

6-30-18 Articles and Headlines

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BMJ 2018 May 30; 361:k1998

Few Long-Term Effects of Neuroborreliosis (LYME DISEASE)

In a 30-year study, documented B. burgdorferi central nervous system infection showed little effect on morbidity or mortality.

As the season for tick-borne infections begins to heat up, so do concerns about the long-term effects of Lyme disease, especially in those cases involving the central nervous system. This retrospective study involved all 2067 Danish patients with a diagnosis of Lyme neuroborreliosis (LN) between 1986 and 2016. The authors compared mortality, morbidity, educational, and social outcomes in patients with those found in 20,670 age- and sex-matched Danish controls.

Mortality over the 30-year period was not higher among the LN patients or their families, compared with the controls or their families. However, the risk of newly diagnosed hematologic malignancies was threefold higher in the LN population. In addition, the risk of nonmelanoma skin cancers was 50% higher in the study group. These increased risks were not shared by family members.

Increases in rates of hospitalization and outpatient care as well as sick days were seen during the acute disease and recovery phases, as would be expected, but did not continue beyond 2 years. Paradoxically, children with LN achieved higher mathematics grades and higher high school graduation rates than controls.

COMMENT: The authors attribute the higher skin cancer rate to high levels of outdoor activities that would coincidentally expose subjects to both tick bite and UV radiation. No etiologic link is provided to explain the

higher hematologic malignancy rate, but mortality from these malignancies was not increased over that in controls. Overall, these results on a large and well-documented population should bring comfort to those who develop LN disease.

CITATION(S): Obel N et al. Long term survival, health, social functioning, and education in patients with European Lyme neuroborreliosis: Nationwide population based cohort study. BMJ 2018 May 30; 361:k1998. (<https://doi.org/10.1136/bmj.k1998>)

Faust SN et al. Good outlook for patients with confirmed Lyme neuroborreliosis: New study should kick start a more rigorous approach to Lyme research. BMJ 2018 May 30; 361:k2284. (<https://doi.org/10.1136/bmj.k2284>)

J Clin Oncol 2018 Jun 11

Integrating Complementary Therapies with Conventional Breast Cancer Treatment

Evidence supports some integrative therapies during and after breast cancer treatment and discredits others.

Sponsoring Organizations: American Society of Clinical Oncology (endorsing Society for Integrative Oncology's 2017 guidelines)

Background and Objective: Studies examining integrative therapies during and after breast cancer treatment show that some approaches may diminish symptoms and adverse effects of treatment, whereas others are potentially harmful or not beneficial.

Key Recommendations

- Acute radiation skin reaction: Aloe vera and hyaluronic acid cream are *not* recommended.
- Anxiety: Meditation, music therapy, yoga, and stress management (preferably with longer-term group programs) are recommended; acupuncture, massage, and relaxation can be considered.
- Chemotherapy-induced nausea and vomiting: Acupressure, electroacupuncture, ginger and relaxation used with antiemetics can be considered. Glutamine is *not* recommended.
- Depression and mood disturbance: Meditation (particularly mindfulness-based stress reduction), relaxation, yoga, massage, and music therapy are recommended; acupuncture, healing touch, and stress management can be considered.
- Fatigue: Hypnosis and ginseng (with precautions regarding individual product safety and efficacy) can be considered during treatment; acupuncture and yoga can be considered after treatment; acetyl-L-carnitine and guarana are *not* recommended.
- Lymphedema: Low-level laser therapy, manual lymphatic drainage, and compression bandaging can be considered.
- Chemotherapy-induced peripheral neuropathy: Acetyl-L-carnitine is *not* recommended, as it is potentially harmful.
- Pain: Acupuncture, healing touch, hypnosis, and music therapy can be considered.
- Quality of life: Meditation and yoga are recommended; acupuncture, qigong, reflexology, and stress management can be considered; mistletoe can be considered (although only subcutaneous preparations, currently not FDA-approved, have been studied).

- Sleep disturbance: Gentle yoga can be considered.
- Vasomotor/hot flashes: Acupuncture can be considered; soy is *not* recommended, as it lacks efficacy.

COMMENT: At least half of all women with breast cancer use complementary therapies but might not volunteer this information. Primary care and oncology clinicians can nonjudgmentally ask about use and refer to this guideline when discussing efficacy and safety. Certain resources (e.g., yoga, music therapy, meditation instruction) may be geographically or financially unavailable to some women; however, free guidance and demonstrations are increasingly accessible on the Internet.

CITATION(S): Lyman GH et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO Clinical Practice Guideline. *J Clin Oncol* 2018 Jun 11; [e-pub].
<https://doi.org/10.1200/JCO.2018.79.2721>

<https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm>

Autism Rates Edge Higher for Kids

The prevalence of autism spectrum disorders (ASD) among children has increased again, affecting 1 in 59 children in 2014, according to new CDC surveillance estimates.

In 2000-2002, the prevalence among 8-year-olds was estimated to be 1 in 150 children, then in 2010-2012, it increased to one in 68.

Among the other findings from 11 U.S. sites:

- Overall, 85% of children with ASD had developmental concerns documented in their medical records by age 36 months, but only 42% had received a full evaluation by then.
- The median age at diagnosis was 52 months.
- The increase in prevalence could be related to increased detection among minority groups. Disparities between white and black children in identifying autism have narrowed, but still remain for Hispanic children.

In *MMWR Surveillance Summaries*, researchers write: "The observed increase ... underscores the need for continued surveillance using consistent methods to monitor the changing prevalence of ASD and characteristics of children with ASD in the population."

[HTTPS://WWW.CDC.GOV/MMWR/VOLUMES/67/SS/SS6706A1.HTM](https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm)

Folic Acid, Multivitamin Use During Pregnancy Tied to Lower Autism Risk

Use of multivitamin or folic acid supplements before or during pregnancy is associated with reduced risk for autism in the offspring, according to an observational study in *JAMA Psychiatry*.

Using Israeli healthcare databases, researchers assessed prescription supplement use in the 9 months before conception and during pregnancy for 27,000 mothers. Of 45,000 offspring, 1% were diagnosed with autism spectrum disorder.



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After multivariable adjustment, the risk for autism diagnosis was significantly lower among children born to women who took folic acid and/or multivitamins before pregnancy (relative risk, 0.39) and during pregnancy (RR, 0.27), compared with women who didn't supplement. Results were similar when considering folic acid and multivitamin use separately.

The researchers say that epigenetic modifications from supplementation could play a role in the observed association.

<https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2667432>

JAMA Pediatr 2018 May 29

Vitamin D Supplementation in Pregnancy May Benefit Infants

A meta-analysis showed multiple benefits, including a lower risk for being small for gestational age.

Vitamin D supplementation during pregnancy has been studied repeatedly to determine its effects on child health outcomes. Results have varied, prompting this meta-analysis of data from 24 randomized, controlled trials of prenatal vitamin D supplementation including 5400 participants. Although supplement doses and dosing frequencies varied widely among included trials, intervention group doses averaged at least 400 international units (IU) daily.

Multiple outcomes were analyzed, with the following notable findings:

- Prenatal vitamin D supplementation was associated with:
 - Lower risk for newborn being small for gestational age (SGA)
 - Increased neonatal 25(OH)D and calcium levels
 - Increased weight at birth and at 3, 6, 9, and 12 months
 - No increase in neonatal mortality or congenital abnormality
 - No difference in risk for asthma, eczema, respiratory infections, or allergies
- Lower vitamin D doses (≤ 2000 IU/day) were associated with lower mortality, while higher doses (> 2000 IU/day) were not.
- Timing of supplementation (< 20 weeks vs. ≥ 20 weeks gestation) was not associated with risk for SGA or neonatal mortality.

COMMENT: Prenatal vitamin D supplementation typically would fall under the purview of obstetricians, family practitioners, and others caring for pregnant women, but these data remind us to encourage women we see in our practices to ask their prenatal care providers about vitamin D. It is becoming apparent that vitamin D both before and after birth can positively affect child health, and we are in a position to advocate for early exposure for our patients-to-be.

CITATION(S): Bi WG et al. Association between vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: A systematic review and meta-analysis. JAMA Pediatr 2018 May 29; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2018.0302>)



J Am Geriatr Soc 2018 Apr; 66:655

Does Cognitive Training Help People with Memory Disorders?

The answer is yes in a study of patients with mild cognitive impairment but no in another study of patients with mild-to-moderate dementia.

Effective interventions are needed for patients with memory impairment. Medications are ineffective for mild cognitive impairment (MCI) and only slow the deterioration in Alzheimer disease (AD). Two recent single-blind, controlled studies examined the efficacy of cognitive training.

Belleville and colleagues randomized 145 patients with MCI to cognitive training, a psychosocial intervention, or no contact (control). Cognitive training was a specific intervention based on learning new strategies that promote capacities for elaborative encoding and attentional control. The psychosocial intervention was a cognitive-behavioral approach to improve psychological well-being. Both interventions involved eight weekly 2-hour sessions plus a booster after 3 months; analyses were of 127 participants with ≥ 1 posttreatment assessment. Only cognitive training was associated with significant improvements in delayed memory, seen at all time-points (z-score changes: posttraining, 0.35; 3-month follow-up, 0.33; 6-month follow-up, 0.52). No group demonstrated changes in depressive or anxiety symptoms or well-being.

Kallio and colleagues enrolled 147 individuals with mild-to-moderate dementia (AD, 122), who were living at home and attending a day program. They were randomized to a 12-week training program focusing on attention, working memory, cognitive flexibility, and planning (twice weekly for 45 minutes) or daycare as usual (control). The intervention, using paper-and-pencil tasks, was adapted from a cognitive remediation treatment used in individuals with chronic psychiatric illnesses. Both groups deteriorated in global cognition and quality of life through 9 months, with no between-group differences.

COMMENT: These studies are difficult to compare because the therapeutic interventions were not identical. It is not surprising that patients with less severe cognitive problems respond, whereas those with dementia do not. The intervention in the MCI study taught strategies that could be beneficial generally, even for people without cognitive impairment, and showed continued benefit even months later. It is difficult to deduce clinical significance from the reported z-score changes. If a medication demonstrated an equivalent benefit in MCI, it would likely be prescribed to everyone.

CITATION(S): Belleville S et al. MEMO+: Efficacy, durability and effect of cognitive training and psychosocial intervention in individuals with mild cognitive impairment. J Am Geriatr Soc 2018 Apr; 66:655. (<https://doi.org/10.1111/jgs.15192>)

Kallio EL et al. Effects of cognitive training on cognition and quality of life of older persons with dementia. J Am Geriatr Soc 2018 Apr; 66:664. (<https://doi.org/10.1111/jgs.15196>)

Ann Neurol 2018 Mar; 83:472

Does Sleep Affect Cognitive Decline?

Several sleep parameters are associated with changes in cognitive status.



To determine whether variations in sleep parameters affect risk for cognitive decline, researchers conducted a prospective cohort study involving 2893 Korean adults (age, ≥ 60 years). Of these participants, 2238 had normal cognition and 655 had mild cognitive impairment.

Sleep parameters included sleep latency (the time to fall asleep), midsleep time (the midpoint between bedtime and wake time), and sleep duration. Cognition status was determined by consensus criteria. Values of sleep variables and cognition status were determined at baseline and at 4-year follow-up.

Among those with normal cognition at baseline, the risk at follow-up for cognitive decline increased by 40% with long sleep latency (>30 minutes) versus average latency, increased by 70% with long sleep duration (≥ 7.95 hours) versus average duration, and decreased by about 40% with late midsleep time (after 3:00 a.m.) versus average midsleep time. Average values for these variables were within one standard deviation of the median values of the normal cognition group. A change from average sleep latency at baseline to long sleep latency at follow-up doubled the risk for cognitive decline. In those with mild cognitive impairment at baseline, long sleep latency at baseline and follow-up was associated with decreased chance of reverting to normal cognition at follow-up; sleep duration and midsleep time at baseline were not associated with a change in cognitive status.

COMMENT: The unique aspect of this study was the measurement of subjective sleep parameters and cognitive status at both baseline and follow-up assessments. The potential protective association of late midsleep time in normal cognition suggests that circadian rhythm may influence cognitive status. Although more objective sleep measurements are needed, these results suggest that sleep can influence changes in cognitive status, particularly in those with normal cognition.

CITATION(S): Suh SW et al. Sleep and cognitive decline: A prospective nondemented elderly cohort study. *Ann Neurol* 2018 Mar; 83:472. (<https://doi.org/10.1002/ana.25166>)

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JAMA 2018 Jun 12; 319:2333.

Is Oral Fluconazole Use During Pregnancy Safe?

In a population-based cohort of pregnant women, fluconazole use was not associated with excess risk for stillbirth or neonatal death.

We have discouraged use of oral fluconazole during pregnancy since a Danish study showed excess risk for spontaneous abortion and stillbirth among pregnant women who received this drug ([Physician's First Watch Jan 6 2016](#) and *JAMA* 2016; 315:58). Now, investigators address this issue among almost 1.5 million pregnant women in Sweden and Norway between 2006 and 2014. The 0.67% of the cohort who used fluconazole were matched by propensity scores to those women who did not use this agent.

Overall, neither risk for stillbirth (hazard ratio, 0.76 [95% confidence interval, 0.52–1.10]) nor risk for neonatal death (risk ratio, 0.73 [95% CI, 0.42–1.29]) were higher with exposure to fluconazole. Similar results were obtained regardless of fluconazole dose (i.e., ≤ 300 mg or >300 mg). The authors were not able to assess rates of spontaneous abortion.



COMMENT: These data, from a larger cohort than previously examined, should provide reassurance to women who have received oral fluconazole during pregnancy. Topical antifungals, which are also effective for vaginal candidiasis, are still my preference for such women. The unresolved issue is how to manage women with systemic fungal infections during pregnancy (e.g., cryptococcal pulmonary or meningeal disease) who require prolonged therapy. These findings don't shed light on this question; thus, we await further studies that do.

CITATION(S): Pasternak B et al. Oral fluconazole in pregnancy and risk of stillbirth and neonatal death. JAMA 2018 Jun 12; 319:2333. (<https://doi.org/10.1001/jama.2018.6237>)

BMJ 2018 May 23; 361:k1951

Antidepressant Use and Long-Term Weight Gain

In a population-based study, most antidepressant classes were associated with weight gain.

Antidepressants are associated with weight gain in the short term, but little is known about their long-term effects. In this population-based cohort study, U.K. researchers determined the long-term associations between antidepressant prescriptions and weight gain in about 300,000 patients who had three or more body-mass index measurements between 2004 and 2014.

In the year of study entry, 13% of men and 22% of women were prescribed antidepressants. During average follow-up of 6 years, the incidence of $\geq 5\%$ weight gain was significantly higher in participants who were prescribed antidepressants than in those who were not (11.2 vs. 8.1 per 100 person-years). Initially normal-weight participants who took antidepressants were more likely to become overweight, and initially overweight participants were more likely to become obese. All antidepressants except paroxetine were associated with risk for weight gain, with the greatest relative increase seen for mirtazapine.

COMMENT: Although residual confounding is possible in this study, editorialists note potentially important public health implications given the widespread use of antidepressants and the adverse effects of overweight and obesity. Patients who are prescribed antidepressants should be informed of risk for weight gain and given advice on how to minimize it.

CITATION(S): Gafoor R et al. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: Population based cohort study. BMJ 2018 May 23; 361:k1951. (<https://doi.org/10.1136/bmj.k1951>)

Serretti A and Porcelli S. Antidepressant induced weight gain. BMJ 2018 May 23; 361:k2151. (<https://doi.org/10.1136/bmj.k2151>)

