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COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR DEPRESSION

**The Efficacy of Complementary and Alternative Medicine Approaches for the
Treatment of Depression in an Integrative Healthcare Setting**

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Abstract

This retrospective study examined Medical Symptoms Questionnaire (MSQ) symptom checklist pre- and post-treatment scores for patients self-reporting depression at an outpatient integrative healthcare center. Clinical outcomes were compared for three different practitioner groups: patients who utilized complementary and alternative medicine (CAM) only, patients who utilized functional medicine (FM) only, and patients who chose to utilize both types of treatment. Regardless of age, sex, initial severity of depression, or type of practitioner seen, patients' symptom checklist scores were significantly reduced from baseline to the final measure during the one-year study period. Controlling for variability in baseline scores, both CAM and FM approaches seemed to significantly reduce symptoms even for patients with self-reported severe depression. In analyses examining number of visits and severity of depression, patterns varied slightly depending upon the model being tested. Specifically, a higher number of visits prior to the study period predicted slightly greater improvement on final MSQ score for the non-severely depressed group. For number of total visits (both during and prior to the study), results indicated a positive association between number of total visits and final MSQ score, and this association was the same for severe and non-severely depressed patients. Findings indicate a need for further research on the efficacy of CAM and functional medicine treatments for depression.

The Efficacy of Complementary and Alternative Medicine Approaches for the Treatment of Depression in an Integrative Healthcare Setting

Depression is a major health problem affecting people of every age, sex, culture, and walk of life. This common mental disorder is characterized by sadness, loss of interest or pleasure in life, feelings of low self-esteem or guilt, poor appetite or disturbed sleep, low energy, and poor concentration; and tragically, sometimes depression leads to suicide (World Health Organization, 2008; American Psychiatric Association, 2000). The personal costs of depression are significant, with symptoms of emotional distress and physical impairment affecting functioning in daily activities at work and home, in relationships and in social roles (Kessler et al., 2003). The public health burden of depression is also a serious issue; depression is currently ranked the fourth most burdensome disease in the world, and it is predicted that it will be the second most burdensome illness by the year 2020 for all ages, and both sexes (World Health Organization, 2008). The economic burden of depression in the United States, including direct medical costs, suicide-related mortality costs, and workplace costs, was estimated at \$83.1 billion in the year 2000 (Greenberg et al., 2003). A national survey found that people diagnosed with major depressive disorder for at least twelve months concurrently reported an average of 35.2 days in the past year when they were totally unable to work or carry out normal activities due to their depression (Kessler et al., 2003). Current estimates of the public burden of depression do not include costs related to comorbid medical and psychiatric conditions, or the significant sums of money being expended on research. Worldwide, depression affects approximately 121 million people (World Health Organization, 2008). In the U.S., the National Comorbidity Survey Replication (NCS-R) found a lifetime prevalence of major depressive disorder of 16.2%, affecting approximately 32 to 35 million adults; the 12-month prevalence rate

in a related study was reported at 6.6%, affecting upwards of 14 million American adults (Kessler et al., 2003).

Young people aged 15-24 years old have the highest incidence of depression, with a rate of 6.1% diagnosed with major depressive disorder in a one-month study; adults aged 35-44 have the next highest incidence at 5.3% (Blazer, Kessler, McGonagle, & Swartz, 1994). The lowest rates are among those who are 45-54 and 55-70 years of age (Kessler, et al., 2003). Prevalence again rises among the very elderly, aged 85 and above (Nolen-Hoeksema, 2007). Women are approximately twice as likely as men to experience depression, across all age groups (Nolen-Hoeksema, 2007). Additional sociodemographic correlates of depression include being unemployed or disabled, divorced or never married, having less than twelve years of education, and living in or near poverty (Kessler, et al., 2003). Those who have experienced a prior episode of depression are at a high risk for relapse (Nolen-Hoeksema, 2007).

Treatments for Depression

Despite increased awareness of depression, there are still significant barriers to treatment, including stigma about mental health disorders, failure to recognize symptoms, patient attitudes and beliefs about depression, psychosocial circumstances and resources including lack of health insurance, transportation, childcare, and finances; noncompliance, and availability and adequacy of care (Hirschfeld, et al., 1997; Institute for Clinical Systems Improvement, 2006; Nutting, et al., 2002). Pharmacotherapy and/or psychotherapy are considered to be effective in treating depression according to clinical practice guidelines and treatment recommendations depend upon the symptom severity, comorbid conditions, psychosocial stressors, and the patient's preferences and self-efficacy beliefs (Institute for Clinical Systems Improvement, 2006). For severe

presenting symptoms, an initial combination of antidepressants and psychotherapy is recommended (Institute for Clinical Systems Improvement, 2006).

The optimal goal in treating depression is remission of symptoms, since remission is shown to contribute to better long-term outcomes and enhanced functioning in daily life (Trivedi, et al., 2006). However, helping patients achieve remission through treatment has proven to be a tremendous challenge for many reasons. First, remission is inconsistently defined. Remission is generally described as a state of minimal to no symptoms and a return to normal functioning (Frank, et al, 1991, as cited in Israel, 2006). Operationalized definitions of remission vary however, due to an absence of specific biologic markers or tests for depression, differences in instruments used for diagnosis, and variability of measures, cut-off scores, and length of time in various studies of depression treatments (Israel, 2006).

Because most patients with depression do not achieve remission with any type of initial treatment, the National Institute of Mental Health (NIMH) funded the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), the world's largest ecologically valid "real world" study of treatment-resistant depression. STAR*D sought to examine pretreatment predictors of remission as well as complexities involved in delivering adequate treatment (Trivedi, et al., 2006). The study design mimicked clinical practice, giving patients choices about treatment strategies, rather than mandating randomization (Rush, et al., 2006). Because antidepressant treatment may be inadequate much of the time both in dose and duration (Hirschfeld, et al., 1997), the study used a measurement-based care methodology in order to deliver correct dosages over the adequate length of time required for patients to exhibit response to treatment (Trivedi, et al., 2006). During the initial treatment phase, 47% of patients responded to treatment with medication, and 28-33% achieved remission of symptoms. Approximately 40%

of those who achieved remission did so at or after 8 weeks of treatment (Trivedi, et al., 2006). While these remission rates were perceived as robust and were higher than expected based upon previous efficacy studies (Trivedi, et al., 2006), the reality remains that the majority of patients did not achieve remission with a single trial of monotherapy with antidepressants.

Patients are less likely to receive psychotherapy as an initial standalone treatment. Most are treated for depression by their primary care physician, and only about one-third of patients are ever referred to a psychiatrist or psychologist (Rost, Zhang, Fortney, Smith, & Smith, 1998). Approximately 75% of patients are prescribed an antidepressant by their primary doctor (Williams, Rost, Dietrich, Ciotti, Zyanski, & Cornell, 1999). The literature is scant regarding the outcomes of providing psychotherapy as initial treatment (see Segal, Vincent, & Levitt, 2002). In one study, women with recurrent depression received interpersonal therapy (IPT) at the outset of treatment and IPT successively if they did not remit (Frank, et al., 2000). A second comparison group received IPT with a selective serotonin reuptake inhibitor (SSRI) at the outset of treatment. A significantly greater number of women (79%) achieved remission in the sequential treatment group than the second, combination group (66%), with the greatest differences seen in severely depressed patients (81% vs. 58%).

Many patients with treatment-resistant depression require multiple treatments (such as trying different antidepressants, and/or combining with psychotherapy) in order to achieve remission (Rush, et al., 2006). In successive STAR*D treatment phases patients chose which strategies were acceptable to them, including augmentation with an additional medication, adjunctive treatment with cognitive therapy (CT), switching medications, or CT alone. Remission rates were approximately 30%, 14%, and 13% respectively for the second, third and fourth treatment steps (Rush, et al., 2006). Switching to or adding CT after the first unsuccessful

treatment with an antidepressant was generally as effective as switching or adding medications; remission took longer to achieve but was better tolerated than a medication switch (Thase, et al., 2007). With each additional treatment step, the chances of remission became smaller and relapse rates became higher (Rush, et al., 2006). The length of time required to hit upon the ‘right’ treatment can be discouraging to patients, as their symptoms may worsen while multiple treatments are being enacted.

About 33% of patients – a significant minority – have a form of depression which does not remit, even after multiple combinations of treatment (Rush, et al., 2006). Demographic correlates of treatment-resistant depression include being non-Caucasian, male, unemployed, and having low levels education and income (Trivedi, et al., 2006). Situational factors include having more concurrent psychiatric disorders, longer index episodes, more general medical disorders, and lower baseline function and quality of life (Trivedi, et al., 2006).

Given the generally low rates of remission achieved with current best-practice treatments, the question of treatment efficacy is a salient one. Questions also arise regarding the efficacy of antidepressants, particularly given the common practice in pharmaceutical trials of using response (a fifty-percent reduction in symptoms) rather than the more stringent standard of remission as a measure of success. Many trials report efficacious outcomes; however, a recent meta-analysis of antidepressants revealed that when unpublished trial data are included along with published trial results, the benefits of medication over placebo fall below recommended criteria for clinical significance (in this case, the standards set by the U.K.’s National Institute for Clinical Excellence) (Kirsch, et al., 2008). This same study found that efficacy reached clinical significance only in trials with the most severely depressed patients, and that this was due not to

an increased response to the antidepressants, but a decreased response to placebo (Kirsch, et al., 2008).

Despite the challenges faced in treating depression, exciting new research emerging in genomics and related fields is helping to change the ways we think about disease and functioning. Broadening our knowledge of the causes of depression, including genetic biomarkers and their interaction with many other body systems, is already opening up new avenues for more potentially effective and more individualized treatments of depression. This ‘systems biology’ approach to understanding disease, including depression, has implications for a new kind of health care referred to as ‘personalized medicine.’

New Paradigms of Disease, Functioning, & Healthcare

The momentous completion of the sequencing of the human genome provided scientists with an incredible amount of information about whole-gene sequences – but not the knowledge about the functions most genes serve, or how genes and the proteins they encode interact, or what impact environmental factors have upon these processes (U.S. Department of Energy Office of Science, 2006). Perhaps the greatest impact of the Human Genome Project is its influence on the tools and techniques now being used for conducting biological research, within a new paradigm called ‘systems biology’ (Henry, 2003; U.S. Department of Energy Office of Science, 2006). Instead of following the traditional reductionist approach to understanding individual biological components such as neurotransmitter reuptake mechanisms or serotonin molecules, systems biology focuses on all the body’s components, and the interactions among them, as part of a single interactive system (Institute for Systems Biology, 2007b). For instance, researchers using systems biology techniques (e.g., genomics, metabolomics, proteomics) have

begun to shed light on how abnormalities of the serotonin system are only one part of complex chains of molecular events that can cause depression. For example, one study with mice found that overactivity of a specific enzyme in the brain may play a more fundamental role in depression than low serotonin levels (and thus be a potentially faster target for new medications) (Beaulieu et al., 2008). Similar implications for improving antidepressant medications came from a study of an experimental medication that relieved depression symptoms within hours, instead of the usual weeks or months, by targeting the glutamate system (Maeng et al., 2007).

Researchers have also uncovered a clue about how antidepressants might work by altering the structure of molecular “pump” mechanism that maintains neurotransmitter balance (Singh, Yamashita & Gouaux, 2007). Results from the extensive NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study have identified that genetic polymorphisms (variations in certain genes) can affect how individuals respond to antidepressant medications (e.g., Paddock et al., 2007; Perlis et al., 2008). Even more specific connections have also been made; for example, certain antidepressants have been tied to suicidal ideation in men with a particular gene variation (Perlis et al., 2007).

What do these results signify in a practical sense? For one, the new field of pharmacogenomics (the study of how genes affect individuals’ responses to drugs) is being hailed as the advent of a new era of “personalized medicine” (Evans & Relling, 2004; PriceWaterhouseCoopers, 2005). In contrast to traditional medicine’s trial-and-error approach to diagnosis, drug development and wide-spectrum treatments, personalized medicine uses new methods of molecular analysis to analyze a patient’s genetic and environmental profile in order to improve diagnosing and individualize treatment and predictive care (The Personalized Medicine Coalition, 2008). For the treatment of depression, personalized medicine has meant the

development of new genetic tests such as the cytochrome P450 (CYP450) genotyping test, which tests for genes that produce an enzyme necessary for metabolizing certain antidepressant medications (Mayo Clinic, 2006; de Leon, Armstrong, & Cozza, 2006). Genetic biomarker tests such as this one may help physicians in diagnosing specific subtypes of depression, determining which antidepressants won't work for a given patient, and predicting adverse side effects (Mayo Clinic, 2006). The promise of such genetic testing and a genetics-based approach to pharmaceutical development is abundant, moving healthcare toward precisely targeted treatments based upon an individual's unique genetic makeup, rather than just treating symptoms.

As illustrated by the aforementioned examples of research and applications for the treatment of depression, the systems biology model and the advent of personalized medicine are transforming our current views of human health and disease, and may ultimately transform the practice of medicine with practical applications toward predictive, preventative and individualized care (Institute for Systems Biology, 2007a). One of the most exciting aspects of the personalized medicine movement lies in its potential to create an enormous paradigm shift in our current best-practice pharmaceutical treatments. It is argued here, however, that there is also a shadow side to this movement. Personalized medicine's underlying assumption is that pharmacological treatments are still the foremost answer for addressing chronic illness. Although more effective drug therapies may be developed by taking each person's unique genetics into account, this myopic focus on pharmaceuticals means a loss of opportunities for practicing "personalized" care in the broadest sense of the word.

It is challenging to locate scientific literature that takes a broader view. A PubMed search yields 416 results focused primarily on genetic polymorphisms, biomarkers of disease and their

implications for pharmacotherapy. However, it is important to recognize that personalized medicine, by some definitions, is more broadly inclusive of other factors such as a patient's medical history, family history, clinical exam, and other non-genomic diagnostic tests, with the goal of enacting the best treatments and outcomes for that individual (U.S. Food and Drug Administration, 2005). It is proposed here that this definition could be further expanded beyond these biologically-based factors to encompass areas such as a patient's unique life history, beliefs, values, environments, and healthcare preferences. Such a definition would be in keeping with the spirit of the systems biology paradigm which gave rise to the current form of personalized medicine, by considering all components relevant to an individual's health and assessing how these factors interact with one another.

Ideally, it would seem that a pharmacogenomic approach integrated with an even more encompassing view of individual patients, beyond their genetic and molecular makeup, might provide the best model of personalized care. Encouragingly, connections are beginning to form between pharmacogenomic-focused personalized medicine and other existing fields of healthcare that are already seeking to practice "personalized" medicine in its broadest sense (NCCAM, 2007b; Institute for Functional Medicine, 2008b; Veltmann, 2005). Two such approaches that hold promise for the treatment of depression are examined here: functional medicine (FM) and complementary and alternative medicine (CAM).

Comparison of Functional Medicine and CAM

Functional medicine may be briefly defined as a dynamic physiologic and biochemical-based approach to assessing, preventing and treating complex chronic disease. Functional medicine is not a unique field, but rather a cross-disciplinary approach to healthcare (Rountree,

2006). Complementary and alternative medicine generally includes healthcare modalities and products that are not currently considered to be part of conventional medicine (National Center for Complementary and Alternative Medicine [NCCAM], 2007b). CAM modalities vary widely and include such diverse treatments as acupuncture, massage, chiropractic manipulation, herbal supplements, and mind-body therapies, to name a few. FM and CAM approaches have varying definitions and may overlap in many ways, creating potential confusion for research efforts. In particular, their relation to one another is somewhat unclear. CAM does not have fixed boundaries, either within itself or between the CAM domain and conventional medicine – treatments and modalities often overlap (NCCAM, 2007b). Functional medicine, too, is differentially defined. FM can be considered a subset of CAM, classified as an “unconventional Western system” within the CAM domain of “whole medical systems” (Kumar Pal, 2002). (Interestingly, at the time of this writing, the NCCAM website does not list functional medicine anywhere.) Overlap certainly occurs within CAM, as specific nutritional and dietary FM treatments could also be placed within the “biologically-based therapies” CAM category. Other definitions, particularly those advocated by FM practitioners, place FM completely outside of the CAM domain, defining it as “more than ‘holistic’ or ‘alternative’ medicine” (Parcell, 2008). FM is said to create a shared approach to practice, based in Western medical science, that is “available to conventional and CAM practitioners alike” (Rountree, 2006).

Still other definitions attempt to go beyond the CAM vs. conventional medicine perspective, and utilize a clinically relevant classification system to categorize therapeutic approaches and treatments by their primary mode of therapeutic action. In this model of classification, six categories are proposed, including biochemical, biomechanical, mind-body, energy, psychological, and non-local (e.g., prayer, faith healing, shamanism) modes of

therapeutic action (Jones, 2005). In this model, FM is a medical system falling within the “biochemical” category, and does not overlap with any of the other classifications.

For the purposes of the present study, it is proposed that the differences are significant enough between FM and CAM that they can be operationalized as two separate approaches (although they may potentially share some overlapping treatments). FM can be thought of as a unique approach primarily due to its biochemical perspective; in contrast, the CAM approaches examined in this study can all be categorized as “mind-body,” “energy,” “psychological,” or “non-local” modes of therapeutic action (Jones, 2005). A detailed discussion of both FM and CAM follows.

Functional Medicine

Functional medicine (FM) is “personalized medicine that deals with primary prevention and underlying causes instead of symptoms for serious chronic disease” (Institute for Functional Medicine, 2008b). The concepts of functional medicine originated in the early 1980’s and were based upon innovations in the field of molecular medicine. Researchers began to shift focus away from the idea that disease is generally predetermined by our genes, and instead postulated that many different environmental influences exert significant effects on gene expression, giving rise to our biochemical individuality (Jones, Bland, & Quinn, 2006). FM is a discipline-neutral field based in Western medical science, but differs from the conventional medical model by focusing first on assessing and treating dysfunctions that underlie chronic disease, rather than emphasizing diagnosis and pathology (Jones, Bland, & Quinn, 2006; Mechanick, 2005). Functional medicine is a type of “upstream medicine” which takes a patient-centered approach to diagnosis by exploring the antecedents, mediators and triggers of the patient’s specific disease

(Jones & Bland, 2006). Acknowledging that chronic disease is almost always preceded by a decline in functioning as a result of unique lifelong interactions among our genetic predispositions, environment and lifestyle, FM seeks to identify these factors and restore balance among them (beyond just addressing symptoms through medication) as a means of both treating and preventing disease (Jones, Bland, & Quinn, 2006).

Functional medicine advocates a systems biology approach to healthcare, aligning with current research showing how the body's physiological processes and systems interact with each other in complex ways, rather than functioning autonomously (Institute for Functional Medicine, 2008b; Bland, 2006). The principle of biochemical individuality (looking at individual variations in metabolic function that arise from our unique environmental and genetic differences) in FM parallels the emerging personalized medicine paradigm. Instead of following the current path of personalized medicine that primarily employs pharmaceutical interventions to treat symptoms, however, FM takes a more comprehensive approach to assessing and treating underlying dysfunctions. FM assesses each person's fundamental clinical imbalances (e.g., hormonal and neurotransmitter, immune, and inflammatory imbalances), fundamental physiological processes (e.g., transport and circulation, elimination of waste), and environmental inputs (e.g., diet, nutrients, air and water, microorganisms, exercise, trauma, psychosocial factors) (Jones, Bland, & Quinn, 2006). Therapies employed, while based in scientific principles, are flexible and eclectic (Quinn & Jones, 2006). Treatments may include dietary and clinical nutritional therapies; additional complementary and lifestyle interventions may include exercise, mind-body-spirit approaches, botanical medicines, physical medicine, and energy medicine such as acupuncture (Quinn & Jones, 2006). Although the use of medications does not disappear from functional medicine practice, FM has a distinct bias toward lifestyle interventions because of

their long-term role in treating and preventing disease, as well as their lower cost (Quinn & Jones, 2006). Philosophically, FM opposes treating patients by matching a diagnosis to pharmacology, and also points out that pharmacologic research (even that conducted by non-corporate entities such as the NIMH) too often focuses on “single disease – single agent – single outcome” methodologies (Jones, Bland, & Quinn, 2006). Thus a potential incompatibility arises between the field of pharmacogenomics, and FM’s approach to personalized medicine. However, many of the individualized dietary and nutritional interventions offered by FM are based upon knowledge from the field of nutrigenomics (the study of molecular relationships between nutrition and gene response), and functional medicine also stands poised to continue utilizing new discoveries in genomics and proteomics (the study of gene expressions and proteins that regulate metabolic function) for determining new treatments (Bland, 2006; Mechanick, 2005).

As with any presenting symptomology, FM takes a systems biology and personalized approach to the treatment of depression. For instance, in postmenopausal women with depression, the complex interactions of neurotransmitters, hypothalamic/pituitary hormones, the nervous system and the immune system are taken under consideration. Estrogen, progesterone, cortisol, adrenaline, and allopregnanolone (a brain active GABA receptor agonist created from progesterone’s rapid conversion in the liver) may all play a role. The goal of hormone therapy in treating depression is to balance hormone levels by improving metabolism, biotransformation, and excretion of estrogen, rather than simply replacing it (Hays, 2006). In order to determine the best treatment for an individual, the FM practitioner examines the interactions of all functional systems involved as well as assessing environmental, genetic and lifestyle factors. For example, it is helpful to know whether the individual was born to a stressed mother, since fetal brain development in a stressed environment can result in a lifelong struggle with an overactive

hypothalamic-pituitary axis (HPA) system, and high levels of cortisol and adrenaline (Hays, 2006). For an individual with overactivity of the HPA, stress-reduction techniques such as mindfulness-based stress reduction, yoga, meditation or energy medicine may be helpful (Hays, 2006).

Functional medicine is being practiced by many diverse healthcare practitioners trained in its approach, including medical doctors, osteopathic physicians, psychologists, nurses, acupuncturists, nutritionists, naturopathic doctors, chiropractors and many other health professions (Institute for Functional Medicine, 2008a). Although FM shows promise as an individualized treatment approach, barriers to treatment do exist. A notable factor is that functional medicine treatment takes time – time for patient and practitioner to form a relationship in which each party has buy-in to the treatments being selected; and time for interventions treating underlying systemic imbalances to begin showing effects (Semmes, personal communication, March 29, 2008). Additionally, it might appear that interventions such as clinical nutritional supplements would have a lower cost than pharmaceutical interventions, a benefit of functional medicine. However, if a FM practitioner pursued all possible lab work (genomic tests, blood workups, polymorphism profiles) needed to gain a fully individualized picture of the patient, costs would be prohibitive (Semmes, personal communication, March 29, 2008).

Functional medicine is predicated upon evidence-based (or at minimum, science-based) medicine (Liska, 2006), and thus values undertaking clinical research on FM treatments. However, FM's numerous and individualized diagnostic and treatment approaches, "most of which have reasonable underlying science and principles" add complexity to the framework of Western medicine within which they are practiced, and have not been rigorously tested either in

clinical or research settings (Pizzorno, 2006, p. 39; Gant, 2000; Mechanick, 2005). Some research does exist for medical conditions such as cardiovascular disease, inflammatory conditions, menopausal symptoms, arthritis, and fibromyalgia (e.g., Lukaczer, et al., 2005; Lukaczer, et al., 2006; Minich, et al., 2007). However, there is a paucity of research both for functional medicine in general, and the use of functional medicine in treating mental health disorders. Thus a significant opportunity exists for research on functional medicine and depression.

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) includes healthcare modalities and products that are not currently considered to be part of conventional medicine (defined as medicine practiced by holders of M.D. [medical doctor] or D.O. [doctor of osteopathy] degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses) (NCCAM, 2007b). As implied by their name, CAM therapies may be used as adjunctive treatments to conventional care (complementary), or instead of traditional medical treatment (alternative). In response to growing consumer use and the potential promise of CAM therapies, the National Institutes of Health created the National Center for Complementary and Alternative Medicine (NCCAM) in 1992.

Complementary and alternative medicine encompasses a wide range of modalities and systems. Despite vast diversity in approaches to treatment, a commonality is that CAM is often utilized by patients for whom traditional care is not meeting their individual needs (Ritenbaugh, Verhoef, Fleishman, Boon, & Leis, 2003). CAM therapies are patient-centered; treatments are often highly individualized to the specific patient, more so than in conventional medicine (Herman, D'Huyvetter, & Mohler, 2006). Practitioners of CAM often hold a more complex

conceptualization of individualization than the ‘personalized medicine’ suggested by genomics (Ritenbaugh, Verhoef, Fleishman, Boon, & Leis, 2003). In addition to considering unique biologically-based factors, CAM practitioners may personalize treatment based upon factors such as a patient’s life experiences, the patient-practitioner interaction, and patient and practitioner values and expectations (Ritenbaugh, Verhoef, Fleishman, Boon, & Leis, 2003). The CAM field is beginning to combine its research efforts with genetics research in the context of personalized medicine, since the two fields do share the broad goal of being able to tailor patient interventions (NCCAM, 2006; NCCAM, 2007b).

The NCCAM categorizes CAM in five domains: whole medical systems, mind-body medicine, biologically-based practices, manipulative and body-based practices, and energy medicine (NCCAM, 2007b). Whole medical systems are complete systems of theory and practice that have often evolved outside of, and earlier than, conventional Western medicine (NCCAM, 2007b). Examples of whole medical systems include traditional Chinese medicine, Ayurveda, homeopathic medicine and naturopathic medicine. Mind-body medicine, as implied by its name, focuses on how the body and mind interact with one another, and on the effects of mental, emotional, spiritual, social and behavioral factors upon health (NCCAM, 2007e). Mind-body approaches are geared toward promoting self-care and self-healing, and include interventions such as yoga, meditation, art therapy, biofeedback, relaxation, and spirituality (NCCAM, 2007e). Biologically-based practices include treatments such as botanicals, vitamins and minerals, fatty acids, functional foods, whole diets, probiotics, fatty acids, amino acids and dietary supplements (NCCAM, 2007a). Manipulative and body-based practices is a large and heterogeneous group of treatment modalities focused mainly on the structures and systems of the body, including soft tissues, bones and joints, and lymphatic and circulatory systems. Among

manipulative and body-based practices are chiropractic manipulation, osteopathic manipulation, massage, reflexology, and many more (NCCAM, 2007d). Despite being widely varied, this group of CAM therapies shares the common principles that the human body has self-healing and self-regulating tendencies, and its parts function interdependently (NCCAM, 2007d). Finally, the domain of energy medicine involves two types of energy fields: veritable energies, which can be measured, and putative energy fields or the human “biofield,” whose existence has been theorized for centuries but cannot yet be measured with existing instrumentation (NCCAM, 2007c). Energy medicine practitioners believe that illness arises from imbalances or disturbances in the biofield, also known as subtle energy; treatment modalities include acupuncture, qi gong, Reiki, Therapeutic Touch, homeopathy, and distance healing (NCCAM, 2007c). Treatments addressing the veritable energies include magnetic therapy, sound energy therapy, and light therapy (NCCAM, 2007c).

Definitions of CAM can vary widely, and may change continuously. For instance, although NCCAM includes chiropractic manipulation in its CAM definition, a recent study on mental disorders and the use of alternative medicine did not include chiropractic care, considering it to be mainstream rather than CAM since it is largely reimbursable today by third-party payers (Unützer, et al., 2000). Cognitive-behavioral therapy was previously considered CAM, and is still viewed by the CAM paradigm as a type of “mind-body medicine” (NCCAM, 2007e), but is now considered a standard treatment for depression recommended by clinical practice guidelines (National Guideline Clearinghouse, 2006). These variations in defining CAM therapies have made it challenging to assess the current literature in a systematic fashion and draw conclusions about potential treatment efficacy.

Western consumers' increasing use of CAM therapies for a host of conditions is beginning to make a strong anecdotal case for their effectiveness, both alone and in conjunction with conventional medicine. It is estimated that over one-third of Americans use some type of CAM in a given year (Eisenberg et al., 1998). People utilizing CAM therapies often self-refer for mental health reasons. A survey of 262 outpatient psychotherapy clients showed that 64% of respondents reported using at least one CAM therapy in the last 12 months (Elkins et al., 2005). One of the largest groups of people who use CAM treatment are those with self-defined depression and anxiety; the only other group with a chronic condition reporting greater use of CAM are those with back or neck problems. In the nationally representative survey reporting these results, approximately 41% of depressed individuals had used an alternative therapy in the past twelve months, and 27% had seen both a medical doctor and a CAM practitioner for depression during that time period (Eisenberg et al., 1998).

Given these consumer trends and initial research results, NCCAM has encouraged further research on CAM therapies to determine their efficacy and potential adjunctive value to standard practice in the treatment of depression (NCCAM, 2007h). Despite the growing number of consumers seeking out CAM therapies for mental health, however, to date it appears that far more research has been conducted on the efficacy of CAM for medical conditions than for mental health conditions. For example, of the current and recently completed clinical trials listed for acupuncture on the NCCAM website, nearly 90% examine medical conditions, and only a handful of studies examine depression (ClinicalTrials.gov, 2007), signifying that there is still more emphasis on CAM use for bodily ailments rather than mental ones. This imbalance may also underscore the historically dichotomous thinking of Western medicine, both in the medical field and in psychotherapeutic approaches. It may be that the professional norms and ethics of

psychotherapy have contributed greatly to a split in thinking about therapies that involve the body, not just the mind. As the field of psychotherapy developed, touch became taboo in most theoretical orientations, reflecting the Western dualism of mind and body (Nolen-Hoeksema, 2007). Given this history, it is not surprising that mental health care practitioners, physicians, and researchers do not often consider integrating or at least investigating body-oriented or energy-based CAM therapies as part of a treatment plan.

Encouragingly, many of the CAM studies which focused on medical conditions incidentally discovered that some CAM therapies have positive effects on conditions such as anxiety and depression. For instance, upon reviewing the efficacy of massage therapy (MT) in studies on a number of clinical conditions as varied as pregnancy, postoperative pain, and chronic fatigue, Field (1998, as cited in Moyer, Round, & Hannum, 2004) noted that anxiety and depression were both reduced across studies. Building upon this medically-related research, a number of recent studies have specifically investigated CAM therapies for mental health issues; with anxiety and depression being primary areas of study.

Although some of the research shows promising results for CAM therapies for mental health, overall results are mixed and therefore inconclusive (Leo et al., 2007; Moyer et al., 2004; Thachil, Mohan & Bhugra, 2007). It is noteworthy that many early studies had significant methodological flaws which more recent studies have attempted to address (Leo et al., 2007). Limitations include insufficient sample sizes, inadequate subject randomization, lack of clear enrollment criteria, poorly defined outcome measures, and participant and practitioner bias due to lack of blinding (Leo et al., 2007). Additionally, heterogeneous populations in some of the reviewed studies make it difficult to generalize findings (Leo et al., 2007). There has been little examination of potential moderating variables such as participant and therapist expectations,

amount and types of communication during a CAM session, and the influence of personality traits (Moyer et al., 2004). Perhaps most importantly, few studies had adequate follow-up post-treatment to determine whether treatment effects are enduring or whether maintenance sessions are required (Leo et al., 2007; Moyer et al., 2004). An additional limitation to existing research is that few studies examine the efficacy of CAM therapies in combination with antidepressant medications and/or psychotherapy, both common treatments for mental health conditions. Given that growing numbers of consumers, however, are utilizing CAM therapies for mental health conditions, often in conjunction with conventional care (Kessler et al., 2001), it is important to address these limitations and to conduct further research on the combinations of pharmacotherapy and/or psychotherapy with CAM.

Depression has been studied more extensively than other mental health conditions in the framework of CAM treatment. Two CAM therapies in particular, acupuncture and massage, have been examined for their efficacy in the treatment of major depression (Leo & Ligot, 2007; Moyer et al., 2004; Thachil et al., 2006). Acupuncture is a healing practice that has been in existence for over two thousand years in Asian traditions. In the framework of traditional Chinese medicine (TCM) it is used traditionally in combination with herbs, diet, exercise, meditation and massage to treat the whole person; addressing complaints of a physical, emotional, and psychological nature. Acupuncture seeks to correct illness by addressing imbalances in the body's system of energy meridians (subtle energies that are not scientifically measurable), generally with thin needles placed at specific points of the body (see Kaptchuk, 2002). This healing practice is still very much in use and respected in Asian cultures, but the scientific West is slower to embrace healing modalities that have not to date been sufficiently theoretically explained or empirically validated. In comparison to other modalities, however, acupuncture has been supported in a

variety of research studies as an efficacious treatment for increasing mental health. In preparation for a systematic review of acupuncture in treating depression, Leo & Ligot (2007) located 25 studies in the literature, with 9 randomized controlled studies deemed of sufficient methodological quality to include in the final review. Although they identified a number of limitations and mixed results, the results from a number of studies showed promise of efficacy for depression.

Like acupuncture, massage has a long traditional history as a medicinal practice (for a discussion see Moyer et al., 2004). Massage therapy (MT) involves the manual manipulation of muscle and connective tissue for the purpose of facilitating health and relaxation (NCCAM, 2007d). There are numerous theories about how the mechanisms of massage promote efficacious outcomes for health with both physical and mental conditions, but there is mixed support for existing theories (see Moyer et al., 2004). A meta-analysis of massage therapy research showed that of 37 randomized controlled studies analyzed, 21 assessed state anxiety, 8 assessed negative mood, 7 measured levels of the stress hormone cortisol, 7 assessed trait anxiety and 10 assessed depression; findings indicated that the largest effects of massage therapy were reduction of trait anxiety and depression (Moyer, et al., 2004).

While results are mixed and inconclusive due to methodological problems and other limitations, in general the findings seem to indicate that acupuncture and massage may result in positive therapeutic outcomes and that they show potential promise as primary therapy for depression, and/or as an adjunct to conventional treatment. Additional CAM therapies such as St. John's wort, omega-3 fatty acids, S-adenosylmethionine, folate, and 5-Hydroxytryptophan (5-HTP) also show promise of effectiveness, although existing research is still preliminary (see Jorm, Christensen, Griffiths, & Rodgers, 2002; Freeman, Helgason, & Hill, 2004).

Despite the promise shown by acupuncture, massage and other CAM therapies for mental health treatment, there are many social barriers to acceptance and availability of these modalities – another important reason for promoting research on this topic. Conventional practitioners in psychology, for instance, are limited in their knowledge about alternative and complementary therapies and their efficacy (Miller, 2006). Cultural norms, too, promote a ‘doctor knows best’ mentality, meaning patients are not as likely to take responsibility for their own healing and therefore explore all avenues of treatment which may be helpful. If conventional providers are not aware of CAM therapies or do not subscribe to their effectiveness, patients may never become aware that this treatment could help.

The prevalent Western medical model also tends to exclude CAM therapies, not just because of the limited body of empirical evidence, but because care is compartmentalized. The focus on a single physical problem or set of psychological symptoms and the model of specialist care providers often translates as the ‘parts not talking to the whole.’ This lack of holistic approach is reflected in the fact that practitioners often don’t communicate or collaborate, or even know that patients are receiving concomitant care (Druss & Rosenheck, 1999; Eisenberg et al., 1998). Another significant obstacle to acceptance and use of CAM therapies is the current social policy around healthcare. Third-party reimbursement for CAM therapies is only beginning to become available for mental health conditions; one study estimated that only 15% of CAM therapies used in the U.S. are covered by health insurance, and 58% of therapies are not covered at all (Eisenberg, et al., 1998). And yet, despite the need to pay out of pocket for such treatments, consumer demand exists (Kessler et al., 2001).

Changing the Evidence Model

Given the general paucity of research in functional medicine and CAM in contrast to the predominance of randomized controlled trials (RCTs) for pharmaceutical interventions, it is worthwhile to briefly examine why greater numbers of rigorously designed RCTs have not been conducted for these other therapeutic approaches. To answer this question, the widely-held view that RCTs are the ‘gold standard’ for providing evidence-based decision-making about patient care must first be considered. RCTs are indeed a powerful tool for assessing whether a specific treatment works in a well-defined population (Banerjee, 1998). RCT designs can eliminate systematic bias and selection bias by randomizing participants across conditions, and using a no-treatment control condition. Unlike non-experimental designs, RCTs attempt to exert tight control over extraneous or spurious variables, and thus can be used to infer causality. In addition to these strengths, however, RCT designs also have considerable limitations for whole-systems, individualized-treatment paradigms of healthcare such as functional medicine and CAM. The specific therapeutic treatments in these approaches often do not easily lend themselves to randomized, double-blind, placebo-controlled study designs (Ritenbaugh, et al., 2003). The holistic, patient-centered models of CAM and FM can also be construed as philosophically opposed in some senses to the reductionist approach required by RCT designs, which primarily focus on a single intervention for a single condition. This presents significant limitations for research in these areas, resulting in a call for new types of research methods (NCCAM, 2007f; Herman, D’Huyvetter, & Mohler, 2006). A given CAM treatment being studied, for instance, is likely individualized, multifaceted, holistic, and inclusive of important “non-specific” therapeutic effects such as the patient-practitioner interaction and the placebo effect, thus introducing much higher levels of complexity to a study design (Herman, D’Huyvetter, & Mohler, 2006). An

additional limitation with the use of RCT designs is that CAM and other integrative approaches take a broader view of whether a treatment “works,” as determined by more qualitative and intangible outcomes such as patient-reported quality of life and whether patient expectations for treatment have been met (Herman, D’Huyvetter, & Mohler, 2006; Ritenbaugh, Verhoef, Fleishman, Boon, & Leis, 2003). These types of measures, however, have their own limitations, most notably due to the subjective nature of patient self-report. In short, it is challenging for RCT research methodologies to effectively answer the real-world question, “*What* treatment, by *whom*, is the most effective *for this* individual with *that* specific problem, and under what set of circumstances?” (Paul, 1967, p. 111).

While RCT studies have provided important information for determining efficacy and best practices in treatment interventions, the value and application of this paradigm has come under scrutiny as medical research and practice are evolving to include more systems-based approaches (see Herman, D’Huyvetter, & Mohler, 2006; Ritenbaugh, Verhoef, Fleishman, Boon, & Leis, 2003). The ‘one size fits all’ model of RCT research is being challenged in many arenas by the growing recognition that a ‘one size fits some’ approach to healthcare is needed (Alexander, Richardson, Grympa, & Hunkeler, 2007; Pyne, et al., 2004). Pharmacogenomic-based personalized medicine, for instance, is identifying methods to tailor drug interventions based on an individual’s unique genetic profile (The Personalized Medicine Coalition, 2008). Research has shown the importance of recognizing patient preferences for pharmacotherapy and/or psychotherapy, as receptivity to different types of treatment affects health outcomes (e.g., Pyne, et al., 2004). Thus the gap seems to be narrowing between conventional medicine paradigms, and the ‘one size fits some’ personalized approach currently practiced by functional medicine and CAM. As new research methodologies evolve, the body of evidence for these

therapies will become more substantial, in quantity, quality, and clinical applicability. It is proposed here that more relevant research models for alternative therapies may emerge through combining the best features of current gold-standard RCT methods with paradigms of personalized medicine and holistic healthcare, in order to attain scientifically rigorous and credible results that have real-world applicability to individual patients.

As demonstrated by a review of the literature, many studies, including RCT, observational and epidemiological designs, have been undertaken in an attempt to determine the most efficacious conventional treatments for depression. Despite the best efforts of researchers, challenges and problems abound with the existing research, which often has low ecological validity and generalizability to patient populations even if it demonstrates high internal validity. Although recent years have seen an increase in interest and funding there is still a paucity of research on alternative treatments for specific mental health disorders. Given the complexities of sequenced and concurrent treatment strategies, questionable efficacy of antidepressants, and the relatively low remission rates, it seems we are still far from understanding how to most effectively treat depression. It is argued here that alternative treatments, alternative methods of research, and new paradigms of disease and patient care must be considered in order to expand our understanding of depression and to broaden our repertoire of effective and personalizable treatments.

One integrative healthcare center in southern Maine, True North Health Center, has begun to conduct research on the efficacy of functional medicine and CAM treatments practiced in an integrative setting. Two completed unpublished pilot studies assessed general patient improvement over time. One study addressed True North's initiative to create access to health care for low income individuals (Dahlborg, 2007b). Health outcomes were analyzed to determine

the success of an innovative grant program which funds a temporary infusion of care for individuals whose income is significantly below the federal poverty level. The intention of the grant program is to motivate patients to continue with healthier lifestyles and to become more invested in their own health. Patients in the study had been in treatment at True North for an average of 2.2 years ($SD = 1.05$). Descriptively speaking, the results of this study ($n = 12$) did indicate improvement in patients' general physical and mental symptoms between pre-treatment and post-treatment health status scores as measured by a medical symptoms questionnaire. However, these results did not reach statistical significance due to the small number of participants in the sample, a wide variation in patient complaints and conditions, and a lack of power in the statistical analyses. This pilot study also examined whether the type of practitioners seen (FM, CAM, or a combination), number of practitioners seen, or number of visits were significant predictors of improvement; again, none of these variables approached significance.

A second pilot study similarly examined health outcomes during a two-year period for another group of patients who also had to meet income requirements (Dahlborg, 2007a). Statistically significant differences were observed for this sample between pre-treatment and post-treatment scores ($r = .807, p < .001$), for a sample of 36 patients, with lower scores at post-treatment comparative to pre-treatment indicating possible symptom reduction. The same predictor variables as found in the first study were analyzed, and again were not significant. The main limitation in both pilot studies is that neither measured improvement for a specific condition such as depression; such specificity was not possible due to the small sample sizes and limitations of the study design and readily-accessible patient data.

Despite some methodological weaknesses, these two studies illustrate commendable attempts to conduct relevant and credible research on real-world treatment outcomes for

functional medicine and CAM therapies delivered in an integrative and individualized manner. As discussed, little research of this kind currently exists, and is much needed in order to further understanding of collaborative, personalized, efficacious treatments for specific conditions such as depression.

Study Aims

The present study identifies a unique opportunity for examining treatment outcomes for depression at True North Health, using a model of personalized care. True North provides an integrative care setting in which to conduct a pilot study examining the comparative efficacy of two personalized care approaches, functional medicine and CAM. To build upon efforts of the aforementioned pilot studies, this study will attempt to utilize a sample with a larger number of patients; to meaningfully compare the treatment approaches of FM, CAM, and a combination approach; and to focus specifically upon the treatment of a single condition, depression. As previously discussed, depression is chosen for study due to its high prevalence in the general population, and the necessity of exploring better treatments for improving individual quality of life as well as reducing depression's heavy social and economic burdens. This study is particularly relevant and timely for study participants and the larger local communities, as the state of Maine is currently facing enormous budget cuts and the loss of mental health services (Remal, 2008). It is anticipated that study results may provide valuable information for continuous quality improvement initiatives at the healthcare center which is the site of the study. Additionally, results may be suggestive of the relative efficacy of functional medicine and CAM therapies for the treatment of depression, as well as having high ecological validity for these types of therapies as they are practiced in an integrative healthcare setting with a focus on

personalized care. This particular aim is aligned with research priorities of the NCCAM, by examining how CAM therapies function in “real-world” healthcare settings, where patients may present with multiple conditions, and utilize multiple therapies, both CAM and conventional (NCCAM, 2007g).

Specifically, this study will seek to answer the following questions. The question of greatest interest in exploring alternative ways to treat depression is whether depressed patients are improving with FM and CAM; and further, whether the specific type of practitioner seen (FM, CAM, or FM + CAM) is a significant predictor of symptom improvement. The second question addressed is whether number of visits significantly predicts improvement. Third, the level of initial severity of depression (severe or non-severe) will be analyzed for its role in predicting improvement. Finally, the interactions of these three factors in predicting symptom improvement will be assessed.

Methods

Setting

True North Health Center, located in southern Maine, is an integrative healthcare center started in 2002. Its model of care was based upon the concept that healing would be most effectively achieved through a holistic blending of science-based medicine and evidence-based complementary therapies (True North Health Center, 2008a & 2008c). In its stated mission of integrative care, patient education and research, True North seeks to embody personalized medicine in its broadest and most collaborative sense.

At True North, patients are frequently seen by more than one practitioner; staff includes traditional family practice physicians, functional medicine-trained physicians, and CAM

practitioners. It is possible that the barrier of limited practitioner knowledge about alternate therapies may not be as great an issue at True North, since practitioners often refer patients to one another, and also participate in monthly case presentation meetings at which all practitioners share the knowledge and experience of their specific modalities in order to contribute to the improvement of a particular patient. Another significant difference in True North's model lies in integrated health care records (charts), enabling maximum integration and collaboration between practitioners. Since True North does not contract with third-party payers, practitioners are able to spend as much time as necessary with patients (typically 1.5 hours for a new patient evaluation and 45-60 minutes for a follow-up visit, instead of the approximately 8-10 minute time-per-patient allowed by insurers). This may also help address a significant barrier to care since it more easily facilitates building a relationship and understanding of the patient's story, enabling patient and physician to create a treatment strategy suited to that individual (True North, 2008b).

Interestingly, another barrier to use of alternative therapies, namely a cultural reluctance on the part of patients to take responsibility for their own healing, may be indirectly addressed by True North's model. Although a majority of patients report that they receive insurance reimbursement for 60-80% of True North's services (True North, 2008b), the fact that they are required to pay out-of-pocket for services rendered may indicate a greater personal investment in their own health – greater, perhaps, than those who are accustomed to paying a \$20 insurance co-pay. Despite the need for out-of-pocket payments, over 3,000 consumers utilized True North's services last year.

Participants

Participants in this retrospective study were a sample of 164 adult male and female patients who presented for appointments at True North Health Center from the period of January 16, 2007 through January 16, 2008. Patients were included in the initial sample if they had completed two or more administrations of the Medical Symptoms Questionnaire (MSQ) during the study period. Further inclusion criteria were applied in which patients were receiving treatment in one of three categories: from functional medicine (FM) practitioners, from complementary and alternative (CAM) practitioners, or from a combination of both types of practitioners (FM + CAM). The original sample, including both depressed and non-depressed patients ($n = 164$) was reduced to 80 patients who self-reported depression on their first MSQ of the study period.

For the purpose of the present study, depression is operationalized by self-report measure (see *Data*, below). Although operationalizing depression by a DSM-IV-TR diagnosis of major depressive disorder (296.xx) or depressive disorder not otherwise specified (311) was considered, there were limitations to this approach. For instance, in the available data set, it was not clear at what specific point in time a diagnosis had been given. Additionally, it was noted that of those patients who reported severe depression symptoms, only 40% had received a DSM-IV-TR diagnosis of depression. Also, general problems exist with coding for depression, such as deliberate misdiagnosis and non-diagnosis having to do with third-party reimbursement considerations, uncertainty of the diagnosis by primary care physicians, and patient acceptance of mental health diagnoses (Rost, Smith, Matthews, & Guise, 1994; Moore, 2004). In addition to avoiding these diagnostic issues, the present method of sorting patients by self-report provided the benefit of subjective outcome data that may be more closely related to patient functioning

and quality of life (Ritenbaugh, et al., 2003). The utilization of self-report measures in the STAR*D study (the Quick Inventory of Depressive Symptomology–Self-Report [QIDS-SR]) also lends precedence for the use of self-report data in the present study (Rush, et al., 2006).

In the overall study sample ($n = 164$), 83% of patients were female; of the depressed sample ($n = 80$), 89% were female. Ethnicity, employment status and marital status demographics were not available in the existing data set. Participants in the overall sample ranged in age from 17.6 to 73.4 years, with a mean age of 46.0 ($SD = 11.24$). Depressed participants ranged from 22.7 to 69.7 years in age, $M = 44.6$ ($SD = 10.9$).

Patient privacy was ensured following the American Health Insurance Portability and Accountability Act of 1996 (HIPAA) rules, under the guidance of the Executive Director, and all identifying characteristics of patients, such as name and date of birth, were omitted from the data analysis. In accordance with True North's standard practices, patients signed Consent to Treatment forms prior to receiving care. This informed consent form gives explicit permission for blinded, non-identifiable use of patient data in True North's research, outcomes assessment and peer review programs. Because this study did not entail any manipulation of participants or interaction with participants, the study was approved as 'exempt from review' by the Institutional Review Board at the University of New England.

Treatments

Participants received treatment from a variety of practitioners, via self-referral and/or referral from one practitioner to another in alignment with True North's integrative model of care. The functional medicine group included medical doctors, a holistic psychiatrist, a naturopathic doctor, and an advanced nurse practitioner – all trained in the discipline of

functional medicine. The total number of practitioners in this group was six. The CAM group included a licensed clinical psychologist trained in several forms of energy healing, a licensed acupuncturist, a licensed massage therapist, a certified Energy Medicine / Healing Touch practitioner, and two shamanic healers. Seven practitioners comprised the CAM group.

In the sample of depressed patients ($n = 80$), the mean number of visits during the study period for the FM group was 39.4 ($SD = 31.5$), compared to 36.8 ($SD = 20.2$) for the CAM group and 39.5 ($SD = 32.9$) for the FM + CAM group. Overall, the mean total number of treatments for depressed patients (prior to and including the study period) was 39.4 ($SD = 31.5$) for the FM group; 36.8 ($SD = 20.2$) for the CAM group, and 39.5 ($SD = 32.9$) for patients who saw both FM and CAM practitioners. There were no significant differences found between the treatment groups in number of visits. The average length of time as a True North patient was 2.38 years ($SD = 1.62$).

Measure

The Medical Symptoms Questionnaire (MSQ), the health status measure utilized in past pilot studies at True North as well as in the present study, is used by True North practitioners for both clinical and research purposes. The MSQ is a clinical tool for the evaluation of general physical signs and symptoms, both in initial assessment and to monitor progress of therapeutic interventions over time (Bland & Bralley, 1992). The MSQ is a 71-item symptom checklist with a 5-point Likert scale for each symptom, with a rating of 0 being “never or almost never have the symptom” and 4 being “frequently have it, effect is severe.” Fifteen separate domains measure various physical, mental, and emotional symptoms, either for the past 30 days or since the patient’s last visit. Subtotals for each domain are combined into a total score. Scores above 75 are generally associated with substantial symptomology and disability, while patients with scores

below 30 generally have few, or low intensity symptoms (Metagenics, 2008). The version of the MSQ used by True North practitioners was expanded by True North to include two additional domains, addressing four symptoms “for men only” and five symptoms “for women only.” This revision resulted in two scores, the original MSQ Total and a new MSQ Grand Total score. Given the unusual history of the development of the MSQ instrument, as well as its diverse uses at True North, it is discussed in further detail here.

Starting in January 2007, non-clinical as well as clinical practitioners at True North were asked to begin using the MSQ on a consistent basis, asking patients to fill out an MSQ in the waiting room prior to each visit. The overall compliance rate regarding this policy is roughly estimated to be 15% for 2007. Initial compliance was much higher, estimated at 60-70%, but dropped off significantly on the part of practitioners and patients alike (T. Dahlborg, personal communication, March 21, 2008). Clinically, practitioners find the MSQ useful for the initial assessment as well as continuing to track symptoms over time, and evaluating treatment efficacy. A practitioner may reference specific MSQ items and make further inquiry with patients as to the symptoms reported. This can be especially useful when patients report verbally that they aren't feeling better, even though the MSQ scores over time show that the symptoms of their presenting complaint have actually improved. The practitioner is then able to initiate further dialogue to discover additional underlying complaints related to other areas of the MSQ. The MSQ is also clinically useful for identifying lab work diagnostic codes for third-party reimbursement purposes, and for writing consultation letters (B. Hays, personal communication, December 10, 2007).

The Medical Symptoms Questionnaire is currently utilized by many functional medicine practitioners in the U.S. (Institute for Functional Medicine, 2008a), as well as by clinical

detoxification programs (Bland & Bralley, 1992). While not used extensively in research, the MSQ has been used as a measure in case studies (e.g., Luckaczer, 2005) and in one randomized controlled trial on Chinese herbs for enhancing learning and memory (Singh, et al., 2004). Currently, George Washington University Medical Center Division of Integrative Medicine is utilizing the MSQ to screen for comorbidities in a study with fibromyalgia patients (B. J. Semmes, personal communication, March 25, 2008).

Although the MSQ displays high clinical utility and reasonable face validity as a subjective measure of physical symptoms, other types of validity and reliability information are at best unclear due to the lack of detail regarding the instrument's development history. The Medical Symptoms Questionnaire (originally named the Metabolic Screening Questionnaire) was derived from the Cornell Medical Index Health Questionnaire (CMI), using a subset of questions related to symptoms of toxicity, by Jeffrey Bland of the Institute for Functional Medicine (IFM) (Bland & Bralley, 1992). The Cornell Medical Index was developed in 1949 for the purpose of collecting a standardized medical and psychiatric history prior to the interview, with minimal expenditure of a physician's time (Weill Cornell Medical Library, 2005). Through the 1970's, the CMI was widely used throughout the country and was considered to be reputable, reliable and valid; it is a Medical Subject Heading with an extensive bibliography in the PubMed database (Weill Cornell Medical Library, 2005; see also Abramson, 1966).

In order to establish the MSQ as a valid scientific instrument, True North undertook studies to examine its reliability and validity. Although derived from a valid instrument, the MSQ itself had not been validated. To remedy this issue, True North tested the MSQ for reliability and validity in two unpublished studies. (Note that True North tested its own edited version of the MSQ, discussed above, not the original MSQ version from the Institute for

Functional Medicine.) In a two-part reliability study, test-retest reliability was analyzed. In Study 1, 17 patients from True North completed the MSQ on two consecutive days. Pearson product-moment correlations for 58 items were significant at the .01 level of confidence (two-tailed), with correlations ranging from .619 to 1.000. Five items were significant at $p = .05$ (two-tailed), with correlations ranging from .482 to .576. Seventeen items were not computed because one of the variables was constant (Hays & Dahlborg, 2006b). In Study 2, volunteer participants were recruited from a national multidisciplinary practitioner conference. Sixty participants completed the MSQ on two consecutive days. Correlations for 76 items were significant at $p = .01$ (two-tailed), ranging from .458 to 1.000. One additional item was significant at $p = .05$, $r = .301$; the two remaining items were not computed due to lack of variability in the variable (Hays & Dahlborg, 2006b). Given these results, it may be concluded that the MSQ is reliable when administered on two consecutive days.

In a separate study examining the MSQ's convergent validity, scores from 87 True North patients were analyzed for both the MSQ and the online DYNHA SF-36® Health Survey (SF-36) administered on the same day. The SF-36, the most widely-used health status questionnaire in the world, has been psychometrically constructed, normed, and empirically validated with general populations of the U.S. and nine European countries, and it is shown to have high internal consistency and test-retest reliability (see Ware & Kosinski, 2002). The MSQ Subtotal score (in True North's version of the MSQ, this score is equivalent to the "Grand Total" score found in the original MSQ version) was found to exhibit a fairly high inverse correlation with the SF-36 Total score, $r = -0.635$, $p = .000$ (Hays & Dahlborg, 2006a). A negative correlation indicates agreement between the two instruments since they are scored in opposite directions (i.e., a higher score on the MSQ indicates worse symptomology, while a higher score on the SF-

36 indicates better functioning and quality of life). Additional analyses examined the correlations between the two sub-scores of the SF-36 for physical and mental health, and the MSQ Subtotal. The SF-36 Physical Component Summary (PCS) score showed a moderate correlation with the MSQ Subtotal, $r = -.485$, $p = .000$ (two-tailed). The SF-36 Mental Component Summary (MCS) was similarly correlated, $r = -.455$, $p = .000$ (two-tailed) (Hays & Dahlborg, 2006a).

It is worthwhile to note that True North attempted to incorporate the computerized DYNHA SF-36 as a primary health status and outcomes measure, due to the DYNHA's extensive validation and ease of results analysis through database reporting. However, since its introduction at True North, the SF-36 has met with limited acceptance from patients (potentially due to its computerized format) and practitioners (who have expressed a lack of satisfaction with their inability to "see" the computer-generated patient scores) (T. Dahlborg, personal communication, October 12, 2007). Thus, the SF-36 is utilized much less than the MSQ despite an organization-wide effort to implement it.

Data Collection

The initial data set was a convenience sample accessed from a spreadsheet created by True North to track patient MSQ and DYNHA SF-36® Health Survey (SF-36) scores from the time period of January 16, 2007 – January 16, 2008. For the present study, patients from the existing data set were included only if they had completed multiple (two or more) administrations of the Medical Symptoms Questionnaire. Additional inclusion criteria was applied, categorizing patients in three treatment groups: functional medicine, CAM, and FM + CAM. Finally, a sub-sample was created including patients self-reporting depression on their first MSQ of the study period. Participants were instructed on the MSQ to "rate each of the

following symptoms based upon your typical health profile for the past 30 days OR since your last visit.” In this final sample, participants ($n = 80$) either reported a ‘1’ or a ‘3’ on the MSQ depression item, indicating their symptoms of depression were not severe ($n = 50$), or they reported a ‘2’ or ‘4’ indicating severe symptoms ($n = 30$).

It is noteworthy that True North’s data set starts at the time when MSQs were beginning to be more reliably administered to patients, in accordance with a new internal policy aligned with the organization’s research mission. While this policy resulted in a reasonable number of per-visit administrations of the MSQ (29% of visits by depressed patients during the study period), for this pilot data set it presented the potentially problematic issue that the ‘first visit’ MSQ score is not a true ‘pre-treatment’ score. Two steps were taken to address this issue. First, charts were reviewed for patients in the sample to identify whether there was consistent administration of the MSQ prior to 2007. Finding that this was not the case for most patients, another strategy was devised to test whether the number of visits prior to the study period was significantly related to the first visit MSQ score of the study period. For depressed patients, it was found that there was not a significant association between the first self-reported MSQ score and the number of visits prior to the study period, $r(80) = -.12, p = .280$ (2-tailed). Given this finding, it was possible to support the rationale that, for this pilot study, the first MSQ depression score in the data set could be treated as a ‘pre-treatment’ score.

Results

Data Analysis

Statistical Tests. Symptom scores in the data set used in this study were not normally distributed, which was expected since the data represented a clinical population of depressed

patients. However, in order to utilize parametric statistical tests such as the t-test and analysis of covariance (ANCOVA), which assume a normally distributed population, the data were first examined to determine if an underlying normal distribution did occur for the overall amount of change between first and last treatment scores. This “difference score” was normally distributed for amount of improvement, even though scores for this depressed population were skewed. This underlying normal distribution provided rationale for using the parametric tests reported here.

Outliers. All tests for significance of variables predicting symptomatic improvement were analyzed first with all data cases intact, and then with outliers ($n = 2$) removed (patients whose number of total visits was three or more standard deviations above the mean). Because no differences were detected, the original data set was used with outliers included.

Variability of First MSQ Score. The first MSQ score of the study period was treated conceptually as a “baseline” score, since a true baseline or “pre-treatment” measure was not available. Rationale for this approach (described previously in *Methods*, above) is predicated upon the finding that there was no significant association between the first MSQ score of the study period, and number of visits prior to the study. Because the first MSQ score accounted for a significant amount of variance between first and final MSQ scores ($r = .784, p < .001$), all ANCOVA tests used the first MSQ score as a covariate. Note also that all results reported indicate two-tailed probability of significance.

Characteristics of Patients

As previously described, the initial sample included patients who presented for appointments at True North Health Center between January 16, 2007 and January 16, 2008, who had completed two or more administrations of the Medical Symptoms Questionnaire (MSQ).

Further inclusion criteria were applied in which patients were receiving treatment in one of three categories: from functional medicine (FM) practitioners, from complementary and alternative (CAM) practitioners, or from a combination of both types of practitioners (FM + CAM). The original sample, including both depressed and non-depressed patients ($n = 164$) was reduced to 80 patients who self-reported depression on their first MSQ of the study period.

Depressed vs. Non-depressed Patients. To analyze the original patient sample ($n = 164$), a repeated-measures mixed-factorial 2 (depressed vs. non-depressed) x 2 (first MSQ score vs. final MSQ score) ANOVA was conducted in which the first factor was a between-participants variable and the second factor was a repeated measure. This analysis revealed a significant interaction for MSQ scores between depressed and non-depressed patients, $F(1, 162) = 20.89$, $p < .001$, where self-reported depressed patients ($M = 55.81$, $SD = 33.43$) were significantly more symptomatic initially than were non-depressed patients, ($M = 22.52$, $SD = 17.92$). Significant differences were not observed between depressed ($M = 39.77$, $SD = 30.59$) and non-depressed patients ($M = 19.88$, $SD = 20.85$) in final MSQ scores, indicating a differential amount of improvement in both groups, and specifically suggesting greater improvement among depressed patients.

Finally, a chi-square analysis revealed no differences between depressed and non-depressed patients for numbers of patients seeing FM practitioners, CAM practitioners, or a combination.

Severity of Depression. On a 0-4 symptom rating scale for the MSQ “Depression” item, those who reported “1” (“occasionally have it, effect is not severe”) or “3” (“frequently have it, effect is not severe”) were categorized as “Not Severely Depressed” patients ($n = 50$). Those

patients who reported “2” (“occasionally have it, effect is severe”) or “4” (“frequently have it, effect is severe”) were categorized as “Severely Depressed” patients ($n = 30$).

Number of Visits. Overall, depressed patients averaged 9.3 visits during the study period ($SD = 9.54$), and 21.3 total visits ($SD = 25.88$) during the length of time they had been seen as a patient at True North. Non-severely depressed patients averaged 9.6 visits during the study period, $SD = 11.08$, while severely depressed patients averaged $M = 8.7$, $SD = 6.31$. Prior visits averaged 13.0, $SD = 20.5$ for non-severely depressed patients, and 10.4, $SD = 18.4$ for severely depressed patients. For the total number of visits, non-severely depressed patients had $M = 22.60$ visits, $SD = 27.97$; severely depressed patients had $M = 19.07$ visits, $SD = 22.25$. No significant differences were observed between severe and non-severe patients in the number of visits they had at True North, either during the study, prior to the study, or in total.

Type of Practitioner. In the group of non-severely depressed patients, 9 patients saw CAM practitioners, 25 saw FM practitioners, and 16 saw both CAM and FM practitioners. Among the group of severely depressed patients, 3 saw CAM practitioners, 20 saw FM practitioners, and 7 saw both CAM and FM practitioners. Using a chi-square analysis, no significant differences were found between severity of depression and type of practitioner seen, or sex and type of practitioner seen.

Symptomatic Outcomes

As previously noted, the first MSQ score of the study period accounted for a significant amount of variance in final MSQ score. Therefore, all ANCOVA tests reported here used first MSQ score as a covariate. As seen in the following results, the ANCOVA tests confirmed that

first MSQ score is highly correlated with final MSQ score (and thus that the first score predicts the final score).

Analysis was undertaken using a mixed-factor 2 (severe vs. non-severe) \times 2 (first MSQ score vs. final MSQ score) ANOVA in which the first factor was a between-participants variable and the second factor was a repeated measures variable. This analysis revealed a significant main effect for initial vs. final MSQ scores (first MSQ score $M = 57.96$, $SE = 3.77$ and final MSQ score $M = 41.16$, $SE = 3.37$), $F(1, 78) = 43.65$, $p < .001$, indicating that patients improved significantly. However, no interaction effect was observed between severely depressed patients and non-severely depressed patients, indicating that these groups displayed a similar amount of improvement.

Predictors of Symptom Reduction

Demographic Correlates. Since this sample had a larger number of females, a chi-square analysis was performed in order to determine whether there was a relationship between sex and self-reported depressive symptoms on the first MSQ measure. No significant differences were found in observed versus expected frequencies between females and males in self-reported depression. Similarly, a chi-square analysis indicated no significant differences between males and females in symptom severity. An additional chi-square test found no sex differences for type of practitioner seen (FM, CAM, or a combination).

Chi-square analysis also was used to determine whether age was a correlate of depression. For this analysis, age was treated as a categorical variable reflecting the varying levels of risk for depression observed by epidemiological studies for different age groups (ages 15-24, 25-34, 35-44, 45-54, 55-70 and 85 and older) (see Blazer, Kessler, McGonagle, & Swartz,

1994; Kessler, et al., 2003; Nolen-Hoeksema, 2007). No significant differences were observed in frequencies of self-reported depression between these age categories.

Type of Practitioner. In order to answer the main question of whether type of practitioner seen is a predictor of symptom improvement, a single-factor ANCOVA was performed, again controlling for initial MSQ score. Between CAM patients ($M = 36.86$, $SD = 20.20$), FM patients ($M = 39.38$, $SD = 31.53$), and the combined FM + CAM group ($M = 39.48$, $SD = 32.88$), type of practitioner was not found to be a significant predictor of final MSQ score, $F = .259(2, 80)$, $p = .772$. Thus, practitioner type was dropped from further analyses.

Number of Visits and Severity of Symptoms. To answer the question of whether any interactions of number of visits and initial severity of symptoms predicted improvement, three separate two-factor ANCOVA analyses were undertaken to test various interaction models. Each ANCOVA included severity of depression (severe vs. non-severe) and number of visits as predictors and controlled for variability in the first MSQ score. The first analysis examined Severity \times Number of Visits During the Study Period, the second examined Severity \times Number of Visits Prior to the Study Period, and the final analysis examined Severity \times Number of Visits Total.

The model for Number of Visits During \times Severity did not show any significant main effects or interactions predicting improvement, and thus results are not reported here. Results for the model testing Number of Visits Prior \times Severity are shown in *Table 1*. While no main effects were noted for number of visits prior to the study period, a nearly-significant interaction effect was observed, $F = 2.31(6, 80)$, $p = .051$, with number of prior visits for severely depressed patients averaging 49.7 ($SD = 35.3$), and 32.6 ($SD = 24.9$) for non-severely depressed patients. Two partial correlations were used to test for simple effects in order to explore why this

interaction effect occurred, correlating final MSQ score with number of prior visits, controlling for first MSQ score: one for severely depressed patients and one for non-severely depressed patients. Although neither correlation was significant, there was a slightly larger correlation for non-severely depressed people and number of prior visits, $r(47) = .20, p = .168$, than for severely depressed people, $r(27) = .16, p = .403$. These results suggest that higher number of prior visits may be associated with slightly greater improvement on final MSQ score for the non-severely depressed group. Care should be taken in interpreting these results due to the fact that the interaction was just on the edge of being significant. In this case, the effects of the one independent variable, number of prior visits, are qualified by the levels of the second variable, severity, and vice versa. Since there was an interaction but no main effects for these two variables, it is not possible to say that either one has an effect on its own.

TABLE 1
ANCOVA Summary Table for Number of Visits Prior x Severity

	Sum of Squares	df	Mean Square	F	Sig.
Main effects					
First MSQ score	23281.23	1	23281.23	79.35	.000***
Initial severity of symptoms	34.16	1	34.16	.116	.735
Number of visits prior to study	12746.98	29	439.55	1.50	.114
2-way interactions					
Initial severity x number of visits prior	4074.54	6	679.09	2.31	.051*
Residual	12323.38	42	293.41		
Total	193918.00	80			

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 2 shows results from the model testing Number of Visits Total x Severity. Main effects were observed for both variables. For severity of symptoms, a significant main effect was noted, $F = 5.68(1, 79), p < .05$, between self-reported severely depressed patients (final MSQ

score $M = 45.31$, $SE = 2.91$ and non-severely depressed patients ($M = 36.75$, $SE = 2.41$). This main effect indicated that severely depressed patients had worse symptoms than did non-severely depressed patients. A main effect was also observed for number of total visits, $F = 2.62(36, 80)$, $p < .01$. A partial correlation between number of total visits and final MSQ score controlling for initial MSQ score was utilized to interpret this main effect, $r(77) = .185$, $p = .103$. Although the results of the correlation were not significant, a positive association between number of total visits and the final MSQ score was demonstrated. As no significant interaction effect was found between severity and number of total visits, these results suggest that the association between number of total visits and improvement was the same for severe and non-severely depressed patients. Again, caution should be used in interpreting these results, as the pattern of results differ depending upon which variable is analyzed (number of prior vs. total visits). Severity did have a main effect in this model, but not in the model which analyzed number of prior visits.

TABLE 2
ANCOVA Summary Table for Number of Visits Total x Severity

	Sum of Squares	df	Mean Square	F	Sig.
Main effects					
First MSQ score	8198.09	1	8198.09	39.32	.000***
Initial severity of symptoms	1185.12	1	1185.12	5.68	.024*
Number of visits total	19683.10	36	546.75	2.62	.004**
2-way interactions					
Initial severity x number of visits total	3483.97	11	316.73	1.52	.176
Residual	6255.75	30	208.53		
Total	193918.00	80			

* $p < .05$, ** $p < .01$, *** $p < .001$

Discussion

While limited to somewhat broad categories of treatments due to the available pilot data, the main value of the present study lies in its naturalistic examination of the treatment of depression using various integrative approaches to personalized care. As demonstrated by a review of the literature, there is a paucity of research on alternative approaches to treating depression. Methodological limitations abound in the studies that do exist. Perhaps most importantly, philosophical, paradigmatic, and pragmatic issues arise with the application of current randomized controlled trial research methods to systems-based, individualized types of healthcare.

The present research built upon previous pilot studies on treatment outcome efficacy for functional medicine and CAM therapies, and narrows the focus to one specific condition, self-reported depression. This study also sought to place this specific research question in the larger context of current trends toward alternative, personalized treatments – and the debate about how to best measure their effectiveness. A randomized controlled trial of a specific alternative treatment (acupuncture or a functional medicine nutritional intervention, for example) would have yielded important data about the effectiveness of that particular treatment, for the average patient with self-reported depression. Herein lies the crux of the problem researchers encounter while trying to assess efficacy for many alternative treatments – and conventional ones, too, for that matter. The question of “what works?” in the context of RCTs translates, “does this exact treatment work for a large number of people with a specific condition?” In a real-life clinical context, however, all the clinical trial efficacy data in the world seems useless if the treatment does not work for the individual patient who is sitting in the practitioner’s office. How then, do we garner credible evidence for the efficacy and safety of potential alternative treatments,

particularly ones that are delivered in a personalized manner? The current pilot study, although limited in some ways by the available retrospective data, sought to gather preliminary evidence regarding the effectiveness of two alternative approaches for treating depression in as systematic a manner as possible, while also maintaining high external validity, and leaving the door open for future exploration of less-easily defined research questions about why various treatments may be effective.

Overall Symptom Reduction

Results from the present study indicated that people with self-reported depression receiving FM and/or CAM treatments in an integrative healthcare setting showed significant improvement from the initial measure to the final measure of symptoms. This is in itself a promising addition to the literature, as more research on efficacious treatments for depression is needed. In answer to the first part of the primary study question, results demonstrated preliminary evidence that FM, CAM, and a combination of these therapies could be effective in reducing overall symptoms for people with both severe and non-severe self-reported depression.

Demographic Correlates

Although complete demographic information was unavailable for the study sample, it was possible to make some limited comparisons of sex and age with the general population of individuals with depression. Analyses revealed no significant sex differences in the proportions of males and females self-reporting depression on their first MSQ measure. Similarly, no sex differences were noted between severely depressed and non-severely depressed patients. Epidemiology studies consistently report that approximately twice as many females as males suffer from depression, and it is theorized that this highly differential rate of depression may be

due in part to the fact that women are more likely to report symptoms and seek care (Nolen-Hoeksema, 2007). The lack of sex differences in self-reported depression in the present study, then, is contrary to the idea that men are less likely to report symptoms of depression. Although the present study did not specifically address why men and women in this sample were similar in self-reporting depression, one possible explanation may be found in the characteristics of the types of patients who come to True North. First, there is anecdotal evidence that patients at True North have already tried other conventional healthcare approaches elsewhere, and have not improved, but are still motivated to seek effective treatment (Semmes, personal communication, March 29, 2008). Second, given that patients must pay out of pocket, and are not reimbursed by third-party payers for many of the services True North offers, it is likely that this demographic group has access to financial and other resources which may contribute to a greater sense of self-efficacy and personal responsibility for their health. Although purely speculative, these two factors, if true, may help explain why men in the sample were just as likely as women to report depression. A final note of caution in interpreting these results is that the lack of sex differences could also have been due to additional biases inherent in a non-randomized sample.

It is also interesting to note that no sex differences were detected in the types of practitioners chosen. Again, this may be due to the particular biases and characteristics of patients who seek alternative care at a holistic healthcare center, but it is notable that CAM use, for instance, is generally more common among women than men (Eisenberg, et al., 1998). It would be intriguing to conduct further research to specifically examine the lack of sex differences for this sample, as compared to the general population using alternative therapies.

In future studies, further analysis of the existing data set, and/or extension of the present longitudinal data set beyond the one year study period, should also include demographic

information such as race, employment status, and marital status in order to better place study results within the existing literature on depression and the use of alternative therapies for mental health issues.

Initial Severity of Depression as a Predictor of Symptom Reduction

As noted, severely depressed patients started out with worse self-reported symptomology than did non-severely depressed patients, and both groups improved significantly. Encouragingly, in addition to the observation that both groups experienced significant reduction in symptoms, severely depressed patients showed a similar amount of improvement as non-severely depressed patients. Although information on specific patterns of depressive symptoms and episodes is not available in the current data set, it is possible that those patients reporting severe depression may actually have treatment-resistant depression. Anecdotally, according to practitioners at True North, patients often seek care there only after they have tried other means of conventional care and not found relief (Semmes, personal communication, March 29, 2008). If this is true, and patients with severe self-reported (possibly treatment-resistant) depression are improving – and even improving similarly to non-severely depressed patients – the study results suggest that FM and CAM may show promise even for treatment-resistant depression.

Number of Visits as a Predictor of Symptom Reduction

The results of the analysis testing severity of symptoms (severely depressed vs. non-severely depressed) and number of visits prior to the study period indicated that non-severe patients, who had a greater number of prior visits, showed slightly greater improvement than severely depressed patients. The somewhat contradictory results of the test of severity of

symptoms and number of total visits (including visits before the study period) showed that the association between improvement and number of visits was the same for severely and non-severely depressed patients. Conceptually, the results for the ‘visits prior’ analysis are indicative that both severity and number of visits have a role in predicting symptom improvement, but their predictive strength depends on the levels of one variable in relation to the other variable. Specifically, non-severely depressed patients averaged a greater number of visits prior to the study period, and also exhibited slightly greater improvement. The ‘visits total’ analysis, however, seems to suggest that while total number of visits and initial severity both have an effect upon symptom improvement, these two variables do not interact with one another. Specifically, both non-severely and severely depressed patients are able to achieve similar improvement with a higher number of visits.

Care should be taken in interpretation of the results of these two models, as the inconsistency in findings may indicate that other factors are having a predictive effect. It is likely, for instance, that controlling for first MSQ score removed enough of the variance in the final score that severity and number of visits were not able to consistently predict improvement.

A notable limitation of this variable (number of visits) as a predictor of improvement arises from that fact that it is not known how long patients were in treatment specifically for depression (or even if they were specifically being treated for depression as a primary health concern). Also, number of visits does not reflect how many weeks a patient had been in treatment. Thus, in the present study, no comparison can be made to existing research results which measure response to treatment or symptom remission during trial periods spanning specific numbers of weeks.

Type of Practitioner as a Predictor of Symptom Reduction

The second part of the main study question asked whether the specific type of practitioner significantly predicted improvement. Intriguingly, all patients in the study – regardless of differences in severity of depression, initial MSQ score, sex, or age – improved no matter which type of practitioner they saw. Due to the nature of the pilot data as well as the fact that specific FM and CAM interventions in the study varied widely, it is not possible to definitively identify the potential active therapeutic ingredients specific to FM and CAM which could be hypothesized as contributing to patient improvement. It is possible, however, to speculate that some of the commonalities between FM and CAM, including the environment in which these treatments were delivered, may be potential contributors to the effectiveness of these therapies.

It should be noted that the broad treatment definitions in this study present both strengths and limitations. It is possible that many types of treatment may have been delivered although the exact treatments are not defined in the existing data set (e.g., acupuncture, massage, dietary and nutritional interventions, hormone therapy, mindfulness-based techniques, and energy healing techniques). In some cases this may mean the lines are also blurred between conventional care and alternative therapies. Specifically, the study's treatment definitions may be limited by the inclusion of a psychologist in the CAM group, so defined by True North in the aforementioned pilot studies because this practitioner includes CAM therapies such as Emotional Freedom Technique, Therapeutic Touch, Voice and Sound Healing, and various mindfulness techniques in her practice. Treatment definitions may also have been confounded between conventional care and alternative care if, for example, a patient who was already taking antidepressants came to True North for treatment and continued with medication in addition to adjunctive treatments.

Additionally, specific FM and CAM treatments may sometimes overlap; for instance, clinical nutritional interventions such as folate or omega-3 fatty acids utilized by a FM practitioner may be considered CAM treatments.

As previously discussed, it is also unclear from the literature how much of FM rests upon ‘conventional’ medical theory, and how much it strays into the realm of ‘alternative’ medicine by utilizing interventions not yet supported by strong clinical data (Mechanick, 2005). A great deal of the literature on functional medicine treatments comes from researchers affiliated with the Institute for Functional Medicine (IFM), which currently appears to be the sole source of training in the FM approach. Although the IFM is a non-profit educational organization, its founder Jeffrey Bland, a nutritional biochemist, is also the chief science officer of the for-profit company Metagenics, Inc. Metagenics manufactures and distributes science-based medical foods and nutraceuticals to healthcare professionals. As with any overlap between scientific research and other arenas, a cautionary note is in order regarding a potential conflict of interest for FM research. Additionally, there is currently no regulatory body for the practice of functional medicine. The IFM website makes an up-front disclaimer in its practitioner database, placing the onus upon the healthcare consumer to fully investigate the education, credentials and licensure of their chosen provider. Additional research on FM treatments by third parties would significantly strengthen empirical support for this approach.

Despite the limitations surrounding lack of knowledge about exact treatments in the present study, speculations may be made regarding potentially therapeutic ingredients – particularly those common to FM and CAM. A strength of the broadly-defined FM and CAM treatments in this study is found in the shared philosophical approach to individualizing care for each patient. For example, one patient’s acupuncture treatment may be quite different from the

next patient's, and may differ depending on that patient's particular needs of the moment. The indication that all patients in the study improved despite wide variations in treatments may lend general credence, not only to the promise of FM and CAM approaches, but also the possibility that personalization of care may be an important common factor in improvement.

Another unique aspect of the current study was the integrative healthcare setting in which treatments were delivered. Practitioners often refer patients to other practitioners in-house, and collaborate on providing care, creating enhanced opportunities for personalized care. Monthly case presentation meetings facilitate the sharing of knowledge and experience between treatment approaches. As with many psychotherapeutic approaches, the patient is viewed as a unique individual whose life story, values, beliefs and expectations regarding treatment and healing are viewed as significant factors in the therapeutic process. Also similar to most psychotherapeutic orientations, the patient-practitioner relationship and interactions are considered to be active elements of treatment (see Corey, 2005). Specifically, True North's model as well as FM and many CAM therapies have parallels with person-centered psychotherapy. Each approach places importance upon therapist variables such as congruence, trustworthiness and empathy, and patient variables such as empowerment and willingness to invest in one's own well-being (Corey, 2005; Leyton, 2006; True North Health Center, 2008c). These factors are often lumped under the category of 'non-specific' treatment effects in the research literature (Herman, D'Huyvetter, & Mohler, 2006), but have been demonstrated as active therapeutic ingredients in the psychotherapy literature (e.g., Watson, 2002). Although the present study was not able to address questions of why specific therapies were effective in treating self-reported depression, perhaps some explanation can be offered from the particular commonalities of these non-specific treatment effects.

Additional Strengths and Limitations

Operationalization of Depression. As previously discussed, a strength of the present study is that it built upon previous real-world pilot studies which were limited to assessing reduction of general medical symptoms; this study narrowed the field to focus upon one specific condition, self-reported depression. The operational definition of depression in the present study has both strengths and weaknesses. Depression was operationalized by self-report on the first symptom questionnaire measure of the study period, with patients reporting “depression” as a symptom (of varying frequency and severity) using a 0 – 4 rating scale. Thus, the study sample may not have included individuals who were depressed but did not report it on the first MSQ measure, because of the stigma associated with depression, or the fact they were having a good day, or some other factor. These individuals may have exhibited more of the somatic symptoms of depression, even though they did not specifically say they were depressed (the present study does not examine this possibility, although further research could utilize the same data to answer this question). The present study does, however, identify individuals who clearly self-identified that they were depressed (at least at the first MSQ). Patient self-report, although sometimes biased by factors such as perceived stigma, can be a reputable measure of symptoms.

The use of DSM-IV-TR diagnoses of major depressive disorder or depressive disorder, not otherwise specified, was considered as a means of operationalizing depression for this study. As discussed, conflicts existed in the data set between those who had received DSM-IV-TR diagnoses, and those who self-reported depression. Specifically, it was noted that of those patients who reported severe depression symptoms, only 40% had received a DSM-IV-TR diagnosis of depression. Of those reporting either severe or non-severe depression, only 13% had received a diagnosis. On the other hand, of the individuals categorized as ‘non-depressed’ in the

sample, approximately 4% had received a diagnosis, but did not self-report being depressed on the first MSQ measure. Given these conflicting data as well as general issues associated with diagnosing depression (see *Introduction*), it was decided to utilize self-report data to operationalize depression. It was also felt that this method was more in keeping with the patient-centered, personalized approaches both of FM and CAM, and of True North's approach to care.

Future research could explore the causes of the observed differences between clinical diagnoses and self-reported depression, including issues such as diagnostic prevalence and accuracy, patient acceptance of diagnoses, perceived stigma of a depression diagnosis, practitioner and patient beliefs and values, patient self-efficacy regarding health, and how alternative approaches such as FM and CAM specifically conceptualize, label, and treat depression. It would also be instructive to examine differential symptom reporting and reduction, and possible predictors of improvement between individuals who self-report depression but are not diagnosed, with those who have received a clinical diagnosis, as well as those individuals who did not self-report depression but do have a diagnosis.

Treatment Outcomes. In many studies of efficacious treatments for depression, the outcome measure is 'response' to treatment, meaning a fifty percent reduction in symptoms. In the more recent real-world STAR*D study, the outcome measure was defined more stringently as 'remission,' in other words a complete or nearly complete lack of symptoms (Trivedi, et al., 2006). The goal of remission is a more meaningful one for treating depressed patients, and thus is the optimal way for research to measure treatment efficacy. A weakness of the present study is its use of reduction of symptoms, not remission, as an outcome of treatment. Further, 'reduction' is ambiguously measured as a statistically significant difference between first and last MSQ scores. Due to the nature of the MSQ as a general symptom questionnaire (not condition-

specific), it was not possible to define specific symptoms of depression and therefore to create a standardized definition of either ‘response’ or ‘remission.’ While the use of the MSQ lends high external validity in many ways, it also contributes to weak internal validity of the study. Future research utilizing additional and/or improved measures would address this issue by providing a stricter definition of patient improvement.

Given the non-controlled study design and the ambiguity of the measure of symptom improvement, it could be argued that the patients in this sample would have gotten better over time without treatment, with MSQ scores regressing toward the mean. However, results of the STAR*D study suggest otherwise. Patients with depression, particularly treatment-resistant depression, often require multiple treatments in order to achieve remission, and with each additional type of treatment the chances of remission become smaller and the chances of relapse become higher (Rush, et al., 2006). Thus, in the current study it is impressive both that severely depressed patients showed statistically significant improvement, and that severely depressed individuals improved as much as non-severely depressed patients did.

Measure. The Medical Symptoms Questionnaire, the self-report measure used for categorizing study participants as severely or non-severely depressed, as well as for measuring outcomes of overall symptom reduction, has both strengths and weaknesses. As the extensive background in *Methods* indicates, although no published literature exists, unpublished studies provide evidence that the MSQ is reliable in terms of internal consistency, and exhibits construct validity as a measure of overall health status and functioning. The MSQ has good clinical validity for assessing patient symptoms and tracking progress, and its use in this study lends external validity for generalizing to other practitioners using this same measure. However, the MSQ was not designed to be a condition-specific measure so is somewhat limited in its ability to

measure depression. Depression is only one item on an 80-item checklist (and was utilized as a categorical method based upon only one MSQ administration) and therefore may not be a particularly reliable way to categorize patients as being depressed. The MSQ's strength as a subjective patient-report measure that truly indicates overall functioning and quality of life is bolstered by its correlation with the heavily utilized and validated DYNHA SF-36 measure. Therefore, the MSQ may be a reasonably good measure of self-perceived overall symptom improvement even if it is not as predictive of depression specifically.

An additional limitation is that only one type of measure was used in the study. Future prospective research with self-reported depressed patients might also include a specific checklist measure of depression such as the Beck Depression Inventory or the Hamilton Rating Scale for Depression (both used in the NIH's STAR*D trials), or the PHQ-9, a nine-item depression scale of the Patient Health Questionnaire, which True North has considered utilizing. This checklist could routinely be given to patients as a pre-treatment measure if the practitioner noted that the 'depression' item was rated on the first MSQ. Either of these checklists would lend greater reliability and validity to measuring depressed patients' symptom reduction throughout treatment.

Pilot Data. This study was limited in some ways by the use of a retrospective sample of pilot data. The first criterion for inclusion was simply that a patient had taken at least two MSQs so their symptomatic outcomes could be compared. Biases may exist with this sample; for instance, the sample may be biased toward those patients who agreed to fill out the MSQ and toward practitioners who routinely use the MSQ. The sample consists of only a small subset of all True North patients who took the MSQ – by no means a representative sample. Also, as noted the data set is missing some useful variables such as demographics, detailed diagnostic

information, and course of depression for each patient. Additionally, since the data set was retrospectively used as a snapshot of patient outcomes over a one-year period, it did not truly reflect patients' symptom status at beginning or end of specific treatment protocols. However, as demonstrated, since the first MSQ score of the study period did not significantly differ depending on how many visits a patient had previously, it could effectively be viewed as a 'pre-treatment' score for the purposes of this pilot study.

Study Design. This study was based on self-report and retrospective, and therefore was not tightly controlled. The study design did not include a conventional-care control group. Patients were not randomized to treatment groups or blinded to treatment; the study also lacked a control group or waitlisted group for comparison of treatment / no-treatment conditions. In patients with severe depression, however, it is unethical to withhold treatment as these patients are at high risk for suicide. The STAR*D trial used a sequential, cross-over study design in order to address this issue (Trivedi, et al., 2006). Although internal validity was not particularly strong, and results are not necessarily generalizable to other populations, the study has high mundane realism at least for the healthcare center at which it was conducted, and possibly other integrative settings providing functional medicine and CAM therapies.

Discussion and Conclusions

Within the broad context of treating depression, this small study contributes ecologically valid preliminary evidence for the effectiveness of integrative, personalized, alternative treatments for self-reported depression. Little research of this kind exists, although guiding organizations in the field of complementary and alternative medicine are calling for further real-

world research into the use and effectiveness of alternative treatments (NCCAM, 2007g; see Ritenbaugh, et al., 2003).

Results for the primary study question indicated that all depressed patients showed significant symptom reduction, regardless of which type of practitioner was seen. While at first glance these results may seem uninteresting in terms of the conclusions that can be drawn about FM and CAM specifically, the main takeaway from the study is that self-reported depressed patients at True North, receiving widely varied treatments in a collaborative and integrative setting, appear to be getting better. Although it is beyond the purview of the present study to answer why this is the case, results are suggestive that some commonalities of FM and CAM, and possibly the common philosophies and environment in which these treatments are delivered, are potential contributors. It has been argued here that important commonalities likely include True North's collaborative patient-centered approach, the importance placed upon the therapeutic relationship of practitioner and patient, and the time that is spent personalizing treatments to each individual. These are among the so-called non-specific treatment ingredients that randomized controlled trial designs find difficult to study. Hopefully, new methods of research addressing systems-based, individualized healthcare will strive to further explore the effects of these variables on patient outcomes.

This study provides a rare one-year longitudinal snapshot of patient outcomes at a holistic healthcare center committed to conducting research to inform its continuous quality improvement initiatives. It is exciting to consider the possibilities for additional research questions utilizing the present data set, and/or an extension of the data including additional variables and a multi-year timeframe. Future studies could be conducted with tighter study

methodology in order to increase internal validity and generalizability to other settings and populations.

A study, for instance, examining specific CAM or FM therapies (e.g., acupuncture, massage, or a particular nutritional intervention) for depression, administered in a personalized manner in an integrative care setting, would be a valuable addition to the existing literature, as would a comparison of these therapies to conventional treatments. The NCCAM is also encouraging research on the cost-effectiveness of integrative and alternative care as compared to conventional settings such as primary care. Research proposals are also being sought to examine some of the non-specific treatment variables such as consumers' decision-making process in the use of CAM and other non-medical therapies, and consumer beliefs, values and attitudes about choice of treatment (NCCAM, 2007g). Larger sample sizes, prospective study design, and creativity in pursuing new research methods may make it plausible to examine such questions.

In conclusion, the present study has attempted to take a 'one-size-fits-some' approach to examining the relative efficacy of two alternative approaches for treating self-reported depression. This small contribution to the evolving paradigm of personalized healthcare highlights the need for creative, credible research methodologies for evaluating individualized therapies in clinical settings. It is hoped that the results of this real-world study will have practical clinical applicability for the delivery of functional medicine and CAM therapies, and pave the way for future research on alternative therapies for the treatment of depression.

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