SECTION III

Disease-Specific Reviews

CHAPTER VII

Asthma

Asthma is a chronic, inflammatory disease of the airways that has dramatically increased in incidence over the past 15 years in both developed and developing countries. The global burden of asthma is considerable. Its effects include reduced quality of life, lost productivity, missed school days, increased health care costs, the risk of hospitalization and even death *(1)*.

While effective treatments that have been shown to dramatically reduce asthma morbidity are available, they are effective only when properly used by patients. Because human behaviour is the necessary interface between good therapies and therapeutic effectiveness, both clinical researchers and clinicians should understand the factors associated with patient adherence. This chapter discusses adherence issues in asthma, with a particular focus on adherence to preventive therapy, such as inhaled corticosteroids (ICSs). The prevalence of non-adherence to preventive therapy and patient factors associated with non-adherence are reviewed. Finally, we suggest some directions for future field research.

1. Defining nonadherence to asthma therapy

Assessing and understanding patient adherence in the management of asthma requires an appreciation of the diversity and complexity of adherence behaviour. Adherence to medication can be defined as the degree to which use of medication by the patient corresponds with the prescribed regimen.

Patients who regularly and consistently follow the prescribed regimen demonstrate adherent use. Adherence to medication is not a dichotomy, however, and patients can demonstrate a wide variety of patterns of medication use. The efficacy of asthma therapies can be modulated by these adherence patterns in several ways.

The most obvious form of nonadherence is chronic under-use, i.e. the patient consistently uses less medication than is prescribed. Chronic under-treatment of asthma may lead to poor control of symptoms and greater reliance on *pro re nata* (PRN) treatments for the relief of acute asthma symptoms.

Patients may also have an erratic pattern of adherence, in which medication use alternates between fully adherent (usually when symptomatic) and under-use or total non-use (when asymptomatic). Patients with erratic adherence may present for treatment of acute asthma although they apparently adhere completely to their prescribed regimen. Some patients relying solely on inhaled beta-agonists for symptom relief may be prone to over-use during acute bronchospasm. This may cause a patient to delay seeking care, or lead to complications associated with excessive use of beta-agonists *(2)*.

Patients may exhibit a different pattern of adherence to each of the various medications prescribed for the management of their asthma. For example, a patient may under-use the prescribed prophylactic anti-inflammatory ("controller" or "preventer") medications while remaining appropriately adherent to the regular taking of the beta-agonist. Adherence to an asthma action plan that outlines how and when both controller and reliever medications should be taken and when to seek urgent care has been shown to be one of the most effective forms of asthma self-management *(3)*. Finally, in order for medications delivered by metered dose inhaler (MDI) to control asthma optimally, the patient must adhere to the instructions for correct MDI use, or use an MDI spacer. Although MDI adherence has rarely been assessed in clinical or research settings, those studies that have examined patterns of MDI use by patients have suggested that poor technique is widespread (resulting both from inadequate instruction and patients' forgetfulness), and that improved MDI adherence can influence asthma management *(4)*.

2. Rates of adherence to inhaled corticosteroids and other drugs for the prevention of asthma

Extensive research conducted in Australia, Canada, the United Kingdom, the United States and elsewhere has found that nonadherence with asthma therapy is widespread, and is a significant risk factor for asthma morbidity and mortality. Because of the limited sensitivity and specificity of self-reported measures of adherence *(5)*, some of the most convincing studies have used objective measures, such as pharmacy databases, medication measurement and electronic medication monitors to assess adherence behaviour.

Conservative estimates indicate that almost half of the prescription medications dispensed yearly are not taken as prescribed *(6)*. The real-life response to a clinician's prescription of preventive therapy will include a range of undesirable patient behaviours, including a failure to fill the initial prescription, erratic use or under-use of therapy, and premature discontinuation of therapy. Studies indicate that primary nonadherence (not filling initial prescriptions) ranges from 6–44% *(7–12)*.

Even when patients fill prescriptions for asthma medications, studies of secondary nonadherence (rates of medication use) suggest that long-term rates of adherence to preventive therapies (e.g. controller or preventer medications) among adult patients are often poor. Spector et al. *(13)*, one of the first investigative teams to use an electronic medication monitor to examine adherence to MDI-delivered medications, followed 19 adult asthmatic patients using an anti-inflammatory drug for 12 weeks. Patients adhered to the four-times-daily regimen for a mean of 47% of the days, with a range of 4.3% to 95%. Patients were also asked to maintain asthma diaries as part of this study, and a comparative analysis of electronic data and diary data found that subjects over-reported their appropriate use of medication in

their diaries more than 50% of the time. In a similar study, Mawhinney et al. *(14)* studied adherence in adult asthmatic patients over a 3–4 week period. Adherence to the medication as prescribed was observed, on average, for 37% of the days, and under-use on more than 38% of the days monitored. Yeung et al. *(15)* used an electronic monitor to follow patients' use of inhaled corticosteroids over a period of 2–3 weeks. When patients were aware that they were being monitored, 60% of them were fully adherent, 20% were partially adherent (taking just 70% of the prescribed dose) and 20% were totally non-adherent. However, when patients were unaware of the monitoring, 6 out of 11 took between 30% and 51% of the prescribed doses.

Several studies have suggested that low-income, ethnic-minority patients (primarily African American) in developed countries may have lower rates of adherence to asthma therapy. Celano et al. *(16)* examined adherence to anti-inflammatory medication delivered by MDI in low-income, urban, primarily African American children with asthma. Adherence to treatment administered by MDI was estimated by weighing canisters and calculating the ratio of the number of puffs used over the study period to the number of puffs prescribed. Estimated MDI adherence in this study was 44% for all participants and only12% of the children had rates above 75%. In a group of 80 asthma patients, treated under the Medicaid scheme, who were repeat users of the emergency department or overnight hospitalization, only 46% had been prescribed ICSs and only 43% had a written action plan *(17)*. Less than half of children with asthma living in Tennessee, receiving treatment funded by Medicaid, had a prescription for oral corticosteroids filled following an emergency department visit or a period of hospitalization for asthma *(18)*.

Low rates have also been reported from studies that used different measurement systems. Coutts, Gibson and Paton *(19)* in the United Kingdom published the first study to examine children's adherence to anti-inflammatory therapy using an electronic medication monitor that recorded and stored the date and time of each use. Children (aged 9–16 years) were monitored for 2–6 months and asked to maintain asthma diaries as well as to use the monitored inhaler. Despite symptomatic asthma, underuse of the inhaled corticosteroids was observed on 55% of the study days. In a second study from the United Kingdom, Gibson et al. *(20)* used electronic monitoring to evaluate the adherence of preschool children to inhaled prophylactic medication. Median adherence was 100% on 50% of study days, and an overall median of 77% of the prescribed doses were taken during the average 2-month monitoring period. It is important to realize that the poor adherence observed occurred in the children of a group of parents who had a clear understanding that adherence was being monitored, and who had been provided with careful explanations of the importance of adherence to prophylactic medications. The authors noted that this poor adherence might reflect persistent misunderstandings or concerns about the side-effects of the medications.

Jonasson et al. *(21)* reported from Sweden on adherence to inhaled budesonide administered with a in 163 children (aged 7–16 years) with mild asthma who were participating in a randomized, double-blind clinical trial. Mean daily diary-card adherence was 93% over the 12-week study, whereas inhaler dose-counting recorded only 77% adherence. Milgrom et al. *(22)*, in the United States used electronic monitors to study of the adherence of school-aged children to inhaled corticosteroids. The participants were unaware of the function of the electronic device. Diary-card data showed that patients reported taking all doses on a median of 54% of study days and at least one dose on 97% of study days. However, electronic records of inhaled corticosteroid use showed a median of only 5% of study days on which all inhaled corticosteroid doses were taken and a median of 58% of days on which at least one dose was taken. The participants skipped all inhaled corticosteroid doses on a median of 42% of days and almost half of them missed their inhaled corticosteroids completely for more than a week at a time.

3. Forms of nonadherence

Understanding patient non-adherence to ICS therapy requires the recognition that there are different forms of non-adherent behaviour with diverse contributory factors. Careful clinical interviewing can reveal these problems and set the stage for identifying appropriate strategies for ameliorating them.

Erratic non-adherence. Perhaps the form of non-adherence that is most common and most acknowledged by patients and providers is doses missed because of forgetfulness, changing schedules or busy lifestyles. Patients who exhibit erratic nonadherence understand their prescribed regimen and would often like to adhere appropriately. However, they find it difficult to comply because the complexity of their lives interferes with adherence, or because they have not prioritized asthma management. Patients who have changing work schedules or chaotic lifestyles may have difficulty establishing the habit of a new medication regimen. For some patients Monday–Friday adherence presents no problem, but weekends or holidays disrupt medication routines. Strategies to improve erratic adherence centre on simplification of the regimen (e.g. once-a-day dosing), establishing new habits through linking (e.g. keeping the MDI next to the toothbrush) and cues and reminder aids (e.g. pill organizers).

Unwitting nonadherence. Many patients may be inadvertently nonadherent to the prescribed therapy because they have failed to understand fully either the specifics of the regimen or the necessity for adherence. Studies have found that patients frequently forget instructions given to them by a physician during a clinic visit (23). MDIs, unlike pill bottles, do not usually have attached labels with dosing instructions. In asthma management it is common for patients to misunderstand the difference between PRN medication and daily medication. Or, they may interpret the prescription for "ICS twice every day" as meaning "ICS twice every day – when you have symptoms".

Patients may overuse their inhaled beta-agonist because they have never been given clear guidelines for when and how to adjust controller medications or seek medical assistance when asthma control worsens. The ubiquity of unwitting non-adherence is illustrated by the findings of a study by Donnelly et al. *(24)*. The investigators interviewed 128 Australian parents of children with asthma about their knowledge about the disease, attitudes, beliefs and knowledge of asthma medications. Only 42% of parents had a basic understanding of the mode of action of beta-agonists, 12% for methylxanthines, 12% for cromoglycate and 0% for inhaled corticosteroids. Approximately half of the parents reported that sodium cromoglycate and inhaled corticosteroids were used to prevent asthma attacks, while 40–50% were unsure of the mode of usage. Most of the parents reported using antibiotics, antihistamines and decongestants in treating their child's asthma. The authors suggested that this poor parental understanding of asthma medications may result from inadequate communication between doctor and patient and this misunderstanding may contribute to the high prevalence of nonadherence to asthma treatments.

In a study in the Netherlands of adult asthmatics and patients with chronic obstructive pulmonary disease, Dekker et al. *(25)* found that 20% of the patients using pulmonary medications admitted that they did not know the prescribed daily dosage. Twenty-nine per cent thought that their regular daily medication was actually to be used "short-term" or "as needed". Only 51% correctly perceived that their medications were to be taken regularly.

Intelligent nonadherence. Sometimes patients purposely alter, discontinue, or even fail to initiate ICS therapy. This deliberate non-adherence is called intelligent non-adherence, reflecting a reasoned choice, rather than necessarily a wise one (26). Patients who feel better may decide that they no longer need to take prescribed medications. Fear of perceived short- or long-term side-effects of ICS may cause some patients to reduce or discontinue dosing. Patients may abandon a therapy because taste, complexity or interference with daily life may convince them that the disadvantages of therapy outweigh the benefits. Patients may find that some variation of the prescribed therapy works better than the doctor-prescribed regimen. Given the well-documented underuse of ICS, the fact that ICS therapy is as successful

in the management of asthma as it is, suggests that many patients manage quite well with altered or reduced doses. This deliberate nonadherence, like any other pattern of nonadherence does not necessarily result in worsening asthma. In every clinical practice there are patients who have knowingly altered their prescribed therapy, yet their health professional may never discover this modification. Regardless of the reason for nonadherence to medication, the necessary first step towards addressing the problem is identifying it through effective, open-ended communication between patient and provider. Only careful interviewing and active listening will equip the provider of asthma care with the information necessary to establish and reinforce adherence to appropriate medication. The time constraints placed on clinicians by managed care represent a serious barrier to carrying out this recommendation.

4. Factors associated with adherence to asthma treatment

Severity of asthma. Because of the significant burden of symptoms and the risk associated with severe asthma it would seem logical that patients with severe disease would have a greater incentive for, and hence a greater likelihood of adhering to prescribed therapy. Conversely, it could be argued that for some asthmatic patients more symptomatic disease is the consequence of inadequate adherence to treatment. For example, Milgrom et al. (22) demonstrated in a study of paediatric asthmatic patients that prednisone bursts were more common in those patients who were found by electronic monitoring to be the least adherent to therapy with inhaled anti-inflammatory medication.

It has also been suggested that the immediate awareness of active asthma symptoms should serve as a cue for improved adherence to medication. Mann et al.*(27)* tested this hypothesis by measuring the relationship between patient adherence to Q.I.D. beclomethasone and periods of increased severity of asthma. Ten adult patients with moderate-to-severe asthma were monitored over a 9-week period using an electronic device attached to the MDI to measure adherence to inhaled medication, and peak flow monitoring to measure airflow obstruction. The authors concluded that compliance with inhaled corticosteroids was not modulated by asthma severity (as measured by peak expiratory flow), or by patient-reported symptoms.

Patients' beliefs about inhaled corticosteroids and asthma. The relationship between beliefs about asthma and adherence to preventive therapy was clearly illustrated in a study by Adams et al. *(28)*. The investigators interviewed adult patients in Wales, United Kingdom, using qualitative interviewing strategies and identified three common self-perspectives among this group: asthma deniers/distancers, asthma accepters, and pragmatics. Each of these perspectives was associated with very different beliefs held by the patients about the nature of asthma and the use of preventive medication. This analysis suggested that an asthmatic patient's self-perception of his or her disease may influence his or her adherence to preventive asthma therapy.

Parents and patients who are concerned about using corticosteroids may under-dose or discontinue long-term use in an effort to be "steroid-sparing". Boulet *(29)* conducted a telephone survey of over 600 adult asthmatic patients in Canada to find out about patients' perceptions about the role of ICS in the treatment of asthma and the potential side-effects of this therapy. The investigators found that patients frequently had misperceptions about the role of ICSs, even if they had recently used them. For example, over 40% of patients believed that ICS opened up the airways to relieve bronchoconstriction, while less than a quarter of the patients reported that ICS reduced airway inflammation. This fundamental misunderstanding of the mechanism of ICS suggests that these patients may also have failed to understand the underlying chronic inflammation that characterizes asthma and the need for preventive therapy. Forty-six per cent of the patients interviewed indicated that they were reluctant to take ICS regularly and only 25% of patients reported that they had discussed their fears and concerns about ICS with their primary care provider. Misconceptions about the side-effects and long-term consequences of ICS use

were also common. However, when the true side-effects of inhaled corticosteroids were explained, most of the patients reported being reassured. Boulet *(29)* concluded that information about the safety and usefulness of ICS does not seem to have reached many patients with asthma. This study also suggests that health care providers should discuss with patients any possible concerns about ICS therapy that might interfere with adherence.

In a similar study conducted in the United States, Chambers et al. *(30)* surveyed 694 largely symptomatic asthmatic patients aged 18–49 years who had been prescribed ICS in 1995–1996. The most notable finding in this survey was the low level of self-reported adherence with therapy. Sixty-two per cent of patients reported less than regular twice-daily ICS use. Thirty-six per cent of the patients endorsed the option "some days I use it at least twice, but on other days I don't use it at all", while 22% reported that they no longer used ICS. Four per cent of patients claimed that they had never used ICS. Those who were less than fully adherent were asked to state their reasons for not using ICS, and the reason most frequently cited was that they used therapy only when they believed they needed it. This study suggests that many patients with asthma believe that their asthma is an episodic rather than a chronic disease, and that therapy is necessary only when there is disease exacerbation.

Psychological models of disease management have suggested that adherence to medication may be related to the patient's perceived vulnerability to the negative consequences of illness, with an increased sense of risk being associated with better adherence. In paediatric research, several studies have suggested that parents who consider their children's health to be fragile or vulnerable (whether based on real events or not) will be vigilant and will adhere to health care recommendations. Spurrier et al. *(31)* examined the relationship between the asthma management strategies used by 101 parents of children with asthma and the perceptions of these parents of their child's vulnerability to illness. The study found that after controlling for the frequency and severity of asthma symptoms, those parents who felt their child had greater vulnerability to illness were more likely to use regular preventive medications, take the child to the doctor and keep him or her home from school. The authors suggested that one possible explanation of this finding is that "parents who do not perceive their child to be medically vulnerable may discontinue administering regular medication…" *(31)*.

Regimen factors in asthma therapy. A number of studies across a range of chronic diseases have found that certain characteristics of the prescribed treatment regimen are strongly associated with patient adherence. In general, the longer the duration of therapy, the more frequent the dosing, and the more complex the regimen (e.g. multiple devices or tasks), the poorer the adherence of the patient (32). Actual or perceived side-effects of treatment and the cost of therapy can also reduce adherence levels.

In recent years considerable effort has been directed towards developing an effective and safe once-a-day therapy for asthma because of its presumed advantage in promoting patient compliance. However, although there is convincing evidence that doses that must be administered more than twice a day lead to decreased adherence *(19)*, the data is equivocal on the superiority of once-a-day dosing over twice-a-day dosing *(33–35)*. Adherence considerations apart, once-daily asthma therapy appears to be preferable for most patients. Venables et al. *(36)* studied patient preferences in asthma therapy and found that 61% of patients expressed a preference for once-a-day treatment, 12% preferred twice-a-day treatment and 27% expressed no preference. While preference may not necessarily lead to improved compliance, it may well reduce the burden of therapy and enhance the quality of life of the patients.

5. Adherence in special populations

Children. There can be great diversity among families in how medication is managed. The responsibility for administration of medication generally shifts as a child grows, from total parental management for a young child, to shared medication management for a school-aged child, to complete self-management for an adolescent. Day-care providers, grandparents and siblings may assume the responsibility for reg-

ular delivery of asthma medication in some households. In chaotic, troubled families there may be confusion as to who has the primary responsibility for medication monitoring. The age at which a child is capable of assuming responsibility for remembering to take daily medication is highly variable, and is more a reflection of the child's maturity and personality than his or her chronological age. In some families children may be expected to manage their own medication early, less because the child has demonstrated sufficient responsibility, than because the parent believes the child is old enough to do it. For older children and adolescents, asthma management has the potential for turning into a battle in the war of independence. Research on juvenile diabetes, haemophilia and rheumatoid arthritis has emphasized the particular vulnerability of adolescents to problems with adherence to medication (37,38). Family conflict and a denial of disease severity in an adolescent with severe asthma should therefore suggest a patient at a high risk for nonadherence to therapy.

Elderly patients. Some barriers to adherence to therapy are more common in older patients and warrant particular attention in clinical management. For example, although patients of any age may forget to take their medication, for some older patients memory difficulties may be exacerbated by other medications or early dementia. In addition, older patients are often receiving treatment for several other chronic health conditions simultaneously. The resulting polypharmacy is a well-recognized problem for many elderly patients, presenting both pharmacological and adherence risks (39). The treatment of multiple ailments can result in complicated and burdensome medication regimens that require medications to be taken many times per day. Clinicians treating older patients for asthma should carefully review all prescribed medications, be attentive to potential memory difficulties, and assist the patient in integrating ICS therapy into his or her existing regimens.

Cultural differences. Culture and lay beliefs about illness and treatment can also influence the acceptance of asthma therapies by patients and their families. Divergent cultural beliefs can affect health care through competing therapies, fear of the health care system or distrust of prescribed therapies.

Income. While income per se does not predict adherence, the co-variates of poverty and inner-city living may make adherence to asthma self-management more difficult. Barriers to adherence related to low income can include inconsistent primary health care, inability to pay for asthma medications, lack of transport, family dysfunction and substance abuse *(40–43)*.

In some countries, patients may not be able to afford preventive asthma therapies. Research suggests that these cost barriers may lead some patients to treat their disease only during periods of exacerbation, or to reduce their dosage to "stretch" their medication.

6. Interventions to improve adherence to asthma therapy

Haynes et al. *(44)* recently reviewed the results of randomized controlled trials of interventions to promote adherence to pharmacological regimens across a range of chronic diseases, including asthma, where both adherence and clinical outcome were measured. This rigorous review found that over half (10/19) of the interventions for long-term treatments reviewed were associated with significant improvements in adherence; however, the magnitude of the improvements in adherence or clinical outcome was generally not large. The authors concluded that successful interventions to promote adherence were complex and multi-faceted and included combinations of counselling, education, more convenient care, self-monitoring, reinforcement, reminders, and other forms of additional attention or supervision. Specific intervention strategies that can be used for promoting adherence to therapy are outlined below.

Educational strategies. Asthma is a complex disease and requires education of the patient and his or her family if it is to be managed successfully. Knowledge of the regimen is necessary, but not sufficient in itself, to ensure patient adherence. Several studies have emphasized the central role of effective communication between patients and health care providers in promoting adherence *(45,46)*.

Written instructions about the asthma regimen that are culturally appropriate and adapted to suit the patient's level of literacy should be a core part of every interaction with the patient. For older patients, comprehension and recall of information on how to take medication has been shown to be significantly improved when medication-taking instructions were clear, presented as lists rather than paragraphs, used pictures or icons in combination with written medication instructions and were consistent with patients' mental representations of medication taking *(47)*.

Self-management programmes that include both educational and behavioural components have been developed *(48)*. The educational formats use basic learning principles to promote adherence with asthma therapy. Key points in the most recent set of treatment guidelines have included the following:

- education of the patient beginning at the time of diagnosis and integrated into every step of asthma care;
- patient education provided by all members of the team;
- teaching skills for the self-management of asthma by tailoring the information and the treatment approach to fit the needs of each patient;
- teaching and reinforcing behavioural skills such as inhaler use, self-monitoring and environmental control;
- joint development of treatment plans by team members and patients;
- encouragement of an active partnership by providing written self-management and individualized asthma action plans to patients; and
- encouraging adherence to the treatment plan jointly developed by the interdisciplinary team and the patients.

These self-management programmes have demonstrated their effectiveness in decreasing symptoms, school absence and emergency care as well as improving asthma knowledge. However, little is known about the direct effects of these programmes on adherence. Future educational programmes will need to include objective monitoring of adherence in order to examine their effectiveness in promoting it.

Behavioural strategies. Behavioural strategies are those procedures that attempt to promote adherence behaviours directly by using techniques such as reminders, contracting and reinforcement (49). The use of reminders has been shown to be helpful in maintaining adherence both in asthmatic children followed in an asthma clinic and asthmatic children followed as outpatients after inpatient asthma rehabilitation *(50,51)*. Providing feedback to patients regarding adherence to medication is an important behavioural clinical strategy. Informing patients that they will be objectively monitored for adherence has been shown to be effective in improving adherence in outpatient clinics *(15)*, at follow-up visits after inpatient rehabilitation *(52)* and in clinical trials *(53)*. Reinforcement is an essential component of all behavioural strategies. Reinforcement refers to any consequences that increase the probability of the behaviour being repeated. Dunbar et al. suggested, that a clinician's time and attention to the patient may be the most powerful available reinforcer *(49)*. The length of time a patient spends with the clinician is positively related to adherence *(54)*. Investigators have used contracts to include the families of asthmatic children. In this setting, patients receive reinforcement from those people who are most significant to them and most readily available at the time the health behaviour occurs *(55)*.

Tailoring of therapy. Tailoring the therapy to the patient is a strategy that is sometimes overlooked by health care providers. Tailoring refers to fitting the prescribed regimen and intervention strategies to specific characteristics of the patient. It is another effective behavioural method used to improve adherence *(55)*. Whenever possible, negotiating a therapy that the patient is able to follow should be a first priority. Some example of ways in which the therapy may be tailored include exploring the patient's

schedule, beliefs, and preferences *(56)*; simplifying the dosing regimen *(57)*; altering the route of administration(58), and using adherence aids *(59)*.

Maintenance interventions to achieve adherence. Achieving and maintaining adherence over long periods of time difficult for both patients and clinicians. Investigators in the management of childhood and adult asthma have developed self-management programmes to enable a patient and his or her family to manage asthma efficiently and effectively over time in conjunction with their health professional. Self-management programmes for adult and childhood asthma have been shown to reduce asthma morbidity and costs, and may be useful in promoting and sustaining long-term adherence to therapy *(60–63)*.

A group of investigators developed and tested the effectiveness of a psycho-educational self-management programme for severely asthmatic children that was delivered in an inpatient setting *(64)*. Patients were admitted to the programme if they met morbidity criteria in the year prior to admission that included a minimum of three hospitalizations, four emergency visits, four corticosteroid bursts and agreement of the families to participate in self-management meetings. The rehabilitation intervention included medical assessment and management, physical activity training, education about asthma for

Table 1 Factors affecting adherence to asthma treatment and interventions for improving it, listed according to the five dimensions and the interventions used to improve adherence

Asthma	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Vulnerability of the adolescent to not taking medications; family conflict and denial of severity of disease in adolescents *(37)*; memory difficulties in older patients; polypharmacy in older patients *(39)*; cultural and lay beliefs about illness and treatment; alternative medicines; fear of the health care system; poverty; inner-city living; lack of transport; family dysfunction *(40)*	List-organized instructions; clear instructions about treatment for older patients *(47)*
Health care team/health system-related factors	(–) Health care providers' lack of knowledge and training in treatment management and/or an inadequate understanding of the disease; short consultations; lack of training in changing behaviour of nonadherent patients	Education on use of medicines; management of disease and treatment in conjunction with patients *(48)*; adherence education *(58)*; multidisciplinary care *(48)*; training in monitoring adherence; more intensive intervention by increasing the number and duration of contacts *(49)*
Condition-related factors	(–) Inadequate understanding of the disease *(29)*	Patient education beginning at the time of diagnosis and integrated into every step of asthma care *(48)*
Therapy-related factors	(–) Complex treatment regimens; long duration of therapy; frequent doses *(32)*; adverse effects of treatment	Simplification of regimens *(57)*; education on use of medicines *(48)*; adaptation of prescribed medications *(55,56,58)*; continuous monitoring and re-assessment of treatment *(15),(52,53)*
Patient-related factors	(–) Forgetfulness; misunderstanding of instructions about medications; poor parental understanding of children's asthma medications; patients' lack of perception of his or her own vulnerability to illness *(31)*	patients' lack of information about the prescribed daily dosage/ misconceptions about the disease and treatments (29); persistent misunderstandings about side-effects (29); drug abuse *(40)*

SMBG, self-monitoring of blood glucose; (+) factors having a positive effect on adherence, (–) factors having a negative effect on adherence

the child and family, and a sequence of family interviews designed to facilitate home-management of the illness and promote adherence to medication. These individuals were followed as outpatients for 4 years; they received 3 to 4 medications concurrently and achieved a marked reduction in hospitalization, emergency care, oral corticosteroid use and total costs of asthma by maintaining adherence, as measured by monitoring theophylline levels at outpatient visits.

7. Discussion

Because adherence with therapy is an integral part of the effective management of asthma, all international public health efforts to improve asthma outcomes should include educational strategies for both patients and health care providers that target the promotion of adherence. Regular adherence to ICS therapy is dependent on the patient's acceptance that asthma is a chronic disease requiring preventive treatment. Patients must also feel that the prescribed therapy is effective in achieving the desired treatment goals and is safe for long-term use. Several studies have confirmed that the beliefs that patients hold about their asthma and the therapy prescribed for it are closely associated with the likelihood of adherence. When patients do not perceive that their asthma is chronic or that it requires preventive treatment, adherence with therapy is generally episodic.

Effective communication between patients and providers has been identified as having an important influence on patients' adherence. Most health professionals lack the training to change the behaviour of nonadherent patients. Educational efforts sponsored by both public and private sources are needed to improve the communication skills of health professionals so as to promote adherence to the treatments recommended for asthma.

Limited evidence from studies of adherence to asthma therapy among immigrant populations in developed countries suggests that use of alternative medicine and lay beliefs may significantly reduce adherence to therapy. Watson and Lewis *(68)* reported that inhaled corticosteroids were available in only 15 of 24 countries surveyed in Africa and Asia, and when available the median (range) cost of a 50 _g beclomethasone inhaler was 20% (6.8–100%) of the average local monthly income. Additional research is needed on the rates of adherence and barriers to adherence in developing countries.

Guidelines on the management of patients with asthma may be modified in the future following the development of accurate and affordable systems for monitoring anti-inflammatory medication. By objectively evaluating the adherence of symptomatic patients, those who are nonadherent may be identified, appropriately treated and counselled in an accurate, efficient and cost-effective manner *(69)*.

8. Conclusions

Nonadherence to regimens for asthma treatment may have several causes including inadequate knowledge and skill on the part of the patient, and inadequate awareness of the problem, or lack of skill to address it, on the part of the health professional. Patients must have a basic understanding of their illness and its treatment if we are to expect even minimal adherence. Achievement of adherence requires considerable effort from both the patient and caregiver. To perform the daily tasks necessary for successful control of their asthma, patients must be well motivated and convinced that their own behaviour will result in improved health, a concept referred to as self-efficacy. Simply giving information to patients is unlikely to change behaviour; health care providers must understand the psychological principles that underlie self-management training and comprehend that motivating patients requires more than informing them briefly about the prescription that has just been written. At the core of these principles is the need to establish treatment goals that can be embraced both by health professionals and patients in a partnership that requires regular and reciprocal communication. Patients will not perform the work necessary to achieve goals they do not understand or do not view as necessary and important.

Once appropriate goals have been established, most patients require assistance in determining how to evaluate their changing symptoms and how to use their written action plan to make effective decisions about daily self-management behaviour.

9. References

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CHAPTER VIII

Cancer (Palliative care)

In most parts of the world, the majority of cancer patients suffer an advanced stage of the disease, which unfortunately is not responsive to curative treatment. Nearly 75% of patients with advanced cancer experience pain, very often in conjunction with many other symptoms, such as asthenia, anorexia and malnutrition, skin problems, dry mouth or thirst, constipation, nausea or vomiting, anxiety, low mood, depression, confusion and sleeplessness *(1,2)*. For such patients, the only available management is palliative care, which focuses mainly on pain relief *(3)*.

Palliative care is an approach that improves the quality of life of patients through the prevention and relief of suffering. To meet the multiple and varying needs of the patients, it is believed that the care should be holistic, multidisciplinary, and family – as well as patient –centred. The aims of palliative care are achieved by:

– providing relief from pain and other distressing symptoms;

– affirming life and regarding dying as a normal process;

– intending neither to hasten nor to postpone death;

– integrating the psychological and spiritual aspects of patient care;

– offering a support system to help patients live as actively as possible until death;

– offering a support system to help the family to cope during the patient's illness and during bereavement;

– using a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;

– enhancing quality of life, and possibly also positively influencing the course of illness; and

– starting palliative care early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and including those investigations needed to better understand and manage distressing clinical complications *(4)*.

Palliative care is still a neglected area worldwide and several million cancer patients suffer needlessly every day as a result *(5)*. Most cancer patients in developing countries receive inadequate palliative care and less than 10% of the resources committed to cancer control in these countries are available to them *(1)*. Palliative care remains far from satisfactory, mainly because of:

– an absence of national policies on cancer pain relief and other aspects of palliative care;

– the lack of education for health care providers, policy-makers, administrators and the general public;

– the concern that the medical use of morphine and related drugs will fuel the problem of drug abuse in a community and result in increased restrictions on prescription and supply;

– limitations on the supply and distribution of the drugs needed for the relief of pain and other symptoms, particularly in developing countries;

– restrictions imposed by the adoption of regional, district or hospital formularies, which contain insufficient drugs for the control of pain and other symptoms;

– the shortage of professional health care workers empowered to prescribe analgesics and other drugs for palliative care; and

– the lack of financial resources for research and development in palliative care *(1)*.

Pain relief is a key component of a comprehensive palliative care programme. Relief from cancer pain can be achieved in about 90% of patients, but unfortunately pain is often poorly managed. Pain relief may be achieved by drug use, but may also include various other means: psychological approaches, pathological processes (e.g. nerve degeneration) and modification of daily activities. The pharmacological approach to the palliative care of cancer patients uses a variety of drugs for managing symptoms. These include non-opioid analgesics (mild analgesics and nonsteroidal anti-inflammatory drugs), opioids for moderate to severe pain, ulcer-healing drugs, antispasmodics, corticosteroids, bronchodilators, laxatives, antiemetics, antifungals, antidepressives and hypnotics among others.

Data from studies by Miaskowski, Du pen and Ward et al. *(6–8)* indicate that one of the main factors contributing to the undertreatment of cancer pain is the patients' lack of adherence to the therapeutic regimen. The study by Ward et al. *(8)* showed that a third of the patients they monitored delayed or omitted many prescribed doses. This reflects the fact that patients often take their doses at intervals longer than those prescribed, commonly longer by hours, but sometimes by days and occasionally by weeks. The clinical and economic consequences of these lapses in dosing are uniquely difficult to measure due to the complexity of treatment and the severity of disease.

Because more than 90% of palliative care is provided on an outpatient basis, it is critically important for clinicians to know how their patients adhere to their regimen for analgesics or other palliative therapies, and if possible, they should also know which effective interventions are available for improving adherence. The aim of this chapter is to summarize the available literature on adherence to palliative care and provide answers to some of these questions.

1. Definitions and epidemiology of adherence

Published studies were considered for inclusion here if they reported relevant epidemiological or economic data on adherence to one of the therapies usually used in palliative care. A search on adherence to cancer palliative care was made using Medline (1990–2002). Some reviews and reports from international and national organizations were also included. The search retrieved only studies that evaluated adherence to pain relief in palliative care.

Adherence was usually not explicitly defined in the articles retrieved, but referred to generally as "patients following medical recommendations". In operational terms, the variables of adherence were defined as: "not filling a prescription," "not taking medication," "errors in dosage," "reducing medication," "taking extra medication" and "taking additional nonprescribed medication" *(6,7,9,10)*.

The studies reviewed here used several different methods to estimate the adherence of patients to their medication. These methods, which can be used either separately or in combination, include review of medical records, patient self-report, family report, residual pill counting, electronic measurement devices, prescription refill rates, biological markers in serum or urine, assays to quantify medications or their metabolites and therapeutic outcome *(6,9)*.

Few studies have provided data on the level of adherence of oncology patients to their pain relief, and the methods used to calculate these adherence rates were not always described. Zeppetella et al., reported that 40% of patients with cancer adhered to pain relief drugs *(9)*. Miaskowski et al. reported adherence rates for opioid analgesics. Cancer patients prescribed relief on an around-the-clock basis took an average of 88.9%, while those who were prescribed relief on an as-needed basis had an adherence rate of about 24.7% *(6)*. Du Pen et al. reported that adherence of oncology patients to their prescribed opioid therapy was between 62% and 72% *(7)* and Ferrell et al. reported a mean adherence rate of 80% *(10)*.

2. Factors and interventions affecting adherence

Non-adherence is a problem that has many determinants; the responsibility for adherence has to be shared by health professionals, the health care system, the community and the patients. Many studies have identified the factors affecting adherence, and we have grouped these into five dimensions: socioeconomic-related factors, health care team/health system-related factors, condition-related factors, treatment-related factors and patient-related factors, as shown in Table 2.

Many factors, such as lack of knowledge about pain management *(5,11)*, misunderstanding instructions about how to take drugs*(9)*, complex treatment regimens *(9)*, anxiety about adverse effects *(12)*, inadequate understanding by health professionals of drug dependence *(13)* and long distance from the treatment setting, among many others, have been shown to be significant barriers to adherence, and should be taken into account when developing interventions.

Several interventions have been designed to improve adherence to medications for the relief of cancer pain. Some of them target specific factors as described below.

– *Patient cooperation.* This is achieved by educating the patient about pain and the management of side-effects, and encouraging the active participation of the patient in his or her own pain treatment *(9)*.

– *Therapeutic relationship.* good relationships between health professionals and patients should be encouraged *(14)*.

– *Simplification of regimens.* The use of once-daily, or at most twice-daily, preparations is desirable wherever possible *(9)*.

– *Adaptations of prescribed medications.* The patient should agree on a medication formulation and medication should be chosen not only for the clinical indication, but also to suit the patient, taking into account his or her lifestyle and preferences *(15)*.

– *The role of home care nurses.* Home care nurses can play an important role in educating patients and their families about pain management, in administering medications and providing support and counselling *(16–18)*.

Failure to address the barriers affecting pain management may lead to therapeutic failure and poor quality of life for the patient.

Table 2 Factors affecting adherence to palliative care for cancer and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Cancer	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Long distance from treatment setting	Optimizing the cooperation between services; assessment of social needs *(3)*; family preparedness *(3)*; mobilization of community-based organizations
Health care team/health system-related factors	(–) Lack of knowledge of health professionals about pain management; inadequate understanding of drug dependence by health professionals *(5)*; health professionals' fears of investigation or sanction *(19)*; poor delivery of care education to the patient *(20)*; poor delivery of care education to family and caregivers *(20)*; reluctance of health professionals to prescribe opioids for use at home *(20)* (+) Good relationship between patient and physician *(14)*	Training of health professionals on adherence *(20)*; pain education component in training programmes *(13)*; support to caregivers; multidisciplinary care; follow-up consultation by community nurses *(20)*; supervision in home pain management *(20)*; identification of the treatment goals and development of strategies to meet these goals
Condition-related factors	(–) Nature of the patient's illness; poor understanding of the disease and its symptoms	Therapeutic patient education *(11)*
Therapy-related factors	(–) Complex treatment regimens; taking too many tablets *(9)*; frequency of dose; having no treatment instructions *(9)*; misunderstanding instructions about how to take the drugs *(9)*; bad tasting medication; adverse effects of treatment *(9)*; inadequate treatment doses; perceived ineffectiveness *(9)*, unnecessary duplicate prescribing *(9)* (+) Monotherapy with simple dosing schedules *(9)*	Simplification of regimens *(15)*; education on use of medications *(9)*; giving clear instructions *(9)*; clarifying misunderstanding about the recommendation of opioids; patient-tailored prescriptions *(9,15)*; continuous monitoring and re-assessment of treatment; assessment and management of side-effects; coordination of prescribing *(9)*
Patient-related factors	(–) Forgetfulness *(9)*; misconceptions about pain *(11,12)*; difficulty in taking the preparation as prescribed *(9)*; fear of injections *(11)*; anxieties about possible adverse effects *(12)*; no self-perceived need for treatment *(9,12)*; feeling that it is not important to take medications *(9,12)*; undue anxiety about medication dependence *(11)*; fear of addiction *(14)*; psychological stress	Interventions to redress misconceptions about pain treatment and to encourage dialogue about pain control between patient and oncologist *(9,11)*; exploration of fears (e.g. about addiction) *(9,11)*; assessment of psychological needs *(3)*; education on use of medications *(11)*; behavioural motivational intervention *(11)*; good patient–provider relationship *(14)*; self-management of disease and treatment *(11,16–18)*; self-management of side-effects *(16–18)*

AEDs, anti-epileptic drugs; (+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence.

3. Conclusions

Definitions and measurements of adherence vary widely; this prevents comparisons between studies and populations. There is little information on the adherence to palliative treatment of patients with cancer, and it covers only treatments for relief of pain. The available information reports adherence rates ranging from 24.7% to 88.9%. A general programme of palliative care must include the management of adherence in order to improve the effectiveness of the interventions and ensure an acceptable quality of life for this group of patients.

More research on adherence to palliative care is required in the following areas:

– epidemiology of adherence, especially to medicines other than those for pain relief;

– determination of the most appropriate methods and definitions for the measurement of adherence to analgesic medications;

– determining the additional factors that contribute to a patient's level of adherence to all required therapies; and

– studies evaluating interventions to improve adherence to all required therapies.

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CHAPTER IX

Depression

Depressive disorder is one of the most prevalent forms of mental illness, and is of major public health importance *(1)*. It is characterized by abnormal and persistent low mood, accompanied by other symptoms including sleep disturbance, loss of appetite, suicidal thoughts, impaired concentration and attention, guilt and pessimism. Symptoms vary in severity, and the pattern of illness can range from an isolated and relatively mild episode, through recurrent episodes of moderate severity, to chronic and persistent severe illness. Owing to its prevalence, and to health system factors, primary care practitioners see most of the patients with depression and few are referred to specialist psychiatric services, even when they are readily available.

Although psychological treatments of proven efficacy are available for the management of depression, the most common form of treatment worldwide is antidepressant medication. For patients with a definitive diagnosis of depression, pharmacotherapy guidelines advocate that treatment should continue for at least 6 months following remission of symptoms. Furthermore, among patients who have suffered two or more episodes of significant depression within 5 years, long-term preventive treatment is suggested *(2)*.

The clinical effectiveness of drug therapies for depression is limited by two groups of factors; patient adherence to the recommended protocol, and under-diagnosis and/or suboptimal treatment by primary care doctors. Both groups of factors appear to be relatively common, but the focus here is on adherence. However, the diagnosis and treatment cannot be ignored as they are likely to interact with, or to mediate, adherence.

This chapter discusses research methods, the overall prevalence of adherence, predictors of adherence and the efficacy of interventions designed to improve adherence. A bibliographical search was made using Medline (1990–2001). A total of 287 articles were identified and evaluated.

1. Research methods: measurement of adherence and sampling

As is the case when attempting to measure patient behaviour in many other contexts, it is difficult to derive accurate estimates of patient adherence to medication for depression. Across studies, several techniques have been used including clinician estimation or patient self-report, pill-counting, estimation of blood levels of drug, metabolite or tracer substance, and the use of electronic monitoring systems that record pill dispensing. Two studies directly compared methods of measurement. In 1990 Kroll et al. using a small sample of patients with mixed diagnoses, demonstrated that levels of medication in the blood correlated with clinical outcome, and that many patients who claimed to be taking a medication regularly had low levels of it in their blood *(3)*. In 2000, George et al. compared four methods of assessment in depressed patients treated by primary care practitioners, and were able to show that an event monitoring system (EMS) that electronically counted the amount of medication dispensed from its container was the most sensitive method of measuring adherence, although the specificity of a patient report of non-adherence was also high *(4)*. Estimations of plasma levels of drugs and their metabolites were less useful. Although these types of measure overcome some of the bias associated with either physician estimation or patient self-report, they still lack some of the features required of a "gold-standard" measure (i.e. being direct, objective and unobtrusive).

The second important methodological issue is the nature of the patient samples studied. Much research has been conducted among hospital outpatients or inpatients, or patients recruited into randomized trials to test the efficacy of medications. This pre-selection bias makes it very unlikely that the patients in these studies represent the true population of depressed patients receiving treatment in primary care settings. This makes it hard to generalize from the results of these studies.

2. Rates of adherence

Many studies have attempted to estimate the prevalence of adherence using different methods in a variety of patient samples. Early studies in primary care settings in the United Kingdom indicated that up to two-thirds of depressed patients who started courses of tricyclic drugs stopped taking them within a month. Peveler et al. assessed a large population of patients receiving tricyclic medication in primary care settings in the United Kingdom using EMS, and found that around 40% had discontinued treatment within 12 weeks *(5)*. In 1990, McCombs et al. attempted to assess adherence in a large sample of depressed Medicaid-funded patients in California, United States, but found it difficult to separate patient adherence from physician adherence to treatment guidelines *(6)*. Katon et al. assessed the extent to which patients of a HMO, on receiving prescriptions for antidepressant drugs, actually obtained supplies of medication. They reported that only 20% of patients who had been prescribed tricyclic drugs filled four or more prescriptions within 6 months, while 34% of patients who had been prescribed newer antidepressants did so *(7)*. Lin et al. assessed a very large sample of HMO patients 6–8 weeks after starting treatment and found that 32–42% had not filled their prescriptions *(8)*.

In a sample of patients with psychiatric disorders receiving prophylactic lithium treatment for unipolar and bipolar affective illness, Schumann et al. found that 43% of patients had discontinued their medication within 6 months *(9)*. Ramana et al. interviewed patients discharged from hospital following admission for depression and found that at 18 months about 70% were "compliant", although this study also noted problems with physicians under-prescribing according to guidelines *(10)*.

Gasquet et al. conducted a large telephone survey of the general population in France *(11)*. He reported that 15% of the subjects admitted to early termination of their treatment, and 22% admitted to reducing their dose.

3. Predictors of adherence

Frequency of dosing. In an early study in a psychiatric outpatient practice in the United Kingdom, Myers & Branthwaite randomized patients into groups that received their treatment once daily or three times daily, or chose one of the two schedules. Adherence was assessed by pill count and interview *(12)*. There was no overall difference in reported adherence between patients receiving once-daily or three-times-daily doses, but those who elected to take their medication three times daily reported better adherence than the rest. This suggests that the element of personal control over choice of dose, rather than the frequency of dosing itself was influential. A recent study has suggested that prescribing a once-weekly dose of enteric-coated fluoxetine may lead to better adherence than a once-daily dose *(13)*; thus substantial gains in convenience may also improve adherence.

Education. Lin et al. reported that patients were more likely to continue to take their medication during the first month of treatment if they had received specific educational messages, namely that they should take their medication daily, that they might notice no benefit for the first 2–4 weeks, that they should continue even if they felt better and that they should not stop medication without consulting their doctor. They also received advice about how to seek answers to questions about medication *(14)*. The impact of such advice has not been evaluated prospectively.

Drug type. There has been considerable interest in the question of whether or not different antidepressant drugs are associated with better or worse adherence. A naturalistic study of claims data of 2000 patients suggested that adherence may be poorer in patients treated with tricyclic antidepressants, and that the provision of family, group or individual psychotherapy may improve adherence *(15)*.

Several meta-analyses of randomized trials have also addressed this question. Montgomery and Kasper reviewed 67 trials and reported that the numbers of patients who discontinued their treatment because of side-effects were 5% lower in patients treated with selective serotonin reuptake inhibitors (SSRIs) than in patients treated with tricyclics *(16)*. Anderson and Tomenson reviewed 62 trials and also found a marginally lower discontinuation rate in patients treated with SSRIs, but commented that the difference was probably too small to be of clinical significance *(17)*. Hotopf et al. reporting the results of another meta-analysis suggested that even this small difference might be due to the preponderance of older tricyclic drugs used in most of the early trials, and that it would disappear if the comparison was made with newer tricyclic and heterocyclic medicines *(18)*. Although the generalizability of meta-analysis may be limited by the characteristics of the patient samples in the trials reviewed, these results suggest that drug type may not be a particularly influential variable.

Co-medication. Furukawa et al. conducted a meta-analysis of trials comparing combinations of antidepressants and benzodiazepines with antidepressants prescribed alone for periods of up to 8 weeks and reported a marginal benefit of co-prescribing benzodiazepines. Any potential benefit must be offset against the possible clinical disadvantages such as the development of dependence on benzodiazepines *(19)*.

Psychiatric co-morbidity and personality traits. Keeley et al. reported from a small study in family practice, that patients with more frequent somatoform symptoms were more likely to be non-adherent to drug treatment *(20)*. Ekselius et al. reported that sensation-seeking personality traits were associated with lower blood-levels of antidepressant drug, though not with lower self-reported adherence, in patients participating in a randomized trial *(21)*.

4. Interventions to improve adherence

As mentioned above, one difficulty in the study of depression therapy is that unsatisfactory treatment may reflect a combination of poor patient adherence and medical advice that is inconsistent with expert guidelines. To be clinically effective, interventions should ideally deal with both aspects of quality improvement. In 1999, Peveler et al. were able to show that two brief sessions of counselling provided by a primary care nurse could greatly reduce rates of discontinuation of treatment at 12 weeks (from 61% to 37%), but clinical benefit was only seen in a post hoc analysis of the subgroup of patients receiving adequate doses of medication *(5)*. A small feasibility study also suggested that similar benefits could be obtained by telephone counselling *(22)*. Information alone, provided by leaflet *(5)* or by repeated mailings *(23)*, did not appear to be effective in improving rates of adherence.

Most other studies have tested complex, multi-faceted, interventions designed to improve the overall quality of care. For example, Katon et al. *(24–27)* evaluated the impact of increased involvement of secondary care specialist staff and closer surveillance of patients receiving treatment in primary care. They reported improved adherence, boosting the proportion of patients receiving an adequate dose of their medication at 90 days to 75%, but although this group initially had better clinical outcomes, these benefits were no longer evident at 19-month follow-up. Subsequent work has shown that a relapse prevention programme can also improve longer-term outcome *(28)*.

Table 3 Factors affecting adherence to treatment for depression and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Depression	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	No information was found	No information was found
Health care team/health system-related factors	(–) Poor health education of the patient (+) Multi-faceted intervention for primary care	Multidisciplinary care *(24–27)*; training of health professionals on adherence; counselling provided by a primary care nurse *(5)*; telephone consultation/counselling *(22)*; improved assessment and monitoring of patients *(24)*
Condition-related factors	(–) Psychiatric co-morbidity (+) Clear instructions on management of disease *(14)*; nature of the patient's illness; poor understanding of the disease and its symptoms	Education of patient on use of medicines *(14)*
Therapy-related factors	(–) High frequency of dose *(13)*; co-prescribing of benzodiazepines *(19)*; adequate doses of medication *(5,24–27)* (+) Low frequency of dose *(13)*; clear instructions on management of treatment *(14)*	Education on use of medicines *(14)*; patient-tailored prescriptions *(13)*; continuous monitoring and re-assessment of treatment *(28)*
Patient-related factors	(–) Personality traits *(20,21)*	Counselling *(24)*; relapse-prevention counselling; psychotherapy *(15)*; family psychotherapy *(15)*; frequent follow-up interviews *(28)*; specific advice targeted at the needs and concerns of individual patients *(24)* (+) Factors having a positive effect on adherence; (–) factors having a negative effect on adherence.

AEDs, anti-epileptic drugs; (+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence.

5. Clinical implications and need for further research

Ten years ago research in this field was limited, but considerable progress has since been made. Although by no means complete, we now have data for estimating the extent of the problem, and there is an increasing awareness of its clinical and social impact and of the fact that high levels of patient adherence to treatment and physician adherence to best-practice protocols are important co-determinants of treatment outcome. There is broader recognition that, at least for those patients with severe and recurrent illness, a chronic disease model should be adopted.

Furthermore, practitioners treating patients with depression can be guided by several recent findings that are summarized below.

– If the problem of poor adherence is not addressed, 30–40% of patients will discontinue their medication early (after 12 weeks), regardless of perceived benefits or side-effects.

– Simple to follow advice and education such as that tested by Lin et al. *(14)* is beneficial, and such advice should be given both in the early phase of treatment *(5)* and repeated at later stages *(28)*.

– If patients admit to poor adherence, then it is highly likely that they are not taking their medication as prescribed; if they report good adherence, but lack of clinical progress suggests that adherence may nevertheless be a problem, the most sensitive method of detection is electronic monitoring.

– There is at best only weak evidence that treatment with the newer antidepressants leads directly to better rates of adherence and this is therefore probably not a material factor in drug choice.

– Improved patient outcomes in primary care are probably best achieved through complex interventions such as those used by Katon et al. comprising improved assessment and monitoring of patients and relapse prevention counselling, together with specific advice targeted at the needs and concerns of individual patients.

A considerable research agenda still remains. More accurate estimations of the prevalence of adherence are needed in addition to research to address and measure the different forms that poor adherence may take, e.g. patients missing doses, taking "drug holidays", substituting agents, changing dosing, not filling prescriptions or discontinuing treatment early. The ways in which primary care physicians assess depression and deliver treatment should be further explored to identify determinants that explain adherence (and nonadherence) behaviours. Electronic event monitoring systems offer a useful approach to measuring some forms of adherence. An improved understanding of the relationships between health beliefs and medication-taking behaviour should lead to more robust theoretical frameworks, and to more effective methods of improving adherence, which can be added to existing techniques. Depression management programmes of the type pioneered by Katon and others in the United States require evaluation in other health care systems to ascertain whether their apparent benefits are transferable to other situations.

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CHAPTER X

Diabetes

1. Introduction

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action or both *(1)*. Diabetes is highly prevalent, afflicting approximately 150 million people worldwide *(2)*, and this number is expected to rise to 300 million in the year 2025 *(3)*. Much of this increase will occur in developing countries and will result from population ageing, unhealthy diet, obesity and a sedentary lifestyle {Glasgow & Anderson 1999 74 /id}*(4)*. In developed countries, such as the United States, diabetes has been reported as the seventh leading cause of death *(5)*, and the leading cause of lower extremity amputation, end-stage renal disease and blindness among persons aged 18–65 years *(6–9)*. It has been estimated that diabetes costs the United States economy more than 98 billion dollars per year in direct and indirect costs *(5,10)*. It has also been estimated that low-income families in the United States supporting an adult member with diabetes devote 10% of their income to his or her care, and that this figure rises to 25% in India *(11)*.

There are four known subtypes of diabetes mellitus *(1)*.

– Type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes, accounts for 5 to 10% of all diagnosed cases of diabetes *(12)*. Type 1 diabetes, caused by failure of pancreatic beta-cells to

produce insulin, can afflict both children and adults who will require daily injections of insulin. Inadequate use of insulin results in ketoacidosis and this inevitable consequence limits the extent to which patients can ignore recommendations to take exogenous insulin and still survive. Ketoacidosis is a significant cause of mortality in young persons with type 1 diabetes *(13,14)*. Patients with diabetic ketoacidosis often require hospitalization and, in most instances, poor adherence to insulin therapy is the suspected cause *(15,16)*.

– Type 2 diabetes, previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, may account for about 90% of all diagnosed cases of the disease. It is typically associated with being overweight and is caused by insulin resistance. For patients with type 2 diabetes, weight control, by means of dietary and physical activity regimens, is the cornerstone of the treatment. However, pancreatic beta-cell function decreases over time, so many patients will eventually require treatment with oral medications or exogenous insulin.

– Gestational diabetes develops in 2 to 5% of all pregnancies, but disappears postpartum (17). Risk factors include race/ethnicity and a family history of diabetes and obesity.

– Other specific types of diabetes result from specific genetic syndromes, surgery, drugs, malnutrition, infections and other illness, and account for 1 to 2% of all diagnosed cases of diabetes.

2. Treatment of diabetes

The goals of diabetes treatment are to keep blood glucose levels as near normal as possible while avoiding acute and chronic complications *(7,18)*. Because the normal homeostatic control mechanisms are disrupted in patients with diabetes, food intake, emotional stress and changes in physical activity can cause blood glucose to become too low or too high leading to the acute complications of hypoglycaemia or hyperglycaemia. In addition, inappropriate nutrition and insufficient physical activity increase the risk of developing the long-term complications of diabetes, especially heart disease. Keeping blood glucose within a target range requires feedback in the form of self-monitoring of blood glucose. Patients with type 1 diabetes must carefully balance food intake, insulin and physical activity. Patients with type 2 diabetes are often prescribed oral medications that increase insulin production, decrease insulin resistance, or block carbohydrate absorption and may have to take exogenous insulin to achieve adequate metabolic control. Because improved metabolic control ends the spilling of glucose in the urine, patients who do not reduce their food intake will gain weight thus increasing insulin resistance, risk for heart disease and other obesity-related complications *(19,20)*.

3. Definition of adherence

Contemporary perspectives on diabetes care accord a central role to patient self-care, or self-management. Self-care implies that the patient actively monitors and responds to changing environmental and biological conditions by making adaptive adjustments in the different aspects of diabetes treatment in order to maintain adequate metabolic control and reduce the probability of complications *(21)*. The self-care behaviours involved in achieving adequate metabolic control and avoiding long-term complications are: home glucose monitoring (in blood or urine); adjustment of food intake, especially of carbohydrates, to meet daily needs and match available insulin; administration of medication (insulin or oral hypoglycaemic agents); regular physical activity; foot care; regular medical monitoring visits, and other behaviours (i.e. dental care, appropriate clothing, etc.) that may vary depending on the type of diabetes *(18)*.

Against this background of illness-related demands, adherence is conceptualized as the active, voluntary involvement of the patient in the management of his or her disease, by following a mutually agreed course of treatment and sharing responsibility between the patient and health care providers *(22)*. Hentinen *(23)* described adherence to self-care as an active, responsible and flexible process of self-management, in which the patient strives to achieve good health by working in close collaboration with health care staff, instead of simply following rigidly prescribed rules. Other terms have been proposed such as "collaborative diabetes management" *(24)*, "patient empowerment" *(25)* or "self-care behaviour management" *(23,26–28)*. Another important concept is "inadvertent nonadherence" which occurs when a patient believes he or she is adhering to the recommended treatment but, through errors in knowledge or skill, is not doing so *(29)*.

4. Prevalence of adherence to recommendations for diabetes treatment

From the study of adherence to treatments for diabetes, it is apparently important to assess the level of adherence to each component of the treatment regimen independently (i.e. self-monitoring of blood glucose, administration of insulin or oral hypoglycaemic agents, diet, physical activity, foot care and other self-care practices) instead of using a single measure to assess adherence to the overall treatment. This is because there appears to be little correlation between adherence to the separate self-care behaviours, suggesting that adherence is not a unidimensional construct *(21,30)*. This finding has been reported for both type 1 and type 2 diabetes *(31)*. Furthermore, there appear to be different relationships between adherence and metabolic control for persons with different types of diabetes *(32)*. Consequently, the following section on adherence rates has been organized to reflect these two issues. First there is a discussion of adherence to each element of the regimen which is followed by an analysis of adherence by diabetes type.

A. Adherence to treatment for type 1 diabetes

Self-monitoring of glucose. The extent of adherence to prescribed self- monitoring of glucose levels in blood varies widely, depending on the frequency or aspect assessed in the study. For example, in a sample of children and adolescents with type 1 diabetes *(33)*, only 26% of study participants reported monitoring glucose levels as recommended (3–4 times daily), compared to approximately 40% of the adults with type 1 diabetes *(34)*, Similar findings were reported in a Finnish study (n = 213; patients aged 17–65 years), in which 20% of the study participants monitored their blood glucose as recommended, and 21% of respondents made daily or almost daily adjustments to their insulin dosage according to the results of self-monitoring of blood glucose. Only 6% reported never performing the prescribed blood glucose tests *(35)*, A study conducted in the United States replicated the latter result in patients with type 1 diabetes (mean age = 30 years), of whom 7% reported *never* testing their glucose levels *(21)*.

Other studies have assessed adherence based on incorrect performance (intentional or unintentional) of the component behaviours involved in glucose monitoring in urine or blood. One study reported that up to 80% of adolescents made significant mistakes when estimating glucose concentrations in urine *(36)*. Between 30% and 60% made errors in the timing procedures involved in self-monitoring of blood glucose *(37)*. Others inaccurately reported concentrations; up to 75% may under-report actual mean concentrations of blood glucose, while up to 40% have been found to over-report or invent phantom values *(38)*. Other studies have found that between 40% and 60% of patients fabricated results *(39,40)* and 18% failed to record their results *(40)*. In recent years, the development of blood glucose meters with electronic memory has made it more difficult, though not impossible, for patients to fabricate the results of blood-glucose monitoring.

Administration of insulin. The prevalence of adherence to insulin administration varies widely. In a study conducted in Finland *(35)* most of the respondents reported adhering to insulin injections as scheduled either daily (84%) or almost daily (15%). Other studies have framed the adherence question differently.

Rates for "never missing a shot" varied from 92% in a sample of young adults *(21)* to 53% in a sample of children *(41)*; while 25% of adolescents reported "missing insulin shots within 10 days before clinic visit" *(42)*.

A study conducted by Wing et al. *(37)* assessed the quality of performance of insulin administration (intentional or unintentional errors). The use of unhygienic injections was noted in 80% of patients and the administration of incorrect doses of insulin in 58%. In studies assessing the intentional omission of insulin to control weight, Polonsky et al. *(43)* reported that 31% of study participants (n = 341; female patients aged 13–60 years) admitted to intentional omission of insulin, but only 9% reported frequent omission to control weight. More recently, Bryden et al. *(44)* reported that 30% of female adolescents (but none of the males in the sample) admitted under-using insulin to control weight.

Diet. The results of research on adherence to prescribed dietary recommendations have been inconsistent. In studies by Carvajal et al. *(45)* in Cuba, and Wing et al. *(37)* in the United States, 70–75% of study participants reported not adhering to dietary recommendations; while in a study in Finland by Toljamo et al. *(35)*, adherence to dietary recommendations was high: 70% of participants reported always or often having a regular main meal, while only 8% reported always having irregular mealtimes. In answer to questions regarding the foods prescribed, over half of the participants reported assessing both the content and amount of food that they ate daily (48%) while 14% of the respondents did not evaluate their food at all. Christensen et al. reported similar findings *(46)*: 60% of study participants (n = 97) adhered to the number and timing of planned meals, while only 10% of patients adhered to planned exchanges, 90% of the time.

Physical activity and other self-care measures. Literature on the extent of adherence to prescribed recommendations for physical activity among patients with type 1 diabetes is scarce. One study conducted in Finland indicated that two-thirds of study participants (n = 213) took regular daily exercise (35%) or almost daily exercise (30%), while 10% took no exercise at all. *(35)* In the same study, only 25% of study participants reported taking care of their feet daily or almost daily, while 16% reported never taking care of their feet as recommended *(35)*.

B. Adherence rates for type 2 diabetes

Glucose monitoring. In a study conducted to assess patterns of self-monitoring of blood glucose in northern California, United States, 67% of patients with type 2 diabetes reported *not* performing self-monitoring of blood glucose as frequently as recommended (i.e. once daily for type 2 diabetes treated pharmacologically) *(34)*. Similar findings were observed in a study conducted in India, in which only 23% of study participants reported performing glucose monitoring at home *(47)*.

Administration of medication. Among patients receiving their medication from community pharmacies (n = 91), adherence to oral hypoglycaemic agents was 75%. Dose omissions represented the most prevalent form of non-adherence; however, more than one-third of the patients took more doses than prescribed. This over-medication was observed more frequently in those patients prescribed a once-daily dose *(48)*. Similar adherence rates of between 70 and 80% were reported from the United states in a study of oral hypoglycaemic agents among a sample of patients whose health insurance paid for prescribed drugs *(49)*. Dailey et al. *(50)* studied 37 431 Medicaid-funded patients in the United States, and used pharmacy records to show that patients with type 2 diabetes averaged about 130 days per year of continuous drug therapy, and that at the end of 1 year, only 15% of the patients who had been prescribed a single oral medication were still taking it regularly.

Diet. In a study conducted in India, dietary prescriptions were followed regularly by only 37% of patients *(47)*, while in an American study about half (52%) followed a meal plan *(51)*. Anderson & Gustafson *(52)* reported good-to-excellent adherence in 70% of patients who had been prescribed a high-carbohydrate, high-fibre diet. Wing et al. *(53)* showed that patients with type 2 diabetes lost less weight than their nondiabetic spouses and that the difference was mainly due to poor adherence to

the prescribed diet among the diabetic patients. Adherence to dietary protocols may depend upon the nature of the treatment objective (e.g. weight loss, reduction of dietary fat or increased fibre intake).

Physical activity. Several studies have reported on adherence to prescribed physical activity. For example, in a study in Canada of a sample of patients with type 2 diabetes randomly selected from provincial health records, few respondents participated in informal (37%) or organized (7.7%) physical activity programmes *(54)*. A survey in the United States found that only 26% of respondents followed a physical activity plan *(51)*. A study assessing the attitudes and adherence of patients who had completed outpatient diabetes counselling observed that only 52% exercised on three or more days per week after the counselling programme was completed *(55)*.

C. Adherence to treatment for gestational diabetes

One study was found that had assessed adherence to treatment for gestational diabetes. Forty-nine pregnant women with pre-existing (overt) diabetes (68% with type 1 and 32% with type 2 diabetes) were assessed, using self-report, on their adherence to a number of self-care tasks on three occasions during pregnancy (mid-second, early third and late third trimester) *(56)*. In general, the participants reported being adherent. However, there was considerable variation across different regimen components: 74 to 79% of women reported always following dietary recommendations, compared to 86 to 88% who followed the recommendations for insulin administration, 85 to 89% who followed the recommendations for managing insulin reactions and 94 to 96% who followed those for glucose testing.

5. Correlates of adherence

Variables that have been considered to be correlates of various adherence behaviours in diabetes can be organized into four clusters.

– treatment and disease characteristics;

– intra-personal factors;

– inter-personal factors; and

– environmental factors.

A. Treatment and disease characteristics

Three elements of treatment and of the disease itself have been associated with adherence: complexity of treatment, duration of disease and delivery of care.

In general, the *more complex the treatment regimen* is, the less likely the patient will be to follow it. Indicators of treatment complexity include frequency of the self-care behaviour – i.e. the number of times per day a behaviour needs to be performed by the patient. Adherence to oral hypoglycaemic agents has been associated with frequency of dosing. Higher adherence levels were reported by patients required to take less frequent doses (a once-daily dose), compared to those prescribed more frequent doses (three times daily) *(48)*. Dailey et al. *(50)* showed that patients prescribed a single medication had better short-term and long-term adherence rates than patients prescribed two or more medications.

Duration of disease appears to have a negative relationship with adherence: the longer a patient has had diabetes, the less likely he or she is to be adherent to treatment. Glasgow et al. *(21)* studied a sample of patients with type 1 diabetes (mean age = 28 years), and found that level of physical activity was associated with duration of disease. Patients who had had diabetes for 10 years or less reported greater energy expenditure in recreational physical activities and exercising on more days per week than those with a longer history of diabetes. Patients with a longer history of diabetes also reported eating more

inappropriate foods, consuming a greater percentage of saturated fats and following their diets plans less well. More recently, in a study conducted in both Polish and American children with type 1 diabetes *(41)*, duration of disease was also associated with adherence to insulin administration, as children with a longer history of diabetes were more likely to forget their insulin injections compared to children who had been diagnosed more recently.

Delivery of care for diabetes can vary from intensive treatment delivered by a multidisciplinary diabetes team, to outpatient care delivered by a primary care provider. Yawn et al. *(57)* observed interactions between patients and providers in a family practice setting and reported that patients with diabetes seen specifically for their diabetes received more counselling on diet and adherence than patients with diabetes seen for an acute illness. Kern and Mainous *(58)* found that although physicians preferred to follow a planned, systematic strategy for treating diabetes, acute illness and failure of patients to adhere forced them to spend less time on diabetes care.

Adherence can also be affected by the setting in which care is received. Piette *(59)* examined the problems experienced by patients in accessing care in two public health settings in the United States and found that the cost of care was a major barrier to access, especially for patients in a community treatment setting. Perceived barriers to access to care were also associated with poor metabolic control.

B. Intra-personal factors

Seven important variables have been associated with adherence: age, gender, self-esteem, self-efficacy, stress, depression and alcohol abuse.

Age of the patient has been associated with adherence to physical activity regimens in a sample of patients with type 1 diabetes *(21)*. Compared to younger participants, patients over 25 years of age reported exercising on fewer days per week, and spending less time (and expending fewer calories) in recreational physical activities. There were no associations reported between age and adherence to other self-care measures.

Age has also been associated with adherence to insulin administration in a study of adolescents with type 1 diabetes. The investigators found that older adolescents were more likely to mismanage their insulin (missing shots) than their younger counterparts *(42)*. In a study assessing adherence to self-monitoring of blood glucose, younger adolescents reported monitoring their blood glucose concentrations more frequently than did the older ones *(60)*. Older adults also may practice better self-management than younger adults *(61)*.

Gender has also been associated with adherence. The men in a sample of patients with type 1 diabetes *(21)* were found to be more physically active than the women, but they also consumed more calories, ate more inappropriate foods and had lower levels of adherence as assessed using a composite measure of diet.

Self-esteem has been associated with adherence to self-management of diabetes among patients with type 1 diabetes. High levels of self esteem were related to high levels of adherence to physical activity regimens, adjustment of insulin doses and dental self-care *(62)*. Murphy, Thompson & Morris *(63)* found that lower self-esteem in adolescents with type 1 diabetes was associated with less frequent testing of blood glucose.

Self-efficacy has been studied in relation to adherence to prescribed treatments for diabetes. In a combined sample of patients with type 1 and type 2 diabetes in Canada *(64)*, a measure of diabetes-specific self-efficacy beliefs was found to be the strongest predictor of energy expenditure suggesting a positive relationship between self-efficacy and adherence to prescribed physical activity. Senecal, Nouwen & White *(65)* reported that beliefs in self-efficacy were a strong predictor of adherence and that both self-efficacy and autonomy predicted life satisfaction. Ott et al. *(66)* found that self-efficacy predicted adher-

ence to diabetes care behaviours in adolescents with type 1 diabetes. Aljasem et al. *(67)* showed that self-efficacy beliefs predicted adherence to a prescribed regimen in 309 adults with type 2 diabetes after controlling for health beliefs and perceptions of barriers.

Stress and emotional problems are also correlated with adherence. Fewer minor stressors were associated with higher levels of adherence to insulin administration and diet in women with gestational diabetes *(56,68)*. In a study using a diabetes-specific stress scale in a combined sample of adults with type 1 and type 2 diabetes *(69)*, stress was found to be significantly associated with two aspects of the diet regimen (diet amount and diet type). However, no associations were found between stress and adherence to physical activity regimens or glucose testing in this sample. Peyrot et al. *(70)* reported that psychosocial stress was associated with poor adherence to a prescribed regimen and poor metabolic control in a mixed group of patients with type 1 and type 2 diabetes. Mollema et al. *(71)* reported that patients who had an extreme fear of insulin injections or self-monitoring of blood glucose had lower levels of adherence and higher levels of emotional distress. Schlundt, Stetson & Plant *(72)* grouped patients with type 1 diabetes according to the problems they encountered in adhering to prescribed diets and found that two of the groups of patients – emotional eaters and diet-bingers – had adherence problems related to negative emotions such as stress and depression.

The incidence of *depression* has been observed to be twice as high among persons with diabetes than in the general population *(73)*. Patients with depression are more likely to experience complications of diabetes *(74)*, have worse glycaemic control *(75)*, and be less adherent to self-care behaviours than patients who are not depressed. Depression is also associated with higher costs of medical care in patients with diabetes *(76)*.

Patterns of alcohol use *(alcohol abuse)* have been related to the quality of diabetes self-management. Johnson, Bazargan & Bing *(77)*, studied 392 patients with type 2 diabetes from ethnic minority groups in Los Angeles, CA, and found that alcohol consumption within the previous 30 days was associated with poor adherence to diet, self-monitoring of blood glucose, oral medications and appointment-keeping. Cox et al. *(78)* examined alcohol use in 154 older men with diabetes and found that greater alcohol use was associated with poorer adherence to insulin injections.

C. Inter-personal factors

Two important inter-personal factors: the quality of the relationship between patients and providers of care, and social support have been found to correlate with adherence. Good communication between patient and provider has been related to improved adherence. Among patients with type 2 diabetes, adherence to administration of oral hypoglycaemic agents and glucose monitoring were significantly worse in patients who rated their communication with their care provider as poor *(79)*.

Social support has been the subject of much research. Greater social support was found to be associated with better levels of adherence to dietary recommendations and insulin administration in women with gestational diabetes *(68)*. Parental involvement, as a measure of social support, has also been associated with adherence to blood glucose monitoring. Adolescents and children with type 1 diabetes, who experienced greater parental involvement with their blood glucose monitoring, reported higher levels of daily checks of blood sugar concentrations *(60)*. McCaul et al. *(21)* followed a sample of adolescents and adults with type 1 diabetes. For both adults and adolescents disease-specific social support was associated with better adherence to insulin administration and glucose testing. For the adolescent group only, general family support was associated with adherence to insulin administration and glucose testing. The study found no association between any of the social support measures and adherence to diet and physical activity regimens. Other studies have shown a relationship between poor social support and inadequate self-management of diabetes *(80–84)*

D. Environmental factors

Two environmental factors – *high-risk situations and environmental systems* – have been linked to poor adherence in patients with diabetes. Self-care behaviours occur in the context of a continually changing series of environmental situations at home, at work, in public, etc., which are associated with different demands and priorities. As their circumstances change, patients are challenged to adjust and maintain their self-care behaviours. Patients are frequently called upon to choose between giving attention to diabetes self-management or to some other life priority. Situations associated with poor adherence have been called "high-risk" situations *(85)*.

Schlundt, Stetson & Plant *(72)* created a taxonomy of high-risk situations that posed difficulties for patients following diet prescriptions. The situations included: overeating in response to people, place and emotions; situations associated with under-eating, and difficulty in integrating food intake according to social context, time of day and place. Schlundt et al. *(82)* described10 high-risk situations for poor dietary adherence that included social pressure to eat; being alone and feeling bored; interpersonal conflicts, and eating at school, social events or holidays. Schlundt et al. *(83)* identified 12 categories of high-risk dietary situations in adults with type 1 and type 2 diabetes: these included resisting temptation, eating out, time pressure, competing priorities and social events. Other studies have also shown that environmental barriers are predictive of adherence to various aspects of diabetes self-care *(34,67,86)*.

Many environmental factors that influence behaviour operate on a larger scale than the immediate situation confronting a person *(87)*. These environmental systems include economic, agricultural, political, health care, geographical, ecological and cultural systems *(88)*. The large-scale environmental changes that occurred in the twentieth century created the current epidemic of obesity and type 2 diabetes *(89–91)*. These changes included increased availability of inexpensive fast foods high in fat, salt and calories *(92)*, and the mechanization of transport systems *(93,94)*. Changes in economic and political systems have allowed women to move into the workforce, yet these same changes have altered the composition of families and the way in which families deal with food selection and preparation *(95,96)*. Large corporations spend billions of dollars each year on marketing foods high in fat and calories *(97)*. Increasing segments of the population spend many hours per day in sedentary activities. These activities have been linked to obesity in both children and adults *(98–101)* and to the risk of developing type 2 diabetes *(102)*.

Some authors have described the current environment as "toxic" to healthy lifestyles *(103,104)*. The rates of both obesity and diabetes are rapidly increasing in developing nations and are likely to be associated with urbanization, mechanized transportation and widespread changes in food supply. The same factors that encourage sedentary lifestyles and the over-consumption of food, and lead to obesity and diabetes, probably also make it difficult for people who do develop diabetes to adhere to best-practice protocols.

Many people in developed nations, including the poor and members of ethnic minority groups, have to some degree been bypassed by the economic prosperity of the twentieth century. It is these groups that have been most adversely affected by the environmental changes that lead to disparities in health status *(105,106)*. Even living in a poor community can contribute to poor health outcomes *(107)*.

Given the powerful influence of these larger social factors, it is important to avoid over-attributing the responsibility for adherence to patient-related factors or to health care providers *(108)*. A patient's ability to manage his or her behaviour, achieve tight metabolic control and prevent the long-term complications of diabetes is determined by a host of intra-personal, interpersonal and environmental factors that interact in ways that are not yet understood *(109)*.

6. Interventions

Almost any intervention that is designed to improve metabolic control in diabetes or to reduce the probability of acute or chronic complications does so by influencing patient self-care or self-management behaviours. Early efforts focused on patient education *(110)*, but more recently, the importance of psychological and behavioural interventions has been stressed as a result of the growing recognition that knowledge alone is insufficient to produce significant changes in behaviour *(111)*.

Elasy et al. *(112)* developed a taxonomy for describing educational interventions for patients with diabetes based on a thorough review and analysis of the literature published between 1990 and 1999 which revealed the great diversity of interventions employed to improve self-management of diabetes.

Brown conducted a meta-analysis of studies that had tested interventions to improve self-management of diabetes, and found a recent trend towards combining patient education with behavioural intervention strategies. Combining behavioural techniques with the provision of information was found to be more effective than interventions that provided only information. In general, the literature supports the conclusion that diabetes education results in at least short-term improvements in adherence and metabolic control *(113)*, but more research is needed to learn which interventions work best with different types of patient and for specific behaviours *(111,112)*.

Beyond interventions that focus on individual patients, two other approaches can be used to improve the self-management of diabetes – interventions that target health providers and interventions at the community or systems level. Several studies have reported that physicians and other health care providers deliver less-than-optimal care to patients with diabetes. There have been several corresponding studies of attempts to modify professional behaviours and attitudes in ways that might lead to improved patient outcomes. Kinmonth et al. *(114)* trained nurses to provide patient-centred diabetes care, and showed that patient satisfaction was improved although metabolic parameters were not. Olivarius et al. *(115)* in a study of Danish physicians used goal-setting, feedback and continuing education and found that the patients of the physicians who had received this intervention had improved metabolic parameters compared to the patients of the physicians in the control group. In a series of studies, Pichert and colleagues showed that a training programme for nurses and dieticians resulted in improved their education and problem-solving skills *(116–118)*. Other studies of training for health care providers have not documented any changes in patient behaviour or metabolic control *(119)*.

Systems interventions can change the way in which environmental determinants influence the self-management behaviour of patients with diabetes. Systems interventions can focus on economic determinants, such as changing Medicare policy to pay for medical nutrition therapy *(120)*. Health care delivery systems are also a target for intervention by means of changing programmes, policies or procedures to improve quality of care and outcomes for patients. For example, Hardy et al. *(121)* implemented telephone reminders to patients in order to improve appointment-keeping behaviour.

The chronic care model is a systems approach to improving the quality of care for patients with chronic diseases such as diabetes *(122)*. Feifer *(123)* conducted a cross-sectional analysis of nine community-based primary care practices and showed that providing system supports to health providers resulted in better care of patients with diabetes. Wagner et al. *(124)* modified the way in which care was provided to patients with diabetes in primary care clinics and showed that these systemic changes resulted in better achievement of treatment goals, improved metabolic control, greater time spent on diabetes education and enhanced patient satisfaction. Wagner *(125)* intervened using a continuous quality care approach combined with the chronic care model in 23 health care organizations and documented improvements in diabetes care and patient outcomes in many of them.

Clearly, the solution to the problem of poor adherence must involve a combination of approaches that include intensive efforts to modify the behaviour of individuals with diabetes together with intelligent efforts to make changes in the larger environmental systems that shape and modify behaviours *(126)*.

Table 4 Factors affecting adherence to therapy for the control of diabetes and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Diabetes	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Cost of care *(59)*; patients aged over 25 years *(21)* (adherence to physical activity); older adolescents (insulin administration) *(42)*; older adolescents (SMBG) *(60)*; male (adherence to diet) *(21)*; female (adherence to physical activity) *(21)*; environmental high-risk situations *(72,82,83,85–89,92,93,95,98,102,103,105)* (+) Patients aged less than 25 years *(21)* (adherence to physical activity); younger adolescents (insulin administration) *(42)*; younger adolescents (SMBG) *(60)*; male (adherence to physical activity) *(21)*; female (adherence to diet) *(21)*; social support *(21,68)*; family support *(21)*	Mobilization of community-based organizations; assessment of social needs *(21,68)*; family preparedness *(21)*
Health care team/health system-related factors	(–) Poor relationship between patient and physician *(79)*	Multidisciplinary care; training of health professionals on adherence *(114,116)*; identification of the treatment goals and development of strategies to meet them; continuing education; continuous monitoring and re-assessment of treatment *(115)*; systems interventions: health insurance for nutrition therapy *(120)*, telephone reminders to patients *(121)*, chronic care models *(122–125)*
Condition-related factors	(–) Depression *(73)*; duration of disease *(21,41)*	Education on use of medicines *(110,113)*
Therapy-related factors	(–) Complexity of treatment *(48,50)* (+) Less frequent dose *(48)*; monotherapy with simple dosing schedules (50); frequency of the self-care behaviour *(48,50)*	Patient self-management *(112)*; simplification of regimens (48,50); education on use of medicines *(110,112,113)*
Patient-related factors	(–) Depression *(75)*; stress and emotional problems *(70–72)*; alcohol abuse *(77)* (+) Positive self-esteem (62,63) /self-efficacy *(64–67,78)*	Behavioural and motivational interventions *(111,112)*; assessment of psychological needs *(111)*

SMBG, self-monitoring of blood glucose; (+) factors having a positive effect on adherence, (–) factors having a negative effect on adherence

7. Methodological and conceptual issues in research on adherence to treatment for diabetes

In a review of methodological and conceptual issues relevant to measuring adherence in patients with diabetes, Johnson *(127)* suggested that the prevalence of adherence may vary across the different components of the diabetes regimen and the patient's lifespan, during the course of the disease, as well as

between diabetes populations (i.e. type 1 and type 2). Johnson also noted the conceptual problems encountered in defining and measuring adherence including:

– the absence of explicit adherence standards against which a patient's behaviour can be compared;

– inadvertent nonadherence attributable to miscommunication between patient and provider and deficits in the knowledge or skills of the patient;

– the behavioural complexity of the diabetes regimen; and

– the confounding of compliance with diabetes control.

Furthermore, the multiplicity of measurements used to assess adherence (i.e. health status indicators; provider ratings; behavioural observations; permanent products, and patient self-reports, including behaviour ratings, diaries and 24-h recall interviews) also makes comparison of studies troublesome. Johnson concluded that a measurement method should be selected on the basis of reliability, validity, non-reactivity, sensitivity to the complexity of the diabetes regimen behaviours and measurement-independence from the indicators of health status. Glasgow et al. *(30)* also noted the methodological shortcomings of studies on diabetes self-care correlates, the lack of clear conceptualizations and the failure to differentiate between regimen adherence, self-care behaviour and metabolic control, as well as the empirical–atheoretical nature of many studies that lacked a comprehensive model or theory.

The present review of studies reported from 1980 to 2001, has revealed that research on adherence to treatment for diabetes yields some inconsistent findings. These inconsistent results may have several causes including variability in:

– research designs (e.g. longitudinal as opposed to cross-sectional studies) and study instruments;

– sampling frames employed for study recruitment;

– the use of general measures (e.g. general stress) as opposed to more specific ones (e.g. diabetes-specific stress);

– sample sizes (in some studies the small samples used decreased the likelihood of detecting significant associations between the variables; and

– lack of control of potentially confounding variables.

8. Conclusions

Poor adherence to treatment is very prevalent in patients with diabetes, and varies according to the type of non-adherence being measured, and across the range of self-care behaviours that are components of treatment. Thus prevalence rates should be assessed by type of behaviour. Additionally, prevalence rates may vary by diabetes subtype (i.e. type 1, type 2 or gestational), and also appear to be influenced by other factors such as age, gender and level of complexity of the treatment regimen. Adherence, or the variables affecting adherence, may vary according to nationality, culture or subculture. Therefore, these factors should also be taken into account when assessing the prevalence of adherence in populations of patients with diabetes.

The lack of standard measurements prevents comparison being made between studies and across populations. Much work needs to be done to develop standardized, reliable and valid measurement tools.

Data from developing countries concerning the prevalence and correlates of adherence in patients with diabetes are particularly scarce. The pressing need to undertake more research in developing

countries is emphasized by the WHO estimates indicating that by the year 2025 the largest absolute increase in prevalence rates of diabetes worldwide will occur in developing countries. Patients and providers of care in developing nations face additional barriers to achieving adequate diabetes self-care because of poverty, inadequate systems for delivering health care, and a host of other priorities that compete for national and individual attention.

More research needs to be conducted on adherence in women with gestational diabetes, and in study populations that include minorities and ethnic groups. Also, cross-cultural comparison studies should be encouraged. However, when making comparisons between different ethnic groups or countries, a number of aspects should be taken into account and controlled for, including types of health care system, health care coverage and socioeconomic macro- and micro-factors, as well as language and cultural differences. Adequate translation and validation of study measurements are required when using questionnaires developed in another country.

It is also important to point out not only the large number of factors that affect adherence behaviours in patients with diabetes, but also that the complex interactions that take place between them affect both adherence and metabolic control. Multivariate approaches to data are required to obtain more accurate representations of the relevant predictors and correlates.

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CHAPTER XI

Epilepsy

1. Introduction

Epilepsy is a common neurological disease affecting almost 50 million people worldwide *(1,2)* 5 million of whom have seizures more than once per month *(3)*. Approximately 85% of people afflicted with epilepsy live in developing countries. Two million new cases occur in the world each year. The results of studies suggest that the annual incidence in developed countries is approximately 50 per 100 000 of the general population whereas in developing countries this figure is nearly doubled to 100 per 100 000 *(1)*.

In developing countries few patients with epilepsy receive adequate medical treatment, and an estimated 75 to 90% receive no treatment at all *(4)*. The treatment of epilepsy in developing countries remains far from satisfactory, mainly because of:

– the general lack of medical personnel;

– non-availability of medications; and

– lack of information and/or education on epilepsy for both patients and medical staff *(1,4,5)*.

Epilepsy is characterized by a tendency to recurrent seizures and it is defined by two or more unprovoked seizures (generally within 2 years). Seizures may vary from the briefest lapses or muscle jerks to severe and prolonged convulsions. They may also vary in frequency, from less than one a year to several per day *(1)*. The risks of recurrent seizures include intractable epilepsy, cognitive impairment, physical injury, psychosocial problems and death *(6)*. Children suffer mainly from idiopathic generalized epilepsy and absence, myoclonus and generalized tonic–clonic seizures are the most common forms of seizure

seen in children. In adults, symptomatic partial epilepsy is the most common form, and it may cause simple partial, complex partial, or secondarily generalized tonic–clonic seizures *(3)*. Convulsive or tonic–clonic status epilepsy is of major concern as it is associated with a mortality rate of 5–15% *(7)*.

The aim of antiepileptic drug (AED) therapy is to achieve freedom from seizures. The treatment goals for patients with epilepsy are to prevent the occurrence of seizures, prevent or reduce drug side-effects and drug interactions, improve the patient's quality of life, provide cost-effective care and ensure patient satisfaction *(6,8)*. Much of the treatment of epilepsy is aimed at creating a balance between prevention of seizures and minimization of side-effects to a level that the patient can tolerate *(6,9)*. Although AED therapy does not offer a permanent cure, successful therapy can eliminate or reduce symptoms. The most commonly used AEDs are (in aphabetical order): carbamazepine, ethosuximide, phenobarbital, phenytoin and valproic acid. New AEDs such as gabapentin, lamotrigine, leviteracetam, felbamate, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide have a role in the management of the 20–30% of patients with epilepsy who remain refractory to conventional drug therapy *(9)*. About 25% of patients with epilepsy have intractable seizure disorders, of those between 12 and 25% are candidates for surgery *(3)*.

The direct costs attributable to epilepsy include physician visits, laboratory tests, emergency department visits, antiepileptic drugs and hospitalizations. Indirect costs include working days lost, lost income, decreased quality of life, the cost of failed therapy and side-effects of drugs *(6)*. Garnett et al., referring to the "Epilepsy Foundation of America data", reported that the annual direct and indirect costs of epilepsy exceeded $12.5 billion. The direct costs of epilepsy are significantly lower for patients whose epilepsy is controlled than for those whose disease is not controlled *(6)*.

Recent studies in both developed and developing countries have shown that up to 70% of children and adults newly diagnosed with epilepsy can be successfully treated (i.e. their seizures can be completely controlled for several years) with antiepileptic drugs. After 2–5 years of successful treatment, drugs can be withdrawn in about 70% of children and about 60% of adults without relapse occurring *(1)*. In the case of treatment failure it is crucial to establish whether the failure is a result of inappropriate drug selection, inappropriate dosing, refractory disease or poor adherence to the therapeutic regimen *(3,6)*.

Good adherence to treatment and proper health education are fundamental to the successful management of epilepsy *(10,11)*. Poor adherence to prescribed medication is considered to be the main cause of unsuccessful drug treatment for epilepsy *(2,3,12–18)*. Nonadherent patients experience an increase in the number and severity of seizures, which leads to more ambulance rides, emergency department visits and hospitalizations *(12,19)*. Nonadherence therefore results directly in an increase in health care costs, and reduced quality of life *(19)*.

The aim of this chapter is to describe the prevalence of adherence (or nonadherence), to treatment for epilepsy, to identify the factors affecting adherence to anti-epilepsy treatment, and to discuss the interventions that have proven effective for improving adherence.

A search on adherence to anti-epilepsy therapies was made using Medline (1990–2002). Reviews and reports from international and national organizations were also included. Publications were considered for inclusion if they reported on one of the following: prevalence data on rates of adherence (or nonadherence), factors affecting adherence, interventions for improving adherence, and information on how poor adherence rates affect illness, costs and treatment effectiveness. Of the 99 studies retrieved by the search, 36 were reviewed for this report.

2. Adherence to epilepsy therapy

Adherence was not usually defined in the published studies, but referred to generally as patients following medical recommendations. Authors generally considered adherence in behavioural terms,

whereby the patient had an active and informed role to play in a therapeutic situation *(13,20)*. In this sense, adherence to prescribed medication was seen as a health-promoting behaviour *(21)*.

The types of non-adherence were described as follows: reduced or increased amount of single dose; decreased or increased number of daily doses; extra dosing; incorrect dosing intervals; being unaware of the need for life-long regular medication; taking duplicate medication; taking discontinued medication; discontinuing prescribed medication; regularly forgetting to take medication, and incorrect use of medication *(18,20,22)*.

Medication use was assessed by review of medical records; patient self-report; family report; pill counts; prescription refill rates, and biological markers, including serum, urine and saliva assays to quantify medications or their metabolites *(2,11,12,14,23–26)*. The best indicator of adherence is believed to be serum levels of anticonvulsant drugs *(18,27)*. Other methods of monitoring adherence, such as electronic measures are not discussed further here because of the lack of published studies in this area. In several studies, patients whose serum levels were outside the therapeutic range were classified as nonadherent *(19,23,28)*. However, serum levels are not a perfect measure. Although blood levels of anticonvulsant medications can be measured, it is difficult to translate them into comparable measures of adherence for patients on different medications and doses. Furthermore, sub-therapeutic levels of a drug in the serum can be due either to poor compliance or the need for a higher dosage *(2)*. Patients with impaired absorption or rapid or ultra-rapid metabolism can have low serum levels even if their intake of AEDs is regular and according to prescription *(11,26,29)*.

Dowse et al. and Leppik et al. reported that indirect measures such as patient interview, tablet counts and prescription refill records gave no indication of the true amount of the drug present in the body and could be inaccurate or biased *(18,19)*. However, using the measurement of drug concentration in blood alone, except in cases of extremely low adherence and variability of drug intake, is not sufficient to detect incorrect drug intake. Therefore, the use of clinical markers and self-reported adherence should also be considered *(11)*.

3. Epidemiology of adherence

Adherence can vary from an occasional missed dose to chronic defaulting on medication regimens *(21)*. Adherence to antiepileptic drugs in patients with epilepsy generally ranges from 20 to 80% *(12,19–21)*. Some studies reported different ranges of adherence for adult patients (40–60%) and children (25–75%) *(3,12)*.

4. Factors affecting adherence and interventions used to improve it

Non-adherence is a problem that has many determinants and the responsibility for adherence must be shared by health professionals, the health care system, the community and the patients. Many studies have identified factors affecting adherence, and these have been grouped into the five dimensions described in section II (see Table 5).

– socioeconomic-related factors;

– health care team/health system-related factors;

– condition-related factors;

– treatment-related factors, and

– patient-related factors.

Many factors, such as misunderstanding instructions about how to take the drugs *(6,12,20,23,26)*, combined antiepileptic medication, complex medication regimens *(3,12,26,30)*, forgetfulness *(6)*, duration, and previous treatment failures *(14)*, fear of dependence *(20)*, feeling stigmatized by the epilepsy *(20)*,

inadequate or nonexistent reimbursement by health insurance plans *(19)* and poverty *(6)*, among many others, have been shown to be significant barriers to adherence, and should be taken into account when developing interventions.

Contrary to expectations, a study by Mitchell et al. *(14)* found that frequency and duration of seizures and previous treatment failure, which are usually thought to be valid prognostic indicators of low adherence, did not affect adherence to treatment. Also, the severity of seizures was not significantly associated with any adherence outcome. However, families reporting less parental education, illiteracy, lower income and high levels of stressful life events were more likely to adhere to treatment.

Some interventions have been designed to improve adherence to anti-epilepsy medications. Some of them target specific factors, such as:

– the therapeutic relationship (increasing communication between patient and health professional) *(2,15,16,18,19,23)*;

– giving full instructions about the treatment and discussing the pros and cons of treatment with the patient *(19)*;

– reducing the number of medications and the frequency of doses *(3)*;

– suggesting memory aids, linking doses to events in the patient's daily schedule, and alarmed watches or pill cases *(3,14,16,31)*;

– motivating patients to incorporate drug adherence into their lifestyles *(6,32)*; and

– providing a regular, uninterrupted supply of medicines in developing countries *(33)*.

Education in the diagnosis and management of epilepsy was found to be effective in improving recruitment of patients into treatment programmes and in improving drug adherence, or markedly reducing nonadherence *(5)*. The use of educational materials, regular interviews, instructions from nurses and physicians about methods of incorporating drug administration into patients' daily lives, a real partnership between physician and patient, and patient self-management of epilepsy treatment, have all been found to improve adherence to AED therapies *(6,11,14,16,18)*. Other helpful measures were: clear information about the treatment, including giving full instructions; discussing the pros and cons of treatment; reinforcing the value of treatment; explaining and repeating the rationale for the regimen; involving the patients in planning their regimens, and explaining the results of medical tests.

Good adherence education may be based on:

– stressing the importance of adherence at the time the therapy is initiated;

– emphasizing the consequences of nonadherence;

– spending adequate time with the patient;

– enquiring about adherence at each visit;

– motivating patients to incorporate drug adherence into their lifestyles;

– designing and implementing intervention strategies to improve adherence to self-medication.

These latter strategies include simplifying the regimen with careful explanation of the dosing schedule; reducing the number of medications and the frequency of doses; improving the medication routine through cognitive cueing and through structuring the task and the environment; providing the patients with control and choices; suggesting memory aids; linking doses to events in the patient's daily schedule, or using alarm watches, calendar packs, pill cases, or specialized dose dispensers.

Encouraging patients to develop their own methods to improve maintenance, after educating them about the nature of epilepsy and the need for long-term therapy, may help them to incorporate drug administration into their daily lives. It is important to note that patients from different cultures require different educational approaches to improve adherence *(15)*. In developing countries it is necessary to maintain a regular, uninterrupted supply of medicines *(33)*, to provide drugs at subsidized costs and to organize effective distribution systems *(27)*.

Table 5 Factors affecting adherence to treatment for epilepsy and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Epilepsy	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Long distance from treatment setting *(27)*; under 60 years old *(12,20)*; teenagers *(20)*; poverty *(6)*; illiteracy *(6)*; unwillingness to pay the cost of medicines *(6,23,27)*; high cost of *(21,34)*; local beliefs or beliefs about the origin of illness *(6,27)*. (+) Elderly patients (over 60 years old) *(20)*; children from family reporting less parental education *(14)*; non-English speaking in an English-speaking community *(14)*; lower income *(14)*; recent immigrants *(14)*.	Assessment of social and career needs *(3)*
Health care team/health system-related factors	(–) Inadequate or non-existent reimbursement by health insurance plans *(19)*; irregular or poor drug supply *(27,27)*; lack of free medicine supplies *(33)*; poorly developed health services *(27)*; lack of education about AEDs *(21,26,34,35)*. (+) Good relationship between patient and physician *(20)*	A regular, uninterrupted supply of medicines in developing countries *(33)*; good patient–physician relationship *(6,11,14,16,18)*; instruction by nurses and physicians about methods of incorporating drug administration into patient's daily life; training health professionals on adherence; adherence education *(11,14,16,19,31)*
Condition-related factors	(–) Forgetfulness *(6)*; memory deficits *(12)*; duration, and previous treatment failures *(14)*; high frequency of seizures *(14)*.	Education on use of medicines (5,14,31); suggesting memory aids *(3,14,16,19,26,31)*
Therapy-related factors	(–) Complex treatment regimens *(3)*; misunderstanding instructions about how to take the drugs *(6,12,20,23,26)*; adverse effects of treatment *(6,9,16,20–23,27)*. (+) Monotherapy with simple dosing schedules *(2)*	Simplification of regimens; single antiepileptic therapy (monotherapy) *(3,16,19,30)*; education on use of medicines; patient-tailored prescriptions *(36)*; clear instructions; use of educational materials; monitoring and re-assessment of treatment *(6,11,14,16,18)*
Patient-related factors	(–) Disbelief of the diagnosis *(16,22)*; refusal to take medication *(34)*; delusional thinking *(16,31)*; inconvenience of treatment *(21,34)*; denial of diagnosis *(21,34)*; lifestyle and health beliefs; parental worry about child's health *(29)*; behavioural restrictions placed on child to protect his/her health *(29)*; fear of addiction *(20)*; doubting the diagnosis *(20)*; uncertainty about the necessity for drugs *(20)*; anxiety over the complexity of the drug regimen *(20)*; feeling stigmatized by the epilepsy *(20)*; not feeling that it is important to take medications *(20)*. (+) Parent and child satisfaction with medical care *(29)*; not feeling stigmatized by the epilepsy *(20)*; feeling that it is important to take medications(20); high levels of stressful life events *(14)*.	Self-management of disease and treatment *(37–39)*; self-management of side-effects *(6,11,14,16,18)*; behavioural and motivational intervention; education on adherence *(6,32)*; providing the patients with control and choices; assessment of psychological needs *(3)*; frequent follow-up interviews *(11,16)*

AEDs, anti-epileptic drugs; (+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence.

5. Conclusions

Poor adherence to drug therapy is one of the primary causes of treatment failure.

Forgetfulness of patients that may or may not be linked to memory difficulties, refusal to take medication and side-effects are the factors most commonly associated with decreased adherence. The impact of epilepsy and the side-effects of its treatment on cognition and of limited or compromised cognition on adherence deserve more attention.

The use of memory aids, linking doses to events in the patient's daily schedule or watch alarms, calendar packs, pill cases or specialized dose dispensers may be helpful tools to increase adherence to treatment in patients who regularly forget to take their AEDs. However, no studies demonstrating this were found in the literature search.

Communication with the patient about medication regimens and the value of treatment is extremely important. It can facilitate the identification of problems and barriers to adequate adherence, and help with treatment planning. Also a real partnership between the physician and the patient is needed to set and achieve goals related to treatment outcomes and adherence.

More research on adherence to anti-epileptic therapies is required to:

– deepen our understanding of the epidemiology of adherence;

– provide clear and consistent definitions of adherence;

– evaluate interventions to improve adherence; and

– collect data on adherence in developing countries.

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CHAPTER XII

Human immunodeficiency virus and acquired immunodeficiency syndrome

Of those patients suffering from HIV/AIDS, approximately one-third take their medication as prescribed *(1)*. Even when patients fully comprehend the consequences of nonadherence to medications, adherence rates are suboptimal *(2,3)*. Good adherence is a decisive factor in treatment success.

Unlike other chronic diseases, the rapid replication and mutation rate of HIV means that very high levels of adherence (e.g. ≥ 95%) are required to achieve durable suppression of viral load *(4–6)*. Recent studies of patients with HIV/AIDS have reported low adherence rates, similar to those seen for other chronic diseases. Suboptimal adherence may rapidly lead to resistance, which can then be transmitted to other people *(7–10)*. The potent and effective new combinations of antiretroviral agents, known as highly active antiretroviral therapy (HAART), have proven efficacious in reducing viral load and improving clinical outcomes. However, the large number of medications involved, the complicated dosing requirements, and the suboptimal tolerability make adherence difficult. Because of the great importance of adherence to antiretroviral treatment of HIV, good strategies for maximizing adherence are essential.

There is no doubt that HAART is one of the most celebrated treatment advances in recent medical history. Nucleoside reverse transcriptase inhibitors (usually two) when combined with non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or both, are highly effective in reducing viral replication and improving clinical outcomes *(11,12)*. In patients with HIV/AIDs, these multidrug regimens, although remarkably efficacious, result in HIV treatment having the most complicated regimens that have ever been prescribed for conditions requiring continuous open-ended treatment *(13)*.

Many researchers believed initially that HAART would completely eradicate the virus from the host *(14,15)*. However, low levels of viral replication persist in small reservoirs even when viral loads are undetectable. Resting memory T-cells, which harbour proviral DNA, survive for far longer than originally thought *(5,6,16–18)*.Therefore, adherence to HAART must be almost perfect to achieve lasting viral suppression. Paterson and colleagues *(6)* found that adherence at levels less than 95% independently predicted viral resistance, hospital admissions and opportunistic infections. Even among patients who reported adherence rates of ≥95%, 22% experienced virologic failure during the study period. In another study, Bangsberg and colleagues *(4)* found that none of the individuals with adherence greater than 90% progressed to AIDS, whereas 38% and 8% of those with adherence rates £50% and 51–89%, respectively, progressed to AIDS. Missing even a single dose in a 28-day reporting period has been shown to predict treatment failure *(5)*.

Nonadherence to HAART can have important public health implications. Drug resistance can be transmitted to other persons during high-risk activity, which can then limit therapeutic options *(7–10)*. Some studies have reported that as many as 80% of isolates from newly infected people are resistant to at least one class of currently approved antiretroviral medications, and that 26% of isolates are resistant to several classes of medication *(18)*. Although these estimates are at the higher end of the spectrum, they nonetheless suggest that transmission of drug-resistant strains is increasing *(10)*.

Because adherence of patients with HIV to antiretroviral medications is essential for both clinical effectiveness and public health, research in this area has burgeoned over the past few years.

1. Types of nonadherence

Nonadherence can take many different forms *(19)*. The patient may simply fail to fill the prescription. If the prescription is filled, the patient may incorrectly time the medication or take the wrong dose because he or she misunderstood, or forgot, the health professional's instructions. Patients may also forget a dose completely or prematurely terminate the medication. Moreover, patients may self-adjust their regimen because of side-effects and toxicity or personal beliefs.

2. Challenges in assessing adherence

It is easy for health professionals to miss adherence problems because patient self-reports of adherence tend to be exaggerated *(20,21)* due perhaps both to a recall bias and a desire to please the provider and avoid criticism. Some patients have been known to dispose of their medication before a scheduled check on their adherence to it so as to appear to have adhered *(22)*. Inadequate adherence coupled with biased reporting is ubiquitous across medicine *(23)*. Conversely, patients who report problems with adherence are rarely trying to mislead their providers *(24)*.

In addition to the misreporting of adherence by patients, estimates of adherence made by health care providers are also usually over-optimistic *(25,26)*. Moreover, providers of health care are not able to predict very accurately which patients will adhere. Many providers believe that factors associated with socioeconomic status, such as lack of education and poverty are good predictors of nonadherence. However, predictors of adherence vary greatly across populations and settings and no one factor has been consistently associated with nonadherence across all studies *(27)*.

3. Predictors of adherence

Four types of factor have generally been found to predict problems with adherence to medication: regimen characteristics, various patient factors, the relationship between provider and patient and the system of care. The following section focuses on the first three factors; a discussion of factors associated with the system of care is beyond the scope of this report.

A. Regimen-related factors

Complexity of regimen. For many chronic diseases, research has shown that adherence decreases as the complexity of the medication regimen increases (i.e. the number of pills per dose and number of doses per day; the necessity to observe strict requirements related to the intake of food, and the existence of special requirements regarding fluid intake). Adherence to HIV medications is an extremely complicated process that includes both the drugs themselves and the adjustments to daily life necessary to provide the prerequisite conditions for effective drug therapy *(13)*. Some regimens require several doses of medication per day together with various requirements or restrictions on food intake and other activities. These complexities, in addition to the problems of toxicity and side-effects, can greatly influence an individual's willingness and ability to adhere to the therapy *(28–31)*.

Many health professionals believe that pill burden strongly influences adherence. However, the effect of pill burden on adherence is closely associated with disease stage. Symptomatic individuals perceive a higher risk for complications of nonadherence to medication, than do asymptomatic patients *(32)*. Dosing schedules and food restrictions or requirements appear to have a more pervasive influence on adherence than pill burden. In the treatment of many diseases, once-daily or twice-daily doses are preferred *(33,34)*. For instance, Eldred and colleagues *(33)* found that patients on twice-daily doses or less reported better adherence (>80%) and were more likely to take their medications when away from home. Paterson and colleagues *(6)* also found that a twice-daily dose was associated with better adherence than a three-times-daily dose. However, other studies have failed to confirm this association, including the large Health Care Services Utilization Study with more than 1900 participants *(35)*. Wenger and colleagues demonstrated that the "fit" of the regimen to an individual's lifestyle and schedule, as well as the individual's attitude towards treatment were better predictors of adherence than dosing schedule *(35)*. It is likely, however, that fewer doses do allow for easier "fitting" of medications into an individual's schedule.

Regimens that involve close monitoring and severe lifestyle alterations together with side-effects may lead not only to frustration and treatment fatigue, but also ultimately to noncompliance *(36)*. Regimens requiring fewer alterations in lifestyle patterns (e.g. fewer pills per day and fewer dietary restrictions) are likely to have a positive influence on adherence to medication.

To the extent possible, regimens should be simplified by reducing the number of pills and frequency of therapy, and by minimizing drug interactions and side-effects. This is particularly important for patients with strong biases against many pills and frequent dosing. There is evidence that simplified regimens that require fewer pills and lower dose frequencies improve adherence *(37)*. When choosing appropriate regimens, the patient's eating habits should be reviewed and the specific food requirements of the regimen discussed so that the patient understands what is required before his or her agreement to such restrictions is sought. Regimens requiring an empty stomach several times per day may be difficult for patients suffering from wasting, just as regimens requiring a high fat intake may be difficult for patients with lactose intolerance or fat aversion.

Side-effects. Side-effects have also been consistently associated with decreased adherence and patients who experience more than two aversive reactions are less likely to continue their treatment *(38)*. HAART regimens usually have temporary side-effects including transient reactions (diarrhoea and nausea) as well as longer-lasting effects (i.e. lipodystrophy and neuropathy). The extent to which side-effects alter a patient's motivation to adhere to a treatment regimen depends greatly on the specific contextual issues surrounding the individual. The literature on side-effects clearly shows that optimal adherence occurs with medications that remove symptoms, whereas adherence is reduced by medications that produce side-effects *(13,27)*. Although HAART may greatly increase quality of life in symptomatic individuals, it probably has a negative effect on quality of life in asymptomatic individuals *(39)*.

Patients quickly discontinue therapy or request changes of medication if they experience side-effects *(40)*. Whether real or perceived, side-effects account for more regimen changes than does treatment failure *(30,40,41)*. One large study of more than 860 HIV-positive patients in Italy reported that more than 25% of treatment-naive patients discontinued their treatment within the first year because of toxicity and other side-effects *(30)*. Another study in France found that the patients' subjective experience of side-effects within the first 4 months of treatment predicted nonadherence more than any other predictors, including sociodemographic variables, number of medications or doses per day *(42)*. The symptoms that cause the most distress are fatigue, diarrhoea, nausea and stomach pain, most of which can be successfully treated *(30,42)*.

One serious side-effect that may affect adherence to HIV medications is lipodystrophy. Kasper and colleagues *(43)* found that 37% of their respondents either stopped or changed their medications because they developed lipodystrophy. Of those who were adherent, 57% stated that they had seriously considered discontinuation of therapy, while 46% stated that they would change medications if symptoms worsened.

Lipodystrophy affects between 30% and 60% of persons on HAART *(44,45)*. Physical manifestations vary greatly but can include fat accumulation on the upper back and neck (buffalo hump), under the muscles of the abdomen (crix belly or protease paunch), lipomas and breast enlargement; it may also cause peripheral wasting of fat in the face, legs, arms and buttocks *(46–48)*. Physiologically, these physical deformities are usually preceded by hyperglycaemia, insulin resistance, hypercholesterolaemia and hypertriglyceridaemia. The exact relationship of these physiological changes to lipodystrophy is unclear. Nonetheless, lipid abnormalities must be treated and this can increase the complexity and side-effects of already complex regimens. Selecting regimens that do not contribute to dyslipidaemia or lipodystrophy may allay fears of disfigurement and support adherence.

In the light of these findings, simplified regimens with fewer pills and fewer doses, and that minimize side-effects, are desirable for achieving maximum adherence *(38)*.

B. Patient-related factors

A patient's behaviour is the critical link between a prescribed regimen and treatment outcome. The most effective regimen will fail if the patient does not take the medication as prescribed or refuses to take it. Consequently, all things being equal, the most important factors influencing adherence are patient-related *(27)*.

Psychosocial issues. Perhaps more than anything else, life stress can interfere with proper dosing of protease medication regimens *(49,50)*, and such stress is experienced more often and to a greater degree by individuals of low socioeconomic status. Although studies of most demographic characteristics of patients have generally failed to establish consistent links with adherence to medication, some recent studies have described several variables that have a possible association. Adherence is apparently most difficult for patients with lower levels of education and literacy, and a few studies have reported lower adherence among blacks and women, although this finding has not been consistent *(38)*. Women have cited the stress of childcare as being related to missed doses *(36)*. The abuse of alcohol and intravenous drugs and the presence of depressive symptoms have also been linked with poor adherence to medication.

Although some studies have demonstrated that a history of substance abuse is unrelated to adherence *(51,52)*, active substance abuse is one of the stronger predictors of non-adherence *(53,54)*. Nevertheless, even active substance abusers can achieve good adherence if the provider takes the time to address the patient's concerns about the medications, including anticipation of, and management of, side-effects. Mocroft and colleagues *(52)* demonstrated that intravenous drug abusers were significantly less likely to begin antiretroviral therapy, but among those who did, the response to therapy was similar to that of other exposed groups.

Psychological distress has also been shown to affect adherence. Depression, stress, and the manner in which individuals manage stress, are among the most significant predictors of adherence, but correlations with other psychiatric comorbidities are weaker *(6,53–57)*. Hopelessness and negative feelings can reduce motivation to care for oneself and may also influence a patient's ability to follow complex instructions. Adolescents living with HIV who reported high levels of depression demonstrated lower adherence than did their peers who were not depressed *(56)*. These findings are similar to those of studies on other chronic conditions that have demonstrated a relationship between adherence and depression *(58)*.

Just as social support acts as a buffer for many psychosocial problems, it also affects adherence behaviour. Patients with supportive friends and families tend to adhere to HAART better than those without these supports *(6,59,60)*. In addition to the support that can be provided by clinic staff in the form of a good relationship between providers and patients, recommendations for improving adherence often include providing a telephone-counselling line where messages can be left for nurses, and enlisting the support of pharmacists *(61)*. It is important to encourage patients to involve family and friends in their care, and to follow up on referrals to support groups, peer-counselling and community-based organizations.

Several psychosocial predictors of acceptable levels of adherence to HIV medications have been identified in a large-scale, multisite investigation of HAART *(62)*. These include:

– availability of emotional and practical life support;

– the ability of patients to fit the medications into their daily routines;

– the understanding that poor adherence leads to resistance;

– the recognition that taking every dose of the medications is important; and

– feeling comfortable taking medications in front of other people.

Such psychosocial aspects of treatment may be easily overlooked yet have been documented as being crucial to consistent adherence to HIV medication regimens.

Patient-belief system. A patient's knowledge and beliefs about disease and medicine can influence adherence. Understanding the relationship between adherence and viral load and between viral load and disease progression is integral to adherence behaviour *(53)*. Wenger and colleagues *(35)* found better adherence in patients who believed antiretroviral medication to be effective. Negative beliefs regarding the efficacy of HAART may also affect adherence behaviour. For example, many African Americans were found to be reluctant to take zidovudine because they believed that it was toxic. Siegel and colleagues *(63)* showed that African American men were more likely than Caucasian men to report scepticism about medications and their ability to adhere to those medications. Other beliefs such as those regarding interference with the actions of HAART by alcohol and drugs can also affect adherence *(64)*.

The list below, adapted from the NIH Antiretroviral Guidelines *(62)*, lists additional patient- and medication-related strategies to improve adherence.

– Inform patient, anticipate, and treat side-effects.

– Simplify food requirements.

– Avoid adverse drug interactions.

– If possible, reduce dose frequency and number of pills.

– Negotiate a treatment plan, which the patient understands and to which he or she is committed.

– Take time, and use several encounters, to educate the patient and explain the goals of therapy and the need for adherence.

– Establish the patient's readiness to take medication before the first prescription is written.

– Recruit family and friends to support the treatment plan.

– Develop a concrete plan for a specific regimen including dealing with side-effects and relate it to meals and the patient's daily schedule.

– Provide a written schedule with pictures of medications, daily or weekly pillboxes, alarm clocks, pagers or other mechanical aids to adherence.

– Develop adherence support groups, or add adherence issues to the regular agenda of support groups.

– Develop links with local community-based organizations to help explain the need for adherence using educational sessions and practical strategies.

– Consider "pill trials" with jelly beans.

Confusion and forgetfulness are major obstacles in achieving adherence to HIV medication regimens. Difficulty in understanding instructions has also been reported to affect adherence. Requirements and or restrictions on the intake of food and water, or the temporal sequences of dosing can be confusing. Misunderstandings may arise as a result of a complex regimen, and/or from poor instructions from the health care provider. In the AIDS Clinical Trial Group, 25% of the participants failed to understand how their regimens were to be taken *(53)*. In another study, less adherent individuals reported significantly greater confusion over how many pills to take and how to take them *(41)*.

The most commonly cited reason for nonadherence is forgetfulness *(51,53,65)*; for example, Chesney and colleagues *(53)* reported that 66% of their respondents gave this as the main reason for nonadherence. Ostrop and colleagues *(51)* demonstrated that not only is forgetfulness the most common reason for nonadherence, but also that the middle dose in a three-times-a-day regimen is the most commonly forgotten. Although other studies have not confirmed this finding, doses are more commonly missed in three-times-daily regimens than in once-daily or twice-daily regimens.

Patient–provider relationship. A meaningful and supportive relationship between the patient and health care provider can help to overcome significant barriers to adherence *(37,59,66)*, but few providers routinely ask about adherence or offer counselling *(67)*. Factors that strengthen the relationship between patient and provider include perceptions of provider competence, quality and clarity of communication, compassion, involving the patient as an active participant in treatment decisions and convenience of the regimen *(27)*. Conversely, patients become frustrated with health care providers when misunderstandings occur, treatment becomes complex, the patient is blamed for being a "bad patient" or side-effects go unmanaged. These frustrations may lead to poor adherence. Specific strategies for clinicians and health teams, as suggested by the NIH Antiretroviral Guidelines *(62)* are listed below.

– Establish trust.

– Serve as educator, source of information, ongoing support and monitoring.

– Provide access between visits for questions or problems by giving the patient a pager number, and arranging for coverage during vacation periods and conferences.

– Monitor ongoing adherence; intensify management during periods of low adherence (e.g. by means of more frequent visits, recruitment of family and friends, deployment of other team members, referral for mental health or chemical-dependency services).

– Utilize health team for all patients, for difficult patients and for those with special needs (e.g. peer educators for adolescents or for intravenous drug users).

– Consider the impact of new diagnoses (e.g. depression, liver disease, wasting, recurrent chemical dependency), on adherence and include adherence intervention in their management.

– Enlist nurses, pharmacists, peer educators, volunteers, case managers, drug counsellors, physician's assistants, nurse practitioners and research nurses to reinforce the message of adherence.

– Provide training on antiretroviral therapy and adherence to the support team.

– Add adherence interventions to the job descriptions of HIV support-team members; add continuity-of-care role to improve patient access.

4. A framework for interventions to increase adherence

Experiences with HAART suggest that adherence is arguably the most important issue in successfully managing HIV/AIDs. A multifaceted approach to improve adherence is the most likely to be beneficial, particularly a combination of actively involving patients in their own health care decisions, provision of appropriate supports, multidimensional educational programmes that teach behavioural skills to the patient to enhance his or her adherence, and tailoring of the regimen to fit the patient *(13,27,68)*.

The provider must accurately assess both the patient's willingness to adhere in the context of possible side-effects, and his or her willingness to overcome potential barriers to taking the medications as prescribed. Furthermore, it is essential that the patient adequately understands the importance of adherence and the serious consequences of nonadherence (i.e. treatment failure, or in some cases, disease progression, drug-resistance or death).

Especially for a disease such as HIV, where poor adherence can cause resistance, it may prove wise to delay active treatment until the patient understands the demands of the regimen and feels truly committed to it. One way in which to gauge a person's readiness to adhere to a regimen, identify specific barriers to adherence, and to simultaneously strengthen the patient–provider relationship is to ask the patient to adhere to a trial run of the regimen. This may be done using vitamin pills or jelly beans, with different tablets or different-coloured beans representing the various medications. Such a trial can give patients a perspective on how dosing schedules and other complexities, such as food restrictions or requirements will fit into their daily routine. A trial lasting a few weeks is usually sufficient for assessing a patient's ability to stick to the regimen and overcome the barriers. However, such a trial run is unable to mimic possible side-effects.

For children who rely on the support of caregivers to maintain their adherence, the caregivers must believe the rationale for the regimen and assume responsibility for maintaining it. Moreover, every attempt should be made to involve the children in the decision-making process to the extent of their capability. Although young infants may have little influence on adherence, older children can have more influence on whether or not they take their medications as prescribed.

Whether developed or acquired, resistance complicates treatment decisions. As a variant becomes progressively resistant to current medications, the therapeutic options become limited. Then the only solution is to select medications from a new treatment class or prescribe medications from existing classes that have demonstrated efficacy against variants resistant to current medications. However, forced selection limits the ability to fit a regimen to patients' lifestyles and schedules.

Ideally, the health practitioner should work together with the patient to select a regimen that will fit into his or her lifestyle. If more than one regimen may be appropriate for a given patient, providers may want to discuss the regimen, the number of pills, the dosing schedule, instructions and potential side-effects with the patient. This discussion will foster a more collaborative and positive relationship between the practitioner and the patient, which is likely to enhance adherence *(68)*. Once the regimen is decided upon, practitioners must make certain that patients fully understand the dosing schedules and instructions.

Rather than associating doses of medication with times of the day, fitting the regimen to the patient's lifestyle calls for working with the patient to associate medication doses with routine activities performed at the times that the medication should be taken *(41)*. For example, morning doses can be associated with morning rituals (e.g. brushing teeth or reading the newspaper), and evening doses can be associated with evening routines (e.g. children's homework or watching television news programmes). In general it is likely that accomplishing this "fit" will be easier with regimens that require infrequent dosing (i.e. once or twice a day). However, the principle of associating medications with daily activities can also accommodate more frequent and complex regimens.

The most simple, effective and potent regimen will fail if patients experience side-effects that they perceive as problematic and terminate their medications. At the time that the regimen is prescribed, health professionals should be proactive and provide strategies to help patients manage any side-effects that may occur *(69)*. Given that experiencing side-effects is associated with nonadherence, providers and their team members should remain in close contact with the patient during early treatment with a new regimen to allow for the timely identification and management of all side-effects and toxicities. A further advantage of this approach is that it provides an opportunity for reinforcing adherence behaviour. A powerful reinforcer of adherence behaviour is positive feedback regarding medication efficacy *(70)*. Consequently, laboratory and other tests should be conducted soon after the initiation of treatment to show the extent to which it has been effective.

Health care providers and their teams should address the patient-related factors and psychosocial issues associated with nonadherence. While these may vary across conditions, screening for active substance abuse and depressed mood would be appropriate in many patient groups. Finally, enlisting the support of family members and "significant others", or employing "treatment buddies" to administer medications can greatly enhance adherence.

An example of a currently operational comprehensive approach to AIDS care, which includes access to free voluntary tests and counselling, the provision of zidovudine or nevirapine for the prevention of mother-to-child transmission, diagnosis and treatment of opportunistic infections, social assistance and directly observed provision of HAART (DOT-HAART) by trained community health workers to the most severely ill patients, has been implemented by Farmer et al. in a poor rural area in Haiti where HIV infection is endemic *(71,72)*.

Preliminary reports have suggested that adherence rates are almost 100%; 86% of patients have no detectable virus in peripheral blood. Clinical outcomes have been excellent in all patients receiving DOT-HAART, enabling up to 90% of them to resume daily activities within 3 months of initiation of treatment. Also hospitalization rates have decreased by more than half since the start of the programme and a sharp decline in mortality has been observed *(73)*.

The implementation of demonstration projects of good HIV/AIDS care practice, using targeted research or evidence-based quality improvement processes, is urgently needed for effectively fighting against the disease. As Pablos-Mendes stated, "research need not hold back care, we should learn by doing" *(74)*.

Table 6 Factors affecting adherence to therapy for HIV/AIDs and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

HIV/AIDs	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Women: stress of childcare *(36)*; low income (49); African American men *(63)*; lack of social support *(6)* (+) Support of family and friends *(6)*; Caucasian men *(63)*	Family preparedness (6); mobilization of community-based organizations; intensive education on use of medicines for patients with low levels of literacy; assessment of social needs
Health care team/health system-related factors	(–) Lack of clear instructions from health professionals; Poor implementation of educational interventions *(61)* (+) Good relationship between patient and physician; support of nurses and pharmacists *(61)*	Good patient–physician relationship *(61,68)*; multidisciplinary care; training of health professionals on adherence; training of health professionals on adherence education; training in monitoring adherence; training caregivers; identification of the treatment goals and development of strategies to meet them *(68)*; management of disease and treatment in conjunction with the patients; uninterrupted ready availability of information; regular consultations with nurses/physicians; non-judgemental attitude and assistance; rational selection of medications *(62)*
Condition-related factors	(–) Asymptomatic patients *(32)* (+) Symptomatic patients *(32)*; understanding the relationship between adherence and viral load *(53)*	Education on use of medicines *(53,62)*; supportive medical consultation; screening for co-morbidities; attention to mental illness, as well as abuse of alcohol and other drugs
Therapy-related factors	(–) Complex treatment regimens *(28)*; close monitoring; severe lifestyle alterations *(36)*; adverse events *(36)*; adverse effects of treatment *(27)*; lack of clear instructions about how to take the medications *(30,38,40–43,53)* (+) Less frequent dose *(6,33)*; fewer pills per day; fewer dietary restrictions *(36)*; fitting medication to individual's lifestyle *(35)*; belief that medication is effective *(35)*	Simplification of regimens; education on use of medicines; assessment and management of side-effects *(37,38)*; patient-tailored prescriptions *(41,68)*; medications for symptoms *(27)*; education in adherence *(68)*; continuous monitoring and re-assessment of treatment *(70)*; management of side-effects *(69)*
Patient-related factors	(–) Forgetfulness *(53)*; life stress *(6,6)*; alcohol use; drug use *(53)*; depression *(6)*; hopelessness and negative feelings; beliefs that alcohol and drug use interfere with medications *(6,64)* (+) Positive beliefs regarding the efficacy of antiretroviral medications *(35)*	Monitoring drug and/or alcohol use; psychiatric consultation; behavioural and motivational intervention *(68)*; counselling/psychotherapy; telephone counselling; memory aids and reminders; self-management of disease and treatment *(68)*

(+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence

5. Conclusions

The problems of adherence are ubiquitous across medicine. Because adherence is a complex process, attempts to improve it need to be multifaceted. Factors such as the complexity of the treatment regimen, patient-related factors and the relationship between the patient and the provider of care all affect adherence.

Health care providers should work to establish a collaborative treatment relationship with their patients. This can be fostered by involving the patients in selecting regimens with dosing schedules, pill burdens and side-effects that they believe are tolerable and will "fit" into their daily lives. Pharmaceutical companies are currently working diligently to develop once-daily and twice-daily regimens with fewer side-effects and higher tolerability that will better achieve this fit. Providers should openly discuss with patients their readiness to follow treatment, the potential barriers to adherence and possible solutions to problems. While the provider and his or her team can be a source of support, other possible sources (including family, friends, and formal support services) should also be discussed with patients.

Clinicians should also be aware of the prevalence of mental health disorders and disorders related to psychoactive substance abuse in certain HIV-infected populations, as inadequate mental health treatment services may jeopardize the ability of affected individuals to adhere to their medical treatment. Appropriate attention to mental illness, as well as to abuse of alcohol and other drugs could greatly enhance adherence to medical treatment of HIV. Social and living conditions, fit of regimen to lifestyle, availability and nature of social support and treatment expectations can also affect adherence.

No patient should be excluded from consideration for antiretroviral therapy simply because he or she exhibits a behaviour, characteristic or risk factor that might be judged as predictive of nonadherence *(62)*. The health care team should make all possible efforts to ensure that patients adhere to therapies. Awareness of patients' risk factors for nonadherence can help to guide clinicians in tailoring regimens to maximize adherence.

Poor adherence to a regimen is only one of several possible reasons for its failure. Others that must be assessed include initial resistance to one or more of the therapeutic agents, altered absorption or metabolism, and multi-drug pharmacokinetics that adversely affect levels of therapeutic drugs. It is therefore important to assess patient adherence carefully before changing antiretroviral therapy. Case managers, social workers and other health care providers involved in the care of the patient may assist in this evaluation.

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CHAPTER XIII

Hypertension

Clinical trials have demonstrated that the treatment of mild-to-moderate hypertension can reduce the risk of stroke by 30 to 43% *(1–4)* and of myocardial infarction by 15% *(5)*. Other costly consequences of untreated hypertension can also be prevented or minimized by effective treatment. Examples of the benefits of treatment include reduction in risk of cardiac failure, reduction in incidence of dementia *(6)*, preservation of renal function and prevention of blindness in diabetic patients with hypertension *(7–9)*.

Traditionally, the term compliance has been employed to mean the extent to which the patient, when taking a drug, complies with the clinician's advice and follows the regimen *(10)*. However, the new era of patient-oriented care has led to the use of this term being questioned, and alternative terms such as adherence, persistence and concordance have been suggested *(11–14)*.

In addition to the confusing terminology in the area of adherence, there has been controversy over the use of 80% as a cut-off point to distinguish adherence from non-adherence. In most studies, non-adherence has been considered to occur when patients do not take ≥ 80% of their prescribed antihypertensive drugs *(15,16)*.

Whatever the definition, poor adherence to treatment is the most important cause of uncontrolled blood pressure *(13,14,17)* and only 20 to 80% of patients receiving treatment for hypertension in real-life situations are considered to be "good compliers" *(18)*.

1. Prevalence of adherence to pharmacotherapy in patients with hypertension

Despite the availability of effective treatment, over half of the patients being treated for hypertension drop out of care entirely within a year of diagnosis *(15)* and of those who remain under medical supervision only about 50% take at least 80% of their prescribed medications *(16)*. Consequently, because of poor adherence to antihypertensive treatment approximately 75% of patients with a diagnosis of hypertension do not achieve optimum blood-pressure control *(13,18)*.

Estimates of the extent to which patients adhere to pharmacotherapy for hypertension vary between 50 and 70%. This variation relates to differences in study groups, duration of follow-up, methods of assessment of adherence and drug regimens used in different studies. For example, studies that defined adherence as an 80% ratio of days on which medication was dispensed to days in the study period, reported adherence rates ranging from 52 to 74% *(19,20)*. Other studies that have investigated discontinuation of antihypertensives have reported adherence rates of 43 to 88% *(21–24)*. Furthermore, it has been estimated that within the first year of treatment 16 to 50% of patients with hypertension discontinue their antihypertensive medications, and among those who continue their therapy in the long term, missed doses of medication are common *(25)*. These figures differ for newly-diagnosed patients and those with chronic, long-standing hypertension *(26)*.

Another source of variation that could explain the differences in rates of adherence is the method used to measure adherence. Examples of methods used include calculating the percentage of pills taken in a specific time period, the percentage of patients taking 80% of their pills, the improvement in number of pills taken, the drop-outs from treatment and follow-up, and the missed appointments. There are also indirect proxy measures such as change in blood pressure and the achievement of target blood pressure *(27)*.

2. Impact of adherence on blood pressure control and cardiovascular outcome

Good adherence has been associated with improved blood pressure control *(17)* and reduced complications of hypertension *(28,29)*. For example, in one study, health education interventions for urban-poor patients with hypertension were introduced sequentially in a randomized factorial design to a cohort of 400 ambulatory outpatients with hypertension over a 5-year period. The interventions resulted in an improvement in adherence, which was associated with better blood pressure control and a significant reduction (53.2% less) in hypertension-related mortality rates *(28)*.

In another study, patients who did not adhere to beta-blocker therapy were found to be 4.5 times more likely to have complications of coronary heart disease than those who did *(23)*. However, whether this increased complication rate was directly related to poor adherence to antihypertensive medication is not certain.

3. Adherence to non-pharmacological treatment

The efficacy of non-pharmacological therapy, including reduction in dietary salt intake, weight reduction, moderation of alcohol intake and increased physical activity, in lowering blood pressure has been shown by several studies *(30,31)*. In general, among small, well-supervised and motivated groups of patients receiving counselling on moderate salt restriction, most of the patients followed the regimen *(30,32,33)*. There is limited information, however, on adherence to other lifestyle measures intended to lower blood pressure. Most of the problems related to adherence to non-pharmacological treatment are currently assumed to be similar to those related to adherence to antihypertensive drug therapy and this is an area that warrants further investigation.

4. Factors contributing to adherence

Many factors have been shown to contribute to adherence and these have been extensively reviewed *(34–36)*. The asymptomatic and lifelong nature of the disease are undoubtedly two of the most important factors contributing to poor adherence. Other potential determinants of adherence may be related to:

– demographic factors such as age and education;

– the patient's understanding and perception of hypertension (37);

– the health care provider's mode of delivering treatment;

– the relationships between patients and health care professionals;

– health systems influences; and

– complex antihypertensive drug regimens (38).

Poor socioeconomic status, illiteracy and unemployment are important risk factors for poor adherence *(39,40)*. Other important patient-related factors may include understanding and acceptance of the disease, perception of the health risk related to the disease, awareness of the costs and benefits of treatment, active participation in monitoring *(41)* and decision-making in relation to management of the disease *(42)*.

The influence of factors related to the health care provider on adherence to therapy for hypertension has not been systematically studied. Some of the more important factors probably include lack of knowledge, inadequate time, lack of incentives and feedback on performance. Multifaceted educational strategies to enhance knowledge, audit with feedback on performance, and financial incentives are some of the interventions that should be tested for their effectiveness *(43–45)*.

The responsibility for adherence must be shared between the health care provider, the patient and the health care system. Good relationships between the patients and their health care providers are therefore imperative for good adherence. Empathetic and non-judgemental attitude and assistance, ready availability, good quality of communication and interaction are some of the important attributes of health care professionals that have been shown to be determinants of the adherence of patients *(46)*.

Health systems-related issues also play an important role in the promotion of adherence. In most low-income countries supplies of medications are limited and they often have to be bought out-of-pocket. Strategies for improving access to drugs such as sustainable financing, affordable prices and reliable supply systems have an important influence on patient adherence, particularly in economically disadvantaged segments of the population *(47)*. Focusing on improving the efficiency of key health system functions such as delivery of care, financing and proper pharmaceutical management can make a substantial contribution to improving the adherence rates of patients with hypertension and patients with chronic illnesses in general.

Some of the better-recognized determinants of adherence to antihypertensive therapy are related to aspects of the drug treatment itself *(46,48–55)* and include drug tolerability, regimen complexity, drug costs and treatment duration.

Some investigators have speculated that poor adherence can be explained in part by properties of the medications such as tolerability. However, a discrepancy has been noted between data on adherence in relation to drug tolerability that are obtained from randomized controlled trials and those obtained from observational studies. For example pooled results from head-to-head randomized controlled trials that recorded discontinuation of medications due to adverse events have demonstrated that significantly fewer patients discontinued treatment with thiazide diuretics compared to those treated with beta-blockers and alpha-adrenergic blockers *(46,48)*. However a recent review based on observational

studies has reported that initial treatment with newer classes of drug such as angiotensin II antagonists and angiotensin converting enzyme inhibitors and calcium channel blockers favoured adherence to treatment *(22)*.

It has been argued that information on adherence and the factors that contribute to it is better obtained from observational studies than from randomized clinical trials *(49)* because the stricter selection criteria and structured protocols used in randomized clinical trials may preclude generalization to patient behaviour in the real world. The role of drug tolerability in adherence to antihypertensive medication remains a topic for debate *(50–53)* and warrants further investigation.

The complexity of the regimen is another treatment-related factor that has been identified as a possible cause of poor adherence. Frequency of dosing, number of concurrent medications and changes in antihypertensive medications are some of the factors that contribute to the complexity of a regimen and these have been investigated in many observational studies *(46)*. Fewer daily doses of antihypertensives *(56,57)*, monotherapies and fewer changes in antihypertensive medications (less treatment turbulence) have all been associated with better adherence *(54,55)*.

5. Interventions for improving adherence

Adherence to treatment recommendations has a major impact on health outcomes and the costs of care for patients with hypertension. However, evidence to support any specific approach or intervention for improving patient adherence to antihypertensive drugs or prescribed lifestyle changes is lacking *(27)*.

Adherence to long-term medication regimens requires behavioural change, which involves learning, adopting and sustaining a medication-taking behaviour. Strategies such as providing rewards, reminders and family support to reinforce the new behaviour have been found to improve adherence in chronic illnesses *(58–60)*. Such behaviour-related interventions are likely to be key to improving adherence to antihypertensive medications and should be explored rigorously in clinical trials.

Until better insight into adherence is obtained, multifaceted measures to assist patients to follow treatment with antihypertensives have to be adopted. Health care providers need to be made aware of the low rates of adherence of patients with hypertension. They should receive training on how to counsel patients in a constructive and non-judgemental manner with the primary goal of helping the patient to adhere better to the treatment schedule.

Health care providers should also be trained to make a rational selection of antihypertensive drugs. The drug selected should be available, affordable, have a simple dosing regimen, and ideally, should not interfere with the quality of life of the patient.

Wherever feasible, patients should be taught to measure and monitor their own blood pressure and to assess their own adherence. Patients need to understand the importance of maintaining blood pressure control during the day and to use their drugs rationally. Furthermore, they need to learn how to deal with missed doses, how to identify adverse events and what to do when they occur.

Table 7 Factors affecting adherence to treatment for hypertension and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Hypertension	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Poor socioeconomic status; illiteracy; unemployment; limited drug supply; high cost of medication *(46,48–55)*	Family preparedness *(58–60)*; patient health insurance; uninterrupted supply of medicines; sustainable financing, affordable prices and reliable supply systems
Health care team/health system-related factors	(–) Lack of knowledge and training for health care providers on managing chronic diseases; inadequate relationship between health care provider and patient; lack of knowledge, inadequate time for consultations; lack of incentives and feedback on performance (+) Good relationship between patient and physician *(46)*	Training in education of patients on use of medicines; Good patient–physician relationship; continuous monitoring and re-assessment of treatment; monitoring adherence; non-judgemental attitude and assistance; uninterrupted ready availability of information; rational selection of medications; training in communication skills; delivery, financing and proper management of medicines; pharmaceuticals: developing drugs with better safety profile; pharmaceuticals: participation in patient education programmes and developing instruments to measure adherence for patients
Condition-related factors	(+) Understanding and perceptions about hypertension *(37)*	Education on use of medicines *(58)*
Therapy-related factors	(–) Complex treatment regimens *(38,46,48–55)*; duration of treatment; low drug tolerability, adverse effects of treatment *(46,48–55)* (+) Monotherapy with simple dosing schedules; less frequent dose (56); fewer changes in antihypertensive medications *(54)*; newer classes of drugs: angiotensin II antagonists, angiotensin converting enzyme inhibitors, calcium channel blockers *(22)*	Simplification of regimens *(38,46)*
Patient-related factors	(–) Inadequate knowledge and skill in managing the disease symptoms and treatment; no awareness of the costs and benefits of treatment; non-acceptance of monitoring (+) Perception of the health risk related to the disease *(37)*; active participation in monitoring *(41)*; participation in management of disease *(42)*	Behavioural and motivational intervention *(58–60)*; good patient–physician relationship; self-management of disease and treatment *(58)*; self-management of side-effects; memory aids and reminders *(58–60)*

(+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence

6. Conclusions

Patients need advice, support and information from health professionals in order to be able to understand the importance of maintaining blood pressure control during the day, to use their drugs rationally, to learn how to deal with missed doses, how to identify adverse events and what to do when they occur. Sharing this responsibility with health professionals is a must – the patient does not need to cope alone.

There is a direct need for research to fill gaps in knowledge on adherence. In general such research should aim at gaining a better understanding of the determinants of adherence discussed above so that effective interventions that address barriers can be developed.

In addition, research should focus on the following important areas:

- validation and standardization of various measures of adherence to prescribed drug therapy and non-pharmacological therapy for hypertension;
- development of valid and reliable questionnaires to obtain information on determinants of adherence;
- investigation of health-related quality-of-life indicators related to patients' adherence to antihypertensive therapy;
- identification of predictors of adherence to pharmacological and non-pharmacological therapy;
- determination of the factors related to behaviour that influence adherence to antihypertensive therapy, such as patient preferences and patient beliefs;
- identifying common risk factors for nonadherence in patients with hypertension, in both developing and developed countries, to study strategies for improving patient adherence;
- understanding of behaviour change principles and mechanisms that promote adherence;
- development of interventions to that promote adherence to antihypertensive medication;
- development of materials to involve patients more in managing and regulating their adherence and therefore their hypertension; and
- determination of the reductions in costs and hypertension-related complications resulting from adherence to antihypertensive therapy – issues that are relevant to the needs of patients, managed care organizations and governments.

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CHAPTER XIV

Tobacco smoking

1. The burden of tobacco smoking

The health risks of tobacco use, particularly cigarette smoking, are well-recognized. Tobacco smoke is the single most important factor contributing to poor health, and it is widely believed that a reduction in the prevalence of tobacco smoking would be the single most effective preventive health measure *(1)*. An estimated 70–90% of lung cancer, 56–80% of chronic respiratory diseases and 22% of cardiovascular diseases are attributable to tobacco smoking *(2)*.

Cigarette smoking remains the most important preventable cause of premature death and disability worldwide *(3)*. Each year, tobacco use causes some 4.9 million premature deaths *(2,4)*. Whereas until recently this epidemic of chronic disease affected the wealthy countries, it is now rapidly becoming a problem in the developing world *(5)*. About 80% of the world's 1.1 billion smokers live in low-income and middle-income countries. By 2030, seven out of every 10 deaths from smoking will occur in low-income countries *(6)*.

The available evidence suggests that free trade in tobacco products has led to increases in tobacco smoking and other types of tobacco use, but measures to reduce its supply are difficult to implement. However, interventions to reduce the demand for tobacco are likely to succeed. These include higher tobacco taxes, antismoking education, bans on tobacco advertising and promotion, policies designed to prevent smoking in public spaces or workplaces, and pharmacological therapies to help smokers to quit *(5,6)*.

Hundreds of controlled scientific studies have demonstrated that appropriate treatment can help tobacco users to achieve permanent abstinence. Millions of lives could therefore be saved with effective treatment for tobacco dependence.

2. Clinical guidelines and therapies available for tobacco smoking cessation

Effective smoking-cessation therapy can involve a variety of methods, such as a combination of behavioural treatment and pharmacotherapy *(4)*. A number of strategies have been developed to help smokers to quit. These include self-help manuals, individual or group counselling, aversive conditioning, hypnosis, clonidine, nicotine replacement therapy *(7)* and the use of antidepressant medications.

The most widely reported treatment is nicotine replacement therapy (NRT), which is available in the form of nicotine gum, nicotine patches and, more recently, as an oral inhaler. Nicotine replacement therapy is an established pharmacological aid to quitting smoking and it has consistently been shown to almost double the rate of quitting, irrespective of additional interventions *(8)*. Many studies have confirmed these findings *(1,7,9–18)*. A brief description of each of the NRTs is given below.

Nicotine gum delivers nicotine through transbuccal absorption. The gum should be discarded, not swallowed, after 30 minutes. The patient can chew another piece when there is an urge to smoke *(19)*. The total recommended dose is 10 to 12 pieces of gum daily for 1–3 months. After 3 months, a gradual withdrawal from gum use is recommended, with completion of treatment within 6 months *(20)*.

Transdermal administration of nicotine is available in three active forms (21, 14 and 7 mg), each steadily delivering an average of 0.7 mg nicotine per cm^2 per 24 h *(21)*. The strength of the patch is reduced gradually (by reducing the size of the patch) over the course of therapy, 8–12 weeks per 24 h treatment or 14–20 weeks per 16 h treatment (with patches that are worn only during the day) *(19)*. To reduce the likelihood of local skin irritation, the manufacturers recommend that the patch site be changed daily and that the same site is used not more than once every 7–10 days *(19,22,23)*.

The 1996 Smoking Cessation Clinical Guideline, which compared the use of NRT patches to nicotine gum, considered the patch easier to use and also more likely to enhance adherence *(24)*.

Oral nicotine inhalers consists of a disposable cartridge containing 10 mg nicotine and 1 mg menthol inserted in a plastic mouthpiece. Nicotine is delivered at a rate of 13 mg of nicotine/puff (80 puffs = 1 mg). The recommended dose is 6–12 cartridges over 24 h *(10)*. In one study, participants were encouraged to decrease use of the inhaler after 4 months, but were permitted to continue treatment for 18 of the 24 months *(10)*.

Behavioural therapies have been used in combination with NRTs, to enhance adherence to treatment and to help patients stop smoking. The therapies employed have included individual counselling, group therapy sessions and telephone hotline support, all of which provide encouragement, guidance, and strategies to combat urges and cravings to smoke. The intensity of the behavioural sessions varied between studies (e.g. weekly or daily, lasting between 15 minutes and 1 hour, and provided by a nurse, a physician or an MS/PhD therapist *(5,7,8,11,12,15,17–20,24–26)*. Pharmacists have also been proposed as potential providers of information and guidance concerning NRTs and tobacco in general *(27)*.

3. Definitions

Smoking cessation is generally defined as complete abstinence from the use of smoked tobacco. The duration of the studies varied from 12 weeks to 24 weeks, and used patient self-report questionnaires or interview data to assess quitting smoking. Almost all studies confirmed the self-reported data using one or more of the following biological measurements: expired carbon monoxide £ 10 ppm from the quitting day until the end of treatment and follow-up *(1,3,10–12,15,17,21,25,26,28–32)*, salivary cotinine levels £ 20 ng/ml *(3,11,13,16,24,28,31,33,34)* and urinary cotinine levels of 317 ng/ml or less *(21)*.

Adherence to smoking cessation therapy. The most widely used definition of adherence to treatment was "using the nicotine replacement therapy continuously at the recommended dose in the instructed manner for the entire 16-h *(17)* (or 24-h) time period" *(1,10,12,13,17,20,29,30,32,35,36)*.

Some studies assessed adherence by comparing the number of used and unused systems returned each week with the number of days that had elapsed between visits *(18,21,29)*. Others counted the total number of days on which patients did not use the systems during the treatment period, more than 5 days missed, or not wearing patches at night, were considered non-adherence *(7)*.

Others defined adherence as "perfect compliance with treatment protocol and/or not missing any scheduled follow-up visits" *(1,8,18)*. Bushnel et al. defined adherence as attending ≥ 75% of smoking cessation classes *(26)*.

Few reports provided detailed data on adherence such as number of prescribed doses taken during a monitored period, monitored days during which the correct number of doses were taken or whether or not the prescribed intervals between doses taken were respected.

Drop-out. Patients may drop out from treatment for several reasons. These include patient-related factors, physician decision and adverse effects of the drug. Regardless of the reason for dropping out, patients who do so are usually found to be smoking at follow-up *(25)*.

The way in which dropouts are handled can make it difficult to compare studies in this area. It is important to consider the reasons for dropping out to achieve accurate estimates of adherence. Those who drop out for reasons related to the treatment need to be distinguished from those who dropped out for reasons related to the study itself. Some patients drop out because they experience adverse events or withdrawal symptoms. As with studies in other therapeutic areas, these patients should be classified as non-adherent. Another important reason for dropout is the failure to stop or reduce smoking despite following the treatment. Many relapsed smokers stop using the prescribed NRT *(37)* when they fail to quit smoking despite having been adherent to NRT *(21,36)*. We consider that these patients should be counted as treatment failures for the purpose of calculating smoking cessation rates, but not for adherence rates. Side-effects were the main reason given for dropout in the studies reviewed *(1,9,11–13,16–18,22,35–40)*. Other patient-related reasons for stopping therapy were failure to recall the receipt of a prescription *(20)*, unwillingness to continue in the study *(1,9,10,13–17)* lack of a self-perceived need for treatment and lack of a perceived effect of treatment *(1,9,13,16,36–40)*. Physicians reported discontinuation of therapy due to lack of efficacy or complete failure to stop or to reduce smoking after therapy had been started *(1,3,8–10,17,18,21,22,24,29,36–38,41–43)* and elevated carbon monoxide *(17)*.

4. Epidemiology of adherence

The prevalence of adherence to smoking cessation therapy varied widely between studies (5–96%) and also varied between countries as shown in Table 8.

Table 8 Rates of adherence to smoking cessation therapy reported by country

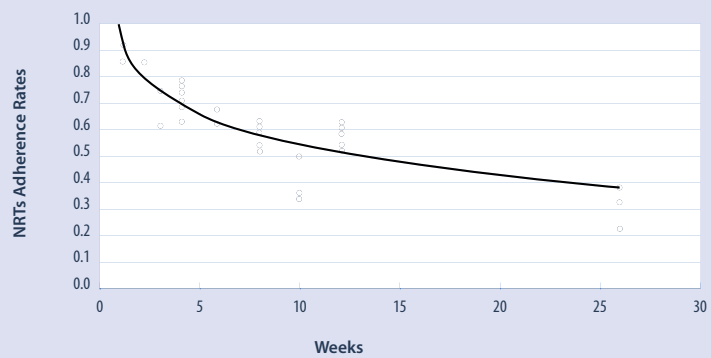
Country	No. of v alues reported	Mean	Standard deviation	Minimum	Maximum
Australia	8	0.57	0.25	0.19	0.83
Denmark	23	0.59	0.14	0.33	0.86
Italy	1	0.34	.	0.34	0.34
New Zealand	4	0.86	0.16	0.63	0.96
Switzerland	2	0.53	0.10	0.46	0.60
United Kingdom	11	0.62	0.17	0.40	0.91
United States	31	0.52	0.23	0.05	0.96

This variation can be explained by the use of different interventions, adjunctive support and populations studied.

Figure 4 includes only studies that reported time-series data. It suggests that adherence to smoking cessation therapies is a logarithmic function of number of weeks. The suggested trend line shows a rapid decrease in adherence rates during the first 6 weeks and a very slow decrease after 24 weeks. (Adherence rates after week 20 are related to adherence to follow-up visits rather than therapy.)

Many studies have found a positive linear correlation between adherence and cessation rates *(3,7,12,14,15,20,24,25,31–33,36,37,39,44)*. Both adherence and smoking cessation rates increased significantly when NRT was combined with antidepressant pharmacotherapy *(3)*.

Figure 1 Adherence rates over time



NRT, nicotine replacement therapy

5. Factors affecting adherence

Some baseline variables apparently influence adherence to therapy. In one study, mean daily cigarette consumption, expired carbon monoxide, plasma nicotine and cotinine, and Fagerstrom Tolerance Questionnaire (FTQ) *(44)* scores were significantly higher in the dropout group than in the adherent group *(1)*. Alterman et al. *(25)* concluded that greater dependence on tobacco was associated with less patch use, indicating that patients who smoked more cigarettes were less adherent to treatment with patches.

Depression is an important psychological factor associated with cessation of smoking. A higher prevalence of depressive symptoms would theoretically increase the risk of nonadherence to treatment *(45)*. Differing results of studies of this association have been reported. Some studies showed that smokers with a history of major depression who were not depressed at the time of a 4-week treatment programme had a lower abstinence rate than did smokers without a history of depression. In another study, smokers with a history of major depression in an 8-week multicomponent cognitive behavioural group plus nicotine-gum programme, had a significantly higher abstinence rate than smokers with a history of depression who were treated with nicotine plus a standard programme of information *(3,45)*. Ginsberg et al. suggested that cognitive–behavioural sessions emphasizing group cohesion and social support among smokers with a history of depression maintains adherence in this population *(45)*. A satisfactory explanation of this link will require further research *(3,24,31)*.

Other variables, such as gender, racial or ethnic background, history of psychiatric pathology *(25)*, weight gain *(29,30)*, craving and withdrawal symptoms are reported as being potential predictors of patch adherence. However, because there are no validated measures of these variables, the available data are insufficient to assess their effects on adherence.

During an NRT programme, investigators observed some factors that had a positive effect on adherence. These included motivation *(25)*, attendance at cessation classes, access to free NRT, higher education levels, older age, advice from physicians *(26)*, and more frequent contact with physicians and pharmacists *(35)*. These factors were also reported as predictive of success in stopping smoking. The analysis of the studies showed that these factors have proven to be statistically significant in increasing abstinence rates, but there is no measure proving their association with adherence.

6. Interventions for improving adherence

The most frequently employed interventions for improving adherence reviewed were NRT, antidepressant therapy, pharmacist intervention, psychosocial/behavioural support and counselling, and diet counselling (low-calorie diet). Adjunctive psychosocial treatment or behavioural advice has been successfully used to support smoking cessation programmes *(25)*.

Although Alterman et al. showed that patients receiving more intense adjunctive psychosocial or medical treatment were more adherent to treatment with patches *(25)*, overall, the data reviewed suggested that minimal behavioural support also results in similar or higher adherence rates, at least for some types of smoker. Minimal behavioural support might offer a cost-effective way to implement first-line smoking cessation programmes at a population level. More controlled studies including cost-effectiveness analysis are needed to clarify this issue.

The monitoring of therapeutic drug levels, NRT and/or antidepressant may also be useful. This feedback might be used to identify poorly adherent patients for whom more intensive adherence-enhancing interventions would be helpful *(46)*.

Intensive anti-smoking campaigns, such as the "Truth Denormalization Ads" might be extremely useful, especially among teenagers, as they change the social attitude towards tobacco smoking.

Table 9 Factors affecting adherence to smoking cessation therapy and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Tobacco smoking	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) High treatment cost *(41)* (+) Higher education levels, older age *(41)*	Social assistance *(25)*
Health care team/health system-related factors	(–) Unavailability for follow up or lost to follow up (1,8,10,11,17,21); failure to recall the receipt of a prescription *(20)* (+) Access to free nicotine-replacement therapy; more frequent contact with physicians and pharmacists *(35)*	Pharmacist mobilization (41); access to free NRT; frequent follow-up interviews *(35)*
Condition-related factors	(–) Daily cigarette consumption; expired CO, plasma nicotine and cotinine levels; Fagerstrom Tolerance Questionnaire (FTQ) scores *(44)*; greater tobacco dependence *(25)*; psychiatric co-morbidities; depression *(3,25)*; failure to stop or reduce smoking during treatment *(1,3,8–10,17,18,21,21,22,24,29,36,36,37,37,38,41–43)*	Education on use of medications; supportive psychiatric consultation *(3,25)*
Therapy-related factors	(+) Attendance at behavioural intervention sessions *(26)*; adverse events *(1,9,16,37–40)* or withdrawal symptoms *(1,9,11,12,12,13,16–18,22,35–40)*	NRT; antidepressant therapy; education on use of medications; adherence education; assistance with weight reduction *(29)*; continuous monitoring and re-assessment of treatment; monitoring adherence *(46)*
Patient-related factors	(–) Weight gain *(29)* (+) Motivation *(25)*; good relationship between patient and physician *(41)*	Adjunctive psychosocial treatment; behavioural intervention *(1,9,10,10–13,16–19,21–23,25,29,29,30, 32,38,39,47–52)*; assistance with weight reduction *(29)*; good patient–physician relationship *(41)*

CO, Carbon monoxide; NRT, nicotine replacement therapy; (+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence

7. Cost, effectiveness and cost-effectiveness of adherence

There are few data available concerning the health economics of adherence to smoking cessation therapy. Westman et al. *(7)* reported that 4 weeks of high-dose and 2 weeks of low-dose nicotine treatment were cost-effective and sufficient to enhance cessation. This 6-week intervention achieved 6-month abstinence rates comparable with those of studies offering 12 or more weeks of treatment.

There is some debate as to whether it is necessary to have health professionals available in the clinic providing supportive counselling *(7,53,54)*. However, the literature search suggested that providing minimal or moderate support resulted in higher adherence rates than providing no support. A separate discussion is required to decide which of the professionals in the health care team should be responsible for the provision of this support.

8. Conclusions

Adherence to NRTs and to other treatments for tobacco dependence is very low in the long-run (<40%), but it shows a strong positive correlation with better cessation outcomes. Unfortunately, these long-term cessation outcomes are still unsatisfactorily low (<20%). The data presented in this chapter are based mainly on clinical trials and three population-based studies. Therefore the data on adherence and cessation rates presented here might be over-optimistic.

In order to improve the accuracy and comparability of measured adherence rates, further research is needed to establish explicit definitions of "adherence to treatment" and treatment dropout. A clearer understanding and distinction between the different factors that influence dropout is also needed.

The patterns of both adherence to therapy and cessation rates over time suggest that interventions for improving adherence would be more cost-effective the earlier they are introduced into the programme (i.e. during the first 3 weeks).

Surprisingly, lack of access to cheap NRTs has been reported as an important reason for smokers in developed countries failing to quit. This is unexpected because the cost of NRTs is usually equivalent to the cost of smoking. Substituting the demand at the same price should not be a reason not to adhere.

There are few data available for identifying effective adherence-promoting interventions, but the use of antidepressant drugs and psychosocial behavioural supports has shown good results. Studies to evaluate the cost-effectiveness of interventions for improving adherence are required.

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CHAPTER XV

Tuberculosis

The World Health Organization (WHO) declared tuberculosis (TB) a global public health emergency in 1993 and since then has intensified its efforts to control the disease worldwide *(1)*. Despite these efforts, there were an estimated 8.7 million new cases of TB worldwide during 2000 *(2)*. The rapidly increasing rates of HIV infection, combined with escalating poverty and the collapse of public health services in many settings have contributed to this serious situation *(3)*.

The therapeutic regimens recommended by WHO have been shown to be highly effective for both preventing and treating TB *(4)*, but poor adherence to anti-tuberculosis medication is a major barrier to its global control *(2,5,6)*. Tuberculosis is a communicable disease, thus poor adherence to a prescribed treatment increases the risks of morbidity, mortality and drug resistance at both the individual and community levels.

The purpose of this chapter is to describe the current insights into patients' treatment behaviour and the methods adopted by health providers to enhance adherence to anti-tuberculosis treatment. This has been done with the aim of contributing to the generation of knowledge leading to the production of guidelines for enhancing adherence to prescribed medication in patients receiving long-term care.

1. Definition of adherence

In terms of TB control, adherence to treatment may be defined as the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment.[7]

Adherence may be measured using either process-oriented or outcome-oriented definitions. Outcome-oriented definitions use the end-result of treatment, e.g. cure rate, as an indicator of success. Process-orientated indicators make use of intermediate variables such as appointment-keeping or pill counts to measure adherence *(7)*. The extent to which these intermediate outcomes correlate with the actual quantities of prescribed drugs taken is unknown *(8)*.

The point that separates "adherence" from "nonadherence" would be defined as that in the natural history of the disease making the desired therapeutic outcome likely (adherence) or unlikely (nonadherence) to be achieved. There is as yet no empirical rationale for a definition of nonadherence in the management of TB. Therefore, the definition of adherence to TB treatment needs to be translated into an empirical method of monitoring both the quantity and timing of the medication taken by the patient *(9)*. At the individual level this is desirable, but at the population level a more pragmatic approach is needed. Thus, the success of treatment, that is, the sum of the patients who are cured and those who have completed treatment under the directly observed therapy, short course (DOTS) strategy, is a pragmatic, albeit a proxy, indicator of treatment adherence.

2. Factors that influence adherence to treatment

Many factors have been associated with adherence to TB treatment including patient characteristics, the relationship between health care provider and patient, the treatment regimen and the health care setting *(10)*. One author has defined non-adherence as "an unavoidable by-product of collisions between the clinical world and the other competing worlds of work, play, friendships and family life" *(11)*. Factors that are barriers to adherence to TB drugs can be classified as shown below.

A. Economic and structural factors

TB usually affects people who are hard to reach such as the homeless, the unemployed and the poor. Lack of effective social support networks and unstable living circumstances are additional factors that create an unfavourable environment for ensuring adherence to treatment *(12)*.

B. Patient-related factors

Ethnicity, gender and age have been linked to adherence in various settings *(13–15)*. Knowledge about TB and a belief in the efficacy of the medication will influence whether or not a patient chooses to complete the treatment *(16)*. In addition, cultural belief systems may support the use of traditional healers in conflict with allopathic medicine *(10,17)*. In some TB patients, altered mental states caused by substance abuse, depression and psychological stress may also play a role in their adherence behaviour.

C. Regimen complexity

The number of tablets that need to be taken, as well as their toxicity and other side-effects associated with their use may act as a deterrent to continuing treatment *(18)*. The standard WHO regimen for the treatment of TB involves using four drugs for an initial "intensive phase" (2–3 months), and two or three drugs for a further "continuation" phase (6–8 months). Drugs may be taken daily or "intermittently" three times a week.

D. Supportive relationships between the health provider and the patient

Patient satisfaction with the "significant" provider of health care is considered to be an important determinant of adherence *(19)*, but empathic relationships are difficult to forge in situations where health providers are untrained, overworked, inadequately supervised or unsupported in their tasks, as commonly occurs in countries with a high TB burden *(20)*.

E. Pattern of health care delivery

The organization of clinical services, including availability of expertise, links with patient support systems and flexibility in the hours of operation, also affects adherence to treatment. Many of the ambulatory health care settings responsible for the control of TB are organized to provide care for patients with acute illnesses, and staff may therefore lack the skills required to develop long-term management plans with patients. Consequently, the patient's role in self-management is not facilitated and follow-up is sporadic.

3. Prediction of adherence

If the individuals at risk for poor adherence could be identified early in their management, health care providers should, in theory, be able to intervene by tailoring the provision of treatment to enable such patients to continue their therapy. Unfortunately, the available evidence indicates that health care providers are unable to predict accurately which patients are likely to be nonadherent *(21–23)*.

The literature describes over 200 variables associated with patients who default on treatment. Many of the cited determinants of adherence are unalterable, and the demonstration of a consistent association between characteristics such as gender, age group or literacy and adherence does not lead to a logical approach on how to remedy the situation. Furthermore, demographic, social and other patient characteristics often relate poorly to the patient's intention or motivation and do not explain why some TB patients adhere to treatment despite having several unfavourable characteristics. Patients with TB apparently fluctuate in the intensity of their motivation to complete their treatment and admit to considering defaulting many times during their long course of therapy *(24)*.

Many epidemiological studies have explored correlates of adherence, often examining the issue from a biomedical perspective. Within this framework the TB patient has sometimes been seen as a recipient of a treatment regimen, who should obey the instructions of the health care worker. Nonadherent patients who do not conform to these expectations have sometimes been regarded as "deviant". This approach ignores the fact that treatment behaviour is complex and is influenced by a host of factors including the patients' sociocultural setting, health beliefs and subjective experience of the illness.

Numerous psychosocial constructs have been proposed that have attempted to provide a conceptual model for thinking about health behaviour (24–28). The information–motivation–behavioural (IMB) skills model (29) which integrates information, motivation and behavioural skills in explaining behaviour has, however, attracted some attention as a potentially useful guide to developing interventions for enhancing adherence to TB treatment. The IMB model demonstrates that information is a prerequisite for good adherence, but is not sufficient in itself to change behaviour. Motivation and the development of behavioural skills are also critical determinants of behavioural change.

4. Strategies to improve adherence to treatment

Concurrently with the efforts to improve our understanding of factors affecting adherence to TB treatment, numerous measures have been introduced in different settings in an attempt to improve it *(30,31)*.

A. Classification of interventions

The interventions for improving adherence rates may be classified into the following categories:

– Staff motivation and supervision – includes training and management processes aimed at improving the way in which providers care for patients with tuberculosis.

– Defaulter action – the action to be taken when a patient fails to keep a pre-arranged appointment.

– Prompts – routine reminders for patients to keep pre-arranged appointments.

– Health education – provision of information about tuberculosis and the need to attend for treatment.

– Incentives and reimbursements – money or cash in kind to reimburse the

expenses of attending the treatment centre, or to improve the attractiveness of visiting the treatment centre.

– Contracts – agreements (written or verbal) to return for an appointment or course of treatment.

– Peer assistance – people from the same social group helping someone with tuberculosis to return to the health centre by prompting or accompanying him or her.

– Directly observed therapy (DOT) – an identified, trained and supervised agent (health worker, community volunteer or family member) directly monitors patients swallowing their anti-TB drugs (see below).

B. Directly observed treatment as a component of the WHO DOTS strategy

The concept of "entirely supervised administration of medicines", first developed by Wallace Fox in the 1950s *(32)*, is now known as directly observed therapy (DOT). DOT was first adopted in TB drug trials in Madras (India) and Hong Kong as early as the 1960s *(33)* and is now widely recommended for the control of TB *(34–36)*. WHO recommends DOT as one of a range of measures to promote adherence to TB treatment *(37)*.

DOT has always meant much more than "supervised swallowing". Different projects in countries with a high prevalence of TB have shown that removing the socioeconomic barriers to DOT faced by patients increases adherence and cure rates *(38,39)*. In a country where the prevalence of TB is low, such as the USA, DOT programmes are complex and have several components including social support, housing, food tokens and legal measures and are highly cost-effective *(35,40)*.

Since 1991, WHO has promoted the strategy of "directly observed therapy, short course" (now known as the DOTS strategy) *(32)*. "DOTS" is the brand name for a comprehensive technical and management strategy consisting of the following five elements:

– political commitment;

– case detection using sputum microscopy among persons seeking care for prolonged cough;

– standardized short courses of chemotherapy *under proper case-management conditions including DOT;*

– regular drug supply; and

– a standardized recording and reporting system that allows assessment of individual patients as well as of overall programme performance *(41)*.

Table 10 Factors affecting adherence to treatment for tuberculosis and interventions for improving it, listed by the five dimensions and the interventions used to improve adherence

Tuberculosis	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) Lack of effective social support networks and unstable living circumstances *(12)*; culture and lay beliefs about illness and treatment *(10,17)*; ethnicity, gender and age *(13)*; high cost of medication; high cost of transport; criminal justice involvement; involvement in drug dealing	Assessment of social needs, social support, housing, food tokens and legal measures (35,40,41); providing transport to treatment setting; peer assistance; mobilization of community-based organizations; optimizing the cooperation between services
Health care team/health system-related factors	Health care team/health system-related factors (–) Poorly developed health services; inadequate relationship between health care provider and patient; health care providers who are untrained, overworked, inadequately supervised or unsupported in their tasks *(20)*; inability to predict potentially non-adherent patients *(21)* (+) Good relationship between patient and physician *(19)*; availability of expertise; links with patient support systems; flexibility in the hours of operation	Uninterrupted ready availability of information; flexibility in available treatment; training and management processes that aim to improve the way providers care for patients with tuberculosis; management of disease and treatment in conjunction with the patients; multidisciplinary care; intensive staff supervision *(42)*; training in adherence monitoring; DOTS strategy *(32)*
Condition-related factors	(–) Asymptomatic patients; drug use; altered mental states caused by substance abuse; depression and psychological stress (+) Knowledge about TB *(16)*	Education on use of medications *(43)*; provision of information about tuberculosis and the need to attend for treatment
Therapy-related factors	(–) Complex treatment regimen; adverse effects of treatment; toxicity *(18)*	Education on use ofmedications; adherence education; tailor treatment to needs of patients at risk of nonadherence; agreements (written or verbal) to return for an appointment or course of treatment; continuous monitoring and re-assessment of treatment
Patient-related factors	(–) Forgetfulness; drug abuse, depression; psychological stress (+) Belief in the efficacy of treatment *(16)*; motivation *(24)*	Therapeutic relationship; mutual goal-setting; memory aids and reminders; incentives and/or reinforcements *(44,45)*; reminder letters *(46)*, telephone reminders *(47)* or home visits *(48)* for patients who default on clinic attendance

a) DOT, directly observed therapy; TB, tuberculosis; (+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence

C. Evidence for the effectiveness of interventions aimed at improving adherence

Unfortunately, there is a lack of rigorous experimental research on the effects of interventions to promote adherence to TB treatment. Quantitative research asks questions about efficacy and effectiveness. The choice of an appropriate experimental design methodology (whether individual or community randomization) depends on the nature of the intervention under evaluation. Quantitative research should be complemented by in-depth qualitative research to answer questions about why an intervention had an effect in a particular setting.

The extent to which DOT alone and various individual social support measures contribute to adherence is unknown. On the one hand, randomized controlled trials have shown no difference in adherence between TB patients randomly allocated to DOT alone or to self-administered treatment. Two recently published systematic reviews reported 16 randomized trials, of which only half were in countries with a high disease burden *(8,49)*. These reviews showed that DOT alone ("supervised swallowing") did not always promote adherence, and therefore the results do not support the use of this intervention in isolation from the other factors affecting adherence (e.g. good quality of communication between patient and health providers, transport costs and lay health beliefs about TB).

On the other hand, programmatic studies of the effectiveness of the DOTS strategy have shown high rates of treatment success *(2,50–52)*. In practice, the trial design necessary to properly evaluate the contribution of DOT alone to the effectiveness of the overall DOTS strategy requires assessment of the social aspects of patient support that surround DOT (as "supervised swallowing"). The outcomes of programmatic evaluations of the effectiveness of implementation of the DOTS strategy better reflect the social, behavioural and economic factors related to the patient, the health care services and characteristics of treatment.

Many other interventions have been found to significantly improve adherence. One study found that reminder letters sent to patients who failed to attend clinic, appeared to be of benefit even when patients were illiterate *(46)*. Another study reported that home visits by a health worker, though more labour-intensive, may be more effective than reminder letters for ensuring that defaulters complete their treatment *(48)*. Yet another study showed that prospective telephone reminders are useful for helping people to keep scheduled appointments *(47)*. Such studies are often location-specific and therefore often produce results that cannot be generalized. For example, studies demonstrating the benefit of telephone and mail reminders are of little relevance in many of the countries with a high prevalence of TB because most patients do not have telephones or mail boxes.

While one trial found that assistance by a lay health worker increased adherence to a first appointment *(44)*, a subsequent study showed no impact on completion of preventive therapy at 6 months *(53)*. Studies in the USA have suggested that monetary incentives are an effective method for improving adherence. Appointment-keeping was significantly improved in homeless men *(44)* and in drug users *(45)* by offering US $5 in payment for returning to a clinic for TB evaluation, but the results of a study of offering monetary incentives to people recently discharged from prison were inconclusive, partly due to its small size *(54)*.

The evidence for an independent effect of health education on adherence of patients to treatment is weak. One trial did suggest some benefit *(55)* but the design of this study was flawed because individuals receiving health education were contacted or seen every 3 months, whereas those in the control group were seen only at the end of the study period. The relative contributions of health education and increased attention in this study are therefore hard to separate. A trial to examine the impact of intensive education and counselling on patients with active TB did, however, find a trend towards increased treatment completion rates for the patients who received intensive education and counselling compared with those who received routine care *(43)*. The study by Morisky and colleagues *(56)*, lent no support to the authors' claims for the benefit of health education as the results were confounded by the effects of a monetary incentive used in tandem with the educational intervention. In a more recent trial that has helped to disaggregate these effects *(45)* health education alone was found to be no better than routine case management for improving appointment-keeping and the impact of education combined with a monetary incentive was indistinguishable from that of the monetary incentive alone.

Finally, an intervention directed at clinic staff rather than patients was studied. Patients attending clinics in which staff were closely supervised were more likely to complete treatment than those attending clinics with only routine supervision of staff *(42)*.

5. Questions for future research

Useful research into human behaviour should take into account a wide range of approaches to enquiry, including qualitative and quantitative research methods. A review of the current literature on adherence to TB treatment has revealed a variety of research objectives, ranging from social and anthropological to clinical and programmatic studies. Further studies should be designed with the following aims.

– Define the theoretical models that underlie interventions to promote adherence to TB therapy.

– Describe the extent of various patterns of adherence (patients who take their medication sporadically, regularly take less than prescribed, and those who discontinue it completely).

– Explore the "active ingredients" of effective alliances between health providers and patients in a variety of sociocultural settings.

– Identify time-points in the case management at which different types of adherence strategy may have increased impact.

– Determine the efficacy and cost-effectiveness of specific interventions to improve adherence, as part of a complex health intervention necessary to achieve a high rate of treatment success.

– Priority should be given to studies in middle- and low-income countries to ensure the relevance of interventions to the settings in which most of the TB caseload occurs.

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