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Review article

Treatment non-adherence in pseudo-refractory epilepsy

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ABSTRACT

Non-adherence to antiepileptic drug treatment strongly affects the outcome of epilepsy and is frequently clinically unrecognized. This review addresses current knowledge on medication-taking behavior in people with epilepsy, as well as the importance of tailoring interventions to the individual patterns of non-adherence.

Non-adherence can be categorized as non-initiation, poor execution (accidental or intentional) or non-persistence and are related to clinical characteristics and health care barriers. All available methods to assess adherence are hampered by shortcomings. Self-reports are indirect and subjective. Pill-counts, electronic bottle-tops and pharmacy records are objective, but indirect measures of drug ingestion. Therapeutic drug monitoring is both direct and objective, but pharmacokinetic and diurnal variability must be taken into account.

Young adults with generalized epilepsy may be particularly vulnerable to non-adherence. The drug burden in the form of polytherapy, multiple dosing and side effects are obvious obstacles. Poor understanding of the principles of prophylactic treatment as well as drug costs may be important in people with low socioeconomic status. Depression is also associated with low adherence. In people with multihandicaps, failed oral intake may be due to behavioral or physical problems, as well as insufficient education of the caregivers.

Non-adherence often results in seizure breakthrough and hospital admissions, but the consequences may be more dramatic. It is the leading cause of status epilepticus in people with epilepsy, and the association with sudden death (SUDEP) is clear.

The management of poor drug-taking behavior should be based on the identification of the specific causes in each individual and corresponding multiprofessional interventions. Non-adherence to antiepileptic drugs needs more clinical and scientific attention.

Contents

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Introduction

Poor adherence to prescribed treatment is considered one of the most serious obstacles to the management of epilepsy (Faught, 2012; Samsonsen et al., 2014). It is of major importance to acknowledge that uncontrolled epilepsy does not necessarily reflect drug-resistant epilepsy. Recently, the International League Against Epilepsy defined drug-resistant epilepsy as uncontrolled seizures in spite of adequate trials of at least two tolerated, appropriately chosen and appropriately used antiepileptic drug (AED) schedules (Kwan et al., 2010). Hence, this problem was addressed, but the fact that adherence failure often is a clinically underestimated cause of seizure breakthrough should receive more attention (World Health Organization, 2003; Samsonsen et al., 2014).

The terminology of medication-taking behavior has changed over time and has become more differentiated and concise (Eatock and Baker, 2007). The term compliance has fallen into discredit as it suggests an element of passive obedience, whereas concordance merely relates to the patient's understanding and approval of a treatment plan. Adherence has replaced compliance, as it is a more exact term in the meaning of the implementation of an agreed medical treatment, its initiation and execution as prescribed. Lack of adherence may be intentional or non-intentional. Persistence denotes maintenance of treatment without stopping it against medical advice. In front of a patient with failed drug intake, this terminology should be born in mind, because the various patterns of non-adherence in the form of intended or accidental drug omission, as well as non-concordance and non-persistence, require different approaches by health care providers.

This review briefly addresses the relation of non-adherence to various clinical characteristics, as well as the importance of tailoring interventional strategies to the individual patient profile.

Assessment of adherence

Adherence can be measured by subjective and objective methods, as well as by direct and indirect approaches (World Health Organization, 2003; Osterberg and Blaschke, 2005, Paschal et al., 2008; Faught, 2012) (Table 1). All have shortcomings, but combined methods may enhance the recognition of non- adherence (Smithson et al., 2012, Chapman et al., 2014, 2015).

Self-reporting obviously relies heavily on the patient's perception of his or her own adherence. It has been demonstrated that many patients who self-report as adherent, in fact are not (McAuley et al., 2015). In a recent study based on therapeutic drug monitoring in consecutive emergency hospital admissions for seizures, more than 40% of obviously non-adherent patients who were specifically asked for medication failure, claimed regular intake (Samsonsen et al., 2014). Questionnaires are simple and inexpensive, but a major obstacle is that patients who do not follow prescribed regimens also tend to report their behavior inaccurately (Paschal et al., 2008). Memory impairment as well as the patients' effort to appear responsible are important limitations. The best known patient self-report scales are the Morisky Medication Adherence Scale (four or eight items) (Morisky et al., 1986; Shallcross et al., 2015) and the Medication Adherence Rating Scale (10 items) (Chapman et al., 2015).

Objective strategies like pill counts and surveillances of prescription refill rates, are useful alternatives, but have shortcomings. Counting the number of pills left in the bottles is the most common method used in drug trials, but is obviously not always a good measure of the amount of ingested medication. Prescription refill rates, such as the Medication Possession Ratio (the percentage of time a patient has access to medications) have been frequently used to identify those who order their medications less frequently than expected (Faught et al., 2008). Pharmacy databases may give useful information on prescription initiation, refill and discontinuation, but this approach is dependent on a modern health care system not available in many countries, and does not guarantee that the medication is used. The use of electronic bottle tops is expensive, and also does not ensure the intake of AEDs (Eatock and Baker, 2007; Paschal et al., 2008).

Therapeutic drug monitoring stands out as the single best way of measuring adherence (World Health Organization, 2003; Samsonsen et al., 2014). It is direct, objective and easy to understand, whereas costs, availability, individual pharmacokinetic variability as well as so-called "white-coat adherence" prior to scheduled visits, constitute relative disadvantages. Serum concentration measurements in the immediate postictal phase compared with trough values in seizure-free periods, may demonstrate non-adherence at one point in time. The method of using series of concentration/dose ratios introduces a new standard for measuring non-adherence over time even with changed dosing, provided there is approximate linear pharmacokinetics of the analyzed drugs (Samsonsen et al., 2014; Lie et al., 2015)

Demographic factors

Several studies have shown that adolescents and young adult patients with epilepsy are at particular risk of non-adherence (Buck

Table 1
Common measures of adherence to antiepileptic drugs.

Method	Advantages	Limitations
Self-reports/questionnaires	Inexpensive/easy to use	Subjective/indirect/memory and cognitive deficits/efforts to appear responsible
Prescription refill rates	Objective/inexpensive	Indirect/does not reflect intake/dependent on health care and insurance system
Pill-counts	Objective/inexpensive/easy to use	Indirect/subject to manipulation
Electronic bottle tops	Objective/easy to use	Indirect/expensive/low availability/subject to manipulation
Therapeutic drug monitoring	Objective/direct/easy to understand/part of routine in many countries	Pharmacokinetic variability and interactions/diurnal variation/control values needed for comparison/sensitive to "white coat" adherence