Brief report

Adjunctive osteopathic manipulative treatment in women with depression: a pilot study

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The authors assessed the impact of osteopathic manipulative treatment (OMT) as an adjunct to standard psychiatric treatment of women with depression. Premenopausal women with newly diagnosed depression were randomly assigned to either control (osteopathic structural examination only; n = 9) or treatment group (OMT; n = 8). Both groups received conventional therapy consisting of the antidepressant paroxetine (Paxil) hydrochloride plus weekly psychotherapy for 8 weeks. Attending psychiatrists and psychologists were blinded to group assignments. No significant differences existed between groups for age or severity of disease. After 8 weeks, 100% of the OMT treatment group and 33% of the control group tested normal by psychometric evaluation. No significant differences or trends were observed between groups in levels of cytokine production (IL-1, IL-10, IL-2, IL-4, and IL-6) or in levels of anti–HSV-1, anti–HSV-2, and anti-EBV antibody. There was no pattern to the osteopathic manipulative structural dysfunctions recorded. The findings of this pilot study indicate that OMT may be a useful adjunctive treatment for alleviating depression in women.

(Key words: osteopathic manipulative treatment, depression)

Homeostasis is an integrated process that involves the interactions of the brain and the immune system. The effect of thought (neural transmission and transmitters) on homeostasis is being explored in depression and other altered mental states. However, the influence of procedural touch, including osteopathic manipulative treatment (OMT), on psycho- neuroimmunologic status has been vastly ignored. Historically, the early OMT studies by Andrew Taylor Still, MD, DO, were among the first studies that supported the view that there is an integration between the nervous system, behavior, and the immune system (the viscerosomatic relationship).[1-4] In the Still-Hildreth Sanatorium, researchers conducted several studies that noted a relationship between the presence and location of spinal lesions and dementia praecox (schizophrenia). Researchers who have studied other forms of procedural touch in patient care have reported various outcomes, including elevated mood states, shortened hospital stays, and relief of depression, especially in the elderly.[5,6]

Depression is the most prevalent disorder in psychiatry[7] and poses a major public health problem. Community prevalence studies indicate that 5% of people in the US population satisfy the criteria for defined psychiatric depression, with 2% to 3% of the population at any given time hospitalized or seriously afflicted with depression.[8] Demographically, women present for treatment for depression three times as often as men.[9] The 3:1 female-to-male ratio is not, however, attributable to a greater degree of help-seeking behavior among females. Instead, this excess of females with depression appears to be strongly associated with women of childbearing age.[9] It had been postulated that this gender and age focus may be mediated through biologic mechanisms, specifically through hormonal effects on the brain.[10,11] However, because of considerable evidence that the endocrine system, neurotransmitters, and the immune system collaborate as mediators of depression, attention has been redirected to a neurobiologic basis for depression.[10-18]

Behavioral changes also affect this interaction and thus modify immune function. The results of this behavioral-neuroimmune interaction are measurable. Negative affective states have been demonstrated to depress antibody levels, while positive affective states have the opposite effect on antibody levels, such as those for herpes simplex virus (HSV) types 1 and 2 and Epstein-Barr virus (EBV).[18] Psychologic stress has also been demonstrated to influence the duration and/or severity of diseases—for example, oral and genital herpes, which are controlled by the T cell–mediated immune system.[18-20] Other studies have found that the risk for cervical hyperplasia due to human papillomavirus (HPV) significantly increases in women who experience negative affective states.[19]

The negative effects of psychologic stressors on the immune system can be alleviated through relaxation training. Patients who have undergone such training seem to demonstrate increased natural killer (NK) cell activity and decreased antibody titers to herpes simplex virus, an indication of a functioning T cell–mediated immune system.[20,21] One of the ways that OMT could impact the neuro-immune "cross-talk" that occurs is by modulating the release of neuropeptides. Receptors for neuropeptides can be found on leukocytes as well as in the brain.[10,14,15,17] In turn, the binding of neuropeptides to leukocytes stimulates the production of cytokines (IL-1, IL-2, IL-4, and IL-6).[14,17] These cytokines can bind specifically to the hypothalamus and pituitary. Their psychoneural activities, taken together, include promoting anorexia, as well as stimulating and inhibiting the release of corticotropic hormone, β-endorphin, thyroid-stimulating hormone, growth hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, and other pituitary hormones.[14,15] Thus, these cytokines can, through feedback mechanisms, act directly and indirectly to stimulate or inhibit production of neuropeptides as part of a neuro-endocrine-immunologic feedback mechanism.[14] The result of these interactions is a measurable alteration in behavior and immune function.[17,19]

Other studies indicate that individuals who disclose troubling personal problems (catharsis) are better off, immunologically speaking, than those who do not.[11] Lymphocyte proliferation and levels of IL-1, IL-2, IL-4, IL-6, and interferon are also affected by mental state.[11,13] Lymphocyte responsiveness to mitogens is depressed in bereaved widowers and hospitalized patients with major depressive disorder.[16] Thus, alterations in behavior or psychologic state result in and are inexorably linked to changes in the function of the immune system—resulting in alterations in T cell subpopulations, B cells, and NK cell function.

Studies over the past 15 years have demonstrated that there is bidirectional communication between the brain and the immune system.[14,17] Neuroendocrine efflux from the pituitary and hypothalamus can influence immune cellular function and cytokine release. Conversely, cytokines and chemokines have been demonstrated to affect neural, endocrine, and behavioral processes. Thus, Pavlovian conditioning, as well as behavioral and emotional status, influence immune response and responsiveness.[21] Current conventional treatment of individuals with moderate depression usually includes antidepressant drugs as an adjunct to psychiatric counseling.[22] Because there is a direct connection between behavior and the nervous and immune systems, it is reasonable to expect that OMT, which affects neural transmission, would have an impact on behavioral states. Further, it is reasonable to expect that such alterations can be monitored through assessment of immunologic status.

Materials and methods

This study was a prospective, experimental, blinded, controlled study to examine the efficacy of OMT as an adjunctive therapy in the treatment of depression in women. The Institutional Review Board of Midwestern University approved the study protocol. Once informed consent was obtained, patients were randomly assigned to control or treatment groups. Premenopausal females considered for enrollment as research subjects were 20 to 50 years of age, included several ethnic groups, and had presented to affiliated clinics and hospitals complaining of depression. A concerted effort was made to enroll only those individuals who had neither experience with nor knowledge of OMT and who had no previous history of depression or other psychiatric disorder.

After providing informed consent, subjects received physical examinations—including a blood sample. A portion of the collected blood was submitted for clinical diagnostic testing to ensure the overall health status of the study subjects. This testing included a complete blood count with differential, lipid profile (cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein, chylomicrons, and LDL/HDL), sedimentation rates, and urinalysis. At this time, study subjects also were reminded to refrain from taking any medications—including nonsteroidal anti-inflammatory drugs, sleep medications, over-the-counter herbal preparations, or opioids—for the duration of their enrollment in the study. Serum was collected and stored at −70°C before determining cytokine and antibody levels. A minimum of duplicates of 2 samples (before and after study) was assessed per study subject. Patient enrollment criteria are given in *Figure 1*, and the demographics of patients who completed the study are presented in the *Table*.

Enrollment in the study was for a minimum of 8 weeks (both for the control and treatment groups) to ensure attainment of pharmacologic levels of the antidepressant medication. From the initial cohort (n = 31), a complete database was achieved for 17 of the patients. Attrition from the study stemmed from failure to cooperate with blood draws, refusal to take the antidepressant, and/or failure to keep appointments for psychiatric counseling. All patients who dropped out of the study did so by the third week of their enrollment. All patients (control and treatment groups) received the antidepressant paroxetine (Paxil) at a dosage of 20 mg/day and weekly psychologic counseling by counselors who were blinded as to whether the patient received OMT or was part of the placebo control group.

Data entry and analysis was also carried out in a blinded fashion. To ensure that diagnostic procedures, OMT treatment group, and immunologic assessment were properly blinded, interpretations were conducted using evaluation forms and sample specimens that contained no reference to the subjects, and the interpreter was blinded as to the source of the data. After interpretations of both psychiatric and immunologic data were recorded, the data from the records were entered by computer into a statistical file for analysis. The veracity of the use of OMT in treatment of depression was determined from the statistical findings only. Psychiatric treatment was conducted in the form of weekly, half-hour sessions. The type of counseling therapy that study subjects received was standardized

to minimize confounding variables that might arise from the use of different psychiatric counseling modalities. Specifically, each study subject received counseling therapy that combined cognitive therapy and neurolinguistic programming.

Both modes of therapy are considered standard procedures in the treatment of depression. In addition, both modalities have demonstrated effectiveness in precipitating neuro-immune interactions that result in measurable changes in immunologic response and responsiveness.[23-25] The principles of neurolinguistic programming were used to help the patients develop positive self-identities and to assist them in ordering chronologically chaotic and fragmented recollections, thus helping to provide continuity and establish goals.[23,24] The addition of cognitive therapy to the neurolinguistic programming assisted patients in altering long-held beliefs and distorted thought patterns based on such beliefs, which can cause and perpetuate depression.[25]

Patient mental status was measured using scores generated on the Zung Depression Scale.[7] The Zung scale, which is used in primary care outpatient settings to assess depression, was administered at the beginning, midpoint, and end of the study.

All study subjects received osteopathic structural examination three times during the study—at the beginning, middle, and end. The osteopathic structural examination was used as the placebo control. The structural examination incorporates both touch and verbal interaction with the patient. Thus, it controls for changes that may occur in the treatment group as a result of this interaction alone. The authors recognize that this study does not include a control for OMT as a type of procedural touch. However, the intent of this study is not to compare OMT to other types of procedural touching (for example, massage, hand-holding) but to ascertain the effectiveness of using OMT as an adjunctive treatment modality for individuals with depression. After the use and relevance of OMT has been established, then com-

INCLUSION CRITERIA
- Premenopausal females, 20-50 years of age
- Presentation consistent with moderate depression

EXCLUSION CRITERIA
- Coexisting infectious disease, medical or surgical conditions
- Suspected or known malignancy
- History of nonevaluated trauma
- History of drug abuse (Other medications must be evaluated for impact on the study.)
- Signs of genitourinary or gastrointestinal disease
- History of recurrent unresolved back pain
- All symptoms and signs of a herniated nucleus pulposus
- ☐ Specific dermatomal patterns of paresthesia (sensory loss)
- ☐ Straight-leg-raising test having at least one of the following:
  —50% of normal
  —Cross-over pain
  —Positive bowstring sign
- ☐ Two of the following neurologic signs:
  —Deep tendon reflex alteration
  —Muscle wasting
  —Weakness
  —Sensory loss
- Use of muscle relaxants or pain medication 8 hours before examination
- History of lumbosacral surgery, fractures, or recent (48 h) spinal manipulation
- > 30% of ideal weight
- History of work-related injury or accidental injury with unresolved legal action
- Pregnant or suspected pregnancy
- Uncooperative subject
- Anxiety disorders
- History of seizure disorder
- Service in the Middle East during the Gulf War

Figure 1. *Inclusion and exclusion criteria.*

parisons of OMT with other types of procedural touch would be both warranted and necessary.

For the control group, the standardized structural examination took 30 minutes per subject. For the treatment group, the standardized structural examination was incorporated into a total clinician-patient interaction time of 30 minutes. The osteopathic structural examination required assessment of 142 structural examination points as either a positive or a negative finding.[26-29] The following were determined: shoulder heights, iliac crest heights, greater trochanter heights, pelvic side shift, spinal lateral curves-type I mechanics, cervical individual mechanics (occiput through C7), thoracic individual vertebral mechanism (T-1 through T-12), lumbar individual vertebral mechanics (L-1 through L-5), sacral mechanics ileo-ileal mechanics, psoas muscle tension, and performis tension. Positive findings had the following: segmental motion (seated, prone, supine)

and tissue texture abnormality (hypertonicity, lack of homogeneous quality, stringy-ropey-boggy quality). These data were grouped into the nine clinical regions of diagnostic osteopathy and summed to yield numbers of positive findings per somatic region. Additional analysis involved subdividing the larger regions into two or three subregions.

The complete variable list for the osteopathic structural examination comprised the following: cervical lordosis; thoracic kyphosis; lumbar lordosis; mastoid process; scapula; ilium; standing flexion; lateral curve greater than 10°; pelvic side shift; trapezius; scalenes; left arm restriction; right arm restriction; left elbow restriction; right elbow restriction; left wrist restriction; right wrist restriction; left fingers restriction; right fingers restriction; left leg restriction; right leg restriction; left knee restriction; right knee restriction; left shoulder restriction; right shoulder restriction; upper thoracic restriction, T-1 to T-4; C-2 through T-12,

Table Patient Demographics		
	Osteopathic manipulative treatment group (n = 8)	Control group (n = 9)
Age, y	23-56	23-59
Mean age, y	44.6	49.6
Ethnicity, %	African-Americans, 25 White/non-Hispanic, 75	African-Americans, 55 White/non-Hispanic, 33 Asian, 11
Marital status, %	Married, 75 Divorced, 12.5 Widow, 12.5	Married, 44 Single, 22 Divorced, 33

each, left and right in both flexion and extension; midthoracic restriction; lower thoracic restriction; upper lumbar restriction; lower lumbar restriction; sacroiliac tenderness; psoas tightness; gluteal tightness; hamstring tightness; upper cervical restriction; midcervical restriction; lower cervical restriction; occiput posterior; atlas; rib cage restriction; innominate restriction; pubic symphysis; cranial rhythm impulse amplitude; and cranial rhythm impulse frequency.

Structural examinations and OMT were administered by student physicians under the guidance of physician instructors. No specific OMT protocol was applied, to more accurately mimic clinical practice. For the test group, treatment followed the structural examination. The specific treatment procedures depended on the nature of the dysfunction and were left to the discretion of the student physician administering the treatment. Treatments were limited by time (20 minutes) to control for the length of time the control group received structural examinations (sham treatments). The specific lesions that were treated, and how they were handled, was a clinical decision made by the student physicians in consultation with their attending faculty. OMT treatments included counterstrain, cranial

treatment, direct treatment, exaggeration treatment, fascial release, Galbreath treatment, indirect treatment, inhibitory pressure treatment, lymphatic pump, mandibular drainage, muscle energy treatment, myofascial treatment, and positional release treatment. Overall, most students opted to use low-impact techniques, such as soft tissue and facial release techniques performed on a find-and-fix basis.

Assessment of immunologic status was achieved by measuring endogenous patient levels of IL-1α, IL-1β, IL-2, IL-6, and IL-4 using commercial ELISA kits (Quantikine HS IL-4, sensitivity <10pg/mL; Quantikine IL-2, sensitivity <7pg/mL; Quantikine IL-1α, sensitivity <0.5 pg/mL; Quantikine HS IL-1β, sensitivity <0.1 pg/mL; Quantikine HS IL-6, sensitivity <0.094 pg/mL) obtained from R&D Systems (Minneapolis, Minn). Measurement of anti–HSV-1 and anti–HSV-2 and EBV immunoglobulin G (IgG) antibody levels was accomplished using Clin-ELISA kits (DiaSorin, Stillwater, Minn).

Outcome measures, such as degree and rate of change in immunologic status readout measures and changes in osteopathic structural lesions, were correlated with the extent of patient recovery from

depression. Parametric tests to determine statistical significance between control and treatment groups were performed using one-way analysis of variance followed by Tukey-Kramer post-hoc analysis.

Results

Of the 17 women in whom depression was diagnosed and who completed the study, eight received OMT and nine were part of the control group. Psychometric measures (Zung Depression Scale) for all study subjects were similar for both groups at the start of the study (*Figure 2*). At the conclusion of the study, both groups showed significant improvement in their Zung Depression Scale scores as compared to their scores at the start of the study. The individuals who received OMT reverted to the normal range of the Zung Depression Scale by week 8 (*Figure 3*). In contrast, although the other group showed improvement, more than 70% of the control patients still had signs of moderate depression at the end of the eighth week of psychiatric treatment.

Overall, no significant differences were found intraindividual or interindividual or between groups, nor in relation to the Zung Depression Scale score for endogenous production of IL-1α, IL-1β, IL-2, IL-4, and IL-6 or IgG anti–HSV-1 and anti–HSV-2 and EBV. For all patients, the levels of cytokines and antiviral antibodies failed to show significant changes with regard to beginning and endpoint levels. While some individuals did have slightly higher levels of cytokines or antiviral antibodies at the beginning as compared with the endpoint measurements, these changes were not significant at the $P < .50$ level. The one exception was the individual in the OMT group with the highest Zung Score (73 initial Zung Depression scale score vs 48 final Zung score) at the start of the study, who exhibited a 23% decline in anti–HSV-1 antibody levels.

A basic analysis of the presence of osteopathic somatic dysfunction was performed using information from the initial and final sessions for six experimental subjects and five control subjects. The remaining test subjects and controls were excluded from the analysis because of
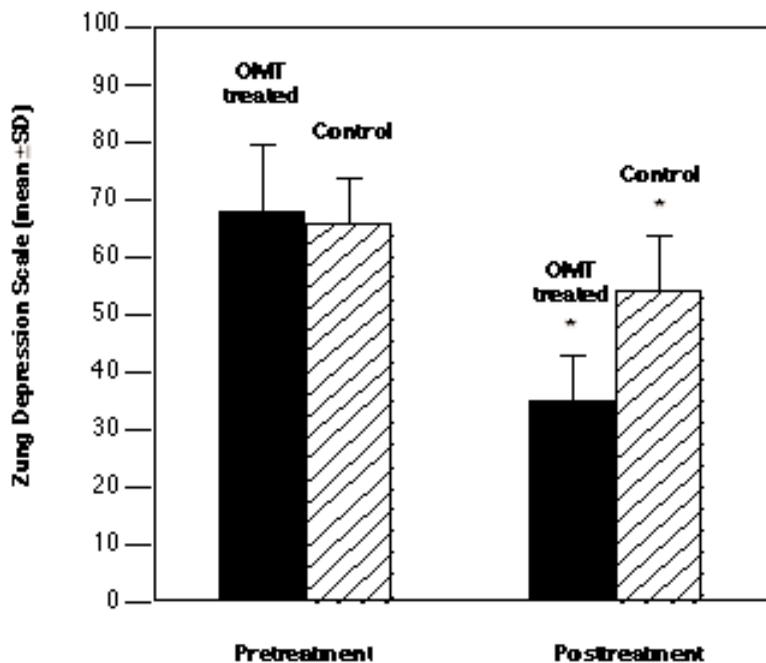
Figure 2. *Effect of osteopathic manipulative treatment on depression. The effect of osteopathic manipulative treatment (treatment group; n = 8) vs. structural examinations (control group; n = 9) on premenopausal women who had depression was assessed before and after an 8-week course of psychiatric counseling and antidepressant drug therapy (using paroxetine [Paxil] hydrochloride). Scores less than 50 = normal; * indicates significant difference, P < .001. Intragroup mean initial and final results were significantly different from each other, as were intergroup mean final Zung Depression Scale results.*
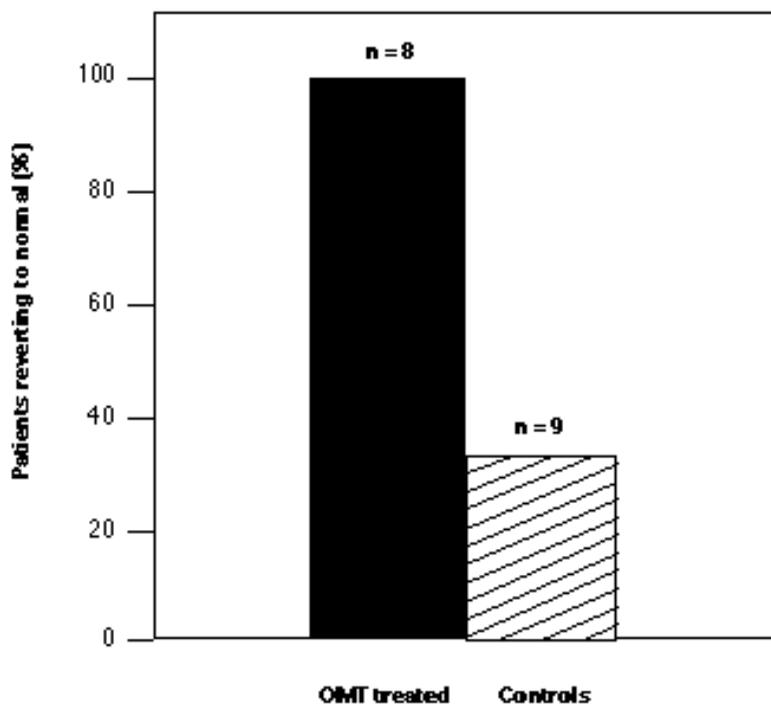

Figure 3. *Impact of osteopathic manipulative treatment on positive outcomes in the treatment of women with depression. The outcomes of patients who received osteopathic manipulative treatment (n = 8) vs. controls (n = 9) reverted to normal by psychometric measure using the Zung Depression Scale.*

musculoskeletal charting inconsistencies. Although the small study group size precluded statistical analysis of structural lesion maps, simple examination of the data indicated that there were no specific trends with regard to type of dysfunction or number of dysfunctions at the initial or final structural examinations—in either the treatment group or the control group. Of interest was the fact that after OMT treatment, four of the six treatment subjects registered an increase in the rate of their cranial rhythmic impulse. In three of these four test subjects, the rate was double their initial cranial impulse rate.

Comments

Although the sample size was small, the findings of this study indicate that OMT may have use as an adjunct to standard psychiatric therapy in relieving depression—at least as measured by the Zung scale. The data from this study provide the basis for further review of the role of pri-

mary care in the treatment of patients with depression, through the use of OMT. Should larger studies confirm this data, the enhanced or accelerated "cure rate" that was measured as a result of OMT could be useful in increasing patient health status. In addition, this accelerated rate of improvement in patients with depression might lead to a decreased burden on the healthcare system by providing cost-effective care for a serious and prevalent chronic disease.

Further clinical trials should also attempt to assess the therapeutic value of other forms of touch therapy and massage to ascertain whether the changes observed were the result of the specific effects of OMT or some other factor, such as the therapeutic effect of touch in general. This trial did attempt to control for the potential therapeutic effects of touch through the use of the osteopathic structural examination, the time frame for which was extended to be equivalent to that of the treatment group's structural examination and treatment. Because of the limited number of study subjects, however, we could neither fully control for the effects of touch nor completely evaluate the benefits of OMT and sham treatment (osteopathic structural examination) by creating a "no-touch" control group.

Although depression is associated with depressed immune responsiveness, we were unable—with a single exception—to measure any significant changes with regard to the in situ levels of cytokines or antibodies directed against HSV and EBV. However, other types of studies have demonstrated that a relationship exists between the depressive state and levels of immune response modifiers (such as cytokines). These same studies have shown a relationship between depression and levels of antibodies directed against viruses of the Herpesviridae (for example, EBV and HSV), which are used as readout measures of the cell-mediated immune response.[26,27] The lack of significant findings in this regard with our study subjects could be attributed to a combination of factors, including the small patient population size, the lack of a latent viral infection, and the sensi-

tivity level of the detection systems.

It is worthy of mention that the sole patient for whom significant measurable changes were observed was also the patient with the greatest percent change in Zung Depression Scale score. This may indicate that for meaningful information on in situ cytokine and antiviral antibody production, patient populations with more severe disease will need to be tested. Other studies indicate that a more sensitive measure of the effects of stress and depression on immunologic function may be required to measure the response of isolated lymphocytes to mitogenic stimuli. We have found in other studies of stress and immune responsiveness that differences in stress interventions could be measured through this protocol. With sufficient technical assistance, both protocols could be used; thus, both the in situ and in vitro function of lymphocyte function could be assessed.

Some differences were noted between the treatment and control groups in the initial and final evaluations of osteopathic dysfunctions in the thoracic region. During the initial and final structural evaluations, most (80%) of the subjects in the OMT treatment group had restricted movement in vertebrae of the upper thoracic region (T-1 through T-4), and restrictions in the midthoracic (T-5 through T-8) and lower thoracic (T-9 through T-12) regions. In contrast, the control group had fewer restrictions of motion in all three thoracic regions. There was no significant difference between groups with respect to their mean presenting Zung Depression Scale scores. No other apparent differences were noted when comparing type, region, and number of dysfunctions during the initial and final structural examinations. Some study subjects, regardless of group assignment (treatment vs. control) improved in number or region of dysfunctions, while others showed no improvement.

Prior research indicated an average cranial rhythmic impulse (CRI) of 6.42 in people with depression.[30] The results presented here support the concept that the CRI rate decreases in individuals with depression. The mean rate of the CRI in the group who received OMT increased

from 6.2 cycles/min (range, 4 to 12 cycles/min) at the start of the study to 8.83 cycles/min (range, 3 to 12 cycles/min) at the conclusion of the study. The mean CRI rate of the control group was 5.2 cycles/min (range, 3 to 8 cycles/min) increasing to 6.8 cycles/min (range, 3 to 10 cycles/min) at the conclusion of the study. The cycle of motion of the CRI normally occurs between 10 to 14 times per minute and may be decreased by psychiatric conditions.[30] Both groups had mean CRIs below 10 cycles/min before and at the conclusion of the study. However, half of the OMT group subjects (n = 6) had increases in their CRI to 10 cycles/min over the course of the study. In contrast, only one of the control group subjects (n = 5) attained a CRI rate of 10 cycles/min. These preliminary findings raise the possibility that the CRI may be useful as an independent readout of an individual's status of depression. Clearly, further studies are needed to confirm or refute this hypothesis and to confirm the efficacy of OMT in the treatment of depression.

It would be presumptive to make conclusions concerning the efficacy of OMT as an adjunctive therapy for the treatment of depression. Although the outcomes of this study were promising, future studies should continue to examine the effect of OMT on immune responsiveness—with the ultimate goal of using measured changes as independent readout measures of the effectiveness of OMT and of general mental health status. Future studies could also focus more closely on the changes observed in cranial rhythms. A broader patient population is needed to verify the positive effects that OMT seems to have on recovery from first-episode depression. A broader study group also is needed to determine whether gender and chronicity of the depressed state can be affected by OMT.

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