

6-2-18 headlines and articles

1. **The Power of Word Choice to Motivate or Alienate Parents During Health Counseling**
2. **Supplemental Vitamin D Reduces Wheezing Risk in Black Premature Infants**
3. **Many Colorado Cannabis Dispensaries Are Recommending the Drug in Early Pregnancy**

Cannabidiol for Drop Attacks in Lennox–Gastaut Syndrome

4. **As-Needed Inhaled Steroids plus Long-Acting Bronchodilators for Mild Asthma**
5. **Nicotine Dependence Can Be Measured in Adolescent E-Cigarette Users**
6. **Does Endometriosis Raise Risk for Developing Ovarian Cancer?**

Probiotics for Mania

7. **Hysterectomy: When Practice Makes Perfect**
8. **Furosemide Linked to Fractures in Children with Congenital Heart Disease**

Endometrial Evaluation in Women with Postmenopausal Bleeding

9. **What Is the Best Treatment for Symptomatic Patent Ductus Arteriosus?**

Acad Pediatr 2018 Apr; 18:342

The Power of Word Choice to Motivate or Alienate Parents During Health Counseling

For obesity counseling, Latino parents found some weight descriptors, such as “unhealthy weight,” motivating, and others offensive.

Latino children are disproportionately affected by obesity but are less likely than non-Latino children to receive obesity counseling. Although it is well known that derogatory weight terms should be avoided, it is not known which terms are the most motivating to diverse patient populations.



Over 500 parents who identified as Latino or Hispanic were recruited from a safety-net hospital's pediatric clinics and completed a survey asking whether they found a selection of weight descriptors desirable, motivating, or offensive (about half were in English, half in Spanish). The most desirable/motivating and least offensive English terms were “unhealthy weight” and “too much weight for his/her health;” the corresponding Spanish terms were “demasiado peso para su salud” and “demasiado peso para su edad.” These terms were deemed especially desirable by families with lower education and by parents born outside the U.S. The commonly used clinical terms “high BMI” and “overweight” were rated as not motivating in both English and their Spanish translation. Parents were most offended by “chubby,” “fat,” “gordo,” and “muy gordo.”

COMMENT: These findings are an excellent reminder that our clinical jargon or attempts to use colloquialisms in health counseling may not be received in a manner that motivates or empowers parents. Without the benefit of survey results like this to guide our word choice during counseling on sensitive topics (e.g., mental health, feeding, media use, or discipline), it may be best to ask parents which terms they prefer, and interpreters can be asked to use these terms consistently.

CITATION(S): Knierim SD et al. Latino parents' perceptions of pediatric weight counseling terms. Acad Pediatr 2018 Apr; 18:342. (<https://doi.org/10.1016/j.acap.2017.09.006>)

JAMA 2018 May 22/29; 319:2086

Supplemental Vitamin D Reduces Wheezing Risk in Black Premature Infants

Supplementing black premature infants' diets with 400 IU/day vitamin D was associated with a 34% reduced risk for recurrent wheezing.

Black premature infants are known to have high rates of postnatal wheezing. To determine the efficacy of vitamin D supplementation in this setting, investigators conducted a randomized, controlled trial involving 300 black infants born at gestational age ≥ 28 weeks and < 37 weeks at four urban hospitals.

Half of the infants were provided 400 IU/day of vitamin D until 6 months' adjusted age and the other half were maintained on dietary sources of vitamin D alone. Prior to randomization, all had received oral vitamin D supplementation in formula or human milk until they were getting 200 IU of vitamin D daily.

At 12 months' adjusted age, 31% of the infants receiving supplemental vitamin D had recurrent wheezing, compared with 42% of those receiving dietary intake alone (odds ratio, 0.66; $P=0.02$). No significant differences were observed in emergency room visits, hospitalizations for respiratory infections, or adverse events. Circulating 25(OH)D concentrations were not significantly different between the two groups.

COMMENT: Although the mechanism is unknown, early vitamin D supplementation reduced the risk for recurrent wheezing episodes during the first year of life in black infants born prematurely. No serious adverse events occurred that were attributable to vitamin D therapy. These data are not generalizable to nonblack premature infants.



CITATION(S): Hibbs AM et al. Effect of vitamin D supplementation on recurrent wheezing in black infants who were born preterm: The D-Wheeze randomized clinical trial. JAMA 2018 May 22/29; 319:2086. (<https://doi.org/10.1001/jama.2018.5729>)

Greer FR. Prenatal vs infant vitamin D supplementation and the risk of wheezing in childhood. JAMA 2018 May 22/29; 319:2081. (<https://doi.org/10.1001/jama.2018.5726>)

Many Colorado Cannabis Dispensaries Are Recommending the Drug in Early Pregnancy

By Joe Elia, Edited by André Sofair, MD, MPH, and William E. Chavey, MD, MS

Many cannabis dispensaries advise taking marijuana to prevent morning sickness, despite warnings against its use in pregnancy, according to a survey of licensed Colorado facilities.

Researchers posing as women with nausea in their first trimester called roughly 400 Colorado dispensaries. They asked, "Are there any products that are recommended for morning sickness?"

Nearly 70% recommended cannabis products in various forms, with medical dispensaries more likely to make this recommendation than retail dispensaries (83% vs. 60%). Unprompted, only about a third of the dispensaries counseled talking with a clinician; however, when prompted, over 80% recommended that the patient do so.

Reporting their findings in *Obstetrics & Gynecology*, the researchers note that the American College of Obstetricians and Gynecologists warns that clinicians "should be discouraged from prescribing or suggesting" marijuana around pregnancy or lactation.

"Women should be cautioned," the authors write, that advice from dispensaries "might not necessarily be informed by medical evidence."

LINK(S): [Obstetrics & Gynecology article](#) (Free PDF), [CDC's web page on "What You Need to Know about Marijuana Use and Pregnancy"](#) (Free)

N Engl J Med 2018 May 17; 378:1888

Cannabidiol for Drop Attacks in Lennox–Gastaut Syndrome

A randomized, placebo-controlled trial shows a significant reduction in sudden drop seizures.

Drop seizures — generalized tonic, atonic, and severe myoclonic — occur frequently (usually multiple times a day) and are often the most severely disabling seizures of patients with secondary generalized epilepsies such as Lennox–Gastaut syndrome (LGS). When patients are ambulatory, drop seizures can result in falls. Other than surgical transection of the corpus callosum, medical and other therapies (vagal nerve stimulation and ketogenic diet) rarely provide meaningful seizure control.

In a multicenter, placebo-controlled trial, investigators tested cannabidiol (CBD) for efficacy in the treatment of drop seizures in patients with LGS. They randomized 225 patients aged 2 to 55 years to one of two doses of oral cannabidiol (10 mg/kg or 20 mg/kg) or placebo, added to patients' existing therapy (median, 3 antiepileptic drugs) for 3.5 months, after a 28-day baseline period (median number of drop seizures during baseline, 85).

The primary endpoint, median percent reduction in drop seizures, was 42% with 20 mg/kg of cannabidiol, 37% with 10 mg/kg, and 17% with placebo. The [table](#) shows the results of secondary endpoints.

COMMENT: These important results show that CBD can be beneficial as an adjunctive treatment for a severe seizure type in both adults and children with LGS. Conversely, the findings reveal that CBD, for all of its notice by the public and in the media because of its relationship to marijuana, is simply another “drug” that has some benefit but also dose-related side effects like all other antiseizure medications. As the authors acknowledge, 49% of the patients were taking clobazam, one of the more effective medications for drop seizures. Clobazam levels are increased by CBD; thus, an unknown proportion of efficacy and side effects might be attributed to elevated CBD levels.

CITATION(S): Devinsky O et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *N Engl J Med* 2018 May 17; 378:1888. (<https://doi.org/10.1056/NEJMoa1714631>)

Secondary Outcomes with Cannabidiol vs. Placebo in Lennox–Gastaut Syndrome

	CBD 20 mg/kg	CBD 10 mg/kg	Placebo
50% or greater reduction, n (%)	30 (39)	26 (36)	11 (14)
75% or greater reduction, n (%)	19 (25)	8 (11)	2 (3)
Free of drop seizures, n (%)	5 (7)	3 (4)	1 (1)
Liver aminotransferase increase > 3X upper limit of normal, n	11	3	0
Withdrew from study, n	6	1	1
Patient/caregiver global impression of change (improvement), n (%)	43 (57)	48 (66)	33 (44)
Significant adverse effects, n (%)			
• Somnolence	25 (30)	14 (21)	4 (5)
• Decreased appetite	21 (26)	11 (16)	6 (8)
• Diarrhea	12 (15)	7 (10)	6 (8)

NEJM
Journal
Watch

N Engl J Med 2018 May 17; 378:1877

As-Needed Inhaled Steroids plus Long-Acting Bronchodilators for Mild Asthma

This combination was as effective as daily inhaled steroids for preventing exacerbations.

Current asthma guidelines recommend daily low-dose inhaled steroids for patients with mild persistent asthma, but patients with minimal symptoms can be reluctant to use daily medications. In two new blinded, industry-sponsored studies, researchers compared as-needed therapies with maintenance therapies.

In the first trial, 3849 adolescent and adult patients with mild asthma were randomized to one of three groups: (1) as-needed terbutaline (an inhaled, dry-powder, short-acting β -agonist used in Europe) with no daily controller, (2) as-needed budesonide/formoterol, (a fixed combination of an inhaled steroid [ICS] plus a fast-acting long-acting β -agonist [LABA]) with no daily controller, or (3) daily budesonide plus rescue terbutaline. Patients were followed for 1 year with daily medication reminders and frequent visits. For the primary endpoint of asthma control, as-needed budesonide/formoterol was superior to as-needed terbutaline but was inferior to daily budesonide plus rescue terbutaline. The rates of severe exacerbations that required systemic corticosteroids were similar in the as-needed–budesonide/formoterol and daily-budesonide groups (0.07 and 0.09 exacerbations annually), but the as-needed group used only 17% as much ICS as did the daily group. Both budesonide therapies were superior to as-needed terbutaline (0.2 exacerbations annually).



In the second trial, 4215 asthma patients were randomized to as-needed budesonide/formoterol only or to daily budesonide with rescue terbutaline. Patients were followed for 1 year with no medication reminders and occasional visits. The primary endpoint of severe exacerbations was similar in the two groups (0.11 and 0.12 annually), but the daily-budesonide group had modestly improved symptom control at the expense of a 75% higher mean daily ICS dose.

COMMENT: Although as many as three quarters of asthma patients are deemed to have mild asthma, the term “mild” is misleading, because these patients account for one third of all severe exacerbations. For patients in whom symptom control is the main concern and among those with moderate-to-severe asthma, daily ICS is the best option; for patients with mild intermittent asthma, a short-acting β -agonist is sufficient. But for patients with mild persistent asthma who would rather not use daily medication but still need protection from exacerbations, as-needed budesonide/formoterol is an attractive option. An editorialist estimates that, if mild asthmatic patients in the U.S. did not use expensive daily ICS inhalers, asthma medication costs would be lowered by US\$1 billion annually; however, this approach is not FDA approved, and, in the U.S., we have only a metered-dose inhaler version of budesonide/formoterol (Symbicort) instead of the dry-powder device used in these studies.

CITATION(S): Bateman ED et al. As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018 May 17; 378:1877. (<https://doi.org/10.1056/NEJMoa1715275>)

Lazarus SC. On-demand versus maintenance inhaled treatment in mild asthma. N Engl J Med 2018 May 17; 378:1940. (<https://doi.org/10.1056/NEJMe1802680>)

O'Byrne PM et al. Inhaled combined budesonide–formoterol as needed in mild asthma. N Engl J Med 2018 May 17; 378:1865. (<https://doi.org/10.1056/NEJMoa1715274>)

Drug Alcohol Depend 2018; 188:60

Nicotine Dependence Can Be Measured in Adolescent E-Cigarette Users

A four-question tool could help clinicians demonstrate symptoms of dependence in teens who think that vaping is nonaddictive.

Adolescents are more likely to use e-cigarettes (“vape”) than to smoke cigarettes, yet there are no data on whether e-cigarette users demonstrate nicotine dependence. To investigate this issue, investigators administered an anonymous survey about tobacco product use to almost 3000 high school students that included a four-item measure of nicotine dependence validated in adult vapers. The items were (paraphrased here): craving gets intolerable if I haven't vaped for a few hours, I drop everything to get e-cigarettes, I vape more before going into a situation where vaping isn't allowed, and I reach for e-cigarettes without thinking about it. Response options ranged from “never” to “almost always.”

Among 520 students reporting past-month vaping (50% female; mean age, 16 years; 85% white), the mean age at first e-cigarette use was 14.5 years, and 22% also smoked cigarettes. On average, students vaped on 13 of the past 30 days, and three fourths reported use of nicotine e-liquid. The mean e-cigarette dependence



score (range, 0–4) was 2.3, and older current age, younger age at initiation of vaping, vaping more frequently, using nicotine e-liquid, and concomitant cigarette smoking were each associated with a higher score.

COMMENT: The authors note that over half of the sample displayed at least one symptom of dependence and conclude that this four-item measure is valid for use in adolescents. They base that conclusion on observed similarities in dependence risk factors and symptom rates between these e-cigarette users and populations of adolescent cigarette smokers. From a clinical perspective, I think these questions can be used to elicit symptoms of dependence among teen users and challenge the belief of some that e-cigarettes are nonaddictive.

CITATION(S): Morean ME et al. Assessing nicotine dependence in adolescent e-cigarette users: The 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for electronic cigarettes. *Drug Alcohol Depend* 2018; 188:60.

(<https://doi.org/10.1016/j.drugalcdep.2018.03.029>)

Obstet Gynecol 2018 Jun; 131:1095

Does Endometriosis Raise Risk for Developing Ovarian Cancer?

Yes, especially the ovarian subtype of endometriosis (i.e., endometrioma); however, absolute risk for ovarian cancer remained low.

To investigate the relation between various types of endometriosis and risk for ovarian cancer, Finnish investigators used nationwide data in a study of some 50,000 women with surgically confirmed endometriosis diagnosed between 1987 and 2012 (follow-up, 839,000 women-years). Endometriosis subtypes included ovarian, peritoneal, and deep infiltrating.

Compared with women who did not have endometriosis, those with the condition were at significantly higher risk for developing ovarian cancer (standardized incidence ratio [SIR], 1.8) although absolute risk for ovarian cancer remained low (approximately 2 additional cases of ovarian cancer per 10,000 women years of follow-up). The magnitude of the association varied for different ovarian cancer types (clear cell SIR, 5.2; endometrioid SIR, 3.2; serous SIR, 1.4; mucinous SIR, 0.9). The ovarian subtype of endometriosis (i.e., endometrioma) was associated with the highest risk for ovarian cancer (SIR, 2.6), particularly clear cell (SIR, 10.1) and endometrioid (SIR, 4.7) ovarian cancer. Isolated peritoneal endometriosis was associated with slightly increased risk for ovarian cancer that did not reach statistical significance (SIR, 1.3).

COMMENT: In the U.S., endometriosis has been diagnosed in about 8% of women aged 15 to 45. This study helps to clarify that women with ovarian endometriosis — but not peritoneal endometriosis — are at increased risk for ovarian cancer (although longer follow-up in a larger cohort is required to clinch this finding). Some ovarian endometriosis lesions harbor genetic changes (e.g., *ARID1A* mutations) that may also occur in ovarian cancers. In the future, molecular analysis of ovarian endometriosis specimens might help to identify those women at highest risk for developing ovarian malignancies.



CITATION(S): Saavalainen L et al. Risk of gynecologic cancer according to the type of endometriosis. *Obstet Gynecol* 2018 Jun; 131:1095. (<https://doi.org/10.1097/AOG.0000000000002624>)

Bipolar Disord 2018 Apr 25

Probiotics for Mania

In a placebo-controlled study, patients taking a specific combination of probiotics had fewer and shorter rehospitalizations.

The microbiome has important roles in inflammatory response and neurologic functioning. Because some patients with acute mania have elevated levels of inflammation, these researchers tested the effects of a probiotic combination on relapse in patients recently discharged following hospitalization for mania.

In the double-blind study, 66 patients continued their medication regimens and were randomized to receive 24 weeks of either *Lactobacillus rhamnosus* strain GG plus *Bifidobacterium animalis* subsp. *lactis* strain Bb12 or placebo. An inflammation score, calculated at baseline, was developed from four measures — immunoglobulin G (IgG) class antibodies to the NR2 peptide fragment of the NMDA receptor; IgG class antibodies to gliadin; IgG class antibodies to the Mason-Pfizer monkey virus gag protein; and IgM class antibodies to *Toxoplasma gondii*.

Rehospitalization rates were significantly higher with placebo than with probiotics, 51.1% vs. 24.2%. Days hospitalized also favored the probiotic group (8.3 vs. 2.8 days), as did time to first rehospitalization. Probiotic patients with higher baseline levels of inflammation had an even lower rate of first hospitalization and an approximately 90% reduction in risk for hospitalization. No serious adverse effects were reported.

COMMENT: This impressive study demonstrates that this probiotic combination, presumably by modulating central nervous system inflammation through the gut–brain axis, has therapeutic effects on patients with mania. The study focused only on mania and not mixed states, hypomania, or depression. The researchers used a specific combination of strains, obtained from a company in Denmark. As the combination was well tolerated, there seems no reason not to try it with our patients. In the U.S., probiotics with the specific species used in the study are available.

CITATION(S): Dickerson F et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. *Bipolar Disorder* 2018 Apr 25; [e-pub]. (<https://doi.org/10.1111/bdi.12652>)

Obstet Gynecol 2018 May 7; 131:981

Hysterectomy: When Practice Makes Perfect



In a New York state study, morbidity and mortality were highest for hysterectomies performed by very low-volume surgeons.

Patients treated by higher-volume surgeons have superior perioperative outcomes (NEJM JW Womens Health Sep 2016) and *Am J Obstet Gynecol* 2016; 215:21) — but what about the low end of the range? Investigators used New York statewide data to assess perioperative outcomes for hysterectomies performed from 2000 through 2014 (including all surgical approaches). Surgeons were classified as very low volume if they performed one procedure per year; hospitals with <40 annual hysterectomies were classified as low volume.

Among 7797 surgeons performing 434,125 hysterectomies, 3197 (41%) were very low-volume surgeons (who performed 1% of these procedures). Complication rates for very low-volume versus other surgeons were 32.0% versus 9.9% (adjusted risk ratio, 1.9, $P<0.001$). Rates of intraoperative (e.g., genitourinary or gastrointestinal tract injuries), surgical site (e.g., hemorrhage), and medical complications (e.g., thrombotic, pulmonary) as well as transfusion and prolonged hospital stay were 3 to 4 times higher for very low-volume surgeons. In-hospital mortality was 2.5% versus 0.2% (ARR, 2.9, $P<0.001$).

COMMENT: As the authors note, fewer hysterectomies are being performed and more women who need gynecologic surgeries are being referred to surgical subspecialists; hence, for many general OB/GYNs, hysterectomy volume has decreased. Taken together with the outcomes reported here, these trends suggest that a surgeon's volume should be factored into decisions made by patients, referring physicians, and credentialing organizations.

CITATION(S): Ruiz MP et al. Outcomes of hysterectomy performed by very low-volume surgeons. *Obstet Gynecol* 2018 May 7; 131:981. (<https://doi.org/10.1097/AOG.0000000000002597>)

J Pediatr 2018 May 9

Furosemide Linked to Fractures in Children with Congenital Heart Disease

Risk for fracture was 87% higher in adherent furosemide users than in matched nonusers.

Furosemide, a diuretic frequently prescribed for children with heart disease, is known to increase urinary excretion of calcium and is suspected to be associated with bone fractures in adults.

To determine whether furosemide use is associated with fractures in children, investigators reviewed data in the Texas Medicaid Database from 2008 through 2014 on 3912 patients (<12 years old) with congenital heart defects (CHD), cardiomyopathy, or heart failure. Of these, 254 (6%) were adherent furosemide users ($\geq 70\%$ medication possession ratio), 724 (19%) were nonadherent users ($< 70\%$ MPR), and 2934 (75%) were propensity-score-matched nonusers. Few other diuretics were coadministered.

Results at a median follow-up of about 3 years were as follows:



- Incidence of fracture was higher in adherent and nonadherent furosemide users than in nonusers (9.1% and 7.2% vs. 5.0%; $P < 0.001$).
- Risk for fracture was 87% higher in adherent users than in nonusers and was 54% higher in nonadherent users than in nonusers.
- Risk for fracture was higher in children with a dual diagnosis of CHD/cardiomyopathy or CHD/heart failure than in those with CHD only.
- Risk for fracture was higher in white children than in black or Hispanic children.
- Risk for fracture was higher in children receiving versus not receiving proton-pump inhibitors (PPIs).

COMMENT: Children with CHD who are receiving furosemide have excess risk for fractures, especially if they have cardiomyopathy, are white, and take PPIs. Unfortunately, because this was a claims-data study, little information was available on the types or mechanisms of fractures that occurred.

CITATION(S): Heo JH et al. Increased fracture risk with furosemide use in children with congenital heart disease. J Pediatr 2018 May 9; [e-pub]. (<https://doi.org/10.1016/j.jpeds.2018.03.077>)

Obstet Gynecol 2018 May; 131:e124

Endometrial Evaluation in Women with Postmenopausal Bleeding

ACOG continues to recommend transvaginal ultrasound as an initial assessment.

Sponsoring Organization: American College of Obstetricians and Gynecologists (ACOG)

Target Population: Women's healthcare providers

Background and Objective: Although postmenopausal vaginal bleeding is common — and endometrial cancer is the most common gynecologic malignancy in U.S. women — the great majority of women with postmenopausal bleeding do not harbor uterine neoplasia. Nonetheless, prompt initial evaluation is important.

Key Recommendations

- Transvaginal ultrasound (TVUS) is appropriate for initial evaluation of postmenopausal bleeding. If the endometrium has a sonographically measured thickness ≤ 4 mm, further evaluation might not be necessary. If bleeding persists or recurs, endometrial sampling is indicated.
- Obesity, uterine position, or myometrial abnormalities may preclude satisfactory endometrial assessment with TVUS. In these cases, postmenopausal bleeding should be evaluated with sonohysterography, office hysteroscopy, or endometrial sampling. If such sampling yields insufficient tissue for diagnosis, further evaluation might not be necessary, provided subsequent TVUS demonstrates an endometrial thickness ≤ 4 mm and bleeding does not recur.
- When postmenopausal women without bleeding undergo TVUS for indications such as pelvic pain or adnexal pathology, an endometrial thickness > 4 mm may be incidentally found. In this setting, additional endometrial assessment is not routinely indicated (although patient-specific factors and imaging findings may warrant further evaluation).



COMMENT: Optimal evaluation of women with postmenopausal bleeding should identify the small proportion who have endometrial neoplasia while minimizing the use of invasive procedures in those with benign causes of such bleeding. These guidelines should help clinicians reach this goal.

CITATION(S): American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 734: The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstet Gynecol* 2018 May; 131:e124. (<https://doi.org/10.1097/AOG.0000000000002631>)

JAMA 2018 Mar 27; 319:1221

What Is the Best Treatment for Symptomatic Patent Ductus Arteriosus?

High-dose oral ibuprofen is superior to other medical options for closure of a clinically significant PDA.

Delayed closure of the patent ductus arteriosus (PDA) commonly occurs in extremely preterm infants (<29 weeks gestation), and in some infants, it can compromise pulmonary function and systemic blood flow. However, decisions regarding if, when, and how to treat a hemodynamically significant PDA remain a topic of considerable debate. Researchers conducted a meta-analysis of randomized trials published between 1980 and 2017 that compared various medical strategies (indomethacin, ibuprofen, acetaminophen) to each other, placebo, or no treatment for closure of a hemodynamically significant PDA. Bayesian network meta-analysis techniques were used to estimate the relative efficacy of 14 variations of therapy, including intravenous, oral, high-dose, and low-dose regimens.

The authors identified 68 trials involving 4802 infants. Overall, high-dose oral ibuprofen (15–20 mg/kg followed by 7.5–10.0 mg/kg every 12–24 hours for a total of 3 doses) was superior to standard-dose intravenous ibuprofen or indomethacin in closing the PDA (odds ratios, 3.59 and 2.35) and avoiding surgical ligation and was not associated with higher rates of necrotizing enterocolitis. Placebo or no treatment was the least effective option for closing the PDA but was not associated with higher risk for death or morbidity compared to any of the active treatment modalities.

COMMENT: For infants receiving treatment for a hemodynamically significant PDA, high-dose oral ibuprofen appears to be the most effective medical option for closing the ductus and avoiding surgical ligation and other morbidity. However, the findings of this meta-analysis should also drive ongoing and future investigations into whether active or expectant management of the hemodynamically significant PDA improves long-term outcomes for preterm infants.

CITATION(S): Mitra S et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: A systematic review and meta-analysis. *JAMA* 2018 Mar 27; 319:1221. (<https://doi.org/10.1001/jama.2018.1896>)