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The impact of medication regimen factors on adherence to chronic treatment: a review of literature

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Abstract This article reviews recent literature in chronic illness or long-term health management including asthma, contraception, diabetes, HIV disease, and hypertension/cardiovascular disease, mental disorders, pain, and other diseases to determine the relationship between regimen factors and adherence to medications. The authors conducted an electronic literature search to detect articles published between 1998 and 2007. Articles were included if they pertained to a chronic illness or to contraception, included a clear definition of how adherence was measured, and included regimen factors as primary or secondary explanatory variables. Methodology of the studies varied greatly, as did methods of measuring adherence and regimen factors. Surprisingly few of these articles concerned (1) chronic treatment, (2) regimen factors such as dosing, pill burden, and regimen complexity, and (3) adherence measured in a clear manner. Most studies failed to use state-of-the-art methods of measuring adherence. Despite these flaws, a suggestive pattern of the importance of regimen factors, specifically dose frequency and regimen complexity, emerged from this review.

Keywords Medication compliance · Adherence · Chronic illness · HIV/AIDS

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Introduction

For more than three decades, researchers and physicians have sought to understand and improve patient adherence to medication regimens for the treatment of chronic illness, including maintenance of prophylactic or health management regimens. Adherence, usually defined as the extent to which the patient's medication-taking matches the prescribed regimen, has evolved from a clinical afterthought to a dependent measure in controlled clinical trials. Furthermore, adherence has become a target of intervention. The impact of non-adherence varies across chronic illnesses, and ranges from minimal to very significant. Increased morbidity and mortality have been observed among those non-adherent to antihypertensive, glycemic control, and antiretroviral regimens. Poor adherence to one form of long-term health management, contraception, typically results in undesired pregnancy (Pinter 2002). A recent World Health Organization report states that because the magnitude of non-adherence and the scope of its sequelae are so alarming, more health benefits worldwide would result from improving adherence to existing treatments than by developing new medical treatments (WHO 2003).

Researchers have identified several classes of correlates of adherence to long-term medication regimens, including *patient factors* such as depression, health literacy, or substance use disorders, *environmental or contextual factors* such as social support and socioeconomic status, and *clinician factors* such as clear communication and time spent explaining the disease and the treatment, and *patient–clinician relationship factors* such as trust. In addition, researchers have identified *disease factor*s such as chronicity, symptom prominence, and response to treatment, *health care delivery factors* such as the wait for appointments or medications, convenience of the pharmacy and

clinic, and *treatment regimen factors* such as pill burden, regimen complexity, side effects, duration of needed treatment, and dosing schedule (Ickovics and Meisler 1997). More recently, *environmental factors* such as weather, social support, poverty, migration, and homelessness have been considered as factors affecting adherence (Balint and O'Donnell 2007; Gerald et al. 2007; Mai and Eng 2007; Misra and Ganda 2007; O'Shea et al. 2007). The WHO report found that the main barriers to adherence related to regimen factors were dose frequency and side effects, and emphasized the need for the health system to develop less frequent dosing and to mitigate side effects (WHO 2003).

A significant volume of research on correlates of adherence, including dosing, has accumulated. Many reviews and clinical articles have included suggestions to reduce the complexity of the regimen, usually by decreasing the number of doses per day (Haynes et al. 2002; McDonald et al. 2002), while others have concluded that there is no systematic difference between the effects of changing doses and other behavioral interventions (Peterson et al. 2003). There are two published reviews on the impact of dosing schedules on adherence in chronic illness (Claxton et al. 2001; Richter et al. 2003). Claxton and colleagues reviewed literature that measured adherence via electronic monitoring to determine whether adherence measured using this "gold standard" varied by daily dosing. They reviewed 76 studies with an aggregated compliance rate of 71%, ranging from 34% to 97% across illnesses. Adherence was significantly higher among patients taking medications with a once-daily dosing schedule compared to thrice or more frequent dosing. They found no difference between once- and twice-daily dosing schedules, nor between twice and thrice-daily dosing schedules. They concluded that simpler, less frequent dosing regimens led to improved adherence with a variety of medications.

Similarly, Richter et al. (2003) found that reductions in daily doses were related to improvements in adherence, with single doses preferable to multiple doses. They also found that twice-daily dosing had an advantage over more frequent dosing in adherence outcomes. They generated a table of characteristics of drugs, disease state, and patient characteristics that make medications good candidates for once-daily dosing. They concluded that drugs with a long duration of action and without increased side effects due to daily dosing are good candidates for a daily dosing schedule based on these *drug characteristics*. They concluded that when symptom control was the target of medications, when non-adherence posed a threat due to disease progression or development of drug resistance, or when multiple tablets or doses are typically required per day, that the *disease state characteristics* merited once-daily dosing formulations. Lastly, they posited that patient groups with multiple chronic illnesses or those with cognitive or physical limitations would benefit greatly from once-daily dosing, based on these *patient characteristics*.

Previous reviews of regimen factors and adherence were imprecise due to methodological limitations in the measurement of adherence. During the last ten years, electronic monitoring of adherence became a near gold-standard in some illnesses, leading to a need for an updated understanding of adherence under conditions of improved measurement. Additionally, regimens for many illnesses have changed considerably. The increasing availability of new formulations of medications, including extended-release and modified-release products, and formulations requiring only weekly or monthly dosing, may lead to simplification of regimens. Because patients often misunderstand regimen instructions (Hanchak et al. 1996), it is possible that medications formulated to reduce or simplify dosing may result in increased adherence. Lastly, while studies of adherence were in vogue 30 years ago, there has been a resurgence of interest in adherence during the last decade due to the emergence of HIV/AIDS as a prevalent chronic illness, and due to the recognition that the treatment of chronic illnesses consumes most of the medical care resources of the developed world. Given these developments, we believe an updated review of the newest literature about adherence in major chronic illnesses is warranted. The purpose of this article is to conduct an updated systematic review of recent literature in chronic illness or long-term health management including asthma, contraception, diabetes, HIV disease, and hypertension/cardiovascular disease, mental disorders, pain, and other diseases to determine the relationship between regimen factors and adherence to medications.

Methods

We conducted an electronic literature search using the *PubMed, Medline*, and *PsycInfo* databases to detect articles published during the 9-year period between 1998 and 2007 using primary keywords "medication adherence and regimen factors," "medication compliance and regimen factors", and ancillary search terms including "pill burden," "dosing," and "regimen complexity." In addition, the search included the terms medication adherence/compliance, dosing, regimen, and pill burden with the name of each condition requiring chronic treatment. Articles were included if they pertained to a chronic illness or to contraception, included a clear definition of how adherence was measured, and included regimen factors as primary or secondary explanatory variables. Using this process, we selected 1,361 articles for abstract review; only 325 merited further review. Additional articles were gleaned from

the reference lists of the 325 reviewed articles. We selected a final set of 61 articles that met the inclusion criteria. Most articles we rejected discussed the likely adherence and regimen relationship, but failed to include explicit measurement of adherence. Others addressed a disease or issue not requiring chronic medication treatment. Despite the vast literature on medication adherence in general, surprisingly few articles directly address both adherence and specific regimen factors in chronic treatment.

Methodology of the studies varied greatly, ranging from observational reports of convenience samples to stringently sampled patients who completed validated adherence measurement specifically for the study. Methods of measuring adherence and regimen factors also varied greatly, including self report, physician and nurse report, collateral report, medical records review, pharmacy claims data review, psychosocial measurement of adherence using validated measures, pill counts, appointment returns, pharmacy refills, and electronic monitoring of pill cap openings. Many regimen factors such as definitions of dosing (e.g., once-daily, twice daily, three times daily, four times daily) were relatively standard. We review findings on the relationship of adherence to regimen factors for each condition requiring chronic treatment.

Results

Asthma and pulmonary disease

Only four studies focused explicitly on the relationship between regimen factors (dosing) and adherence in the area of asthma and pulmonary disease. In a dose-ranging study of asthmatic patients, there was no compliance advantage to once-daily fluticasone propionate by discus compared to twice-daily dosage, but there was an efficacy disadvantage to the once-daily dosing regimen, leading the authors to recommend against the once-daily regimen (Purucker et al. 2003). In a study to compare adherence rates of oral versus inhaled medications for asthma, Kelloway et al. (1994) found no compliance differences between twice per day regimens versus thrice or more per day regimens for either prescribed theophylline or two inhaled anti-inflammatories. Mann et al. (1992) compared adherence to twice-daily versus four-times-daily dosing of flunisolide inhalers for 16 adult asthmatics. Patients were instructed to take two puffs per dose, and the most common behavior among the four-times-daily group was to take six puffs each dose, essentially tripling the recommended dose. They concluded that compliance was better for the twice-daily dosing regimen. Dolce et al. (1991) characterized medication regimens for chronic obstructive pulmonary disease and found that greater complexity of regimens, often including both dosing and time-dependent inhaled medications, was related to poorer adherence, based on patient reports of stopping or forgetting medications, overusing some inhaled medications, or using inhaled medications with improper technique. However, this early study did not use standardized adherence measurement nor provide tabular data for direct examination of the adherence–regimen relationship.

In summary, the adherence–regimen relationship has rarely been explicitly addressed in the asthma or pulmonary disease literature, with only one study (Mann et al. 1992) using a form of electronic monitoring of adherence. The few existing studies have found that the lowest dose does not always relate to better adherence and is not usually the recommended regimen. Existing studies have mixed results in terms of an adherence benefit to fewer daily doses, and there may be lower adherence with complex regimens requiring multiple types of medications.

Contraception

Contraception is the deliberate use of barrier, hormonal, or natural methods to reduce the risk of pregnancy for the sexually active woman. Although contraception does not signify a disease state, a discussion of contraceptive medications is included here due to the need for chronic "treatment" and excellent adherence to achieve pregnancy prevention.

The oral contraceptive pill was introduced in the 1960s, and choices for contraception have proliferated, especially during the last decade. Most newer products are longer-acting formulations of estrogen–progesterone products, delivered via a variety of vehicles. Researchers developed most of these methods to address the most common reason for non-adherence, simple forgetting. Newer methods tend to reduce doses to weekly or monthly or longer in the case of implanted devices.

The contraceptive patch offers a once-weekly alternative to daily contraceptive pills. This extended-release form of contraception is equivalent in efficacy and leads to superior adherence (Burkman 2002; Sicat 2003). Dittrich et al. (2002) found that three tested doses of the contraceptive patch had superior compliance compared to contraceptive pills in a randomized trial. In another study of the patch, the odds ratio of compliance with the patch versus pill was 2.1 (95% CI, 1.8–2.3) (Gallo et al. 2003). Similarly, a study of the contraceptive ring, which is used intra-vaginally for 21 days, found excellent adherence (86%) to this simplified regimen (Dieben et al. 2002).

The literature on contraception focuses primarily on efficacy, but effectiveness in the population is dependent on adherence. The growing literature on adherence in this area will bring needed attention to what factors determine

adherence. The few studies reviewed suggest that forms of contraceptive medications that reduce forgetting and user error show superior rates of adherence, and ultimately, better prevention of unwanted pregnancy. Unfortunately, no studies in this area used electronic monitoring to measure adherence.

Diabetes

In the area of diabetic care, researchers have sought to determine which dosing schedule yields the best adherence and glycemic control. Donnan et al. (2002) used a retrospective cohort design to explore adherence to oral hypoglycemic medication among adult type 2 diabetics. They found that regimen complexity including more frequent dosing was related to poorer adherence. Another study found that the frequency of insulin doses influenced compliance (Paes et al. 1997). The adherence rate for the patients taking a dose once-daily was 79%, while for the patients taking doses three times daily was only 38%. Dezii et al. (2002) evaluated adherence to prescribed therapy, comparing once-daily dosing and twice-daily dosing of glipizide in patients with type 2 diabetes. Adherence in both groups was suboptimal, but was higher in the once-daily dosing group (60.5%) than the twice-daily dosing group (52%). Because their rates of persistence with therapy also favored the once-daily group despite more pills required in the single dose, they concluded that dosing frequency exerts a greater impact on patient adherence and persistence than pills per dose. Kardas (2005) also evaluated once-daily and twice-daily dosing of sulfonylureas. Adult patients with type II diabetes in Poland previously treated with glibenclamide were randomized to gliclazide MR once-daily or glibenclamide twice daily. Adherence to these regimens was measured using MEMS® electronic monitoring caps in several ways. Overall compliance was better in gliclazide MR (93.5%) than glibenclamide (87.2%). Furthermore, 77.6% took ≥90% of doses versus 56.3% of glibenclamide group.

The number of missed doses was almost twice as high in the glibenclamide group (17.5% vs. 9.3%). Finally, diabetes control (as measured by HBA_{1c}) improved over time in the once-daily dosing group.

Grant et al. (2003) conducted an intervention to improve adherence to diabetic care. They used a pharmacist-delivered intervention including review of proper use of the patient's regimen of medications, identification of medication barriers, and medication discrepancy, with reports electronically forwarded to the patient's physician. Patient self-reports of medication adherence were very high, reflecting correct dosing on 6.9 of 7 days on average, so there was likely a ceiling effect that limited the ability to detect any improvements made due to the intervention. Among patients with medication discrepancies, however, the authors found that confusion about dosing (timing or frequency) was a predictor of non-adherence. Poor adherence may be related to misunderstanding of the regimen. Consistent with this idea were the findings of two additional studies that identified misunderstanding or poor comprehension of the prescribed regimen as confounders of adherence (Bedell et al. 2000; Hanchak et al. 1996).

In sum, the growing literature on the relationship of regimen factors to adherence in diabetes strongly suggests that fewer doses per day improves adherence. Only two studies in this area (Grant et al. 2003; Kardas 2005) used electronic monitoring to measure adherence, which is especially surprising given the availability of blood glucose meters to monitor long periods of blood glucose readings. Based on a few studies in the diabetes and adherence literature, it seems likely that one source of non-adherence is misunderstanding of regimens when multiple doses per day are required.

HIV and AIDS

In HIV/AIDS care, the urgency of addressing non-adherence stems from the recognition that even episodic non-adherence can lead to viral mutations and drug resistance. Nearly perfect adherence (95%) is required for this group of patients to achieve and sustain viral suppression, maintain immune health, and slow disease progression. The goal of therapy for HIV is undetectable viral load, which is strongly associated with good adherence. Achieving this goal with consistent high adherence for life is a daunting prospect, especially when considering the population. People with HIV/AIDS are increasingly female, people of color, and injection drug users and their partners, all disenfranchised groups with multiple sources of stigma and fewer health care options.

Most of the literature-addressing adherence in HIV disease, which has shown explosive growth, addresses patient factors that contribute to non-adherence. However, researchers are paying increased attention to regimen factors such as dosing. Stone et al. (2001) found that many patients misunderstood their medication regimens. Poor understanding correlated with increasing regimen complexity, including increased doses per day, and those with such misunderstandings were less adherent. Specifically, patients with three or more doses daily were more likely to have missed doses in the past 3 days, OR 1.4, 95% CI, .9–2.3. These findings echo those of Paterson et al. (2000), who found that 63% of individuals with twice-daily dosing achieved 95% electronically monitored adherence to dosing and timing compared with 45% with thrice-daily dosing, $P < .04$.

Golin et al. (2002) studied a mostly male county hospital sample using a prospective design. They found a significant and moderate bivariate correlation between dose frequency per day and adherence ($r = –0.25$, $P = 0.006$). In this study doses ranged from two to five per day, with a mean of 2.8. Molassiotis et al. (2003) identified 13 factors that explained half the variance in adherence in their sample of Hong Kong HIV patients, most of whom were taking triple drug combinations. In addition to psychosocial factors, twice per day dosing (versus once per day dosing) were the only regimen factor identified as a predictor of non-adherence. Eldred et al. (1998), in an early study of combination therapy adherence, found that dosing frequency was related to better adherence; patients on twice-daily regimens were more adherent than those on thrice-daily regimens (odds ratio = 1.44; 95% confidence interval 1.01–1.96). Wohl et al. (2003) reported in a study of directly observed therapy among prisoners that any regimen requiring more than one medication per day resulted in sub-optimal adherence that would not likely maintain viral suppression. Trotta et al. (2002) identified that achieving undetectable HIV viral load was strongly associated with fewer daily pills in a meta-analysis of 23 RCTs examining triple combination therapy for HIV. Multi-drug formulations with two the three antiretroviral medications in one tablet have resulted in improved adherence compared to their multiple pill, multiple dose predecessors (Eron et al. 2000; Katlama et al. 2001).

In the past several years, once-daily dosing of HIV medications has become possible. Few published studies have examined the role of once-daily regimens on adherence. However, in a study of individuals with undetectable viral load (<50) and good baseline adherence receiving one of several specified regimens of stavudine and lamivudine, Portsmouth and colleagues (2005) found that the adherence of patients on twice-daily regimens decreased over the study period compared to those individuals on once-daily dosing schedules. The baseline adherence of these patients was quite high in both groups, but MEMS® caps monitoring revealed a significance difference between the two groups on all adherence variables across time with those on twice-daily dosing dropping from 98.5% pill taking compliance at baseline to 97.7% at 24 weeks ($P < 0.03$) and correct dosing compliance dropping from 96.3% at baseline to 92.6% at 24 weeks, ($P < 0.01$). The evidence that fewer daily doses results in superior adherence to HIV regimens is strong and consistent.

Simpler daily dosing is not the only consideration for adherence among those taking antiretroviral therapy. Recent studies have identified regimen complexity, not just doses per day, as a critical determinant of HIV medication adherence (Fogarty et al. 2002). Flandre et al. (2002) studied the adherence and outcomes of patients enrolled in a trial of triple therapy contrasted to dual-medication treatment. They found that adherence was lower in patients staying on triple combination treatment compared to those on a two-drug regimen. Paterson et al. (2000) found that less complex regimens (fewer doses, with fewer food or storage restrictions) were associated with greater adherence. Witteveen and Van Ameijden (2002) conducted a qualitative study in which Amsterdam drug users with HIV discussed their barriers to optimal adherence. These patients raised significant concerns about complex regimens that did not fit into their routines; they reported great difficulty with thrice-daily regimens, reporting most often missing the middle dose.

In a study addressing another aspect of regimen complexity, McNabb et al. (2003) found that patients who missed a dose of one medication typically missed the time-linked dose of another medication, and concluded that the dosing schedule was related to electronically monitored adherence. Shoptaw et al. (2002) reported that HIV medication adherence among gay male methamphetamine users was related to the number of different medications in the regimen and the number of doses per day. Participants in a qualitative study identified several regimen complexity factors as contributing to non-adherence (Murphy et al. 2000). Twenty-one percent ($n = 8$) reported that adherence was hindered by having "too many pills to take," "being confused" about the number of pills to take and when, and "forgetting how many pills you already took." All of these factors, while reported by a minority, suggest that fewer pills and/or fewer doses might facilitate adherence by reducing regimen complexity. Wilson et al. (2001) found that there was greater within-patient variability in adherence (lower reliability coefficients) among patients taking four to five rather than one to three antiretroviral medications ($P < .05$). Another aspect of regimen complexity that may undermine adherence is the definition of a missed dose in the context of combination therapy. Patients and providers do not agree on what constitutes a missed dose in HIV care, and these misunderstandings can often lead to non-adherence (Sankar et al. 2007). Similarly, 11% of participants in the Murphy study reported they doubled up on a dose due to missing a dose, and 8% were "confused about the dose."

A few studies have found that specific demographic characteristics may interact with regimen factors to influence adherence. Ferguson et al. (2002) reported that there were racial differences in the impact of regimen factors on adherence. They found that Caucasian participants were more likely than African-Americans to report that the schedule of antiretroviral medications was inconvenient, and to state that they were taking too many medications. Halkitis et al. (2003) reported a study of treatment, access, and adherence among ethnically diverse men who have sex

with men, and found no relationship in this sample between the number of medications or the number of pills per day and adherence.

In general, the evidence that more complex regimens lead to lower rates of optimal adherence is strong, although this relationship may vary across sub-samples. Men who have sex with men and men of color may not demonstrate the same decrement in adherence when taking complex regimens, but confirmatory studies are necessary before these findings should influence clinical care.

There may be an interaction between cognitive impairment or depression and regimen complexity that hampers adherence in HIV disease. Hinkin et al. (2002) examined the impact of regimen complexity among HIV+ patients with and without cognitive impairment. They found that while adherence rates were low overall, the cognitively impaired group had significantly lower adherence than their non-impaired peers. Regimen complexity also demonstrated a main effect, and there was a significant interaction between cognitive impairment and regimen complexity. Patients with cognitive impairment and complex dosing schedules showed the poorest rates of adherence. These results suggest that for the subset of patients with mild to moderate cognitive dysfunction, simplified regimens with fewer doses will facilitate necessary adherence. This is highly pertinent because HIV disease can produce a dementia process in which perceptual motor speed and higher order processing is diminished. In contrast, Ammassari et al. (2003) found that depression, rather than neuropsychiatric impairment, accounted for increased odds of non-adherence. Although these findings seem contradictory, clinicians are aware that mild depression and mild neurocognitive impairment share many features, and that these features (memory difficulties, psychomotor slowing, motivational deficits) may affect adherence regardless of the neuropsychiatric source.

In summary, the large literature on the relationship of regimen factors and adherence in HIV disease is methodologically strong, and indicates that higher dose frequency and greater regimen complexity result in poorer adherence. Nearly all of the HIV medication adherence studies used either electronic monitoring of adherence, or direct observation of medication taking. There is an urgent need for medication combinations and formulations that reduce doses per day and regimen complexity for the treatment of HIV disease. Methods used to quantify adherence in HIV positive samples could be adapted for other chronic illnesses.

Hypertension and cardiovascular disease

In the area of hypertension and cardiovascular disease, researchers have examined a number of medications, primarily antihypertensive agents, for adherence correlates. Dunbar-Jacob et al. (2003) investigated medication adherence among patients with cardiovascular disease, focusing on SES and economic predictors of adherence. They found that most of the study participants were on once-daily or twice-daily regimens, and that adherence was inversely correlated with the number of doses per day, with increasing dosing related to poorer adherence. This finding repeats those reported in an earlier study by Eisen et al. (1990). They also found that adherence to once-daily antihypertensive medication was higher (84%) than to thrice-daily dosing (59%) among 105 hypertensive patients. Similarly, Lee et al. (1996) found that African American patients in the AASK cohort, being followed for hypertension and kidney disease, were more adherent to once per day than twice per day regimens measured by electronic monitoring (49% vs. 5% adherence, $P < .001$).

Chapman and colleagues (2005) evaluated the adherence of more than 8,000 adults receiving simultaneous antihypertensive (AH) and lipid-lowering (LL) treatment. They measured adherence as the maximum proportion of dates with medication available based in pharmacy refill data in each 3-month period following the initiation of therapy. Adherence was defined categorically, with patients with at least 80% of days potentially covered during the 3-month period categorized as adherent. Even with this generous definition of adherence, adherence rates were low, dropping from 45% at 3 months to 36% at 12 months after initiation of AH/LL combination therapy. Patients taking no other medications were almost twice as likely to be adherent as those taking six or more medications.

Yiannakopoulou et al. (2005) conducted an observational, cross-sectional study on 1,000 Greek hypertensive patients. They measured compliance by self-report based on several questions asked within 2 days of hospital admission (whether they take medications as prescribed). If patients acknowledged missing doses, their non-adherence was queried further with a structured interview with precoded answers, presumably by someone other than the physician, to determine the type of non-adherence and reasons for non-adherence. Compliance in this sample was positively related to several factors: urban dwelling, younger age (<60 years old), level of education, and having a private doctor outside of the hospital or public health care system. Furthermore, compliance was more common among those taking one tablet per day than those taking more than one tablet (37.8% vs. 8.2%, $P < .005$). In contrast, George and Shalansky (2007) found that a higher number of medications predicted good adherence in a study of 350 clinic patients with congestive heart failure. They reviewed refill adherence data in a prescription claims database, with non-adherence defined as <90% mean refill

adherence. They found that the use of medications twice or less daily predicted non-adherence. The authors suggest that, in this population, taking more medications may require a higher level of attention to routine and therefore improve adherence. Patients with congestive heart failure have highly structured routines and restrictions on activity, diet, and medication, and more medications may indicate more severe illness and relate to more attention to adherence.

Iskedjian and his colleagues conducted a meta-analysis of dose frequency and adherence to anti-hypertensive medications. They included eight studies with over 11,000 subjects, the majority of whom had BID (n = 4,405) or TID (n = 4,147) dosing, with the remainder having once-daily dosing (n = 1,830) (Iskedjian et al. 2002). They found that the mean adherence of those with once-daily dosing, 91.4%, exceeded adherence among those with multiple daily doses (83.2%); $Z = 4.46$, $P < .001$. However, there was no advantage found for BID dosing versus dosing schedules of three or more times per day. In this area, there is clear evidence that once-daily dosing results in superior adherence compared to multiple daily dosing, but it is less clear whether there is a decrement in adherence for each additional dose per day. Moreover, based on the existing research, the number of concurrent medications may contribute to adherence or non-adherence. Three of the seven included studies in this area (Dunbar-Jacob et al. 2003; Eisen et al. 1990; Lee et al. 1996) used electronic monitoring to measure adherence.

Mental disorders

Most research on medications for mental disorders has not addressed adherence in a systematic way. Rather, studies have observed adverse events and tolerability of extended-release and controlled-release medications in comparison to their immediate-release forms. In the area of depression, extended-release and immediate release forms of fluoxetine, venlafaxine and paroxetine have been compared, and some studies have included assessments of patient adherence. Generally, extended-release forms of these medications are similar in safety and efficacy, with mixed results on side effects. While venlafaxine has no tolerability advantage according to its package insert, the controlled-release form of paroxetine has lower rates of nausea than the immediate-release form (Golden et al. 2002). Burke and McArthur-Miller (2001) demonstrated that weekly dosing of fluoxetine was comparable to daily dosing for the continuation of treatment of depression. Masand (2003) suggests that the lower rate of unpleasant side effects of new antidepressant extended-release and long-acting products may result in increased adherence, but this has not been formally measured.

Poor adherence has long plagued the treatment of psychotic disorders, and medications available in a depot, long-acting form, or in a once-daily dose, have been explored with the aim of reducing intolerable side effects while increasing treatment efficacy. For example, Chengappa et al. (2003) found that once-daily doses of quetiapine compared favorably to twice-daily dosing in terms of tolerability and efficacy. Adherence was not directly measured but was posited to be better among those on once-daily dosing. There were no studies examining regimen components as explanatory factors of adherence in the area of mental disorders, and no studies that used electronic monitoring to measure adherence.

Chronic pain

Most studies of pain concerned the appropriate dose to achieve analgesia while avoiding negative outcomes like addiction, rather than studying adherence and dosing/regimen relationships. This has resulted in no published studies that specifically examine whether adherence to analgesic treatment varies by regimen factors. For example, a typical study is Hays et al. (1994), who found that controlled-release hydromorphone resulted in equivalent analgesia when compared to immediate-release hydromorphone. The authors posit that adherence would be enhanced due to the fewer doses required, but do not provide evidence of this relationship.

Morley et al. (2003) conducted a double-blind study of 10 vs. 20 mg methadone to determine its efficacy as a treatment for chronic neuropathic pain. They reported "high compliance", but adherence was not measured or described in a standardized manner (Morley et al. 2003). In an older study, Kubacka and Juhl (1985) explored attitudes about medication dosing among patients with chronic pain or hypertension. Although patients preferred once-daily dosing for non-painful conditions, they preferred multiple doses daily for analgesics. However, this study was conducted when most pain medications were not available in extended-release formats, and these preferences may have indicated patients' concern that their pain would be undertreated if they took fewer daily doses.

In summary, in the area of adherence to analgesic medication for chronic pain, no published studies addressed the possible relationship of adherence to regimen factors nor did any use electronic monitoring to measure adherence. This is particularly problematic in the understanding of chronic pain treatment given that patients with pain may undertake or overtake their medications. Both forms of non-adherence could be detected by electronic monitoring. Patients in the mid 1980s expressed concerns that their pain might not be properly addressed with once-daily dosing, but there are no recent studies of patient

attitudes toward modern, long-acting opioid analgesic formulations. Much work remains in the area of adherence in chronic pain to better characterize the nature of and correlates of non-adherence.

Other disorders

The treatment of *H. pylori* requires a complicated regimen of four different drugs, and has been plagued by high rates of non-adherence. Lee and colleagues conducted a randomized controlled trial (RCT) to determine whether compliance differed between standard care and a program of enhanced compliance care (Lee et al. 1999). They found that although the intervention and control group did not differ, adherence varied by the frequency of dosing and the total number of pills. A follow-up survey of a subset of subjects revealed that 26% of patients reported that frequent dosing had reduced their ability to comply with the four drug treatment, while 22% reported that the number of pills required reduced their compliance. Although results of only one study are not conclusive, it appears that adherence to *H. pylori* treatment is reduced with increasing dose frequency and pill burden.

Treatment regimens for the management of ulcerative colitis, a chronic illness included in a group of inflammatory bowel diseases, can be complicated and intrusive. One systematic review of research pertaining to the treatment of ulcerative colitis has been published (Kane 2006). This review described non-adherence and dosing/regimen issues as contributing to non-adherence, but it appears that studies in this area did not include any form of electronic monitoring. The author recommends simplifying regimens and making them less intrusive to improve adherence to these treatments.

Discussion

At the time that we wrote this article, there were 110,218 articles containing "adherence" or "compliance" in the PubMed/National Library of Medicine database, 18,885 of which contain these terms in the title, presumably as the primary focus of the article. However, surprisingly few of these articles concern (1) chronic treatment, (2) regimen factors such as dosing, pill burden, and regimen complexity, and (3) adherence measured in a rigorous manner. For some chronic treatment conditions, the search was extended to earlier years due to a paucity of recent studies yet still resulted in only 61 studies. Despite the prior recognition of the importance of regimen factors, few recent published studies exist in this area.

Other than in diabetes and HIV/AIDS, where research on adherence as a primary outcome is more common, most studies failed to use state-of-the-art methods of measuring adherence. This means that more subtle adherence–regimen relationships may be undetected, due to overly crude measurement of adherence. This is particularly problematic given the advancements in the measurement of adherence made possible by electronic monitoring. In most of the areas reviewed, electronic monitoring methods to assess adherence were under-utilized. More rigorous adherence measurement methods are usually not used unless adherence is studied as a primary outcome variable, but in most areas, adherence is still studied only as a secondary consideration, or as a covariate. Therefore, studies often do not allocate research resources to this method of measurement, which can be more costly, and requires more sophisticated analyses, than other methods. In addition to methodological weaknesses in some literatures, another concern is the relative absence of attention to adherence in chronic patient populations including those with mental disorders and chronic pain. In these areas, adherence remains relatively ignored, casting doubt on the validity of response rates in many efficacy and effectiveness studies in those fields.

Despite these flaws, a clear picture of the importance of regimen factors, specifically dose frequency, has emerged from this review. While this conclusion is not novel, it is based on literature in HIV and diabetes that included sensitive measures of adherence, adding to confidence in the importance of reducing dose frequency. In most areas (with the exception of asthma/pulmonary disease), there is some evidence that greater dosing frequency is associated with poorer adherence. In some literatures, including that on diabetes, hypertension, and HIV/AIDS, there is strong, consistent evidence that increases in dose frequency and regimen complexity (multiple medications, multiple doses, specific dietary or time requirements) are related to poorer adherence. There are *no* studies showing poorer adherence among groups with lower dose frequencies. However, there are some reasons that once daily dosing may be contraindicated for certain patients. Specifically, some patients may metabolize medications too rapidly, potentially resulting in trough levels of medication that are not therapeutic (and in the case of HIV treatment, represent a risk for the development of resistance), while others may be slow metabolizers for whom once-daily dosing could result in excessive blood levels. Among non-compliant patients who take some of their doses but not others, they may retain some benefit from 50% compliance. However, it could be argued that these may be the very patients who would benefit from once daily dosing. That is, if they remember to take one of two doses currently, they could be expected to take the one prescribed dose in the future. The real concern would be for those with a pattern of skipping days of medication, rather than doses, such that a daily dosing regimen could result in a sub-therapeutic level of

medication within one day of non-adherence. More studies are needed in nearly all chronic conditions to identify those patients who would benefit or possibly be harmed by once daily dosing. However, based on this review, we conclude that to achieve optimal adherence for the greatest number of patients with a variety of conditions requiring chronic treatment, there is a pressing need for efficacious medications and treatments that require the fewest doses per day.

This review has also identified regimen complexity as a likely determinant of adherence. Unfortunately, in most chronic illnesses, investigators have not measured regimen complexity until very recently; however, there are a few exceptions. George et al. (2004) described the development of the Medication Regimen Complexity Index (MRCI), which aims to measure such regimens accurately. The MCRI is a 65-item instrument that includes the number of drugs, dosage frequency, administration instructions, and prescribed dosage forms. When used with 134 medication regimens for COPD, the instrument showed evidence of high interrater reliability and temporal stability for total score and sub-sections ($r \geq .9$). When the authors assessed convergent and discriminant validity, total MCRI scores correlated significantly with the number of drugs in regimen but not patient's age or gender (George et al. 2004).

Similarly, Martin et al. (2007) developed the Antiretroviral Regimen Complexity (ARC) Index. The ARC Index provides a method for quantifying regimen complexity in HIV care and encompasses number of medications, dosing schedule (number of pills per dose and number of doses per day), method of medication administration (liquid, pill, or injection), medication instructions, medication preparations (e.g., refrigeration or reconstitution). Different weights are assigned for each variable depending on the level of complexity (Martin et al. 2007). These weight values are totaled, yielding a single score for the ARC index. In the original scale development and validation studies, 2-week temporal stability reliability was high ($r = 0.98$), as was interrater reliability ($r = 0.97$; Martin et al. 2007). The instrument showed evidence of construct validity (Ranking of regimens by raters was consistent with the order of ARC index scores. The authors recommend the use of the ARC Index for a wide range of health professionals, and use of this index may assist in examining the relationship between regimen complexity and adherence (Martin et al. 2007). Methodological advances such as these should be incorporated in studies of adherence in these and other chronic diseases.

Even when simple regimens are available, there will still be a need for clinical care strategies and methods that lead to better adherence. In most areas of chronic illness, there are few behavioral methods targeting improved adherence with known efficacy. HIV care is an exception. In this area, efficacious behavioral methods to influence patient adherence to medications have been identified and reviewed (Amico et al. 2006; Rueda et al. 2006; Simoni et al. 2006).

Simoni et al. (2006) conducted a meta-analysis on 19 RCTs of adults receiving behavioral interventions that included outcome data and were published between 1996 and 2005 including 1,800 patients. Participants in intervention arms were 1.3 times more likely to report undetectable viral load and 1.5 times more likely to report at least 95% adherence than those in the control arms. Studies with greater effect sizes tended to provide educational information on HAART and engage participants in discussions regarding expectations, beliefs, and motivations, but the specific contributions of intervention components were not identifiable. A second meta-analysis included 24 studies published in peer-reviewed journals between 1996 and 2004, and found that behavioral interventions had moderate effects on adherence, with considerable between-study variability. Studies targeting participants with lower adherence rates at baseline were associated with greater changes in adherence behavior that did not decay over time (Amico et al. 2006).

A Cochrane review on HIV treatment adherence found that of 19 studies, 10 interventions had beneficial effects on adherence (Rueda et al. 2006). Successful interventions included individual rather than group delivery, and practical medication management skills training that may have included memory aids. Unfortunately, the authors reported that they were unable to assess the effects of quality on study outcomes because there were so few studies of good quality based on Consort criteria. In summary, even in the area with the most attention to influencing patient adherence, HIV care, only about half of studies find that behavioral interventions are helpful, and the mechanisms of action remain unknown. Additionally, there is little effectiveness data on how to improve adherence outside of clinical trials. Intervention components that appear promising include personalized discussion, motivational interactions, and practical skills development.

Unfortunately, while evidence in favor of some behavioral interventions is accumulating in HIV care, it is still fair to say that there is an absence of evidence that behavioral interventions will result in meaningful improvements in adherence (Fogarty et al. 2002). Given that, the intervention most likely to result in optimal adherence for the greatest number of patients is simplification of the medication regimen. Prescribing clinicians can assist patients to become optimally adherent by remaining current with medication development and utilize formulations that allow clinical efficacy while reducing dosing and/or regimen complexity. Pharmaceutical companies should be encouraged to develop combination medications that reduce overall pill burden and regimen

complexity, as well as extended-release formulations of existing efficacious medications to allow reduced dosing. For those areas of medicine lacking low frequency dosing alternatives, novel strategies to overcome forgetting may enable patients to achieve optimal adherence.

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