

# ADHERENCE TO PRESCRIBED ORAL MEDICATION IN ADULT PATIENTS UNDERGOING CHRONIC HEMODIALYSIS: A CRITICAL REVIEW OF THE LITERATURE

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## Abstract

**Objective:** Poor adherence to complex multimodal therapies is a widely recognized problem in the daily care of dialysis patients, contributing to excess morbidity and mortality of this population. While a few studies have been devoted to understanding patient nonadherence, their results were somewhat controversial. The goals of this review are to quantify nonadherence to certain oral medications, to raise awareness of factors that may cause problems in a patient's adherence to this treatment, and to describe strategies that may be used to improve adherence to prescribed pharmacotherapy.

**Methods:** A systematic literature review in the MEDLINE and PubMed database (1971-2008) was performed. Quantitative studies, which accurately indicated the total percentages of nonadherence to oral medication in adult patients receiving chronic hemodialysis, were identified.

**Results:** A total of 19 studies fulfilled the search criteria. Rates of nonadherence to the oral medication ranged from 3 - 80%. More than half of the included studies reported nonadherence rates of  $\geq 50\%$  (mean 67%). The use of phosphate binding therapy was the prevalent surveyed oral medication. Self reports, structured interviews, and predialysis serum phosphate levels were the most frequent assessment tools used to record adherence rates. Limitations of the reviewed studies included small patient cohorts, inconsistent definitions of adherence, and a lack of standardized methods for measuring nonadherence.

**Conclusions:** Nonadherence to oral medication in hemodialysis patients is still an underestimated, but life-threatening behaviour.

**Key words:** Adherence, compliance, hemodialysis, medication, prescription

## INTRODUCTION

The prevalence and incidence of chronic kidney disease stage V (end-stage renal disease) are continuously increasing, particularly in elderly patients [1]. End-stage renal disease (ESRD) is not simply a mono-organ failure, but rather a systemic disorder affecting a number of other organ systems. Despite significant advances in the technology of renal replacement therapy (RRT), no current modality of blood purification

serves as a substitute for all renal functions. RRT undoubtedly contributes to long-term survival. However, morbidity and mortality of maintenance dialysis patients remain high: only about one third of the US hemodialysis (HD) patients are alive after 5 years [2]. Cardiovascular diseases are the leading cause of death in ESRD patients [3]. Notably, patients with ESRD have a very high prevalence of cardiovascular disease risk factors such as diabetes and hypertension, but they are also exposed to other non-traditional, uremia-related cardiovascular disease risk factors, particularly derangements in calcium and phosphate metabolism [4]. Given the complexity of these cardiovascular risk factors in ESRD patients, it presents a challenging target for therapy. To modify these risk factors such as hypertension or secondary hyperparathyroidism, the HD patient has to take an average of 6-12 tablets per day [5, 6, 7].

Successful RRT of ESRD patients relies on patient adherence to various aspects of the therapy, such as attendance to the number of sessions prescribed to achieve the optimal dose of RRT, restriction of fluid intake, following dietary guidelines, and adherence to complex medical regimens [8, 9, 10, 11]. There is solid evidence that adherence of ESRD patients correlates with morbidity and mortality [12]. Specifically, skipping treatment and poor dietary adherence are strongly associated with greater risk for death [13]. Unfortunately, poor adherence (compliance) with prescribed medication is a widely recognized problem in daily practice, but few studies have been devoted to understanding patient nonadherence to medication [14]. Furthermore, criteria to assess nonadherence to prescribed oral medications are often arbitrary and are not linked to defined clinical outcomes.

The goals of this literature review are: i) to quantify nonadherence to drugs preventing or treating secondary hyperparathyroidism, or to antihypertensive drugs, ii) to raise awareness of factors that may cause problems in patient adherence to these treatment programs, and iii) to describe strategies that may be used to improve adherence to prescribed medication.

## MATERIALS AND METHODS

We conducted a systematic literature review in the online databases MEDLINE and PubMed (1971-2008) using a comprehensive list of relevant search terms

(adherence/nonadherence, compliance/noncompliance, medication/drug, dialysis/hemodialysis, renal replacement therapy, end-stage renal disease/chronic renal failure) to identify studies on oral medication adherence among adult HD patients. We limited our review to those articles that accurately indicated total percentages or rates of nonadherence to oral medication in the HD population. The systematic literature research identified a total of 387 published articles that contained a combination of the search terms in the abstract. The vast majority (368) of these articles were qualitative studies, review articles, or case reports. Articles focusing on pediatric adherence (patients under 18 years of age) were excluded.

## RESULTS

Only 19 studies reported total rates of nonadherence to oral medication among adult HD patients. Key information is summarized in Table 1.

The selected articles showed a wide variation with regard to the sample size, varying from a minimum of 19 patients [15] to a maximum of 6251 patients [16]. Seven out of 19 studies (37%) included a total number of less than 50 patients.

Phosphate binders (PB, 18/19 studies), antihypertensive drugs (AHT, 11/19 studies), or oral calcium supplementation including the vitamin D analog calcitriol (CAS, 8/19 studies) were the prevalent surveyed oral medications.

Self reports or structured interviews (patient self reports, PSR, 16/19 studies, 84%) were the most frequently used tools to assess adherence rates. Predialysis serum phosphate (9/19 studies, 47%) was commonly used as an adherence indicator for patients taking the oral prescribed phosphate binding medication. Limit values for predialytic phosphate levels showed a broad amplitude from >4.5 mg/dl [15] to >7.5 mg/dl [16]. Only two studies by Curtin and coworkers [17, 6] used medication event monitoring devices (MEMS) to monitor patient's adherence.

Quantitative rates of nonadherence to oral medication substantially varied in the reviewed studies, and estimates of the percentage of nonadherent participants ranged from 3 - 80%. More than half of the included studies (11/19, 58%) reported nonadherence rates of  $\geq 50\%$  (mean 67%).

A history of long-term HD [18], older age (>65 years) [17], higher educational level [19], lower medication costs [20, 21], as well as little concerns about potential adverse effects were identified as markers for adherence. Among psychosocial variables an internal locus of control orientation (defined as a high expectation that one's actions have a causal relationship with the produced consequences) [15] and perceived barriers were most significantly associated with good adherence [22].

## DISCUSSION

To determine the frequency and prevalence of nonadherence in patients with ESRD undergoing HD, a clear-cut and consistent definition of these terms is essentially needed.

Owing to the inconsistencies in uniform definitions, widely divergent results have been obtained in different studies, so that as many as 80% of HD patients may be considered noncompliant with oral medication [23, 24, 8, 18]. The data of the selected 19 studies revealed that the calculated median is closer to 50% [25].

Standardized adherence parameters that can be easily measured and verified would be desirable to achieve reproducible and accurate rates of nonadherence. Nonadherence rates to oral medication are most frequently assessed by predialytic serum phosphate levels. However, serum phosphate level is not only influenced by the phosphate binder therapy itself, but also by diet restrictions, dialysis attendance and residual renal function, revealing the lack of specificity particularly in regard to comorbid illness and the patient's nutritional status. This could be a possible explanation for the weak correlations between adherence rates estimated by self reports and phosphate measurements.

To date, there is little consensus among researchers about standardized methods for measuring nonadherence. Assessment tools for evaluation of adherence in the HD population include direct and indirect monitoring methods (summarized in Table 2).

Microelectronic monitoring devices (MEMS) [26] are recently introduced microchips incorporated into drug container caps and offer a reliable and objective source of adherence data [27, 28]. MEMS are expensive, but monitoring 1 or 2 medications, chosen as "sentinel" drugs, is usually sufficient to determine adherence [26, 29]. Marked differences in rates of nonadherence as measured by the MEMS versus self reports were observed: MEMS recorded 52% of the HD patients as repeatedly nonadherent for antihypertensive medication and 70% as repeatedly noncompliant for phosphate binder medication, whereas evaluation of self reports only identified 12% and 8%, respectively [17, 6].

Factors associated with nonadherence in HD patients, mainly based on expert opinion, are similar to those for other chronic conditions and can be subdivided into demographic, clinical and psychosocial predictors (summarized in Table 3) [30].

Among the most frequently assessed demographic predictors of oral medication adherence, age seems to be a strong predictor of nonadherence in patients with ESRD undergoing HD in most, albeit not all studies. Some articles reported that older age, particularly > 65 years, was associated with higher levels of adherence [31, 32, 24, 33, 23, 34]. This is in contrast to recent observations, reporting an emerging cognitive impairment and dementia in the aging dialysis population [35, 36].

The complexity of the prescribed medication regimen is another crucial predictor of nonadherence, as prescribed number of doses seems to be inversely related to adherence [26]. Unfortunately, once-daily dosing as latterly introduced in the therapy for HIV-infected patients as well as for transplant recipients is unrealistic for the multimorbid adult HD patient [37, 38].

In addition to treatment complexity and high pill burden, also the size and taste of phosphate binding tablets may impact adherence to prescribed oral med-

Table 1. Studies in a chronological order focusing on adherence to prescribed oral medication in adult HD patients.

Study, year	Included patients	Medication type	% Non-adherent	Nonadherence definition /assessment	Results
Wenerowicz, 1978 [15]	19	PB	60	P >4.5 mg/dl PSR (questionnaire)	Patients with internal locus of control <sup>1</sup> orientation showed higher compliance than with external locus
Cummings, 1982 [51]	116	PB	70	P >5.5 mg/dl PSR (interview)	Situational factors and psychosocial variables major contributors to adherence
Betts, 1988 [52]	46	PB	74	P >5 mg/dl PSR (questionnaire)	Length of time on HD, age, educational level and response to illness not significantly related to adherence
Weed-Collins, 1989 [22]	30	PB	64	P >5.5 mg/dl PSR (questionnaire)	Perceived barriers (“forgetting” and “being away from home”) most significant predictors of compliance, women significantly more compliant
Blanchard, 1990 (53)	40	PB, CAS, Vits	28	PSR (questionnaire)	Majority of HD patients knew dosing schedules but knowledge about drug treatment was grossly deficient
Bame, 1993 [23]	1230	PB, AHT, CAS	50	P >6.0 mg/dl	Prevalence of noncompliance consistent with previous studies; older age and higher income associated with compliance
Kaplan, 1994 [7]	30	PB, AHT	67	PSR (questionnaire) Reporting missing a dose	Drug selection and medication compliance contained greatest number of potential problems
Cleary, 1995 [18]	51	AHT, PB, CAS, Vits	61	P >4.5 mg/dl (interview)	Patients with long-term HD more compliant with AHT and CAS than with PB
Lin, 1997 [54]	86	PB, CAS	24 – 61	P >4.59 mg/dl, PSR, nurses' assessment	Multidimensional Health Locus of Control (MHLC) scale had only slight influence on measures of compliance
Curtin, 1997 [17]	135	AHT, PB	42 – 80	MEMS	Patients ≤ 65 yrs made more dosing errors with AHT and missed taking PB on more days than patients > 65 yrs
Leggat, 1998 [16]	6251	PB	22	P >7.5 mg/dl	Younger patients and smokers with higher rates of noncompliance; blacks significantly less noncompliant than whites
Curtin, 1999 [6]	135	AHT, PB	73	PSR, pill count, MEMS	African-Americans with higher rates of noncompliance
Caraballo Nazario, 2001 (19)	53	AHT, PB, CAS	75	PSR, Reporting missing a dose (structured interview)	Significant association between compliance and educational level
Horne, 2001 [55]	47	AHT, PB, CAS	57	PSR, Reporting missing a dose (self report)	Nonadherence correlated with concerns about potential adverse effects of medication
Tomasello, 2004 [56]	129	PB	38-51	PSR (taking < 80% of medication), P >5.5 mg/dl	Compliance did not account for the large difference in prescribed pill burden
Rahman, 2004 [57]	205	AHT	23	PSR, Reporting missing a dose	Good adherence to AHT therapy
Holley, 2006 [20]	39	AHT, PB	21	PSR, Reporting missing a dose (structured interview)	Inadequate prescription coverage, lack of transportation, and medication cost contribute to noncompliance
Lindberg, 2007 [58]	144	AHT, PB, CAS, Vits	80	Discrepancy between self-report and medication list	Deviation between consumption and prescription in chronic HD patients
Hirth, 2008 [21]	5478	AHT, PB, CAS	3 *.- 29 **	Reporting cost-related nonadherence (questionnaire)	Cost-related nonadherence varies across countries, substantial international variation

*Abbreviations:* PB Phosphate binder, AHT Antihypertensives, CAS Ca supplements including calcitriol, Vits Vitamins, MEMS medication event monitoring system, \* Japan, \*\* USA; <sup>1</sup>defined as a high expectation that one's actions have a causal relationship with the produced consequences

Table 2. Standard assessment tools for evaluation of adherence in the HD population.

Direct monitoring methods	Indirect monitoring methods
assays of drug concentrations in biological fluids	patient self-reports (structured interviews, questionnaire)
use of markers incorporated into pills	compliance ratings by nurses
direct observation of pill taking	prescription refills
	pill counts
	microelectronic monitoring devices (MEMS)

Table 3. Factors associated with nonadherence in HD patients.

<b>Demographic factors</b>	age sex / gender educational level marital status / living arrangements race / ethnicity income / employment status cost / payment / insurance / socioeconomic situation smoking / drinking / drug abuse religion / religiosity
<b>Clinical factors</b>	length of time on hemodialysis chronicity / chronic conditions diabetic status former transplant history treatment regimen complexity / high tablet burden tablet size and taste treatment side effects
<b>Psychosocial factors</b>	health beliefs / knowledge / motivation self-esteem cognitive behaviour / function health locus of control <sup>1</sup> social support and family dynamics psychiatric illness anxiety / depression coping style patient-physician relationship

<sup>1</sup>defined as a high expectation that one's actions have a causal relationship with the produced consequences.

Note: These factors are mainly based on expert opinion.

Table 4. Strategies to improve HD patient's adherence to oral medication.

Improvement of interaction with the attending physicians and the nursing staff
Maintenance of contact with the patient and the patient's family (empathy on adherence, trust)
Continuous education of the patient about the disease and its treatment
Establishment of the goals of therapy
Improvement of patient motivation
Awareness of medication-taking behaviour
Reduced complexity of treatment regimens (once-a-day formulations)
Early diagnosis of cognitive impairment

Note: While interventional studies are lacking in the HD population, the proposed strategies are predominantly based on expert opinion.

ication [39]. Novel compounds prescribed for phosphate binding in ESRD patients could circumvent high pill burden in the future. If the calcium- and aluminium-free lanthanum carbonate could provide ef-

fective phosphate control with a lower tablet burden has to be elucidated [40].

HD patients are commonly affected by secondary hyperparathyroidism (SHPT), in which 3 well-known

factors are usually involved: hypocalcemia, hyperphosphatemia, and calcitriol deficiency. Anecdotal reports showed that HD patients who receive any injectable vitamin D formulation have a survival advantage over comparable patients who receive no injectable vitamin D [41]. The intravenous administration of vitamin D or vitamin D analogs should further improve adherence in therapy for SHPT in HD patients. Several new vitamin D analogs, e.g. paricalcitol (19-nor-1,25(OH)2D2), have been developed and investigated with the rationale to treat SHPT with a reduced risk of hypercalcemia and hyperphosphatemia [42].

Psychosocial variables, such as the extent of depression [43] and social support or family dynamics [44], are frequently related to outcome in ESRD patients treated with HD [45]. Particularly in regard to prescribed oral medication, an internal locus of control orientation [15] and perceived barriers (especially forgetting and being away from home) were significant predictors of compliance [22].

Patient motivation, empathy and trust are essential key factors to optimize patient adherence. As stated in "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" [46], the "*most effective therapy prescribed by the most careful clinician will control the disease only if the patients are motivated*". In the development of empathy, attending physicians and the nephrology nursing staff play a pivotal role. Particularly, nephrology nurses are ideally placed to establish a partnership with the chronic HD patient [11]. The HD patient requires consistent and repeated education about their disease, treatment, and risks and benefits of adherence [47]. Interventional studies evaluating possible strategies to improve prescribed oral medication adherence are so far lacking in the dialysis population [48]. However, a single structured drug education program for HD patients yielded significant increases in medication knowledge and adherence within a control group [49]. To minimize nonadherence, interventions need to focus on both patient factors and the extent to which relationships and system problems compromise the patient's ability to adhere to medication treatment [50].

Taken together, a wide spectrum of useful strategies to improve medication adherence have been proposed, but most of them were not proved by interventional studies (summarized in Table 4). A patient-centered approach, including the removal of barriers to adherence, with improved communication, simplification of medication regimen, ongoing education, and the use of MEMS have been recommended as strategies to improve medication adherence. However, up to now, no single strategy has been definitely proven to yield universal and/or long lasting improvements in adherence.

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