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EDITORIAL

The Fujii story

A chronicle of naive disbelief

Martin R. Tramèr

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In this issue of the *European Journal of Anaesthesiology*, the editors retract 12 articles from the Japanese anaesthetist Dr Yoshitaka Fujii (Table 1). The 12 articles are part of 183, all authored by Fujii, that have been retracted during the last few months in a variety of journals. Scientific anaesthesiology has been recently rocked by the Reuben and Boldt affairs, and Fujii represents another blow to the reputation of scientific journals. We are all shocked that this has happened again and it is perhaps appropriate to step back a moment, and critically appraise the chain of events.

It does not come as a surprise to us that systematic reviewers were among the first to become suspicious of Fujii, with his significant output, and the conspicuous pattern of his research papers. In 2001, Kranke *et al.*¹ published a letter in *Anesthesia and Analgesia* with the odd title ‘*Reported data on granisetron and postoperative nausea and vomiting by Fujii et al. are incredibly nice!*’. In common with most experts in postoperative nausea and vomiting (PONV), Kranke had become increasingly irritated with Fujii, who was producing an astonishing number of articles dealing with the antiemetic efficacy of the 5HT₃ receptor antagonist granisetron in patients undergoing surgery. Even for those who lacked expertise in the critical appraisal of clinical studies, it must have become evident that the Fujii trials were fundamentally different from most other published studies. They were all of the same (limited) size; they were always almost (but only almost) identical; they addressed always the same issues; and, perhaps most strikingly, they reported on very similar numbers of efficacy and drug-related harm. Although there were never obvious duplicates, these trials were clearly not ‘natural’. Kranke *et al.*,¹ in their letter, presented a simple but convincing mathematical approach that provided strong evidence that Fujii’s data

had been fabricated. They had analysed the reported headache frequencies (a common adverse effect of 5HT₃ receptor antagonists) in 21 granisetron trials that had been published by Fujii at that time. They knew that in real life, with binominal distribution, a certain variability was expected. What their analysis found was that the close resemblance of Fujii’s published results was unlikely to have arisen by chance. They concluded that ‘there must be an underlying influence causing such incredibly nice data reported by Fujii *et al.*’¹ Subsequently, Fujii was invited by the editors of *Anesthesia and Analgesia* to publish a reply that satisfied nobody, and the affair was closed. It was not clear, though, why Kranke *et al.* had not said outright that Fujii was fabricating data. Also, reading their letter today, it seems odd that this analysis was not given a full report. Today, we know that at that time, editors and peer reviewers of various high ranking anaesthesia journals did not want Kranke *et al.* to declare overtly that there was something rotten here.

One year later, Kranke *et al.* published in *Acta Anaesthesiologica Scandinavica* a meta-analysis of 27 granisetron trials.² In a subgroup analysis, they compared the Fujii trials, which at that time made up about two thirds of all granisetron trials, with granisetron trials from other authors. The Fujii trials reported a significantly improved antiemetic efficacy of granisetron. Kranke concluded that results of meta-analyses could be significantly skewed by one dominating centre.² At that time, at least three different affiliations were listed on Fujii’s various publications: Tokyo Medical and Dental University School of Medicine; Toride Kyodo General Hospital; Ibaraki; and University of Tsukuba Institute of Clinical Medicine. Clearly the Fujii phenomenon was not about the impact of a single centre but that of an individual. In addition, the main interest here was not to prove the antiemetic efficacy of granisetron (who cares about granisetron?), but to show that somebody was fabricating data. To top it all, in an accompanying Editorial, Kranke’s analysis was

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Table 1 Retracted articles by Fujii *et al.*

1. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Antiemetic efficacy of prophylactic granisetron, droperidol and metoclopramide in the prevention of nausea and vomiting after laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled trial. <i>Eur J Anaesthesiol</i> 1998; 15 :166–171
2. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Effective dose of granisetron for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. <i>Eur J Anaesthesiol</i> 1998; 15 :287–291
3. Fujii Y, Toyooka H, Tanaka H. Efficacy of thoracic epidural analgesia following laparoscopic cholecystectomy. <i>Eur J Anaesthesiol</i> 1998; 15 :342–344
4. Saitoh Y, Tanaka H, Fujii Y, <i>et al.</i> Posttetric burst count and train-of-four during recovery from vecuronium-induced intense neuromuscular block under different types of anaesthesia. <i>Eur J Anaesthesiol</i> 1998; 15 :524–528
5. Saitoh Y, Fujii Y, Ueki M, <i>et al.</i> Accelerographic and mechanical posttetric count and train-of-four ratio assessed at the great toe. <i>Eur J Anaesthesiol</i> 1998; 15 :649–655
6. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Antiemetic efficacy of prophylactic granisetron compared with perphenazine for the prevention of postoperative vomiting in children. <i>Eur J Anaesthesiol</i> 1999; 16 :304–307
7. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Prophylactic therapy with combined granisetron and dexamethasone for the prevention of postoperative vomiting in children. <i>Eur J Anaesthesiol</i> 1999; 16 :376–379
8. Fujii Y, Takahashi S, Toyooka H. Milrinone enhances the contractility of fatigued diaphragm in dogs: a dose-ranging study. <i>Eur J Anaesthesiol</i> 1999; 16 :600–604
9. Fujii Y, Tanaka H. Granisetron reduces postoperative vomiting in children: a dose-ranging study. <i>Eur J Anaesthesiol</i> 1999; 16 :62–65
10. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Prevention of postoperative nausea and vomiting with combined granisetron and droperidol in women undergoing thyroidectomy. <i>Eur J Anaesthesiol</i> 1999; 16 :688–691
11. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. <i>Eur J Anaesthesiol</i> 2000; 17 :64–68
12. Fujii Y. Effects of diltiazem compared with nicardipine on diaphragmatic fatigability <i>in vivo</i> . <i>Eur J Anaesthesiol</i> 2003; 20 :575–576

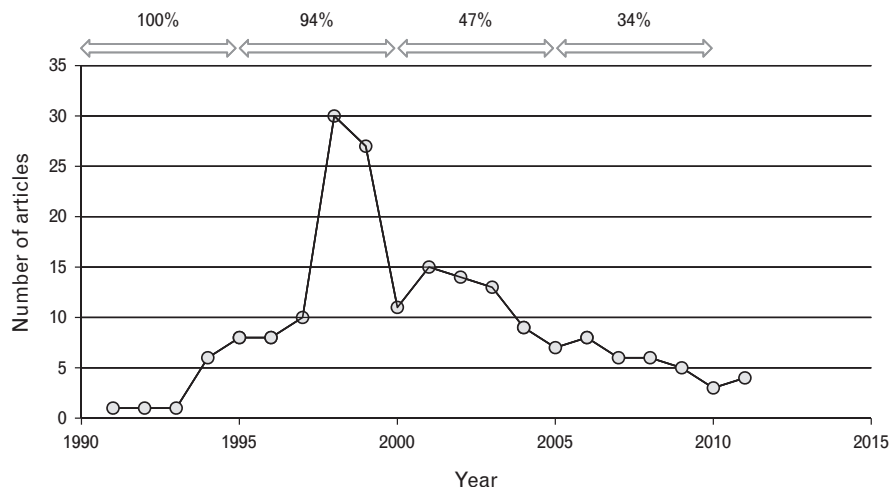
dismissed. It argued that different baseline risks in the granisetron studies may have been responsible for the observed differences in outcomes.³ In conclusion, Kranke *et al.* were allowed to publish their alarming analyses, but the Editorial approach significantly blunted their impact.

Interestingly, in the years that followed, the number of studies published by Fujii dropped dramatically, and the proportion of those published in anaesthesia journals, compared with non-anaesthesia journals, decreased sharply from almost 100% before 2000 to less than 35% after 2005 (Fig. 1). At this time, neither editor nor institution had started an official enquiry into Fujii's strange production line. It seemed that the editors of most anaesthesia journals had come to a mutual agreement that the best way to deal with the problem

was to ignore it, and to ban future Fujii studies from their journals. The last Fujii article in *Acta Anaesthesiologica Scandinavica* and the *British Journal of Anaesthesia* appeared in 2002, in the *European Journal of Anaesthesiology* in 2003, in *Anaesthesia and Intensive Care* in 2004, in the *Canadian Journal of Anesthesia* in 2005, and in *Anesthesia and Analgesia* in 2007. Between 2006 and 2009, Fujii still managed to publish seven articles in the Japanese journal *Anesthesia and Resuscitation*. However, a variety of ENT, surgery, ophthalmology, gynaecology, and pharmacology subspecialty journals had become the host of Fujii's fraudulent articles.

How did the PONV experts around the world, who could not escape the Fujii phenomenon, deal with the problem? In 2002, when a multidisciplinary panel of

Fig. 1



Retracted articles by Fujii *et al.* from 1991 to 2011. Percentages are percentages of Fujii articles published in anaesthesiology journals over four 5-year periods.

experts met in Florida to set up the first international PONV guidelines,⁴ it was suggested by some panel members that publications from Fujii should not be cited. Until then, Fujii had published as first author almost 70 randomised controlled trials dealing with PONV. The total number of randomised patients added up to more than 7200, which extrapolated to almost 1000 patients for each year, an incredible production machine. The trials made up almost the entire granisetron PONV literature at that time. There were some hesitant voices among the PONV panel members who were asking, without much conviction, where the evidence for any wrongdoing was and whether we had the right to accuse an author of misconduct, and to ignore his significant contribution to science, in the absence of a proper investigation. Despite these voices, the first PONV guideline paper was published without any reference to Fujii.⁴ The chapter dealing with granisetron listed four references from other authors. Fujii did not get a single mention in that guideline paper, nor was there any explanation as to why we did not wish to cite his papers. Nobody – neither editors, nor peer reviewers nor readers, nor the manufacturer of granisetron, or even Fujii himself, asked why we had so overtly ignored his articles. Fujii had become invisible.

Three years later, in 2005, the international expert panel met again to update the first PONV guidelines.⁵ Between the first and the second guideline, Fujii had published as first author an additional 20 randomised trials dealing with PONV, with an additional 1895 randomised patients. Eight of these trials tested ramosetron, a new generation 5HT₃ receptor antagonist. As at that time the efficacy of ramosetron for the control of PONV had not been tested by any other author, the expert panel simply decided to ignore it in the guidelines; the real reason was that we did not want to cite Fujii. Thus, in the second guideline paper, neither Fujii nor ramosetron was mentioned, nor was it explicitly explained what the reasons were for these omissions.⁵ Once again, nobody cared enough to question it. Everybody seemed to agree.

During subsequent years, some authors were prepared to publish systematic reviews about PONV issues that uncritically included Fujii data.^{6–8} One of them, Carlisle and Stevenson,⁸ published a Cochrane review in 2006 and included 69 Fujii references. Regarding the granisetron data they wrote: ‘The most important aspect of results for granisetron that readers should take into account is the marked asymmetry of the Funnel plots. These asymmetries suggest that the effect of granisetron is overestimated (versus placebo) and that there is not a reliable difference between granisetron and other antiemetics.’ Still in 2012, Tang and Malone⁹ justified the inclusion of 14 Fujii trials into their granisetron meta-analysis arguing: ‘These (i.e. Fujii’s) studies were not excluded because: (1) criticisms seemed to be solely

coming from the same group of authors and may not be representative of surgical/anesthetic experts; (2) consistent results obtained by Fujii *et al.* may not necessarily justify the suspicion that they were producing fraudulent data; and (3) journals that have published work by Fujii *et al.* have not retracted their publications.’

Nevertheless, starting in 2010, several significant things happened almost simultaneously. Although they all seemed to have contributed to Fujii’s end, it is speculation as to whether they actually influenced each other. In 2010, Moore *et al.*¹⁰ published a thought-provoking Editorial in *Anaesthesia* dealing with research fraud. They presented a simple event rate scatter using the data from the previously published Kranke meta-analysis, suggesting that the granisetron data from Fujii came from smaller trials and showed greater favourable effects for granisetron, whereas data from other authors were from larger trials showing a less dramatic effect of granisetron. This editorial came out of the blue but may have triggered further discussion of Fujii. Then, in 2011, something remarkable happened; Fujii was audacious enough to submit an article to the *Canadian Journal of Anaesthesia*. This time the editors alerted the Chair of the Department of Anaesthesia at Toho School of Medicine, the affiliation of that paper, and expressed their concern regarding the implausibility of certain elements of the data presented in Fujii’s article.¹¹ An internal investigation at Toho University revealed that this article had no ethical approval, and the authenticity of the data, nor the study itself could be established. This event launched a more extensive review by the Faculty of Medicine at Toho University. The ball had definitely started rolling. Finally, in 2012, Carlisle¹² set out to present a huge statistical analysis that convincingly reinforced the previous message from Kranke *et al.* It looked as if the earlier Editorial by Moore had triggered Carlisle’s ambition to nail Fujii down, some years after he had included, perhaps a bit naively, all the available Fujii trials into his Cochrane PONV analysis.⁸

This was the end; in April 2012, 23 journal editors under the lead of Steve Shafer from *Anesthesia and Analgesia* (who had acquired experience in such things during the Boldt affair) published a ‘Joint Editorial Request’ asking the institutions under whose auspices Fujii’s research was conducted to determine the authenticity of all his studies.¹³ Subsequent inquiries led by the various Japanese institutions came to the conclusion that of the 192 papers listed in the Joint Editorial Request, nine were authentic. For 183 papers, either original research data could not be found or there was no evidence of approval from an ethics committee. The response from each institution, as well as an analysis of Fujii’s published research by the Japanese Society of Anesthesiologists, is available online.¹⁴ The last institutional response came from Tsukuba University. As nine of the 12 Fujii papers published in the *European Journal of Anaesthesiology* go

back to that affiliation (the other three are from Toride Kyodo General Hospital), we had to wait until now to officially retract these remaining articles, published in the Journal between 1998 and 2003. No manuscript by Yoshitaka Fujii remains in the archives of the *European Journal of Anaesthesiology*.

It has taken more than a decade from the first clumsy blowing of the whistle to the end of Fujii's aspirations. Why was he allowed to publish almost 200 fraudulent articles? There may be several reasons. Fujii has published in a variety of domains: PONV; prevention of propofol injection pain; a diaphragmatic contractility model in dogs; neuromuscular blockade; and airway management. The same editors and peer reviewers do not necessarily share these domains. Fujii's articles were affiliated with seven institutions. This may explain why nobody felt responsible for him. Those who tried early on to alert a wider readership to the obvious irregularities were unable to disseminate a clear message. Fujii has changed target journals during his career. During his last 5 years of publication, almost two thirds of 39 articles were published in journals outside anaesthesia: for instance, *International Journal of Gynecology and Obstetrics*, *Surgical Endoscopy*, *Clinical Therapeutics* or *Otolaryngology Head and Neck Surgery*. It is likely that editors and peer reviews of those subspecialty journals were unaware of the controversy that accompanied Fujii. Finally, over the years in question, many of those who felt strongly that Fujii was cheating, were not effective enough to stop him. They may not have been aware of the steps to be undertaken when fraud is suspected. They may have felt that ignoring him was the easiest way to deal with the problem.

Fujii is not the first and he is unlikely to be the last. He follows Scott Reuben whose detection in 2009 led to the retraction of 21 articles published between 1996 and 2008.¹⁵ Also Joachim Boldt who was unmasked in 2011, when 88 articles published between 1999 and 2011 were retracted.¹⁶ By comparison, Fujii's activities spanned 20 years and led to the retraction of 183 articles. What is most disturbing is that it took 13 years following Kranke's warning for the appropriate action to be taken. The idea of tracking fraud using mathematical models was not new,¹⁷ but Carlisle's huge second analysis, with its overwhelming amount of fraudulent data accumulated over 20 years should not have been necessary. If Kranke had not been effectively silenced, this Editorial might not have been written. Were editorial staff simply naïve to believe in Fujii? There is a natural reluctance to rock

the boat, and the fraudster uses this to advantage. A more robust attitude is needed, and for this we must recognise the missing factor in this case – courage to speak out and address the problem.

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