THE SPINE JOURNAL
A Multidisciplinary Journal of Spinal Disorders

Embargoed For Release
June 17, 2013 at 5:00 p.m. EDT

Contact: Nicolle Heller
(630) 230-3650 or nheller@spine.org

Response to Long-Awaited YODA Report on Controversial Spinal Fusion Product

Attribution: Eugene Carragee, MD, Editor in Chief of *The Spine Journal*

The YODA (Yale University Open Data Access Project) report published today in the *Annals of Internal Medicine* is the latest and saddest shock to Medtronic's biologics product, human recombinant bone morphogenetic protein-2 (InFuse and other formulations). YODA's two independent groups found that *"rhBMP-2 provided little or no benefit compared to bone graft and may be associated with more harms, possibly including cancer…"* But what is even more troubling, the groups found that the Medtronic-associated authors "*misrepresented*" efficacy and underreported complications *"for both on-label and off-label indications"* and *"selected analyses and results that favored rhBMP-2 over ICBG."* The YODA groups confirm the findings of *The Spine Journal's* editorial review of 2011.

To put the YODA findings in perspective, one must understand the carnival-like promotion that preceded BMP-2's fall from grace. Market boosters advertised that the BMP-2 product went beyond all other medical innovations. Perhaps confusing Infuse with penicillin or the polio vaccine, one zealot proclaimed: "InFuse, the single most successful biologic product ever launched in orthopedics and possibly ever in medicine."

Before its fall from grace, the hyperbolic fever of BMP-2 promotion turned spinal conferences into Elmer Gantry-styled revival meetings. In that context, it is difficult to exaggerate the contrast in both style and content of the YODA groups' remarkable findings. In a triumph of understatement, the YODA group informs us that ten years after its development *"it is difficult to identify a clear indication for BMP-2 use in spinal fusion."* Ten years after penicillin was developed, people were saying it had saved a quarter-million lives in World War II. Ten years after the polio vaccine, braces had disappeared from grammar schools. Ten years after BMP-2's introduction, the YODA group could not identify a single compelling indication for use—but we know it can kill you in the cervical spine and probably can promote cancer, which can then kill you.

It is astonishing to recall the lavish praise for BMP-2 use by some Medtronic-associated surgeons just a few years ago. When the product was approved, surgeon and researcher Dr. Scott Boden declared, "The age of BMP has arrived." Then *within three months of FDA approval* in July of 2002, Dr. Thomas Zdeblick and Dr. J Kenneth Burkus reported that InFuse had become their *exclusive* bone grafting method for anterior lumbar fusions: *"With its superiority, InFuse Bone Graft may now become the new gold standard for replacing autograft bone."* Propelled by a "superiority" *The Spine Journal* and two YODA groups all agree never existed, Infuse was foisted from approval to gold standard in three months.

Years following FDA approval, Dr. Boden reported unparalleled product safety, "the only known risk [of on-label use] involves development of transient increases in antibodies." Even more emphatically, the author of many industry-sponsored publications, Dr. Burkus reported that "[n]o adverse events have been linked to the use of rhBMP-2." Regarding the same early work by Burkus and Zdeblick the YODA group finds*: "Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication and underreporting."* Say it ain't so, Joe.

(more)

Perhaps not by coincidence, the recent Senate Finance Committee investigation named these three surgeons, Boden, Burkus and Zdeblick, as having among the most lucrative financial ties with Medtronic, ranging from $10 to $35 million each. According to US Senator Charles Grassley, Medtronic "*maintained significant, previously-undisclosed financial ties with physicians who authored studies about InFuse, making $210 million in payments to physicians over a 15-year period."*

The Merry-Go-Round

In reviewing both the Senate and YODA documents, the important "checks and balances" of clinical research were seriously undermined. For critical early publications of Infuse, an extraordinary merry-go-round of comprehensively conflicted faces are found where independent checks should have provided critical review. In some instances, it seems investigators with strong financial ties helped design a trial, and then acted as surgeons who monitored their own complications. To complete the circuit the same surgeon/investigator would co-author the paper and then submit the manuscript for review to…well…*himself* as chief or section editor of the journal. In some cases the editor in chief of the journal approving his own paper was also the developer and the royalty holder on products being investigated. It would be hard to envision a situation more likely to produce, as the YODA group found, "journal publications select[ing] analyses and results that favored rhBMP-2 over ICBG."

The end result of this process was that important BMP-2 complications were "underreported" or just plain "missing." As YODA project director Dr. Harlan Krumholz delicately puts it, *"Evidence suggests that some data are not missing at random." The Annals* editors are more blunt: *"Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and underreporting."* Ouch.

What happened?

The BMP-2 story has come full circle: several years after "*early journal publications misrepresented the effectiveness and harms"* came the "FDA Warning of Life-Threatening Complications with BMP-2," then three (or is it now four?) whistle-blower lawsuits, allegations of fraudulent BMP-2 research at the Army's premier medical center, retraction of a landmark BMP-2 paper, *The Spine Journal* 2011 focus issue, the AMPLIFY FDA denial for cancer concerns, a scathing Senate Finance Committee Report and now the YODA project. This "market correction," if there is one, took over a decade. The public needs better safeguards against conflicted and tainted medical research.

It is ultimately disappointing that after 15 years of largely self-congratulatory research, we have only indirectly discovered BMP-2's many potential complications. At present these "concerns" regarding higher rates of cancer, sterility, wound problems and nerve injury remain poorly described. The suggested reason for this gap in our understanding, if true, is simply appalling: these complications were systematically "misrepresented," "underreported" or just "missing" from the first decade of publications. The research to better understand those complications and risks is still before us.

What do we do now?

So where are we? As the *Annals* editors state, "*after systematic evaluation and synthesis of all available evidence, both systematic reviews published here independently conclude that rhBMP-2, compared with iliac crest bone grafting, does not improve pain or function and increases adverse events, possibly including cancer*." A surgeon would need a truly exceptional case to use BMP-2 when the data supporting its use are marginal and the scant complications data we have comes through potentially biased filters at every level. If the complications monitoring processes were as biased as the analyses and reporting processes have proven to be, then data YODA was given fundamentally and systematically misrepresent the risk of BMP-2 use. Is there reason to assume otherwise?

(more)

At present, Medtronic-sponsored surgeons may finally retire the line that "this product is completely safe, don't worry about it" but I would not count on it. Instead, it is up to journals, medical societies and the honest surgeons everywhere to say "enough is enough." Before we routinely put in our patients any more BMP-2 (or the next "single most successful product ever launched in orthopedics and possibly ever in medicine") we should require convincing data proving it really is better and safer than what we have now. To do this we will need unbiased presentation and accessible data, sometimes to the level of the individual patient. Unless we remain vigilant, medical publications will continue to devolve into information-laundering machines and clinical studies become infomercials for their corporate sponsors. We will need estimates of authors' financial associations and bias that are not printed for laughs. Until redeemed in time, the legacy YODA may leave us is the impression unvetted, industry-sponsored trials is as reliable as late night-TV weight-loss pitches.

The Spine Journal *is an international, multidisciplinary journal that publishes original, peer-reviewed articles on research and treatment related to the spine and spine care, including basic science and clinical investigations. With a 3.290 Impact Factor,* ***The Spine Journal*** *is the top-rated spine journal and the third-ranked orthopedic journal in the world. Published online continuously and printed monthly by Elsevier, Inc.,* ***The Spine Journal*** *is the scientific publication of the North American Spine Society (NASS). NASS adheres to a policy of editorial independence for the journal's editorial board, which follows guidelines of the International Committee of Medical Journal Editors, Committee on Publication Ethics and other best editorial practices.*

###