

# Letters to the Editor

## Prescribing Cholinesterase Inhibitors for Alzheimer Disease: Timing Matters

**Original Article:** Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms

**Issue Date:** June 15, 2017

**See additional** reader comments at: <https://www.aafp.org/afp/2017/0615/p771.html>

**To the Editor:** As subspecialists in geriatric psychiatry and pharmacy, we appreciate this concise and informative review of pharmacologic and nonpharmacologic therapies for Alzheimer disease. We would, however, like to make a suggestion regarding the information in Table 1 on administration of cholinesterase inhibitors. The authors recommend administering donepezil (Aricept) at bedtime and other oral cholinesterase inhibitors, specifically galantamine (Razadyne) and rivastigmine (Exelon), once or twice daily depending on whether the formulation is extended release.

The most common adverse effects of cholinesterase inhibitors include nausea, diarrhea, vomiting, decreased appetite, dyspepsia, anorexia, muscle cramps, fatigue, insomnia, dizziness, headache, and asthenia.<sup>1-3</sup> Taking these medications with food, preferably a full meal, can mitigate these gastrointestinal effects. Therefore, we recommend taking cholinesterase inhibitors with food whenever possible to improve tolerability. Furthermore, administering these medications with a meal delays drug absorption, which reduces the peak plasma and brain concentrations, thereby decreasing the risk of all acute adverse effects.<sup>4</sup> Fortunately, the package inserts for galantamine and rivastigmine recommend dosing with meals.<sup>2,3</sup> However, the package insert for donepezil mentions only nightly dosing.<sup>1</sup> When donepezil is administered nightly, plasma levels of the drug peak in three to four hours,<sup>5</sup>

likely contributing to the incidence of insomnia and abnormal dreams.

The only justification we are aware of for nightly dosing is that peak blood levels and their accompanying adverse effects would occur while patients are asleep and, therefore, would go unnoticed. However, nausea can rouse one from sleep, and another common adverse effect, bradycardia, could predispose patients to nocturnal falls when moving from the bed to the toilet.

We recommend administering donepezil in the morning with a meal, and oral forms of galantamine and rivastigmine once or twice daily, depending on the formulation, with meals.

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**Editor's Note:** This letter was sent to the authors of "Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms," who declined to reply. ▶

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**This series** is coordinated by Kenny Lin, MD, MPH, Deputy Editor.

## Contraception Should Be Addressed with Women Who Have Sex with Women

**Original Article:** Preventive Health Care for Women Who Have Sex with Women

**Issue Date:** March 1, 2017

**Available online at:** <https://www.aafp.org/afp/2017/0301/p314.html>

**To the Editor:** I appreciated this timely article, but the authors neglect to mention a crucial element of prevention in women who have sex with women (WSW): contraception.

Unintended pregnancy is a very real problem among WSW. As a family physician providing full-scope family planning services for women, I often hear from patients who identify as lesbian or bisexual (often seeking therapeutic abortion after consensual sex or rape) that their previous physicians neglected to offer contraception because “they thought I didn’t need it.”

The authors point out that “a self-identity of being lesbian does not automatically exclude male sex partners,” and that “97% of women who report same-sex sexual behavior have had or still have male sex partners.” We can imagine that WSW may be likely to prefer certain contraceptive methods; be less likely to be offered certain methods (e.g., tubal ligation) because of different patterns of interaction with the health care system; and have different concerns about and barriers to accessing emergency contraception or therapeutic abortions.

At the very least, the SORT: Key Recommendations for Practice table should have included an item about offering contraceptive counseling. All family physicians should be attentive to this oft-neglected area of prevention in the WSW population.

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**In Reply:** A discussion of contraception is important for every woman of childbearing age. As we discussed in our article:

- A self-identity of being lesbian or WSW does not automatically exclude male sex partners.
- About 50% to 97% of women who report same-sex sexual behavior have had or still have male sex partners.
- Among the 7% of women who reported a same-sex sexual relationship, 50% self-identified as heterosexual.

We also emphasized that the physician must ask WSW frank questions about sexual activities. In Table 4, we listed these questions to use as part of a culturally competent history:

- Are you having or have you ever had sex with women, men, or both?

- Have you ever been pregnant?
- Do you have oral sex? Vaginal sex? Anal sex? Other types of sex?
- Do you use barrier protection such as condoms?
- Are there times you do not use barrier protection?
- Do you use another method of birth control? (if sexually active with men)
- Do you (or does your partner) have any plans to conceive in the next 12 months?

These questions should lead the physician to have a pertinent discussion about the need for contraception for WSW.

The SORT table focused on health issues that are disproportionately represented in WSW. Although we certainly agree that WSW should be asked about contraception, we believe that we addressed this issue throughout the article.

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## Lymphadenopathy in Children and Young Adults May Be Due to a Periodic Fever Syndrome

**Original Article:** Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis

**Issue Date:** December 1, 2016

**See additional** reader comments at: <https://www.aafp.org/afp/2016/1201/p896.html>

**To the Editor:** I read with interest Drs. Gaddey and Riegel’s excellent review article on unexplained lymphadenopathy. To the complex differential diagnosis of this common problem, I would add an increasingly recognized entity known as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenopathy). Also known as Marshall syndrome, this symptom complex was first described in 1987<sup>1</sup> and was initially thought to be a rare disease seen only in children. Over the past decade, however, it has been increasingly reported among young adults.

A typical episode is characterized by abrupt onset of fever, chills, sore throat or mouth pain, and tender cervical lymph nodes; in other words, a rather typical presentation of strep throat! A prodrome of fatigue may precede the fever. In the case of PFAPA, rapid strep test results are negative, throat culture yields no growth, and heterophile antibody test results are normal. Further testing might reveal moderate leukocytosis and an elevated erythrocyte sedimentation rate. Marshall syndrome does not respond to antibiotics.

The recurrent nature of Marshall syndrome sets it apart from more mundane illnesses and suggests one of the periodic fever syndromes. Episodes may occur every month or so and last four to five days, with complete resolution

between each course of illness. The case definition specifies six recurrences. Exclusion of cyclic neutropenia is accomplished by a complete blood count. The pathophysiology of PFAPA has yet to be defined, although it appears to be a type of autoinflammatory disorder, with decreased numbers of activated T cells accompanying monthly flare-ups.

Physicians who provide continuity of care are in the best position to recognize PFAPA and initiate proper treatment. Once diagnosed, a single dose of oral prednisone (1 mg per kg) results in rapid resolution of current symptoms. However, there is some concern that this treatment leads to more frequent occurrences.

In carefully selected cases, tonsillectomy (with or without adenoidectomy) has been shown to bring about lasting remission.<sup>2</sup> Cimetidine (Tagamet) has also been employed to induce remission with some success. More recently, the drug anakinra, which acts on interleukin-1, shows promise.

The diagnosis of Marshall syndrome is one of exclusion, and a high index of suspicion is required. The prognosis of patients diagnosed with PFAPA is excellent, with most persons achieving spontaneous remission over time.<sup>3</sup>

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## Cerebrovascular Disease as a Cause of Dizziness

**Original Article:** Dizziness: Approach to Evaluation and Management

**Issue Date:** February 1, 2017

**See additional** reader comments at: <https://www.aafp.org/afp/2017/0201/p154.html>

**To the Editor:** I appreciated the thorough discussion of dizziness. In discussing cerebrovascular disease as a cause, the authors did not include subclavian steal. In our rural tribal health center, we have had a handful of cases that presented as vertigo and intermittent disequilibrium. In most cases, the diagnosis was suggested by carotid and vertebral

artery Doppler ultrasonography showing reversal of flow and retrograde flow in the vertebral arteries. Follow-up magnetic resonance or computed tomography angiography showed subclavian stenosis. The patients were successfully treated with percutaneous stenting. One patient needed to be stented multiple times and still has difficulty. Furthermore, the cardiologist consulting on the case was falsely reassured by similar blood pressures in both arms, not realizing that the patient had subclavian stenosis bilaterally.

A recent study that followed 232 patients over a decade showed that 16% of patients restenosed and required restenting.<sup>1</sup> Symptoms included dizziness, imbalance, visual disturbance, syncope, and upper extremity exertional ischemia.

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**In Reply:** We appreciate Dr. Renwick bringing attention to another central cause of dizziness. In our article, we wanted family physicians to think about more serious causes of dizziness, especially vertebrobasilar ischemia, if a patient had any brainstem symptoms such as diplopia, dysarthria, weakness, or clumsiness. As Dr. Renwick noted, subclavian artery stenosis could be considered in patients with dizziness and symptoms of upper extremity exertional ischemia.

In the study Dr. Renwick cited, the patient's blood pressure was taken in both arms if subclavian artery stenosis was suspected.<sup>1</sup> An interarm difference of 15 mm or greater strongly suggests subclavian artery stenosis. The next diagnostic step would be an imaging study of the subclavian and vertebrobasilar arteries. Significant obstruction can be treated with percutaneous transluminal angioplasty, which may relieve the dizziness.<sup>1</sup>

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## The Need for Systems of Care and a Trauma-Informed Approach to Intimate Partner Violence

**Original Article:** Intimate Partner Violence

**Issue Date:** October 15, 2016

**Available online at:** <https://www.aafp.org/afp/2016/1015/p646.html>

**To the Editor:** We appreciated Drs. DiCola and Spaar's update on intimate partner violence (IPV). The critical update of our 2011 review of this topic in *American Family Physician*<sup>1</sup> noted new evidence supporting screening women of childbearing age for IPV, leading the U.S. Preventive Services Task Force to move from a finding of insufficient evidence to moderate certainty that screening is effective.<sup>2</sup> Primary care must now meet the challenge of operationalizing this recommendation and continuing to push toward a more holistic approach to trauma-informed care.

One obstacle to moving forward has been the time burden on physicians to effectively respond to IPV disclosures. Our 2014 systematic review, however, noted that effective interventions are delivered by nurses, social workers, advocates, and educators providing support, education, safety planning, problem solving, and resource navigation that requires only minutes to hours of time.<sup>3</sup> With adequate support, primary care physicians themselves do not need to shoulder the full burden of IPV response. However, principles of trauma-informed care require that physicians be attuned to the possibility that past or current trauma may impact patients' health and health care.

For the field to reach its full potential in primary care, the next steps will need to be built on an understanding of the experience of trauma across the patient's life span. Stressors experienced during childhood increase the lifetime risk of risky behaviors, revictimization, and poorer health outcomes. A trauma-informed approach historically focused on secondary and tertiary responses would also embrace approaches to primary prevention charged with not only engaging survivors of abuse and adversity, but also the potential perpetration of abuse and violence among our patients.<sup>4,5</sup>

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**In Reply:** We appreciate Drs. Cronholm and Dichter's response to our IPV update. Many family medicine practices have embraced a team-based approach, in which physicians are able to focus their time and energy on addressing the complex ways trauma affects patients' health and on primary prevention. It is still important to recognize, however, that family physicians outside of academic medical centers and large health networks have limited resources. Many times, the "team" consists only of the physician and a small office staff. Even in this setting, it is important for medical education to include the practical details of screening and intervention, along with the ongoing paradigm shift toward recognizing the effects of trauma across the life span and across the families and communities we serve. What is most important is that the question is asked, rather than who asks it.

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## NNTs Misleading for Onychomycosis Treatments

**Original Article:** Topical Antifungals for Treatment of Onychomycosis [FPIN's Help Desk Answers]

**Issue Date:** November 1, 2016

**See additional** reader comments at: <https://www.aafp.org/afp/2016/1101/p734.html>

**To the Editor:** The authors of this article asked, "What is the rate of resolution of onychomycosis treated with topical antifungal agents?" Although the agents discussed are effective for treating onychomycosis, the number needed to treat (NNT) of 7 to 17 is potentially deceptive. Expressing effectiveness as an actual cure rate would have been more direct, clear, and patient centered.

For example, the study on efinaconazole 10% topical solution demonstrated complete cure rates of only 15% to 18% after one year.<sup>1</sup> By comparing efinaconazole cure rates with vehicle cure rates of 3.5% to 5.5%, the NNT is indeed 7 to 10. However, it would also be correct to state that 82% to 85% of patients who used efinaconazole 10% topical solution for 52 weeks did not have a complete cure. Given that the cost of

efinaconazole is approximately \$600 for a single 4-mL bottle,<sup>2</sup> the low absolute cure rate would make the value of this treatment quite low.

Similarly, the study comparing cure rates of tavaborole 5% topical solution with those of placebo yielded an NNT of 13, which might make tavaborole 5% topical solution seem more favorable than if the actual cure rates of 6.5% to 9.1% after 48 weeks of treatment were emphasized.<sup>2</sup> Given that the cost of a single 4-mL bottle of tavaborole 5% topical solution is approximately \$600,<sup>2</sup> and that more than 90% of patients using this treatment would not have a complete cure, the value of this treatment also seems quite low.

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**Editor's Note:** Estimated retail cost for one treatment course based on information obtained at <http://www.goodrx.com> (accessed May 4, 2018).

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**In Reply:** We appreciate Dr. Fallert's interest in our article. In fact, we did report the absolute cure rates. The NNT offers clinical utility for physicians to understand how these topical agents for onychomycosis compare with vehicle over 48 weeks of daily treatment. Space constraints kept us from discussing the costs of these treatments and their comparative value. The bottom line is that topical treatment options for onychomycosis have limited effectiveness and high costs. We hope that our article will help guide family physicians in selecting appropriate treatments for their patients.

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