Cochrane for Clinicians

Putting Evidence into Practice

Pharmacologic Interventions for Apathy in Patients with Alzheimer Disease

Jeanmarie B. Rey, MD, and Virginia B. Kalish, MD, Fort Belvoir Community Hospital, Fort Belvoir, Virginia

Author disclosure: No relevant financial affiliations.

Clinical Question

Is methylphenidate (Ritalin) safe and effective for reducing apathy in patients with Alzheimer disease (AD)?

Evidence-Based Answer

Methylphenidate may improve apathy in select patients with AD (mean difference [MD] = −4.99 on the apathy evaluation scale [AES]; 95% confidence interval [CI], −9.55 to −0.43), although the clinical significance associated with these findings remains unclear and the evidence is considered low quality. The risk of developing an adverse effect is no more likely with methylphenidate than with placebo (relative risk [RR] = 1.28; 95% CI, 0.67 to 2.42).[1] (Strength of Recommendation: B, based on limited-quality patient-oriented evidence.)

Practice Pointers

AD is a debilitating, prevalent, and costly condition affecting 5.7 million Americans.[2] Behavioral and psychological symptoms of dementia such as apathy are common and among the most troubling aspects of dementia care. Apathy is a state of reduced motivation affecting goal-directed cognitive activity, goal-directed behavior, and the accompanying emotional response.[3] Apathy is a highly prevalent and persistent behavioral and psychological symptom of dementia and is associated with disability, poor health, caregiver burden, and mortality.[4,5] The objective of this review was to assess the safety and effectiveness of pharmacotherapies for the treatment of apathy in patients with AD.

This Cochrane review included 21 randomized controlled trials (published between 1998 and 2017) involving 6,384 participants.[1] The authors looked for any placebo-controlled trials investigating pharmacologic treatments in persons with AD or mixed AD (i.e., AD with vascular pathology) reporting an effect on apathy. Of the 21 trials, only four reported apathy as a primary outcome measure; three of these featured an examination of methylphenidate, whereas one featured modafinil (Provigil). Apathy outcomes were measured using the AES or the neuropsychiatric inventory apathy subscale (NPIa). The AES is scored from 0 to 42 and the NPIa from 0 to 12, with higher scores on each indicating greater apathy.

Methylphenidate (20 mg taken daily for two to 12 weeks) may have improved apathy compared with placebo in those with AD who had clinically significant apathy at baseline (MD = −4.99 on the AES; 95% CI, −9.55 to −0.43). This finding was present only with use of the AES. When apathy was measured using the NPIa, methylphenidate did not improve apathy (MD = −0.08; 95% CI, −3.85 to 3.69). Methylphenidate may have had slight benefits for cognition based on the Mini-Mental State Examination (MD = 1.98; 95% CI, 1.06 to 2.91). There appeared to be no difference between methylphenidate and placebo in the risk of developing an adverse effect (RR = 1.28; 95% CI, 0.67 to 2.42). Overall, the data regarding methylphenidate were considered low quality. The one small trial (n = 22) that evaluated whether modafinil was effective for treating apathy in patients with AD had insufficient evidence.

The remaining 17 trials included in this meta-analysis did not investigate apathy as a primary outcome measure. These studies provided low- or very-low-quality evidence on cholinesterase inhibitors, atypical antipsychotics, antidepressants, valproate (Depacon), and two pharmacotherapies from research trials that were discontinued, mibampator (not available in the United States) and semagacestat (not available in the United States). Given the small number of studies within each

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, Assistant Medical Editor.

A collection of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 11.

drug class, as well as the risk of bias and imprecision of these studies, no evidence exists to support the use of these medications for apathy in AD.

Currently, there are no guidelines with recommendations regarding the pharmacologic treatment of apathy in AD. Nonpharmacologic therapies remain the cornerstone strategy for behavioral and psychological symptoms of dementia. Based on this review, a trial of methylphenidate may be reasonable in a patient with AD who has clinically significant apathy. Physicians are encouraged to exercise caution given the risk of medication noncompliance and mishap in the cognitively impaired, as well as potential drug-drug and disease-drug interactions (e.g., agitation, open-angle glaucoma, hypertension, other cardiovascular conditions) in this aging population.

The practice recommendations in this activity are available at http://www.cochrane.org/CD012197.

This article reflects the opinions of the authors alone and does not reflect the opinion of the Department of the Army, Air Force, Defense Health Agency, Department of Defense, or the U.S. government.

References

1. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctôt KL. Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database Syst Rev.* 2018;(5):CD012197.
2. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2018;14(3):367-429.
3. Robert P, Onyike C, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104.
4. van der Linde RM, Matthews FE, Dening T, Brayne C. Patterns and persistence of behavioural and psychological symptoms in those with cognitive impairment: the importance of apathy. *Int J Geriatr Psychiatry*. 2017;32(3):306-315.
5. Steinberg M, Shao H, Zandi P, et al.; Cache County Investigators. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2008;23(2):170-177.

Prophylactic Vaccination Against Human Papillomavirus to Prevent Cervical Cancer and Its Precursors

Corey Fogleman, MD, and Laura Leaman, MD,
Family and Community Medicine Residency Program, Lancaster, Pennsylvania

Author disclosure: No relevant financial affiliations.

Clinical Question

Is prophylactic vaccination against human papillomavirus (HPV) safe and effective in preventing HPV infection and resultant cervical cancer precursors?

Evidence-Based Answer

HPV vaccination in women 15 to 26 years of age prevents the development of cervical intraepithelial neoplasia (CIN) 2 and CIN 3 in women regardless of previous HPV exposure (number needed to treat [NNT] = 39). No serious adverse effects are associated with administration of the HPV vaccine.[1] (Strength of Recommendation: C, based on consistent disease-oriented evidence.)

Practice Pointers

Cervical cancer is the fourth most common cancer in women worldwide, with more than one-half of this type of cancer occurring in women younger than 45 years. Persistent HPV infection can progress to CIN, with a subsequent 12% to 30% probability of CIN 3 (i.e., the highest grade CIN) progressing to invasive cancer.[2] Cytology screening programs have decreased the incidence and mortality related to cervical cancer, but the treatment of high-grade CIN (i.e., CIN 2 or greater) remains a source of patient morbidity. Therefore, the primary prevention of high-grade CIN lesions with prophylactic HPV vaccination has the potential to reduce morbidity and mortality related to HPV infection.

This Cochrane review involved 26 randomized controlled trials and 73,428 international women 15 to 45 years of age.[1] Included trials evaluated vaccine effectiveness and safety for the monovalent, bivalent, or quadrivalent HPV vaccines; the nonavalent HPV vaccine was not included. The surrogate primary outcome of high-grade CIN and adenocarcinoma in situ (AIS) incidence following prophylactic vaccination vs. placebo was evaluated, because assessment for the development of invasive cervical cancer would require prohibitively large and long-term studies. Although all but one trial were funded by the respective vaccine manufacturers, most trials were assessed to be at low risk of bias.

In women 15 to 26 years of age, HPV vaccination provided protection against persistent high-risk HPV types 16/18 infection at six and 12 months, as well as the development of CIN or AIS. Although women were HPV negative at study enrollment, the vaccine seems to prevent dysplasia. Even when HPV status was unknown, the vaccine still prevents CIN 2 (NNT = 60) and CIN 3 (NNT = 113). A subset of trials determined that significant protection against CIN 2 and CIN 3 was still afforded by receipt of only one or two doses of the bivalent and quadrivalent vaccines.

SUMMARY TABLE: REPRESENTATIVE TREATMENT OUTCOMES WITH PLACEBO VS. HPV VACCINE

High-risk HPV status at study initiation	Risk with placebo	Risk with HPV vaccination	Number needed to treat (95% CI)	Number of participants (number of studies)	Quality of evidence
Negative					
CIN 2	28.7 per 1,000	10.6 per 1,000	55 (46 to 77)	25,180 (5)	High
CIN 3	10.9 per 1,000	2.3 per 1,000	*	20,719 (3)	Moderate
CIN 2 and 3 combined	39.6 per 1,000	12.9 per 1,000	*	—	—
Irrespective of risk					
CIN 2	55.9 per 1,000	39.1 per 1,000	59.5 (42 to 119)	35,779 (4)	High
CIN 3	26.6 per 1,000	17.8 per 1,000	113 (74 to 520)	35,489 (3)	Moderate
CIN 2 and 3 combined	82.5 per 1,000	56.9 per 1,000	39 (27 to 97)	—	—

CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.

*—Could not be calculated based on numbers provided.

Only two studies included women 24 to 45 years of age. HPV vaccination in this age group did not appear to provide protection against CIN 2, and there were no data on CIN 3 or AIS.

Short-term local adverse effects (pain, erythema, or swelling at the injection site) were more common in women who received the vaccine vs. the control, but no serious adverse effects were observed. There was no increased risk of miscarriage among women who became pregnant during the trials.

Criticisms of this review have suggested that it does not include enough data about the nonavalent vaccine nor enough unpublished data; that authors of this review may not have adequately assessed risk of bias; and that the original reviews may have underestimated the risks and/or severity of adverse effects of HPV vaccine.[3] In response, the Cochrane editors commissioned an independent review, which concluded that this analysis contained enough data to report the stated outcomes; that bias was adequately assessed; and that the risks and adverse effects were appropriately estimated.[4]

The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend prophylactic HPV vaccination for all girls 11 to 12 years of age, with catch-up vaccination for girls 13 to 26 years of age for the primary prevention of cervical cancer.[5] Recently, the U.S. Food and Drug Administration expanded the approved age range to include women 27 to 45 years of age.[6] Ideally, adolescent girls should be vaccinated before their first sexual contact to allow for the highest vaccine effectiveness, but vaccination will still protect against CIN or AIS regardless of previous HPV exposure.

The practice recommendations in this activity are available at http://www.cochrane.org/CD009069.

Editor's Note: The numbers needed to treat reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

References

1. Arbyn M, et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Syst Rev.* 2018;(5):CD009069.
2. McCredie MR, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008; 9(5):425-434.
3. Jørgensen L, et al. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. *BMJ Evidence-Based Medicine.* https://ebm.bmj.com/content/23/5/165. Accessed December 2018.
4. Tovey D, et al. Cochrane's Editor in Chief responds to a *BMJ Evidence-Based Medicine* article criticizing the Cochrane review of HPV vaccines. https://www.cochrane.org/sites/default/files/public/uploads/cochrane_hpv_response_3sep18.pdf. Accessed December 2018.
5. CDC. Immunization schedule for adults (19 years of age and older). https://www.cdc.gov/vaccines/schedules/easy-to-read/adult.html. Accessed December 2018.
6. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm. Accessed December 2018. ■