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Review

Future development of a depot antiepileptic drug: What are the ethical implications?

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ABSTRACT

Depot medications have been used for long-term treatment of many different medical conditions (schizophrenia, opioid addiction) and for prevention of pregnancy (birth control). In addition, proposals for depot medication for antidepressants have been made as a possible treatment for chronic depression. For the treatment of chronic epilepsy, there are currently no depot antiepileptic drugs (AEDs). However, there may be a role for them. Depot AEDs could improve medication adherence rates, thereby reducing the morbidity and mortality that are associated with ongoing seizures. This could help to reduce hospital costs for people with epilepsy. Potential patient populations that could benefit from a depot AED include patients with forgetfulness, socioeconomic barriers to access of daily oral medications, impaired gastric absorption or dysphagia, comorbid epilepsy and psychiatric disease, and personal preference to avoid the inconvenience of taking a medication daily or even multiple times per day. In this article, we review reasons to create a depot AED and the outcomes of doing so in the context of the pillars of bioethics: beneficence (to act in a patient's best interest), autonomy (to respect a patient as an individual and honor their preferences), nonmaleficence (to do no harm), and justice (to treat all persons fairly and equally).

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1. Introduction

Long-acting depot formulations of oral medications have been developed as a way to minimize frequency of administration, improve adherence, and stabilize blood levels. The advantage of stable serum levels of medication is that it improves efficacy, helps to avoid withdrawal, and reduces the toxicity that is associated with the peak levels that can occur with oral dosing. The first depot, a long-acting injectable antipsychotic called fluphenazine enanthate, was developed in 1966. Many other long-acting antipsychotic formulations were produced in the following years [1]. Shortly thereafter, a long-acting depot birth control, medroxyprogesterone acetate, was developed [2]. Its use eventually became widespread. More recently, a long-acting extended-release injectable formulation of naltrexone was developed to treat opioid addiction [3]. Use of depots in other settings, such as depression, has also been discussed [4]; however, this is not yet commercially available.

For the treatment of chronic epilepsy, there have been proposals for several alternative methods of antiepileptic drug (AED) administration other than long-acting injectable formulations. These methods include AED administration through skin patches, an AED implantable device (similar to the nexplanon/implanon for birth control), and an implantable pump that continuously infuses the AED directly into the cerebrospinal fluid or to the region of seizure onset. Although proposed, none of these novel techniques have been implemented in the clinical setting [5]. In 2012, an experiment in rats reinvigorated the interest in the potential of AED depot drug delivery. In this in vivo experiment, ethosuximide loaded nanogels were found to suppress spike–wave discharges when subcutaneously injected into 5 Long Evan rats [6].

There are several potential benefits of a long-acting medication for patients with epilepsy. First, a long-acting antiseizure medication could reduce concerns about adherence to a medical regimen. Studies have shown that in people with epilepsy, nonadherence significantly increases emergency department visits and rates of hospitalizations [7]. Improved adherence reduces the morbidity and mortality from seizures, including cases of sudden unexpected death in epilepsy (SUDEP). Thus, we propose that there is a need for the development of a depot AED. Herein, we provide case examples of patients who could benefit from a depot formulation of an AED and discuss both the reasons to create one and the consequences of doing so using the pillars of bioethics: beneficence (to act in a patient's best interest), autonomy (to respect a patient as an individual and honor their preferences), nonmaleficence (to do no harm), and justice (to treat all persons fairly and equally) [8]. This discussion pertains to the clinical care of patients

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with epilepsy, but does not address the ethical aspects of drug development or clinical research. While we do not know of any efforts to produce an AED in depot form, we hope that by reviewing the reasons to create one and the consequences of doing so, we will foster interest in the creation of this formulation of an AED.

2. Case examples

2.1. Case 1

A 58-year-old woman with refractory localization-related epilepsy with a high seizure burden despite trials of multiple AEDs frequently waits 3 days after running out of pills before refilling her prescriptions. At multiple clinic visits, she continues to require repeated education regarding the importance of medication adherence and the risks of medication nonadherence despite the chronic and refractory nature of her epilepsy.

2.2. Case 2

A 72-year-old man with non-small-cell lung cancer and known brain metastases complicated by symptomatic epilepsy is currently getting chemotherapy which has been complicated by frequent episodes of nausea and vomiting causing him to be unable to tolerate his AEDs.

2.3. Case 3

An 18-year-old woman with a genetic epilepsy syndrome who has one to two nocturnal generalized seizures per month despite adherence to her three-times-a-day AED regimen is starting college and requests a long-acting AED to simplify her daily routine and minimize potential missed doses.

2.4. Case 4

A 47-year-old undomiciled man with chronic schizophrenia and polysubstance abuse with symptomatic epilepsy secondary to a traumatic brain injury, now with schizophrenia well managed on an antipsychotic depot, has multiple visits to the local emergency department each month with breakthrough seizures in the setting of medication nonadherence.

3. Discussion

3.1. Issues of beneficence

The success of depot medications in other chronic diseases demonstrates that there is potential for people with epilepsy to benefit from AED depot development. As compared with oral antipsychotics, depot antipsychotics were found to be associated with lower risk of relapse, suicide, rehospitalization, and incarceration in a systematic review by Khan et al. of the landmark studies Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), European First Episode Schizophrenia Trial (EUFEST), A Comparison of Long-Acting Injectable Medications for Schizophrenia (ACLAIMS), and Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) [9]. Additionally, in a study examining 65 patients whose most common reason for starting risperidone depot was noncompliance, Najim et al. found an association between the depot prescription and reduction in number and length of hospital admissions [10].

The potential for benefits from an AED depot is obvious when considering the prevalence of AED nonadherence. The exact percentage of noncompliance in people with epilepsy varies across studies and geographic regions. However, nonadherence is a worldwide problem. It occurs in both developed and less developed nations. In the US, recent studies suggest that nonadherence occurs in about 33% of people with epilepsy [11]. In one cross-sectional study of 450 patients with epilepsy in Northwest Ethiopia, 38% were nonadherent as measured by the Morisky Medication Adherence Scale (MMAS) [12]. Factors that were significantly associated with AED nonadherence included being on treatment for 6 or more years; having to pay for AEDs as compared with receiving AEDs free of charge; lacking health information about their illness from healthcare providers; or having poor social support, perceived stigmatization of AED use, and side effects [13]. A large German study of 31,317 people with epilepsy similarly found that one-third of patients were poorly adherent based on the medication possession ratio [12]. Adherence was more common in patients who lived in West Germany, had learning disabilities, and were treated with new rather than old and brand-name versus generic AEDs. Interestingly, among the most common AEDs prescribed, the highest rate of compliance was for patients on levetiracetam while the lowest was for patients on valproate. As one would expect, the adherence rate was lower for patients taking medications 2 or more times a day. The authors concluded that administration of new, well-tolerated drugs in simple dosage regimens improved AED adherence. In a 131-patient study in China, 5%, 70%, and 25% showed high, medium, and low adherence, respectively. The reasons for nonadherence included forgetfulness (54%), seizure-free period for a period (49%), and fear of adverse drug effects (28%) [14]. Another study in rural India with 120 patients classified participants as highly adherent, moderately adherent, or nonadherent. Of the moderately and highly adherent patients, 47% and 13%, respectively, reported forgetfulness as the reason for missed medications. Of the 29% of patients who were classified as nonadherent, 81% reported that they assumed that the drug was harmful, 73% felt cured of the disease, and 73% wanted to avoid side effects [15]. Although nonadherence due to the desire to avoid side effects would not be addressed by a depot AED, nonadherence due to forgetfulness and barriers to medication access, as illustrated in case 1, could be avoided with a depot AED.

Antiepileptic drug nonadherence has profound clinical and economic repercussions. As would be expected, a recent animal epilepsy model showed that nonadherence has a direct correlation with reduced seizure control [16]. Nonadherence is a primary risk factor for emergency department visits and hospitalizations in patients with epilepsy [17]. RANSOM, a landmark retrospective study of 33,658 patients in 388,564 AED-treated quarters demonstrated an over threefold increased risk of mortality in the 26% of patients nonadherent to AEDs as compared with the patients who were adherent to AEDs. Nonadherence was also associated with a significantly higher incidence of visits to the emergency room, hospital admissions, injuries secondary to motor vehicle accidents, and fractures [18]. In another retrospective study of 10,892 patients, Davis et al. found that the 39% of patients who were nonadherent had an increased likelihood of hospitalization and emergency room admission associated with increased healthcare costs [19].

Notably, there is substantial psychiatric comorbidity in patients with epilepsy [19,20]. Some studies estimate that psychiatric disorders can be identified in 25–50% of patients with epilepsy and that the prevalence is higher among patients with poorly controlled seizures [21]. From the proven benefits of antipsychotic depots, we may be able to extrapolate that AED depots may also provide benefits for a select group of patients, as illustrated in case 4 [20,22]. Moreover, there is the possibility that controlling seizures would make psychiatric symptoms better as well. Mendez et al. found that psychotic symptoms often emerge temporally with increased seizure activity [23], so improved seizure control could potentially reduce psychotic symptoms in patients with both epilepsy and a psychiatric disorder.

In addition to the clinical benefits of AED depots, the financial incentives must be considered. The potential cost savings of AED depot development is substantial. Data from RANSOM (discussed above) demonstrated that nonadherence was associated with increased cost because of inpatient ($4320 additional cost per quarter, 95% confidence interval (CI) = $4077–$4564) and emergency department services

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