Responding to the challenge of clinically relevant osteopathic research: efficacy and beyond

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Abstract

The osteopathic profession has been challenged over the past decade to provide clinically relevant research. The conduct of evidence-based osteopathic research is imperative not only for scientific, economic, and professional reasons, but also to drive health care policy and clinical practice guidelines. This paper summarizes recent studies in response to the osteopathic research challenge, including clinical trials registered with ClinicalTrials.gov and a systematic review and meta-analysis of osteopathic manipulative treatment (OMT) for low back pain. The concept of the OMT responder is introduced and supported with preliminary data. Within the context of a pain processing model, consideration is given to genomic (e.g., the catechol-O-methyltransferase gene) and psychological (e.g., depression and somatization) factors that are associated with pain sensitivity and pain progression, and to the role that such factors may play in screening for OMT responders. While substantial progress has been made in osteopathic research, much more needs to be done.

Keywords

osteopathy; osteopathic medicine; osteopathic manipulative treatment (OMT); low back pain; genomics; catechol-O-methyltransferase (COMT); pain processing

1. The osteopathic research challenge

In a recent *Journal* editorial, Lucas and Moran raised critical questions regarding the relevancy of contemporary osteopathy research in the evolving healthcare environment.[1] Their ultimate challenge to the osteopathic profession was to provide the "*numbers*" supporting the clinical effectiveness of osteopathy, or osteopathic manipulative treatment (OMT) as it is better known in the United States. They aptly identified important consumers of the numbers, including researchers, universities, health insurers, government agencies, and the media, with the latter noted to exert considerable influence over public opinion and, potentially, policy. The recent media attention afforded the Ernst and Canter[2] systematic review of systematic reviews of spinal manipulation and its conclusion that "*data do not demonstrate that spinal manipulation is an effective intervention for any condition,*" illustrates their point.

The osteopathic profession in the United States has been similarly challenged in the past decade. In 1997, Goldstein editorialized that the profession should foster evidence-based osteopathic medicine.[3] In 1999, following publication of a major randomized controlled trial of OMT in the *New England Journal of Medicine*,[4] Howell commented that "*the long-term*

survival of osteopathic medicine will depend on its ability to define itself as distinct from and yet still equivalent to allopathic medicine. That argument may best be articulated not in theoretical terms, but by demonstrating treatment outcomes."[5] Apparently, Howell's "*outcomes*" relate to osteopathic medicine as Lucus and Moran's numbers relate to osteopathy.

1.1 Ongoing osteopathic clinical trials

The American response to such osteopathic research challenges has grown considerably over time. Just 10 years ago, the evidence base for OMT was virtually non-existent. In contrast, at the end of 2006, a search of the ClinicalTrials.gov database maintained by the National Institutes of Health identified six ongoing randomized controlled trials involving OMT and five other trials that had been completed or were no longer recruiting subjects. These clinical trials are summarized in Table 1, which reveals the wide variety of conditions being evaluated for OMT efficacy. Most trials involve comparisons of OMT with placebo or active treatments, and a majority of trials report using a double-blind methodology. A flurry of OMT research reports should be forthcoming in the near future based on these recently completed trials and those that are scheduled to stop recruiting subjects in 2007.

1.2 Systematic review and meta-analysis of osteopathic manipulative treatment outcomes

As suggested by Lucas and Moran,[1] the numbers are particularly germane to systematic reviews and meta-analyses (SRMAs), which lie at the top of the evidence pyramid and often drive healthcare policy decisions, such as payment for various clinical services. In that regard, the Ernst and Cantor study[2] noted above pre-dated the first and only known SRMA specifically addressing OMT, published by Licciardone and colleagues in 2005.[6] The overall findings of the latter study, which assessed the efficacy of OMT in treating low back pain, are presented as a forest plot in Figure 1. The subjects who received OMT experienced a greater reduction in low back pain compared with those subjects who did not receive OMT (mean effect size, −0.30; 95% confidence interval, −0.47 – −0.13; P=.001). Thus, OMT provided clinically relevant and statistically significant reductions in low back pain.

Beyond these overall findings, the SRMA subgroup analyses yielded three important results. First, in those randomized controlled trials in which OMT was compared with other active or placebo treatments, the OMT group continued to demonstrate clinically relevant and statistically significant reductions in low back pain (mean effect size, −0.26; 95% confidence interval, −0.48 – −0.05; P=.02). This finding supports the conclusion that benefits of OMT in treating low back pain cannot be attributed merely to the placebo effect. Second, comparable OMT effects were observed in randomized controlled trials conducted in the United States (mean effect size, −0.31; 95% confidence interval, −0.52 – −0.10; P=.004) and in the United Kingdom (mean effect size, −0.29; 95% confidence interval, −0.58 – −0.00; P=.05). Because osteopathic physicians in the United States and osteopaths in the United Kingdom have disparate clinical practice rights by law, these comparable findings support the validity of the SRMA in isolating the treatment effects attributable to OMT, exclusive of other co-treatments such as prescription drugs. Finally, OMT effects increased over time (mean effect size, −0.28; 95% confidence interval, −0.51 – −0.06; P=.01 for short-term outcomes; mean effect size, −0.33; 95% confidence interval, −0.51 – −0.15; P<.001 for intermediate-term outcomes; and mean effect size, −0.40; 95% confidence interval, −0.74 – −0.05; P=.03 for long-term outcomes). These findings suggest the possibility that OMT benefits are cumulative, yielding augmented analgesic responses over time. Licciardone and colleagues are presently conducting a comprehensive SRMA project aimed at assessing the efficacy of OMT for a variety of clinical conditions. More than 2000 bibliographic citations have been identified and evaluated for potential inclusion in that study.

2. The osteopathic manipulative treatment responder

The variability among similar patients in response to a given pain treatment has perplexed health care providers and payers alike for many years.[7] At present there is no consensus on what constitutes a favorable response to a given treatment for low back pain. However, Assendelft and colleagues in collaboration with the Cochrane Collaboration's Back Editorial Board, recommended that a mean pain reduction of 10 mm on a 100-mm visual analogue scale (VAS) be considered clinically relevant when comparing spinal manipulation with control treatments.[8] Using their assumption of a 25-mm standard deviation on such scales, the clinically relevant effect size in comparison with a "perfect" placebo that provides no therapeutic effect is (10 mm – 0 mm)/25 mm, or 0.40. However, perfect placebos are rarely encountered in pain studies. In fact, a review of clinical trials involving placebo treatment vs. no treatment arms found an effect size of 0.27 associated with placebo treatment in pain studies.[9] Thus, an effect size of 0.67 (0.40 + 0.27) or a 17-mm (0.67 effect size × 25-mm SD) pain reduction on a 100-mm VAS may be used to identify responders to OMT.

As there is little published work on the response to OMT, data from the North Texas clinical trial[10] involving OMT in subjects with chronic low back pain were re-analyzed to determine if OMT responders could be identified. This re-analysis focused on the 48 subjects who were randomly allocated to the OMT + usual care (UC) group, as opposed to the sham manipulative treatment + UC group or the UC only group. The OMT + UC subjects included 33 women and 15 men having a mean age (SD) of 49.0 (11.6) years. A total of 32 (67%) subjects completed the entire 6-month protocol. Using the 17-mm pain reduction criterion established above, 13 OMT subjects (27% of randomized subjects and 41% of trial completers) were identified as OMT responders at the 6-month exit visit. A comparison of these OMT responders and 19 non-responders with regard to VAS pain scores over time is depicted in Figure 2. This provides graphical evidence to support the existence of the OMT responder. Further, statistical analysis confirmed significantly different pain outcomes over time in OMT responders and non-responders ($P<.001$ based on group × time interaction in repeated measures analysis of variance).

3. Genomic considerations in osteopathic manipulative treatment response

With the advent of genomic medicine and greater recognition of host-environment interactions in the etiology of and response to disease,[11] another challenge for osteopathic research will be to use emerging technologies to help identify OMT responders. This osteopathic research challenge is currently foreshadowed by analogous developments in pharmacogenomics.[12] Responses to drug therapy are quite variable, ranging from complete disease remission to fatal adverse events. Such pharmacologic variation may be attributed to many factors, including disease susceptibility, drug metabolism, drug transport, and target-organ response. Genomics offers the promise of individualizing drugs and dosages for a given patient. Similarly, genomics may help identify OMT responders and better guide their individualized treatment.

With regard to pain sensitivity, recent studies have shown a link between gene polymorphisms (often referred to as single nucleotide polymorphisms, or SNPs) and pain phenotypes. In 2003, Zubieta and colleagues found that the gene encoding for catechol-O-methyltransferase (COMT) modulates pain sensitivity.[13] Subjects homozygous for the met^{158} allele of the COMT polymorphism ($val^{158}met$) showed diminished regional μ-opioid system responses to pain compared with heterozygotes who, correspondingly, showed diminished responses compared with val^{158}homozygotes. Importantly, they found that diminished μ-upload system responses to pain were associated with higher sensory and affective ratings of pain, thereby suggesting that the COMT $val^{158}met$ polymorphism influences the human experience of pain and may underlie interindividual differences in response to pain.

In 2005, these findings were extended by Diatchenko and colleagues,[14] who studied haplotypes of the COMP gene. Haplotypes are sets of SNPs on a single chromatid that are statistically associated. They reported that three haplotypes of the COMT gene were associated with the risk of developing myogenous temperomandibular joint (TMJ) disorder. These haplotypes, which comprise 96% of the human population, were designated as low (LPS), average (APS), or high pain sensitivity (HPS). The relative risk of developing TMJ disorder was 2.3 (95% confidence interval, 1.1 – 4.8) in subjects having only HPS and/or APS haplotypes compared with subjects having at least one LPS haplotype. In addition to COMT, other high priority candidate genes for human neuropathic pain (and the molecules that they encode) include: IL1B (interleukin 1β), IL6 (interleukin 6), NOS1 (neuronal nitric oxide synthase), NOS2A (inducible nitric oxide synthase), OPRM1 (μ-opioid receptor), SLC6A4 (serotonin transporter), BDKRB2 (bradykinin receptor 2), 2TNFα (tumor necrosis factor α), GDNF (glial-derived nerve factor), and PDYN (prodynorphin).[15] Additional research is needed to elucidate the role that such genes and molecules may play in the etiology of somatic dysfunction and pain, and in the response to OMT.

4. Psychological considerations in osteopathic manipulative treatment response

With regard to pain treatment, third-party payers often require pretreatment psychological screenings to help identify patients at risk for poor outcomes.[7] Thus, another challenge for osteopathic research is to develop a psychological profile of OMT responders, particularly with regard to chronic pain disorders. The stages of pain processing model developed by Wade and colleagues,[16, 17] as schematically represented in Figure 3, may be used to glean some insight into the multiple factors associated with low back pain. Intensity, the initial stage of pain, is dependent upon sensory-discriminative sensitivity to noxious stimuli and, as indicated above, may be related to host genetic and molecular factors. The next stage of pain processing involves unpleasantness, which reflects the immediate affective response to the painful sensation. Chronic pain results in suffering, which is strongly related to higher cognitive processes, including negative beliefs and emotions. Several prospective studies have assessed psychological factors thought to play a role in the progression of low back pain [18–23]; however, not until Pincus and colleagues conducted a systematic review was there a critical appraisal of the relevant scientific evidence.[24] Depression (often labeled as "distress," and comprised of depressive symptoms, depressive mood, or psychological distress) and somatization were the primary psychological factors implicated in the transition to chronic low back pain. The last stage of pain processing involves overt behavioral expressions of pain, such as functional disability. Studies of psychological factors, including those associated with pain processing, may not only help disentangle the specific effects (i.e, those attributable to OMT) from the non-specific effects (i.e., those attributable to placebo), but may also be useful in addressing the potential interaction between OMT and placebo responses.[25] Thus, this represents a crucial area of osteopathic research.

5. Conclusion

A pain processing model such as that presented above provides a useful framework for considering the multifactorial etiology and progression of chronic pain disorders, such as those often treated with OMT. Consequently, in studying the response to OMT, this framework enables integration of both emerging scientific disciplines such as genomics and more traditional disciplines such as psychology. For example, the COMT haplotypes described above serve as key regulators of pain perception, cognitive function, and affective mood by altering the mRNA secondary structure that modulates protein expression.[26] Thus, genetic factors may help explain multisomatoform pain disorders that share neural abnormalities that amplify sensory stimuli and increase the risk of mood disorders.[27] While substantial progress

has been made in osteopathic research during the past few years, particularly involving clinical trials to assess OMT efficacy, much more basic and translational research is needed to move beyond the status quo in osteopathic research.

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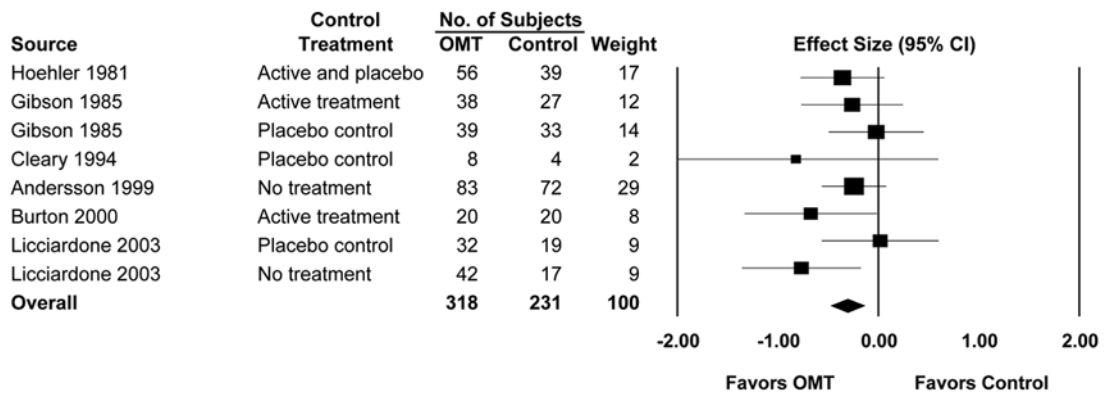
Figure 1.
Osteopathic manipulative treatment (OMT) of low back pain. CI denotes confidence interval. (Reproduced with permission from Licciardone and colleagues.[6] Source citations for meta-analysis are provided therein.)
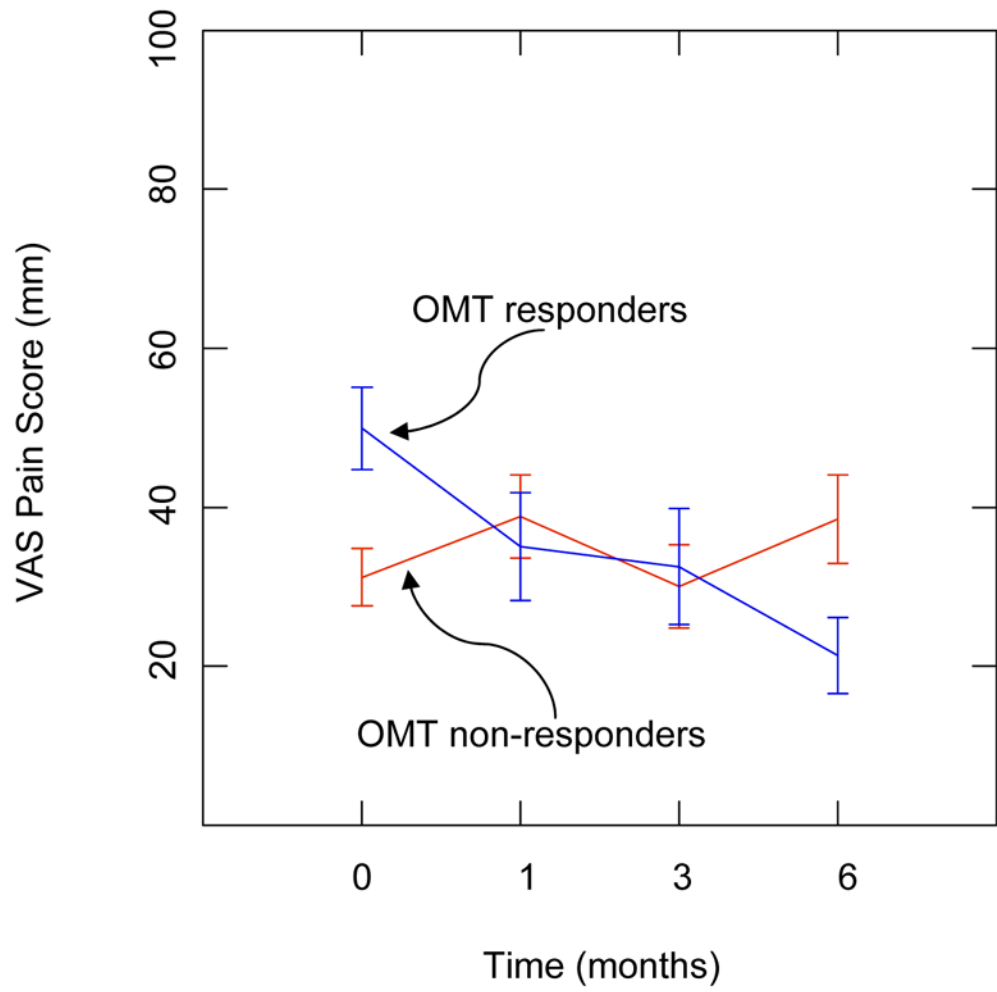
Figure 2.
Pain outcomes over time in osteopathic manipulative treatment (OMT) responders and non-responders. VAS denotes visual analogue scale.
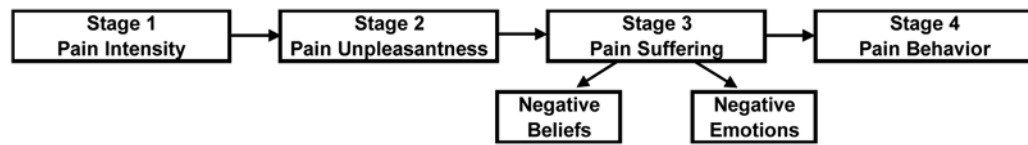
Figure 3.
Stages of pain processing. (Adapted from Wade and colleagues.[16, 17].)

Table 1

Osteopathic clinical trials registered with ClinicalTrials.gov according to size.[*]

Target Disorder or Condition	ClinicalTrials.gov Identifier	Status	NIH Funded	Phase	N	Start Date	End Date[†]	Blinding	Control	Assignment
Chronic low back pain	NCT00315120	Ongoing	Yes	III	488	Aug 2006	Oct 2010	Double	Placebo	Factorial
Pneumonia	NCT00258661	Ongoing	No	NS	360	Mar 2004	Jul 2007	Double	Placebo	Factorial
Carpal tunnel syndrome	NCT00394043	Ongoing	Yes	II	138	Oct 2006	Jan 2010	Double	Placebo	Parallel
Low back pain	NCT00394264	Ongoing	No	II	100	Oct 2006	Dec 2007	Single	Active	Parallel
Muscle tension	NCT00403936	Completed	No	NS	100	Apr 2005	May 2005	Single	Active	Cross-over
Pregnancy	NCT00298935	Completed	No	NS	99	Jul 2003	May 2006	Double	Placebo	Parallel
Postoperative nausea and vomiting	NCT00387361	Ongoing	No	II	60	Oct 2006	Mar 2007	Double	Placebo	Parallel
Low back and hip pain	NCT00410397	Ongoing	No	NS	20	Dec 2006	Feb 2007	Single	Placebo	Parallel
Emphysema	NCT00034112	Completed	Yes	II	NS	Apr 2001	Mar 2002	NS	Placebo	Parallel
Spastic cerebral palsy	NCT00011024	Completed	Yes	II	NS	Sep 1998	Jun 2004	NS	NS	NS
Otitis media	NCT00010465	Completed	Yes	II	NS	NS	NS	Double	Placebo	NS

[*] Information as reported in December 2006; NIH denotes National Institutes of Health; NS, not specified.

[†] Based on data entry closure date.