

# Managing patient adherence and quality of life in epilepsy

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**Abstract:** Patient adherence to medication continues to be a cause of concern within the medical profession. This review examines the various methods of quantifying the level of patient adherence, progress in predicting causes of non-adherence, and the implications for its management. Contributions from the medical, health belief, and psychosocial models are discussed in order to highlight how the concept of adherence has changed over time. The impact of epilepsy, seizures, and taking antiepileptic drugs (AEDs) on both adherence and quality of life are also explored. The volume and quality of previous research conducted has enabled a number of predictive factors to be identified, from which various strategies have been developed. While this review concentrates on potential strategies in managing treatment adherence within epilepsy, findings can equally be applied to other chronic conditions.

**Keywords:** adherence, compliance, antiepileptic drugs, epilepsy, QOL

## Introduction

In assessing the effectiveness of prescribed medication there is a strong emphasis on the ability of the patient to adhere to the regime recommended by the clinician (Trostle 1988; Donovan and Blake 1992). Various tools have been developed to measure adherence but have limitations (Vermeire et al 2001). Most research has concentrated on quantifying levels of compliance/adherence without first defining what is meant by both terms (Vermeire et al 2001).

For individuals with epilepsy, adherence to medication is crucial in preventing or minimizing seizures and their cumulative impact on everyday life. Non-adherence to antiepileptic drugs (AEDs) can result in breakthrough seizures many months or years after a previous episode and can have serious repercussions on an individual's perceived quality of life (Baker et al 1997).

Reasons for non-adherence are complex and multilayered (Donovan and Blake 1992; Mitchell et al 2000). Patients can accidentally fail to adhere through forgetfulness, misunderstanding, or uncertainty about clinician's recommendations, or intentionally due to their own expectations of treatment, side-effects, and lifestyle choice. There are various strategies suggested for managing patient adherence but these are highly dependent on the reasons why a patient has not followed clinician advice initially (Conrad 1985).

## Terminology Compliance

As Becker and Maiman (1975, p11) state "...patient non compliance has become the best documented but least understood health related behaviour". Donovan and Blake (1992, p507) state how compliance is to "...obey, submit, defer or accede to instructions". Trostle (1988) describes how medical compliance can be seen as an ideology with pre-conceived assumptions about the role of doctor and patient. The relationship between the clinician and patient is one of unequal power dynamics

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with the traditional definitions of compliance constructed within the medical model (Barofsky 1978).

While clinicians are the “gatekeepers” in providing medication, the patient is the one who ultimately decides whether they adhere to the recommended regime (Donovan 1992). The traditional medical model assumes that once the medication regime is recommended by the clinician it is then the responsibility of the patient to follow it; if patients do not comply then the factors why need to be examined. In other words the problem lies with the patient (Garritty 1981).

Social scientists have recognized how compliance is rooted in this clinician perspective and have attempted to examine the concept from a patient standpoint. The medication regime recommended has to be interpreted by the patient, who examines how the advice can be incorporated into their lifestyle and “self regulates” their drug taking schedule (Conrad 1985). A health belief model hypothesized by Becker and Maiman (1975) (Figure 1) includes the most frequently examined aspects of compliance (age, drug regime, peer effects, doctor relationship) interacting with an individual’s motivations, and perceived benefits or costs of adherence to medication. To Donovan and Blake (1992) this weighing up of severity of symptoms and symptom relief juxtaposed against risks of treatment illustrates how non-compliance can be deliberate and the result of patients actively making decisions about their own treatment.

## Adherence

The gradual shift away from using the term compliance has been encouraged due to the possibility of a patient somehow being labeled as “deviant” for not following a recommended drug regime (Conrad 1985). In contrast, adherence, while not a perfect term (Barofsky [1978] describes it as what is expected of the patient as opposed to compliance being told what to do) at least implies a more mutual arrangement of co-operation and agreement but is still prone to the same difficulties in determining how it is measured. The concept of both compliance and adherence is further complicated when it is broadened to include general lifestyle changes that have been recommended to promote optimum health alongside a drug regime. Kobau and DiIorio (2003) in their study found that patients who were adherent to their medication schedule often failed to adapt their general lifestyle (getting enough sleep, reducing alcohol intake,

avoiding stress) which could be just as detrimental to seizure control and overall health.

## Concordance

Recently the concept of concordance has been promoted as a possible replacement to the notions of compliance or adherence, advocating a decision-making process where patients can feel more comfortable with their treatment (Marinker and Shaw 2003). Crucially, the philosophy of concordance has been embraced by the Department of Health’s Task Force on Medicine Partnership whose preliminary reviews feature contributions from both patients and patient support groups such as the National Society for Epilepsy (Carter et al 2005). The promotion of concordance involves re-thinking the relationship between clinician and patient, and this is likely to be a gradual process. While there has been an emphasis on re-training the medical profession, patients have been accustomed to working within the compliance model and may themselves take some time to adjust to the notion of concordance when they are encouraged to make more decisions about their care (Bissell et al 2004).

We will use the term adherence throughout this review as while compliance implies a purely clinician’s perspective we cannot assume that every patient-clinician interaction has embraced the principles of concordance whereby the patient’s decisions have had priority (Marinker and Shaw 2003). This is especially important when it is considered that most research highlighted in this review pre-dates the Department of Health’s decision to advocate the principles of concordance or has been conducted outside the UK. Adherence and concordance reflect a different process of decision making about treatment and health outcomes but ultimately, however, once treatment has been decided there will still be a need to measure whether the treatment regime has been effective both in terms of treating the condition and the relative cost (Trostle 1988).

Similarly, there needs to be a distinction between adherence and concordance in *how* they are measured. Concordance suggests that the relationship between patient and treatment provider is measured rather than direct health outcomes (Bissell 2004). Research cited in this review has measured outcomes in terms of levels of adherence to medication; it is not clear to what extent patients have been able to negotiate treatment decisions, particularly in the case of clinical studies where patients have been asked to adhere to a specific recommended regime.

## Measuring adherence

### Classification

Adherence research has involved the use of various criteria in categorizing levels of adherence in patients. In a review of adherence studies, Vermeire et al (2001) report that adherence has largely been measured using process-orientated definitions involving number of doses missed or taken incorrectly rather than looking at the end result to health. As Farmer (1999) in his review of adherence measures states, the cut off point determining whether someone is classed as adherent or not has an important role in assessing drug effectiveness for clinical practice and clinical trials. However, if the importance of adherence is to ensure the best outcome for the patient it may be more beneficial to measure it in terms of the level required for a desirable end result for the individual (Vermeire et al 2001). The adherence level to enable positive health outcomes varies depending on the particular illness; for example, Read et al (2003) report that to manage HIV a rate of 95% or greater is needed continuously over a long period of time, much higher than most chronic conditions.

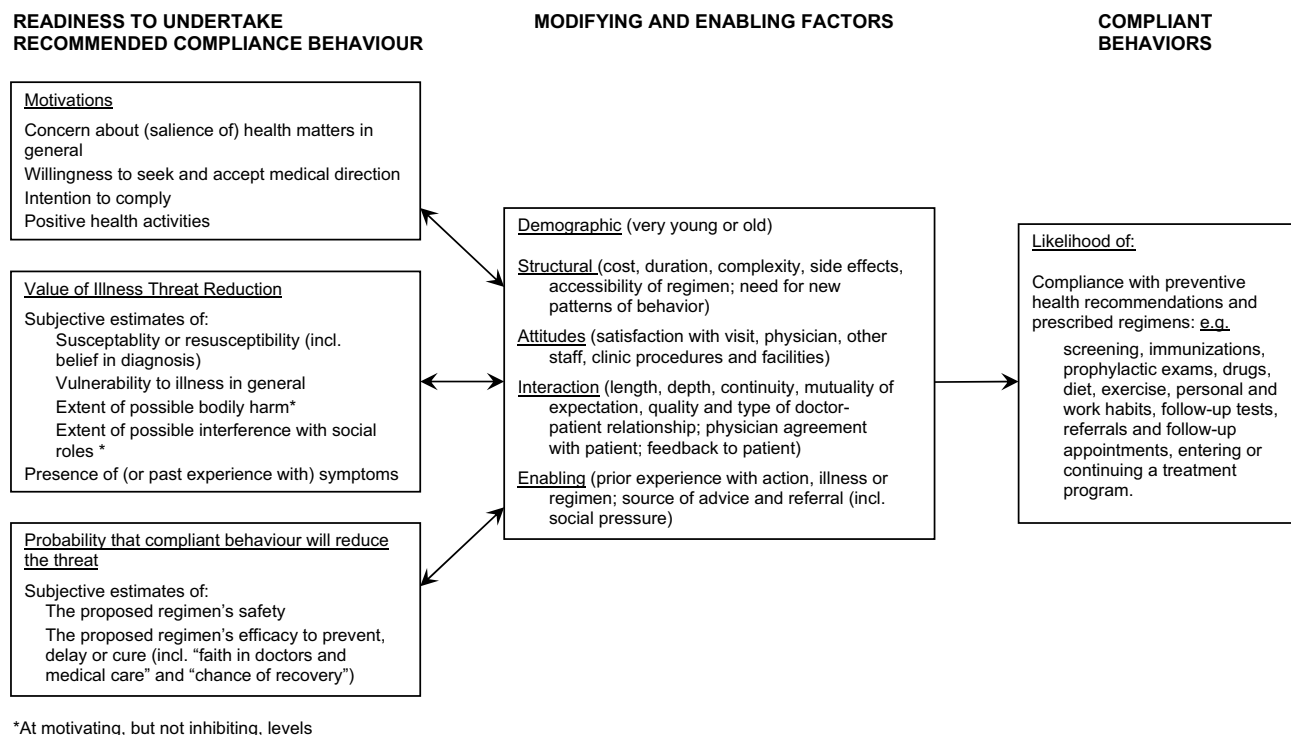
How adherence is classified is highly dependent on the method employed to measure it. Measuring adherence can be divided into direct (blood levels, observation of drug

taking) and indirect methods (patient reporting through questionnaires and diaries, pill counts, electronic monitoring), and all have varying advantages over each other (Osterberg and Blaschke 2005). Certain methods can investigate only the consumption of medication over a certain time but not how a particular regime was followed (Farmer 1999).

### Methods

Research into patient adherence has been undertaken continuously from the 1970s. Various factors have been identified as to why patients alter their medication-taking behavior but an agreed definition or gold standard for measurement remains elusive (Vermeire et al 2001). Adherence has been measured in numerous ways including drug plasma levels (Specht et al 2003), patient self reporting either anonymously or reported to clinician (Cramer et al 2002; Doughty et al 2003), electronic monitoring (Cramer et al 1989a, 1995), pill counting, and hair analysis (Williams et al 1997). Each has important limitations with their accuracy in assessing the level of adherence.

Measuring blood drug levels provides an objective measurement of whether medication has been taken and



**Figure 1** Model hypothesized by Becker and Maiman (1975) for predicting and explaining compliance behavior. Reprinted with permission from Becker MH, Maiman LA. 1975. Sociobehavioural determinants of compliance with health and medical care recommendations. *Med Care*, 13:10-23. © 1975 Lippincott Williams & Wilkins.

whether the level present is effective but is disadvantaged by “white coat adherence” – a patient may be adhering to the regime for only a day or two before an appointment (Feinstein 1990). In the case of epilepsy, AED serum levels can be obtained but this does not provide detailed information about patient adherence over time and is valid only for certain types of drugs which do not include many of the so called “second generation” AEDs (Walters et al 2004). Despite this, medical personnel still request and rely on these measures as an indicator of non-adherence (Walters et al 2004).

Pill counting can be unreliable. Cramer et al (2002) highlight that there are problems for patients to work out whether they have taken the wrong number of tablets, as counting the number of tablets left in a bottle and trying to work out how many should be left is not always straightforward (Cramer et al 2002). In a study by Paes et al (1997), looking at electronic monitoring of oral antidiabetic medication, patients were recorded as having problems with taking too much medication on some days and then having no medication at all in preceding or succeeding days. This effect was more pronounced in the group of patients who were taking once-daily doses of medication; this suggests that patients could not always recall whether they had taken their dose and highlights how pill counts would assume adherence when the actual medication taking behavior posed a significant risk to the individual's health (Paes et al 1997).

Pharmacy records held on computerized systems are a useful source of data when looking at adherence over larger patient populations (Steiner and Prochazka 1997). The expected time between prescription refills can be compared to the rate at which a patient actually returns for more medication. Christensen et al (1997) developed an algorithm to calculate a patient's adherence to antihypertensive drugs based on computerized pharmacy records and found that they were able to calculate adherence levels in 89% of 5500 prescriptions dispensed. Steiner and Prochazka (1997) state that using pharmacy records measures the *acquisition* of medication rather than consumption of medication and this differentiates it from pill counting. However, like the pill count method there needs to be an awareness of which facet of adherence is being measured. The quantity of medication acquired or assumed taken is only one aspect of adherence, but the timing of medication can be equally critical (Choo 1999).

As Choo et al (1999) highlight, the method of measuring adherence is dependent on how the variations in adherence

can affect health outcomes. Pharmacy records cannot be used for some chronic conditions which involve frequent changes of dose or for medications prescribed on a p.r.n. basis and also cannot gauge the effectiveness of a drug between dose intervals (Steiner and Prochazka 1997). The recording of the medication regime in patient notes may also not reflect the actual prescription details held on the computer system. Christensen et al (1997) found that drug name was correct, but that 14%–21% of the time the dosage recorded was different and verbal instructions about dosage were not mirrored in the prescription. These issues are of particular relevance to adherence in epilepsy where it is quite common for dosage to be changed and where incorrect timing of doses can lead to inadequate drug levels potentially causing a breakthrough seizure to occur (Specht et al 2003).

Patient reporting relies on the patients accurately recalling when doses were missed and/or if they were taken outside the recommended interval. The mechanisms of patient self-reporting are also complex with a wide variety of methods used including diaries, interviews, and standardized interview techniques (Farmer 1999). Critical to data collected using patient reporting is the approach used by the interviewer or how questions are worded (Farmer 1999). The reality of the medication-taking routine followed can differ widely from the patient's reports. Buelow and Smith (2004) compared patient reporting alongside data collected from a Medication Event Monitoring System (MEMS) cap which recorded the timing of when medication was taken and found that patients who believed that they managed their medication schedule effectively did not in fact adhere completely to recommendations.

Use of MEMS (Medication Event Monitoring System) devices answer many of the criticisms leveled at other methods of measuring adherence. They allow adherence to be more strictly defined by both number of pills missed and intervals between doses. Electronic monitoring cannot guarantee that medication was actually consumed but as Cramer et al (1989a) suggest, a patient who has remembered to open the bottle at the correct interval would be unlikely to then not take the medication. Even this drawback of assuming medication was taken has been addressed with research into adherence to asthma medication with flow sensors being incorporated into the device (Tashkin 1995). Unfortunately, electronic monitoring can realistically be used for only a limited time as it requires data to be downloaded at regular intervals and the cost prohibits long-term use (Osterberg and Blaschke 2005).

## Adherence in epilepsy

### Prevalence of epilepsy

While failing to adhere to treatment plans can adversely affect individuals with any general medical condition, the consequences of not taking medication can be more immediate with epilepsy. Epilepsy as a chronic condition relies heavily on adherence to medical advice in order to maximize an individual's quality of life by controlling seizures more effectively while avoiding unwanted side-effects (Baker et al 1997). Epilepsy also represents one of the more common neurological conditions with an estimated incidence of 4–10 people per 1000, with higher incidences of epilepsy among infants and the elderly (Sander 2004). Epilepsy Action estimate that epilepsy affects around 1 out of every 131 people in the UK population.

### Treatment

Of those diagnosed with epilepsy the vast majority are treated with AEDs and approximately 70% can become seizure-free once the most effective regime is followed (Sander 2004). Monotherapy is viewed as the initial and preferential option for treating epilepsy, the choice of drug depending on seizure type and effectiveness of the drug balanced against possible side-effects (Browne and Holmes 2004).

It is difficult to find estimates of how many people are on monotherapy or polytherapy at any one point in time. A US study of 314 adults found that 44% of patients were on monotherapy with the remaining 56% of patients on polytherapy (Yeager et al 2005). Similar proportions were found in a European study assessing the quality of life of over 5000 patients: 47% of patients were reported to be receiving monotherapy, 36% were taking 2 AEDs (12% were on 3, 1% 4 or more, and 4% were not receiving medication). The drugs most commonly taken were carbamazepine (53%), sodium valproate (33%), and phenytoin (25%) (Baker et al 1997).

### Investigating the extent of non-adherence

It is generally believed that adherence rates with acute conditions are much higher compared with chronic conditions (Osterberg and Blaschke 2005). Adherence in epilepsy has often been compared with other chronic conditions such as asthma and diabetes due to their outward manifestation of symptoms and the potential consequences of non-adherence being very apparent compared with other

disorders which may have no symptoms or any immediate consequences (Cramer et al 1989a). In the Claxton et al (2001) review of 76 studies across various chronic medical conditions the problem of adherence to drug regimes was prevalent regardless of medical condition. Mean adherence rates ranged from 51%–80% depending on drug regime and how adherence was measured. As an example a prospective study of asthma patients defined non-adherence as patients taking less than 70% of doses over a specific time period or who left out all doses for 1 week or longer, and even with this criteria 51% were non adherent (Bosley et al 1995).

While chronic illness requires long-term medication regimes and regular contact with the health system, due to time and financial constraints it is often studied for only a limited period of time, which has led to the call for longer-term study using a combined methodology approach (Casebeer and Verhoef 1997). The study of adherence to medication with chronic conditions has been limited to short-term monitoring of medication-taking which may not be representative of actual behavior, and it has been shown that even in the interval between appointments there is a marked decline in adherence levels (Cramer 1990). The level of adherence to AEDs also has to consider the length of time a patient has been taking medication. In a study of 661 epilepsy patients, 71% had missed a dose at least once at some point during their treatment but nearly half of the overall sample had been taking AEDs for more than 10 years (Cramer et al 2002).

Electronic monitoring of adherence has allowed researchers to look at a patient's AED medication-taking behavior on a day-to-day basis. Cramer et al (1989a) defined non-adherence in terms of omitting scheduled doses and found that 76% of doses were taken as prescribed. There was evidence of patients attempting to compensate for doses missed by clustering doses, which meant that overall 92% of tablets prescribed were taken but not at the specified interval (Cramer et al 1989a). Fisher (2000) found that 20% of respondents to their survey reported that they adjusted medications on their own either by altering the dose or the schedule. There are also differences in levels of adherence across countries, with a recent study showing that 18%–53% stated that they never missed their AED medication at entry to the study (Doughty et al 2003).

Non-adherence to medication is not restricted to involving taking too few doses or at the wrong time, patients can also be judged as non-adherent by taking too large a dose or too many tablets whether accidental or deliberate. A survey of 2031 respondents who had epilepsy reported



that 91% of patients never took more than the dose prescribed but the remaining 9% did occasionally (Doughty et al 2003). If patients' perceptions of AED taking do differ from reality this 9% may be an underestimate of what is actually happening. The true extent of overconsumption may be much higher, as individuals can accidentally take too much medication by mistakenly thinking that they had forgotten to take an earlier dose (Paes et al 1997).

## Relationship between non-adherence and seizures

Non-adherence to AED medication is not a modern phenomenon. Trostle (1988) cites the example of a Dr Gowers who, in 1881, reported on patients with epilepsy admitted to hospital with recurrence of seizures due to apparent non-adherence. The consequences of non-adherence to AEDs can be immediate and devastating to an individual's quality of life (QOL). People with epilepsy are acutely aware of the potential repercussions of not following a drug regime. In a survey conducted in 2002 of 661 patients with epilepsy 45% stated that they had a seizure when missing a dose and only 32% of responders had informed their doctor if they had missed any doses (Cramer et al 2002). This is a worrying statistic, as it can give the false impression that the drug regime is ineffective and persuade the clinician to alter the management of medication unnecessarily (Schroeder et al 2006). The other difficulty is that it has been shown that patients do not always accurately remember whether any doses were skipped, which can also lead the clinician to believe that the drug regime needs to be altered (Buelow and Smith 2004).

While non-adherence may cause a seizure to occur there are many individuals who do not adhere to medication and do not experience seizures and vice versa, as Shope et al (1988) note this is a source of frustration to clinician and patient alike. As mentioned previously, mistimed doses can also be defined as non-adherence and can also result in a seizure. Cramer et al (1995) reported how patients who stayed up late would take a dose just before bedtime, which may have been up to 15 hours since their previous dose by which time drugs levels may have become ineffective in preventing a seizure. Some patients who have not experienced seizures for some time start to gradually reduce their adherence to their medication, as they believe taking it to be unnecessary, particularly if they have skipped doses previously with no seizure occurring (Cramer et al 2002).

Gomes and Maia (1988) used questionnaires to ask individuals with epilepsy a number of questions related to

medication-taking and reported that 61.4% of the group agreed with a statement asking whether they reduced or stopped medication to see what happened. Patients may not perceive non-adherence as the main attributing factor in seizures occurring. When patients were asked if anything increased the likelihood of a seizure 41% mentioned stress/emotion, 19% fatigue, and only 13% stated medication missed (Hayden et al 1992). From a health economics perspective non-adherence can also involve additional costs to the health service due to the staff and resources required to deal with admissions to hospital because of seizures or seizure related injuries (Buck et al 1997b).

## QOL and epilepsy

QOL adherence is prone to difficulties in establishing how it is defined and measured. The World Health Organization define it as an "...individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHO 1997). The WHOQOL group have produced various tools designed to measure QOL, which consist of key "domains" designed to assess the impact of illness on health. Even with this definition there is still debate about what these domains include and how applicable they are across all illnesses or conditions (Bowling 1995).

Gilliam et al (1997) asked patients with moderately severe epilepsy to list any concerns with their epilepsy and found a mean of 6.2 concerns were listed by each individual. Driving, independence, and employment were the areas listed most often and rated as the most important. While seizures and treatment were also mentioned these domains were not regarded as the main concerns by patients (Gilliam et al 1997). There is limited opportunity here to explore all the domains of QOL and how they are measured. However, it is important to acknowledge that QOL depends on more than seizure control and treatment. It has become increasingly apparent that what an individual considers to be a successful outcome goes beyond prevention of seizures only (Sander 2005).

In managing QOL it is recognized that individuals with epilepsy are a heterogeneous population. Patients who are classed as refractory, for example, will report a greater negative impact on their quality of everyday life compared with those whose epilepsy is well controlled (Wheless 2006). For the estimated 70% who become seizure free epilepsy appears to impact less on their everyday life (Jacoby 1992) and they may even have similar quality of life to the

population in general (Leidy et al 1999). Even in the absence of seizures it is the unpredictability of epilepsy generally that impacts on quality of life (Jacoby 2000). In a study comparing quality of life of school children with epilepsy and asthma (active and inactive) the epilepsy group were affected more negatively than the asthma group regardless of whether their epilepsy was active or not (Austin 1996). The epilepsy group experienced greater social stigma over a number of domains compared with both the inactive and active asthma groups. It could be feasibly concluded that the nature of a seizure as opposed to an asthma attack accounted for this difference (Austin 1996).

## Seizures

Seizure frequency has been shown to be one of the main factors involved in how a person with epilepsy perceives their degree of stigma and their quality of health generally (Baker et al 1997). In the European Quality of Life study, 51% of people with epilepsy experienced some level of stigma but those with frequent seizures were three times more likely to experience high levels of stigma and even those having infrequent seizures experience more stigma than those who were classed as seizure free (Baker et al 1997). Patients with tonic-clonic seizures alongside other type of seizures are significantly more likely to feel stigmatized (Ratsepp et al 2000). Individuals with uncontrolled seizures in addition to the stigma experienced are also less likely to be in employment or more likely to encounter problems within their employment (Chaplin et al 1998). Seizures also have an impact on how the impact of epilepsy is perceived. Sixty-three per cent of respondents working part time or who were unemployed attributed this to their epilepsy particularly if they were having frequent seizures (Ratsepp et al 2000).

## Injuries

Apart from seizures themselves, injuries that occur as a consequence of having a seizure also have implications for an individual's health. Buck et al (1997a) reported on various injuries that were common such as burns and scalds, and revealed that 24% of the group had incurred head injuries and a further 10% experienced dental injuries during the previous year. A study surveying people with epilepsy throughout Europe found similar proportions of injuries – 27% had experienced a head injury with 13% reporting dental injuries (Baker et al 1997). Kirby and Sadler (1995) recorded data from adult emergency rooms over a 1-year

period in Canada and reported that 15% of seizures resulted in injury or death.

## Antiepileptic drugs and side-effects

Unfortunately, AEDs have the potential to produce side-effects singularly, and in combination with each other, as well as interacting with other prescribed medication. Common reported side-effects of AEDs include tiredness, dizziness, weight gain or loss, acne, and rash along with other less common but serious effects such as toxicity, hepatic failure, and teratogenicity (Sander 2004; Perucca and Meador 2005). The vast majority of patients will experience at least one side-effect while being on AED medication. Baker et al (1997) reported that only 12% of patients involved in the European Study of Quality of Life stated that they experienced no side-effects. Various side-effects were reported including hair loss, weight gain, trouble with teeth and gums, and problems with vision. Side-effects relating to the central nervous system (CNS) such as attention, memory, or concentration problems were also reported in significant numbers (Baker et al 1997). The issue of side-effects remains a fear for patients when following a drug regime. Side-effects experienced by patients whether actual or perceived increases the likelihood of non-adherence (Buck et al 1997b).

## Social impact of taking AEDs

The characteristics of side-effects experienced affect non-adherence. Side-effects that are perceived to compromise or interfere with an individual's social skills discourage adherence (Conrad 1985). Most AEDs have some CNS associated side-effects which in turn are likely to affect an individual's psychosocial functioning (Buck et al 1997b). Psychomotor processing, attention, and memory can all be affected to varying degrees by AEDs (Perucca and Meador 2005). This is of particular relevance to children and adolescents who are striving for peer acceptance (Buck et al 1997b). In a survey of 47 school children and adolescents, half of the group felt embarrassed about their epilepsy and a third felt excluded by peers (Anderson et al 2000). In addition, taking AEDs was resented by half of the children and sleepiness was reported as one of their main concerns about taking the medication (Anderson et al 2000).

One further complication is the role of side-effects in contributing towards accidental injury. Although seizures can result in injury, experiencing side-effects might also be a contributing factor in patients injuring themselves (Buck et al 1997a). In a matched patient and control study, those

who reported injuries in the patient group mostly took two or more drugs (van den Broek and Beghi 2004). Lawn et al (2004) also found number of AEDs taken to be a risk factor. However both Lawn et al (2004) and van den Broek and Beghi (2004) conclude that while the relative risk of accident or injury among people with epilepsy is high compared with the general population, the risk is attributable mostly to seizures and their frequency.

The actual physical act of having to take medication can increase the levels of stigma experienced by the patient. Taking AEDs reminds the individual that they have epilepsy and they may resort to keeping pill-taking in public to a minimum or disguise the purpose of the medication (Conrad 1985). Although patients may recognize the importance of adherence in avoiding seizures and injuries, drug-taking itself can be felt to be equally stigmatizing.

## Factors affecting adherence

While the debate continues about the correct terminology to use, research has continued to attempt to explain why certain people show adherent behavior compared with others, and different studies have attempted to identify characteristics that can predict adherence (Buck et al 1997b; Mitchell et al 2000; Kyngas 2001; Cramer et al 2002; Asadi-Pooya 2005). Buck et al (1997b) identified various factors indicative of those who were likely to show adherence (Table 1). As previously stated, these factors do not work in isolation. Shope (1988) used the model hypothesized by Becker and Maiman (1975) and found that while adherence was affected by doctor–patient relationship, level of social support, familiarity with drug regime, and age, the patients who believed their treatment to be effective and those who had more knowledge about their seizures and treatment, for example, were more likely to show adherence.

## Seizure type and frequency

As discussed previously, the quality of life for people with epilepsy can differ according to seizure type and severity but the effect on adherence is less clear. Specht et al (2003) encouraged patients who had had seizures to come into hospital in order to assess drug levels and found that out of the non adherent group those with generalized tonic clonic seizures appeared to show less adherence compared to other seizure types. However, as Specht et al (2003) state, this finding has to be interpreted with caution as people having GTC seizures were more likely to see a clinician straight after one occurring compared with other types of seizures.

Paradoxically, Shope et al (1988) found that self-reported adherence among those adults whose seizures were well controlled was higher than in those who classified themselves as having a more severe seizure disorder, whereas their pediatric research showed increased adherence in the group who had more frequent seizures. Jones et al (2006) have recently reported that in their group of patients with epilepsy, a negative correlation could be detected between seizure frequency and adherence. Gopinath et al (2000) also found this in their study of 200 patients with epilepsy.

## AED regime

Throughout the research literature it has been concluded that drugs taken less frequently daily is a significant aid to adherence (Kruse et al 1991; Paes et al 1997; Claxton et al 2001; Cramer 2002). Frequency of dose seems to be an important factor regardless of what the medication is for. Kruse et al (1991), investigating adherence to fertility medication, found that adherence was significantly improved when the frequency was reduced from four times daily to twice daily. With AEDs Cramer et al (2002) calculated that the odds of missing a dose increased by 27% each additional time a drug was expected to be taken daily. This further supports the study of Cramer et al (1989a) using a Medication Event Monitoring System (MEMS) over a total period of 3428 days, which found that adherence rates dropped considerably between those taking AEDs once daily and four times daily (Table 2).

Doughty et al (2003) collected data from 2031 people across Europe who were switched from sodium valproate to depakine chrono. When questioned, 88% of patients at baseline stated that they would prefer to take medication once daily (89% 3 months later after the drug switch). Again, differences in levels of adherence were affected according to how many times a day medication was taken (Doughty et al 2003). The possibility of only taking AED medication once a day is an attractive proposition for patients who can more easily fit this into their everyday routine and minimize their chances of forgetting to take doses (Doughty et al 2003).

The number of different tablets to be taken daily is also an important element in examining adherence rates. Buck et al (1997b) noted a significant difference in adherence, with those on polytherapy more likely to adhere. Cramer et al (1995), in a study about dose frequency and adherence, reported that the number of different medications to be taken was not a factor affecting adherence, simply because if a



**Table 1** Buck et al (1997b) factors affecting compliance with AED regimes

	Frequency miss taking AEDs:			
	Never %	<once a month %	at least once a month %	
Age:				
Under 60 ( <i>n</i> = 460)	66	18	17	$\chi^2 = 26.14$
60 or over ( <i>n</i> = 180)	86	8	6	$P < 0.00001$
Teenager ( <i>n</i> = 25)	52	32	16	$\chi^2 = 6.66$
Over 20 ( <i>n</i> = 615)	72	14	14	$P < 0.05$
How important to take drugs as prescribed:				
Very important ( <i>n</i> = 597)	76	15	9	$\chi^2 = 100.50$
Fairly/not at all important ( <i>n</i> = 64)	29	17	53	$P < 0.00001$
Reported feelings of stigma:				
Yes ( <i>n</i> = 245)	66	19	15	$\chi^2 = 6.82$
No ( <i>n</i> = 394)	74	13	13	$P < 0.05$
No. of drugs				
Monotherapy ( <i>n</i> = 467)	68	17	15	$\chi^2 = 13.61$
Polytherapy ( <i>n</i> = 190)	82	9	9	$P < 0.01$
Side-effects due to AEDs:				
Yes ( <i>n</i> = 326)	67	18	16	$\chi^2 = 9.6$
No ( <i>n</i> = 328)	77	12	11	$P < 0.01$
How perceive general practitioner:				
Easy to talk to ( <i>n</i> = 394)	73	14	14	$\chi^2 = 6.58$
Not easy ( <i>n</i> = 63)	57	24	19	$P < 0.05$
Have regular arrangement to see GP about epilepsy:				
Yes ( <i>n</i> = 69)	81	19*		$\chi^2 = 4.61$
No ( <i>n</i> = 382)	68	32		$P < 0.05$

\* Although there was no significant difference between never missing, missing less than once a month or missing at least once a month and having a regular arrangement to see GP, the difference was significant when the 'frequency missed' variable was collapsed into two categories: whether missed at all or never missed.

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patient remembered they were due to take a dose they took them all at the same time. Yeager et al (2005) analyzed adherence by measuring the relative complexity of taking AEDs. Everyday routine was affected by the guidelines in taking medication, in particular whether they needed to be taken alongside food or not. The nature of AED management in introducing and withdrawing drugs also complicated the drug regime, with some medication requiring an increase over a set time period with another drug reducing in dose over time (Yeager et al 2005).

Another adherence issue less frequently reported is related to examining why patients sometimes take more

doses or higher doses than recommended. Patients can be psychologically reliant on antiepileptic medication as a method of reducing the amount of concern associated with having seizures (Conrad 1985). For some patients, taking AEDs may have been regarded as no longer necessary by the clinician but patients fear the consequences should they stop treatment, with a relapse having implications for employment and overall quality of life (MRC AEDWS Group 1992). Detailed interviews of people with epilepsy have also revealed that patients take additional doses when they feel that a seizure may be triggered, such as during periods of stress or tiredness (Conrad 1985).

**Table 2** Cramer et al (1989a,b) compliance rates for prescribed dosing regimes

Dosage*	No. of Patients	Mean No. of Days Observed	Mean (SD) Compliance Rate, %†‡	Range, %
QD	3	191	87‡ (11)	73-99
BID	12	161	81§ (17)	44-100
TID	7	102	77§ (12)	52-90
QID	4	52	39 (24)	3-68
All	26	132	76 (21)	3-100

\*QD indicates once daily; BID, twice daily; TID, three times a day; and QID, four times a day.

†P<.01 by analysis of variance.

‡P<.01 vs QID group by Student's *t* test with Bonferroni multiple comparison correction.

§P<.05 vs QID group by Student's *t* test with Bonferroni multiple comparison correction.

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## Patient characteristics

Research examining adherence in individuals with any chronic condition requiring medication has been analyzed in terms of various characteristics such as socio-economic background, age, and attitudes to medication-taking which have similarly been investigated with epilepsy (for example Buck et al 1997b; Britten 1994). While it appears that there are no significant differences between genders, the age of the patient is a factor, with adolescents considered less likely to adhere (Cramer et al 1995; Buck et al 1997b; Anderson et al 2000; Asadi-Pooya 2005).

## Children and adolescents

Adherence levels for children and adolescents are highly dependent on the level of support from parents. Kyngas (2001) reports that this support was a strong predictor for adherence in teenagers with epilepsy. From the first diagnosis of epilepsy, family are encouraged to help by monitoring seizures and medication and are involved in the initial explanation of the importance of adherence (Schachter 1999). Shope (1988) looked at parent-reported adherence compared with drug serum levels and reported that although 95% of parents believed medication prescribed reduced their children's seizures and 83% reported no problems in giving medication to their children, the blood results showed that only 57% had adhered to the drug regime.

Parents who had a good knowledge of seizures and treatment and who sought out information about epilepsy had a positive impact on their children's adherence, but surprisingly, parents who had higher expectations about their children's academic achievements showed less adherence (Shope 1988). Austin et al (1996) investigated QOL in youth with epilepsy and proposed that their poorer academic progress compared with children with asthma could be due

to the neurological effects of epilepsy and/or the AED medication which could negatively affect cognitive functioning and therefore academic achievement as a result. This might be a possible reason why parents may not encourage their children to take medication as prescribed.

Other family influences beyond parents can also affect adherence. While Asadi-Pooya (2005) reported that the number of people in a family could negatively affect adolescent adherence, Kyngas (2000) found no significant effect. This might be explained by cultural difference – Asadi-Pooya's study was based in Iran and Kynga's in Japan. However, the nature of the family environment extends beyond the number of people or who it comprises. Asadi-Pooya (2005) noted that families with a positive history of epilepsy were likely to adhere less to medication. Perhaps surprisingly, teenagers and children from poorer families and those who reported stressful life events were more likely to adhere (Mitchell et al 2000). Mitchell et al (2000) also found that families classified as being in a higher socio-economic category were more likely to be non-adherent, which lends weight to the theory that non-adherence can be intentional rather than a reflection of difficulties in accessing medical advice or an inability to understand (Mitchell et al 2000).

Teenagers with epilepsy appear to adhere less to medication. Buck et al (1997b) reported how 52% of teenagers reported that they never missed medication compared with over 72% of over 20s. In scales used by Kyngas (2000), only 37% were ranked as showing good levels of adherence with medication. The reasons why teenagers are less likely to adhere are complex. This age group may feel increased levels of stigma associated with taking AEDs (Buck et al 1997b), or may simply be at an age when parental responsibility for ensuring adherence has been relinquished to the adolescent who may simply forget

to take the medication (Anderson et al 2000). Anderson et al (2000) reported that 18 out of the 19 adolescents in their study forgot to take medication at some point.

Adherence also depends on how taking medication interferes with everyday life as viewed from the patient's perspective, despite simultaneously acknowledging the importance of following the drug regime (Buck et al 1997b). Younger people who believed that epilepsy was not affecting social well-being were more adherent to medication. Adolescents experiencing no perceived adverse effects on their social well-being combined with parental support and physician support, are factors believed to predict 97% of those likely to show good adherence (Kyngas 2001).

## Doctor–patient relationship

As noted earlier, an important aspect of the level to which patients adhere is determined by their perception of their relationship with the clinician. Patients' decision-making relies heavily on whether their expectations of the clinician are met at each visit (Garrity 1981). It appears that successful interactions with medical personnel can increase adherence. Buck et al (1997b) highlighted how, while the number of visits was unimportant, the patient feeling that they could regularly talk to an understanding GP about epilepsy was a key factor.

Gopinath et al (2000) investigated the patient perspective of the doctor–patient relationship and found that both the number of visits and effective communication between the two promoted adherence. Kyngas (2001) studied 13- to 17-year-olds with epilepsy and reported how 60% of the group believed the physician to be interested in the epilepsy rather than the individual and that medical personnel gave orders rather than negotiating a care plan. However, as Gopinath et al (2000) emphasize, in India and throughout the world, physicians' allocated time to consult with the patient has become increasingly limited due to pressures on resources.

## Psychosocial factors

Psychological factors such as anxiety or depression may need to be investigated when adherence to medication is poor. Bosley et al (1995) found that among their group of individuals with asthma there was a significant relationship between depression and the level of adherence. Attitudes and perceptions about medication generally can influence how likely it is for an individual to be adherent (Britten 1994). Britten conducted in-depth interviews with patients and revealed that patients feared becoming dependent on medication, worried about having to take it for life, and

some experienced a level of shame in having to take certain medication.

Interwoven with all these factors of adherence is the element of stigma. Stigma can adversely affect the ability or perceived ability of a person to manage their epilepsy in all aspects of self care (DiIorio et al 2003). The relationship between stigma and management of epilepsy is complex. In the DiIorio et al (2003) study high stigma levels were associated with a number of socio-economic variables such as unemployment, low income, and less education. High levels were also associated with whether the seizures were well controlled and if they had had a seizure in the previous year (DiIorio et al 2003).

While there has been a focus on patient characteristics in order to predict who is likely to be non-adherent, patient characteristics are unable to provide a complete picture. These contributing factors, while important, do not work in isolation and a new approach may be to examine the characteristics of situations which can trigger non-adherence (Trostle 1988). There is already evidence available to show how everyday environments such as school can affect medication management (Anderson et al 2000). The workplace is another situation which may hinder adherence. The MRC Antiepileptic Drug Withdrawal Study noted that a significant number of people who were still taking AEDs felt that it affected work in some way (MRC AEDWS 1992). Employer attitudes towards individuals with epilepsy may also discourage the desire to inform them of their epilepsy (Jacoby et al 2005). This is an important consideration for people who need to take their medication at work.

## Strategies

Previous proposed strategies have centered on improving the effectiveness of communication between clinician and patient. Opportunities for patients to discuss their epilepsy treatment and any side-effects regularly with their GP improve levels of adherence (Buck et al 1997b). A recent Norwegian study using a nurse-led intervention program over 2 years showed that adults with epilepsy benefited from having regular opportunities to discuss their condition, and showed marked improvements in QOL compared with the group who were not in the intervention program (Helde et al 2005). Interestingly, scores related to medication effects showed a significant improvement in the intervention group (Helde et al 2005). Having the opportunity to discuss any fears of medication and possible side-effects could potentially result in a greater level of adherence (Britten 1994).

For patients who are unclear about the importance of following AED routines, various programs may be of benefit particularly in cases involving children and adolescents (Buck et al 1997b; Asadi-Pooya 2005). Educational programs may be a method of improving adherence; patients with more knowledge about seizures and treatment do appear to show higher levels of adherence (Shope et al 1988). Gopinath et al (2000) take this one step further and suggest wider dissemination of information about epilepsy, lifestyle, and treatment through public education.

Decreasing the frequency of taking AEDs has been shown to reduce the times patients forget to take medication (Cramer et al 1995). Moreover the negative effects on social relationships experienced by school-aged children can be lessened if AEDs do not have to be taken during school time (Anderson et al 2000). However, Paes et al (1997) did not recommend this as a strategy in their study of diabetic patients due to the possibility of a patient overconsuming medication on one day and having no therapeutic coverage on others. Adherence to timing of doses proves to be even more critical in once-daily regimes, as variance in the time medication is taken could result in 36 hours with no coverage (Claxton et al 2001). Claxton et al (2001) recommend talking to patients about the duration of action of individual drugs and emphasize the importance of taking medication at similar intervals.

Where appropriate, a switch to a sustained-release form of an AED could allow a drug to be taken less frequently. Research has shown that this results in fewer side-effects, greater levels of adherence, and improvement in patient-reported quality of life (Doughty et al 2003; Ficker et al 2005). The desire to minimize side-effects can be a factor in explaining why patients omit medication or experiment with the time interval of doses (Donovan and Blake 1992).

If drug regimes cannot be simplified further, blister packs/pill organizers/multi-compartment medication devices have been viewed as a possible method of improving adherence. This may be of benefit for some individuals who have difficulty remembering to take various medications daily, but evidence of their effectiveness is limited and incurs extra costs for the NHS (National Health Service – UK publicly funded health service) (McGraw 2004).

More innovative ways of providing feedback to patients about how they are managing their medication schedule could be considered. As mentioned previously, blood level monitoring shows recent doses taken prior to attending the clinic, but a patient may have been omitting many doses previously without this being apparent (Williams et al 1997).

Williams et al (1997) used hair analysis to show the adherence pattern for carbamazepine over a period of 6 months, which highlighted any irregular dose taking during over this time. This approach counteracts the drawbacks of blood testing at clinic visits where only a snapshot of adherence is possible.

Specht et al (2003) measured post-ictal serum levels of AEDs to assess adherence and suggested that this provided useful feedback to the clinician (in terms of possible pharmacoresistance) and patient in explaining why a seizure had occurred. Similarly, through use of a MEMS cap for a short period of time patients could be presented with details of inconsistencies in their drug regime (Cramer et al 2002).

Patients' perceptions about how well they can self-manage their own health (DiIorio et al 2003) and their attitude to medication generally (Britten 1994) can and should be discussed with clinicians. In some cases psychosocial intervention and counseling may reduce the level of stigma and encourage patients to feel more positive about their ability to control their health (DiIorio et al 2003). Enhancing self-efficacy has also been shown to make an individual likely to engage in behaviors more beneficial in minimizing the impact of epilepsy on everyday life (Kobau and DiIorio 2003).

Finally, patients may be fully aware of the importance of taking AED medication and the benefits gained by altering their lifestyle choices in order to prevent seizures, but will make a decision about the degree to which they follow advice (Conrad 1985). As Conrad argues, patients only have a small amount of time in contact with the clinician in their "patient role", after which they return to the practicalities of their everyday routine where their adherence fluctuates based on how they feel their medication affects their QOL.

## Summary

Adherence to medication regardless of medical condition remains an important problem in treatment. Factors that have been discussed here – side-effects, drug regime, family support, impact on everyday life, relationship with the clinician – are unlikely to be the only predictors of adherence. While adherence to treatment within the context of epilepsy has been the focus of this review, these factors can equally be applied to various chronic conditions.

Strategies to manage adherence originate from different perspectives. While the medical model may advocate less complex drug regimes, the use of measured pill containers, and minimization of side-effects, the psychosocial model analyzes non-adherence in terms of patient attitudes to



**Table 3** Summary of proposed recommendations for improving adherence

<b>AED regime</b>	Anderson et al (2000)	Enable tablets to be taken once or twice daily to reduce forgetfulness and prevent children having to take medication at school
	Asadi-Pooya (2005)	Make drug regime less complex to improve adherence – preferably once daily dose.
	Cramer et al (2002)	Use simplest drug regime possible in terms of dosage and number of tablets
	Doughty et al (2003)	A switch from standard formulation to slow release drugs (sodium valproate to depakine-chrono) produces fewer side-effects and increases adherence.
<b>Doctor–patient relationship</b>	Britten (1994)	Establish patients' feelings and thoughts about medication in general, discuss fears and problems in taking medication.
	Buelow and Smith (2004)	Examine the decision making process that patients use in managing their medication.
	Donovan and Blake (1992)	Doctor and patient should develop treatment regime together. Patients should be clearer about their needs and expectations of their treatment plan.
	Mullen (1997)	Clinicians should adopt non-judgmental attitudes to patients, allow patients to describe actual drug taking behavior, and reach agreement about dose options with initial prescriptions seen as a “trial”.
<b>Education/ interventions</b>	Buck et al (1997b)	Use of educational programs to provide information about epilepsy, AEDs, adherence, and patient decisions, tailor programs for adolescents.
	Gopinath et al (2000)	Increase the level of public education about epilepsy, particularly antiepileptic drugs and lifestyle behaviors.
<b>Feedback</b>	Cramer et al (1995)	In clinical trials involving AEDs, data from MEMs caps can be used to provide feedback to patients to show actual drug taking behavior.
	Specht et al (2003)	Postictal serum levels can be used as feedback to patients in order to avoid seizures and promote adherence.
<b>Self care management</b>	Barofsky (1978)	Develop self-care ability of a patient from a young age, enable “socialization” with the health care system via school health education programs.
	Conrad (1985)	Ensure patients feel in control in regulating medication regimes and their relative impact on everyday life
	Dilorio et al (2003)	Combat stigma experienced by patients through interventions designed to reduce stigma and promote self care.
	Kobau and Dilorio (2003)	Increase levels of self-efficacy through interventions/programs to improve ability to self manage care.

medication, stigma, family and peer influences, and ability to manage self care. Neither model can adequately improve adherence independently. Perhaps the best approach is to offer a “menu” of adherence-enhancing strategies (Vermeire et al 2001). However, what is increasingly clear from both models is that total adherence is an unrealistic goal. The emphasis has shifted away from total adherence towards a compromise with both patient and clinician involved in a joint process of treatment negotiation and decision-making in order to achieve the best outcome for the individual.

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