

6-1-19

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## Question: What is the FDA's current stand on cannabis and cannabis-derived compounds? Part I

**Answer:** The following was released on December 20, 2018 from the FDA. Provided below are excerpts; you are encouraged to read the complete statement that can be found at the website at the end of the statement.

### Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds.

"The Agriculture Improvement Act of 2018 (AIA) changes certain federal authorities relating to the production and marketing of hemp, defined as cannabis (*Cannabis sativa L.*), and derivatives of cannabis with extremely low (less than 0.3 percent on a dry weight basis) concentrations of the psychoactive compound delta-9-tetrahydrocannabinol (THC). These changes include removing hemp from the Controlled Substances Act, which means that it will no longer be an illegal substance under federal law.

Just as important for the FDA is what the law *didn't* change: Congress explicitly preserved the agency's current authority to regulate products containing cannabis or cannabis-derived compounds. In doing so, Congress recognized the agency's important public health role with respect to all the products it regulates. This allows the FDA to continue enforcing the law to protect patients and the public while also providing potential regulatory pathways for products containing cannabis and cannabis-derived compounds.

This increasing public interest in these products makes it even more important for the FDA to clarify its regulatory authority over these products. In short, we treat products containing cannabis or cannabis-derived compounds as we do any other FDA-regulated products — meaning they're subject to the same authorities and requirements as FDA-regulated products containing any other substance. This is true regardless of the source of the substance.

In view of the proliferation of products containing cannabis or cannabis-derived substances, the FDA will advance new steps to better define our public health obligations in this area.

In particular, we continue to be concerned at the number of drug claims being made about products not approved by the FDA that claim to contain CBD or other cannabis-derived compounds. Among other things, the FDA requires a cannabis product (hemp-derived or otherwise) that is marketed with a claim of therapeutic benefit, or with any other disease claim, to be approved by the FDA for its intended use before it may be introduced into interstate commerce. Cannabis and cannabis-derived products claiming in their marketing and promotional materials that they're intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases are **considered new drugs or new animal drugs** and must go through the **FDA drug approval process for human or animal** use before they are marketed in the U.S. (Emphasis added)

We'll take enforcement action needed to protect public health against companies illegally selling cannabis and cannabis-derived products that can put consumers at risk and are being marketed in violation of the FDA's authorities. The FDA has sent warning letters in the past to companies illegally selling CBD products that claim to prevent, diagnose, treat, or cure serious diseases, such as cancer. Some of these products were in further violation of the FD&C Act because they were marketed as dietary supplements or because they involved the addition of CBD to food."

**Editor's Note: The excerpts in answer to this question will be continued next week.**

<https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys>

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## Hip Fracture After Menopause Was Associated with High Intake of Vitamins B<sub>6</sub> and B<sub>12</sub>

Women who took high doses of both B<sub>6</sub> and B<sub>12</sub> had 50% higher risk than those who had low intake.

In prior studies of B<sub>6</sub> and B<sub>12</sub> supplementation, researchers reported excess hip fracture risk among supplement users. To confirm these results in a large population, investigators used data from the Nurses' Health Study. They assessed more than 75,000 postmenopausal women at baseline and every 2 years from 1984 through 2014 (mean follow-up, 21 years) for a wide range of clinical variables; dietary analyses were performed every 4 years.

Median intakes (dietary plus supplements) of vitamins B<sub>6</sub> and B<sub>12</sub> were 3.6 mg/day and 12.1 µg/day, respectively. About 9% of the population had high intake of B<sub>6</sub> (≥35 mg/day) and about 24% had high intake of B<sub>12</sub> (≥20 µg/day). Nonpathological hip fractures occurred in 2300 participants. High intake of both B<sub>6</sub> and B<sub>12</sub> was associated with nearly double the crude incidence of hip fracture compared with low intake of both vitamins (19 vs. 10 per 10,000 person-years) but statistical adjustment attenuated the relative risk to about 1.5.

**COMMENT:** We don't have a known mechanism by which B<sub>6</sub> or B<sub>12</sub> would cause fractures, so inferring a causal association would be purely speculative. However, nutritional supplements do not seem to benefit people without diagnosed nutritional deficiencies, and excessive intake of some vitamins and minerals can be harmful. Therefore, this study reminds us to question patients explicitly about nutritional supplement use and counsel them accordingly.

**CITATION(S):** Meyer HE et al. Association of high intakes of vitamins B<sub>6</sub> and B<sub>12</sub> from food and supplements with risk of hip fracture among postmenopausal women in the Nurses' Health Study. *JAMA Netw Open* 2019 May 3; 2:e193591. (<https://doi.org/10.1001/jamanetworkopen.2019.3591>)

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## Charcoal Toothpaste May Do Harm and Not Much Good

Charcoal toothpaste may be having a moment as a go-to brightening and whitening tool, but some dentists say these products might actually damage tooth enamel. At a minimum, any claims charcoal toothpaste marketers make have no scientific evidence behind them, the authors of a paper in the *British Dental Journal* warned. "The evidence highlighting any potential benefits of charcoal toothpaste over regular toothpaste is severely lacking," said Dr. Joseph Greenwall-Cohen of the University of Manchester Dental School in the UK, one of the coauthors.

<https://www.reuters.com/article/us-health-toothpaste-charcoal/charcoal-toothpaste-may-do-harm-and-not-much-good-idUSKCN1SM2M3>

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## Sugary Beverage Consumption and All-Cause Mortality

In a longitudinal study, drinking a lot of sugar-sweetened beverages and 100% fruit juice was not healthful.

High consumption of sugar-sweetened beverages is associated with coronary heart disease (CHD) risk factors. Using dietary recall and death reports from a U.S. longitudinal cohort study, researchers investigated the effect of "sugary beverages" on CHD-related and all-cause mortality. More than 13,000 participants (mean age, 64; 70% overweight or obese; 50% current or former smokers), without baseline CHD, stroke history, or type 2 diabetes, were assessed.

Mean sugary beverage consumption was 8.4% of total calories, split roughly equally between sugar-sweetened beverages and 100% fruit juice (which are essentially identical in sugar content). During a median 6-year follow up, 1000 deaths from any cause and 168 CHD-related deaths occurred. The authors conducted a wide range of analyses in which they adjusted for many sociodemographic, behavioral, and dietary risk factors. For example, high consumption of sugary beverages ( $\geq 10\%$  of total calories as sugar) compared with low consumption ( $< 5\%$  of total calories) was associated with 44% higher risk for CHD-related death. The relative risk for all-cause mortality increased by 24% for every additional 12-ounce consumption of 100% fruit juice.

**COMMENT:** Elevated mortality appears to be associated with 100% fruit juice as well as sugar-sweetened beverages. One possible reason is that their similar sugar content has the same adverse metabolic effects on lipids and central fat deposition. Another explanation is that sugary beverages, including fruit juice, could replace calories from foods with higher nutritional value.

**CITATION(S):** Collin LJ et al. Association of sugary beverage consumption with mortality risk in US adults: A secondary analysis of data from the REGARDS study. *JAMA Netw Open* 2019 May 3; 2:e193121. (<https://doi.org/10.1001/jamanetworkopen.2019.3121>)

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*Ann Intern Med* 2019 Apr 23

## Metformin Might Help Maintain Weight Loss Long Term

*After 15 years follow-up, both patients who received metformin and patients who received intensive lifestyle modification had sustained weight loss.*

Although metformin has short-term weight-loss benefits, less is known about its ability to sustain long-term weight loss. Using data from the Diabetes Prevention Program Outcomes Study (which involved  $> 2700$  prediabetic, obese or overweight participants who were randomized to receive metformin, intensive lifestyle intervention, or placebo; *NEJM JW Gen Med* Mar 15 2002 and *N Engl J Med* 2002; 346:393; *NEJM JW Gen Med* Jan 15 2010 and *Lancet* 2009; 374:1677), investigators evaluated  $\approx 1000$  participants who had lost at least 5% of their baseline weight within the first year. Twenty-nine percent of the metformin group, 63% of the lifestyle-intervention group, and 13% of the placebo group had lost the weight required to be included in this post hoc analysis.

Participants were followed for 15 years. Sustained weight loss was reported for 56% of the metformin group and for 43% of the lifestyle-intervention group. However, because fewer patients in the metformin group had achieved sufficient weight loss during the first year to be included in the analysis, long-term weight loss was more common in the lifestyle-intervention group than in the metformin group (27% vs. 16%). Both the metformin and lifestyle-intervention groups outperformed the placebo group.

**COMMENT:** How should we apply results from weight-loss interventions in this highly selected population (with few unemployed or low-income participants)? Intensive lifestyle interventions — for motivated patients — might have the greatest likelihood of conferring long-term sustained weight loss. However, metformin might also sustain weight loss longitudinally, especially when preceded by short-term weight loss.

**CITATION(S):** Apolzan JW et al. Long-term weight loss with metformin or lifestyle intervention in the Diabetes Prevention Program Outcomes Study. *Ann Intern Med* 2019 Apr 23; [e-pub]. (<https://doi.org/10.7326/M18-1605>)

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## New Alzheimer-Like Disorder Described

*A working group describes and discusses limbic-predominant age-related TDP-43 encephalopathy as a dementia disorder.*

Limbic-predominant age-related TDP-43 encephalopathy (LATE), a recently recognized encephalopathy, has features of Alzheimer disease but is distinct from it. It's still a disease without an agreed-upon name, according to a *Brain* review.

A working group on LATE describes it as “proteinopathy of advanced age, especially in subjects older than age 80.” The protein has a molecular weight of 43 kilodaltons and usually is found in the cell nucleus, but in LATE, it's also found in the cytoplasm.

The disease brings on “substantial disease-specific cognitive impairment ... of the Alzheimer's type.”

The authors, citing the presence of the proteinopathy in over 20% of people older than 80, say “the public health impact of LATE is likely to be quite significant.”

**COMMENT — NEUROLOGY:** *Jennifer Rose V. Molano, MD*

This consensus statement adds new information on the complexity and heterogeneity of pathological substrates that underlie dementia. As the authors report, in vivo biomarkers for LATE may assist not only in identifying appropriate participants for clinical trials but also in determining the natural history for those with dementia due to this underlying pathology. Because LATE occurs primarily in those over age 80, we need a better understanding of the risk factors for this condition.

**CITATION(S):** Nelson PT et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. *Brain* 2019 Apr 30; [e-pub]. (<https://doi.org/10.1093/brain/awz099>)

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*BMJ* 2019 Apr 29; 365:l1516

## Preeclampsia as a Harbinger of Maternal Renal Disease

*Particularly when it occurs early in gestation, preeclampsia predicts subsequent chronic kidney disease.*

Preeclampsia is a systemic pregnancy-related condition associated with multiple organ system dysfunction, including renal malfunction. Earlier reports suggested excess risk for subsequent renal disease among patients with preeclampsia, but other findings have been inconsistent. Using a nationwide health database, Danish investigators followed a cohort of >1 million pregnant women from 1978 through 2015.

During a mean follow-up of 18.6 years per woman, 3901 cases of chronic renal disease were identified. Risk for subsequent chronic renal disease was more than doubled in women with a history of preeclampsia compared with those delivering at comparable gestational ages without preeclampsia. Among women with a history of preeclampsia associated with delivery at <34 weeks, this risk was elevated 3.9-fold and was highest during the 5 years after a pregnancy (as opposed to decades later).

**COMMENT:** The findings of this large study support the recommendation that women with a history of preeclampsia should be monitored for kidney disease for at least the first 5 years following pregnancy, particularly if preeclampsia

occurred early in pregnancy. Presumably, early detection of deterioration in renal function would facilitate measures to delay progression of kidney disease.

**CITATION(S):** Kristensen JH et al. Pre-eclampsia and risk of later kidney disease: Nationwide cohort study. *BMJ* 2019 Apr 29; 365:l1516. (<https://doi.org/10.1136/bmj.l1516>)

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*Ann Neurol* 2019 May; 85:653.

## **MS Relapses and Long-Term Worsening of Disability**

*A large data set raises questions about the impact of relapses on long-term disability.*

Investigators sought to determine the influence of relapses on disability worsening in patients with multiple sclerosis (MS) according to the Expanded Disability Status Scale (EDSS) and the MS Functional Composite (MSFC), using a single-center clinical database that included annual assessments of patients seen since 2004.

Of 480 patients with relapsing-remitting MS or clinically isolated syndrome, 407 had complete visits through year 5 and 372 through year 10. Worsening EDSS score at the annual visit occurred in 30% of those with a relapse and 23% of those with no identified relapse. At the following confirmation year, EDSS worsening was not different between those with versus those without relapses. Relapses in the first 6 years were unrelated to disability worsening at a median of 11 years, which occurred in 38% of patients with vs. 36% without relapses. Significant (20%) worsening on the 25-foot timed walk occurred in more years with relapses than in years without relapses (9% vs. 6%), as did worsening on the 9-hole peg test (16% vs. 12%), but again, relapses had no long-term effect on walking times or peg-test performance. The paced auditory serial addition test had a nonsignificant association with relapse years (13% vs. 11%) and no long-term association with relapse. More patients with than without an annual relapse had gadolinium-enhancing lesions (47% vs. 25%). A new T2 lesion was not associated with short- or long-term worsening on the EDSS. Brain atrophy was associated with long-term disability and relapse-free progression.

**COMMENT:** Patients with MS appear to worsen long-term regardless of relapses and T2 lesion accumulation. Relapses represent inflammatory events within neurologically eloquent regions of the central nervous system, such as optic nerves, brain stem, and spinal cord. Many affected brain regions do not have a describable symptom but contribute to loss of axons/neurons. Brain atrophy does appear related to worsening, highlighting the neurodegenerative component of this disease and its importance with continued follow-up. Clinicians need to pay careful attention not just to inflammatory activity, but also to the insidious progression of MS.

**CITATION(S):** Cree BAC et al. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol* 2019 May; 85:653. (<https://doi.org/10.1002/ana.25463>)

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*Brain* 2019 Mar 1; 142:633

## **Characterizing Cervical Spine Lesions in Multiple Sclerosis**

*Spinal cord lesions may be diagnostic and prognostic in MS.*

The cervical spine is an eloquent region of central nervous system tissue that is frequently involved in multiple sclerosis (MS). To further characterize the spatial characteristics of MS cervical spine lesions and correlate lesion burden with clinical status, investigators conducted a retrospective, multicenter study involving 642 adult MS patients with primary

progressive MS (PPMS), secondary progressive MS (SPMS), relapsing-remitting MS (RRMS), or clinically isolated syndrome (CIS).

Results were as follows:

- Cervical spine lesions were identified in 99% of PPMS patients, 95% of SPMS patients, 90% of RRMS patients, and 77% of CIS patients.
- Lesion counts were higher in PPMS and SPMS patients than in RRMS patients or CIS patients.
- Lesions in white matter were larger than those in gray matter and were larger in PPMS and SPMS patients than in RRMS or CIS patients.
- Median Expanded Disability Status Scale (EDSS) scores were higher in PPMS and SPMS patients (6.0 for both) than in RRMS patients (2.9) or CIS patients (1.0); 44% of the variance in EDSS scores was explained by the normalized lesion volume in motor tracts.
- Patients with higher EDSS scores had lesions within motor tracts; those with lower EDSS scores had lesions in sensory tracts.
- Lesions were most common in the posterior columns; lesions in the lateral funiculus were associated with more severe disability.

**COMMENT:** Cervical spine lesions are very common, which should aid in the diagnosis of MS due to the greater specificity of spine lesions compared with brain T2 lesions. The spine lesions increase in number and volume as the disease progresses, and lesion volume is a key variable for disability. Careful analysis of cervical-spine lesions may be one consideration in MS diagnosis and prognosis.

**CITATION(S):** Eden D et al. Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. *Brain* 2019 Mar 1; 142:633. (<https://doi.org/10.1093/brain/awy352>)

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*Neurology* 2019 Apr 16; 92:e1811

## **Real-World Comparison of Dimethyl Fumarate and Teriflunomide for Relapsing Multiple Sclerosis**

*A study funded by the Danish MS Society suggests key differences between these oral treatments.*

Few head-to-head studies of multiple sclerosis (MS) treatments are available. To compare efficacy outcomes with dimethyl fumarate (DMF) versus with teriflunomide (TFL), investigators assessed data from the Danish MS Registry. Of 2236 patients, 1469 were on TFL and 767 on DMF. Statistical analyses included a propensity score with multivariable logistic modeling. Average follow-up was 2.0 years.

Adjusted annualized relapses rates were 0.19 for TFL and 0.11 for DMF. Mean Expanded Disability Status Scale score changes were minimal: 0.03 for TFL and -0.02 for DMF. DMF-treated patients were 7% more likely to remain free of 6-month confirmed disability worsening than TFL-treated patients at 4 years. Discontinuation for disease breakthrough was 22% for TFL and 11% for DMF. Discontinuation for adverse events was 18.5% for TFL and 18.0% for DMF.

**COMMENT:** This large, single-country, retrospective, open-label, propensity-adjusted analysis associated DMF with lower relapses rates and a lower incidence of worsening disability than TFL. Treatment discontinuation, whether for efficacy or tolerability, appeared to favor DMF as well. Currently, five oral therapies are available for MS; this study helps to elucidate the difference between two of them in a real-world clinical setting.

Dr. Naismith has received honoraria for consulting/speaking for Biogen and Genzyme.

**CITATION(S):** Buron MD et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. *Neurology* 2019 Apr 16; 92:e1811. (<https://doi.org/10.1212/WNL.00000000000007314>)

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*Clin Gastroenterol Hepatol* 2019 May 8

## **Cholesterol Levels Increase with Tofacitinib Use for Ulcerative Colitis**

*New data confirm elevation of cholesterol but show no increase in cardiovascular events.*

Tofacitinib is a Janus kinase inhibitor recently approved for treating moderate-to-severe ulcerative colitis. A known side effect of this drug class is an elevation in lipid levels. It is unclear whether this elevation is seen in patients taking tofacitinib for ulcerative colitis and, if so, whether it has any clinical consequence.

In an industry-supported study, investigators analyzed lipid concentrations and major adverse cardiovascular events from the known registration trial data. Over 1000 patients with tofacitinib exposure of up to 61 weeks were included. After 8 weeks of treatment, there was greater increase from baseline in total cholesterol, HDL, and LDL levels in patients on tofacitinib versus placebo, and these levels remained elevated through week 61. The mean change in total cholesterol was approximately 35 mg/dL at week 8. The incidence rate for cardiac events was low at 0.24 per 100 person-years, and patients experiencing these events had other cardiovascular risk factors.

**COMMENT;** The safety profile of any new medication is always of great interest to clinicians and patients. This large observational review of registration trial data does show that there is a sustained increase in all components of lipids. A total increase of 35 mg is high, and while this may be alarming to some practitioners and patients, it does not appear that these elevations translate into any meaningful clinical outcomes for the majority of patients. In perspective, as the authors point out, the cardiovascular event rate was 0.24 per 100 for tofacitinib and is 0.51 per 100 for those exposed to anti-tumor necrosis factor agents. Also, the majority of major adverse cardiovascular events occurred in those with multiple risk factors. It remains to be seen who the ideal patient is for this type of therapy.

**CITATION(S):** Sands BE et al. Tofacitinib treatment is associated with modest and reversible increases in serum lipids in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2019 May 8; [e-pub]. (<https://doi.org/10.1016/j.cgh.2019.04.059>)

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*BMJ* 2019 May 14; 365:l1652

## **Hormone Therapy's Range of Effects on Breast Cancer Risk in Transgender Individuals**

*In a Dutch study, breast cancer risk in transgender women was higher than in cisgender men, but lower than in cisgender women; in transgender men, risk was lower than in cisgender women.*

Transgender individuals commonly receive hormone therapy (HT), but the effects of such treatment on breast cancer risk remain uncertain. Therapy for transgender women (male sex at birth, female gender identity) usually includes estrogen, while transgender men (female sex at birth, male gender identity) usually receive testosterone. Investigators at a clinic serving >95% of transgender people in the Netherlands assessed risk for breast cancer in 2260 transgender women and 1229 transgender men receiving HT compared with risk in the general population from 1972 to 2016. Median age at HT initiation was 31 (transgender women) and 23 (transgender men); median follow-up was 13 and 8 years, respectively.

Among transgender women, 18 cases of breast cancer (15 invasive; median age at diagnosis, 50) had occurred after a median of 18 years on HT. Standardized incidence ratios (SIRs) for invasive tumors were 46.7 compared with cisgender men and 0.3 compared with cisgender women. Among transgender men, 4 cases of invasive cancer (median age, 47) were diagnosed after a median of 15 years on HT; SIRs were 58.9 compared with cisgender men and 0.2 compared with cisgender women. Median age at breast cancer diagnosis among all transgender patients was lower than in cisgender women.

**COMMENT**: In this large study, estrogen therapy in transgender women was associated with a marked increase in breast cancer incidence compared with cisgender men (in whom breast cancer is uncommon). However, among transgender women and transgender men receiving HT, breast cancer risk was substantially lower than in cisgender women. Among individuals who have been using HT for  $\geq 5$  years, guidance suggests beginning biennial screening mammography at age 50 for transgender women as well as transgender men without mastectomy ([Center of Excellence for Transgender Health](#)). These important findings support such guidance.

**CITATION(S)**: de Blok CJM et al. Breast cancer risk in transgender people receiving hormone treatment: Nationwide cohort study in the Netherlands. *BMJ* 2019 May 14; 365:11652. (<https://doi.org/10.1136/bmj.11652>)

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*Lancet* 2019 May 2

## For Gonorrhea, Gentamicin Was Less Effective Than Ceftriaxone

*In a randomized trial, intramuscular gentamicin was especially poor at curing rectal and pharyngeal gonorrhea infections.*

Rapid development of antibiotic-resistant *Neisseria gonorrhoeae* hampers effective control efforts (the current recommended therapy is a single 500-mg dose of intramuscular [IM] ceftriaxone). To investigate gentamicin as an alternative, investigators conducted a randomized noninferiority trial of ceftriaxone versus a single 240-mg IM dose of gentamicin in 720 participants (mean age, 30; 81% men) with positive tests for genital, pharyngeal, or rectal gonorrhea who were recruited at 14 sexual-health centers in England.

Overall, infection had cleared at 2 weeks in 98% of the ceftriaxone group compared with 91% of the gentamicin group; however, the adjusted risk difference of 6.4% in favor of ceftriaxone did not meet the prespecified noninferiority margin of 5% for gentamicin. Against genital gonorrhea, gentamicin performed relatively well (cure rates, 98% [ceftriaxone] and 94% [gentamicin]); by contrast, against rectal (98% and 90%) and pharyngeal (96% and 80%) infections, gentamicin performed poorly. Both drugs were well tolerated, although more pain at the injection site was reported by gentamicin recipients (probably reflecting the larger injection volume).

**COMMENT**: This large, rigorous study takes gentamicin off the table of options for gonorrhea therapy. New drugs (preferably oral, such as zoliflodacin [*NEJM JW Infect Dis* Jan 2019 and *N Engl J Med* 2018; 379:1835]) — are urgently needed, as are studies to clarify why cure rates differ by anatomic site.

**CITATION(S)**: Ross JDC et al. Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): A randomised non-inferiority trial. *Lancet* 2019 May 2; [e-pub]. ([https://doi.org/10.1016/S0140-6736\(18\)32817-4](https://doi.org/10.1016/S0140-6736(18)32817-4))

Kirkcaldy RD and Workowski KA. Gentamicin as an alternative treatment for gonorrhoea. *Lancet* 2019 May 2; [e-pub]. ([https://doi.org/10.1016/S0140-6736\(19\)30244-2](https://doi.org/10.1016/S0140-6736(19)30244-2))

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