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REVIEW

To adhere or not, and what we can do to help

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Abstract Two factors predict treatment outcome, how effective the treatment is and whether the patient takes or follows the treatment plan. As clinicians or scientists, we strive to develop newer and more effective treatments, both pharmacological and non-pharmacological to improve treatment outcome in our patient population. Adherence is the single most modifiable factor associated with treatment outcome, yet how often is the issue of adherence addressed in clinical consultations? The best treatment is rendered useless if not adhered to. Initial adherence rates are low and get worse with time, but methodological difficulties in studies make it difficult to determine both the clinical implication of suboptimal adherence and successful strategies. Further research should apply more rigour to the area of definition and measurement, be sufficiently powered and long term, and measure possible confounders, to allow for an understanding on the link and impact between adherence and clinical outcome. This article reviews some of the main issues with regard to adherence and cost implications of suboptimal adherence and suggests future directions.

Keywords Adherence · Concordance · Compliance · Treatment effectiveness

What is adherence and what is the relevant terminology?

Adherence, as defined by the World Health Organisation reflects "the degree to which the person's behaviours, taking medication, following a diet and or executing lifestyle changes, correspond with the agreed recommendations of a health care provider" [1]. Embedded within this definition is the perception that adherence is non-judgemental, it assumes a clinician–patient relationship based on partnership and mutual respect. Interchangeable terms include alliance, concordance and fidelity. Compliance, although sometimes used interchangeably, is somewhat different as agreement has not been established jointly between both parties. Adherence is not an all or nothing concept, nor is it static. Although research reports more often refer to medication, it pertains equally to behavioural interventions. Suboptimal adherence is viewed by clinicians as a major treatment obstacle, and in some cases the most prominent barrier to treatment effectiveness, leading the authors to coin non-adherence as "America's other drug problem" [2]. Arbitrary terms, e.g. partial, suboptimum and optimum adherence, without clear definitions make comparison across studies difficult. What exactly was measured and for how long? For example, the total number of pills taken per day, or averaged over a longer period; the actual mg dosage taken as a percentage of prescribed dose; was the timing of medication taken reviewed? Equally does the categorisation used consider the changing treatment regime based on progress made, reappraisal of on going need, emerging side effects or change in circumstances of the patient, or agreement to disagree about treatment indicated? All of these scenarios may lead to valid changes in baseline treatment plan and may not be proof of adherence issues.

What is the significance of adherence in health care?

The shift in disease burden worldwide from acute to chronic illness requiring long-term adherence emphasises

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the potential personal, societal and economical consequences of non-adherence. In the USA non-adherence is estimated to cost $300 billion/year [3]. In medical settings, non-adherence has been shown to severely compromise the effectiveness of treatments and is related to increased hospital visits, unnecessary hospitalisation and increased expression of disease, morbidity and mortality [4–6]. In addition, medication non-adherence limits advances in biomedical technology as studies testing new products fail to find positive effects, not due to lack of efficacy, but rather to lack of drug exposure.

The benefits of adherence are not as clear-cut in some psychiatry studies. On the one hand, patients who adhere more to the treatment have reported improved psychological functioning, better overall quality of life and a 50 % lower hospitalisation rate [4]. Better medication adherence predicted better outcomes in some studies of children with ADHD [7]. Similarly, non-adherence to anti-psychotic medication was predictive of suboptimal response and more severe relapses in a psychotic cohort [8]. However, not all studies report an association between improved adherence and outcome. The seminal multimodal treatment of ADHD (MTA) study examined the effectiveness of four treatment arms over a 14-month period, with naturalistic follow-up for another 36 months [9]. Whilst there was a positive correlation between adherence and outcome, this did not extend to the other treatment arms, behavioural or combined. Another smaller ADHD study also failed to find an association between adherence and clinical outcomes [10].

These puzzling and contradictory findings may be due to methodological issues in the categorisation of adherence referred to above. In the MTA study when adherence was defined using physiological measures, it was positively associated with clinical outcome but not when defined by parental report [5]. Intriguingly, in the TORDIA (Treatment of Resistant Depression in Adolescents) study, the researchers found a modest dose response relationship with clinical outcome when adherence was measured using self-report but not drug plasma levels [11]. This counter-intuitive finding whereby an accurate (physiological) measure of adherence faired less well than a subjective rating (self report) suggests that others factors rather than the medication itself may be at play. In cardiovascular studies, adherence itself, irrespective of whether with active drug or placebo, is strongly linked to outcome [12]. Personal, family or environmental factors which facilitate a person's readiness or ability to adhere may be the factors associated with better outcome, rather that the treatment itself. This is particularly true if treatment outcomes are defined in broad terms, such as quality of life, improved peer or family relationships and better grades in school, which may have less to do with immediate treatment (medication) effect and more to do with behavioural and cognitive change or a combination of both. The natural history of an illness may suggest links with successful treatment when in fact remission was independent of treatment offered/taken. Studies of short duration may fail to detect an association between adherence and outcome, even when present but delayed. Whilst treatment studies using an RCT design aim to control for all these confounders, such potential and ill-understood confounders have not received systematic study. These factors may be more salient to psychiatric conditions where behavioural and cognitive changes may have a more prominent role in treatment.

How is adherence measured?

There is no gold standard to measure adherence. 'Simple methods are not accurate and accurate methods are not simple.' For psychotherapeutic intervention, attendance at sessions may be reported, but should this be extended to cover in-session participation, degree of behavioural change or homework completed between sessions? In drug studies, subjective rating scales of medication taken are most commonly used. Generally, they are recognised to be over-estimates unless reporting non-adherence. In the TORDIA study, there was minimal agreement between self-report and drug plasma levels [11]. Even parental as opposed to child report is not linked with increased reliability. In the MTA study, parental report correlated with saliva drug measures in only half of the cases [9]. Any form of recall must be considered as a guide at best.

Objective methods, often supported by patient/parent recall, are the standards used in many medication studies. Remaining dosage units are returned to the clinician each visit and can be counted; however, tablets gone are not necessarily consumed and do not give any information about the timing or the pattern of missed doses. A medication event monitoring system electronically records the time and date when medication bottles have been opened. It is expensive and there is no guarantee that bottles opened equate with medication taken. Pharmacy databases documenting the rate of refills, while useful and cheap, have similar limitations. Direct observation of treatment is most accurate but also most difficult and costly, often reserved for use in treatment of infectious diseases such as TB and HIV where ambiguity is less well tolerated, and where adherence has clear medical and economic advantages [13]. Using a nontoxic biological marker which is added to the medication and which can be measured in either saliva or blood levels is effective and accurate, but costly. This was used in the TORDIA study, and highlighted the poor correlation with patient self-report and biological measure [11].

How prevalent is non-adherence?

Surveys differ in estimated rates of non-adherence and vary between country and illness group. Rates are recognised to be lower in developing countries [14]. Adherence rates deteriorate with time and are generally worse for chronic illness regimes and for lifestyle change, where rates of 50 % have been reported [4, 15]. Research, targeting physical health or smoking behaviours in children, concur with the adult literature on non-adherence being a significant impediment to effective treatment [16]. High rates of non-adherence are also associated with chronic mental health disorders. Rates of 30–60 % were reported in adults [17] with a 40 % rate of medication discontinuation within 12 weeks [18]. Similarly, in the TORDIA study almost half of the adolescents (49.5 %) reported low adherence rates [11].

In a review of 17 ADHD publications, Chacko and colleagues estimated that between 1/3 and 2/3 of youth do not adhere consistently to medication regimes [19]. The average time to discontinuation was found to be 4 months [20] with full compliance lasting only 2 months. Another study, also in children with ADHD, found the majority had discontinued medication within the year, with as many as one in five discontinuing after the first prescription [21]. Devatharshny and colleagues [22] followed up 71 children with ADHD over a 3-year period. The authors reported an adherence rate, defined as taking medication more than 5 days per week, of just over half (52 %). In the MTA study, adherence to the medication regime was defined as the family attending more than 85 % of follow-up medication appointments over the 18-month study period; 78 % of children met these criteria. A smaller number, 63 %, of families were adherent to the behaviour regime, defined as attendance at more than 75 % of sessions. With regard to the combined groups, only 61 % were adherent. In this study, for whatever reasons (despite free evidence-based treatment), more than one-quarter of the patients or families were non-adherent.

What are the determinants/predictors/associated factors of non-adherence?

The WHO considers adherence to be a 'multi-determined phenomena determined by the interplay of 5 sets of factors' or domains, namely: social and economic, patient related, disease or condition related, treatment related and clinician or health system related [1].

Socioeconomic factors include factors such as gender, age, marital status, race, poverty, literacy, low levels of education, unemployment and lack of effective social supports, but in themselves are not independent predictors of adherence [23]. In both medical and psychiatry settings, younger children have been found to be more adherent than their older peers, possibly due to increased parental input [22]. In fact, children who assume 'sole' responsibility for their illness early in life adhere less than their older peers [1]. A more recent study, reporting very low adherence rates of 19 %, found that adherence rates amongst black and Hispanic youth were much lower than in white non-Hispanic youth [10].

Cultural and lay beliefs about illness and medication have a huge influence on adherence. In Western society, medical treatments may be perceived to be linked with authority and power and/or perceived as dictums which threaten patient autonomy and freedom. They may create a fear of dependence to be resisted at all costs, leading to a counter-reaction, described by some researchers as the "Reactance theory" [24]. However, in other cultures, the sense of dependence is welcome, and a view that the doctor "knows best" is accepted and followed.

The knowledge and belief that the patient has about their illness and their perceived need for treatment understandably influence their wish to follow recommended treatment guidelines. The patient (or parent) has to recognise that he/she (their child) has an illness; they must be motivated to manage it and have a certain level of confidence in their efficacy to do so. Each must have positive expectations regarding the benefits of treatment. For example, parents of Caucasian boys with ADHD are more likely to believe that their sons have a biological disease which requires medication than parents of female children or children of other races, and they are more likely to be adherent [25]. Illnesses that are ego-syntonic, like anorexia nervosa or mania, where the illness may be welcomed, clearly bring huge challenges to help seeking and adherence. A patient who has no insight into the fact that they have an illness which could benefit from treatment will be reluctant to engage in a treatment programme which may involve medication, behavioural change and attendance at clinics.

The illness must pose a 'disease threat', be sufficiently severe to arouse the need for treatment, must be perceived as being resolvable and that remedial action is linked with a fast effect and a noticeable reduction of symptoms [26]. This immediate or notable treatment effect may explain some of the findings in children with ADHD, where adherence rates are reported to be higher with severe ADHD symptoms at baseline [22], with faster acting medication [27, 28] and following a greater initial response to treatment [29]. In diseases where prognosis is poor, adherence rates are low [26, 30].

Patients with mental illness may pose particular risks for treatment adherence. This may be due in part to the illness itself, where the patient may have minimal insight, symptoms may be ego-syntonic and previous treatment may

have been without consent. Desired outcomes may be initially negative, such as at the initiation of behavioural intervention or in psychotherapy where painful memories are brought into consciousness and may lead to non-adherence. Many mental health illnesses are chronic with periods of relapse and remission making it difficult to identify treatment-specific effects, maintain and positively reinforce treatment adherence. Adherence rates are known to drop after the first 6 months of therapy and often even earlier. Motivation to take medication when well or in remission becomes increasing difficult. In addition, the effects of interventions may be less tangible, more distal and hard to specify. A person with diabetes who forgets his/her medication may be reminded by a sudden onset of unpleasant physical symptoms which remit in a timely fashion following treatment. Such a dramatic effect is less likely following mental health interventions. Society is less tolerant of psychiatric treatment, especially medical, depriving individuals of wider support networks. However, as MH practitioners, we are uniquely skilled to encourage the behavioural changes necessary that complement optimal adherence.

Treatment-related factors include practical issues, such as the treatment setting, accessibility, flexibility of opening hours and waiting times. Specific issues, such as cost, complexity and duration, of the treatment regime predict adherence. Patients may have concerns or anxieties about the side effects of treatment, medical or social, real or perceived, common or rare, with different side effects being more salient for different groups. This is of particular relevance to the adolescent group, where pressure to conform to social norms is high. A side effect of weight gain, acne or fatigue may be intolerable in a young adolescent, but may be of little consequence to an older person. Stigma around the illness itself, the concept of taking medication or worries regarding confidentiality or privacy also influences adherence. Interference with other personal choices or lifestyles can have an adverse effect, again perhaps particularly salient in the adolescent group where peer pressure and less healthy lifestyle choices such as excess alcohol and drug consumption are prominent. Treatment which is required to be supervised by another person may either increase or decrease the likelihood of adherence, depending on the individual responsible and the relationship between them. For example, an ADHD parent with his/her own executive function deficits or an unconvinced parent may have difficulty in facilitating adherence in an ADHD child.

Factors within the clinician or the health-care system are also important to consider. Research has shown that if patients like their clinician, perceive them to have a more affiliate style of communication and feel engaged in the process, they are more likely to be compliant [31–34]. Equally if a clinician provides continuity of care and specifically asks about adherence, he will be rewarded [31]. Attitudes and beliefs of staff and lack of training in adherence-related issues may be significant barriers to treatment adherence [14].

What can be done to improve adherence?

A number of studies have been carried out looking at ways to improve adherence. Studies using an RCT design, providing data on both adherence and clinical outcomes, with at least a 6-month follow-up period, were the subject of two separate Cochrane reviews [35, 36]. Strategies included providing reinforcements for compliance, reducing cost barriers by free dispensing, increasing motivation, providing counselling, family therapy or additional supportive care. Short-term interventions were more successful than longer-term interventions. Of the ten studies reviewed, only four were associated with improved adherence which led to a better clinical outcome [36]. Despite the amount of effort and resources consumed, longer-term interventions were less effective. Of the 83 studies reviewed, less than half (44 %) led to improved adherence and only 25 interventions (30 %) led to improved clinical outcomes. The researchers concluded that interventions required to increase adherence were generally complex, expensive and not very effective, at least in the longer term. We should not abandon these efforts but rather ensure that these become integrated into clinical practice in an ongoing way. Strategies such as providing information about the illness and medications, reminding the patients about taking their treatment, establishing more convenient and less complex care, either at home or work, changing hours of practice, and attention to the route and timing of administration are within our scope. Irrespective of outcome, psycho-education to parents, patients and family about the illness, and explicit treatment instructions and expectations are considered essential.

In 2001, the National Institute of Mental Health proposed the Unified Theory of Behaviour Change Model to assist with adherence issues as they pertain to both medical and non-medical management [37]. This model disentangles immediate from more distal determinants of behavioural change and considers how the clinician can become aware of person-specific determinants and include them in strategies to optimise adherence. They suggest as immediate factors: a patient's willingness to 'perform the behaviour', for example take medication, or engage in behavioural experiments; whether the patient has the requisite knowledge or skills, i.e. a child's ability to swallow a tablet or a parent's understanding of 'time out' procedures, a fundamental component of parent management, and the

presence of any environmental constraints which prohibit them carrying out the behaviour, e.g. a child needing transport to the clinic. The behaviour must be salient so that they do not forget to carry it out and that any habitual or automatic processes present are not a barrier, e.g. a person who habitually overeats at nighttime might need to be mindful of this and have distractions in place. Distal determinants of a person's readiness to engage in the treatment plan are more deep rooted. These include their attitude towards the required behaviour, their normative beliefs, i.e. what others think about the behaviour or their illness, and their expectancies about change. A parent who has a fundamental distrust of medication may be more sceptical about positive outcomes and their ambivalence may impede prioritising full adherence. The illness or treatment may challenge their self-concept and contribute to a lack of confidence in their ability to execute the new behaviour.

Strategies for children, adolescents and adults will differ. Working with a younger child to improve adherence may involve working with parents, the child, teachers and significant others, and facilitating behavioural change in all. Adult's beliefs, priorities and capabilities may dictate adherence to the treatment plan. As a child gets older, the treatment alliance and responsibility will shift more towards the adolescent. Strategies with adolescents may use a cognitive Socratic approach, be more accepting of differences in opinions, accept errors of judgement and encourage expression of ambivalence. Motivation to change on the part of a child or parent is a critical determinant to any given behaviour and behavioural change. As such, the therapeutic technique of motivational interviewing, and at what stage of change the person is at, has been very successfully applied to the concept of adherence [38]. The 'Pre-contemplation' period establishes the patient's perception of the problem and discrepancies between their view and the view of others, including the clinician's. Research has shown that positive perceptions of either their predicament [25] or their clinician [31, 33] have been linked with better treatment adherence. The clinician continues to educate them about their disorder and the pros and cons of suggested treatment regimes. Maintaining engagement and communication at this stage is key, rather than discharging the 'non-complaint' patient. During the 'Contemplation' phase, ambivalence and indecisiveness are normalised and they are encouraged to consider what they can do to effect change. With 'Preparation', the clinician may encourage and support the patient/family to think of specific goals and identify barriers which may impede or delay progress. In the 'Action' phase, the patient is praised for action taken towards treatment adherence, and difficulties and barriers continue to be identified along with strategies to overcome them. The last stage, the 'Maintenance' phase, focuses on how to cope with episodes of non-adherence and recognise the advantages of the new behaviour. These strategies apply equally well to medication regimes and to other therapeutic modalities. Short courses and on-line training opportunities in motivational interviewing are readily available [39–41].

The most important aspect in optimising adherence is to ensure that the original assessment and diagnostic formulation are accurate so that the correct evidence-based treatment plan can be developed, informed by the expertise of the clinical, shaped by the available resources and established collaboratively with the patient (family) so that it is acceptable and appropriate to their lifestyle and core beliefs. The treatment plan should be considered a reference guide which will change over time and in response to the illness trajectory and other circumstantial changes and guided by the mutually agreed time frame and definition of clinical outcomes.

Identification of factors contributing to suboptimal adherence will allow strategies to be developed to address these. Individual factors such as low socioeconomic class, gender and marital status may not be possible to change, but an understanding of the increased risk of non-adherence in this group might encourage systematic enquiry about adherence on every visit, brain-storming and problem-solving when difficulties arise, and looking for social supports to assist. There may be differences culturally in how the patient and clinician conceptualise illness and treatment which may lead to adherence difficulties. Correct information about the illness and treatment regime need to be shared in a sensitive and understandable way, with due respect to issues of confidentiality (e.g. if an interpreter is used), gender of clinician and compatibility with traditional healing methods. Appreciation and respect for cultural values and beliefs has been shown to lead to better adherence, outcome and reduced cost [42].

Stigma, self and public, are a major barrier to individuals seeking and adhering to treatment. Some evidence exists for the beneficial effect of reducing stigma at an individual and societal level through media campaigns, education and cognitive reframing [43]. Ongoing public education about the benefits of various interventions in mental health is crucial to allow a cultural change and reduce the ever present stigma associated with mental illness.

Establishing the readiness of the patient to engage in treatment, where they are in the 'stages of change' model, and developing intervention pertinent to that stage will be most meaningful. Factors within the clinician or the service should be addressed when relevant, such as opening times, ease of access, waiting times, privacy and ensuring a patient-friendly and age-appropriate environment. Transition of care across services, therapeutic style and ethos, and

issues of confidentiality and clinician expertise should be reviewed. The treatment regime itself should be considered, with an effort to make it simple, affordable and acceptable [36]. Simple strategies such as providing written instructions, attention to taste and size of medication, reminders, use of self-monitoring and using nonverbal material can make a significant difference, especially in younger children or those with learning difficulties. Flexibility about one or other parent attending groups, offering late appointments to facilitate working parents, and sensitivity to wider family and school issues will maximise engagement. When medication is part of the regime, due care should be given to choosing medication with the most efficacy and with least adverse side effects. Being reflective about our own practice and persuasions is also crucial to ensure the treatment recommendations made are indeed multi-modal and developed from a bio-psycho-social understanding of mental illness.

Conclusion

Adherence is a ubiquitous and dynamic process, an aspect of all therapeutic interventions, and needs to be reviewed and enquired about on a regular basis during clinical consultations. Individual patient-specific factors which determine adherence behaviour may have as much impact on treatment outcomes as the treatment. The actual level of impact of suboptimal adherence on treatment outcome is unknown due to methodological issues in studies conducted. Whilst strategies used to improve adherence are often only short lived, we should continue to incorporate these into everyday clinical consultations. Future studies should explicitly define adherence rates, be sufficiently powered and have sufficient follow-up time to allow for associations, if present, to be established. Potential confounders such as beliefs/behaviours which influence both adherence and other lifestyle choices need to be measured. To combat adherence difficulties, individualised patient-tailored interventions are necessary as it is clear that adherence is not standard across patient groups or disorder type and not static with time, and no one size fits all. Patients with MH difficulties may be particularly vulnerable to non-adherence and need to be supported in a non-judgemental fashion. Motivational style interviewing as a therapeutic technique may offer specific advantages in optimising adherence. Specific training in optimising adherence and further research in this area should be rewarded by improved clinical outcomes for our patients. Given that mental illness contributes substantially to the global burden of disease, and that treatments are often long term, investment in applied research into adherence is of crucial clinical and economic importance.

Conflict of interest None.

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