Ethical Considerations for the Use of Next-Generation Alzheimer Drugs in Symptomatic and At-Risk Patients

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ABSTRACT

This article presents a case in which a patient with mild Alzheimer disease requests a prescription for a newly developed Alzheimer disease drug, after which the patient's daughter inquires about its potential usefulness as a prevention strategy for herself. The article discusses the physician's responsibility to balance the ethical principles of beneficence, nonmaleficence, and respect for patient autonomy when evaluating requests for medications from patients with neurocognitive disease as well as from asymptomatic but at-risk patients.

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Case

Note: This is a hypothetical case and drug.

A 75-year-old woman presented to the memory clinic for her annual follow-up visit, accompanied by her 50-year-old daughter. The patient had been diagnosed with mild, symptomatic Alzheimer disease (AD) 4 years prior and had been stable on donepezil 10 mg/d for the past 2 years. The patient had a strong family history of AD. She lived independently, but her daughter advised her about her finances and phoned her daily, reminding her to take her donepezil. At the follow-up visit, her Mini-Mental State Examination (MMSE) score was 24 out of 30.

At the conclusion of the examination, the patient asked whether a recently approved drug for AD would be useful for her condition. The patient's daughter then asked whether she should begin taking the drug herself to try to prevent onset of neurocognitive symptoms because of her strong family history of AD. The daughter provided the neurologist with a printout of information she had located on the Internet describing the medication as a monthly IV medication costing thousands of dollars per dose to be used only in patients with biomarker evidence of amyloid pathology. During clinical trials, 5% of patients developed either cerebral edema or intracerebral hemorrhage.

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DISCUSSION

This case, while about a hypothetical patient and drug, is realistic considering the pace of research in Alzheimer disease (AD) for asymptomatic at-risk individuals¹ and individuals with prodromal symptoms,² mild cognitive impairment due to AD,³ or mild dementia due to AD.⁴ Neurologists may soon be facing such clinical and ethical dilemmas with their patients who have AD. Any time physicians recommend a new therapeutic intervention, they must engage their patients in an informed consent process. Adult patients with decision-making capacity (or surrogates, acting on the patient's behalf, if patients lack capacity) have a right to self-determination. Patients must be apprised of the risks and benefits of a proposed therapy and given adequate information to decide whether the proposed intervention aligns with their personal values. Shared decision making is often appropriate and allows the physician to guide the patient to make the choice most compatible with the patient's values and desires. This shared decision-making model eschews paternalism, respects patient autonomy, and acknowledges that patients typically desire some guidance from their physicians in making sense of the information that must be considered for a truly informed decision. In addition to respecting a patient's autonomy rights, physicians must also consider the dual effects of beneficence and nonmaleficence. Beneficence calls on physicians to act to propose interventions that promote patients' well-being, while nonmaleficence requires physicians to minimize patient harm.

Although traditionally recommendations for therapy come from physicians, physicians are now routinely managing the expectations of patients who research therapies on the Internet. Neurologists must grapple with the same ethical considerations regardless of the source of the request for therapy. Additionally, neurologists must remember that they are their patients' fiduciaries and must always act in their patients' best interests. Especially when a request for a given therapy comes from the patient, the physician must resist the urge to act paternalistically and dismiss the request outright. However, the physician need not concede to the demands of a patient in the false belief that a patient's right to autonomy trumps sound clinical judgment. Physicians are not acting paternalistically when they refuse to give in to a patient's medically unreasonable request. Like all therapies, the requested therapy must be medically appropriate, meeting the demands of beneficence by maximizing benefit and the demands of nonmaleficence by minimizing harm.

In this hypothetical case, the patient's request and her daughter's request present quite different ethical challenges. The patient's request is truly a routine matter of clinical judgment. If the US Food and Drug Administration (FDA) approved this new (hypothetical) medication for people like this patient who have mild AD, then the issue is really about ethical demands on a physician when providing informed consent for a therapy with which the physician has no experience. When proposing a new therapy unfamiliar to the physician, the demands of medical professionalism, which include the physician's fiduciary obligations to work in the patient's best interest, require the physician to consult peer-reviewed publications and pay particular attention to inclusion and exclusion criteria used in phase 3 trials as well as to the efficacy and safety data of the new medication as compared to placebo. The physician should explain to the patient that there may be insufficient postmarketing data to establish safety

beyond the length of the study and in patients whose demographics and medical comorbidities differ from the studied population.

This particular hypothetical drug also requires expensive diagnostic tests as part of the patient selection process. Thus, if the patient meets the clinical criteria for using this therapy, she may be an appropriate candidate for this newly approved therapy. The informed consent process would have to include an honest and thorough review of the not-insignificant risks associated with this therapy. Even if the patient possesses decision-making capacity, the patient should be encouraged to involve her daughter in the informed consent process since this treatment requires marshaling considerable cognitive and material resources, and the patient appears to rely on her daughter considerably. If the neurologist deems the patient lacking in capacity for this decision, the patient should still assent to the intervention even while the patient's surrogate decision maker provides consent.

The daughter's request for a preventive treatment using this therapy would be considerably more complicated if the FDA did not approve this therapy for people like her, who have a strong family history of AD, but who currently do not exhibit symptoms of the disease. Although they may prescribe medications off-label, physicians, as their patients' fiduciaries, must ensure that their therapeutic recommendations meet the same ethical and clinical standards as on-label prescribing. However, clinicians at the vanguard of off-label prescribing of recently approved medications typically will not possess robust evidence supporting the therapy's off-label use. The more serious the risk of harm from an intervention and the less well-founded is the evidence of benefit, the less prudent it would be for a physician to recommend such off-label treatment. Thus, the risks of harm of nonintervention must be considerably greater than the risks for active intervention in order to warrant recommending a relatively untested therapy.

CONCLUSION

Although the patient's request for the (theoretical) new medication may be reasonable, the neurologist should not concede to the daughter's request at this time, even if the daughter has the financial resources to pay out-of-pocket for this costly intervention. If new data emerge from high-quality trials suggesting that this treatment is effective in preventing AD in presymptomatic at-risk people, the physician should reconsider this request at that point. The neurologist may probe to see if the daughter is interested in participating in a trial for at-risk people, and she can be referred to an appropriate research center. Additionally, the encouraging results of nonpharmacologic interventions combining physical activity, cognitive training, optimal nutrition, and medical care over 2 years in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study provide strategies to stave off the onset of dementia.⁵ Similar studies are underway in North America and Europe.⁶ Some countries, such as Australia, are already implementing national plans to prevent AD based on interventional epidemiology data.⁷ The daughter in this case should be educated about these nonpharmacologic interventions.

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