

Challenges and Opportunities for Improvement

Epilepsy: Patient Adherence to Medications



Introduction

Lack of adherence to treatment regimens is an important problem in many therapeutic areas. Nonadherence to antiepileptic drugs (AEDs) can result in increased frequency of seizures. It is estimated that 30-80% of patients with epilepsy exhibit some form of nonadherence. The reasons for nonadherence are diverse and include memory problems, difficulties with pill burden, failure to understand treatment instructions, and socioeconomic barriers. Currently, there is a significant unmet need in addressing nonadherence to antiepileptic drugs. This unmet need provides an opportunity to develop products and programs aimed at combating nonadherence in patients with epilepsy.

Recognizing the need to improve adherence, Aprecia called upon an advisory board of epilepsy experts to discuss the critical factors of adherence in epilepsy treatment, and to introduce the group to products and programs designed to foster improved adherence to epilepsy medications.

The following advisory board members were interviewed for this research:

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The following report is a summary of major topics discussed during the advisory board meeting. The key findings in this report are further supported by the medical literature and additional one-on-one market research performed by Access Medical and Aprecia Pharmaceuticals. As a matter of policy, the members of the advisory board do not support any specific product.

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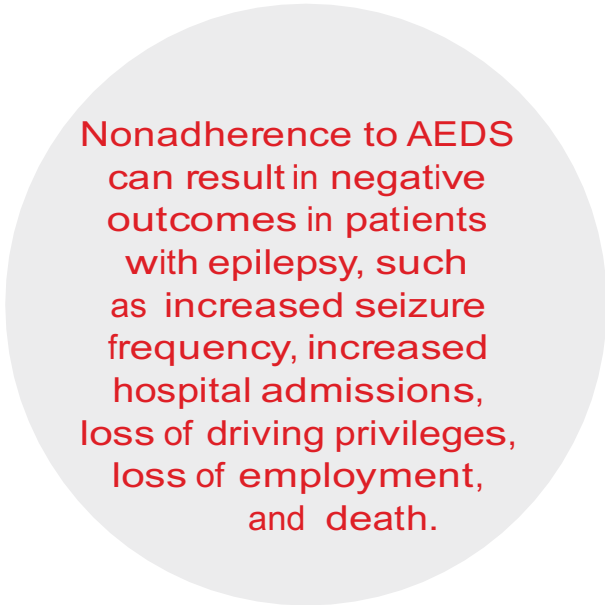
The Problem of Nonadherence to AEDs

Epilepsy is a term used to describe a group of neurologic conditions that result in a chronic tendency to experience recurrent and unprovoked seizures. Successful treatment of epilepsy requires vigilant self-management, including strict adherence to anti-epileptic drugs (AEDs). Adherence is defined as the extent to which a person's behavior coincides with medical or health advice.^{2,3} Nonadherence to AEDs can result in negative outcomes in patients with epilepsy, such as increased seizure frequency, increased hospital admissions, loss of driving privileges, loss of employment, and death.⁴⁻⁷

Chronic diseases such as epilepsy require long-term adherence to prevent negative outcomes. Maintaining adherence over a long period can be challenging for many patients. It is not surprising that many patients become non-adherent, which can range from the patient not taking medication exactly as prescribed to completely discontinuing all medications.^{8,9} The rate of nonadherence is estimated to be between 30-80% of patients, depending on the patient population being analyzed.¹⁰ In addition, up to 30% of patients being treated are categorized as having intractable epilepsy.¹ A patient is labeled as having intractable epilepsy if they fail 2 or more medications provided to them at their optimal dosage.^{1,11} Patients with this classification have additional hardships including restrictions on driving.¹² Non-adherence with these patients is enhanced by the feeling that the drugs are not controlling the seizures, and thus the patient can believe it is not important to take them as directed.¹³ Thus, adherence to a prescribed medication is important for the patient's quality of life.

Regardless of the reason for nonadherence, the success of AED therapy is dependent upon a patient's ability to take their prescribed treatment regimen. Medication nonadherence is considered the single greatest cause for treatment failure and often does result in an increased frequency of seizures.¹⁴ The consequences of nonadherence to AEDs can be immediate and devastating to a patient. The factors that contribute to nonadherence are unique to each patient population and perhaps to each individual patient. Nevertheless, it is possible to categorize several general barriers to adherence.

First, nonadherence can be due to patient-related factors such as age, individual patient habits, beliefs about medications, and socioeconomic conditions. The observed contributors to nonadherence are often unique to different age groups. For example, many pediatric patients have low self-management skills and need to rely on caregivers. Based on cross-sectional studies using self-report, the rate of nonadherence in pediatric populations is between 12% and 35%.¹⁰ One study found that the rate of nonadherence in newly diagnosed children with epilepsy during the first month of therapy is approximately 21%.⁸ This result is alarming because children and parents are most likely to adhere to their treatment regimen in the initial stages of management.⁸ In adolescent patients, one study found that only 52% of teenagers reported that they never missed medication compared



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with over 72% of adults aged 20 years or more.¹⁵ In elderly patients, forgetfulness, having the ability to drive to procure the medications, and difficulty swallowing may contribute to nonadherence.⁴ In addition to age, patient habits can also dictate whether a patient will take their medications. Missing medications may be either intentional or unintentional, depending on whether the patient believes that their medications are helpful. Finally, the socioeconomic status of a patient can determine whether the patient has the financial ability to obtain the medication.¹⁶ A recent study identified and characterized trajectories of adherence in children with newly diagnosed epilepsy over the first 6 months of therapy in order to determine socio-demographic and epilepsy-specific predictors of adherence trajectories. This study found that socioeconomic status was a strong predictor of adherence, with lower socioeconomic status associated with higher nonadherence.⁹ Cost burdens can also negatively effect the adherence of adult patients, as these patients are more likely to be unemployed or underemployed and have insurance that charges higher copays.¹³

A second general category for contributors to nonadherence is healthcare professional-related factors such as patient-physician relationships. Successful interactions with medical personnel can increase adherence. In order for the patient to adhere to a treatment regimen, they must first understand the doctor's directions. Open communication is important, and prescribers must be able to ask their patients if they are taking their medications without sounding judgmental or accusatory. Educational programs that foster better communication skills may help improve patient adherence.¹⁶ In general, physicians do not receive specific training on how to speak about self-management with their patients.¹⁷

A third set of barriers to adherence are factors related to the disease, such as severity of the illness and frequency of symptoms. Unlike many diseases, adherence in epilepsy can be measured in seizures, which is an all or none event.¹⁶ A missed dose of a single AED can result in a seizure for some patients but not for others.¹⁶ Some patients who have not experienced seizures over an extended period of time may conclude that the AEDs are not necessary and then stop taking AEDs, particularly if they have skipped doses previously with no seizures.^{4,5,16} In epilepsy, it remains unclear what the optimal level of adherence is to remain seizure-free.

Finally, properties of the medication including safety, side effects, efficacy, and dosing can contribute to nonadherence. Common side-effects of AEDs include fatigue, behavioral changes, dizziness, dry mouth, weight gain or loss, acne, and rash along with other less common but serious effects such as hepatic failure, gastrointestinal effects such as nausea or vomiting, and teratogenicity.^{4,18-20} Most patients will experience at least one side effect to an AED,²¹ and some patients intentionally alter their medication schedules to avoid side-effects.^{4,22} For example, a patient might turn a twice-a-day regimen into once-a-day at night to avoid drowsiness.¹⁶ On the other hand, patients might question the efficacy of a medication if they are still experiencing seizures.¹⁶ Finally, the physical act of having to take AEDs can increase nonadherence. For example, the stigma associated with epilepsy can cause some patients to minimize or discontinue pill-taking in public.⁴ Difficulty in pill swallowing, especially with large pills often prescribed in the treatment of epilepsy, can be difficult in children, the elderly, and patients with dysphagia.

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Interventions to Help Address Nonadherence

Studies designed to assess adherence to AEDs vary greatly in the literature. Currently, there is not a standard method by which to measure patient adherence to AEDs. Examples of different methods used in various studies include using self-report, parent-report, pill counts, pharmacy refill data, and use of electronic monitors, such as the medication event monitoring systems (MEMS) caps™, in which a computer chip is embedded in a specially designed pill cap.¹⁴

Some studies have focused on improving doctor-patient relationships as a way of increasing adherence. One study found that assessment of the appropriateness of a proposed treatment for an individual patient should include an exploration of the patient's preferences towards the medicines being prescribed.^{23,24} Another study found that transitioning to a sustained-release formulation of a drug resulted in greater adherence.²⁵ Clinical trials in other chronic diseases that require long-term treatment including hypertension, diabetes, depression, and HIV/AIDS, have shown that improved doctor-patient relationships can result in increased rates of adherence. A recent randomized clinical trial has shown that improving specific patient and clinician behaviors such as close monitoring of disease control parameters and timely treatment adjustments to achieve individualized goals, can improve disease control and quality of life among patients with multiple conditions and complex healthcare needs.²⁶

Other studies have focused on education programs as a method of improving adherence. One study investigated if adherence could be improved by counseling, disease and drug informational leaflets, self monitoring of medication of adherence and seizures, and mailed reminders for missed appointments and drug refills in 53 hospital outpatients.²⁷ Although this study found significant improvements in medication adherence and serum drug levels, there was no significant association for patient education and the frequency of seizures. These education programs can focus on both patient education and physician education.

Few studies have examined medication-related factors as a way of improving adherence. One study using a questionnaire of 2031 respondents from 8 European countries found that using an extended-release formula of a medication resulted in a reduction in reported side effects, an improvement in the level of adherence, and a modest improvement in patient satisfaction.²⁸

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ZipDose® Technology

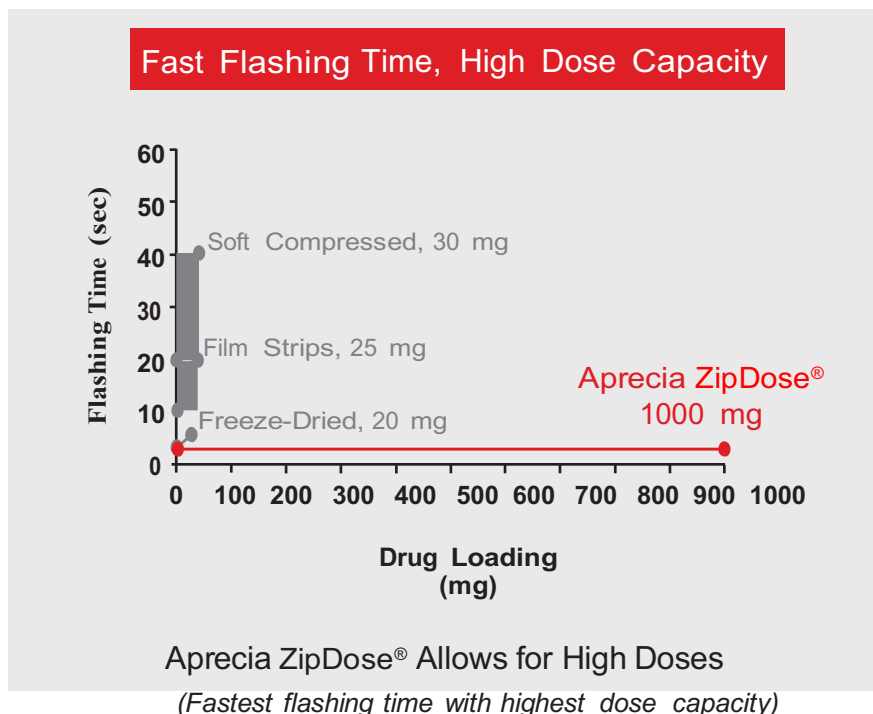
Aprecia Pharmaceuticals has helped to develop a new approach to potentially assist patients with adherence issues by offering a new fast-melt dosage delivery form of AED medications. Aprecia's formulations are based on a breakthrough technology platform that uses 3 dimensional printing (3DP). Originally developed and patented by the Massachusetts Institute of Technology, Aprecia owns a worldwide license to the pharmaceutical use of 3DP technology.

Aprecia's technology achieves a paradigm shift in precisely engineered drug release profiles. Because 3DP is a fundamentally different manufacturing process, it opens a new route to pharmaceutical product development in which superior control of internal structure and external appearance is realized.

ZipDose® formulation is a versatile fast-dispersing dosage form that offers a new route to developing high-dose products with fast flashing times, unique taste masking, and immediate-release or extended-release combinations.

At least some patients, particularly pediatric and geriatric patients, have trouble swallowing large pills. In addition, some of these patients have a fear that pills can get stuck in their throats. A fast-melt dissolving tablet can help alleviate these problems.²⁹ ZipDose® offers an alternative to large hard tablets for both pediatric and geriatric populations. This next-generation fast-melt dosage form will dissolve in the mouth of a patient in 1 to 5 seconds with a sip of water. In contrast to liquid preparations, this form is pre-measured and spill-proof, and can be carried in single-unit blisters for portability.

ZipDose® formulations have the unique ability to administer a high dose with a rapid flash time (Figure 1). The ZipDose® formulation can accommodate up to 1000 mg of medication while still retaining a rapid flash time of 1 to 5 seconds. This level of dosage capacity and fast flash time is unprecedented.



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It is expected that the easy-to-swallow ZipDose® formulation will help promote patient adherence by improving both the patient and caregiver experience with administration. ZipDose® alleviates pill burden by a different tactic than reducing the number of tablets or the dosing frequency—the actual experience of taking the medication becomes more pleasant and the effort for each and every dosing event is reduced, changing how patients relate to and feel about the act of taking their medicine.

Preliminary market research indicates that physicians are enthusiastic about utilizing the ZipDose® formulation. After learning about and taste-testing the ZipDose® product, experts in epilepsy adherence indicated a willingness to try the new formulation with their patients. The advisors were asked to provide feedback on the ZipDose® technology. Responses were uniformly positive, with one advisor commenting *“Where did it go? Holy cow. That’s pretty cool.”*

While enthusiastic about the technology, the experts offered important considerations regarding tablet characteristics that can impact nonadherence. The size of a pill is an important consideration for both pediatrics and geriatrics.¹⁷ Additionally many patients, especially children, are sensitive to taste. Aprexia product development teams seek to identify and achieve optimal tablet size, taste and dispersion targets as part of each target product profile. The ZipDose® formulation was identified by the expert advisors as providing an important alternative to current dosage forms, especially for children, the elderly, and other patients who have difficulty swallowing.

Summary

Adherence to medications regardless of medical condition is essential to successful treatment. The factors associated with nonadherence include patient-related factors, difficulties with communication between the patient and healthcare provider, disease-related factors, and medication-related factors such as pill burden and side-effects. It is likely that a multi-faceted approach tailored to each individual patient will be required to combat nonadherence in patients with epilepsy. As a part of this multi-faceted approach, the use of easy-to-swallow dosage forms, such as the ZipDose® formulation, may play an important part of future programs to help improve patient adherence to medications in epilepsy.



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