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Biol Psychiatry 2019 Jan 9

First-Episode Psychosis? Take Your Vitamins

Reducing homocysteine levels with a vitamin cocktail has potential benefits.

Elevated homocysteine levels have been reported in schizophrenia, and homocysteine reduction by higher vitamin doses has been reported to improve symptoms in schizophrenia. In a 12-week, randomized, double-blind, placebo-controlled Australian study, researchers provided a single pill combining standard supplement doses of vitamin B_6, vitamin B_{12}, and folic acid to 100 patients with a first episode of any psychotic disorder. All patients continued their usual treatment, including antipsychotic drugs.

Vitamins, but not placebo, increased red cell folate levels and decreased homocysteine levels. At 12 weeks, the two groups showed no differences in positive and negative symptoms or overall neurocognition. However, attention/vigilance declined in placebo patients while remaining stable in vitamin patients. This benefit with supplementation was mainly evident in patients with baseline elevated homocysteine levels, patients with affective psychoses, and women, who also showed improved processing speed. In a test of four genetic variants in folate-metabolizing enzymes, no group differences were seen.

COMMENT: These results, combined with other earlier findings, suggest that this vitamin preparation could be helpful in higher doses to patients with elevated homocysteine levels, particularly in those with affective psychoses. The other health benefits of lowering homocysteine levels are already known. It is sometimes claimed that methylfolate is more beneficial than folate, but in this study, folate did at least enter red cells, and its effect was independent of alleles of folate-metabolizing enzymes. Little seems to be lost by suggesting the addition of supplements in high doses to patients with affective psychoses, especially women (because an effect could have been evident in men with higher doses).

CITATION(S): Allott K et al. The vitamins in psychosis study: A randomized, double-blind, placebo-controlled trial of the effects of vitamin B_{12}, B_6 and folic acid on symptoms and neurocognition in first-episode psychosis. Biol Psychiatry 2019 Jan 9; [e-pub]. (https://doi.org/10.1016/j.biopsych.2018.12.018)

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Acad Pediatr 2019 Jan 10

Rapid Increase in Use of Commercial Direct-to-Consumer Telemedicine for Children

Users of these services were less likely to receive recommended preventive care and more likely to use urgent care services, raising concern for fragmentation of care.

Direct-to-consumer (DTC) telemedicine is an on-demand service in which physicians (usually outside the medical home) treat common, acute complaints through telephone or video conferencing. Access to such services for children is increasing, as most large U.S. companies provide DTC telemedicine through their health plans; however, the American Academy of Pediatrics (AAP) has cautioned that DTC telemedicine outside the medical home can lead to fragmentation and lower quality of care.

To examine use of these services by children, researchers analyzed claims from a large national health plan for acute care visits to DTC telemedicine and primary care providers (PCPs). From 2011 to 2016, DTC telemedicine visits increased from 38 to 24,409 per year. The most common primary billing diagnoses were infections of the nose/sinus (24%), mouth/throat (16%), and ear (9%). Roughly 6% of telemedicine visits were for children <2 years of age. Compared with children using PCPs, those using telemedicine were more likely to be from rural areas, to live in lower-income neighborhoods, to not receive preventive visits, and to have visited other acute care venues (urgent care clinics and emergency departments).

COMMENT: This study supports AAP concerns that DTC telemedicine is associated with care fragmentation. However, we still need to know more about the quality of care provided by DTC telemedicine and the effects on child outcomes when care is delivered outside the medical home versus incorporated into it. I found it interesting that DTC telemedicine providers were less likely than PCPs to bill for "unspecified viral illness" and instead billed for specific infections, such as

throat or sinus. Therefore, it would be helpful to know whether DTC telemedicine providers prescribe more antibiotics (perhaps unnecessarily) compared to PCPs.

CITATION(S): Ray KN et al. Use of commercial direct-to-consumer telemedicine by children. Acad Pediatr 2019 Jan 10; [e-pub]. (https://doi.org/10.1016/j.acap.2018.11.016)

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JAMA 2019 Jan 22; 321:256

A Low–Free-Sugar Diet Improves Nonalcoholic Fatty Liver Disease

Limiting free-sugar intake for 8 weeks significantly reduced hepatic steatosis and serum alanine aminotransferase levels in adolescent boys with NAFLD.

Current treatment recommendations for children with nonalcoholic fatty liver disease (NAFLD) are exercise and a healthy diet. To determine the effect of lowering free-sugar intake in children with NAFLD, investigators conducted a multicenter, randomized, controlled, open-label trial involving 40 boys (aged 11–16 years; 95% Hispanic) with a clinical or pathological diagnosis of NAFLD and evidence of active disease. Participants received an 8-week course of either a study-provided low–free-sugar diet (<3% of calories as sugar) or a usual diet. The primary outcome was change in hepatic steatosis.

Free-sugar intake declined more with the study diet than with the usual diet (11% to 1% vs. 14% to 9%; $P<0.001$), as did hepatic steatosis (25% to 17% vs. 21% to 20%; $P<0.001$). Serum levels of alanine aminotransferase, aspartate aminotransferase, and g-glutamyl transpeptidase also declined significantly more with the study diet than with the usual diet. Serum measures of insulin resistance did not change significantly with the study diet. Mean body weight declined by 1.4 kg with the study diet and increased by 0.6 kg with the usual diet ($P=0.002$).

COMMENT: A very low free-sugar diet produced impressive improvements in hepatic steatosis and liver function in only 8 weeks. The rigor and tight study control of the diet is unlikely to be attained and sustained in daily living. Nonetheless, we should recommend a low-sugar diet for patients with NAFLD, especially one that avoids sugared beverages and juices.

CITATION(S): Schwimmer JB et al. Effect of a low free sugar diet vs usual diet on nonalcoholic fatty liver disease in adolescent boys: A randomized clinical trial. JAMA 2019 Jan 22; 321:256. (https://doi.org/10.1001/jama.2018.20579)

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Obstet Gynecol 2019 Feb; 133:343.

Fingerstick Blood Samples for Laboratory Assay of Fertility Hormones: A Key Advance?

The ability to measure hormone levels in reconstituted fingerstick samples will enhance testing's flexibility.

Hormone testing, a linchpin of reproductive health care, relies on venipuncture to obtain blood samples. Fingerstick sampling is more convenient — but is it accurate? In an industry-sponsored study, researchers compared samples collected contemporaneously by venipuncture and fingerstick from 130 women (age range, 18–40) on menstrual cycle day 3. Fingerstick samples were reconstituted after drying on filter paper at collection. All samples were measured for anti-müllerian hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, testosterone, thyroid-stimulating hormone, and free thyroxine using standard commercially available immunoassays.

The correlation between venipuncture and fingerstick samples ranged from 0.99 to 1.00 for each hormone.

COMMENT: This study documents the efficacy of utilizing fingerstick blood samples to measure several key reproductive hormones. The approach provides the flexibility to allow patients to collect samples at home and mail them in for measurement. If broader experience verifies these promising findings, it will reflect a key advance in laboratory testing. However, if companies start suggesting that women collect their own samples for measurement even before seeing a provider, reproductive counselling and treatment will become more challenging.

CITATION(S): Burke EE et al. Concordance of fingerstick and venipuncture sampling for fertility hormones. Obstet Gynecol 2019 Feb; 133:343. (https://journals.lww.com/greenjournal/Abstract/2019/02000/Concordance_of_Fingerstick_and_Venipuncture.15.aspx)

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JAMA Oncol 2018 Dec 1; 4:1700

Are Circulating Tumor Cells Predictive of Late Recurrence of ER-Positive Breast Cancer?

The presence of CTCs 5 years after diagnosis was associated with a 13-fold higher risk for recurrence.

To determine if the presence of circulating tumor cells (CTCs) in the blood can predict late recurrence of ER-positive breast cancer, investigators conducted a secondary analysis of a prior randomized, double-blind, phase III trial (E5103) involving women with high-risk HER2-positive, node-negative or node-positive disease who received doxorubicin and cyclophosphamide followed by paclitaxel, with or without bevacizumab. A total of 547 patients in the E5103 study were eligible to participate in the present secondary analysis (EL112) if they were free from recurrence 4.5 to 7.5 years after enrollment in E5103.

A CTC assay result was positive (≥1 CTC/7.5 mL of blood) for 18 (5.1%) of 353 patients with ER-positive disease; 23 (6.5%) of 353 patients had a clinical recurrence. Recurrence rates in the CTC-positive and CTC-negative groups were 21.4% and 2.0%, respectively. In a multivariate analysis, a positive CTC assay result was associated with a 13.1-fold higher risk for recurrence. Of 23 patients with recurrence, 30.5% had a positive CTC assay result at a median of 2.8 years before clinical recurrence.

COMMENT: Identifying which patients are at late risk for recurrent disease may lead to strategies that include prolonged duration of endocrine therapy in ER-positive disease or alternative systemic therapies. CTC analysis, circulating tumor DNA assessment, or molecular assays that are currently available or in development may offer clinicians some insight into the long-term risks that individual patients face.

CITATION(S): Sparano J et al. Association of circulating tumor cells with late recurrence of estrogen receptor–positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 2018 Dec 1; 4:1700. (https://doi.org/10.1001/jamaoncol.2018.2574)

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JAMA Pediatr 2018 Dec 28

Intranasal Ketamine Noninferior to Intranasal Fentanyl for Pediatric Pain

Ketamine caused more adverse events, but they were mild and transient.

Intranasal ketamine has been compared with intranasal fentanyl for pain reduction in the emergency department, but previous studies had important limitations.

Researchers randomized 90 patients aged 8–17 years presenting to one pediatric hospital's emergency department with moderate-to-severe pain from an acute limb injury to receive either intranasal ketamine (1.5 mg/kg) or intranasal fentanyl (2 mcg/kg). The primary outcome was the difference between groups in mean pain reduction on the visual analog scale (range, 1–100 mm) from baseline to 30 minutes after treatment.

Mean pain reduction was similar between groups at 30 minutes (ketamine, −31 mm; fentanyl, −32 mm); ketamine was shown to be statistically noninferior. Rescue analgesia rates were similar between groups, but significantly more patients receiving ketamine experienced at least one adverse event (77% vs. 31%; relative risk, 2.5). All adverse events were classified as mild and transient, the most frequent being drowsiness, dizziness, and unpleasant taste.

COMMENT: Intranasal ketamine has now been studied head to head with intranasal fentanyl in at least three randomized trials, and all have shown ketamine to be noninferior for pediatric pain control when used in subdissociative doses. Side effects are common but mild, making intranasal ketamine a reasonable choice for management of moderate-to-severe pain in the pediatric emergency department, particularly when opioids may be less appropriate (due to tolerance, allergy, or poor opioid sensitivity).

CITATION(S): Frey TM et al. Effect of intranasal ketamine vs fentanyl on pain reduction for extremity injuries in children: The PRIME randomized clinical trial. JAMA Pediatr 2018 Dec 28; [e-pub]. (https://doi.org/10.1001/jamapediatrics.2018.4582)

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CMAJ 2019 Jan 21; 191:E69

Caring for Youth with Gender Dysphoria

This review provides primary care providers with a practical overview of definitions, resources, and management strategies for adolescents with gender dysphoria.

Pediatricians may feel ill-equipped to care for the growing and vulnerable group of children and adolescents requesting care for gender dysphoria — the distress experienced when there is discordance between gender identity and gender assigned at birth. These authors reviewed relevant articles published between 1950 and 2018 to provide guidance for primary care providers. Among the key points:

- The authors endorse gender-affirming care (an approach that "does not view gender variance as pathological").
- Patients and families look to providers for advice on when to initiate pubertal blockade and other aspects of medical management but may also seek guidance on the timing of social transitioning, including change of name and pronouns.
- Guidelines from professional societies advocate not suppressing puberty before spontaneous Tanner II development, in some cases to confirm a diagnosis of gender dysphoria, and to extend the time for decision making before initiation of gender-affirming hormone therapy. However, this point is debated and its impact on bone accrual and other health outcomes is unclear.

COMMENT: This paper compiles evidence for managing gender dysphoria and provides helpful talking points for pediatricians who struggle to understand both the medical and social issues that arise. It also provides definitions of common terms and a list of available resources. Shared decision making among the patient, family, and care providers around decisions for hormone therapy is ideal, and pediatricians can provide invaluable guidance in this process.

CITATION(S): Bonifacio JH et al. Management of gender dysphoria in adolescents in primary care. CMAJ 2019 Jan 21; 191:E69. (https://doi.org/10.1503/cmaj.180672)

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Neurology 2018 Dec 28

Nerve Ultrasound as a Diagnostic Tool in Peripheral Neuropathies

Nerve ultrasound was a reproducible diagnostic test in a prospective multicenter analysis.

Peripheral nerve ultrasound is a relatively new technique for the diagnosis of peripheral nerve disorders. Although much of the experience has been in the context of entrapment neuropathies, a role has been reported for ultrasound in diagnosing other types of neuropathies such as hereditary, immune-mediated, infectious, and axonal neuropathies. The objective of this prospective, systematic, multicenter study was to determine interobserver variability of nerve ultrasound in peripheral neuropathies (PNs).

Twenty patients with acquired chronic demyelinating or axonal polyneuropathy and 10 healthy controls were enrolled at 3 different centers. Experienced sonographers blinded to clinical information and other tests conducted an extensive protocol that included brachial plexus, median, ulnar, fibular, tibial, and sural nerves. Measurement of nerve size was performed. Differences between measurement made by different investigators were small. Brand of sonographic device and hospital site did not contribute to interobserver variability. Ultrasound classification of nerve enlargement was generally good to excellent in the arms but poor to moderate in the legs.

COMMENT: This study shows that interobserver variability of sonographic nerve size is limited. Nerve ultrasound may add complementary information to neurophysiologic studies in the diagnostic workup of peripheral neuropathies and contribute to the understanding of the intersection between structure and function in PNs. Although this was a small study, ultrasound is a reproducible tool, that in time, it may prove to be useful in the diagnosis of neuropathies, with applications in clinical practice and research.

CITATION(S): Telleman JA et al. Nerve ultrasound: A reproducible diagnostic tool in peripheral neuropathy. Neurology 2018 Dec 28; [e-pub]. (https://doi.org/10.1212/WNL.0000000000006856)

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N Engl J Med 2019 Jan 24; 380:389

Levodopa Is Safe but Not Disease Modifying

A comparison of early versus delayed start over 80 weeks shows no difference in Parkinson disease outcomes.

Levodopa remains the single best treatment for Parkinson disease (PD). Whether levodopa has a disease-modifying effect remains unknown. A multicenter, double-blind, placebo-controlled, delayed start trial compared the effects of "early-start" levodopa (100 mg 3 times daily) plus carbidopa (25 mg 3times daily) for 80 weeks versus "delayed-start" levodopa for 40 weeks after receiving placebo for 40 weeks. Mean change from baseline to week 80 in the total Unified Parkinson's Disease Rating Scale (UPDRS) score was the primary outcome.

There were 445 patients randomly assigned. The change in UPDRS score from baseline to week 80 was not significantly different between early and delayed start (early start, −1.0±13.1 points; delayed start, −2.0±13.0 points; difference, 1.0 point. Rates of PD progression, dyskinesia, and motor fluctuations were no different between groups. Although 39% of the delayed-start group received levodopa in the first 40 weeks, a per-protocol analysis also showed no difference in the primary outcome between the groups.

COMMENT: Levodopa remains the most important and effective treatment for Parkinson disease, and its introduction to the PD armamentarium has undoubtedly improved quality of life and reduced morbidity and mortality. The current well-designed, well-executed study addresses the question raised in previous studies of whether levodopa might be neuroprotective. It is not. The current study also bolsters our confidence that levodopa is safe even in early PD and that patients and doctors should not fear prescribing it.

CITATION(S): Verschuur CVM et al. Randomized delayed-start trial of levodopa in Parkinson's disease. N Engl J Med 2019 Jan 24; 380:315. (https://doi.org/10.1056/NEJMoa1809983)

Bressman S and Saunders-Pullman R. When to start levodopa therapy for Parkinson's disease. N Engl J Med 2019 Jan 24; 380:389. (https://doi.org/10.1056/NEJMe1814611)

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Endoscopy 2019 Jan 11

Four-Liter Polyethylene Glycol Bowel Preparation: Still the One

Low-volume prep was associated with worse participation in screening, bowel preparation quality, and lesion detection compared with standard-volume prep.

Low-volume bowel preparation ("prep") regimens are attractive because they are better tolerated by patients and have comparable effectiveness with standard-volume, 4-liter regimens. However, it is unknown whether low-volume preps are associated with better participation in colonoscopy-based screening programs. To find out, investigators randomized over 13,500 Poland residents to prep regimens of 0.3 L sodium picosulfate with magnesium citrate or standard-volume (4 L) polyethylene glycol (PEG) and then invited them to undergo colonoscopy as part of a population-based screening program. Results were as follows:

- Participation rates were not significantly different between groups (16.6% for low-volume vs. 15.5%).
- Participation was more likely in men and those living close to the endoscopy center or in affluent areas.
- Compliance was better with the standard-volume prep (97% vs. 95%).
- Adequate bowel prep was less frequent in the low-volume group overall (79% vs. 86%) and in the proximal colon (80% vs. 87%).
- Adenoma and advanced adenoma detection were similar, but the low-volume group had lower advanced adenoma detection in the proximal colon and lower advanced serrated polyp detection overall and in the proximal colon.
- Nearly 39% of patients did not use split regimens, but the proportion was similar between groups.

COMMENT: Because of the pragmatic health-services design of this randomized, controlled trial, patients were not aware they were participating. Thus, the finding of similar participation in screening is less surprising, and important outcomes such as tolerability and willingness to repeat could not be assessed. Nevertheless, the findings of worse prep quality and lesion detection with the low-volume option are striking. It remains to be seen whether these findings are attributable to a class effect or specific to the agent used in this study, but for now 4-liter PEG remains the gold standard.

CITATION(S): Pisera M et al. The impact of low- versus standard-volume bowel preparation on participation in primary screening colonoscopy: A randomized health services study. Endoscopy 2019 Jan 11; [e-pub]. (https://www.thieme-connect.com/products/ejournals/pdf/10.1055/a-0748-5479.pdf)

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Obstet Gynecol 2019 Jan; 133:27

Rates of Syphilis in Pregnancy Are Rising

Nonetheless, half of pregnant women with syphilis report no risk factors.

Because congenital syphilis is a serious but preventable condition, all pregnant women are routinely tested for syphilis at the initial prenatal visit with a recommendation to retest high-risk women during the third trimester.

CDC data show that the number of pregnant women with syphilis increased from 1561 to 2508 between 2012 and 2016. However, only 51% of pregnant women with syphilis reported having a risk factor, suggesting that individual history is

not an accurate predictor of a positive test. The most common risk factors were prior sexually transmitted diseases (STDs; 43%) and more than one sexual partner (30%) within the past year.

COMMENT: Women may not disclose sexual or drug-related risk factors, potentially undermining the ability of such factors to predict syphilis infection. However, STD transmission depends on both partners' behavior, so individual behavior has limited ability to predict STD status. The rise in syphilis among pregnant women reflects a generalized syphilis epidemic in the U.S. (with the largest increases among men who have sex with men). Forthcoming strategies are likely to include routinely testing pregnant women during the third trimester and at delivery. CDC guidelines address treatment of syphilis diagnosed during pregnancy.

CITATION(S): Trivedi S et al. National trends and reported risk factors among pregnant women with syphilis in the United States, 2012–2016. Obstet Gynecol 2019 Jan; 133:27. (https://doi.org/10.1097/AOG.0000000000003000)

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Walgreens to Pay $269 Million on Claims It Overcharged Federal Programs

Walgreen's Boots Alliance has agreed to pay more than $269 million to settle federal and state lawsuits that accused it of overbilling federal healthcare programs. Two separate settlements were approved. In the first settlement, Walgreens agreed to pay $209.2 million to the U.S. and several state governments for improperly billing Medicare, Medicaid, and other programs for hundreds of thousands of insulin pens it dispensed to program beneficiaries who did not need them. In the second settlement, Walgreens agreed to pay $60 million to settle claims that it overbilled Medicaid by failing to disclose and charge the lower drug prices it offered the public through a discount program.
https://www.wsj.com/articles/walgreens-to-pay-269-million-on-claims-it-overcharged-federal-programs-11548204714

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