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Brain 2019 Sep 1; 142:2800

Cognitive Effects of Cannabis in Multiple Sclerosis

What effect does discontinuation of cannabis have on cognition in patients with MS?

Prior research has suggested that cannabis can affect cognitive function in patients with multiple sclerosis (MS). Investigators recruited 40 patients with MS who used cannabis (via smoking, vaping, or ingestion) starting after their MS diagnosis and had global cognitive impairment and randomized them to cannabis withdrawal (CW) or cannabis continuation (CC). Cognitive testing and brain functional MRI (fMRI) were performed at baseline and 28 days.

Participants used the drug an average of at least four times per week. At baseline, performance on the Brief Repeatable Neuropsychological Battery was similar between the two groups. On retesting, the CW group improved in all cognitive domains, whereas the CC group did not change. fMRI demonstrated no between-group differences at baseline but higher activations in four brain regions in the CW group than in the CC group at 28 days.

COMMENT: Cannabis use is growing among patients with MS and other neurologic diseases. MS itself often causes cognitive issues, including decreased short-term memory, processing speed, multitasking, and word finding. This study demonstrates that, in patients with MS and cognitive deficits, cannabis withdrawal is associated with improvements on

cognitive testing and with greater brain activation by fMRI. Patients should be counseled on this effect when discussing the pros and cons of medical marijuana.

CITATION(S): Feinstein A et al. Coming off cannabis: A cognitive and magnetic resonance imaging study in patients with multiple sclerosis. *Brain* 2019 Sep 1; 142:2800. (<https://doi.org/10.1093/brain/awz213>)

JAMA Netw Open 2019 Sep 4; 2:e1911944

To Improve Sleep Duration in Teens, Combine Biology with Psychotherapy

Early morning light flashes during sleep plus cognitive-behavioral therapy improved teens' sleep patterns and duration.

Short sleep duration in teenagers (retiring late and rising early for school) is driven by both biological rhythms and psychological difficulty and causes cognitive and emotional difficulties. Researchers conducted a two-phase, randomized, controlled trial to improve sleep initiation and total sleep duration in 9th to 12th graders with self-reported sleep difficulties.

All participants were encouraged to retire an hour earlier. In phase one, 72 participants received 4 weeks of brief light flashes every 20 seconds or sham light during the last 3 hours of sleep. Students in phase one reported that light flashes were noticed or were sleep-disturbing. Thus, in phase two, 30 students received 4 weeks of light flashes or sham light for the last 2 hours of sleep, combined with 4 weekly sessions of cognitive-behavioral therapy (CBT; psychoeducation, sleep hygiene, stimulus control, motivational interviewing).

Light therapy alone was ineffective in phase one but when combined with CBT in phase two moved sleep initiation 50 minutes earlier, lengthened sleep by 43 minutes, and increased subjective evening sleepiness, compared with sham light. Phase-two participants did not report that light was noticed or disturbed their sleep.

COMMENT: This elegant study illustrates how biologically driven “eveningness” sleep patterns and nonbiological difficulties in going to sleep early enough in sleep-deprived teens weaken their abilities to alter their eveningness patterns. CBT alone cannot override the biological “wake” signal that likely occurs when teens attempt to retire earlier. Providing phototherapy during sleep removes problems with teens' treatment adherence and motivation, but CBT is still required to get teens to go to sleep earlier. This intervention needs to be replicated. The novel light source needs to be commercialized but has the potential to improve sleep in sleep-deprived teens and, by implication, improve cognitive and emotional problems due to inadequate sleep.

CITATION(S): Kaplan KA et al. Effect of light flashes vs sham therapy during sleep with adjunct cognitive behavioral therapy on sleep quality among adolescents: A randomized clinical trial. *JAMA Netw Open* 2019 Sep 4; 2:e1911944. (<https://doi.org/10.1001/jamanetworkopen.2019.11944>)

Pediatrics 2019 Oct 10

New Links Between Autism and Congenital Heart Disease

Children with autism showed particularly high rates of atrial and ventricular septal defects.

Developmental delays are estimated to affect about half of children with congenital heart disease (CHD), but links between autism and CHD are difficult to study because of the rarity of both conditions. To address this, researchers used a very large military health system database to examine the records of tens of thousands of children.

Autism cases (8760 children) were defined as children who had ICD-9 diagnostic codes of autism over two or more clinical encounters. These children were each matched with three controls (totaling 26,280 children) in the database by age, sex, date of birth, and enrollment time frame. Cases and controls were then reviewed for 54 different ICD-9 codes for CHD and related surgical procedures.

After adjustment for confounders such as prematurity and known genetic syndromes, children with autism had 33% higher odds of having CHD compared with controls. Associations were strongest for atrial septal defect (ASD; odds ratio, 1.97) and left heart obstructive lesion (OR, 1.42), as well as ventricular septal defect (VSD; OR, 1.28). Other CHDs — including atrioventricular septal defects, conoventricular defects, anomalous pulmonary venous return, and Ebstein anomaly — were not associated with autism.

COMMENT: Regardless of whether these links between autism and certain types of CHD are due to common genetic causes or cerebral hypoperfusion in utero or during infancy, developmental surveillance in this higher-risk population is important. Many hospitals provide CHD neurodevelopmental follow-up, but this may not cover children with minor ASDs and VSDs. Over and above language development, primary care clinicians may want to ask about social problems such as difficulty making friends, difficulties with transitions, rigid behavior, and repetitive mannerisms. Any parent or teacher concerns warrant referral for diagnostic evaluation.

CITATION(S): Sigmon ER et al. Congenital heart disease and autism: A case-control study. *Pediatrics* 2019 Oct 10; [e-pub]. (<https://doi.org/10.1542/peds.2018-4114>)

N Engl J Med 2019 Oct 17; 381:1547.

Long-Term Benefit of Early Statin Therapy for Familial Hypercholesterolemia

Improved low-density lipoprotein levels and reduced cardiovascular event risk were shown after 20 years of statin treatment in children with FH.

The long-term benefit of initiating early statin therapy in children with familial hypercholesterolemia (FH) is unknown. Now, researchers report outcomes 20 years after statin therapy initiation at ages 8 to 18 years (mean age, 14 years) in 184 patients with FH. Mean age at follow-up was 32 years. Comparison groups were 77 unaffected siblings and 156 affected parents.

At 20-year follow-up, results were as follows:

- Most (79%) of the participants with FH reported still taking statins.
- Mean LDL cholesterol level was 161 mg/dL (down from 237 mg/dL at study start) compared with 121 mg/dL in unaffected siblings.
- Mean progression of carotid artery intima-media thickness was not different between participants with FH and their unaffected siblings.
- Among affected parents, 26% had a cardiovascular event prior to age 40 years, while 99% of the patients who began early statin therapy were free of cardiovascular events after 20 years of therapy.
- One participant with FH who discontinued statin therapy had an episode of angina pectoris requiring an intervention.
- Seven percent of affected parents died before age 40 years. No cardiovascular deaths occurred in the study group starting statins as children.

COMMENT: These data provide convincing evidence of the value of early statin therapy in children with FH. A family history of FH should alert us to screen our patients for hypercholesterolemia at around age 8 years and initiate statin therapy as soon as hyperlipidemia is found.

CITATION(S): Luirink IK et al. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med* 2019 Oct 17; 381:1547. (<https://doi.org/10.1056/NEJMoa1816454>)

Pediatrics 2019 Oct; 144:e20192528.

New ADHD Clinical Practice Guidelines

Much is unchanged from prior guidelines, but there is a new emphasis on comorbid conditions and practice implementation.

Sponsoring Organization: The American Academy of Pediatrics (AAP)

Background

AAP guidelines for managing attention-deficit/hyperactivity disorder (ADHD) in children 4 to 18 years of age, previously revised in 2011, have now been updated based on a review of the literature from 2011 to 2016. This update documents that around 7% to 15% of children have ADHD and that the disorder is twice as common in boys than in girls. It also shows that the most common comorbid conditions are language and learning disorders, that boys are more likely than girls to have externalizing behaviors (aggression, disruptive behavior), and that girls more likely than boys to have internalizing symptoms (anxiety and depression).

Key Recommendations

- Providers should initiate ADHD evaluations for children presenting with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.
- Diagnoses should be based on DSM-5 criteria across more than one setting by gathering rating scales from parents, guardians, teachers, other school personnel, and mental health clinicians.
- For children younger than 4 years of age with ADHD symptoms, referral for parent behavioral management training (PBMT) should be made.
- Providers should screen for comorbid conditions — such as anxiety, depression, disruptive behavior, substance use, developmental conditions, and physical conditions — and manage them directly or with referrals to subspecialists.
- Management using a chronic care/medical home model is recommended, including coordination of care with school personnel or therapists.
- Treatment should include PBMT and school supports for 4- to 6-year-olds; PBMT, school supports, and medication for 6- to 12-year-olds; and school supports, medications, and transition supports for >12-year-olds. Teens should be screened for substance abuse.

COMMENT: Although much is the same about these guidelines, it is worth reading the accompanying process-of-care algorithm to facilitate their implementation in your practice. I find that the most crucial processes are identifying skilled local PBMT providers, coordinating care with teachers, and managing comorbid mood and learning issues.

CITATION(S): Wolraich ML et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2019 Oct; 144:e20192528. (<https://doi.org/10.1542/peds.2019-2528>)

Surgical Management of Pelvic Organ Prolapse Might Not Require Removing the Uterus

A uterine sparing technique, sacrospinous hysteropexy, was associated with low likelihood of recurrent symptoms or prolapse.

To test the long-standing thesis that successful surgical treatment of women with pelvic organ prolapse (POP) requires uterine removal, investigators randomized 204 women with POP (mean age, 62) to vaginal hysterectomy (VH) or a uterine sparing technique, sacrospinous hysteropexy (SH). In the VH group, the apex of the vagina was attached to the uterosacral ligaments with sutures; in the SH group, the posterior side of the cervix was attached to the right sacrospinous ligament. In both groups, repair of vaginal wall defects was performed if indicated.

At 5 years' follow-up, a composite measure of surgical success (no prolapse of vaginal tissue beyond the hymen, absence of bulge symptoms, and no repeat surgery or pessary use) occurred in 76% and 87% of women in the VH and SH groups, respectively (a statistically significant difference). Prolapse of the vaginal apex causing bothersome bulge symptoms or necessitating repeat surgery occurred in 8% and 1% of the women in the VH and SH groups, respectively.

COMMENT: This study demonstrates that vaginal hysterectomy is not a necessary element of successful POP surgery. Conservation of the uterus — performed by attaching the posterior cervix to the sacrospinous ligament — provides a durable cure for prolapse of the vaginal apex, reducing the postoperative likelihood of recurrent bothersome bulge symptoms or repeat surgery.

CITATION(S): Schulten SFM et al. Sacrospinous hysteropexy versus vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage 2 or higher: Observational follow-up of a multicentre randomised trial. *BMJ* 2019 Sep 10; 366:l5149. (<https://doi.org/10.1136/bmj.l5149>)

Consensus Statement Says Testosterone Therapy Is Warranted in Women with Hypoactive Sexual Desire Disorder

Further research applicable to the general population of women remains a priority.

Although testosterone administration has no definitive indications in women — and FDA-approved testosterone-containing products for women are lacking — clinicians have prescribed various preparations to alleviate a variety of symptoms in women despite uncertain benefits and risks. A task force representing several international societies has developed a position statement based on findings from randomized controlled trials lasting ≥ 12 weeks.

Key points include:

- Testosterone therapy is indicated only for postmenopausal women with hypoactive sexual desire disorder (HSDD), with evidence suggesting moderate therapeutic effects.
- Doses yielding premenopausal physiologic blood levels of testosterone should be used.
- Although available data have not documented severe adverse events, the long-term safety of testosterone therapy has not been established.
- The diagnosis of HSDD involves complete clinical assessment but does not entail measurement of serum testosterone concentrations.
- In the absence of any approved product for women, products approved for men can be used at doses appropriate for premenopausal women (with monitoring of serum testosterone concentrations).
- Compounded testosterone preparations are not recommended.

COMMENT: Above all, this consensus statement points to the current limited use of exogenous testosterone in women: The recommendations are limited to postmenopausal women with documented HSDD. Additional research with broader applicability should be foremost.

Andrew M. Kaunitz, MD, is an author of this consensus statement and Editor-in-Chief of *NEJM Journal Watch Women's Health* but had no role in selecting or summarizing this article.

CITATION(S): Davis SR et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab* 2019 Oct 1; 104:4660. (<https://doi.org/10.1210/jc.2019-01603>)

JAMA Netw Open 2019 Aug; 2:e1910154.

Does Menopausal Hormone Therapy Prevent Loss of Muscle Mass?

Probably not: Analysis suggests minimal effect of HT in maintaining lean body mass.

Age-related loss of muscle mass (sarcopenia) is an important predictor of impaired mobility. Because declining estrogen levels during the menopausal transition are associated with accelerated sarcopenia, menopausal hormone therapy (HT) has been proposed as a strategy to prevent this loss of lean body mass (LBM). Investigators identified 12 randomized trials of menopausal HT in which changes in LBM were assessed. Among 4474 participants, mean age was 58 and median follow-up was 2 years.

Loss of LBM in HT recipients was 0.06 kg less than that in nonrecipients. This small between-group difference associated with HT was not statistically significant and not thought by the investigators to be clinically relevant for the average postmenopausal woman.

COMMENT: As the authors note, sarcopenia in menopausal women is associated with diminished physical activity and protein intake — and HT's lack of substantive efficacy in preserving LBM may reflect that it does not directly address these declines. While the authors speculate that HT might be useful in preventing sarcopenia in women who enter menopause with deficient LBM, they also point out that HT's impact on LBM has not been assessed in this subgroup. I agree that, in general, while maintenance of LBM is important as women age, strategies other than HT (for example, resistance exercise) should be explored to accomplish this goal.

CITATION(S): Javed AA et al. Association between hormone therapy and muscle mass in postmenopausal women: A systematic review and meta-analysis. *JAMA Netw Open* 2019 Aug; 2:e1910154. (<https://doi.org/10.1001/jamanetworkopen.2019.10154>)

Estrogen-Progestin Therapy Elevates Risk for Breast Cancer — Should This Influence Clinical Practice?

No; benefits will outweigh risks for many menopausal patients who, through discussion of research findings and shared decision making, can make informed choices about HT use.

Hormone therapy (HT) is the most effective treatment for bothersome menopausal vasomotor symptoms. However, after initial publication of findings from the Women's Health Initiative (WHI) randomized clinical trial in 2002, which found that estrogen-progestin therapy (EPT) increased risk for cardiovascular events and breast cancer among women aged 50 to 79 at enrollment (*NEJM Journal Watch Womens Health* Nov 2013 and *JAMA* 2013 Oct 2; 310:1353), use of HT plummeted in the U.S. and globally. Subsequently, the estrogen-alone trial in women with hysterectomy showed that conjugated estrogens (for a median of 7 years) did not increase breast cancer risk. Both regimens raised risk for stroke and

venous thromboembolism but lowered risk for fractures and diabetes. Thus, HT has a complex risk-benefit pattern, with studies suggesting more-favorable profiles in younger than older women.

Although observational studies over the past several decades have linked HT to increased breast cancer risk, the specific associations with HT formulation, route of delivery, and duration have been poorly studied. In a recent meta-analysis ([Lancet Aug 29 2019 \[e-pub\]](#)), investigators used individual participant data from 58 observational studies reported between 1992 and 2018 to quantify the strength of the relation and the roles of these factors in the HT–breast cancer connection.

All systemic HT formulations (including those using oral conjugated equine estrogens or estradiol or transdermal estradiol) were associated with excess risk for breast cancer. Use of EPT was associated with a greater risk for breast cancer than was estrogen-only therapy (ET). Type of progestogen did not appear to affect these associations. Vaginal estrogen was not associated with increased risk. Assuming the reported associations are causal, the authors estimated the absolute risk for breast cancer up to age 70. For never-users of HT and women who initiated EPT at age 50 and continued for 5 years, risks were 6.3% and 8.3%, respectively; the two percentage-point difference indicates one additional breast cancer case per 50 treated women. At 10 years of HT use, risks were approximately twice that at 5 years.

For EPT, both the randomized WHI trial and this new *Lancet* analysis of observational data indicated an increased risk for breast cancer. However, in contrast to the *Lancet* report, the WHI did *not* find that ET (conjugated equine estrogens alone) increased this risk — in fact, risk was significantly reduced after long-term follow-up. Could the excess risk found in observational studies be exaggerated due to inherent limitations of the study design? In observational settings, women using HT tend to undergo mammographic screening more frequently and consistently than nonusers. In contrast, in the WHI trial (and in most randomized trials of HT), both users and nonusers underwent uniformly standardized mammographic screening. Thus, the excess breast cancer risk in observational studies could reflect increased mammographic detection of nonlethal cancers. In addition, breast cancer incidence appears to increase with longer-duration HT use. Accordingly, one advantage that observational studies have over randomized trials (usually limited to 5–7 years of treatment) is their ability to assess extended use. The differences in mammographic screening between users and nonusers of HT are likely to persist and may even increase cumulatively over follow-up.

Wrap-Up

Understandably, women are often concerned about breast cancer risk as they make decisions about HT; however, such decisions should be guided by the big picture. On an absolute scale, many of the risks associated with HT are modest. Furthermore, with 18 years' cumulative follow-up, the WHI's findings on total mortality as well as overall cancer mortality with HT use are reassuring, especially for women younger than 60 ([NEJM Journal Watch Womens Health Oct 2017](#) and [JAMA 2017 Sep 12; 318:927](#)). The largest hazard ratio associated with HT use corresponds to an elevated risk for venous thromboembolism — and using transdermal rather than oral estrogen appeared to attenuate this risk.

For many women, risks associated with HT are offset by reductions in symptoms, improved quality of life, and benefits in other health outcomes, such as fractures. The net effects of HT are most favorable for recently menopausal women who have moderate to severe vasomotor symptoms and low or average risks for breast cancer, cardiovascular disease, and venous thromboembolism. Women at above-average risk for the latter conditions may want to avoid HT and consider nonhormonal options for symptom management. In sum, women deserve reliable information in order to make informed decisions — aligned with their personal preferences — on whether the potential benefits of HT are likely to outweigh the potential risks.

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Prevalence of Chronic Hypertension in Pregnant Women: A Sharp Increase

Rising maternal age has largely driven the upswing, per an observational study using 4 decades of data.

Chronic hypertension is associated with both adverse fetal and maternal outcomes. To determine how chronic hypertension rates in pregnant women have changed from 1970 to 2010, investigators analyzed data from the National Hospital Discharge Survey compiled by the CDC.

The analysis included women with in-hospital deliveries at ages 15 to 40 (>151 million hospitalizations) and with chronic hypertension (according to International Classification of Diseases–8 or 9 codes). Mean prevalence of chronic hypertension was 0.53% in white women and 1.24% in black women. Chronic hypertension was strongly associated with advancing maternal age. Year of delivery was also associated with chronic hypertension; the rate ratio increased until 1990, plateaued for a decade, and then increased again starting in 2000. The rate of chronic hypertension grew by 6% annually; white women had a somewhat higher rate of increase (7%) than black women (4%). According to data from the National Health and Nutrition Examination Survey, chronic hypertension was not linked to secular trends in maternal obesity and smoking.

COMMENT: Unsurprisingly, as maternal age advances, chronic conditions will increase. Hypertension, a commentator notes, is likely an important, preventable, and controllable contributor to the rise in U.S. maternal mortality rates. Despite the study's strengths of a large sample size and analysis of 4 decades of data, greater attention has likely been paid to maternal risk factors (and hence coding) during hospitalizations and delivery in more recent years than previously. Multidimensional interventions are needed to address the prominent disparity between black and white expectant mothers.

CITATION(S): Ananth CV et al. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. *Hypertension* 2019 Sep 9; [e-pub]. (<https://doi.org/10.1161/HYPERTENSIONAHA.119.12968>)

Larsen DM and Tangren JS. Trends in chronic hypertension in pregnancy highlight racial disparities in maternal health. *Hypertension* 2019 Sep 9; [e-pub]. (<https://doi.org/10.1161/HYPERTENSIONAHA.119.13480>)

Gastroenterol Hepatol 2019 Sep 11; S1542-3565(19)30990-5

Pancreatic Enzyme Therapy After Pancreaticoduodenectomy

Supplemental pancreatic enzyme replacement was associated with small gains in weight and nutritional status.

Exocrine pancreatic insufficiency (EPI) can be found in a plethora of patients, including those with chronic pancreatitis or cystic fibrosis as well as those who have undergone roux-en-Y gastric bypass or pancreatic surgery with loss of functional pancreatic parenchyma. The standard treatment for EPI is pancreatic enzyme replacement therapy (PERT).

Investigators have now conducted a multicenter, randomized, double-blind, placebo-controlled trial to assess the effect of PERT on weight gain and nutritional status in 164 EPI patients who had undergone pancreaticoduodenectomy. Patients received 40,000 units of lipase or placebo for three meals a day for 3 months.

Mean weight gain (the primary endpoint) was improved with PERT versus placebo (1.09 kg vs. -2.28 kg; $P<0.001$), as was mean serum levels of prealbumin (10.9 mg/dL vs. 7.8 mg/dL; $P=0.002$). However, the weight gain benefit vanished in the intention-to-treat analysis. The authors therefore concluded that PERT had no significant effect on body weight after pancreaticoduodenectomy.

COMMENT: While I laud the authors for performing this important and well-needed study of PERT to treat EPI following pancreaticoduodenectomy (a very common indication), I have some concerns. First and foremost, the dose of

pancreatic enzymes used (40,000 units of lipase per meal) was quite low, given that most adults require 48,000 to 72,000 units per meal, plus additional doses with snacks. Second, 3 months after pancreaticoduodenectomy may be too short a timeframe to see meaningful improvements in patients, about half of whom in this study had cancer. Although the improvements associated with PERT were shown to be modest, I think that patients with EPI following pancreaticoduodenectomy should be considered for PERT therapy, given the low risk and potential benefits.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Kim H et al. Effects of pancreatic enzyme replacement therapy on body weight and nutritional assessments after pancreatoduodenectomy in a randomized trial. *Clin Gastroenterol Hepatol* 2019 Sep 11; S1542-3565(19)30990-5; [e-pub]. (<https://doi.org/10.1016/j.cgh.2019.08.061>)

Arthritis Care Res (Hoboken) 2019 Sep; 71:1249

Tofacitinib Confers Excess Risk for Herpes Zoster

In patients with rheumatoid arthritis, shingles risk doubled when tofacitinib-treated patients also used glucocorticoids.

Patients with rheumatoid arthritis (RA) often receive therapies that include JAK inhibitors, including tofacitinib (Xeljanz). However, studies have shown excess risk for herpes zoster (HZ) in patients who receive tofacitinib. In this study, researchers used the MarketScan and Medicare databases to determine how risk for shingles varied among 8000 tofacitinib-treated patients, according to concomitant use of methotrexate or glucocorticoids.

Incidence of HZ was lowest among patients who did not take glucocorticoids, regardless of concomitant methotrexate use (≈ 3 cases per 100 patient-years). Incidence of HZ was approximately twofold higher among tofacitinib users who took glucocorticoids, whether or not they also took methotrexate (≈ 6 cases per 100 patient-years). Older age and female sex also were associated with higher risk for HZ, and prior HZ vaccination (with the live attenuated vaccine) was associated with lower risk in a multivariate analysis.

COMMENT: Clinicians should be aware of the association between HZ and JAK inhibitors. The incidence of shingles almost doubles in patients who receive JAK inhibitors and glucocorticoids. In my practice, I aggressively recommend Shingrix vaccination to my RA patients, and this study supports that practice.

CITATION(S): Curtis JR et al. Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. *Arthritis Care Res (Hoboken)* 2019 Sep; 71:1249. (<https://doi.org/10.1002/acr.23769>)
