareness occurs in children at least as frequently as it does in adults [47,48]. The causes and consequences of awareness are, however, not clearly defined in children. It is clear that BIS monitoring can reduce awareness in high-risk adult patients [45], although the differences in the nature of awareness preclude the automatic translation of this fact to children.

Do they improve outcomes in children?

The above is the crucial question in the use of anaesthesia depth monitors in children. To be even more precise, they should improve clinically important outcomes. There are more studies emerging which examine outcomes. Well-designed randomized controlled trials looking at relevant outcomes are the studies which should change clinical practice. The ‘validation studies’ should be best regarded as necessary steps to provide a basis for ethical outcome studies.

Initially studies have examined outcomes found to be improved in adult studies. In a well-designed randomized trial, Bannister et al. [43] demonstrated that BIS-guided anaesthesia resulted in shorter recovery times in older children (although actual discharge times were not reported). More recently, two studies in dental patients found that BIS-guided anaesthesia resulted in substantially reduced recovery and discharge times [49,50]. In another study, 30 children aged 1–11 years were randomized to Narcotrend index-guided and standard-care anaesthesia [51]. The Narcotrend index-guided children had lower propofol consumption, but there was no difference in emergence times. To great credit to the investigators, one of the few studies investigating the AAI-1.6 is an outcome study in which Weber et al. [52] enrolled 20 children aged 3–11 years having strabismus repair in an randomized controlled trial comparing AAI-1.6-guided remifentanil/propofol anaesthesia and standard practice. Propofol consumption and emergence times were shorter in the AEP/2 group (5 vs. 13 min).

Anaesthesia depth monitors may help inadvertent light anaesthesia. In paediatric anaesthesia a major complication of light anaesthesia is laryngospasm. Several studies have examined the possibility of these devices to predict ablation of airway reflexes. In an observational blinded study, Davidson [53] demonstrated no relationship between BIS and glottis closure after stimulation when sevoflurane was used, although paradoxically there was an excellent relationship between BIS and glottis closure when halothane was used. In a very well conducted study, Oberer et al. [54] examined laryngeal reflexes in children anaesthetized with either propofol or sevoflurane at BIS of 40 or 60. For apnoea and cord closure choice of agent or BIS value made no difference, while cough and expiration reflexes were less with lower BIS in the propofol group, but not the sevoflurane group.
In one study, BIS was a poor predictor of complications associated with laryngeal mask airway insertion, while another provided weak and indirect evidence suggesting BIS may be a predictor of complications at laryngeal mask airway removal [55,56].

**Which one is best for children?**

The studies evaluating indices as measures of anaesthesia depth have provided good evidence that BIS, entropy and the Narcotrend index have similar validation or performance characteristics in children compared to adults. In some studies performance has been directly compared and none has appeared to be substantially superior to another. As far as outcome studies, both BIS and the AAI-1.6 have been shown to reduce anaesthetic dose and speed recovery, although in children there have been no head-to-head studies comparing devices and outcomes. Head-to-head studies in adult patients have not consistently found one particular monitor to be superior in outcome measures. No monitors have been evaluated in their capacity to reduce awareness in children and none has been shown to reduce the other complications of light anaesthesia in children. At this stage no preference can be made with certainty between BIS, entropy, AAI-1.6, CIS and the Narcotrend index.

**Where else may they be used?**

There is a growing literature examining the application of anaesthesia depth monitors for procedural sedation and to guide sedation in the intensive care unit.

The need for adequate and safe sedation for distressing procedures in children is now well established. It has been suggested that anaesthesia depth monitors may have a role in improving safety and quality of sedation and recovery. Several studies have demonstrated a correlation between BIS and a variety of sedation scores during procedural sedation [57–65], and the topic has been recently reviewed in this journal [66]. The correlations have been weaker in infants [58] and some studies failed to find any correlation [67]. When using ketamine, no correlation was found [58,65]. Unfortunately many of these studies are difficult to interpret due to wide age ranges, wide variations in sedation cocktails and non-rigorous methods of analysis. There are no randomized studies designed to assess the impact on outcomes. Interestingly, some of these studies have demonstrated very low BIS values when propofol was used, implying the sedation was really general anaesthesia [68,69].

Several studies have evaluated the correlation between BIS and sedation scores in the intensive care unit. In general the BIS provides a moderate correlation with a variety of sedation scores [70–76]. In infants the correlations were not as good and BIS monitoring is not recommended [77,78]. Many of these correlation studies are of limited value due to the lack of any clear gold standard of sedation for comparison, heterogeneous samples and methodological flaws. There are no studies demonstrating improved outcome and consensus guidelines generated by UK Paediatric Intensive Care Society Sedation and Analgesia and Neuromuscular Blockade Working Group do not recommend routine use of anaesthesia depth monitors in the paediatric intensive care unit at this stage [79].

**What are the particular problems?**

There are several particular situations where anaesthesia depth monitors are not accurately associated with anaesthesia depth. These are not peculiar to paediatric anaesthesia and have been recently summarized elsewhere [80]. Some recent studies have indicated children are not exempt from these limitations.

**Effect of neuromuscular blockade**

The most important limitation is the effect for electromyography (EMG) on the scalp EEG. Most EMG occurs in frequencies higher than those used by most depth monitors, but some EMG signal will inevitably bleed down into the higher end of the frequencies where anaesthesia depth monitors operate. Epochs with large amounts of EMG may be rejected, but the EMG signal can never be completely eliminated. The major concern is that EMG signal can be abolished with neuromuscular blocking agents and the loss of his high-frequency signal may be interpreted as an increase in anaesthesia depth; neuromuscular blockers giving a false impression of deepening anaesthesia. There is now ample evidence that this is a real phenomenon [81–85]. There is no reason to think this issue would not be relevant to paediatric anaesthesia. In a recent abstract, Rigouzzo et al. [86] reported 49 children randomized to receive propofol or sevoflurane anaesthesia with remifentanil with or without atracurium. The atracurium groups had lower BIS but only in the propofol group and only with lower doses of propofol.

**Drug specificity**

Xenon, nitrous oxide, high-dose opioids and halothane will all produce sedation or loss of consciousness, without the usual expected changes in EEG derived indices. Simply stated, there are different ways to render a patient unconscious or decrease arousal, which are not always associated with the same changes in EEG activity.

In children the performance of BIS during halothane anaesthesia has been investigated in several studies. In a sample of children aged 2–15 years, Davidson and Czarnecki [87] found the BIS to be significantly higher at 1 MAC of halothane compared to 1 MAC of isoflurane, while the BIS at awakening was the same in both groups. A similar result was found comparing halothane
to sevoflurane [88] and desflurane [39,63]. These results are only partly explained by the greater antinociceptive properties of halothane compared to other volatile agents.

**Paradoxical reactions**

Several of the above studies have demonstrated that the BIS falls steadily as sevoflurane concentration rises, but for concentrations greater than 3% the opposite occurs. Constant et al. [89] designed a study to compare midazolam and clonidine as premedication to reduce agitation in children aged 2–10 years. BIS and EEG were also recorded. In both groups BIS fell with induction. The EEG changes consisted of increase in total power and a shift to lower frequencies (with the clonidine group having a greater shift to the lower frequencies). For induction all children received 8% sevoflurane and while the children were still receiving 8% sevoflurane the BIS fell to very low levels, but then paradoxically rose again. Similarly, Kim et al. [41] studied 81 children divided into age groups 0.5–2, 3–7 and 8–12 years. All received 2, 3 and 4% sevoflurane, and in all age groups BIS decreased from 2 to 3%, but paradoxically rose from 3 to 4% sevoflurane. The likely reason for this paradoxical rise is the increased activity seen in the EEG as sevoflurane concentrations approach levels associated with burst suppression.

**Critically reading the literature**

The literature surrounding anaesthesia depth monitor is quickly expanding. By the time this paper is published another dozen relevant papers will appear. Therefore it is worth highlighting common issues with these studies. Assessing the performance of these monitors is not a simple task. This is especially so in children where volunteers are nonexistent, measures of consciousness and memory are age specific, and assumptions of pharmacokinetic modelling may not be valid. The reader should be alerted to simple errors such as absurdly broad age groups, studies reporting multiple measures in the same child without checking or adjusting for low intra-subject variance and analyses that make unqualified assumptions that the indices are continuous or interval data (wherever possible they should be treated as ordinal scales). Many studies use Smith’s $P_k$. This is one of the better measures, but even it is not without problems; it should only be used with paired data and $P_k$ values from different study populations are not always comparable.

The most interesting problem is algorithm drift. Some of the devices have undergone several upgrades of the software or introduced new sensors. Software includes the specific algorithm and artefact rejection programs. All the software remains proprietary to some degree (entropy being the least ‘secret’). When the algorithms or artefact rejection software are proprietary it is impossible to know exactly how these new versions relate to the old versions. We simply cannot be sure that studies done with older versions of the software are relevant to newer versions of the software. To make matters worse some studies have not clearly indicated which versions were used.

**Conclusion**

In the last few years entropy, the Narcotrend index, AAI and CSI have all followed BIS in measuring anaesthesia depth in children. BIS remains the most widely studied; however, the number of studies is small and there are no head-to-head outcome studies. There is little, but increasing, evidence that these devices work in older children, and that in older children they may improve some outcomes. There is also increasing evidence that these devices do not work in infants. There is some way to go before the exact place of these devices is known in paediatric anaesthesia or which monitor is most suitable.

**References**

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 286–287).


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Correlation of the Bispectral Index

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