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INSIDE

Acupuncture for the Treatment of Insomnia

By Elad Schiff, MD

WITH A PREVALENCE OF 30-35% IN ADULT AMERICANS—10% OF which is assessed as chronic (more than six months) and/or severe—insomnia is the most common sleep complaint reported to physicians.[1] Insomnia is a perception that sleep quality is inadequate or nonrestorative, despite adequate opportunity to sleep, and encompasses many problems, including difficulty falling asleep, sleeping too lightly, sleep being easily disrupted by multiple spontaneous awakenings, or early morning awakenings with inability to fall back asleep.

It is important to note that insomnia is a symptom, not a disease. It is associated with a diversity of medical, psychiatric, and sleep disorders, and usually results from a combination of biological, physical, psychological, and environmental factors. Insomnia is linked with significant morbidity and mortality, including impaired ability to concentrate, poor memory, irritability, decreased ability to enjoy family and social relationships, a doubled risk for fatigue-related motor vehicle accidents, and a higher mortality rate in patients who get fewer than 5 hours of sleep per night as compared to the general population.

Complaints of sleep disruption often are managed by the use of medications such as benzodiazepines and tricyclic antidepressants. Sedatives and oral hypnotics have high abuse potential and can be addicting, in addition to their long list of serious adverse effects. Non-pharmacological interventions for insomnia may be employed to modify sleep hygiene, habits, and expectations (i.e., cognitive behavioral therapy).

TCM for Insomnia

In traditional Chinese medicine (TCM), symptoms are a manifestation of an underlying *qi* (vital energy) imbalance. Insomnia is one such symptom, reflecting imbalance of the mind and its different mental aspects. There are nine major patterns of *qi* disharmony that may manifest with insomnia.[2] Traditionally, patients are categorized into their pattern of *qi* disharmony and treated accordingly with acupuncture and/or herbs. In addition, patients may receive lifestyle

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recommendations such as diet, exercise, body position for sleep, and meditative practices as stress reduction techniques.

Within the paradigm of acupuncture, however, other approaches have evolved in recent centuries. Formulations of acupoints that have been empirically and traditionally associated with powerful hypnotic effects are used in protocols for insomnia treatments. These protocol-based acupuncture treatments for insomnia do not attempt to address the underlying *qi* disharmony. More recently, following the development of French auricular acupuncture therapy and its endorsement in China, many protocols also combine auriculotherapy.

Clinical Trials

A MEDLINE search using the terms acupuncture, acupressure, auricular, sleep, and insomnia yielded a significant number of case reports and case series from the Chinese literature.[3-7] Definition of insomnia, patient age and population, duration of insomnia, underlying disease, acupuncture technique, assessment tools, and outcome measures vary widely between and within these reports; all reported significant positive results.

In the English medical literature several case reports on acupuncture treatment for insomnia exist. Good therapeutic results were stated for a variety of endpoints. For example, in a study by Lee, 16 patients with severe insomnia were treated with auricular acupuncture protocol.[8] Seven auricular points were used in this study: heart, kidney, adrenal, sub-cortex, endocrine, san chiao, and shen men. Additional auricular points (sympathetic, occiput, and gallbladder) were added if tender. Patients were treated three times weekly for an average of 10-12 treatments. Improved subjective outcomes for the treatment of sleep disorder were reported in 15 of 16 patients treated. Beneficial effects were still present three months following the conclusion of treatment.

Shi reported a case series of 28 patients with moderate-to-severe insomnia of at least three months duration.[9] Patients were treated with a combination of individualized and empirical acupuncture. Sixty percent of patients had complete relief of insomnia and the rest experienced marked subjective improvement.

Sleep frequently is disrupted in all stages of HIV disease. In a case series reported by Phillips and Skelton, acupuncture was found to be effective in the treatment of 21 HIV patients, 29-50 years of age, with moderate-to-severe insomnia.[10] Patients were assessed for treatment response using wrist actigraph analysis (used for ambulatory sleep monitoring) and current sleep quality index as a self-reported score. Acupuncture was performed twice weekly for five weeks and was individualized based on TCM pattern differentiation. Auricular and body points were used. Statistically significant improvement was noted for amount of sleep, time awake, and sleep quality in all patients following intervention.

In another open clinical trial, 18 volunteers, age 30-50, with chronic insomnia and subsyndromal anxiety (scoring high in an anxiety rating scale but not fulfilling DSM criteria for anxiety disorder), were treated with individual acupuncture twice weekly for five weeks.[11] Patients were assessed for treatment effectiveness using polysomnography, urinary melatonin sampling, Stanford Sleepiness Questionnaire, anxiety inventory, and a fatigue scale. Following treatment, anxiety and fatigue scores improved significantly. Several polysomnographic parameters also improved, including sleep onset latency, sleep arousal, total sleep time, and sleep efficiency. Additionally, urine analysis showed increases in melatonin production at night and decreases in its production in the morning and afternoon, reflecting normalization of melatonin secretion. The authors of the study concluded that acupuncture may be of value as a therapeutic intervention for insomnia in anxious subjects.

This study also sheds some light on the mechanism by which acupuncture affects sleep. The melatonin urinalysis results suggest that acupuncture may exert its

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therapeutic effects in the setting of insomnia through regulation of melatonin secretion. This finding was also confirmed in rats.[12] In another article, it was postulated that acupuncture, via its effect on the endogenous opioid system, reduces stress and anxiety, enabling better sleep.[13]

Comparative Studies

Comparison studies of varying acupuncture styles for the treatment of insomnia represent an interesting research path yet to be vigorously pursued in peer-reviewed medical literature. Additionally, comparison studies of acupuncture and medication for the treatment of insomnia have not yet been published in peer-reviewed literature. Currently, there are only two randomized controlled trials of acupuncture/acupressure treatment for insomnia in the English medical literature.

The first study evaluated the effectiveness of acupressure in the treatment of insomnia in hemodialysis patients.[14] A high prevalence of sleep complaints is reported in patients with end-stage renal disease (ESRD). In a randomized controlled trial, Tsay and colleagues assessed effectiveness of acupressure in alleviating insomnia in 98 ESRD patients, age 18-65, who scored 5 points or higher on the Pittsburgh Sleep Quality Index (PSQI). Eligible patients were randomized into experimental (n = 35, receiving acupressure plus usual care), placebo (n = 32, receiving sham acupressure, 1 cm from the true acupoints, plus usual care), or control (n = 31, usual care) groups. Three acupoints were chosen from the ears, hands, and feet and massaged for a total of 15 minutes, three times per week for four weeks, when patients received hemodialysis. Assessment tools included the PSQI, a daily sleep log, and the Medical Outcome Study-Short Form 36 (SF-36).

Results indicated that compared to the control groups patients in the true acupressure group improved significantly with respect to subjective sleep quality, sleep duration, habitual sleep efficiency, and sleep sufficiency. There also was a significant difference in subjective sleep quality between the sham acupressure and control groups, possibly due to the non-specific effects of non-acupoint acupressure. Data obtained from the sleep log showed that the acupressure group had significantly decreased awake time and improved quality of sleep at night in comparison with the control groups. SF-36 analysis showed significant improvement for body pain, vitality, social function, role function, total physical component, and total mental component in the acupressure group compared with the control groups.

In the second randomized controlled trial, Suen et al compared different techniques of auricular acupoint stimulation for the treatment of insomnia.[15] In auriculotherapy, either needles are inserted or small seeds are attached to the acupoint. Patients are then asked to intermittently stimulate them manually, to prevent "fatiguing" of the acupoint. It is theorized that magnetic pearls do not need further stimulation after their attachment and are thus more convenient. One hundred twenty elderly participants with chronic insomnia were randomized to three groups. In the first group, 30 patients received auriculotherapy, using junci medulla (the dried stem of perennial plant *Juncus effusus*). Due to its soft texture, it will not induce any physical pressure on the acupoints of the ear. In the second group, 30 patients received seed attachment without manual stimulation. In the final group, 60 patients received magnetic pearls stimulation with each magnetic pearl producing an average of 6.58 mT/~66 Gauss per pearl of magnetic flux.

Seven auricular points that are thought to have an effect on promoting sleep were selected in this study: shenmen, heart, kidney, liver, spleen, occiput, and subcortex. The total treatment course lasted three weeks. Objective assessment of sleep using actigraphic monitoring, and subjective assessment with sleep questionnaires and sleep diary were used. The results of the study showed that only the magnet auriculotherapy group showed significant improvement in terms of the nocturnal sleep time and sleep efficiency. Both the junci and seeds without stimulation groups showed no difference from baseline in these measures. The authors concluded that auricular therapy using magnetic pearls is an effective means for improving the quantity and quality of sleep in the elderly.

A follow-up study showed that treatment effectiveness was maintained at one, three, and six months after initial treatment.[16]

Safety

MacPherson et al conducted a prospective postal audit of acupuncture treatments administered by 574 professional acupuncturists who were members of the British Acupuncture Council.[17] They found no serious adverse events after 34,407 acupuncture treatments. In 2001, White et al reported prospective data from 78 physicians and physiotherapists who administered 31,822 acupuncture treatments.[18] Altogether, only 43 significant events were reported, giving a rate of 14 per 10,000 (95% confidence interval [CI] 8-20/10,000). All adverse events had cleared within one week, except for one incident of pain that lasted two weeks and one report of sensory symptoms that lasted several weeks. None of these events was serious. A total of 2,135 minor events was reported, giving an incidence of 671/10,000 (CI 42-1,013/10,000) consultations. The most common

events were bleeding (310/10,000 [CI 160-590/10,000] consultations) and needling pain (110/10,000 [CI 49-247/10,000] consultations).

Most recently, Melchart et al conducted a prospective investigation of adverse effects of acupuncture in 97,733 patients receiving more than 760,000 acupuncture sessions.[19] The mean (SD) number of inserted needles per session was 12.6 (± 5.1). Mild adverse effects were reported in 6,936 patients (7.10%; 99% CI 6.88%-7.32%). The most frequently reported adverse effects were needling pain and hematoma. Comparison of this adverse event rate for acupuncture with those of drugs routinely prescribed in primary care suggests that acupuncture is a safe form of treatment.[20]

Conclusion

Acupuncture has a history in China of being an effective treatment for insomnia for hundreds of years. Recent studies conducted in Western countries assessing acupuncture's effectiveness for this indication support those historical observations.

Recommendation

There is a paucity of methodologically sound studies on the effectiveness of acupuncture in the treatment of insomnia. However, based on its well-established safety profile, numerous case reports/series, and a few randomized trials, acupuncture treatment may be recommended to patients with insomnia as part of an initial intervention. ❖

Dr. Schiff is a Fellow in the Program in Integrative Medicine, University of Arizona, in Tucson.

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Probiotics for GI Disorders and Antibiotic-Associated Diarrhea in Children

By Bradley C. Johnston, ND, MSc Cand, and Sunita Vohra, MD, FRCPC, MSc

PROBIOTICS REFER TO "FRIENDLY" NON-PATHOGENIC microorganisms intended to benefit the host by improving the properties of indigenous microflora.[1] The rationale behind probiotic administration is based on re-inoculation and normalization of unbalanced indigenous microflora using specific probiotic strains. These friendly microorganisms have been shown to improve microbial balance in the intestinal tract and display both antibacterial and immune regulatory effects in humans.[2,3] They have been administered both prophylactically and therapeutically in an attempt to modify intestinal activity

as well as mucosal, epithelial, and systemic immune activity.[4]

Background

It is hypothesized that many children and adults may have inadequate indigenous microflora because of exposure to overly sterile environmental conditions that result in the development of gastrointestinal (GI) and immunological problems.[5] Compared to a diet that once contained several thousand times more bacteria, today's food is highly processed, pasteurized, and sterilized, resulting in limited exposure to bacteria.[6] The overly hygienic environment in which most children in developed countries reside lacks microbial stimulation, and this may result in an impaired gut barrier that in turn may cause autoimmune, infectious, and inflammatory conditions.[6] This situation also may be associated with various GI disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), infectious diarrhea, *Clostridium difficile* colitis, and antibiotic-associated diarrhea (AAD).

Probiotics for GI Disorders in Children

One of the primary areas of probiotic research in children is for the treatment and prevention of GI disorders. Small uncontrolled trials using *Lactobacillus GG* (*Lactobacillus casei* spp. *rhamnosus*) for the treatment of *C. difficile*-associated diarrhea, which can occur after antibiotic therapy, have demonstrated positive results. Although a number of uncontrolled and controlled trials of *Lactobacillus GG* for *C. difficile*-associated diarrhea in adults have been reviewed,[7] only one small uncontrolled pediatric trial has been reported: In this open label case series of four pediatric patients with recurrent *C. difficile*, *Lactobacillus GG* demonstrated positive results in preventing relapses.[8] In addition, *Saccharomyces boulardii* has demonstrated benefit in adults with *C. difficile* and AAD.[9,10]

Probiotics for the treatment of acute diarrheas, specifically virally induced diarrhea in children, have been extensively studied in randomized controlled trials (RCTs). These trials include a number of probiotic species, both alone and in combination, and have demonstrated decreased severity and duration of diarrhea in a range of socioeconomic populations when administered individually or as part of oral rehydration therapy.[11] A recent meta-analysis of nine RCTs concluded that lactobacillus interventions, including *Lactobacillus acidophilus*, *Lactobacillus bulgaris*, *Lactobacillus GG*, and *Lactobacillus reuteri*, reduced the duration of acute infectious diarrhea by approximately one day in children, with trials of *Lactobacillus GG* making the most substantial contribution to the overall results.[12] For example, of the nine trials, four used the probiotic *Lactobacillus GG* in the treatment groups. However, in a recent RCT, *Lactobacillus GG* was ineffective in children with severe diarrhea admitted to the hospital. The authors hypothesized that prior intestinal colonization from probiotic use may be important, resulting in greater benefits with regard to prevention of virally induced diarrhea rather than treatment.[13] Large RCTs of *Lactobacillus GG* and *S. boulardii* for the prevention of traveler's diarrhea (of viral origin) have demonstrated effectiveness in adults.[14,15]

The prevention of acute diarrhea using probiotics also has been studied in RCTs in infants. Of note, there are safety concerns with exposing neonates and infants to probiotics *(see the Safety section)*. *Bifidobacterium bifidum*, together with *Streptococcus thermophilus* and *Lactobacillus GG*, has demonstrated benefit in preventing nosocomial diarrheas.[11,16] In uncontrolled trials, *Bifidobacterium lactis* and *L. reuteri* (as well as RCTs of *Lactobacillus GG*) have demonstrated a reduction in the incidence of acute diarrhea in children.[11,17]

Diarrhea also is a well-known sequelae of IBD and IBS. The efficacy of probiotics in IBD and IBS has previously been reviewed;[4,18] however, no trials of probiotics for IBS have been reported in children. Two small but promising trials of probiotics for the treatment of children with Crohn's disease have been reported.[19,20] In both open label trials, 10 billion *Lactobacillus GG* colony-forming units (CFUs) were administered twice daily. Malin et al reported that orally administered *Lactobacillus GG* has the potential to increase gut IgA immune response and promote the gut immunological barrier.[19] Gupta et al reported a significant improvement in the Crohn's disease activity index.[20]

Probiotics for Pediatric Antibiotic-Associated Diarrhea

Most antibiotic treatments disturb the colonization resistance of GI flora, resulting in a range of clinical symptoms, of which diarrhea is the most frequent. Specifically, antibiotics that act on anaerobes are most often associated with diarrhea, with aminopenicillins, cephalosporins, and clindamycins resulting in the highest risk of diarrheal side effects.[21] Although the overgrowth of many enteropathogens has been demonstrated in AAD, *C. difficile* overgrowth has become known as the bacterial agent most associated with AAD.[22] Reports in the general population indicate that AAD occurs in approximately 5%-39% of patients between initiation of antibiotic therapy and up to two months after the end of treatment.[21,22] The incidence of diarrhea in children receiving broad-spectrum antibiotics ranges from 20% to 40%.[23]

Table

Common probiotics

Common Probiotics Found in Commercial Products	Common Probiotics Used in Antibiotic-Associated Diarrhea Studies	Common Probiotics Used in Pediatric Antibiotic-Associated Diarrhea Studies
Bifidobacterium	Bifidobacterium	Bifidobacterium
B. bifidum	*B. bifidum*	*B. bifidum*
B. infantis	*B. longum*	*B. infantis*
B. longum		
B. thermophilum		
B. adolescenti		
Clostridium	Clostridium	Clostridium
C. butyicum	*C. butyicum*	*C. butyicum*
Lactobacillus	Lactobacillus	Lactobacillus
L. acidophilus	*L. acidophilus*	*L. acidophilus*
L. brevis	*L. bulgaris*	*L. bulgaris*
L. casei	*L. casei*	*Lactobacillus GG*
Lactobacillus GG	*Lactobacillus GG*	*L. sporogens* with Fructo-Oligosaccharide* (FOS)
L. cellobiosus	*L. paracasei*	
L. curvatus	*L. plantarum*	
L. delbruecki subsp. *bulgaris*	*L. reuteri*	
L. fermentum		
L. plantarum		
L. reuteri		
L. salivarius		
L. sporogens		
Streptococcus	Streptococcus	
Lactis salivarius subsp. *thermophilus*	*S. thermophilus*	
Yeasts	Yeasts	Yeasts
Saccharomyces boulardii	*Saccharomyces boulardii*	*Saccharomyces boulardii*
Saccharomyces cerevisiae		

* FOS = a prebiotic, non-digestible food ingredient (i.e., principally oligosaccharides found in foods such as beans and lentils) that may beneficially affect the host by selectively stimulating the growth of beneficial bacteria (i.e., lactobacillus, bifidobacterium) in the colon.

Two recent meta-analyses on probiotics provide evidence to suggest probiotics prevent AAD in the general population.[24,25] Results strongly favored probiotic co-administration with antibiotics for the prevention of diarrheal side effects.

There are more than 30 strains of probiotics commonly used, yet little is known about the strains or doses that yield the most beneficial results for the prevention of AAD *(see Table)*. *Lactobacillus GG*, one probiotic strain that has been extensively studied for many GI disorders, has demonstrated benefit in two pediatric randomized controlled trials for AAD. *Lactobacillus GG* has been the focus of probiotic research because of its proven safety, its resistance to stomach acid and bile, and its ability to temporarily colonize the human intestine.[26] To date, a systematic review of probiotics for pediatric AAD has not been conducted. To address this need the authors of this article published a protocol in the Cochrane Database of Systematic Reviews to assess probiotics as an adjunct to antibiotics for the prevention of AAD in children.[27]

A systematic search of MEDLINE identified two RCTs that evaluate *Lactobacillus GG* for the prevention of AAD in children.[28,29] These two studies (n = 307) provide evidence that 10-20 billion CFUs of *Lactobacillus GG* per day significantly decrease the incidence of diarrhea in children. Furthermore, both studies indicate that children administered *Lactobacillus GG* who became ill had diarrhea (> 2 loose bowel movements per day) for a significantly shorter duration of time, approximately three quarters of a day less than those administered placebo. However, clinical heterogeneity was apparent and larger rigorous trials are needed.

Safety

The safest forms of probiotic bacteria are found in many common fermented foods, including yogurt, buttermilk, kefir, tempeh, miso, and sauerkraut.[30] The trials of probiotics for treating pediatric diarrhea reviewed in this article investigate supplemental forms of probiotics. Supplemental forms provide a substantially higher dose of probiotic and appear to be more effective than

fermented foods in treating GI disorders. These studies have investigated a wide spectrum of probiotic supplementation doses, ranging from 1 million to 300 billion CFUs per day, usually taken in powder or capsule form and combined with food or drink.

In a review of 143 trials of the use of several different probiotic strains and doses for a host of health concerns in otherwise healthy individuals, no significant adverse events were reported.[31] Although safety does not appear to be a concern in healthy individuals, case reports of bacteremia with clinical features ranging from septicemia, pneumonia, and meningitis infections have been documented in immunocompromised and severely debilitated individuals using probiotics.[32,33] For example, 82% of 89 cases of adult lactobacillus bacteremia patients in Finland had severe comorbidities.[32] There has been one reported case of meningitis caused by bifidobacterium in an immunocompromised infant and one case report of meningitis caused by *Bifidobacterium breve* in an otherwise healthy neonate.[33,34]

Few reports or controlled trials specifically document the safety of feeding large amounts of probiotics to healthy infants or children for extended periods of time (longer than 1-2 weeks). The most rigorous of the reports, a prospective, double-blind, randomized, placebo-controlled trial of 180 healthy infants 3-24 months of age demonstrated long-term consumption (mean 210 days) of *B. lactis* and *S. thermophilus* (100,000 CFUs per day) was well tolerated and safe.[35] Administration of *Lactobacillus GG* (1-2 billion CFUs per day) has also been evaluated in double-blind placebo-controlled trials in pregnancy and postnatally for six months.[36,37] Although no adverse events were reported in these trials, they did not investigate the effectiveness or potential safety concerns of probiotics in patients with severe debilitating disease or altered immune function. Given the limited amount of information, probiotic use in these populations needs to be closely monitored or avoided until further studies have been conducted.

Conclusion

Re-inoculation and normalization of unbalanced indigenous microflora using specific probiotic strains underlies the rationale of probiotic administration in children. *Lactobacillus GG* has been widely studied in adults and children and possesses the characteristics needed to provide benefits to the host (e.g., resistance to acid and bile, colonization in human intestinal tract). *Lactobacillus GG* at a dose of 10-20 billion CFUs per day appears to be safe and clinically effective at preventing AAD and *C. difficile*-associated diarrhea in otherwise healthy children. Although *Lactobacillus GG* alone or in combination with oral rehydration therapy for traveller's diarrhea has been demonstrated to be effective in adults, trials in children are still needed. *Lactobacillus GG* for the treatment of acute diarrhea in healthy children has repeatedly demonstrated significant results, whereas other probiotic strains such as *L. acidophilus*, *L. bulgaris*, and *L. reuteri* have demonstrated great promise. Meanwhile for the prevention of acute diarrhea, RCTs in healthy infants using *B. bifidum*, together with *S. thermophilus*, as well as RCTs employing *Lactobacillus GG*, have demonstrated benefit in preventing nosocomial diarrheas. Probiotic use in severely debilitated and immunocompromised children and adults should be avoided. Neonates administered probiotics, in particular *Bifidobacterium breve*, should be closely monitored.

Recommendation

Advantages of probiotic co-administration with antibiotics include ease of administration, the potential for increasing the probability of the child completing the antibiotic prescription vs. premature discontinuation of the antibiotic due to diarrheal side effects, and maintenance/restoration of the gut microflora. *Lactobacillus GG* is a novel and apparently worthwhile therapy for the prevention of pediatric AAD. A one-month supply of *Lactobacillus GG* is available in most health food stores and many pharmacies for approximately $20.

Clinicians and parents wishing to prevent AAD in healthy children may consider a strict *Lactobacillus GG* probiotic or a probiotic cocktail that contains up to 20 billion CFUs of *Lactobacillus GG* co-administered with the antibiotic. Larger rigorous trials of *Lactobacillus GG* and other microbes for pediatric AAD are still needed before making wide public health and clinical recommendations for routine use. ❖

Mr. Johnston is a graduate student, and Dr. Vohra is the Director of the Complementary and Alternative Research and Education (CARE) program, Stollery Children's Hospital, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada.

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Creatine to Improve Muscle Strength

By Dónal P. O'Mathúna

ATHLETES, COMPETITIVE AND RECREATIONAL, ARE increasingly using dietary supplements and nutritional aids. Creatine is one of the most popular supplements among competitive athletes. A 2004 survey involving more than 200 varsity athletes at a Division 1 university found that 37.2% reported using creatine.[1] Users were almost exclusively male and used creatine to increase muscle mass and strength. Other surveys found between 28% and 41% of all student-athletes at National Collegiate Athletic Association (NCAA) institutions use creatine, primarily in power sports (boxing, track and field, and those involving weightlifting).[2] Creatine is not included in the list of banned substances adopted just prior to the 2004 Olympics, which, for the first time, had been adopted by all countries and for all sports.[3] However, NCAA institutions are not permitted to provide athletes creatine as a nutritional supplement.[2]

Creatine use among recreational athletes is undocumented, but it is widely advertised and promoted as an aid to building muscle mass and strength. Physicians should be aware of this use and the claims made about creatine. Almost half the athletes in the 2004 Division 1 survey claimed they used creatine "for their health," yet physicians and pharmacists were 10th and 15th, respectively, among those used as sources of information on supplements.[1] The most popular sources were family members, fellow athletes, and strength coaches.

Creatine's role in exercise was discovered in 1847 when wild foxes killed after foxhunts were found to have more than 10 times the amount of creatine in their meat compared to foxes raised in captivity.[4] Soon afterwards, creatine levels were correlated with muscle mass and urinary levels of creatinine, now known to be a byproduct of creatine metabolism. In spite of this early interest, creatine didn't burst onto the athletic scene as a potent ergogenic aid (i.e., a performance-enhancing substance) until the 1990s.

Pharmacology

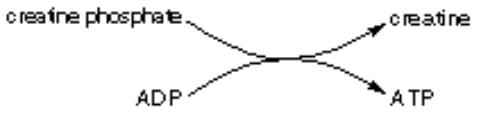
Creatine is made from three amino acids common to protein. On average, people require about 2 g of creatine daily, obtained equally from exogenous and endogenous sources.[5] Humans store 95% of their creatine in skeletal muscle, with more found in fast-twitch muscle fibers than slow-twitch ones.[4]

Creatine is vital to the supply of energy for short-duration, high-intensity exercise, such as sprinting, jumping, power-lifting, and tackling. About 60% of the creatine in skeletal muscle exists as creatine phosphate (CP). Adenosine triphosphate (ATP) supplies energy for muscle contraction as it is converted into adenosine diphosphate (ADP). Muscle ATP stores provide fuel for only a few seconds of exercise, after which CP replenishes ATP *(see Figure)*. Muscle CP stores contain fuel for 4-6 additional seconds of intense exercise, and its rate of replenishment depends on free creatine concentrations.[6] Creatine is thus essential for short, intense, anaerobic exercise. Thirty seconds of rest will half-replenish CP levels, though complete recovery may take up to 3-4 minutes.[7]

Mechanism of Action

The mechanism of action by which creatine supplementation could increase muscle strength and athletic performance is not known with certainty. However, a number of physiological mechanisms have been proposed and are being investigated. Studies have provided evidence that up to 40% of the ergogenic effect could be due to a direct effect of making more creatine and CP available for muscle energy production.[8]

Figure
Role of creatine in energy production



As CP stores are depleted with exercise, increased free plasma creatine would allow faster replenishment of CP stores and thus shorten recovery periods during repeated bouts of intense exercise. Athletes consuming creatine have been found to tolerate higher exercise volumes, which may thereby produce greater strength.[8] Creatine also has been proposed to contribute to muscle fiber hypertrophy, to activate gene expression that leads to muscle growth, and to increase total body water.[8] The latter may influence glycogen levels and increase the rate of muscle protein synthesis and/or decrease the rate of muscle protein breakdown.

These different mechanisms could contribute to increased muscle mass and strength. Variation in their influence could account for one of the ongoing controversies regarding creatine supplementation, namely, the great variability in individual responses to supplementation.

Clinical Studies

Creatine is one of the few ergogenic aids that has been extensively researched. When reviewed in this newsletter in 2000, several dozen small studies showed some ergogenic benefit but with considerable variability.[9] Several hundred studies of creatine have now been published, with one review estimating that 70% of these found at least some ergogenic benefit.[8]

The first meta-analysis of studies examining the impact of creatine on strength performance was published in 2002.[10] Of 66 studies identified, 16 met the inclusion criteria. Only studies measuring strength or power (and not endurance) were included, and all crossover studies were excluded because of controversy over the appropriate washout period. The analysis showed that creatine supplementation improves maximal resistance training performance in previously trained young men. Benefits were found only when supplementation was accompanied by resistance training. Improvements were not found with more complex exercise involving strength, speed, and coordination of several muscles, nor were they found in untrained men, women, or older adults. However, the analysis also reported poor overall study quality, with an average score of 3.5 out of 10 and the best score being 5.5.

A 2003 meta-analysis examined 100 studies.[11] The inclusion criteria were broader than those above, including all randomized, placebo-controlled, blinded studies

that measured any body composition or physical performance outcome. Although the results of individual studies were considerably variable, certain overall patterns emerged. The mean overall improvement after creatine supplementation (5.7% ± 0.5%) was significantly greater than after placebo (2.4% ± 0.4%). The authors concluded that creatine is effective in increasing total and lean body mass, and improving performance in high-intensity, short-duration, repetitive exercise. For example, of the 62 studies examining exercise duration of less than 30 seconds, 45 reported an ergogenic effect from creatine and 17 reported no benefit, for an overall effect size of 0.24 ± 0.02. Eighteen studies examining exercise of 150 seconds or longer found an equal number with and without ergogenic benefits.

A number of other patterns emerged from this meta-analysis. Benefits were greater when supplementation continued at a lower dose after the initial loading dose. Few studies included women, and most of these found no ergogenic benefit. Creatine supplementation led to more pronounced benefit with upper-body exercise than lower-body or overall body exercise. Most studies involved controlled laboratory settings, but the few conducted in the field found creatine to lead to minimal improvement in running, swimming, or jumping performance. This may be due to the weight gain consistently found with creatine supplementation.[8]

Adverse Effects

Creatine frequently leads to weight gain of 1-3 kg, which is believed to be due to intramuscular water retention resulting from an osmotic effect.[11] Numerous anecdotal reports claim creatine supplementation causes gastrointestinal problems, muscle cramping, and renal problems. Controlled studies generally do not support these concerns. A few case studies reported renal problems after creatine supplementation, especially with extended high-dose usage.[12] However, a small study of healthy athletes taking 10 g creatine daily for as long as five years revealed no impaired renal function.[12] Supplement use appears generally safe, although those at high risk for renal disease should be monitored medically.[13]

The NCAA and International Olympic Committee (IOC) do not ban creatine but warn about the risk of contamination with banned substances. An IOC study of more than 600 non-hormonal nutritional supplements purchased in 13 countries found 14.8% to be contaminated with hormones that were not listed on the labels.[14] Tests showed that consumption led to urine levels that would have resulted in positive doping results.

No drug interactions are known, although creatine could interact with other drugs associated with renal toxicity.

Formulation

Creatine is readily available from meat and fish (containing roughly 4-5 g/kg) and therefore is classified as a dietary supplement, not a drug. It is most commonly available as the monohydrate in powder, candy, gum, and liquid. Numerous products combine it with vitamins, nutrients, and supplements, with no evidence of added benefits. Usually, athletes "load" on 20 g creatine per day for 4-6 days (usually 5 g qid), followed by one 2 g daily dose. The same creatine "loading" levels are achieved after 30 days of 3 g/d taken as a single dose.[15]

Conclusion

Oral creatine supplementation has been studied extensively over the past decade. Ergogenic improvements consistently occur with repeated bouts of maximal exertion lasting less than 30 seconds with a few minutes recovery—such as high-intensity weight-lifting, football plays, and short-burst training programs. The metabolic rationale for such benefits is well-established. Those most likely to benefit from supplementation are young, well-trained males. Very little evidence supports improvements with single-bout anaerobic exercise, submaximal exercise, or aerobic exercise. Most studies have been conducted in controlled environments and may not be replicable in competition. Additionally, people vary widely in their response to supplementation, with some being wholly unresponsive.

Recommendation

High-performance athletes involved in high-intensity, repeated exercise of very short duration may benefit from creatine supplementation with 2 g/d. Recreational and endurance athletes probably will not benefit from creatine. Adverse effects are rare, although few long-term studies have been conducted. Clinicians should ask their athletic patients if they take such supplements. Most will probably not be training at the intensity needed to see any benefit. Those who are highly competitive should be cautioned about the risks of contaminated products. Clinicians should remain informed of the latest developments in creatine research, so they can advise their patients, especially those who may be susceptible to renal damage. ❖

Dr. O'Mathúna is a lecturer at the School of Nursing, Dublin City University, Ireland.

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

Acupuncture for PONV

Source: Gan TJ, et al. A randomized controlled comparison of electro-acupoint stimulation or ondansetron versus placebo for the prevention of postoperative nausea and vomiting. *Anesth Analg* 2004;99:1070-1075.

Goal: To determine whether electro-acupoint stimulation (EAS) is an effective alternative to ondansetron (OND) for postoperative nausea and vomiting (PONV) prophylaxis.

Design: Prospective, randomized, sham-controlled study.

Subjects: Seventy-seven patients having major breast surgery under general anesthesia (75 included in analysis).

Methods: Subjects were randomized to one of three groups: active EAS at acupoint P6 using pads (no needles), single dose OND 4 mg IV, or sham acupoint control (pads placed but no EAS). Those not receiving OND IV were given an equivalent volume of saline. EAS was applied 30-60 minutes before induction of anesthesia, and was continued throughout the procedure until the electrodes were removed just prior to waking the patient. Measurements included incidence of nausea and vomiting, use of rescue anti-emetics, postoperative pain, and patient satisfaction. Assessments were made at 0, 30, 60, 90, 120 minutes and at 24 hours (the latter by phone follow-up).

Results: Both EAS and OND use resulted in significantly more procedures not complicated by nausea or vomiting at all, as well as less need for rescue anti-emetics, than the sham control. Subjects who received EAS had a lesser incidence and severity of nausea, and less pain, than patients in the OND and control groups. Patients in the active treatment groups were more satisfied with the management of their PONV than those in the control group.

Conclusion: Both OND and EAS reduce PONV, but EAS appears to be slightly more effective than OND, and has the added benefit of an analgesic effect. Thus, EAS is a viable alternative to the use of OND.

Study strengths: Degree of blinding (a different postop nurse was even used for data collection); enrolled consecutive patients (no selection bias).

Study weaknesses: Complete blinding not possible while subjects were awake.

Of note: Subjects receiving OND fared significantly better than those in the control group, but less well compared to the EAS group; all subjects were told the electrical stimulation unit produces an electrical current they may or may not feel, and the screen of the unit was covered by tape to also blind clinicians and researchers; all patients received fentanyl and midazolam as premedication and the intraoperative anesthetic regimen was standardized; no difference between groups was identified with respect to adverse events or length of stay; a reusable acupoint stimulation unit with disposable electrodes costs about $200, while each administration of OND runs approximately $16; subjects who had previously experienced acupuncture were excluded from the trial, which was performed at Duke University Medical Center.

We knew that: PONV are the most common reasons for low patient satisfaction in the postoperative period; OND use is associated with headache, abdominal pain, and elevated liver function tests; acupuncture effects may be blocked by naloxone; low-frequency EAS (2-4 Hz) causes release of endorphins, while high-frequency stimulation (50-200 Hz) involves release of enkephalins; a 30% placebo response

rate exists when assessing efficacy of anti-emetics; studies in which EAS is offered following induction of anesthesia show less effect on PONV.

Clinical import: Patient satisfaction surveys hold significant sway, as do cost-containment measures, so both practitioners and administrators are likely to be intrigued by the results of this trial. Although a number of papers have compared acupuncture to placebo for PONV, most showing benefits with acupuncture, many suffer from significant methodologic flaws. This well-done study, however, comparing EAS to a well-accepted pharmaceutical agent, creates a persuasive argument that members of the surgical team learn how to perform EAS.

What to do with this article: Make copies to hand out to your peers. ❖

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47. In traditional Chinese medicine, which of the following might be used to treat insomnia?

a. Diet and exercise
b. Stress reduction techniques
c. Acupuncture
d. All of the above

48. Which of the following athletes is *most* likely to benefit from creatine supplementation?

a. Elite athletes involved in high-intensity, repeated exercise
b. Recreational athletes
c. Endurance athletes
d. All of the above

49. *Lactobacillus GG* possesses which of the following characteristics?

a. Resistance to acid and bile
b. Proven safety
c. Ability to colonize the human intestinal tract
d. All of the above

Answers: 47. d, 48. a, 49. d.

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ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Getting a Good Night's Sleep

UNTIL THE 1950S, MOST PEOPLE THOUGHT OF SLEEP AS A PASSIVE, DORMANT PART OF OUR daily lives. We now know that our brains are very active during sleep. Moreover, sleep affects our daily functioning and our physical and mental health in many ways that we are just beginning to understand.

At least 40 million Americans each year suffer from chronic, long-term sleep disorders each year, and an additional 20 million experience occasional sleeping problems. These disorders and the resulting sleep deprivation interfere with work, driving, and social activities. They also account for an estimated $16 billion in medical costs each year, while the indirect costs due to lost productivity and other factors are probably much greater.

Almost everyone occasionally suffers from short-term insomnia. This problem can result from stress, jet lag, diet, or many other factors. Insomnia almost always affects job performance and well-being the next day. About 60 million Americans a year have insomnia frequently or for extended periods of time, which leads to even more serious sleep deficits. Insomnia tends to increase with age and affects about 40% of women and 30% of men. It is often the major disabling symptom of an underlying medical disorder.

Mild insomnia often can be prevented or cured by practicing good sleep habits *(see sidebar, page S2)*. For more serious cases of insomnia, researchers are experimenting with light therapy and other ways to alter circadian cycles.

How much sleep do we need?

The amount of sleep each person needs depends on many factors, including age. Infants generally require about 16 hours a day, while teenagers need about 9 hours on average. For most adults, 7-8 hours a night appears to be the best amount of sleep, although some people may need as few as 5 hours or as many as 10 hours of sleep each day. The amount of sleep a person needs also increases if he or she has been deprived of sleep in previous days. Getting too little sleep creates a "sleep debt," which is much like being overdrawn at a bank. Eventually, your body will demand that the debt be repaid. We don't seem to adapt to getting less sleep than we need; while we may get used to a sleep-depriving schedule, our judgment, reaction time, and other functions are still impaired.

People tend to sleep more lightly and for shorter time spans as they get older, although they generally need about the same amount of sleep as they needed in early adulthood. About half of all people older than age 65 have frequent sleeping problems, such as insomnia, and deep sleep stages in many elderly people often become very short or stop completely. This change may be a normal part of aging, or it may result from medical problems that are common in elderly people and from the medications and other treatments for those problems.

Many studies make it clear that sleep deprivation is dangerous. Sleep-deprived people who are tested by using a driving simulator or by performing a hand-eye coordination task

perform as badly as or worse than those who are intoxicated. Sleep deprivation also magnifies alcohol's effects on the body, so a fatigued person who drinks will become much more impaired than someone who is well-rested. Driver fatigue is responsible for an estimated 100,000 motor vehicle accidents and 1,500 deaths each year, according to the National Highway Traffic Safety Administration.

What does sleep do for us?

Although scientists are still trying to learn exactly why people need sleep, animal studies show that sleep is necessary for survival. For example, while rats normally live for 2-3 years, those deprived of REM sleep survive only about 5 weeks on average, and rats deprived of all sleep stages live only about 3 weeks.

Sleep appears necessary for our nervous systems to work properly. Too little sleep leaves us drowsy and unable to concentrate the next day. It also leads to impaired memory and physical performance and reduced ability to carry out math calculations. If sleep deprivation continues, hallucinations and mood swings may develop. Some experts believe sleep gives neurons used while we are awake a chance to shut down and repair themselves. Without sleep, neurons may become so depleted in energy or so polluted with byproducts of normal cellular activities that they begin to malfunction. Sleep also may give the brain a chance to exercise important neuronal connections that might otherwise deteriorate from lack of activity.

Source: National Institute of Neurological Disorders and Stroke, National Institutes of Health. Available at: www.ninds.nih.gov/health_and_medical/pubs/understanding_sleep_brain_basic_.htm. Accessed on Oct. 18, 2004.

Tips for a Good Night's Sleep

- **Set a schedule:** Go to bed at a set time each night and get up at the same time each morning. Disrupting this schedule may lead to insomnia. "Sleeping in" on weekends also makes it harder to wake up early on Monday morning because it re-sets your sleep cycles for a later awakening.
- **Exercise:** Try to exercise 20-30 minutes a day. Daily exercise often helps people sleep, although a workout soon before bedtime may interfere with sleep. For maximum benefit, try to get your exercise about 5-6 hours before going to bed.
- **Avoid caffeine, nicotine, and alcohol:** Avoid drinks that contain caffeine, which acts as a stimulant and keeps people awake. Sources of caffeine include coffee, chocolate, soft drinks, non-herbal teas, diet drugs, and some pain relievers. Smokers tend to sleep very lightly and often wake up in the early morning due to nicotine withdrawal. Alcohol robs people of deep sleep and REM sleep and keeps them in the lighter stages of sleep.
- **Relax before bed:** A warm bath, reading, or another relaxing routine can make it easier to fall sleep. You can train yourself to associate certain restful activities with sleep and make them part of your bedtime ritual.
- **Sleep until sunlight:** If possible, wake up with the sun, or use very bright lights in the morning. Sunlight helps the body's internal biological clock reset itself each day. Sleep experts recommend exposure to an hour of morning sunlight for people having problems falling asleep.
- **Don't lie in bed awake:** If you can't get to sleep, don't just lie in bed. Do something else, like reading, watching television, or listening to music, until you feel tired. The anxiety of being unable to fall asleep can actually contribute to insomnia.
- **Control your room temperature:** Maintain a comfortable temperature in the bedroom. Extreme temperatures may disrupt sleep or prevent you from falling asleep.
- **See a doctor if your sleeping problem continues:** If you have trouble falling asleep night after night, or if you always feel tired the next day, then you may have a sleep disorder and should see a physician. Your primary care physician may be able to help you; if not, you can probably find a sleep specialist at a major hospital near you. Most sleep disorders can be treated effectively, so you can finally get that good night's sleep you need.

Adapted from: "When You Can't Sleep: The ABCs of ZZZs," by the National Sleep Foundation. For more information, visit www.sleepfoundation.org.