

Editorial

Between evidence and commerce – the case of sufentanil sublingual tablet systems

As a specialist in a field of medicine, occasionally one is obliged to read, and quite often re-read, about aspects of your practise. In this instance, writing this editorial coincided with refreshing our knowledge regarding the literature on gabapentin. Therefore, coincidentally, we came across an article by Steinman et al. that reported how ‘cleverly’ industry promoted the anticonvulsant and antineuropathic drug gabapentin in the 1990s [1]. For their article, Steinman et al. reviewed publicly available court documents from the USA and thus identified three main strategies industry employed to promote gabapentin. The first involved continuing medical educational activities targeting a wide audience, for instance organising local talks and lectures as well as meetings and conferences. The second approach, advisory boards and consultant meetings, was directed at opinion leaders and high-rate anticonvulsant prescribers. Meetings were often held at luxury hotels and participants frequently received honoraria and travel reimbursements. Finally,

Steinman et al. found even research and publication strategies ‘served as key elements in the marketing for the drug [gabapentin]’. Original articles, for instance, were not only used to gain US Food and Drug Administration (FDA) approval, but also as tools to ‘disseminate information as widely as possible’. Review articles and letters to the editor had the same purpose. Often, medical education companies were employed to guide or even directly prepare manuscripts (‘ghost-writing’), and to choose ‘suitable authors’. ‘Suitable authors’ usually already had a commercial relationship with industry and/or were subsequently paid to participate in the publication process. Also, for some articles, sponsorship was not disclosed. Steinman et al. concluded that involving physicians in research and publication helped industry to engage opinion leaders, reward customers and influence prescribing.

Reflecting on Steinman’s article and because of the recent, seemingly omnipresent, advertisements for the sufentanil sublingual tablet system (SSTS), we thought it prudent to gather more information about how the data presented in van de Donk et al.’s review, published in this edition of the journal,

were generated, whether they might be in any way biased, and whether any particular marketing strategy, that might resemble the process Steinman described, was apparent relating to SSTS [2].

Conflict of interest statements

Because Steinman et al. also noted that industry-sponsored original articles preferentially reported results favouring gabapentin, we think it is important review articles should always mention the conflict of interest (COI) statements of each work they include. Interestingly, this is not common practice yet and this struck us as odd. It seems reviews hardly ever provide information on COIs for the research they are basing their messages on. This is despite journals being increasingly diligent in disclosing COI statements for authors of original articles [3]. Although the sense and (perhaps) nonsense of disclosing COIs is still controversial [4, 5], journals are right to ask for as much transparency as possible about potentially important sources of bias. This notion is not only based on evidence, that industry funded research more often than not favours the sponsor’s product [6, 7], but simply reflects good research practice. By

This editorial is accompanied by an article by van de Donk et al., *Anaesthesia* 2018; 73: 231–7.

reporting as many confounders as possible, one allows others to reproduce the reported results [8]. However, omitting such information in review articles, considered a beacon of evidence-based medicine [9], at best dilutes and at worst even contradicts the original journal editors' intentions.

To explore whether the non-provision of individual COI disclosures is indeed standard practice in review articles, we performed a short, albeit crude, survey. On entering the following search terms into PubMed: 'review' (title/abstract) AND 'analgesia' (title/abstract) AND 'date of publication' (2015/01/01–2017/03/29), we retrieved $n = 970$ articles (accessed March 2017). We randomly selected 10% of these ($n = 97$ articles) to look at further; these included systematic and narrative reviews. Despite all articles having COI statements regarding their authors, and many including statements about evaluating the risk of bias in selected articles, none provided information about the funding of the trials they included. It is therefore laudable *Anaesthesia* asked van de Donk et al. to address the issue of industry funding for the four key articles included in their manuscript [10–13]. Regardless of whether single-source funding of undertaken research constitutes an indication for systematically biased evidence, van de Donk et al.'s statement according to Schwid and Gross [8] thus '*ensures that everyone has as much information as possible to critically appraise each report*'. We hope this will serve as a precedent and will be widely adopted in the future.

Multiple reviews

Further, looking through the retrieved titles of the Pubmed search, we were surprised to find seven review articles published between November 2015 and February 2017 regarding the use of sublingual sufentanil nanotablets for the treatment of pain [14–20]. All seven reviews included the same original articles, sometimes citing each other [14, 15, 18, 19] or providing the same figures [14, 17, 19] or similar tables [14, 17, 19]. The publication of seven reviews in 16 months, all independently reviewing the same evidence, led us to consider how many original publications about sublingual sufentanil existed altogether. A further PubMed search (search term: 'sublingual sufentanil' conducted in March 2017) identified seven original articles. Interestingly, they included the four papers cited in van de Donk et al.'s review and importantly all seven articles were funded by the same company (AcelRx Pharmaceuticals Inc., Redwood City, CA, USA). Cross-checking with the USA trial registry 'ClinicalTrials.gov' (<https://clinicaltrials.gov>; search term: 'sublingual sufentanil'), this company had completed 16 clinical trials with SSTS since March 2008. According to 'ClinicalTrials.gov', seven of these studies were still to be published (last accessed 9 April 2017) while nine appeared in the seven original articles found in the described PubMed search. Therefore, just seven original articles have now created eight reviews, including that of van de Donk et al. published in this issue of *Anaesthesia*.

According to Steinman et al.'s article, it appears this is not uncommon practice as it apparently is an important part of industry's promotional strategy [1]. Furthermore, clinical trials frequently cited within 2 years of their publication, are thought not only to endorse the product in question, but also help boost the impact factor of their publishing journals, creating a win-win situation for all parties involved [21, 22].

As much as this discovery feels uneasy, it is important to reflect that although this appears to represent an uneven balance between review and original articles, there is nothing unlawful about this practice. Lexchin et al. outline that, although industry-funded studies were more likely to favour industry's products [6], contrary to common belief, industry-sponsored studies were at least of the same quality as studies supported by other sources [23]. This is an important consideration in the current academic climate where research funding is diminishing, and new drugs are unlikely to be trialled outside of industry sponsorship.

Article quality

Therefore, industry sponsorship aside, are the four SSTS articles cited by van de Donk et al. [10–13] performed with adequate rigor? To evaluate this, 'quality indicators' as suggested by Sackett and Oxman [24] as well as Bero and Rennie [25] were considered to look at: the ethical approval process; the conduct of the research; and the overall quality of the manuscripts.

Ethical approval for the three clinical trials were sought in North Carolina [10–12] and for the pharmacokinetic study in Kansas [13], respectively, despite the company marketing SSTS in the USA being based in California. Both these remote review boards are independent, non-academic, for hire institutions (North Carolina: <http://www.cgirb.com/about/>; Kansas: <https://mlirb.com/>). The Kansas-based Board also advertises its services using a statement from the first author of the sufentanil pharmacokinetic study (<https://mlirb.com/>; last accessed 12 April 2017). This complies with USA law, however seems at odds to European practice where there is extensive governmental policing and regulation.

With respect to the conduct of the individual studies, the descriptions of the randomisation and blinding processes within Jove's [11], Ringold's [12] and Melson's [10], articles were brief. As highlighted by van de Donk et al., Melson's study was an open-label trial. The group allocations for the other three blinded clinical trials took place in recovery following surgery, and after it had been confirmed patients were opioid-sensitive or responders [10–12]. This method is often adopted to ensure the study participant has a known response to the drug in question. However, it could allow for the possibility of biased patient selection. Further, Jove's and Ringold's studies compared sufentanil only with placebo, while Melson used an active comparator (intravenous morphine), albeit at a lower equivalent dose than the test drug. Both control

group approaches have been criticised in the past and could contribute to a favourable trial drug outcome [6, 7, 25].

Finally, when judging the overall quality of the four original manuscripts, both the Jove [11] and Willsie [13] articles included the statement '*editorial assistance was provided...*'. This phrase, according to McHenry, indicates the involvement of a ghost-writer and the possibility of '*misreporting of the data to favour the sponsor's product*' [22].

What is going on?

To summarise, the evidence regarding the sufentanil sublingual tablet system at present involves more reviews than original articles, the ethical approvals for these trials were granted by commercial review boards, the reporting of and some of the research methodology in the clinical trials contain some shortcomings, and for the preparation of two manuscripts, ghost-writers were employed. Hence, there is the possibility that SSTS is being subjected to a promotional tool similar to that seen with gabapentin described by Steinman et al. [1].

However, we also think this case likely reflects a deeper-seated issue regarding research and publishing, where all stakeholders contribute to the problem. As, for instance, at the moment, the tables are turning in the epic race between fraudsters and journals favouring the latter, the onus is more than ever on authors [26, 27]. This is highlighted by a recent example of the use of statistics in this journal [28].

Moreover, journals, far from being the victims, may contribute themselves. Due to their own financial interests, they can become biased also. As Lundh et al. highlight [21], journals like publishing industry-funded trials, because firstly they are cited more frequently and hence help boost a journal's impact factor, and secondly companies often purchase large numbers of reprints which for some journals constitute a considerable part of their total income [21]. An extreme example of this is the creation of journals for the sole purpose of product promotion [29]. Furthermore, some open access e-journals (so called 'predatory journals') are financed by offering prompt publication, often at the expense of a proper review process, in exchange for considerable fees [30]. Even the peer review process, potentially the gate keeper to research integrity, has recently been tainted following a publisher needing to retract 43 papers due to allegations of the peer review process being inappropriately influenced and compromised [31]. Finally, studies reaching the mainstream media may preferentially report research regarding lifestyle issues that have 'positive' data [32]. Therefore, more or less, we all are responsible for the shortcomings in medical research reporting, and currently as readers we search for a way through a dizzying maze of conflicting interests and ever increasing moral expectations. To be fair, some authors have started developing ideas of how to address these issues, but they will take time to be adopted as they involve

a complete change of culture [33–36].

So, how can we address this complex issue currently? As readers, as reviewers and as authors, we need to insist on an academic standard by asking for more transparency. If we don't understand, we should ask for it to be explained and if it doesn't seem plausible, we should ask for the data to show it is. In other words, we need to step back, be curious and cast a critical eye.

Acknowledgements

CB has received an educational grant from TEVA UK as well as consultancy and speaker fees from NAPP Pharmaceuticals Ltd. and Mundipharma GmbH. No other external funding or competing interests declared.

C. Bantel

Consultant/Honorary Clinical Senior Lecturer

Pain Medicine and Anaesthesia

Klinikum Oldenburg AöR

Oldenburg Germany

Imperial College London

London, UK

Email:

carsten.bantel@uni-oldenburg.de

H. C. Laycock

Clinical Lecturer and Advanced

Pain Fellow

Imperial College London

London, UK

Keywords: conflict of interest; pain; sublingual sufentanil

References

- Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Annals of Internal Medicine* 2006; **145**: 284–93.
- van de Donk T, Ward S, Langford R, Dahan A. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. *Anaesthesia* 2018; **73**: 231–7.
- Drazen JM, de Leeuw PW, Laine C, et al. Toward more uniform conflict disclosures—the updated ICMJE conflict of interest reporting form. *New England Journal of Medicine* 2010; **363**: 188–9.
- Thompson DF. Understanding financial conflicts of interest. *New England Journal of Medicine* 1993; **329**: 573–6.
- Rosenbaum L. Understanding bias—the case for careful study. *New England Journal of Medicine* 2015; **372**: 1959–63.
- Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *British Medical Journal* 2003; **326**: 1167–70.
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *Journal of the American Medical Association* 2003; **289**: 454–65.
- Schwid RS, Gross RA. Bias, not conflict of interest, is the enemy. *Neurology* 2005; **64**: 1830–1.
- National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. 1999. www.health.qld.gov.au/__data/assets/pdf_file/0029/143696/nhmrc_clinprgde.pdf (accessed 18/07/2017).
- Melson TI, Boyer DL, Minkowitz HS, et al. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. *Pain Practice* 2014; **14**: 679–88.
- Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system for the management of postoperative pain after knee or hip arthroplasty: a randomized, placebo-controlled study. *Anesthesiology* 2015; **123**: 434–43.
- Ringold FG, Minkowitz HS, Gan TJ, et al. Sufentanil sublingual tablet system for the management of postoperative pain following open abdominal surgery: a randomized, placebo-controlled study. *Regional Anesthesia and Pain Medicine* 2015; **40**: 22–30.
- Willsie SK, Evashenk MA, Hamel LG, Hwang SS, Chiang YK, Palmer PP. Pharmacokinetic properties of single- and repeated-dose sufentanil sublingual tablets in healthy volunteers. *Clinical Therapeutics* 2015; **37**: 145–55.
- Minkowitz HS. A review of sufentanil and the sufentanil sublingual tablet system for acute moderate to severe pain. *Pain Management* 2015; **5**: 237–50.
- Minkowitz HS, Candiotti K. The role of sublingual sufentanil nanotabs for pain relief. *Expert Opinion on Drug Delivery* 2015; **12**: 845–51.
- Babazade R, Turan A. Sufentanil sublingual tablet system for the management of postoperative pain. *Expert Opinion on Pharmacotherapy* 2016; **17**: 2351–7.
- Sacerdote P, Coluzzi F, Fanelli A. Sublingual sufentanil, a new opportunity for the improvement of postoperative pain management in Italy. *European Review for Medical and Pharmacological Sciences* 2016; **20**: 1411–22.
- Babazade R, Turan A. Pharmacokinetic and pharmacodynamic evaluation of sublingual sufentanil in the treatment of post-operative pain. *Expert Opinion on Drug Metabolism and Toxicology* 2016; **12**: 217–24.
- Frampton JE. Sublingual sufentanil: a review in acute postoperative pain. *Drugs* 2016; **76**: 719–29.
- Katz P, Takyar S, Palmer P, Liedgens H. Sublingual, transdermal and intravenous patient-controlled analgesia for acute post-operative pain: systematic literature review and mixed treatment comparison. *Current Medical Research and Opinion* 2017; **33**: 1–12.
- Lundh A, Barbateskovic M, Hrobjartsson A, Gotzsche PC. Conflicts of interest at medical journals: the influence of industry-supported randomised trials on journal impact factors and revenue – cohort study. *Public Library of Science Medicine* 2010; **7**: e1000354.
- McHenry L. Of sophists and spin-doctors: industry-sponsored ghostwriting and the crisis of academic medicine. *Mens Sana Monographs* 2010; **8**: 129–45.
- Kesselheim AS, Robertson CT, Myers JA, et al. A randomized study of how physicians interpret research funding disclosures. *New England Journal of Medicine* 2012; **367**: 1119–27.
- Sackett DL, Oxman AD. HARLOT plc: an amalgamation of the world's two oldest professions. *British Medical Journal* 2003; **327**: 1442–5.
- Bero LA, Rennie D. Influences on the quality of published drug studies. *International Journal of Technology Assessment in Health Care* 1996; **12**: 209–37.

26. Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia* 2017; **72**: 944–52.
27. Loadsman JA, McCulloch TJ. Widening the search for suspect data – is the flood of retractions about to become a tsunami? *Anaesthesia* 2017; **72**: 931–5.
28. Carlisle JB, Loadsman JA. Evidence for non-random sampling in randomised, controlled trials by Yuhji Saitoh. *Anaesthesia* 2017; **72**: 17–27.
29. Hutson S. Publication of fake journals raises ethical questions. *Nature Medicine* 2009; **15**: 598.
30. Kahan S, Kushner RF. New year's resolution: say no to fake journals and conferences. *Obesity (Silver Spring)* 2017; **25**: 11–2.
31. Dyer O. Major publisher retracts 43 papers, alleging fake peer review. *British Medical Journal* 2015; **350**: h1783.
32. Dumas-Mallet E, Smith A, Boraud T, Gonon F. Poor replication validity of biomedical association studies reported by newspapers. *Public Library of Science One* 2017; **12**: e0172650.
33. Triggler CR, Triggler DJ. What is the future of peer review? Why is there fraud in science? Is plagiarism out of control? Why do scientists do bad things? Is it all a case of: "all that is necessary for the triumph of evil is that good men do nothing"? *Vascular Health and Risk Management* 2007; **3**: 39–53.
34. Gupta A. Fraud and misconduct in clinical research: a concern. *Perspectives in Clinical Research* 2013; **4**: 144–7.
35. Carlisle JB, Dexter F, Pandit JJ, Shafer SL, Yentis SM. Calculating the probability of random sampling for continuous variables in submitted or published randomised controlled trials. *Anaesthesia* 2015; **70**: 848–58.
36. Klein AA. What Anaesthesia is doing to combat scientific misconduct and investigate data fabrication and falsification. *Anaesthesia* 2017; **72**: 3–4.

doi:10.1111/anae.14037

Editorial

Time to stop using uncuffed tracheal tubes in children?

Accepted wisdom over the last 50 years has been that uncuffed tracheal tubes should be used in children less than eight years of age. This is because it was thought that the narrowest part of a child's airway is below the vocal cords at the level of the cricoid cartilage. Therefore, an uncuffed tracheal tube that is large enough to seal the cricoid ring, but allow a leak at pressures above 20 cmH₂O, should enable adequate positive pressure ventilation without exerting excessive pressure on the tracheal mucosa that could lead to tissue hypoperfusion.

The results of a Cochrane review [1] comparing cuffed with

uncuffed tracheal tubes are due to be released soon and I await the findings with great interest, but in the meantime, I aim to convince you that cuffed, rather than uncuffed, tracheal tubes should be the preferred choice for children other than neonates.

In 2008, cuffed tracheal tubes were not very popular in the UK. Flynn et al. [2] sent out a questionnaire to paediatric anaesthetists and intensivists, and found that only a very small number of those surveyed routinely inserted a cuffed tracheal tube, because it was perceived that there was minimal benefit to be gained. The most common indication cited for using a cuffed tracheal tube was reduced lung compliance and, even if a cuffed tracheal tube was used, intra-cuff pressure was not

routinely monitored. However, opinion appears to be changing. An electronic survey distributed to members of the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) and the Section of Paediatric Anaesthesia in the Netherlands in 2015 [3] found that, although Dutch anaesthetists were much more likely to use cuffed tracheal tubes, 50% of UK anaesthetists indicated that they were regularly using cuffed tracheal tubes in infants or older children. In the USA, cuffed tracheal tubes are more popular and, in a recent survey of members of the Society of Pediatric Anesthesia [4], 85% of respondents used a cuffed tracheal tube at least 50% of the time in children older than two years of age.

When an uncuffed tracheal tube is selected, this is usually based on the

This editorial accompanies an article by Chambers et al., *Anaesthesia* 2018; 73: 160–8.