An Exploratory Analysis of Gender as a Potential Modifier of Treatment Effect Among Patients in a Randomized Controlled Trial of Integrative Acupuncture and Spinal Manipulation for Low Back Pain

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Abstract

Objective: To identify the potential association of self-reported gender on pain and disability among patients in a randomized controlled trial of integrative acupuncture and spinal manipulation therapy (SMT) for low back pain (LBP).
Methods: In the original study, 100 participants with LBP were randomized to receive acupuncture, SMT, or both combined. Eighty completed treatment and were followed for 60 days. Primary outcome measures were the Roland-Morris Disability Questionnaire and numeric pain scales. This study was a secondary analysis and used regression models to estimate and test for gender-specific differences in outcomes from baseline through end of treatment.
Results: Women assigned to acupuncture averaged a 3.8-point reduction in highest LBP vs 2.0 points for SMT, whereas men assigned to SMT averaged a 3.5-point reduction vs 1.8 points for acupuncture (*P* for interaction = .04). There was a trend toward the same for disability (*P* for interaction = .12). For women, acupuncture alone led to better outcomes without SMT, and for men, SMT alone led to better outcomes without acupuncture. Women who received acupuncture were more likely to experience 50% or greater reductions in disability and pain, whereas men who received SMT were more likely to experience 50% or greater reductions in disability and pain.
Conclusion: An association was found between self-reported gender and response to LBP treatment. Women demonstrated a greater reduction in pain and disability with acupuncture and men with SMT. Future clinical trials should consider sex as a potential determinant of treatment outcomes for LBP. (J Manipulative Physiol Ther 2019;42:177-186)
Key Indexing Terms: *Low Back Pain; Acupuncture; Manipulation, Spinal; Integrative Medicine; Gender Identity*

Introduction

Previous studies report that the lifetime prevalence of low back pain (LBP) globally may be as high as 84%.[1,2] Throughout the industrialized world, LBP is a leading cause of absenteeism, disability, and diminished quality of life[3] and is a major driver of health care costs.[4] In developing nations, the prevalence of LBP and the social and economic impact is profound, and potentially even more disabling due to the high percentage of the work force that engages in manual labor.[3,5-8] The pervasiveness of LBP coupled with the high costs and associated morbidity positions it as one of the most significant contributors to the global burden of disease.[9] In the United States alone, it is estimated that $90 billion is spent annually on the diagnosis and management of LBP,[10] with upward of an additional $20 billion more attributed to lost productivity.[11,12] Despite this remarkable burden, an optimum approach to LBP

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Table 1. *Sex-Specific Frequency Distributions (Numbers and Percents or Means [SDs] and Medians) of Selected Sociodemographic and Health-Status Variables, by Treatment Group (n = 80)*

		Female			Male		
		AOM	DC	AOM + DC	AOM	DC	AOM + DC
Variable	Category	(n = 7)	(n = 16)	(n = 17)	(n = 16	(n = 12)	(n = 12)
Age (y)	Mean (SD)	37.9 (18.6)	44.9 (14.6)	45.1 (14.8)	40.7 (12.5)	42.5 (17.1)	40.5 (17.5)
	Median	31	43.5	46	39	41.5	32.5
SF-36 Physical function	Mean (SD)	58.3 (16.3)	51.2 (26.0)	61.6 (30.4)	69.7 (22.5)	70.9 (27.5)	65.0 (25.7)
	Median	55	55	65	77.5	75	65
SF-36 Role—physical	Mean (SD)	41.7 (40.8)	54.7 (40.0)	46.9 (44.6)	35.9 (37.6)	54.5 (40.0)	50.0 (41.3)
	Median	37.5	75	37.5	37.5	50	25
SF-36 Role—emotional	Mean (SD)	61.1 (49.1)	56.2 (45.1)	51.0 (44.3)	60.4 (40.8)	63.3 (36.7)	55.6 (43.4)
	Median	83.3	66.7	66.7	66.7	66.7	50
SF-36 Mental health	Mean (SD)	65.3 (12.0)	74.7 (21.8)	67.1 (22.3)	71.0 (19.5)	72.0 (19.0)	70.2 (20.3)
	Median	64	80	72	76	72	72
SF-36 Social function	Mean (SD)	60.4 (20.0)	69.5 (29.9)	69.1 (24.7)	72.7 (29.3)	69.3 (29.8)	64.8 (31.5)
	Median	68.75	75	75	81.25	75	75
SF-36 Bodily pain	Mean (SD)	42.9 (17.1)	53.4 (24.3)	54.6 (18.2)	52.2 (21.8)	52.7 (19.9)	56.8 (25.2)
	Median	45	56.25	55	56.25	55	55
SF-36 General health	Mean (SD)	49.2 (24.2)	74.7 (16.2)	62.0 (22.3)	68.1 (26.6)	68.9 (21.8)	60.5 (15.1)
	Median	37.5	75	55	72.5	65	65

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *SD*, standard deviation; *SF-36*, 36-Item Short-Form Health Survey.

treatment has not been identified and predictors of a patient's response to different types of care remains largely enigmatic.[13]

Research is increasingly recognizing the influence of a person's genetic makeup in the treatment of diseases such as cancer. However, very few studies have investigated the role of genetic differences, such as biological sex or gender identity, as a modifier of LBP outcomes.[13] It appears there is an increased prevalence of LBP among women compared with men; however, the literature is heterogeneous and the magnitude of difference reported is variable.[14-19]

Sex or gender differences in clinical outcomes for LBP have been explored for select interventions. Jensen et al reported gender differences in response to a behavioral modification rehabilitation intervention for chronic spinal pain.[20] Pieh et al found that in response to a multimodal pain treatment program that included physicians, psychologists, physical therapists, a nutritionist, a social worker, and a relaxation therapist, women achieved better outcomes than men in pain-related disabilities in daily life.[21] Hansen et al found that men responded better than women to conventional physical therapy for LBP.[22] Similarly, Peterson et al found statistically significant gender differences at 1-month pain levels after chiropractic treatment with greater improvements noted in men than women.[23] The sex or gender differences that have been observed in the literature have led some researchers to suggest that when it comes to risk and prognostic factors for LBP, men and women should be studied separately.[5] A review of current literature suggests that there is also a large gap regarding sex or gender differences and response to care for LBP.

We previously conducted a small-scale randomized controlled trial on an integrative care model for LBP.[24] This study examined whether combining spinal manipulative therapy (SMT) and acupuncture led to better outcomes for LBP than either therapy alone. Participants in all 3 groups experienced clinically meaningful improvements in the primary outcome measures, and no between-group differences in outcomes were observed. However, the study did not consider whether gender was a factor that influenced participants' responsiveness to care.[24]

Objective

The objective of this secondary analysis was to investigate the potential association of self-reported gender on pain and

Table 2. *Sex-Specific Frequency Distributions (Numbers and Percents or Means [SDs] and Medians) of Primary LBP Outcome Variables at Baseline by Treatment Group (n = 80)*

		Female			Male		
		AOM	DC	AOM + DC	AOM	DC	AOM + DC
Variable	Category	(n = 7)	(n = 16)	(n = 17)	(n = 16)	(n = 12)	(n = 12)
Roland-Morris LBP	Mean (SD)	13.4 (5.3)	10.1 (5.4)	9.6 (6.4)	9.0 (6.1)	10.1 (6.1)	8.8 (6.0)
Disability score (0-24)	Median	14	10	10	6.5	11	9
Current LBP	Mean (SD)	4.9 (1.8)	5.0 (2.2)	4.3 (2.2)	4.1 (2.3)	3.8 (2.3)	4.0 (1.9)
(0-10 NRS)	Median	4	5.5	4	4	4	4
Typical LBP last week	Mean (SD)	6.4 (1.7)	5.4 (2.4)	5.8 (2.1)	5.2 (2.1)	5.0 (1.6)	4.8 (1.6)
(0-10 NRS)	Median	7	6	5.5	6	4.5	5
Lowest LBP last week	Mean (SD)	3.1 (1.2)	3.4 (2.3)	2.5 (1.9)	2.7 (1.9)	2.3 (1.8)	2.6 (2.1)
(0-10 NRS)	Median	3	3	2	3	2	2
Highest LBP last week	Mean (SD)	7.4 (1.3)	7.1 (2.3)	7.5 (1.6)	7.0 (1.9)	6.9 (1.7)	7.0 (1.9)
(0-10 NRS)	Median	8	8	8	7	7	7

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *NRS*, numeric rating scale; *SD*, standard deviation.

Table 3. *Sex-Specific Frequency Distributions (Numbers and Percents or Means [SDs] and Medians) of Secondary LBP Outcome Variables at Baseline by Treatment Group (n = 80)* [a]

		Female			Male		
		AOM	DC	AOM + DC	AOM	DC	AOM + DC
Variable	Category	(n = 7)	(n = 16)	(n = 17)	(n = 16)	(n = 12)	(n = 12)
Percent time with LBP	<50% (%)	1 (14.3)	2 (13.3)	4 (25.0)	3 (21.4)	4 (33.3)	3 (25.0)
	50% (%)	2 (28.6)	5 (33.3)	3 (18.8)	6 (42.9)	1 (8.3)	3 (25.0)
	>50% (%)	4 (66.1)	8 (52.3)	9 (56.2)	5 (35.7)	7 (58.3)	6 (50.0)
	Mean (SD)	64.3 (24.4)	61.7 (20.8)	65.6 (30.1)	58.9 (27.0)	62.5 (31.1)	56.2 (21.6)
	Median	75	75	75	50	75	62.5
Days per week with LBP	<7 (%)	3 (43.9)	6 (40.0)	8 (47.1)	8 (50.0)	5 (41.7)	5 (41.7)
	7 (%)	4 (57.1)	9 (60.0)	9 (52.9)	8 (50.0)	7 (58.3)	7 (41.7)
	Mean (SD)	6.0 (1.3)	5.9 (1.6)	5.4 (1.9)	5.9 (1.4)	5.7 (1.8)	6.1 (1.2)
	Median	7	7	7	6.5	7	7
Missed days last week because of LBP	0 (%)	5 (83.3)	13 (100)	13 (81.2)	11 (84.6)	8 (72.7)	8 (88.9)
	1+ (%)	1 (16.7)	0 (0.0)	3 (18.8)	2 (15.4)	3 (27.3)	1 (11.1)
	Mean (SD)	0.2 (0.4)	0.0 (0.0)	0.6 (1.7)	0.2 (0.4)	0.7 (1.3)	0.1 (0.3)
	Median	0	0	0	0	0	0
Pain pills past week because of LBP	Not at all (%)	1 (14.3)	5 (31.2)	7 (41.2)	8 (50.0)	10 (90.9)	6 (54.5)
	A few times (%	6 (85.7)	7 (43.8)	8 (47.1)	7 (43.8)	0 (0.0)	4 (36.4)
	Daily (%)	0 (0.0)	4 (25.0)	2 (11.8)	1 (6.2)	1 (9.1)	1 (9.1)

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *SD*, standard deviation.

[a] Numbers may not total 80 because of missing values; percentages are of nonmissing observations and may not sum to 100 because of rounding.

Table 4. *Estimated Sex-Specific Age-Adjusted Means (95% CIs) of Primary Outcome Variables at 60 Days by Treatment Group: Results From Mixed-Effects Linear Models*

		Female		Male	
Outcome	Treatment	Mean	(95% CI)	Mean	(95% CI)
LBP Disability (0-24)	(1) AOM	6.1	(1.9-10.4)	6.5	(3.8-9.1)
	(2) DC	7.8	(4.8-10.8)	5.0	(1.9-8.0)
	(3) AOM + DC	5.5	(2.5-8.4)	6.7	(3.4-10.0)
			$P_{tx*sex\ interaction} = 0.5467$		
Current LBP (0-10)	(1) AOM	1.6	(0.04-3.4)	3.1	(2.1-4.1)
	(2) DC	2.6	(1.5-3.6)	1.7	(0.6-2.9)
	(3) AOM + DC	2.0	(1.0-3.0)	2.5	(1.3-3.7)
			$P_{tx*sex\ interaction} = 0.0805$		
Typical LBP (0-10)	(1) AOM	2.1	(0.6-3.7)	3.3	(2.2-4.3)
	(2) DC	4.0	(2.9-5.1)	2.3	(1.2-3.5)
	(3) AOM + DC	2.7	(1.6-3.8)	3.1	(1.9-4.3)
			$P_{tx*sex\ interaction} = 0.1879$		
Lowest LBP (0-10)	(1) AOM	1.4	(0.1-2.8)	2.0	(1.1-2.9)
	(2) DC	2.3	(1.4-3.3)	1.0	(0.0-2.0)
	(3) AOM + DC	1.5	(0.6-2.4)	1.4	(0.4-2.5)
			$P_{tx*sex\ interaction} = 0.2572$		
Highest LBP (0-10)	(1) AOM	3.5	(1.7-5.3)	5.4	(4.2-6.6)
	(2) DC	5.1	(3.8-6.3)	3.4	(2.0-4.8)
	(3) AOM + DC	4.0	(2.8-5.2)	4.3	(2.9-5.8)
			$P_{tx*sex\ interaction} = 0.1244$		

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain.

disability among patients in randomized controlled trial of integrative acupuncture and SMT for LBP.

Methods

Study Design

This study was a secondary analysis of data obtained from a clinical trial of integrative acupuncture and SMT for the treatment of LBP.[24] The primary outcome measures were clinically significant improvements in LBP-related pain and disability. The secondary outcomes were decreased missed days of work, days per week with LBP, percentage of time with LBP, and pain pills taken during the past week because of LBP. The trial showed that patients received equivalent clinically significant benefits from the integrative therapy as from acupuncture or SMT alone. This secondary analysis was conducted to determine whether a patient's self-reported gender influenced therapy outcomes. Additional details on the original trial's design, conduct, and analysis may be found in the study published by Kizhakkeveettil et al.[24]

Study Population

Of the 100 randomized participants, 80 (40 female and 40 male) completed treatment and were followed up with through 60 days.

Statistical Analysis

Mixed-effects linear models and ordinary least squares regression were used to estimate gender-specific age-adjusted means and absolute and percentage changes from

Table 5. *Estimated Sex-Specific Adjusted Mean Absolute and Percentage Changes (95% CIs) From Baseline to 60 Days on Primary Outcome Variables by Treatment Group: Results of Ordinary Least Squares Regression Analyses* [a]

		Female		Male		Female		Male	
		Mean		Mean		Mean %		Mean %	
Outcome	Treatment	Change	(95% CI)	Change	(95% CI)	Change	(95% CI)	Change	(95% CI)
LBP disability (0-24)	(1) AOM	4.8	(1.0-8.6)	3.2	(1.2-5.3)	42.6	(-6.2 to 91.4)	42.4	(16.1-68.7)
	(2) DC	2.7	(0.2-5.1)	4.9	(2.3-7.5)	-3.0	(-34.7 to 28.7)	55.6	(22.4-88.8)
	(3) AOM + DC	4.3	(2.1, 6.5)	1.6	(-0.9 to 4.0)	52.8	(24.7-81.0)	26.7	(-5.0, 58.4)
			$P_{tx*sex\ interaction} = 0.1188$				$P_{tx*sex\ interaction} = 0.0286$		
Current LBP (0-10)	(1) AOM	2.9	(1.5-4.3)	1.1	(0.2-2.1)	62.2	(27.4-97.0)	30.4	(6.7-54.1)
	(2) DC	2.1	(1.1-3.0)	2.4	(1.4-3.5)	49.5	(26.5-72.5)	58.6	(29.6-87.7)
	(3) AOM + DC	2.3	(1.4-3.2)	1.8	(0.7-2.9)	58.1	(35.8-80.3)	39.5	(11.8-67.1)
			$P_{tx*sex\ interaction} = 0.1684$				$P_{tx*sex\ interaction} = 0.3187$		
Typical LBP (0-10)	(1) AOM	3.7	(2.2-5.3)	2.0	(0.9-3.0)	63.5	(22.8-104.2)	19.6	(-7.7 to 46.8)
	(2) DC	1.2	(0.1-2.2)	2.8	(1.6-3.9)	20.1	(-8.1 to 48.4)	60.0	(29.5-90.6)
	(3) AOM + DC	2.9	(1.9-3.9)	2.2	(1.0-3.4)	48.0	(21.4-74.5)	40.0	(9.3-70.6)
			$P_{tx*sex\ interaction} = 0.0188$				$P_{tx*sex\ interaction} = 0.0351$		
Lowest LBP (0-10)	(1) AOM	1.6	(0.3-2.9)	0.8	(-0.1 to 1.7)	58.4	(8.4-108.4)	17.3	(-19.1 to 53.8)
	(2) DC	0.8	(-0.1 to 1.6)	1.4	(0.5-2.4)	27.4	(-8.3 to 63.0)	69.5	(27.8-111.2)
	(3) AOM + DC	1.1	(0.3-1.9)	1.3	(0.3-2.2)	38.4	(3.0-73.8)	49.2	(7.7-90.7)
			$P_{tx*sex\ interaction} = 0.3341$				$P_{tx*sex\ interaction} = 0.1406$		
Highest LBP (0-10)	(1) AOM	3.8	(2.1-5.5)	1.8	(0.6-3.0)	50.1	(24.8-75.4)	23.3	(6.1-40.5)
	(2) DC	2.0	(0.9-3.1)	3.5	(2.2-4.8)	30.8	(14.1-47.5)	51.6	(32.3-70.8)
	(3) AOM + DC	3.3	(2.2-4.5)	2.9	(1.6-4.2)	45.9	(29.7-62.2)	37.8	(18.5-57.0)
			$P_{tx*sex\ interaction} = 0.0392$				$P_{tx*sex\ interaction} = 0.0545$		

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain.

[a] Estimates adjusted for age and baseline value of the outcome measure.

baseline to the end of treatment (60 days) on each continuous primary outcome variable (Roland-Morris LBP Disability and 0-10 numeric rating scale [NRS] scores). Log-binomial regression was used to estimate and test the effects of treatments on gender-specific differences in proportions experiencing clinically meaningful changes in disability (3+ points) and pain (2+ points) from baseline to 60 days. Residual diagnostics (eg, residual and Q-Q plots) and influence analyses were conducted in SAS 9.3 (Cary, North Carolina). The normality and independence assumptions of residuals were satisfied, as was the homoscedasticity assumption. Potentially influential observations were removed in sensitivity analyses; parameter estimates derived from the full and reduced models were qualitatively similar. Product terms with treatment group and gender were included in all models to test for interactions between treatment type and gender. Effects were estimated with 95% CIs; *P* values were computed for tests of interaction.

Results

A total of 80 study participants completed the 6 weeks of therapy. There were no significant differences between men and women for age, quality life, LBP-related pain and disability, or any of the secondary outcomes (Tables 1-3).

The effects of treatment appeared to have been influenced by the participants' self-reported gender. Primary outcomes in women tended to be better under acupuncture care, whereas primary outcomes in men tended to be better under SMT (Tables 4-6). For example, women in the acupuncture group experienced an average 4.8-point improvement on the

Table 6. *Estimated Sex-Specific Numbers, Percentages, and Effects (RRs and 95% CIs) by Treatment and Treatment Contrast of AOM Alone vs AOM + DC and DC Alone vs AOM + DC on 3+ Point Reductions in LBP Disability Scores and 2+ Point Reductions in LBP NRS Scores (Clinically Meaningful Improvement) From Baseline to 60 Days (Primary Outcome Point): Results of Log-Binomial Regression Analyses* [a]

		Female				Male				
Outcome	Treatment	n	Percent	RR	95% CI	n	Percent	RR	95% CI	$P_{tx*sex\ interaction}$
Disability	AOM	3	60.0	1.20	0.49-2.91	9	56.3	2.06	0.72-5.93	0.4418
	DC	5	45.5	0.90	0.39-2.09	8	80.0	2.93	1.06-8.08	0.0801
	AOM + DC	7	50.0	1.00	(referent)	3	27.3	1.00	(referent)	
Current LBP	AOM	6	85.7	1.32	0.83-2.10	6	37.5	0.56	0.27-1.19	0.0565
	DC	10	62.5	0.97	0.58-1.62	8	66.7	1.00	0.57-1.76	0.9293
	AOM+DC	11	64.7	1.00	(referent)	8	66.7	1.00	(referent)	
Typical LBP	AOM	7	100.0	undefined	(zero cell)	9	60.0	1.20	0.60-2.42	undefined
	DC	7	50.0	0.67	0.37-1.21	10	83.3	1.67	0.90-3.10	0.0703
	AOM + DC	12	75.0	1.00	(referent)	6	50.0	1.00	(referent)	
Lowest LBP	AOM	3	42.9	1.21	0.42-3.54	4	26.7	0.80	0.25-2.55	0.6043
	DC	7	43.8	1.24	0.53-2.90	6	50.0	1.50	0.56-4.00	0.7733
	AOM + DC	6	35.3	1.00	(referent)	4	33.3	1.00	(referent)	
Highest LBP	AOM	5	71.3	0.81	0.49-1.33	9	60.0	0.72	0.44-1.17	0.7414
	DC	8	50.0	0.57	0.34-0.95	10	83.3	1.00	0.70-1.43	0.0777
	AOM + DC	15	88.2	1.00	(referent)	10	83.3	1.00	(referent)	

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *NRS*, numeric rating scale; *RR*, risk ratio.

[a] RRs greater than 1 indicate higher probability of clinically meaningful improvement in the single vs combined treatment groups; RRs less than 1 indicate lower probability of clinically meaningful improvement in the single vs combined treatment groups.

Roland-Morris scale vs just 2.7 points for women in the SMT group, whereas men in the SMT group had an average 4.9-point improvement vs. just 3.2 points in the acupuncture group (*P* for interaction = .12, *P* for interaction using percentage change as the outcome = .03). Changes in NRS pain ratings followed a similar pattern. For example, women in the acupuncture group had an average 3.8-point change in highest LBP vs a 2.0-point improvement under SMT care, whereas men under SMT care had an average 3.5 point improvement vs 1.8 points in the acupuncture group (*P* for interaction = .04; *P* for interaction using percentage change as the outcome = .054).

For women, the effects from acupuncture care were better alone without the addition of SMT care. For men, the effects of SMT care were better without the addition of acupuncture. For example, for women in the acupuncture group, the improvement in disability dropped from 4.8 to 4.3 points with the addition of SMT care, and for men in the SMT group, the improvement dropped from 4.9 points to 1.6 with the addition of acupuncture. These patterns held whether outcomes were estimated with absolute or percentage changes or when estimating proportions of women and men with clinically meaningful changes in disability and pain during the 60-day treatment period. Among women, clinically meaningful improvements in disability and pain were most likely for those in the acupuncture group and least likely for those in the SMT group, whereas for men, clinically meaningful improvements were most likely for those under SMT care and least likely for those in acupuncture care. For example, 100% of the women in the acupuncture group improved by at least 2 points on the NRS for typical pain compared with just 50% of women in the SMT group, whereas for men, 83% of those in the SMT group improved by at least 2 points vs just 60% for those in acupuncture care. For women under acupuncture care, likelihood of improvement dropped with the addition of SMT care (from 100% to 75%), and for men under SMT care, the likelihood of improvement dropped with the addition of acupuncture (from 83% to 50%).

Additionally, women who received acupuncture care (with or without SMT care) were more likely to experience 50% or greater reductions in disability and pain, whereas men who received SMT care (with or without acupuncture care) were more likely to experience 50% or greater reductions in disability and pain (Table 7). Tables 8 and 9

Table 7. *Estimated Sex-Specific Numbers, Percentages, and Effects (RRs and 95% CIs) by Treatment and Treatment Contrast of AOM Alone vs AOM + DC and DC Alone vs AOM + DC on 50% or Greater Reductions in LBP Disability and LBP NRS Scores From Baseline to 60 Days (Primary Outcome Point): Results of Log-Binomial Regression Analyses* [a]

		Female				Male				
Outcome	Treatment	n	Percent	RR	95% CI	n	Percent	RR	95% CI	$P_{tx*sex\ interaction}$
Disability	AOM	3	60.0	0.93	0.41-2.11	8	50.0	1.10	0.49-2.48	0.7796
	DC	3	27.3	0.42	0.15-1.20	5	50.0	1.10	0.45-2.69	0.1740
	AOM + DC	9	64.3	1.00	(referent)	5	45.5	1.00	(referent)	
Current LBP	AOM	5	71.4	0.93	0.55-1.60	6	40.0	0.63	0.29-1.35	0.4060
	DC	11	68.7	0.90	0.59-1.37	7	70.0	1.10	0.61-2.01	0.5915
	AOM + DC	13	76.5	1.00	(referent)	7	63.6	1.00	(referent)	
Typical LBP	AOM	5	71.4	0.95	0.55-1.65	9	60.0	1.20	0.60-2.42	0.6104
	DC	5	35.7	0.48	0.22-1.02	9	75.0	1.50	0.78-2.88	0.0246
	AOM + DC	12	75.0	1.00	(referent)	6	50.0	1.00	(referent)	
Lowest LBP	AOM	5	71.4	1.11	0.60-2.05	5	38.5	0.55	0.25-1.22	0.1695
	DC	7	50.0	0.78	0.41-1.50	7	70.0	1.00	0.56-1.77	0.5711
	AOM + DC	9	64.3	1.00	(referent)	7	70.0	1.00	(referent)	
Highest LBP	AOM	5	71.4	1.21	0.66-2.24	4	26.7	0.53	0.19-1.47	0.1732
	DC	5	31.3	0.53	0.23-1.22	7	58.3	1.17	0.56-2.45	0.1653
	AOM + DC	10	58.8	1.00	(referent)	6	50.0	1.00	(referent)	

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *NRS*, numeric rating scale; *RR*, risk ratio.

[a] RRs greater than 1 indicate higher probability of 50% or greater reduction in the single vs combined treatment groups; RRs less than 1 indicate lower probability of 50% or greater reduction in the single vs combined treatment groups.

show for each treatment group the sex-specific frequency distributions and means and medians of the secondary outcomes and health-status variables at the primary (60-day) outcome point. Women under acupuncture care (with or without SMT care) tended to report less time in pain, whereas men under SMT care (without acupuncture care) tended to report less time in pain (Table 8). Sex-specific distributions of health status variables at 60 days did not vary appreciably by treatment group (Table 9).

Discussion

Lower back pain is a major contributor to global disability and has proven very difficult to manage from both private practitioners' and public health perspectives. To achieve better outcomes, more accurate predictors of who will respond to which of the many therapies available for treating LBP will be required. This study has uncovered a relationship between self-reported gender and outcomes when treating LBP with acupuncture or SMT. Men responded significantly better to SMT and women significantly better to acupuncture care.

The cause of this modifying effect of gender can only be speculated on at this time. One possible explanation may be the reported association between female sex and hypermobility, possibly owing to hormonal effects.[25] A popular explanation for the effectiveness of SMT is that it releases adhesions in hypomobile joints. Thus, SMT may be less useful as a therapy for women.

Another plausible explanation is related to the association of hypermobility, undiagnosed fibromyalgia, and inflammation in women. Ofluoglu et al found a significant correlation between hypermobility in women and fibromyalgia.[26] Fetami et al discuss how fibromyalgia is associated with chronic LBP and is often overlooked as a cause, particularly in older adults.[27] Women may also be more prone to inflammatory states in general, as seen by their increased incidence of autoimmune diseases.[28] Fairweather et al found that women respond to infection with increased antibody and autoantibody responses compared with men.[29] Oke et al and Kavoussi et al noted that acupuncture may enhance vagus nerve activity, thus reducing inflammation.[30,31] Kavoussi et al also postulated that acupuncture may deactivate inflammatory macrophages.[31] These mechanisms may explain why women would respond better to acupuncture care.

Table 8. *Sex-Specific Frequency Distributions (Number and Percent) and/or Means (SDs) and Medians of Secondary Outcome Variables at the Primary Outcome (60-Day) Point, by Treatment Group (n = 80)* [a]

		Female			Male		
		AOM	DC	AOM + DC	AOM	DC	AOM + DC
Variable	Category	(n = 7)	(n = 16)	(n = 17)	(n = 16)	(n = 12)	(n = 12)
Percent time with LBP	<50% (%)	5 (71.4)	5 (33.3)	8 (50.0)	7 (50.0)	7 (58.3)	5 (41.7)
	50% (%)	2 (28.6)	5 (33.3)	3 (18.7)	2 (14.3)	3 (25.0)	4 (33.3)
	>50% (%)	0 (0.0)	5 (33.3)	5 (31.3)	(35.7)	2 (16.7)	3 (25.0)
	Mean (SD)	28.6 (17.2)	51.7 (29.1)	48.4 (28.1)	50.0 (29.4)	41.7 (30.8)	47.9 (24.9)
	Median	25	50	37.5	37.5	25	50
Days per week with LBP	<7 (%)	5 (71.4)	9 (60.0)	14 (82.3)	8 (50.0)	7 (58.3)	8 (67.3)
	7 (%)	2 (28.6)	6 (40.0)	3 (17.7)	8 (50.0)	5 (41.7)	4 (33.3%)
	Mean (SD)	4.7 (2.4)	5.0 (2.0)	3.9 (2.1)	4.9 (2.3)	4.3 (2.6)	4.9 (2.0)
	Median	5	5	4	6	4	5.5
Missed days last week because of LBP	0 (%)	6 (100)	16 (100)	16 (94.1)	14 (87.5)	11 (91.7)	10 (90.9%)
	1+ (%)	0 (0.0	0 (0.0)	1 (5.9)	2 (12.5)	1 (8.3)	1 (9.1)
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.2 (1.0)	0.2 (0.5)	0.2 (0.6)	0.4 (1.5)
	Median	0	0	0	0	0	0
Pain pills past week because of LBP	Not at all (%)	5 (71.4)	10 (62.5)	12 (70.6)	13 (81.2)	10 (83.3)	8 (72.7%)
	A few times (%)	2 (28.6)	5 (31.2)	4 (23.5)	3 (18.8)	2 (16.7)	3 (27.3%)
	Daily (%)	0 (0.0)	1 (6.2)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Patient satisfaction	Mean (SD)	40.0 (9.0)	42.8 (7.0)	41.4 (7.2)	42.8 (7.4)	46.8 (2.8)	41.8 (3.9)
	Median	43	44.5	42	46.5	47	42

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *SD*, standard deviation.
[a] Numbers may not add to 80 due to missing values; percentages are of nonmissing observations and may not sum to 100 because of rounding.

Limitations

Limitations of this study include the relatively small sample size, the 20% loss of participants to follow-up, the fact that outcome measures used were all self-generated by participants, and that participants were not blinded to treatment. Owing to budgetary and quality control challenges, Chinese herbs were not used in this study despite them being a mainstay of traditional Chinese medicine practices along with acupuncture. Finally, owing to practical limitations, a collaborative model of care was not used in the combined-care group. Instead, the 2 modalities were delivered in parallel without coordination between practitioners.

Another limitation of this secondary analysis stems from the original study screening questionnaire, which only gave participants the choice of entering gender as male or female. There was no provision made for entering other options, such as transgender or nonbinary. Furthermore, participants were not asked to report their biological sex at birth and whether this was different from their gender identity. This may have influenced the difference in the outcomes found between men and women. However, given that less than 1% of US adults identify as transgender, it is unlikely that noncongruent biological sex and gender identity had a significant effect on our findings.[32]

Conclusion

This study was a secondary analysis of data obtained from a clinical trial for integrative therapy that included SMT and acupuncture for LBP. We found that self-reported gender had a significant influence on the treatment outcomes related to pain and disability. Women responded better to acupuncture care and men responded better to SMT. This was the first study reported in the literature of a gender-based difference in response to these therapies for the treatment of LBP.

Table 9. *Sex-Specific Means (Standard Deviations [SDs] and Medians) of SF-36 Health-Status Subscale Scores at the Primary Outcome (60-Day) Point by Treatment Group (n = 80)*

		Female			Male		
		AOM	DC	AOM + DC	AOM	DC	AOM + DC
Variable	Category	(n = 7)	(n = 16)	(n = 17)	(n = 16)	(n = 12)	(n = 12)
SF-36 Physical function	Mean (SD)	75.8 (23.1)	66.0 (23.8)	71.8 (25.2)	78.4 (20.4)	85.4 (22.3)	76.7 (26.4)
	Median	82.5	60	70	87.5	95	90
SF-36 Role—physical	Mean (SD)	64.3 (45.3)	57.8 (43.5)	70.6 (40.7)	54.7 (44.0)	66.7 (35.9)	64.6 (44.5)
	Median	100	62.5	100	62.5	75	87.5
SF-36 Role—emotional	Mean (SD)	52.4 (42.4)	77.1 (39.8)	83.3 (29.8)	64.4 (44.5)	63.9 (38.8)	72.2 (39.8)
	Median	66.7	100	100	100	66.7	100
SF-36 Mental health	Mean (SD)	63.3 (17.6)	80.5 (14.2)	72.9 (21.6)	78.2 (15.0)	75.0 (16.2)	70.3 (26.7)
	Median	58	84	80	80	80	74
SF-36 Social function	Mean (SD)	67.9 (33.0)	80.5 (30.3)	81.6 (26.6)	80.5 (22.3)	81.2 (18.8)	80.2 (26.4)
	Median	75	100	100	87.5	81.25	87.5
SF-36 Bodily pain	Mean (SD)	66.8 (24.9)	67.8 (21.6)	73.1 (19.2)	73.7 (17.8)	75.8 (21.0)	72.3 (22.6)
	Median	77.5	77.5	77.5	77.5	80	77.5
SF-36 General health	Mean (SD)	50.0 (23.4)	77.8 (13.3)	68.8 (20.0)	74.4 (22.5)	74.1 (19.5)	65.8 (21.8)
	Median	40	72.5	70	80	75	65

AOM, acupuncture and Oriental medicine; *DC*, chiropractic; *LBP*, low back pain; *SF-36*, 36-Item Short-Form Health Survey.

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No funding sources or conflicts of interest were reported for this study.

Practical Applications

- Men and women responded differently to the study interventions, with men generally having better outcomes with spinal manipulation therapy and women having better outcomes with acupuncture.
- As observed with medical care for pathological conditions, the possibility that intervention effects may vary by gender has profound implications on the delivery of the most effective care for functional conditions for all patients.
- Clinical trials of interventions for low back pain should be designed to enable the (a) detection of gender differences in treatment effects and (b) estimation of gender-specific effects with adequate precision.

Contributorship Information

Concept development (provided idea for the research): A.K.
Design (planned the methods to generate the results): A.K., K.A.R., G.E.K.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): A.K.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): A.K., K.A.R., G.E.K.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): E.L.H.
Literature search (performed the literature search): A.K., G.E.K.
Writing (responsible for writing a substantive part of the manuscript): A.K., K.A.R., G.E.K., E.L.H.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): A.K., K.A.R., G.E.K., E.L.H.

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