

Editorial

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Combating the Spread of Ineffective Medical Procedures A Lesson Learned From Multiple Sclerosis

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The Information Age has had a staggering effect on the spread and democratization of knowledge. The increased availability of cutting-edge data has accelerated the speed of breakthroughs. Faster communication of major discoveries in science has highlighted the need for scientists and physicians to hone their skills at simple and clear communication of their newfound knowledge to the general public. In medicine, we have realized significant gains by broadening international collaboration and widening the audience for medical knowledge.

However, these advances have come at a cost. The value of expertise has at times been degraded, and the careful judicious review of data has sometimes been compromised in the effort to quickly circulate new findings to the largest possible audience. At times, preliminary concepts that might have previously helped catalyze new thinking—but that still should have been considered provisional—have been inappropriately regarded as signaling a paradigm shift, without the requisite opportunity for expert appraisal. This is an important danger that we need to address.

In 2009, Zamboni et al concurrently published 2 studies^{1,2} on venous stasis in multiple sclerosis (MS). As part of this work, Paolo Zamboni, MD, coined the term *chronic cerebrospinal venous insufficiency* (CCSVI) to describe a phenomena of hypoplasia, intraluminal defects in the internal jugular and azygous veins, and an ill-defined concept that he termed *compression*. The first study¹ described the CCSVI pattern and reported an extraordinarily high frequency of CCSVI findings in patients with all types of MS, with greater than 70% of patients harboring different CCSVI features (compared with 0% to 11% of controls). Zamboni et al¹ also reported that patients with MS had a more than an 1100-fold increase in the odds of having reflux in their internal jugular or vertebral veins. A sister publication² described the observed benefits of an open-label study for

percutaneous balloon venoplasty in patients with MS with identified CCSVI. These publications together suggested that the field had overlooked the possibility that venous pooling in the central nervous system contributed to the pathogenesis of MS. Zamboni, who had begun his foray into MS research as an established expert in vascular disease and treatment, freely acknowledged in later press coverage that the experience his wife had with MS helped motivate him to help to do something transformational. In November 2009, the story of his work was highlighted in a 30-minute video documentary on Canada TV's "W5" program, which was accompanied by an article in *The Globe and Mail*.³ Interest in this emotionally resonant and uplifting program spread rapidly among patient blogs. This in turn prompted the creation of Facebook pages and patient interest groups,³ and soon enthusiasm for the method grew into calls for action. In 2010, based on advocacy from those who had come to strongly believe in the importance of CCSVI, the US National Multiple Sclerosis Society dedicated \$2.4 million, or nearly 7% of its research budget, to studies of CCSVI. Variations in interventional treatment methods to include stenting in addition to venoplasty emerged, with individual centers each adopting their own protocols and techniques. This momentum was not slowed by reports of complications, which included the deaths of 2 Canadian patients⁴ and 1 US patient⁵ (who were treated in Costa Rica and California).

In 2011, the Canadian Institute for Health Research set up a scientific expert working group to investigate the relationship between MS and CCSVI.⁶ This led to a bill in Canadian Parliament to provide special funding for clinical research studies dedicated to further evaluating CCSVI, with a special focus on clinical trials. It did not pass, but the Canadian government ultimately dedicated more than Can\$5 million to funding research in this area. Calls were made to the US National Institutes of Health to commit equivalent resources. The Directorate General for Health and Welfare of the Italian region of Emilia Romagna also provided €2.75 million (\$3.6 million in 2012 US dollars) of funding for a randomized clinical trial, to which patients added donations of €63 000 (\$82 500).⁷ In 2012, *The New York Times Magazine*³ covered CCSVI, at which time it was estimated that up to 20 000 people worldwide had undergone the so-called liberation treatment or some variation thereof for the treatment of MS.

In *The New York Times Magazine* article,³ Robert Fox, MD, captured the general sentiment of MS clinicians and researchers at the time by calling the evidence of the contribution of CCSVI to MS pathogenesis weak. Since the introduction of the concept in 2009, more than 225 articles on CCSVI have been published and indexed (under the search term CCSVI) in the US National Institutes of Health National Library of Medicine research archive PubMed Central. Of these, 211 are related to MS. Most early attempts to independently replicate the findings of Zamboni et al^{1,2} were unsuccessful.^{8,9} Multiple studies found either low rates of CCSVI in cohorts of patients with MS or even higher rates in study participants with neurological diseases other than MS.^{8,9} Furthermore, no correlation was found between markers of disease severity and CCSVI findings. Additional work established that CCSVI could not be detected by a blinded ultrasonographer in patients with clinically isolated syndrome or early relapsing-remitting MS (all of whom presumably had less neurological dysfunction and therefore less obvious clinical status than patients who had advanced MS).¹⁰ Others established by means of gold standard catheter venography that absolutely no evidence for venous compromise existed in MS.¹¹ However, patients who underwent CCSVI treatment continued to report subjective clinical improvement, and the field has therefore been waiting for the final word from 2 concurrent blinded clinical trials funded via the aforementioned mechanisms.

In this issue of *JAMA Neurology*, Zamboni and colleagues¹² report the results of their definitive randomized, double-blind sham-controlled clinical trial. This trial of 115 participants (of whom 76 were randomized to receive percutaneous transluminal venous angioplasty and 39 to receive a sham procedure) finds no benefit for “liberation treatment” for patients with MS, including no benefit in a disability outcome measure that included assessments of walking, balance, hand function, urinary function, and visual acuity. No benefit was seen for treated patients with regards to the percentage of patients who were free of new lesions or the number of new brain lesions observed. The disability outcome measure was novel and not the typical Expanded Disability Status Score or Multiple Sclerosis Functional Composite score, but this option was intentionally chosen by the investigators out of concern that the standard measures of disability would be insensitive to possible benefits. The study was smaller than initially intended, but the results suggested absolutely no benefit to treatment, with the primary end point actually favoring the sham procedure.

The investigators note a remarkable issue: despite a 2:1 randomization, recruitment was partially curtailed because patients were unwilling to enroll in the trial that might require them to undergo a sham procedure and therefore forgo a treatment that the media had emphasized as beneficial. The Canadian randomized clinical trial by Traboulsee et al¹³ presented its own negative result at the Society for Interventional Neuroscience and World Congress of Neurology. These data were also presented to the working group at the Canadian Institute for Health Research, who recommended that what they called “rigorous... gold-standard” data⁶ be reported to the public.

More than 4 decades ago, Richard Dawkins, MA, DPhil, posited the existence of memes and suggested that ideas become self-sustaining, duplicate, and spread in proportion to how much they reaffirm or communicate ideas that are intrinsic to a culture. The CCSVI theory had many of the features of a self-perpetuating idea. It taught distrust of naysayers and nonbelievers. It reaffirmed worry in some quarters that clinicians and the health care industry were conspiring to maintain certain chronic diseases, such as MS, rather than effectively cure them, to ensure patient dependence on the health care and pharmaceutical industries. It also offered some degree of salvation, providing the promise of hope and reassurance to people living with a potentially devastating neurological illness for which cure and definitive treatment remain elusive. It reinforced cultural paradigms and norms, and it thrived in a medical environment in which procedures are sometimes elevated over medicinal therapy because of their allegedly curative capacity. It even traded on the notion that the spread and democratization of information was the reason people were freed from the existing bankrupt and incorrect paradigm of MS as an autoimmune disease.

New medical procedures often spread quickly, in part because it is easier to get approval for the use of a device to treat medical illness than a drug and in part because reimbursement, especially in a fee-for-service model, is generally greater for procedures than for medications.¹⁴ In the modern era, US Food and Drug Administration approval of new drugs typically requires 2 separate randomized double-blinded studies with appropriate assessment and evidence of safety.¹⁴ A detailed review of the methods acceptable for showing efficacy is typically provided by regulatory authorities both before the studies are undertaken and after the studies are complete to ensure that the data support approval.¹⁴ A similar but separate regulatory framework exists in Europe.¹⁴ However, in the United States, no clinical evidence is required to market a procedure involving a low-risk medical device other than a premarket notification to the

Food and Drug Administration; even for higher-risk devices, requirements for randomized clinical trials are sometimes not imposed on manufacturers because of the challenges of randomization and blinding.¹⁴ Clearance requests can be provided for medical devices that merely demonstrate they are substantially similar to products already on market. In Europe, there is greater variation across the member states of the European Union, but rules are similarly less rigid and more permissive than they are for drug treatments.¹⁴ For example, the stents and balloons used for the treatment of venous conditions, such as CCSVI, are typically identical to those that were originally approved for the purpose of arterial stenting without considering the differences in vessel compliance or changes in vein collapsibility on movement. No substantial evidence of their efficacy needs to be provided for manufacturers to market the product or physicians and hospitals to offer a procedure to treat a particular medical condition. The major regulatory control emanates from the judgment of the medical practitioner, availability of a payer to reimburse for the procedure, and concerns for medical liability in acting outside of the standard of care.¹⁴ The recent successes of newer-generation stent retrievers for acute thromboses in cases of stroke and patent foramen ovale closure devices for secondary prevention in narrow indications have only followed years of reimbursed procedures that were likely of no benefit.¹⁵ In addition, procedures such as venous stenting for Ménière disease¹⁶ or idiopathic intracranial hypertension¹⁷ are now increasingly being performed at multiple centers before the results of definitive trials are available.

As clinicians, we owe it to patients to protect them from false advances without appropriate efficacy and safety data, but we are often confronted with a wave of pressure from referring physicians, hospitals, advocacy groups, and the patients themselves. Zamboni et al should be applauded for their clear-eyed evaluation¹² of their earlier theory^{1,2} in a rigorous and definitive fashion. It is difficult to refute one's own prior findings, but the authors have used the right methods to test the CCSVI theory and have yielded an unequivocal result.

We have an epidemic in medicine of these types of stories. As with infectious disease outbreaks, we can best learn how to control spread of ill-advised communicable ideas by reviewing what went wrong in the last occurrence. Hopefully, the field can use this lesson to identify what can be done to inoculate ourselves against similar future events.

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