RELIAS MEDIA

# Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 41, Issue 8, April 30, 2019
ReliasMedia.com

BRIEF REPORT

# Does Physical Activity Lower the Risk of Parkinson's Disease?

***By Ellen Feldman, MD***

*Altru Health System, Grand Forks, ND*

**Dr. Feldman reports no financial relationships relevant to this field of study.**

SYNOPSIS: A systematic review and meta-analysis incorporating more than 500,000 subjects revealed that moderate to vigorous physical activity is associated with a significant reduction in development of Parkinson's disease; this relationship is most pronounced in men.

SOURCE: Fang X, Han D, Cheng Q, et al. Association of levels of physical activity with risk of Parkinson disease: A systematic review and meta-analysis. *JAMA Netw Open* 2018;1:e182421.

*And is not the bodily habit spoiled by rest and idleness, but preserved for a long time by motion and exercise?*
*Plato from Theaetetus, 360 BCE*[1]

In recent years, the importance of exercise to health, well-known for centuries, has become the focus of medical studies attempting to quantify and better understand the nuances of this relationship. Fang et al attempted to clarify an association between physical activity and the risk of Parkinson's disease (PD). Undertaking a broad-based meta-analysis to uncover relationships obscured by the limits of individual trials, they identified eight eligible studies for this investigation.

PD is one of the more common neurodegenerative disorders (ranking second to dementia). The risk for developing the disorder increases with age. Although there is regional variation, the overall estimated prevalence of PD in North America in persons 45 years of age and older is 572 per 100,000. Gender also plays a role; PD is more common in men than in women, with a prevalence of 667 per 100,000 in men compared to 488 per 100,000 in women older than 45 years of age.[2,3]

Fang et al noted that the etiology of PD most likely involves a combination of genetic and environmental factors, and that physical activity is among the modifiable risk factors suspected to play a role in protecting against the development of this disorder. Studies of this relationship have been inconsistent

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott, Acadia, Allergan, AstraZeneca, Avadel, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mylan, and Salix; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Executive Editor Leslie Coplin; Accreditations Manager Amy M. Johnson, MSN, RN, CPN; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

*Internal Medicine Alert* (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.



SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.

**Online only: 1 year (Single user)** with ***free*** *AMA PRA Category 1 Credits™*: $299

**Back issues: $21.** Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 1/15/2019. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 2 AAFP Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

in terms of methodology and outcome, making it difficult to prove an association. In fact, of eight studies identified for review and meta-analysis, only one revealed a statistically significant correlation between physical activity and a reduced risk of PD. Yet, when the pooled group was considered and a standardized approach to measuring physical activity was employed, an association between physical activity and reduced risk of PD became more apparent.

The gender balance within the 544,346 participants across the eight studies was close to equal. More than 2,100 cases of PD developed over the follow-up period. Fewer than one-third of these cases were in women.

According to Fang et al, each study included in the meta-analysis had different cutoffs for the physical activity category, making comparisons and conclusions difficult. To overcome this barrier, the group quantified physical activity from each study using a standardized measure of metabolic activity, termed MET hours. One MET hour represents the amount of energy expended when sitting quietly (approximately 1 kcal/kg/hour). MET hours required for moderate to strenuous activity are in the range of three to six times this baseline.[4] By moving physical activity to a consistent measure of energy expenditure, the authors created categories of physical activity. These categories ranged from minimal physical activity to light physical activity to moderate/vigorous physical activity.

Fang et al reported positive or statistically significant results, as well as results that did not show statistical significance. The results in this study appear much more conclusive for men than for women. There are possibly several factors at work here. It is not unexpected that fewer women overall developed PD in the follow-up period, as this disorder occurs more frequently in men. However, the numbers may not be sufficient to uncover a true relationship between relative risks of PD and exercise or activity level in this gender. Fang et al noted that more studies looking harder at this relationship in women are needed to clarify if the relationship changes with more female participants.

The authors also considered the possibility of reverse causation overall and attempted to control for this. The mean length of the studies was 12 years. This seems sufficient to minimize the risk of mistaking low physical activity due to subclinical PD with low physical activity as a risk factor for PD. Nevertheless, they noted even with a time-lag meta-analysis (excluding the first several years of the study), the relationship between physical activity and reduced risk of PD in men remains consistent. With longer studies in the pipeline, this concern should be laid to rest eventually.

This is a convincing study with immediate clinical application, especially for patients with suspected genetic predisposition to PD. Smoking tobacco and caffeine consumption are among the modifiable risk factors linked to the onset of PD.[5,6] Although both activities appeared to be inversely related to the development of PD, mitigating factors make prescribing or endorsing the use of each (especially cigarettes) less desirable. Exercise, with its known widespread benefits and central role in maintaining wellness, is a more natural fit for a prescription.

Future studies in this arena remain necessary. Robust longitudinal studies incorporating quantifiable and consistent definitions of physical activity verified by means other than self-report should help clarify the relationship between physical activity and reduced risk of PD. However, it is not necessary to wait for such studies to start recommending at least daily moderate to vigorous levels of physical activity to patients. ■

## REFERENCES

1. Plato. Theaetetus. Available online at: https://bit.ly/2FRVjmM. Accessed April 4, 2019.
2. Parkinson's Foundation. Statistics. Available at: https://bit.ly/2KtnrSY. Accessed Feb. 23, 2019.
3. Marras C, Beck JC, Bower JH, et al; Parkinson's Foundation P4 Group. Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Dis* 2018;4:21.
4. University of South Carolina. Arnold School of Public Health Prevention Research Center. The Compendium of Physical Activities. Available at: https://bit.ly/2OQWhnp. Accessed April 4, 2019.
5. Rodriguez T. The Troubling Link Between Parkinson's and Smoking: Can We Deny the Benefits? *Neurology Advisor*, Dec. 10, 2015. Available at: https://bit.ly/2Ti1Bku. Accessed April 4, 2019.
6. Munoz DG, Fujioka S. Caffeine and Parkinson disease: A possible diagnostic and pathogenic breakthrough. *Neurology* 2018;90:205-206.

ABSTRACT & COMMENTARY

# Probiotics Do Not Prevent *C. difficile* Infection in Hospitalized Patients

***By Richard R. Watkins, MD, MS, FACP, FIDSA***

*Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH*

**Dr. Watkins reports no financial relationships relevant to this field of study.**

SYNOPSIS: A retrospective cohort study from a single California hospital revealed the administration of probiotics to patients receiving antibiotics did not reduce the incidence of healthcare facility-onset *Clostridioides difficile* infection.

SOURCE: Box MJ, Ortwine KN, Goicoechea M, Scripps Antimicrobial Stewardship Program (SASP). No impact of probiotics to reduce *Clostridium difficile* infection in hospitalized patients: A real-world experience. *Open Forum Infect Dis* 2018;5:ofy192.

Healthcare facility-onset *Clostridioides difficile* infection (HO-CDI), formerly known as *Clostridium difficile*, is detrimental to patients and healthcare institutions alike. Some data suggest the coadministration of probiotics with antibiotics may reduce the risk for HO-CDI, at least in institutions where the rates are high (> 20%).

As part of a care bundle to reduce HO-CDI, a specific probiotic formulation was recommended for administration to patients receiving antibiotics and judged to be at high risk for HO-CDI at the authors' institution. Thereafter, the researchers sought to determine whether probiotics are beneficial in a hospital with a lower rate of HO-CDI, what they describe as a "real-world" environment.

Box et al conducted a retrospective cohort study at a 400-bed community hospital in La Jolla, CA. Patients were included if they were ≥ 18 years of age, had received at least one dose of antibiotics, and had been in the hospital more three days. The authors excluded patients whose CDI was community-acquired or who had received cefazolin or cefoxitin for surgical prophylaxis. The primary outcome was the incidence of HO-CDI in patients who received IV antibiotics plus probiotics compared to those who received IV antibiotics alone.

Between March 29, 2016, and Sept. 30, 2016, investigators evaluated 1,576 patients treated with IV antibiotics. Of those, 649 received antibiotics plus probiotics and 927 received antibiotics alone. The two groups were well matched in terms of age and ICU stay. However, patients who received probiotics were in the hospital longer, scored higher on the Charleston Comorbidity Index (CCI), and paid more money for antibiotics. The use of acid-suppressing agents was not significantly different between the two groups. HO-CDI occurred in 11 of 649 patients who received antibiotics plus probiotics and in eight of 927 patients who received antibiotics alone (1.8% vs. 0.9%, respectively; $P = 0.16$). The median duration of probiotic use was 8.1 days. Furthermore, in-house mortality was higher in the antibiotics plus probiotics group (53/649) compared to the antibiotics alone group (63/927), although this difference was not significant ($P = 0.32$).

The authors conducted a subgroup analysis to determine if greater exposure to antibiotics in the probiotic group offset a potential benefit. They compared HO-CDI rates in the probiotic group with rates in the top 30% of patients by antibiotic exposure (billed grams of antibiotics) in the group that received antibiotics alone. There was no observed difference in HO-CDI rates between the two groups (five of 284 patients; $P$ = no significance).

## ■ COMMENTARY

This large, retrospective cohort study revealed no benefit for probiotics in preventing HO-CDI. The use of probiotics for CDI prevention has been controversial. The most recent Infectious Diseases Society of America guidelines decline to endorse probiotics as a CDI prevention approach outside clinical trials. The guideline authors cited insufficient data at the time of publication.[1] Based on the results of the Box et al study, their institution removed all probiotics from the formulary. This decision seems rational from a quality standpoint, since probiotics did not demonstrate any benefit and carry associated costs.

There were a few limitations. First, it was conducted at a single community hospital, which may limit its generalizability to other healthcare settings, such as nursing homes, or for outpatients. Second, the authors did not explore the association and outcomes between probiotics and specific antibiotics, including those that are more prone to cause CDI. Third, the retrospective design may have led to bias from unmeasured

confounding factors, such as differences in probiotic prescribing by physicians. Fourth, the finding that the probiotic recipients scored higher on the CCI, stayed in the hospital longer, and received more antibiotics likely indicates these patients were more ill and at higher risk for CDI. This could have skewed the results and led to a type II error. Finally, there was no attempt to discern initial CDI from recurrent CDI. Whether probiotics were beneficial in cases of recurrence is unclear from the study data.

Antibiotic use is the most important modifiable risk factor for CDI. The CDC estimates that 30% of antibiotics are prescribed unnecessarily.[2] Thus, the Box et al study is another nail in the coffin for the idea that probiotics prevent CDI. Instead, it reaffirms that the best way forward to reduce the risk for CDI is through prudent and aggressive antibiotic stewardship efforts.

Rather than conducting more studies on probiotics, it would be more pragmatic if investigators focused on ways to reduce antibiotic use that still leads to successful eradication of infections and positive outcomes. For example, studies that elucidate the least amount of time that antibiotics can be given for a particular infection to result in a cure would be valuable from clinical, quality, safety, and resource use perspectives. ■

REFERENCES


1. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018;66:987-994.
2. Centers for Disease Control and Prevention. Antibiotic use in the United States, 2017: Progress and opportunities. Available at: https://bit.ly/2UpLGVX. Accessed April 4, 2019.


BRIEF REPORT

# Imagine: Multidrug-Resistant Acute Gonococcal Infection


***By Carol A. Kemper, MD, FACP***

*Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center*



**Dr. Kemper reports no financial relationships relevant to this field of study.**

SOURCE: Blank S, Daskalakis DC. *Neisseria gonorrhoeae* – Rising infection rates, dwindling treatment options. *N Engl J Med* 2018;379:1795-1797.


The United States spends an estimated $182 million annually on the treatment of acute gonococcal infection (in 2017 dollars). Imagine what would happen to that dollar figure if we lost ceftriaxone as an effective therapy for gonococcal infection.

Investigators started the Gonococcal Isolate Surveillance Program (GISP) in 1986 to monitor antibiotic resistance in *Neisseria gonorrhoeae* isolates at selected sites throughout the United States. The first evidence of a serious shift in susceptibility patterns occurred in 2007, with evidence of increasing resistance to fluoroquinolones, along with reports of clinical treatment failure. As a result, fluoroquinolones were removed from recommended treatment guidelines for gonococcal infection. Subsequently, increasing minimum inhibitory concentrations to cefixime and other oral cephalosporins were observed. Clinical failures to these agents began to appear. Over the past few years, increasing minimum inhibitory concentrations to azithromycin have been observed.

Currently, resistance to ceftriaxone in the United States remains limited to a handful of cases. Fortunately, all isolates with reduced susceptibility to azithromycin have retained sensitivity to ceftriaxone. Although ceftriaxone retains its efficacy (for now), the threat of evolving resistance to what is virtually the only remaining reliable therapy looms. Should this occur, it is not clear what the best treatment regimen might be — and it may just require days of parenteral treatment.

The editorial by Blank and Daskalakis underscores the threat by laying out the possible consequences of a further shift in gonorrhea susceptibility patterns: 1) younger, sexually active people will be affected disproportionately, potentially resulting in lost wages and even days of hospitalization; 2) increasing risk of refractory pelvic inflammatory disease in young women, with resulting infertility; 3) higher risk to pregnant women and neonates, with serious health consequences and adverse pregnancy outcomes (e.g., blindness in neonates); 4) the use of potentially more toxic agents; 5) more HIV infections; and 6) a stunning increase in the annual cost of STD treatment. Safe and reliable agents are needed urgently for the treatment of acute gonococcal infection. ■

SPECIAL FEATURE

# Update on Treatments for Vulvovaginal Atrophy

*By Rebecca H. Allen, MD, MPH*

*Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI*

**Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.**

Vulvovaginal atrophy, now known as the genitourinary syndrome of menopause (GSM), occurs with the decline of estrogen in the menopausal period. Due to the loss of estrogen, the vulvovaginal tissue becomes thinner, the vagina becomes more alkaline, and vaginal secretions can decrease.[1] Many postmenopausal women report symptoms related to vulvovaginal atrophy, including vaginal dryness, dyspareunia, vaginal burning or itching, vaginal discharge, and urinary tract symptoms.[2] Of course, the condition also can occur occasionally during other low estrogen states, such as lactation and hypothalamic amenorrhea, or among women taking antiestrogenic drugs, often for breast cancer treatment. Women may be asymptomatic or reluctant to discuss the problem with their providers.[3] Whether a woman is sexually active does not always correlate with the degree of symptoms she may experience.

Typically, providers can diagnose vulvovaginal atrophy by physical exam alone. Findings may include labia minora resorption; loss of hymenal remnants; loss of vaginal rugae; fragile, pale, and dry vaginal epithelium; and shortened vagina. The cervix may become flush with the vaginal vault, with the cervical os difficult to identify.[2] When the vagina appears inflamed, the term atrophic vaginitis is used. Since lactobacilli depend on an estrogen-replete environment to thrive and prosper, the pH of the vagina often is elevated above 5.0. Saline wet prep reveals relative acellularity and an increase in the proportion of parabasal cells.[3] In research studies, investigators measure the maturation index, which is the proportion of parabasal, intermediate, and superficial vaginal epithelial cells in each 100 cells on a saline wet prep. Parabasal cells signify the absence of estrogen. Thus, premenopausal women usually have no parabasal cells, whereas women in menopause have a majority of parabasal cells.[4]

The treatment of vulvovaginal atrophy often depends on the severity of the condition. Treatments include vaginal lubricants, vaginal moisturizers, and local vaginal estrogen for patients who do not need or want systemic estrogen therapy. Vaginal moisturizers include components that adhere to the vagina and allow intermittent dosing, while vaginal lubricants typically are used before intercourse.3 First-line treatment for milder symptoms often includes vaginal lubricants to be used at the time of sexual intercourse to reduce friction on delicate tissue. If one lubricant does not work or causes irritation, the patient can try another lubricant (e.g., water-based vs. silicone-based). Coconut oil is another option that is used widely for vulvovaginal lubrication. Often, this is recommended for patients with vulvodynia. Patients also can opt for vaginal moisturizers, which are used several times a week unrelated to the timing of intercourse. Vaginal sexual intercourse can be an important part of therapy, as it maintains vaginal health by regularly increasing blood flow to the vagina. Masturbation and sexual toys can be used if a patient does not have a partner.[4]

Because vaginal lubricants and moisturizers offer some symptomatic relief but do not reverse the maturation index of the vagina, these agents can fail women with more severe symptoms. In these cases, vaginal estrogen or other treatments are needed.[3] Vaginal estrogen is safe and does not increase the risk of cardiovascular disease, breast cancer, endometrial cancer, or all-cause mortality.[5,6] Vaginal estrogen treatments include 4 mcg or 10 mcg estradiol tablets, a three-month estradiol vaginal ring that releases 7.5 mcg daily, and estradiol or conjugated estrogen cream. The most recent estrogen product on the market (Imvexxy) contains estradiol. The novel features of this product are that it does not require an applicator and it is suspended in coconut oil. It also is available in two low doses of estrogen (4 mcg or 10 mcg).

The authors of a Cochrane Review concluded that vaginal estrogen in different forms was superior to placebo for the treatment of GSM (vulvovaginal atrophy), although the quality of the evidence was low, mostly because of small sample sizes.[7] In addition, the authors of a systematic review concluded that "all commercially available vaginal estrogens effectively relieve common vulvovaginal atrophy-related complaints."[8] With correct dosing, the systemic absorption of vaginal estrogen remains in the postmenopausal range and does not require a progestin for the prevention of endometrial hyperplasia and cancer.[3] The use of vaginal estrogen in women with a history of breast cancer should be coordinated with the patient's oncologist.

Prasterone (Intrarosa) is a new non-estrogen topical product on the market for GSM that is approved for the treatment of moderate-to-severe dyspareunia due to menopause. No one has conducted a head-to-head trial of prasterone with vaginal estrogen. The results of one study revealed that prasterone was superior to placebo and improved female sexual function index scores after 12 weeks of therapy.[9] Prasterone is supposed to work through aromatization of androstenedione and testosterone locally in the vagina to estrone and estradiol. Because of its daily dosing and lack of known superiority to estrogen, most experts view this as second-line treatment for patients who do not want to use estrogen. In addition, insurance may not cover as much of the associated costs for newer brand name products (Intrarosa and Imvexxy) compared to more established estrogen products, limiting patient access.

Ospemifene is an oral agent that is indicated specifically for the treatment of moderate-to-severe dyspareunia caused by GSM.[1] Approved in 2013, ospemifene is a selective estrogen receptor modulator that acts as an estrogen agonist in the vagina but does not appear to stimulate breast and endometrial tissue.[10] Typically, this daily oral option is considered for women who prefer not to or cannot use a vaginal product. Similar to prasterone, no one has conducted a head-to-head trial comparing ospemifene with vaginal estrogen. Side effects include hot flashes, with one trial revealing a 7% rate of hot flashes with ospemifene compared to 4% in the placebo arm.[10] All selective estrogen receptor modulators could increase the risk of venous thromboembolism. Neither prasterone nor ospemifene has been demonstrated to be safe for breast cancer patients.

Finally, the use of vaginal laser therapy (microablative fractional laser: carbon dioxide, erbium, YAG, or hybrid technologies) for GSM has been shown to improve symptoms associated with GSM, but it remains controversial.[11,12] Most providers recognize this treatment as the MonaLisa Touch laser. The technology was introduced prior to any randomized, placebo-controlled trials showing safety and efficacy over the long term. The mechanism of action is to create microabrasions in the vaginal epithelium that then stimulate improved vascular supply and collagen development, thickening the vaginal epithelium.[4] In July 2018, the FDA cautioned that it has not approved any energy-based devices to treat vulvovaginal atrophy or vaginal laxity and that the use of these devices could cause vaginal burns, scarring, and dyspareunia.[13] The American College of Obstetricians and Gynecologists and North American Menopause Society agreed with the FDA's cautionary stance, stating that although preliminary data are promising, more research is needed before these devices are used in practice routinely.[14,15] There have been case reports of persistent dyspareunia, vaginal insertion pain, vaginal stenosis, and vaginal lacerations during intercourse after vaginal laser treatment.[16] Because of these safety concerns and the lack of definitive research proving safety and efficacy, women should be counseled about other options prior to resorting to vaginal laser therapy.[12] Since laser therapy to the vagina is considered cosmetic by most insurance companies and is not FDA-approved, health insurers rarely cover the costs of this therapy. Practitioners usually recommend yearly treatments to maintain the beneficial effects of this laser therapy.

As with many clinical conditions, the spectrum of GSM requires the clinician to consider the effect on the patient's quality of life. Although situational lubricants and regular moisturizers effectively pacify many symptoms, local estrogen is a safe, effective, and affordable way to treat the vulvovaginal changes of menopause. ■

## REFERENCES


1. American College of Obstetricians and Gynecologists Practice Bulletin No. 141. Management of menopausal symptoms. January 2014.
2. Minkin MJ, Reiter S, Maamari R. Prevalence of postmenopausal symptoms in North America. *Menopause* 2015;22:1231-1238.
3. Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. *Menopause* 2013;20:888-902.
4. Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: An overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol* 2016;215:704-711.
5. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause* 2018;25:11-20.
6. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause* 2018; Dec. 17. doi: 10.1097/GME.0000000000001284. [Epub ahead of print].
7. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database System Rev* 2016;(8):CD001500.
8. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: A systematic review. *Obstet Gynecol* 2014;124:1147-1156.
9. Labrie F, Derogatis L, Archer DF, et al. Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. *J Sex Med* 2015;12:2401-2412.
10. Portman DJ, Bachmann GA, Simon JA; Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause* 2013;20:623-630.
11. Arunkalaivanan A, Kaur H, Onuma O. Laser therapy as a treatment modality for genitourinary syndrome of menopause: A critical appraisal of evidence. *Int Urogynecol J* 2017;28:681-685.
12. Kaunitz AM, Pinkerton JV, Manson JE.. Women harmed by vaginal laser for treatment of GSM — the latest casualties of fear

and confusion surrounding hormone therapy. *Menopause* 2019; Feb. 19. doi: 10.1097/GME.0000000000001313. [Epub ahead of print].
13. U.S. Food and Drug Administration. FDA Warns Against Use of Energy-Based Devices to Perform Vaginal 'Rejuvenation' or Vaginal Cosmetic Procedures: FDA Safety Communication. Available at: https://bit.ly/2LOGN4h. Accessed April 4, 2019.
14. American College of Obstetricians and Gynecologists Position Statement. Fractional Laser Treatment of Vulvovaginal Atrophy and U.S. Food and Drug Administration Clearance. Available at: https://bit.ly/2HtlvFz. Accessed April 4, 2019.
15. North American Menopause Society. FDA Mandating Vaginal Laser Manufacturers Present Valid Data Before Marketing. Available at: https://bit.ly/2OEWzgz. Accessed April 4, 2019.
16. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: A case series of patient complications following vaginal laser treatment for atrophy. *Menopause* 2019; Jan. 14. doi: 10.1097/GME.0000000000001293. [Epub ahead of print].

PHARMACOLOGY UPDATE

# Brexanolone Injection (Zulresso)

***By William Elliott, MD, FACP, and James Chan, PharmD, PhD***

*Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.*
*Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.*

**Drs. Elliott and Chan report no financial relationships relevant to this field of study.**

The FDA has approved the first drug for the treatment of postpartum depression (PPD). Brexanolone is a synthetic neuroactive steroid gamma-aminobutyric acid receptor-positive modulator. It is identical to endogenous allopregnanolone. Brexanolone will be distributed as Zulresso through a restricted Risk Evaluation and Mitigation Strategy program.

## INDICATIONS

Brexanolone is indicated for the treatment of PPD in adults.[1]

## DOSAGE

Brexanolone is administered through continuous IV infusion over 60 hours.[1] For hours 0 to 4, the dose is 30 mcg/kg/hr; from four to 24 hours, increase the dose to 60 mcg/kg/hr; from 24 to 52 hours, increase the dose to 90 mcg/kg/hr (60 mcg/kg/hr for those intolerant to 90 mcg/kg/hr); from 52 to 56 hours, decrease the dose to 60 mcg/kg/hr; from 56 to 60 hours, decrease the dose to 30 mcg/kg/hr. Brexanolone is available as a single-dose vial (100 mg/20 mL).

## POTENTIAL ADVANTAGE

Brexanolone is the first FDA-approved treatment for PPD.

## POTENTIAL DISADVANTAGES

Brexanolone can cause excessive sedation or loss of consciousness. Patients should be monitored for hypoxia with oximetry.[1] In clinical studies, researchers had to interrupt or reduce the dose in 7% of brexanolone-treated subjects due to adverse reactions (vs. 3% for placebo-treated subjects).[1] Other adverse reactions include dizziness, presyncope, and vertigo. There are no data on the effects of brexanolone on breast milk production or on breastfed infants. However, due to the drug's low bioavailability, infant exposure is expected to be low (1% to 2% of maternal weight-adjusted dosage). Brexanolone requires continuous infusion over 60 hours.

## COMMENTS

Allopregnanolone is an endogenous neuroactive steroid that is a metabolite of progesterone. Allopregnanolone and other metabolites rise steadily through pregnancy and decrease in the postpartum period. Lower levels in the peripheral blood or cerebrospinal fluid have been associated with major depression and anxiety disorders.[2,3] Brexanolone, a synthetic allopregnanolone, was evaluated for efficacy and safety in two randomized, double-blind, placebo-controlled studies.[1,4] Study 1 included subjects with severe PPD (Hamilton Depression Rating Scale [HAM-D] score ≥ 26). Study 2 included subjects with moderate PPD (HAM-D scores = 20-25). Subjects were randomized to brexanolone or placebo. The primary endpoint was mean change from baseline in HAM-D total score at hour 60 (end of infusion). The secondary endpoint was mean change at day 30.

The authors of study 1 compared two doses of brexanolone (60 mcg/kg/hr; n = 38 and 90 mcg/kg/hr; n = 41) to placebo (n = 43). The mean reduction of HAM-D scores at hour 60 was -19.5 from a baseline of 29.0 for patients on the 60 mcg/kg/hr dose and -17.7 from a baseline of 28.4 for patients on the 90 mcg/kg/hr dose. For subjects who took placebo, HAM-D score change was -14.0 from a baseline of 28.6. Mean placebo-subtracted differences were -5.5 ($P$ = 0.0013) and -3.7 ($P$ = 0.025).

In study 2, the authors administered brexanolone at 90 mcg/kg/hr (n = 51) and placebo (n = 53). Reduction in HAM-D scores with brexanolone was -14.6 from a baseline of 22.6 vs. -12.1 from a baseline of 22.7 for placebo-treated patients (mean difference, -2.5; $P$ = 0.016). Generally, mean changes at hour 60 with brexanolone were maintained at day 30.[4] In study 1, 51%

of patients on the 60 mcg/kg/hr dose achieved HAM-D remission (total score ≤ 7) at the end of infusion vs. 16% for placebo-treated patients. In study 2, the HAM-D remission rate was 61% of patients on brexanolone vs. 38% of patients on placebo.

## CLINICAL IMPLICATIONS

In 2012, the prevalence of PPD was 11.5% in the United States.[5] PPD can affect women regardless of age, race, ethnicity, or economic status.[6] If left untreated, PPD can last for months or even years. Suicide accounts for about 20% of PPD deaths and is the second most common cause of mortality in postpartum women.[7]

Current therapy includes cognitive and interpersonal therapy and traditional antidepressants. Traditional antidepressants onset slowly; brexanolone offers a rapid onset and effective treatment. The cost is estimated to be $7,450 per vial, with an average course costing about $34,000. ■

## REFERENCES

1. Sage Therapeutics, Inc. Zulresso Prescribing Information, March 2019. Available at: https://bit.ly/2FuRrtf. Accessed April 10, 2019.
2. Osborne LM, Gispen F, Sanyal A, et al. Lower allopregnanolone during pregnancy predicts postpartum depression: An exploratory study. *Psychoneuroendocrinology* 2017;79:116-121.
3. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol* 2014;113:79-87.
4. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: Two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018;392:1058-1070.
5. Ko JY, Rockhill KM, Tong VT, et al. Trends in postpartum depressive symptoms - 27 states, 2004, 2008, and 2012. *MMWR Morb Mortal Wkly Rep* 2017;66:153-158.
6. National Institute of Mental Health. Postpartum Depression Facts. Available online at: https://bit.ly/2wFEWHO. Accessed April 10, 2019.
7. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health* 2005;2:77-87.

## CME QUESTIONS

**1. Based on the meta-analysis by Fang et al, which of the following statements is true regarding Parkinson's disease (PD) and physical activity?**

a. PD is a neurodegenerative disorder more common in men. This study indicates that more physical activity lowers the risk of this disorder in men and raises the risk of this disorder in women.

b. PD is a neurodegenerative disorder more common in men. This study indicates that more physical activity lowers the risk of this disorder in men, but the relationship is not definitive in women.

c. PD is a neurodegenerative disorder more common in women. This study indicates that more physical activity lowers the risk of this disorder in women, but the relationship is not definitive in men.

d. PD is a neurodegenerative disorder more common in women. This study indicates that more physical activity lowers the risk of this disorder in men and women alike.

**2. Based on the study by Box et al, which of the following statements is true about probiotics and *Clostridioides difficile* infection?**

a. The administration of probiotics to patients receiving antibiotics increased the incidence of healthcare facility-onset *Clostridioides difficile* infection.

b. The authors could not draw definitive conclusions about the relationship between probiotics and *Clostridioides difficile*.

c. The administration of probiotics to patients receiving antibiotics did not reduce the incidence of healthcare facility-onset *Clostridioides difficile* infection.

d. The administration of probiotics to patients receiving antibiotics did reduce the incidence of healthcare facility-onset *Clostridioides difficile* infection.