Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective, Single-Center Analysis

**BACKGROUND:** Intracranial pressure (ICP) is a clinically important variable after severe traumatic brain injury (TBI) and has been monitored, along with clinical outcome, for over 25 yr in Addenbrooke’s hospital, Cambridge, United Kingdom. This time period has also seen changes in management strategies with the implementation of protocolled specialist neurocritical care, expansion of neuromonitoring techniques, and adjustments of clinical treatment targets.

**OBJECTIVE:** To describe the changes in intracranial monitoring variables over the past 25 yr.

**METHODS:** Data from 1146 TBI patients requiring ICP monitoring were analyzed. Monitored variables included ICP, cerebral perfusion pressure (CPP), and the cerebral pressure reactivity index (PRx). Data were stratified into 5-yr epochs spanning the 25 yr from 1992 to 2017.

**RESULTS:** CPP increased sharply with specialist neurocritical care management ($P < 0.0001$) (introduction of a specific TBI management algorithm) before stabilizing from 2000 onwards. ICP decreased significantly over the 25 yr of monitoring from an average of 19 to 12 mmHg ($P < 0.0001$) but PRx remained unchanged. The mean number of ICP plateau waves and the number of patients developing refractory intracranial hypertension both decreased significantly. Mortality did not significantly change in the cohort (22%).

**CONCLUSION:** We demonstrate the evolving trends in neurophysiological monitoring over the past 25 yr from a single, academic neurocritical care unit. ICP and CPP were responsive to the introduction of an ICP/CPP protocol while PRx has remained unchanged.

**KEY WORDS:** Traumatic brain injury, Intracranial pressure, Cerebral hemodynamics, Autoregulation, Outcome

---

Because the management of severe traumatic brain injury (TBI) in the acute phase is focused on reducing further injury from insults such as raised intracranial pressure (ICP) or impaired cerebral perfusion pressure (CPP), ICP monitoring has become an important component in the management of TBI. Through the pioneering work of Guillaume and Janny, Lundberg, and Jennett et al in the middle of the 20th century, clinical ICP monitoring was promoted as a method to optimize the management after TBI. At Addenbrooke’s Hospital (Cambridge, UK), continuous, computer-supported (ie, all data were saved digitally for post-processing) intracranial monitoring was introduced in 1992 and thus has been running for over 25 yr.

Despite a paucity of positive randomized trials, the management of severe TBI has evolved significantly over the last 50 yr. While the first neurosciences intensive care units were opened in in 1932 in Johns Hopkins Hospital (USA) and in the National Hospital for Nervous Diseases (UK) in 1954, it was not until the 1980s and 1990s that the largest academic institutions were equipped with intensive care units to treat TBI patients. People pioneering computer-supported monitoring paved a way
to recognition of ICP as a complex and clinically relevant signal. In the UK, recognition of the importance of preventing cerebral hypoxia and hypotension led to several significant changes in TBI management. Initially, there was a transfer of care for TBI patients from the neurosurgical ward to a specialist neurosciences intensive care unit. Subsequently, there was a focus on ICP and CPP through a dedicated CPP/ICP management algorithm and multimodal brain monitoring. Furthermore, national major trauma units were established to facilitate rapid access to specialized care.

The primary aim of this study was to describe the time-related changes of intracranial physiology (as measured by ICP, CPP, and cerebrovascular pressure reactivity [PRx]) over the past 25-yr period in a single academic institution in relation to incremental changes in management strategies.

METHODS

Study Design and Setting

This study was conducted as a retrospective analysis of a prospectively maintained database cohort (1992-2017), in which high-frequency physiological monitoring data had been archived. Monitoring of brain modalities was conducted as a part of standard patient care and archived in an anonymized database of physiological monitoring. Data on age, injury severity, and clinical status were recorded at the time of monitoring on this database, and no attempt was made to re-access clinical records for additional information. Since all data were extracted from the hospital records and fully anonymized, no data on patient identifiers were available, and therefore formal patient or proxy consent and institutional ethics approval were not required.

Participants

TBI patients with a clinical need for intracranial pressure (ICP) monitoring and computerized signal recordings were included for analysis. A total of 1146 head-injured patients admitted to the Addenbrooke’s Hospital Neurocritical Care Unit between 1992 and 2017 were included. Inclusion criteria were as follows: TBI; computerized invasive monitoring of ICP and arterial blood pressure (ABP) for at least 12 h; admission Glasgow Coma Scale (GCS); and 6-mo mortality data available. Of the 1146 TBI patients with monitoring data, 1112 patients were included for subsequent analysis. Although data on total TBI admissions are not available over the 25 year period, during the period between 2002 and 2017, 2241 patients were admitted to the unit with TBI, of which 1100 had ICP monitors inserted. A total of 569 of the 1100 ICP monitored patients had computerized ICP monitoring (52%).

While some patients in the cohort would be categorized into the moderate TBI group on basis of initial GCS, these patients deteriorated and subsequently required invasive intracranial monitoring and therefore were included in the analysis. Patients were managed according to contemporaneous TBI guidelines. Between 1992 and 1993, patients were managed within the Department of Neurosurgery and general Intensive Care Unit if ventilatory or organ support was needed. A dedicated 12-bed Neurocritical Care Unit was opened in 1994 which was later expanded to 21 beds in 2010 followed by transformation to a major trauma unit and further expansion to 23 beds in 2011.

A protocol aimed at keeping CPP > 70 mmHg and ICP < 20 mmHg using step-wise medical and surgical management was implemented in 1994. In 2003, modifications to ICP and CPP targets were introduced (reduction of CPP target to CPP > 60 mmHg) followed by restricting hyperventilation (end-tidal pCO2 range adjusted from 4-4.5 to 4.5-5 kPa; Figure 1). Introduction of multimodal monitoring including microdialysis and brain tissue oxygenation (PbrO2) occurred in 2002 and 2004, respectively. Assessment of the PRx was a part of multimodal monitoring since 1996, however, it was included in clinical assessment (to assist with prognostication) of TBI in only 1999. Furthermore, since 2012, autoregulation-based CPP targets have been available to try to optimize management as a secondary parameter at the discretion of the clinician. In 2015, blood pressure zeroing was changed from the level of the right aurium to the level of foramen of Monro, as estimated by tragus level.

All patients were sedated, intubated, and ventilated. The step-wise ICP management included positioning and head elevation, prevention of hypotension, and hypoxia and maintenance of end-tidal pCO2 levels, sedation, muscle paralysis, ventriculostomy, osmotic agents, induced hypothermia, barbiturate coma, and decompensate cranioectomy. CPP was maintained at target levels using intravenous fluids, vasopressors, and inotropes. Tight glucose management was achieved with insulin sliding scale, with target blood glucose levels of between 6 and 8 mmol/L (108-144 mg/dl). Seizure management was achieved using phenytoin and levetiracetam as appropriate. Initial GCS was obtained for each patient pre sedation. Patients without point breakdown of GCS were included as data for patients before electronic medical records frequently had only total GCS score. Mortality was assessed at 6 mo post injury.

Data Acquisition

ICP was monitored with an intraparenchymal micro-sensor inserted into the frontal cortex (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, Massachusetts) and arterial blood pressure was monitored in the radial or femoral artery (Baxter Healthcare, Deerfield, Illinois) with a zero calibration at the level of the right aurium (1992-2015) and at the foramen of Monro (2015-2017). Between 1992 and 1996, data trends (1-min time averages) were collected with nonpropriety ICM software developed in-house and 1-min trends were stored.8 From 2002 to 2017, data were collected using ICM©, (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). PRx was monitored from 1996 onwards. PRx was calculated as the Pearson correlation of 30 consecutive 10-s average values of ABP and ICP. CPP was calculated as ABP-ICP. A 10-s average was used to reduce the influence of respiratory and pulse waveforms. A 300-s moving window was used to generate continuous PRx values.

For each patient, the mean values of ICP, CPP, and PRx were calculated for the duration of monitoring. Indicators of secondary insult were obtained using the percentage time with ICP above 20 mmHg, percentage time with CPP below 60 mmHg, and percentage time PRx > 0.25. Plateau waves were identified as an increase in ICP above 40 mmHg, associated with a significant decrease in CPP, for between 5 and 60 min. Severe refractory intracranial hypertension was defined here as an increase in ICP over 40 mmHg for at least 1 h.

Statistical Analyses

Overall time trends in physiological variables were investigated graphically by fitting a generalized additive model to the mean physiological variables vs date-time of monitoring. Means, counts, and proportions across 5-yr epochs (from 1992 to 2017) were analyzed with a 1-way ANOVA, negative binomial regression, and the chi-squared test.
After 1994, the specialist neurocritical care was opened and a specific ICP/CPP protocol was instituted. Modifications to monitoring parameter targets, and the addition of further neuromonitoring modalities have also occurred. ABP, arterial blood pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; NCCU, neurocritical care unit.

### TABLE. Patient Demographics; Long-Term Monitoring Trends After TBI

<table>
<thead>
<tr>
<th>Overall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1112</td>
</tr>
<tr>
<td>Age [years] (mean (sd))</td>
<td>37.96 (17.24)</td>
</tr>
<tr>
<td>Sex = male (%)</td>
<td>867 (78.0)</td>
</tr>
<tr>
<td>GCS ≤ 8 (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>275 (24.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>776 (69.8)</td>
</tr>
<tr>
<td>NA</td>
<td>61 (5.5)</td>
</tr>
<tr>
<td>Decompressive craniectomy (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>620 (55.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>267 (24.0)</td>
</tr>
<tr>
<td>NA</td>
<td>225 (20.2)</td>
</tr>
<tr>
<td>ICP [mm Hg] (mean (sd))</td>
<td>15.96 (9.33)</td>
</tr>
<tr>
<td>CPP [mm Hg] (mean (sd))</td>
<td>76.84 (11.72)</td>
</tr>
<tr>
<td>PRx [a.u.] (mean (sd))</td>
<td>0.07 (0.17)</td>
</tr>
<tr>
<td>Plateau wave presence (%)</td>
<td>383 (34.4)</td>
</tr>
<tr>
<td>Mean number of plateau waves (mean (sd))</td>
<td>1.90 (3.50)</td>
</tr>
<tr>
<td>Severe refractory intracranial hypertension presence (%)</td>
<td>94 (8.5)</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>248 (22.3)</td>
</tr>
</tbody>
</table>

ICP, intracranial pressure; CPP, cerebral perfusion pressure; PRx, pressure reactivity index.

Results

#### Descriptive Data

Summary data are shown in Table. In the current analysis, 1112 patients were included with a mean age of 38; 867 were male and the majority (776) were severely injured on initial GCS assessment. The remainder had a secondary neurological deterioration. The mean duration of monitoring was 114.08 h (SD 102.15) and 248 (22.3%) died. Figure 1 highlights important changes to the intensive care management over the past 25 yr.

#### Main Results

When mean values of ICP are plotted against time of injury, a consistent decrease from values around 19 mmHg to below 12 mmHg are observed over the 25-yr period (Figure 2). The measured CPP showed a distinct increase from ∼70 mmHg in 1994 to above 80 mmHg in 2000 followed by a gradual reduction and stabilization over the next 15 yr at ∼75 mmHg. In the final 2 yr, measured CPP decreased by ∼7 mmHg. PRx remained stable throughout the years of monitoring (1996-2017).

Statistical analysis confirmed significant effects of time (stratified into 5-yr epochs) for CPP and ICP (including a decrease in number of plateau waves and incidence of refractory intracranial hypertension) but not PRx (Figure 3). There was an increase in age of monitored patients over time, however, no change in mortality or GCS (Figure 4). The percentage of monitored patients undergoing decompressive craniectomy was 30% and did not significantly change over the period when data was

respectively. Holms method was used to adjust for multiple comparisons. All data analysis was performed using the R language for statistical computing with the following packages: ‘MASS’, ‘dplyr’, ‘ggplot’.
FIGURE 2. Changes in TBI neuromonitoring variables over 25 yr. A and D, ICP; B and E, PRx; and C and F, CPP (n = 1112; generalized additive model with 95% confidence limits). A, ICP decreases from just below 20 mmHg to below 12 mmHg while C, CPP increases shortly after 1995 from below 70 to greater than 80 mmHg around 2000. B and E, PRx remains unchanged throughout the 20 yr it has been monitored. Key changes in management are indicated by the dotted lines and refer to (in chronological order): Change from ward to NCCU based care (1994); introduction of brain oxygen and metabolism monitoring, relaxation of CO2 and CPP targets (2002-2004), designation of major trauma unit (2012); and switch from ABP transducer zero at heart to brain level (2015). ICP, intracranial pressure; PRx, pressure reactivity index; CPP, cerebral perfusion pressure.

DISCUSSION

Key Results

Of the multiple incremental changes in TBI management over the past 25 yr in this single institution, the introduction of specialized neurocritical care and goal-directed therapy had the most pronounced effects on monitored physiology (year 1994, Figure 2) resulting in increased CPP, decreased ICP, fewer plateau waves, and less time spent outside of ICP or CPP targets. The subsequent introduction of microdialysis, brain tissue oxygenation monitoring, or changes in pCO2 targets and ventilation strategies did not seem to have major immediate effects on ICP, CPP, or PRx. Despite an increasing age of the monitored cohort, the mortality has not significantly changed (∼22%).

Limitations

Due to the retrospective nature of this study, the collection of detailed patient outcome assessment and characterization of patient injury (mechanism of injury, pupil reactivity, computed tomography [CT] findings, prehospital insults etc) was not possible. Therefore, inferences from patient outcome results must be treated cautiously. However, the main purpose of the study was to document changes in trends in the monitored physiological parameters and as such, the available ICP, CPP, and PRx data suffice to address the research question. Furthermore, the modest percentage of patients with ICP monitoring captured in this study (52%) raises the possibility of inclusion bias. In addition, information regarding treatment on a patient-by-patient level may aid in the interpretation of this monitoring data. Unfortunately, such data were unavailable in this database.

Decreasing Mean ICP

The mean ICP decreased over the 25-yr period by 8 mmHg and the percentage of time with ICP over 20 mmHg also decreased from a mean value of >30% of monitoring time to <10%. Because increased ICP is related to cerebral blood flow and metabolism,14,15 effective treatment of raised ICP is a prime directive of neurocritical care after TBI.16 However, defining a precise ICP that warrants treatment is difficult; it is likely the threshold for a damaging ICP will depend on how long the ICP is raised, and whether other cerebral physiological markers are also impaired.17-19 Notwithstanding, the threshold of ICP used in this center was 20 mmHg for escalating treatment.
The decrease seen in ICP over the years could indicate an increase in frequency in treatments, an increase in efficacy of treatments, or perhaps a decrease in the 'baseline' ICP of the monitored cohort. Unfortunately, due to the retrospective nature of the data we do not have exact information on the specific treatments and their timings in each patient. However, the rate of decompressive craniectomy did not change significantly over the past 20 yr. Despite the lack of positive trials on ICP lowering interventions that could be responsible for the results (other than the recent RESCUEicp trial for decompressive craniectomy	extsuperscript{20}), the management of TBI has undoubtedly evolved in most neurotrauma centers, including Addenbrooke's Hospital. Such changes have included preference of hypertonic saline over mannitol; use of multimodal monitoring including better access to EEG allowing for more individualized treatment in difficult cases (including seizure management, glucose supplementation, etc), more rapid access to imaging and treatment of space occupying lesions. Furthermore, with an aging population the age distribution has shifted, albeit modestly, to older patients, potentially contributing to the lower ICP.

**Increasing CPP**

The increase in CPP between 1994 and 1999 is particularly striking and is an example of how the introduction of a management protocol can directly affect patient physiology. CPP-oriented therapy developed from the works of Rosner who...
DONNELLY et al

![Graph](image)

**FIGURE 5.** Changes in CPP corrected to estimate CPP at the level of tragus (n = 1112; generalized additive model). When a 10 mmHg correction is made for the approximate height of the hydrostatic column between the heart and the tragus in the 30 degrees head up position, it is apparent that the highest CPP levels have occurred since switching the zero level of the transducer from the heart to the tragus level CPP cerebral perfusion pressure (2015).

proposed that maintaining CPP at slightly higher values may decrease the stimulus for vasodilatory ICP waves and thus lead to a more stable ICP.\(^{21,22}\) Against this background, it is interesting to note that the average number of plateau waves per patient decreased after the introduction of CPP oriented therapy (Figure 2). It became apparent several years after the promotion of CPP oriented therapy, that maintaining high levels of CPP, although effective in preventing secondary insults as measured by jugular bulb oxygen saturation, had no significant effect on neurological outcome possibly due to acute lung injury related to the use of vasopressors and fluids required to maintain an increased CPP.\(^{23}\) Subsequently most institutions, including Addenbrooke’s Hospital, and the Brain Trauma Foundation\(^{24}\) changed their guidelines to reflect these findings. The decrease of CPP threshold to CPP > 60 mmHg can be again seen in the time trends in Figure 2.

Finally, a 7-mmHg dip in displayed CPP seen after 2015 can be explained by a change in practice, whereby the position of the zero level for the ABP transducer was changed from the level of the right atrium to the level of the foramen of Monro (Figure 2) to give a clearer indication of the perfusion pressure at the level of the brain.\(^{25}\) Interestingly, when a posthoc correction of 10 mmHg is applied, the highest CPP levels were experienced after 2015 perhaps indicating increased use of vasopressors (however, these data are unavailable).

**Unchanged Pressure Reactivity**

Pressure reactivity in this single-center cohort did not change over time (Figure 2). Secondary indices such as PRx derived from continuous monitoring of ICP and ABP can be useful for monitoring various aspects of physiology.\(^{26,27}\) PRx has been proposed as a measure of cerebral autoregulation and has the pragmatic advantage over other more direct methods, in that it can be calculated continuously over time.\(^{28}\) PRx has been demonstrated to be related to patient outcome after TBI (worse autoregulation, worse outcome), has been validated in experimental models against gold-standard static autoregulation analysis, and has been shown to correspond with the PET-based static rate of regulation in adult TBI patients.\(^{29-31}\)

Although we have the ability to easily monitor cerebral autoregulation, our ability to improve it is at present limited. Despite the early promise of some drugs such as statins,\(^{32}\) there are currently none in use for improving autoregulation acutely. In addition, autoregulation can be affected by many physiological and treatment factors including, CO\(_2\), arterial glucose, red blood cell transfusion, and body temperature.\(^{33-36}\) Altering physiological conditions has been proposed as a method to improve overall autoregulation and in this light, the concept of CPP optimal may prove useful.\(^{37-41}\) With this method, the CPP at which autoregulation is the most efficient is actively targeted through the careful titration of vasopressors. Despite conceptual promise, its use in clinical practice has been limited\(^{42}\) due to the lack of prospective clinical studies demonstrating either its safety, or its efficacy (a phase II multicenter trial about feasibility of CPP oriented therapy, has been started this year; http://cppopt.org/).

Nevertheless, as cerebral autoregulation is intrinsically linked to CPP, and hence ICP, one could argue that incremental changes in either of these parameters, as well as good neurocritical care with adequate ventilatory support and maintained systemic homeostasis should have exerted beneficial effect on PRx. The obtained results, together with the confirmed independent association of PRx with outcome, suggest there is still room for developing interventions targeting cerebral autoregulation.

**Admission Patient Characteristics and Mortality**

Despite the increasing age and steady initial GCS over the 25 yr, mortality in the analyzed cohort did not significantly change (Figure 4). While this may have been contributed to the sustained improvement in ICP, and better control of CPP, it should be appreciated that patient outcome and, in particular, mortality are influenced by not only ICP, but also by factors not assessed in this study. These factors include the severity of extracranial injuries, comorbidities, the severity of the primary insult, involvement of critical structures such as the brain stem, as well as patient factors and wishes with respect to withdrawal of care. Indeed, the importance of ICP (and CPP) monitoring after head injury has been challenged with the publication of the BEST TRIP trial.\(^{43}\) It has not been our institutional policy, however, to abandon ICP monitoring. Rather, ICP is used in combination with multimodal monitoring in an interdisciplinary effort (neurointensivists, neurosurgeons, and neurologists) to obtain maximal information about the intracranial physiology and guide specialized therapies.

While the limited nature of the current database prevents detailed analysis of outcome trends over time, our institutional outcomes compare favorably with published data where mortality...
after severe TBI typically exceeds 25% to 30%.20,43-45 Indeed, in a review of severe TBI outcomes in the last 150 yr, Stein et al16 demonstrated that while mortality after head injury decreased significantly in the periods between 1970 and 1990 there was no significant improvement in mortality after 1990; it remained static at around 35%. The reasons for the improvements before 1990 are likely related to the introduction of neurocritical care for head injury patients with good hemodynamic and ventilatory management avoiding hypotension and hypoxemia, rapid access to CT scanning and surgery if required.7 Since 1995, Brain Trauma Foundation Guidelines have been published47-49 and Major Trauma Networks have been set up50 in an attempt to unify care after severe TBI. Some reports suggest improved outcomes with increasing adherence to the Brain Trauma Foundation Guidelines.51,52

In the UK, neurosurgery services have been centralized since 1948 and therefore volumes and guideline adherence are typically high. Previous UK-based studies have demonstrated reducing mortality over time when all patients with TBI were taken into account53 and good overall performance when confronted with prediction models.54 Our data does not strictly confirm this improving trend; however, direct comparison is impossible, as only a selected cohort of patients requiring prolonged computerized intracranial monitoring and neurocritical care was selected for this analysis. Nevertheless, our data, as well as similar studies from other locations44,55 confirm that it has proven difficult to clearly reduce mortality after severe TBI. Potential reasons for a stagnant mortality rate despite an apparent improved neurocritical care and access to neurosurgery include an aging population, better prehospital survival in patients previously dying on the scene, and an increasing frequency of multitrauma or high velocity accidents.

Generalizability

Whether the reported long-term trends in physiology after severe TBI from this single academic institution are applicable to the general severe TBI population is uncertain. Determining geographic and socioeconomic influences on the response of intracranial physiology to changes in management guidelines could represent an avenue for further research and opportunities for improved outcomes.

CONCLUSION

In over 1100 patients, we demonstrate the evolving trends in neurophysiological monitoring over the past 25 yr from a single, academic neurocritical care unit. ICP and CPP were responsive to the introduction of an ICP/CPP goal directed therapy while cerebrovascular pressure reactivity has remained unchanged. Although we treat increasingly older patients now compared to 25 years ago, mortality seems to remain unchanged and low.

Disclosures

These studies were supported by National Institute for Healthcare Research (NIHR, UK) through the Acute Brain Injury and Repair theme of the Cambridge NIHR Biomedical Research Centre, an NIHR Senior Investigator Award to Dr Menon, and an NIHR Research Professorship to Dr Hutchinson. Dr Donnelly is supported by a Woolf Fisher Scholarship (New Zealand). Dr Zeiler has received salary support for dedicated research time from the Cambridge Commonwealth Trust Scholarship, the University of Manitoba Clinician Investigator Program, and the Royal College of Surgeons of Canada—Harry S. Morton Travelling Fellowship in Surgery, during which this project was completed. Dr Hutchinson and Dr Menon were also supported by a European Union Framework Program 7 grant (CENTER-TBI; Grant Agreement No. 602150). Dr Zeiler and Dr Cardim have received PhD funding from the Cambridge Commonwealth Trust. Dr Kollia, Dr Hutchinson, Dr Menon, and Dr Budoshski declare funding from the NIHR Global Health Research Group on Neurotrauma, which was commissioned by the NIHR using Official Development Assistance (ODA) funding (project 16/137/105). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, National Institute for Health Research or the Department of Health. The authors have the following potential conflicts of interest: Dr Czosnyka receives part of licensing fees for ICM+—owned and distributed by Cambridge Enterprise Ltd; paid lectures for: Integra Lifescience Speakers’ Bureau; and is partially supported by: National Institute of Health Research Medtech and In vitro diagnostics Co-operatives in Cambridge. Dr Smielewski receives part of the licensing fees for the software ICM (Cambridge Enterprise Ltd; Cambridge UK), used in this project for data collection and data preprocessing. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Menon has had consultancy, research collaboration, or trial data monitoring interactions with Solvay Ltd; GlaxoSmithKline Ltd; Brainsciences Ltd; Ornim Medical; Shire Medical, and Neurovive Ltd; Calico Inc; Pfizer Ltd; Pressura Ltd; Glide Pharma Ltd; and NeuroPro Ltd.

REFERENCES
