Scanning the Global Literature

In each issue of Global Advances in Health and Medicine, we publish summaries of and commentaries on select articles from journals our editors and other contributors to the journal are reading.

PLACEBO EFFECTS IN MEDICINE¹

For many years, the placebo response has been trivialized and even referred to as an “inert substance.” In a groundbreaking article recently published in The New England Journal of Medicine, Kaptchuk and Miller elucidate mechanisms underlying the placebo response and highlight findings to date regarding placebo effects. They note that placebo effects result from complex neurobiological mechanisms involving neurotransmitters such as endorphins, cannabinoids, and dopamine, not unlike the pathways of common medications. While placebos may provide relief, the authors note that placebos rarely cure. They cite as an example the lack of evidence that placebos can shrink tumors, while noting that placebo interventions may reduce symptoms and side effects of cancer treatments. In highlighting the power of the placebo effect, they also note that symbols such as how the drug is labeled and clinician interactions can dramatically increase the effectiveness of pharmaceuticals. Finally, just as positive expectations can influence positive outcomes, they also describe nocebo effects—psychosocial factors that have the potential to cause adverse consequences. A strong argument is made of the importance of going beyond using placebos as a methodological tool to rigorously studying placebo effects that can help explain how clinicians can be therapeutic agents in the ways they relate to their patients.

Commentary by Mary Jo Kreitzer, PhD, RN, FAAN

Teaching clinicians and health professional students about placebo and nocebo effects and the power underlying the therapeutic alliance between clinicians and patients is essential. Within curricula of health professional schools, there is considerable emphasis on technology and pharmacology and often too little focus on touch, eye contact, presence, trust, caring, and empathy. In fact, it has been found that over the course of medical training, empathy declines rather than increases and threatens the quality of patient care.² In writing about integrative nursing and the importance of person-centered, relationship-based care and the innate capacity of people for health and wellbeing, Kreitzer³ notes the importance of nurses engaging in behaviors that lead to deeper meaning and wholeness;

• engage and support patient and family strengths;
• cultivate presence;
• connect as human beings, recognizing the patient as a person and the self as a person; and
• focus intention for healing and wholeness during ordinary nursing procedures.

Placebo effects in healthcare have been understudied and are critically important. As noted by Kaptchuk and Miller, they are at the core of what makes medicine (and I would add all health professions) a healing profession.

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2. Neumann M, Edelhäuser F, Tauschel D, et al. Empathy decline and its reasons: a systematic review of studies with medical students and residents. Acad Med. 2011 Aug;86(8):996-1009.
3. Kreitzer MJ Integrative nursing: application of principles across clinical settings. Rambam Maimonides Med J. 2015;6(2):1-8.

RANDOMIZED CLINICAL TRIAL ASSESSING IF ADDITIONAL MASSAGE TREATMENTS FOR CHRONIC NECK PAIN IMPROVE 12- AND 26-WEEK OUTCOMES

Previous reviews on the use of massage therapy for neck pain, including several Cochrane reviews, have noted that the included studies used different types and doses of massage, making the optimal dose for both practice and further clinical trials unknown. The purpose of this study was to determine the optimum dose of massage for neck pain. Participants were recruited from group health subscribers with a history of chronic nonspecific neck pain and from the general population of Seattle, Washington. Persons with conditions such as vertebral fracture, metastatic cancer, cervical radiculopathy, a recent automobile accident, pain intensity of less than 4 on an 11 point pain scale and less than 5 on the 0 to 50 Neck Disability Index, contraindications for massage, massage within the last 3 months, massage for neck pain within the last year, or current involvement in litigation were excluded, resulting in 179 participants.

Participants were then randomized to 1 of 6 groups for a primary treatment period of 4 weeks: a waitlist control group or 1 of 5 different dosing schedules of massage: 30-minute treatments 2 or 3 times per week or 60-minute treatments 1, 2, or 3 times per week. Participants then were randomized again to either receive a booster dose of massage consisting of 60-minute treatments once a week for 6 weeks or no additional massage.

Column
No differences by primary treatment group were observed at 12 weeks or later at 26 weeks. Those receiving the booster dose of massage showed improvements in pain and dysfunction at 12 weeks, but these were not significant by 26 weeks. An analysis of subgroups by primary and booster treatments found the booster dose effective only among those initially randomized to one of the 60-minute massage groups.

**Commentary by Martha Brown Menard, PhD, LMT**

Protocol design in clinical studies of massage therapy is quite complex. There is always the issue of which specific techniques to include or exclude, the duration and frequency of individual sessions, duration of the overall intervention, and the clinical experience level of the treating therapists. Previous studies from the group health team of investigators have been thoughtfully designed in these regards and serve as a model for other researchers.

The issue of the optimal dose of massage therapy for various conditions has often raised questions when evaluating individual studies and added to the challenge of determining where the weight of the evidence lies in meta-analyses and systematic reviews. This study is noteworthy for its systematic evaluation of the value of a longer treatment period for massage therapy and provides a useful framework for conceptualizing the optimal dose of massage in future studies.

**REFERENCE**

Cook AJ, Wellman RD, Cherkin DC, Kahn JR, Sherman KJ. Randomized clinical trial assessing if additional massage treatments for chronic neck pain improve 12 and 26 week outcomes. Spine J. 2015 Jun 18. [Epub ahead of print.]

**RURAL STROKE SURVIVORS’ AND CAREGIVERS’ EXPERIENCE OF RECEIVING EDUCATION FROM HEALTHCARE PROVIDER**

It is well known that location (especially the rural/ urban divide) is often a significant influence upon the healthcare use and experience of individuals and communities, and surviving a stroke often requires support and information that may not be either easily accessible, available, or effectively delivered in such settings. One productive response from the health research community to help identify and ultimately address this issue has been to draw upon health social science methods and approaches in order to understand mediating cultural, social, and political dynamics.

In line with this broad work, this paper reporting qualitative fieldwork undertaken in Kentucky with rural Appalachian stroke survivors (n=13) and caregivers (n=12) examines experiences of receiving education from healthcare providers. The interprofessional research team drew upon a descriptive qualitative approach to conduct qualitative content analysis of the participants’ “telling.” Analyses of the qualitative interview data illustrate that healthcare providers were the primary source of education, and both patients and caregivers stressed the importance of effective, clear communication to receiving effective support and care from such providers. Moreover, participants expressed a desire to receive information from multiple sources and described the need for broader information channels such as contact persons and support groups. Analyses showed that communication clearly led to anxiety, fear, and other negative experiences, and challenges to effective communication resided in both provider and patient approaches to receiving and delivering information around care.

**Commentary by Jon Adams, PhD**

Health education, whether provided to the stroke patient or caregiver, is an important factor in helping ensure optimal care and timely interventions for stroke sufferers. As this small qualitative study set in a rural location suggests, the information needs and strategies around effective dissemination to patients and caregivers about stroke are complex. However, as the authors stress, the results from this qualitative study add weight to the identified need for multiple repetitions of information throughout a patient’s stroke journey. While strategies and implementation will obviously vary across circumstances and settings, this qualitative study provides insights and food for thought for all involved in delivering and receiving health education and information post-stroke.

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Danzl MM, Harrison A, Hunter EG, et al. “A lot of things passed me by”: rural stroke survivors’ and caregivers’ experience of receiving education from health care providers. J Rural Health. 2015 Jun 22. doi: 10.1111/jrh.12124. [Epub ahead of print.]

**INTEGRATIVE MEDICINE FOR BREAST CANCER PATIENTS—A PRAGMATIC RANDOMIZED CONTROLLED TRIAL FROM SOUTH TYROL**

Throughout Europe, patients’ demand for complementary and alternative medicine (CAM) is great, and an increasing number of hospitals offer CAM services. The regional healthcare system in South Tyrol, Italy, established a service for CAM at Merano Hospital. To assess the effectiveness of CAM care on health-related quality of life in breast cancer patients, a pragmatic randomized controlled trial was conducted.

Two hundred seventy-five patients with confirmed breast cancer were randomized to receive individualized, multimodal CAM care or conventional care alone. Median time since diagnosis was just over 3 years, and most patients were stage I and II with a favorable prognosis. Standard therapy had been conducted in all or most of the patients, and about one-third had used CAM before. Most of the patients received hormone therapy,
and some also received chemotherapy, radiation, or antibody therapy during the study.

CAM treatments within the trial were individualized according to clinical presentation, needs, and co-treatments. Most frequently applied were acupuncture, homeopathy, dietary advice, phytotherapy, orthomolecular therapy, osteopathy, infusions, and laser and magnetic field therapy. Therapy was provided by physicians, nurses, and physiotherapists. Nearly one fourth of the patients sought additional CAM therapies outside the study. After 6 months, health-related quality of life (primary outcome Functional Assessment of Cancer Therapy-Breast [FACT-B], secondary outcomes FACT-General, Functional Assessment of Chronic Illness Therapy [FACT], Fatigue-Scale, and SF-12) was significantly better in the CAM-treated group than in the control group in all questionnaires (FACT-B: 107.9 vs 102.2, \( P < .001 \)). In particular, physical subscales related to quality of life improved. Thus, complex and individualized CAM was shown to improve quality of life in breast cancer patients.

**Commentary by Gunver Kienle, Dr med**

Randomized controlled trials usually investigate the specific influence of one intervention for one indication in a standardized context. As a result, the context is often experimentally and only partly generalizable to clinical reality. Therefore, pragmatic trials have been called for to investigate the comparative effectiveness of interventions in everyday care. This is particularly necessary for CAM, as CAM interventions are less standardized utilizing a high degree individualized and patient-centered treatment strategies. Still, conducting a pragmatic randomized trial is a challenge, and only a few have been conducted so far for CAM. So this study is a major step. In this study, CAM led to improved quality of life, and the number of patients who sought outside CAM therapy before and during the study shows the need for integrative healthcare. The included patients had a rather good prognosis; the primary diagnosis had been made some years before and conventional anticancer therapies had been provided in most cases. Therefore, the patients presumably were in rather good health. One might speculate that the need for integrative medicine right after the diagnosis or in cases of a less favorable prognosis may be even greater; pragmatic research in this population of cancer patients would be a logical next step in building an evidence based for CAM.

**HEALTHCARE SYSTEM CHANGES REDUCE LATINO PEDIATRIC MORTALITY**

Between 2007 and 2009, adjusted risk of mortality for Latino children at a Memphis, Tennessee, tertiary hospital pediatric intensive care unit was 3.7-fold higher than the risk for white or African-American children. Increased risk was independent of age, gender, diagnosis, infections, or insurance status. Hospital leadership, medical staff, and community stakeholders examined the problem and developed and implemented from 2009 to 2011 a multilevel intervention consisting of (1) cultural competency training for healthcare professionals; (2) increased hiring of bilingual staff; (3) 24/7 interpreter availability; (4) Spanish language education materials and consent forms; (5) engaged palliative care providers for culturally sensitive end-of-life conversations; (6) Latino community outreach to reduce health access barriers; and (7) collaboration with local government and public health agencies to increase preventive services. Compared to the pre-intervention period, the mortality rate for Latino children in the post-intervention period (2010-2012) decreased from 8.6% to 4.0% and no longer differed from that of white or African-American children.

**Commentary by Rob Saper, MD, MPH**

Social, cultural, lifestyle, environmental, genetic, and healthcare system factors contribute to health disparities. This report by Anand et al is a striking example of how disparities can be eliminated through patient-centered initiatives aimed at making a more responsive culturally competent healthcare system. This report shows that “health disparities are not intractable.” Strategic investment of resources; a long-term commitment to change on behalf of leadership, staff, and community partners; and a multilevel strategic systems approach are necessary.

**REFERENCE**

Anand KJ, Sepanski RJ, Giles K, Shah SH, Juarez PD. Pediatric intensive care unit mortality among Latino children before and after a multilevel health care delivery intervention. JAMA Pediatr. 2015 Apr;169(4):383-90.

**BEING LEFT OUT CAN HURT YOUR HEART AND BRAIN**

In addition to the negative psychological impact of overt bullying among adolescents, a growing body of research supports that lack of social acceptance, including being regularly rejected or perceived as unpopular by peers, can result in widespread impairments in mental health that may persist throughout psychosocial development and into adulthood. However, the behavioral and neural basis for responses to being socially excluded are not well characterized. Using a combination of behavioral measures and functional magnetic resonance imaging (fMRI) responses to a virtual ball-tossing game (Cyberball) that experimentally manipulates levels of
inclusion/exclusion, this study conducted in the Netherlands tested the hypothesis that adolescents with a history of chronic peer rejection display enhanced neural responses to social exclusion compared to stable accepted adolescents. Participants (aged 12-15 y) were recruited from a sample of adolescents whom were followed yearly in their classroom since they were 6 years old and included individuals who either had a stable accepted (n=27; 14 males) or a chronic rejected (n=19; 12 males) status among peers from age 6 to 12 years.

All adolescents, regardless of peer rejection history, reported increases in distress after being excluded in the virtual ball-tossing game. However, adolescents with a history of chronic peer rejection showed higher activity in brain regions previously linked to the detection of, and the distress caused by, social exclusion. Specifically, when compared to stably accepted adolescents, chronically rejected adolescents displayed (1) higher activity in the dorsal anterior cingulate cortex (dACC) during social exclusion (ie, ball regularly not thrown to them), and importantly (2) higher activity in the dACC and anterior prefrontal cortex when they were incidentally excluded in a social interaction in which they were overall included (ie, ball thrown to them with equal frequency to others but heightened reaction when excluded because it was simply not their turn to receive). These findings demonstrate that chronic childhood peer rejection is associated with heightened neural responses to social exclusion during adolescence, which has implications for understanding the processes through which peer rejection may lead to adverse effects on mental health over time.

**Commentary by Peter Wayne, PhD**

While a growing body of research has shed light on the negative consequences of overt childhood trauma, less attention has been focused on more subtle forms of chronic social isolation. This study supports that social exclusion can be highly distressing, impacting a fundamental human need to belong and to have some control over our social environment. Findings support that healthy relationships with peers are vital to satisfying these needs across the lifespan and that their absence in adolescence can impact neural structures such as the dACC, which may have implications in lifelong regulation of many key psychological processes including monitoring of conflict, physical pain, and a variety of emotions. These findings also highlight the value of developing and administering creative interventions that promote social inclusiveness and that proactively help identify and provide behavioral resources to individuals who do not have strong social networks.

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Will GJ, van Lier PA, Crone EA, Güroğlu B. Chronic childhood peer rejection is associated with heightened neural responses to social exclusion during adolescence. J Abnorm Child Psychol. 2015 Mar 12. [Epub ahead of print.]