Taking a Broader Perspective on Medication Adherence: The Importance of System Factors

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To Hanne, Lieze, and Sophia,
three little girls who are very important to me.

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Summary

One of the greatest challenges health care professionals, organizations and system will be confronted with in the twenty-first century is the dramatic increase in the number of patients suffering from one or more chronic diseases [1, 2]. It is expected that by the year 2020, chronic conditions will be responsible for 60% of the global disease burden in developed countries [2, 3]. Yet, as the current health care system is largely organized around an acute, episodic model of care, it does not meet the needs of chronically ill patients. Chronically ill patients need a model of care that pays attention to self-management, prevention and continuity of care, which receive limited attention in acute care models [4]. As an answer to the need to shift the model of care, Wagner and colleagues developed the Chronic Care Model. This model provides a guide for the health care organizations and systems to improve the care for their chronically ill patient populations [4, 5]. The World Health Organization (WHO) revised the model to provide a global perspective resulting in the Innovative Care for Chronic Conditions (ICCC) framework [2, 6, 7]. Evidence in a limited number of chronically ill patient populations (e.g., asthma and diabetes) support the effectiveness of implementation of (parts of) the model in view of improved patient outcomes (e.g., better glycemic control, improved HbA_1, BMI, triclgyerides), reduction in the number of hospitalization, less emergency room visits, a reduction in the number of unscheduled visits to physicians as well as reducing days missed at work or school and a reduction of the total costs [4, 8-10].

Suffering from a chronic disease implies that patients have to adopt their health behaviors. One important health behavior for a treatment to be effective is adhering to prescribed medications. Despite its importance, 25% [11] to 50% [12] are non-adherent to treatment regimen. Non-adherence can be defined as “deviation from the prescribed medication regimen sufficient to influence adversely the regimen’s intended effect” [13] (pg. 36). Non-adherence can have serious consequences including poor clinical outcomes, higher (re)hospitalization rates and increased health care costs [12, 14-24].

To reduce the magnitude of non-adherence, it is crucial to know which factors influence patients’ medication adherence. The WHO categorizes the risk factors for non-adherence into: 1) patient-related factors (e.g., self-efficacy, patient’s beliefs

about the efficacy of medications, knowledge, perceived barriers to adhere to regimens); 2) social and economic factors (e.g., social networks, family functioning); 3) therapy-related factors (e.g., symptom distress associated with side effects of the regimen, duration of treatment, dose complexity); 4) condition related factors (e.g., self-care disability, complications, and psychiatric diagnoses, substance abuse); and 5) health care system and health care team related factors [25].

As behavior is influenced by the system in which the patient lives, it is crucial to investigate the role of system factors in explaining adherence. However, until now, system level factors have received relatively little attention to explain medication non-adherence. This may explain the limited explanation in the variability in adherence [26]. A framework which can be used in explaining the influence of system factors on behavior is an ecological model. In an ecological model three levels of influence on patient behavior are identified: 1) the micro level, which encompasses factors related to the interpersonal or face-to-face relationships with health care professionals, as well as social support [2]; 2) the meso level, which refers to the practice patterns or the characteristics of the health care organization where the patient is being treated [2]; and 3) the macro level, which includes the characteristics of the health care system in which a patient lives [2]. This level includes local, state, and national laws and policies related to health. These three levels interact with and dynamically influence each other. Taking factors at these three levels into account in explaining patient behavior is essential. To-date, however, system level factors have received limited attention as potential predictors of patient medication adherence. Furthermore, existing evidence on the influence of these factors on medication adherence has not been compiled. As a consequence, the magnitude of the effect of different system factors on adherence is not known, a clear gap in the growing adherence literature.

This system perspective is also needed when implementing interventions to improve adherence. These interventions can target the patient, the micro level (i.e., the health care provider), the meso level (i.e., health care organizations' practice patterns) and the macro level (i.e., health care policy) [27]. Interventions targeting the patient can be classified as educational/cognitive, counseling/behavioral, or psychological/affective interventions [28]. Although most research to-date has focused on interventions targeting the patient, knowledge concerning which interventions

are used in clinical practice is scare. An example of an intervention targeting the health care provider which may influence adherence to medication is training health care professionals in the use of patient-centered methods (e.g., motivational interviewing) [27]. Interventions targeting the health care organization mainly focus on changing practice patterns. The implementation of chronic care models, which has been shown to result in better patient outcomes, is an example of changing practice patterns [27, 29]. However, the extent to which chronic care models are implemented in practice has not been investigated in certain chronically ill patient populations such as transplantation. One reason for this lack in evidence is the absence of a valid and reliable instrument to assess the level of chronic illness management implemented in the health care organization. Interventions focusing on the health care policy are "higher order interventions affecting health policy, organization and financing of care and quality of care programs" [27]. An example of an intervention focusing on the health care policy is changes in medical insurance coverage for prescription drugs in the US [30].

The overall purpose of this dissertation was to explore the role of system factors in chronic illness management, focusing on medication adherence. Five articles present the results of this work.

First, a systematic review was conducted of quantitative studies addressing factors at the mico-, meso-, and macro levels of the health care system that are associated with adherence to medication regimens in individuals with HIV and organ transplant recipients (Chapter 3). A total of 64 studies (seven in the transplant literature and 57 in the HIV literature) examining the association between characteristics at the micro (i.e., quality of the patient-provider relationship, medication counseling, satisfaction with the health care provider, relationship with health care providers, health care provider disease-specific experience, trust/confidence in the health care provider, clarity of health care provider instructions about medications, accessibility to the health care providers, perceived pressure from the provider to take medications, and perceptions of non-judgmental attitudes of health care providers), meso (i.e., center effects, frequency of health care visits, access to disease-specific services, access to medications, quality of care, and satisfaction with the health care setting) and/or macro (i.e., health insurance, drug costs, distance from and access to clinical site, and

country/continent) level of the health care system and medication adherence were identified. The two factors that were most consistently related to medication adherence in these patient populations were trust in the health care provider (a micro level factor) and access to medications (a meso level factor). Both factors support the importance of continuity of care in the treatment of chronically ill patient populations. Across the factors examined, however, study findings about their relationships to adherence varied. One explanation for this variability may be the wide variability in the methodological approaches utilized in studies (e.g., definition adherence, measurement adherence, study design and methods of analysis).

The second manuscript, a methodological paper, provides an overview of commonly used statistical measures (i.e., effect sizes) for expressing the strength of the relationships between variables such as system factors and adherence behavior (Chapter 4). More specifically, formulas utilized to directly calculate common effect sizes from summary data reported in studies, as well as examples of methods utilized to indirectly estimate the effect size from summary statistics are presented.

Third, a study was conducted to describe the strategies cardiovascular nurses and allied health professionals utilize to assess patients' adherence to their medication regimens and to enhance adherence (i.e., educational/cognitive, counseling/behavioral, or psychological/affective interventions) (Chapter 5). In this study, a 45-item questionnaire designed to assess adherence assessment and interventional strategies utilised in clinical practice was distributed to a convenience sample of attendants of the 10th Annual Spring Meeting of the European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions conference in Geneva (Switzerland) in March 2010. A total of 137 health care professionals were included in the study. Questioning patients about non-adherence during follow-up visits was the method used most frequently to assess adherence. Providing reading materials was the strategy used most frequently to enhance patient medication adherence, followed by training patients about medication taking during their inpatient recovery. Across the categories, educational/cognitive adherence enhancing interventions were used most frequently, followed by counselling/ behavioural interventions. Psychological/ affective interventions were less frequently used.

The fourth study examined adherence assessment strategies as well as the interventions health care professionals report using to improve adherence in transplant patients (Chapter 6). Furthermore this study examined the health care professionals' perceptions about the effectiveness the interventions they utilize. Data were collected at the second International Transplant Nurses Society (ITNS) symposium in Germany held on June 18th – 19th, 2010. Eighty-six participants are included in this study. The most frequently used assessment adherence strategy was questioning patients about non-adherence during follow-up. Training patients to self-administer medications and providing printed adherence information were the most frequent interventions. More specifically, these interventions were used by 79% of the participants. Providing printed medication instructions was the third most frequently used intervention. The intervention perceived as most effective by the health care professionals was medication self-administration training. Comparing the utilization of interventions per category, educational/cognitive interventions were used most frequently, followed by the counseling/behavioral interventions and the psychological/affective interventions. The average effectiveness ratings for the three categories of interventions were very similar.

The final study (Chapter 7) describes the development, the content validity testing as well as the inter-rater reliability testing of the Chronic Illness Management Implementation – Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument. The development of the CIMI-BRIGHT instrument was based on the conceptual framework of World Health Organization's Innovative Care for Chronic Conditions (ICCC) framework, as well as the clinical expertise of the members of the research team. Initial psychometric testing, more specifically content validity and inter-rating reliability testing, were conducted. Content validity was evaluated by 7 experts in chronic illness management. These experts rated the relevance of each item in terms of the construct 'chronic illness management' on a 4-point Likert scale (ranging from 1= not relevant to 4= highly relevant). Content validity indexes were calculated for each item and the survey as a whole. Of the 51 items, 42 were had good content validity. Two of the nine items with low content validity were deleted the remaining seven were revised based on recommendations from the expert reviewers. To evaluate inter-rater reliability, a pilot study was conducted in two transplant programs. The percentage agreement between the participants for total CIMI-BRIGHT instrument

in each center was calculated by averaging the percent agreement on individual items. The percentage agreement in the two centers for the total instrument scores was 84.6% and 74.8% respectively.

Synthesizing the findings of the studies yields the following three key results which contribute to the current state of knowledge. First, there remains a significant knowledge deficit in view of the influence of health care system factors on medication adherence calling for further research investment. Second, nurses' practice patterns in view of adherence-related interventions call for a change in curricula. The health care workforce needs to be equipped with the required competencies for behavioral management. Moreover, practice development focused on integrating behavioral strategies to improve adherence management is needed. Finally, The CIMI-BRIGHT instrument is the first and only tool developed to systematically assess the level of chronic illness management in transplant centers and thus provides a building block for further observational and intervention research in transplantation.

These findings have several implications for future research and clinical practice. Firstly, to fully understand the role of system factors in medication adherence a large multi-continental, multi-country, multi-center study should examine the associations between multiple factors at the micro-, meso-, and macro level and non-adherence to medication regimens. Second, education and training in the utilization of counseling/behavior and psychological/affective interventions are important for health care professionals. It needs to be included in basic education programs, as well as in ongoing professional education and training. Health care curricula need to be revised to include competencies in adherence enhancing interventions. Finally, future studies should continue to examine the psychometric properties of the CIMI-BRIGHT instrument. This instrument has the potential to contribute to our understanding of chronic illness care in transplant centers and to be a useful tool in evaluating the impact of interventions designed to improve chronic illness management in these centers.

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Chapter 1

Introduction

Introduction

In order to achieve good treatment outcomes it is essential that chronically ill patient patients take their medication as prescribed. While patients' medication adherence behavior is known to be influenced by a number of factors, those that have been investigated to-date fail to adequately explain the observed variability in adherence. This may be related to the influence of the patients' environment, i.e., the system in which the patient lives, on medication adherence. System factors have only recently been recognized as potentially important predictors of adherence. To date, there is very limited research examining the impact of system factors on adherence. This dissertation focuses on the influence of system level factors on medication adherence.

Chronic conditions

The dramatic increase in the number of patients suffering from a chronic condition is a major challenge which health care professionals, organizations, and systems face in the twenty-first century [1, 2]. Chronic conditions are defined by the World Health Organization (WHO) as "diseases which have one or more of following characteristics: they are permanent, leave residual disability, are caused by nonreversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care" [3] (pg. 4). According to this definition, chronic conditions cover a broad range of diseases ranging from persistent communicable diseases (e.g., HIV and AIDS), non-communicable diseases (e.g., cardiovascular diseases and cancer), and mental disorders (e.g., depression) to ongoing impairments in structures (e.g., amputations and joint disorders) [2]. Transplant recipients are also a subset of the growing group of chronically ill patients, as they require ongoing management for the rest of their life in order to achieve successful short and long term outcomes after transplantation.

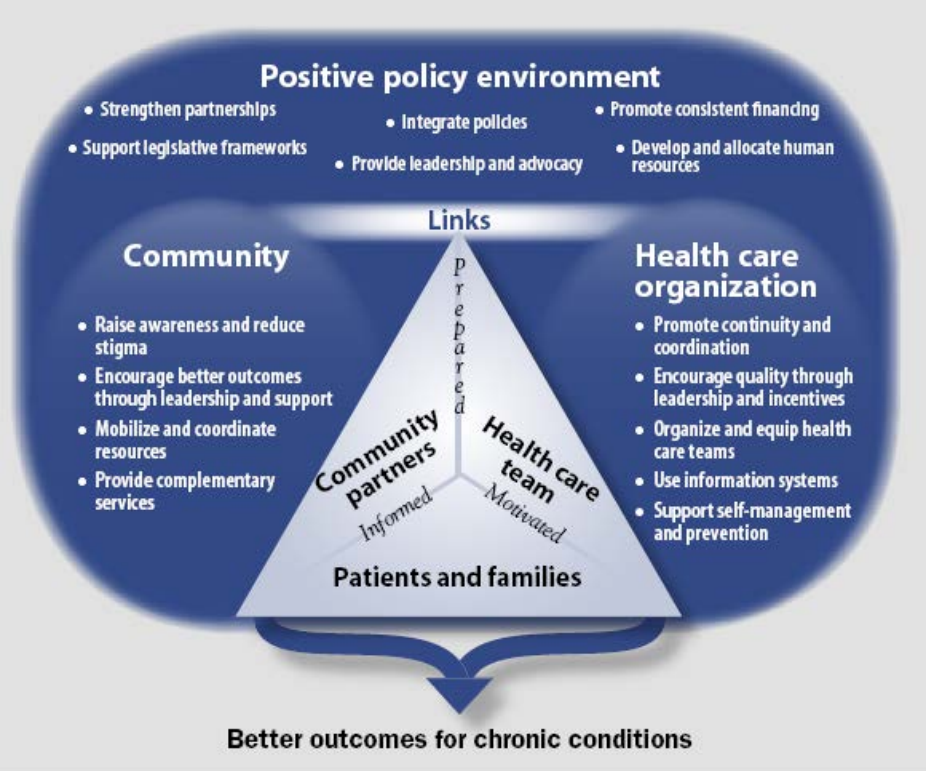
The number of chronically ill patients is increasing globally, and overwhelms high as well as low income countries [1, 2]. This increase is mostly due to the rapid aging of

the population and the greater longevity of persons with many chronic conditions [4]. Currently, more than half of the global disease burden is caused by chronic conditions [5]. It is expected that by the year 2020, chronic conditions will be responsible for 60% of the global disease burden in developed countries [2, 6]. Chronically ill patients are the largest consumers of drugs in the society. The mean number of prescribed drugs per year for a person with no chronic conditions is 2.2; for a patient with one chronic condition this is 11. For a patient with three or more chronic conditions the mean rises to 28.3 [7].

Chronic care model

The shifting balance from patients suffering from acute illnesses to those with a chronic condition requires a shift in the organization of health care. Currently, health care is "organized around an acute, episodic model of care that no longer meets the needs of many patients, especially those with chronic conditions" [2] (pg. 4). The Chronic Care Model, developed by Wagner and colleagues is an answer to the need to shift the model of care. It provides a guide for health care organizations in the management of chronically ill patients [4, 8]. Chronic illness management refers to a model of care that combines the following building blocks: 1) continuity of care; 2) partnerships with patients, families and communities; 3) support for patients in improving their self-management; 4) attention to preventive measures; 5) decision-making support for health care professionals; and 6) availability of clinical information systems [2, 5, 9, 10]. To provide a global perspective, the WHO adapted Wagner's Chronic Care Model. The revised model, the Innovative Care for Chronic Conditions (ICCC) framework (see Figure 1) [2, 11, 12] expanded the community and policy aspects of the Chronic Care Model [11].

Figure 1: Innovative Care for Chronic Conditions Framework [2]



This framework is comprised of fundamental components within the patient, family and the health care provider level; the organization and community level; and the policy level [2, 12]. These components are described as "building blocks", which can be used to help decision makers or those working in the health care system progressively create or redesign health care organizations and systems to expand their capacity to manage long-term health problems [2, 12].

Improved patient outcomes are observed when the care system shifts from acute to a chronic care model for the management of chronically ill patients. Empirical evidence in asthma and diabetes suggests the effectiveness of implementation of the combination of building blocks in chronic care management [8, 10, 13, 14]. The extent to which chronic care management has been implemented and shows efficacy in other chronically ill patient populations such as transplant recipients has not been examined to date.

Health behaviors

Suffering from a chronic condition implies that patients have to adopt new health behaviors or adapt their health behaviors and need to engage in a number of activities to promote physical and psychosocial well-being; interact with health care professionals; adhere to treatment regimens; monitor their health status and make associated care decisions; and manage the impact of their chronic condition on physical, psychological and social functioning [1]. The actions patients perform for themselves in daily life to manage their illness and treatment and to avoid functional and health deterioration are called "patient self-management" [2, 5, 15]. Chronically ill patients have to perform a number of activities in their daily life. After receiving an organ transplant, for instance, patients need to engage in long term health behaviors including medication taking, avoidance of risk factors for cardiovascular disease and cancer, and self-monitoring for signs of rejection and infection, as well as regular follow-up visits to prevent poor outcomes related to rejection, graft loss, mortality and the progression or development of co-morbidities. Adherence (also called compliance) to these health behaviors can be defined as "the extent to which a person's behavior –in terms of taking medications, following a diet, and/or executing lifestyle changes, corresponds with the agreed upon recommendations of a health care provider [3] (pg. 3). In renal transplantation, patients take on average 8 to 10 medications a day [16] with a range from 4 to 16 [17]. Lung transplant recipients take a median of 8 (Q1-Q3: 6-11) non-immunosuppressive medications a day, while for both liver and heart transplant recipients the median was 3 (Q1-Q3: 2-5) [18].

Non-adherence to medication regimen

Definition medication non-adherence

Adherence to prescribed medication regimens is a fundamental prerequisite for a treatment to be effective. In a report of a 2008 Consensus Conference on non-adherence to immunosuppressive medications, Fine and colleagues [19] reported that although non-adherence has been examined a number of times, the absence of a taxonomy has resulted in much conceptual confusion, mainly because most

authors try to identify specific cutoffs or percentages to identify medication intake or drug level. These authors ignore the fact that patients' drug taking behavior is a dynamic process that changes over time. They also fail to distinguish between two important components of adherence-related pharmacotherapy: (1) discontinuation or non-persistence which refers to disengagement from the prescribed regimen and (2) the quality of execution both in terms of taking and timing of medication intake while the patient is engaged with his or her therapeutic regimen [19]. This group of adherence experts in transplantation proposed a new definition specifically of medication non-adherence. They defined non-adherence as followed: "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [19] (pg. 36). In this definition the therapeutic outcome - in contrast to specific medication intake or drug level, is emphasized [19]. For transplantation, research has shown that this clinical meaningful definition for non-adherence is a deviation of > 5% of the daily schedule [20-22].

Prevalence non-adherence

A Cochrane review [23] and a meta-analysis [24] highlight the magnitude of non-adherence to prescribed medication regimens in chronically ill patient populations. On average, 25% [24] to 50% [23] of patients do not take their medications as prescribed. In organ transplantation, 20% to 37% of the patients are non-adherent to their immunosuppressive medications [25-28]. A meta-analysis in transplantation showed an overall non-adherence rate of 22.6 cases per 100 persons per year [29]. Among cardiovascular patients, an average treatment non-adherence rate of 23.4% was reported in a meta-analysis [30]. For HIV patients, estimates of non-adherence to antiretroviral therapy ranged from 30% to 40% [31-34]. While these numbers are influenced by the variability in case finding and assessment methods and operational definitions, they demonstrate that non-adherence is a major issue in many patient populations.

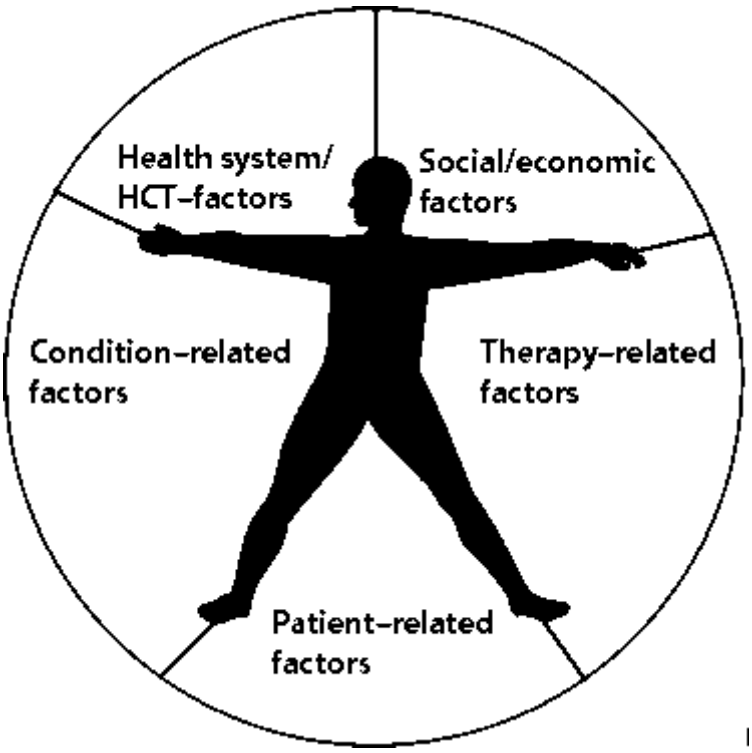
Consequences of non-adherence

Non-adherence to medication treatment can have serious consequences in chronically ill patient populations, including poor clinical outcomes, higher (re)hospitalization rates, and increased health care costs [23, 31, 35-44]. A meta-analysis found that patients who were adherent were 26% more likely to have a good clinical outcome compared to patients who did not adhere to their overall treatment regimen (not only medication adherence) [36]. Non-adherence costs the US health care system an estimated $100 billion annually in direct costs. Indirect costs exceed $1.5 billion in lost patient earnings and $50 billion in lost productivity [45]. It can be assumed that the financial situation for Europe is similar. A recent study in renal transplantation examining the economic costs associated with non-adherence to immunosuppressive medication showed that patients who were persistently non-adherent experienced approximately $21,600 higher medical costs in the first three years after transplantation compared to patients with excellent adherence [43].

Factors associated with patients' non-adherence

To tackle the problem of non-adherence it is crucial to know which factors influences a patient's behavior, i.e., which factors are associated with patients' non-adherence to their prescribed medication regimens. Modifiable factors can then be targeted for intervention. The WHO states that adherence is a multidimensional phenomenon, determined by the interplay of five dimensions (see Figure 2): (1) patient-related factors (e.g., self-efficacy, patient's beliefs of efficacy of medications, knowledge, and perceived barriers to adhere to regimens); (2) social and economic factors (e.g., social networks, and family functioning); (3) therapy-related factors (e.g., symptom distress associated with side effects of the regimen, duration of treatment and dose complexity); (4) condition related factors (e.g., self-care disability, complications, and psychiatric diagnoses such as substance abuse); and (5) health care system and health care team related factors [46].

Figure 2: Five interacting dimensions affecting adherence [46]



Until now, most efforts to understand the remarkably high rates of non-adherence have focused on patient-related, social and economic, treatment-related and condition-related factors [46, 47]. A meta-analysis in transplantation, however, showed that these factors only explain a small part of the variability in non-adherence [29]. This indicates that factors not immediately associated with the patients, but rather with health care providers, the system of care or the characteristics of the health care system as a whole might explain more variability in non-adherence than patient or treatment related factors. Health systems can be defined as "all organizations, people and actions whose primary intent is to promote, restore or maintain health" [48] (pg. 30). However, the influence of health system level factors on patients' non-adherence to medication regimens has not been examined to the same extent as patient-, socio-economic-, treatment- and condition-related factors [46, 49, 50], an obvious gap in the literature.

Theoretical background

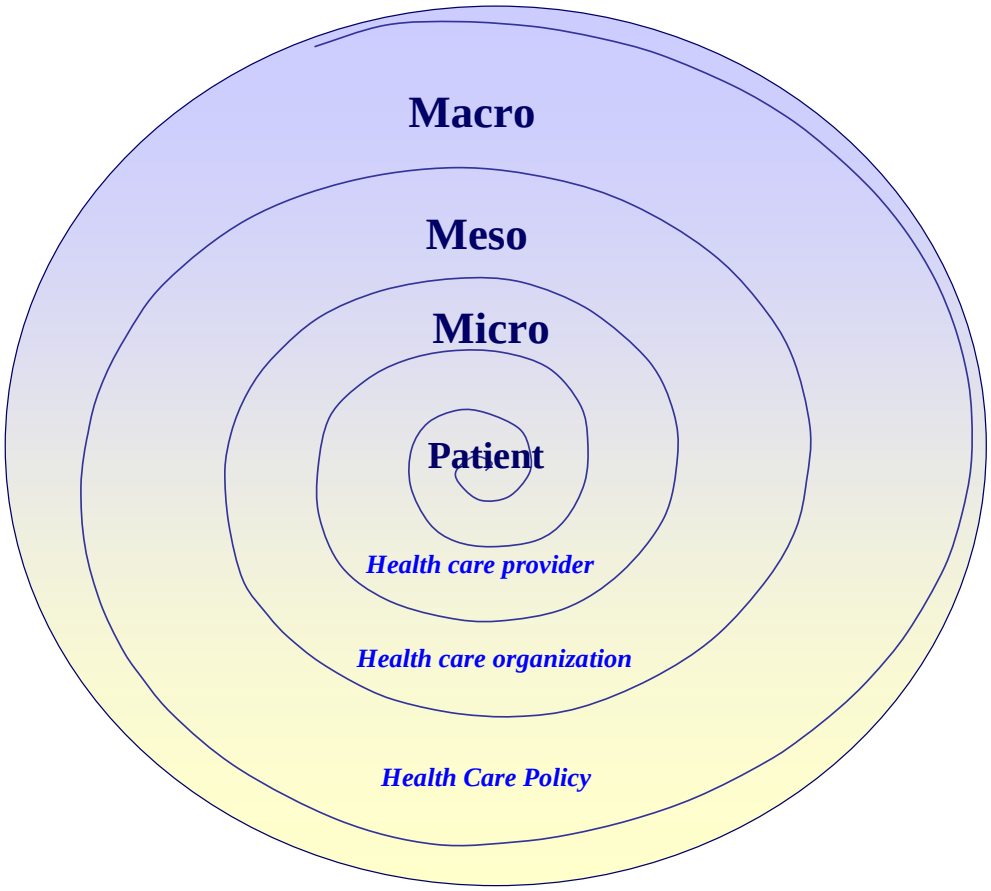
A number of theoretical approaches have been suggested to describe factors influencing a person's behavior (e.g., non-adherence) [51, 52]. A common problem in most of these models is that they ignore the influence of contextual or environmental factors on patients' medication taking behavior [52]. As patient behavior is also influenced by factors from his or her environment, it is crucial to integrate these factors in order to explain behavior.

System thinking and the ecological model

To reach successful behavioral change, it is important that the patient is motivated. However Alemi et al. (2000) also emphasis the importance of the system in promoting change [51]. The system refers to an individual's environment. The process of accounting for the influence of various people, circumstances and historical choices on the behavior that is to be modified is called system thinking or ecological thinking [53, 54]. The concept of ecology originates from public health and psychology [55]. In public health, for instance, environmental influences on diseases have been recognized for centuries [55]. In education, it is acknowledged that predicting achievements of students requires not only consideration of student-related variables such as intelligence, motivation or self-efficacy, but also variables on the level of the teacher, the school, and the educational system [56, 57]. In 1936, Kurt Lewin coined the term ecological psychology to describe the study of the influence of the outside environment on the person [55].

Urie Bronfenbrenner (1979) was the first person who focused specifically on the multiple environmental levels influencing behavior [55, 58]. In Bronfenbrenner's model, behavior is viewed as being affected by, as well as effecting, multiple levels of environmental factors [47, 58]. These different levels can be divided into patient-, the micro-, the meso-, and the macro levels (see Figure 3) [47].

Figure 3: Framework for the review: the ecological model of McLeroy et al. (adapted) [58]



Patient level factors comprise characteristics of the individual, such as knowledge, self-efficacy, and attitudes. This level also incorporates the developmental history of the individual [58]. **Micro level factors** encompasses factors related to the interpersonal or face-to-face relationships with health care professionals, as well as social support [2]. Examples are the quality of communication between the health care professionals and patients and the degree of trust the patient has in the health care professional. **Meso level factors** refer to the practice patterns or the characteristics of the health care organization where the patient is being treated [2]. Examples of a health care organization characteristic or a practice pattern is the time available for consultation or the interventions implemented in daily clinical practice to enhance patients' medication adherence. **Macro level factors** include the characteristics of the health care system in which a patient lives [2]. This level

includes local, state, and national laws and policies related to health (e.g., insurance coverage and regulations on reimbursement for medication).

As depicted in Figure 3, each of these levels interacts with and dynamically influences the other levels. Paying attention to all these levels of patients' environment or system in promoting patients' behavior is essential as the system surrounding the patient is the often reason for success or failure in changing behavior [51]. Kidd and Altman (2000) emphasize the importance of taking environmental factors into account in understanding a patient's adherence to a medication regimen [47]. This need has also been recognized by others. In 1997, an expert panel of the American Heart Association recommended a multi-level approach to improve medication adherence [50] and more recently the American Society of Hypertension recommended a more ecological approach to improve adherence to antihypertensive medications [59]. In addition, policy reports from the WHO and clinical practice guidelines from the National Collaborating Center for Primary Care and Royal College of General Practitioners (UK) strongly advocate using a systems approach that transcends the patient level when dealing with the issue of poor medication adherence [46, 60]. However, as stated before, most studies to date have examined how characteristics of the patient and of the treatment regimen impact adherence. System level factors have not received much attention so far. Furthermore, existing evidence of the influence of these factors on medication adherence has not been compiled. As a consequence, the magnitude of the effect of different system factors on adherence is not known, a clear gap in the growing adherence literature.

Interventions improving adherence

Given the magnitude of non-adherence and its consequences, leading to describing non-adherence with medication as a major public health treat developing, implementing and testing the efficacy and effectiveness of preventive and restorative adherence interventions is a high priority on both policy, research and clinical agendas.

A number of interventions can be implemented to improve patients' adherence. These interventions can target the patient, the micro level (i.e., the health care provider), the meso level (i.e., health care organizations' practice patterns) and the macro level (i.e., health care policy) [3].

Interventions targeting the patient can be classified as educational/cognitive, counseling/behavioral, or psychological/affective interventions [61]. *Educational/cognitive interventions* present information individually or in a group setting, delivering it verbally, in written form, and/or audio-visually. *Counseling/behavioral interventions* shape and/or reinforce behavior, empowering patients to participate in their own care, while positively changing their skill levels or normal routines. *Psychological/affective interventions* focus on patients' feelings and emotions or social relationships and social support [61]. However, not all interventions are supported by strong evidence. A Cochrane review [23] focusing on the efficacy of adherence enhancing interventions and measuring both adherence and clinical outcomes included 70 trials testing 83 interventions for long-term treatments. This review showed that for long-term treatments, only 36 of the 83 interventions were significantly associated with improvements in medication adherence [23], while only 25 led to improvement in at least one treatment outcome [23]. No simple and few complex interventions resulted in improvement in adherence and clinical outcomes [23]. Interventions that were effective to improve adherence for long-term treatments included combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care [23]. In a meta-analysis investigating the efficacy of interventions to improve medication adherence in older adults, Conn et al. (2009) reported that a number of interventions significantly improved medication adherence, but there were large differences in the effect size associate with these interventions [62]. In this meta-analysis, the intervention used most often to improve adherence was education. However, despite an significant improvement in knowledge, these interventions did not improve adherence [62]. Similarly, in "*Adherence to long-term therapies – evidence for action*" the WHO states that adherence interventions at the patient level have usually focused on increasing knowledge, i.e., patient education [3]. However, evidence shows that knowledge alone is not enough to establish and maintain strong adherence behavior [3]. The most effective adherence enhancing interventions

targeting the patient aim to enhance self-regulation or self-management capabilities [3].

Interventions targeting the health care providers (micro level): Although health care professionals have a significant role in promoting patient adherence, only few studies on this topic have been reported in the literature [3]. A recent meta-analysis focusing on physician communication and patient adherence to treatment showed that patients whose physician communicates poorly have a 19% higher risk for non-adherence compared to patients whose physician communicates well [63]. The authors emphasis that interventions focusing on communication training for physicians is essential and effective [63]. Training health care professionals in the use of patient-centered methods has been shown to improve patient satisfaction with treatment and may also improve patients' medication adherence [3]. Health care professionals trained to use goal-setting, feedback and ongoing education had better patient outcomes [3].

Interventions targeting the health care organization (meso level). Interventions targeting the health care organization mainly focus on changing practice patterns. One example of changing practice patterns which has been shown to result in better patient outcomes is the implementation of chronic care models [3, 64]. In the Organization for Economic Co-operation and Development (OECD) report, Hofmarcher and colleagues reported that the chronic care model had positive effects for patient adherence, patient satisfaction, and patient knowledge related to their condition [65]. However, the extent to which chronic care models are implemented in practice as well as their relationship to medication adherence is not yet investigated in certain chronically ill patient populations such as transplant recipients. One reason for this lack in evidence is the absence of an instrument which has the capacity to assess the level of chronic illness management implemented in the health care organization in a valid and reliable manner. Prior to introducing interventions to change practice patterns, it is essential to assess the current state of practice. To date, there is limited research examining which interventions are used in daily practice to enhance patients' medication adherence.

Interventions targeting the health care policy (macro level): Interventions focusing on health care policy are "higher order interventions affecting health policy, organization and financing of care and quality of care programs" [3]. An

example of an intervention focusing on the health care policy is change in medical insurance coverage of prescription drugs in the US. Madden and colleagues investigated the impact of Medicare prescription drug coverage (Part D) on cost-related medication non-adherence [66]. A principle goal of the implementation of Medicare Part D was to increase economic access to medications, especially among vulnerable poor and chronically ill populations [66]. The authors demonstrated that the implementation of Medicare Part D was associated with a significant decrease in the prevalence of cost-related medication non-adherence [66]. The Obama's health care reform [67], which would indefinitely provide immunosuppressive drug coverage for kidney transplant recipients has the potential to decrease cost-related non-adherence. Immunosuppressive drugs for kidney transplant recipients are currently covered for only the first 36 months post-transplant [68].

Non-adherence to medication regimens is a prevalent problem among chronically ill patients and is influenced by a number of factors. However, to-date research on adherence has focused primarily on patient-related factors and those factors failed to explain the broad variability in non-adherence rates. As behavior is influenced by the system in which the patient lives, it is crucial to investigate the role of system factors in explaining adherence. A framework which can be used in explaining the influence of system factors on behavior is the ecological model. However, system factors have not received much attention in explaining medication adherence, and their influence is unclear. The systematic review which is part of this dissertation summarizes current evidence about the role of individual system factors at the health care provider, health care organization, and policy levels in association with medication non-adherence.

Also in view of interventions to improve adherence, a system perspective is needed. Based on this perspective, interventions will target the patient, the health care provider, the health care organization and health related policies. Today most research has focused on patient-centered interventions designed to improve adherence. Even within this domain, our understanding of the interventions that health care professionals use with their patients is limited. This dissertation examined health care providers' reported patient-centered interventions utilized to improve adherence.

The Chronic Care Model, developed by Wagner and colleagues and revised by the WHO emphasizes the importance of a comprehensive system focused approach to improving clinical outcomes in persons suffering of chronic disorders. One of the challenges in doing research on implementation of the chronic care model is the lack of a valid and reliable instrument that can measure the extent to which the model has been implemented in health care organizations or to examine the impact of interventions designed to integrate the model into practice. Another study in this dissertation describes the development and initial psychometric testing of an instrument developed to measure health care professionals' perceptions regarding the implementation of the chronic care model in their clinical setting.

In summary this dissertation will address gaps in the literature by:

- Presenting a systematic review of the evidence describing the association between health care system factors and medication adherence in two chronically ill patient populations, people living with HIV and transplant patients (Chapter 3).
- Providing an overview of commonly used statistical measures for expressing the strength of the relationships between variables such as system factors and adherence behaviour (Chapter 4).
- Describing the adherence assessment strategies and adherence enhancing interventions routinely used by health care providers in caring for cardiovascular patients (Chapter 5).
- Examining adherence assessment strategies as well as the interventions health care professionals report using to improve adherence in transplant patients, as well as their perceptions about the effectiveness the interventions (Chapter 6).
- Describing the development of an instrument designed to assess the level of chronic care implemented in transplant centers as well as its content validity and inter-rater reliability (Chapter 7).

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Chapter 2

Study aims

Study aims

Given the gaps in the evidence regarding the influence of system level factors and medication adherence in chronically ill patient populations, the aims of this research were following:

1) To identify and summarize quantitative studies addressing factors at the micro-, meso-, and macro levels of the health care system that are associated with non-adherence to medication regimens in individuals with HIV and organ transplant recipients (Chapter 3).

2) To provide an overview of the most common used measures of effect sizes and how these are calculated (Chapter 4).

3) To assess the strategies cardiovascular nurses and allied health professionals utilize to assess patients' adherence to their medication regimens, and to assess the strategies they use to enhance their medication adherence (i.e., educational/cognitive, counseling/behavioral, or psychological/affective techniques) (Chapter 5).

4) To identify which strategies transplant health care professionals utilize to assess their patients' medication adherence, to classify the medication adherence enhancing interventions they use (i.e., educational/cognitive, counseling/behavioral, or psychological/affective) and to assess how they perceive their chosen interventions' effectiveness (Chapter 6).

5) To describe the development, the content validity assessment as well as the inter-rater reliability assessment of the Chronic Illness Management Implementation - Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument (Chapter 7).

Chapter 3

System factors as correlates of medication adherence in HIV and transplant populations: a systematic review

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Abstract

Purpose: Medication adherence is influenced not only by characteristics of the individual patient, but also by the micro-, meso-, and macro levels of the health care system. However, most research focuses on patient level factors, which offer limited explanation for medication adherence's broad variability. The aim of this systematic review is to summarize evidence from quantitative studies examining the relationship between micro-, meso-, and macro level health care system factors and medication adherence in organ transplant (Tx) recipients and patients living with HIV – two populations for whom strict medication adherence is essential in preventing poor outcomes.

Methods and Materials: Searches were conducted in PubMed, EMBASE and Cinahl databases. Quantitative studies published in English between January 1999 and December 2009 were included. To be eligible, studies had to investigate medication adherence as an outcome, describe the adherence measurement method used, and report the relationship between one or more micro-, meso-, and/or macro level factors and medication adherence in post-Tx or HIV-positive adults.

Results: Electronic searches returned 5,341 citations. Seven articles in the Tx literature and 57 in the HIV literature met all inclusion criteria. For most of the factors examined, the relationship to medication adherence was not consistent across studies. The micro level factor most consistently related to adherence was trust in the health care provider. At the meso level, it was drug access/dispensing. Cost-related characteristics (macro level), including medication cost, were significantly associated with adherence 50% of the times they were studied.

Conclusions: While the findings of studies examining the relationship between the system level factors and medication adherence are inconsistent, this systematic review provides preliminary evidence to suggest that certain system level factors may contribute to the variability in medication adherence. Due to the limited ability of patient characteristics to explain adherence, it is critical to continue to explore the role of system level factors in explaining medication adherence.

Introduction

Adherence to a prescribed medication regimen is influenced not only by characteristics of the individual patient, but also by system level factors in that person's environment. These determinants can be classified into three levels: micro (i.e., factors related to the health care professional, social support), meso (i.e., factors related to the health care organization or setting in which care is received) and macro (i.e., health care system factors) [1]. Understanding medication adherence requires awareness of all three levels [2, 3]. To date, however, most adherence research has focused on patient level factors (patient, socio-demographic, condition and treatment related matters) with insufficient consideration of those at other levels. Moreover, we are unaware of any previous systematic reviews examining the relationship between such factors and medication adherence. Therefore, our goal was to conduct a systematic review with the aim to summarize evidence from quantitative studies examining the relationship between micro-, meso-, and macro level health care system factors and medication adherence in organ transplant recipients and patients living with the human immunodeficiency virus (HIV).

Background

The World Health Organization (WHO) defines adherence (also called compliance) to long-term therapy as "the extent to which a person's behavior (i.e., taking medication) corresponds with the agreed recommendations of a health care provider" [4] (pg. 3). Although adherence is a fundamental prerequisite for a prescribed treatment to be effective, non-adherence to medication regimens in chronically ill patient populations is very common, with prevalence rates ranging from 22% to 57% [5, 6]. The consequences can include poorer treatment outcomes (including hastened mortality), higher hospitalization rates and increased health care costs [7, 8].

Despite its negative consequences, medication non-adherence in chronically ill patients remains poorly understood. Until now, most efforts to understand it have focused on characteristics of the individual patient (e.g., self-efficacy, knowledge,

intentions), the treatment regimen (e.g., regimen complexity, duration of treatment), socio-economic and demographic related factors (e.g., age, race, marital status), along with condition related factors (e.g., depression, number of co-morbidities) [4, 9]. Factors related to health care provider, health care organization, and the health care system as a whole have received far less attention [2, 4, 10].

This imbalance is well recognized. To tackle medication adherence issues, WHO policy reports and clinical practice guidelines published by the Royal College of General Practitioners' National Collaborating Center for Primary Care strongly advocate system-oriented approaches beyond the patient level [4, 11]. In 1997, an American Heart Association expert panel recommended a multi-level approach to improve adherence [2] and more recently the American Society of Hypertension recommended this approach to improve adherence with antihypertensive medication [12].

Importantly, a meta-analysis in transplantation by Dew et al. (2007) suggests that system level factors have an impact on adherence. In that report, the authors observed that North American transplant patients had higher rates of non-adherence than European ones, a difference to which they suggested health care system factors may contribute [13]. A seven-country study investigating practice patterns in hemodialysis centers found that center characteristics (e.g., size, percentage of highly trained staff) and the country where the dialysis center was located were related to dialysis non-adherence (i.e., failure to attend dialysis sessions) [14, 15]. Schoen et al. (2009) conducted an eleven country survey of primary care doctors, finding wide variations at a national level in practice systems, incentives, perceptions of access to care, use of health information technology and programs to improve quality [16]. In a survey the following year, Schoen et al. found that the eleven countries surveyed also had differing systems of health care coverage, leading to significant differences in access to care, cost burdens and problems with health care insurance [17]. However, they did not investigate the influence of these system factors on medication adherence. In the Swiss HIV cohort study, which did focus on medication adherence, patient followed-up centers, a meso level factor, accounted for significant variability in adherence rates [18]. A meta-analysis focusing on patient treatment adherence and physician communication

across diverse illness populations and settings found that the risk of non-adherence was 19% higher when communication with physicians was poor [19].

The aim of this systematic review is to identify and summarize quantitative studies addressing factors at the micro-, meso-, and macro levels of the health care system that are associated with adherence to medication regimens in individuals with HIV and organ Tx recipients. These populations were selected because both conditions require complex, lifelong medication treatment. Furthermore, medications are life-saving in both populations. In contrast to other chronically ill populations, even minor deviations from the prescribed regimen can seriously impact these patients' clinical outcomes. In transplantation, for instance, non-adherence is associated with poor kidney function, acute rejection, and graft loss [20-23]. In HIV, even slight deviations of the prescribed anti-retroviral treatment regimen (e.g. < 95%) are associated with poorer virological outcomes including higher viral loads, lower CD4 cell counts and the development of HIV drug resistance [24-28].

Conceptual framework for a multi-level approach to a system

An approach whereby several levels of a system are considered when explaining a phenomenon (e.g., adherence) is called an ecological perspective [1, 9] (see Figure 1). From an ecological perspective, a patient's activities overlap numerous settings – within self, within family, with friends, at work, during recreational activities, in the health care setting and within society – each of which influences his or her behavior. As depicted in Figure 1, each level of contact interacts with and dynamically influences the others. When the patient-, micro-, meso-, and macro level factors work effectively within and among themselves, the system is efficient and effective [1].

Micro level

The micro level encompasses factors related both to interpersonal or face-to-face relationships with health care providers and to social support [29], e.g., the degree of trust the patient has in the health care provider and the overall quality of the patient-provider relationship. For the purpose of this review, we focused on micro

level factors related to professional relationships, and not to personal social support factors, the significance of which was confirmed, regarding treatment adherence, in DiMatteo's 2004 meta-analysis of 122 studies [30].

Meso level

The meso level encompasses the characteristics of the health care facility where the patient is being treated [29] (e.g., time available for consultation, treatment team skill mix).

Macro level

The macro level includes the characteristics of the larger health care system and policy that influence how the patient uses the system [29]. These include local, state, and national legislation and policies related to health (e.g., insurance coverage and regulations regarding reimbursement for medication).

Recognizing and understanding factors related to medication adherence are essential to the development of adherence-enhancing strategies, the identification of patients at risk of non-adherence and the design of interventions to target modifiable factors. As each style of intervention targeting medication adherence has significant weaknesses, the most effective systems have combined a number of approaches on the different levels [6, 31]. Such combinations are recommended by policy reports and clinical guidelines [4, 11]. However, to implement interventions effectively, it is essential to know which health care system factors at each level are associated with adherence to medication regimens and which explain the most variability in medication adherence.

Methods

We conducted systematic electronic literature searches of the PubMed, EMBASE and Cinahl databases to identify relevant studies published in English from January 1999 to December 2009. For the PubMed database, for example, our search terms for articles on transplant recipients were: (complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren*

OR concordance OR non-concordance OR concord* OR non-concord*) AND transpl*. For the HIV population: (complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren* OR concordance OR non-concordance OR concord* OR non-concord*) AND HIV. Table 1 shows the specific search strategies utilized for each database. These strategies were kept deliberately broad as there is a wide use of terminology in the literature and we wanted to identify as many studies as possible.

We included studies that met the following eligibility criteria: 1) quantitative analysis; 2) publication between January 1999 and December 2009; 3) publication in English; 4) adult samples (≥ 18 years old) who were Tx recipients or had HIV; 5) use of medication adherence as an outcome; 6) description of adherence measurement methods; and 7) examination and reporting on relationships between micro-, meso-, and/or macro level health care system characteristics and medication adherence. Studies were excluded if 1) they focused on treatment refusal (the medications was never prescribed or initiated); 2) they included institutionalized subjects and did not report findings separately for subjects who were not institutionalized; 3) their participants suffered from psychiatric disorders; 4) they examined a group of factors including those at the patient level but did not report findings separately for the micro-, meso-, and/or macro level factors; 5) they used qualitative designs; 6) they described intervention studies examining only the relationships between the determinants and adherence following an intervention; or 7) they focused on social support. If two or more studies involved the same sample, only one study was included in this review. Decisions on which studies to include were based on the number of system factors examined. We selected those examining the greatest numbers of system factors.

The reference lists of retrieved studies were also examined to identify additional relevant studies. Using a review protocol, a single researcher (LB) reviewed all titles and abstracts to determine their eligibility. If any uncertainty existed, a second researcher (SE) was consulted. Next, both researchers (LB & SE) read and evaluated the full text of the studies corresponding to the selected abstracts.

To extract data from the articles, we developed a data extraction sheet. The following information was extracted: design, sample characteristics, definition of adherence, factor(s) examined, and results. One author (LB) reviewed the extracted

data from the included studies; a second author checked the extracted data (SE). If disagreement occurred, it was resolved by discussion between the two authors.

Quality assessment of studies included in a systematic review is essential to ensure that the original research is systematically appraised and evaluated [32]. To assess the quality of studies included in this review, we adapted a criteria-based checklist used in prior systematic reviews [33, 34]. The result was a list of 15 categorical questions (see Figure 3). Using this checklist, two authors (LB & SE) independently evaluated all included studies. Any disagreements were resolved through discussion.

Data analysis

Adherence definitions, measurements and reporting methods varied across the studies. Therefore, meta-analysis was not performed. Odds ratios (OR) and their 95% confidence intervals (CI) were reported or calculated (Tables 3, 4 and 5) as measures of the strength of the relationship (effect size) between the micro-, meso- and macro level factors and adherence in this systematic review. When studies reported an OR and CI for non-adherence, it was converted into an OR and CI for adherence. If OR were not reported in the article but sufficient data were available, an OR and a 95% CI were calculated 35. If data were insufficient, we contacted the authors and asked them to provide data which would allow us to calculate an OR with a 95% CI. In cases where only p-values were available, a Cohen's d was calculated, then converted to an approximate OR using the Effect Size Generator – Professional Edition version 4.1 software package (Melbourne, Australia). Chi-square tests of independence were utilized to examine the relationship between study characteristics (patient population, study design, continent on which the study was conducted, method of measuring adherence, method of analysis and system factors examined) and reporting a significant relationship between a system factor and adherence.

Results

Study selection

The electronic searches of the three databases returned 5,341 citations (see Figure 2). After eliminating duplicates (HIV n= 515; Tx n= 512), and including additional records identified through other sources, 4,370 citations were screened for eligibility by title and abstract. Of the 4,370 citations, 258 articles were selected for full-text review. Of these, 7 articles in the transplant literature and 58 articles in the HIV literature met all eligibility criteria. One [36] of the 58 HIV studies was, however, excluded because of inconsistencies in the results section and the tables. Our attempts to contact the corresponding author to resolve these inconsistencies were unsuccessful.

Study characteristics

A summary of the characteristics of the included studies is shown in Table 2. Almost half of the studies (n= 29; 45.3%) were conducted in North America; just over one-fifth (21.9%) took place in Europe. Prospective designs were used in 23.4% of the studies. A cross-sectional or retrospective design was used in 76.6% of the studies. Most studies (76.6%) used patient self-reports (either interviews or self-administered questionnaires) to assess medication adherence. Four studies in the HIV population (7%) and none in the transplant population used multiple methods to assess adherence. Of the studies using multiple methods, we used the method that detected the highest prevalence of non-adherence. The studies' adherence assessment periods varied widely, ranging from "ever" to the previous 2 days. The most prevalent time periods were the previous 4 weeks (20.3%), followed by the previous 3 days (14.1%). Most of the included HIV studies focused on micro level factors, while the transplant studies focused more on macro level factors.

Quality assessment

None of the studies fulfilled all 15 of the defined quality appraisal criteria. In HIV, the total quality score ranged from 7 (2 studies) to 14 (7 studies) (Mean= 11.65; SD= 1.75). For HIV studies, the quality scores ranged from 6 (one study) to 14 (3 studies) (Mean= 11.86; SD= 3.13). Almost all articles provided a definition of adherence (see Figure 3). The quality criteria fulfilled by the fewest studies was "information about psychometric properties of used instruments". No studies were excluded on the basis of the quality appraisal.

Micro level factors (health care provider related factors)

The relationship between micro level factors and adherence was analyzed multivariately 46 times across 31 studies, and 17 times bivariately in 5 studies (see Table 3). The majority of these studies (56.5% of multivariately and 76.5% of bivariately) reported that the micro level factor examined was not significantly related to adherence. The factor most commonly examined was the patient-health care provider relationship or some aspect of it (e.g., communication, trust, satisfaction or quality). Of the 56 times where it was examined, 23 (41.1%) showed a significant positive relationship between positive patient-provider relationships and adherence. The specific micro level factor most consistently related to adherence was trust in the health care provider (examined in 8 studies), which was significantly associated with higher adherence in 62.5% of the studies that assessed it. The reported or calculated effect sizes (OR and 95% CI) between micro level factors and adherence are presented in Table 3. Effect sizes were not reported and could not be calculated for 10 of the relationships examined. None of these relationships were statistically significant.

Meso level factors

The relationship between meso level factors and adherence was examined multivariately 24 times across 18 studies and bivariately in two (see Table 4). The factors examined were drug access/dispensing related (n= 4 studies multivariately, 2 bivariately), center differences (n= 7 studies multivariately), visit-related

characteristics (n= 5 studies multivariately), specialty care/case managements (n= 4 studies multivariately), clinic-related factors (e.g., satisfaction, quality of care, or access) (n= 4 studies multivariately). Drug access or the method of dispensing the drugs was the only meso level factor consistently related to adherence, with 75% of the studies that examined it multivariately and both of studies that examined it bivariately reporting significant relationships. Treatment center was significantly related to adherence in 28.6% of the studies examining it multivariately. In most of the studies, the remaining meso level factors were not significantly related to adherence. In all of the studies with non-significant findings, the meso level factor was not significantly related to adherence bivariately and therefore not examined multivariately. Effect sizes were not reported and could not be calculated for eight of the relationships examined. None of the relationships were statistically significant.

Macro level factors

The relationship between adherence and a macro level factor was examined multivariately 26 times in 21 studies and bivariately 4 times in 3 studies (see Table 5). The factor examined most frequently was cost related characteristics (e.g., type of health care coverage, cost to patient for medications). In half (50%) of the cases where it was examined multivariately, no significant relationship was found between this factor and adherence; however, it was significantly related to adherence in two of the three studies that tested for that relationship bivariately. The higher the cost for the patient, the lower the adherence rates. Transportation related issues were examined multivariately in 5 studies, none of which found significant relationships to adherence. One study examined the relationship between the continent and/or country where transplant care was delivered and adherence, with multivariate analysis showing a significant relationship for three of their four comparisons (i.e., the U.S. vs. Europe; the Netherlands vs. Belgium; and Switzerland vs. Belgium). Another study only examined the relationship between the country where the transplant occurred and adherence bivariately and reported no significant relationship. In seven (22.6%) of the 31 cases where a macro level factor's relationship to adherence was examined multivariately, the OR and/or 95% CI were not reported and could not be calculated. None of these seven analyses found a significant relationship between the examined macro level factor and adherence.

Relationships between study characteristics and significant findings

We analyzed for relationships between 5 study characteristics – patient population (HIV/AIDS or transplant), study design (prospective vs. cross-sectional and retrospective), continent on which the study was conducted (North America, Europe or other), method of adherence measurement (self-report or other [e.g., pill count, electronic monitor, blood assay or a combination of methods]), method of analysis (multivariate or bivariate), and the level of the systems factor examined (micro, meso or macro) – and whether a significant relationship was reported between systems factors and adherence. Although study design approached statistical significance, none of the study characteristics were significantly related to the likelihood of finding a significant relationship. Statistically significant relationships were reported in 43.0% of cross-sectional or retrospective studies compared to 24.0% of prospective studies (p= 0.08).

Discussion

To our knowledge, this is the first systematic review of quantitative studies examining the association between micro-, meso-, and macro level health care system factors (see Figure 1) and medication adherence in any population. Overall, the relationships between the factors examined and adherence were inconsistent across the studies, with the majority the relations not being statistically significant. In an attempt to explain the inconsistent findings across the studies, we examined the likelihood of significant relations being reported in relation to a number of study characteristics (study design, patient population, method of measuring adherence, method of analysis and the level of system factor examined). Of these, the only characteristic that approached statistical significance was study design (p= 0.08) with almost twice as many of the relationships examined in cross-sectional or retrospective studies reported as significant than those examined in prospective studies. In this review, however, the proportion of factors examined in prospectively designed studies was relatively small (21.2%). It is possible that other study characteristics not examined in this review (e.g., differences in the definition of adherence or the period over which it was measured) can explain the inter-study variability. The need for a consistent definition of adherence was recognized by the

Ascertaining Barriers for Compliance (ABC) project, a multinational group of researchers and clinicians in adherence research. This group is currently working to achieve international consensus on the terminology used to describe adherence and related concepts, with the immediate goal of standardizing the way adherence is defined, measured and reported [37].

Major variability also occurred in the definitions and measurements of the various micro-, meso-, and macro level factors examined by the studies included in this systematic review. In this review, the factors most consistently related to adherence were drug access (i.e., the better the drug accessibility, the better the adherence rates) and the method of dispensing drugs (e.g., dispensing at the physician's office or off-site). All of the studies examining the relationship between drug accessibility and the dispensing of drugs were conducted in the HIV population.

The only other factor related to adherence in more than half of the studies was trust in the health care provider. The literature contains a number of definitions of trust [38-40]; however, according to Hall et al. (2001), most emphasize "the optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for the truster's interests" [39] (pg. 615). Still, trust in the health care provider is only part of the patient-provider relationship. When the association between the overall patient-provider relationship and adherence was examined, it was only significant in 41.1% of cases.

Another aspect of the patient-provider relationship is communication. Few of the studies in our review specifically examined provider–patient communication. Again, the findings were mixed, with most reporting no significant relation to adherence. In contrast, a recent meta-analysis by Zolnierek & Dimatteo, focusing on physician–patient communication and its association with adherence to treatment regimens for varying medical conditions, concluded that physician communication is significantly positively associated with adherence [19]. More specifically, that meta-analysis linked poor physician communication with a 19% higher risk of non-adherence. Possible explanations for the inconsistency between our findings and those of Zolnierek and Dimatteo include the small number of studies in our review that specifically examined this factor, as well as the methods used to assess communication quality. Future studies should consider using a combination of methods (e.g., patient report and direct observation) to assess patient-provider

communication. Our results suggest that it is not the overall relationship with the health care provider, but rather specific aspects of this relationship (such as trust in the health care provider) that are more important predictors of adherence.

Although the continent and country where patients were followed-up was investigated multivariately in only one study, this factor seems to influence non-adherence. This is consistent with the findings of Dew et al. who reported that non-adherence rates were higher in North-American studies than those from Europe and other continents [13]. Denhaerynck et al. [41, 42] suggest that the differences in adherence found between countries or continents could be based on differences in transcultural factors (e.g., illness beliefs) or differences in health care system characteristics such as health insurance coverage and regulations regarding reimbursement for drugs and medical treatment. In the current systematic review, however, two-thirds of the studies examining cost related factors multivariately found no significant relationship with adherence.

In our systematic review, 3 of the 6 studies examining medication-related costs (50%) reported a significant relationship to adherence. Of these, 2 showed that receiving anti-retroviral therapy (ART) at low or no cost increased the likelihood of adherence. The third [43] showed the opposite – i.e., that receiving the medication for free was associated with lower adherence. The study's investigators speculated that this finding may have occurred because patients who paid for their medications received more counseling and/or had more advanced disease at the time of treatment initiation than those who received their medication at no cost [43]. Consequently, medication cost may have served as a proxy for other system or disease-related factors. In a different patient population, a study of hemodialysis patients in 12 countries reported that medication non-adherence was associated with patients reporting any out-of-pocket costs (R^2= 0.298) and their average out-of-pocket costs (R^2= 0.396) [44]. Another recent study, examining the insurance related experiences of adults in eleven countries in Europe, North-America, Australia and New Zealand, found significant differences in access, cost burdens, and problems with health insurance associated with insurance design [17].

No other factors examined in more than three studies were consistently related to medication adherence. One of the issues we faced in this systematic review was that most of the factors showing a significant relationship to adherence were examined

in a low proportion of studies, which measured those factors in diverse ways. Visit-related factors, for example, were examined as more than 6 months interval between visits in one study, as the number of visits a month in another and as having scheduled appointments in a third study. In addition, a number of factors were only examined in a small number of studies. Such limitations made it difficult to draw confident conclusions about many of the factors' impacts on medication adherence.

Strengths, Limitations, and Research Recommendations

To the best of our knowledge this is the first systematic review comprehensively examine the relationship between health care system factors and medication adherence. This review points out the methodological challenges inherent in comparing findings across studies using difference methods. It identifies the need for additional research to understand the role of health care system factors in medication adherence.

This systematic review has several limitations. The first is that only articles in English were included. As a result, relevant studies may have been missed. Second, the review of citations to select articles for review was conducted by only one individual. Despite the careful procedure followed in searching the literature, it is possible that eligible citations were overlooked. A further limitation is that the gray literature (i.e., studies that are unpublished or not easily located) was not searched. Another is that some factors were not clearly defined in the studies, e.g., scheduled vs. non-scheduled appointments. Further, we limited this review to two chronically ill patient populations.

Because the many methodological differences across the reviewed studies, we strongly recommend conducting a large multi-continental, multi-country, multi-center study to test for associations between factors at the micro-, meso-, and macro level and non-adherence to medication regimens. Another recommendation for further research and its dissemination is that authors of future studies should report the magnitude of the various system factors' effects on adherence.

Conclusion

Most reviewed studies on system factors associated with adherence in the HIV and organ transplant populations were conducted in the HIV population, with little research in transplant populations. While the relationships between the examined system level factors and adherence are inconsistent, this systematic review provides preliminary evidence that at least two of these factors (trust in the health care provider and method of dispensing medications) are important contributors to adherence. Further, considering the limited variability of patient level explanations of non-adherence, it is critical to further explore system level relationships.

Figure 1: Framework for the review: the ecological model of McLeroy et al. (adapted) [1].

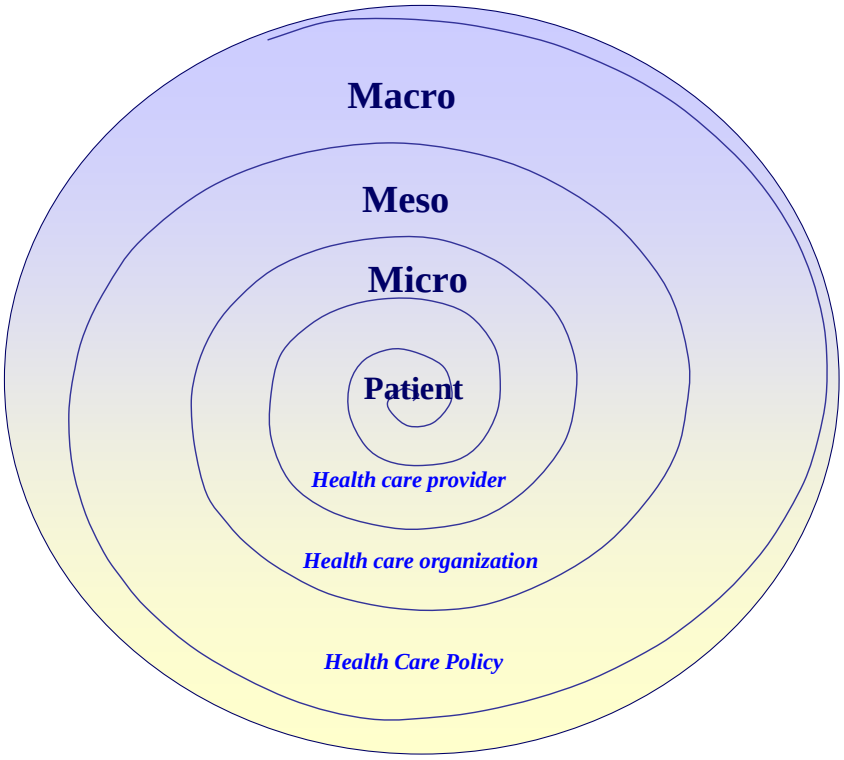

Table 1: Search strategy

Database	Population	Search terms	Number of hits
PubMed			
	HIV	(complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren* OR concordance OR non-concordance OR concord* OR non-concord*) AND HIV	2406
	Transplantation	(complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren* OR concordance OR non-concordance OR concord* OR non-concord*) AND transpl*	1060
CINAHL			
	HIV	(complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren* OR concordance OR non-concordance OR concord* OR non-concord*) AND HIV	837
	Transplantation	(complian* OR noncomplian* OR non-complian* OR adheren* OR nonadheren* OR non-adheren* OR concordance OR non-concordance OR concord* OR non-concord*) AND transpl*	130
EMBASE			
	HIV	'hiv'/mj AND ('compliance' OR compliant OR noncompliance OR noncompliant OR 'non compliance' OR 'non compliant' OR adherence OR	66

	adherent OR nonadherence OR nonadherent OR 'non adherence' OR 'non adherent' OR concordance OR 'non concordance' OR concordant OR 'non concordant')	
Transplantation	('transplantation'/mj OR 'transplant') AND ('compliance' OR compliant OR noncompliance OR noncompliant OR 'non compliance' OR 'non compliant' OR adherence OR adherent OR nonadherence OR nonadherent OR 'non adherence' OR 'non adherent' OR concordance OR 'non concordance' OR concordant OR 'non concordant')	842
Total		5,341

Figure 2: Flow chart of study selection process

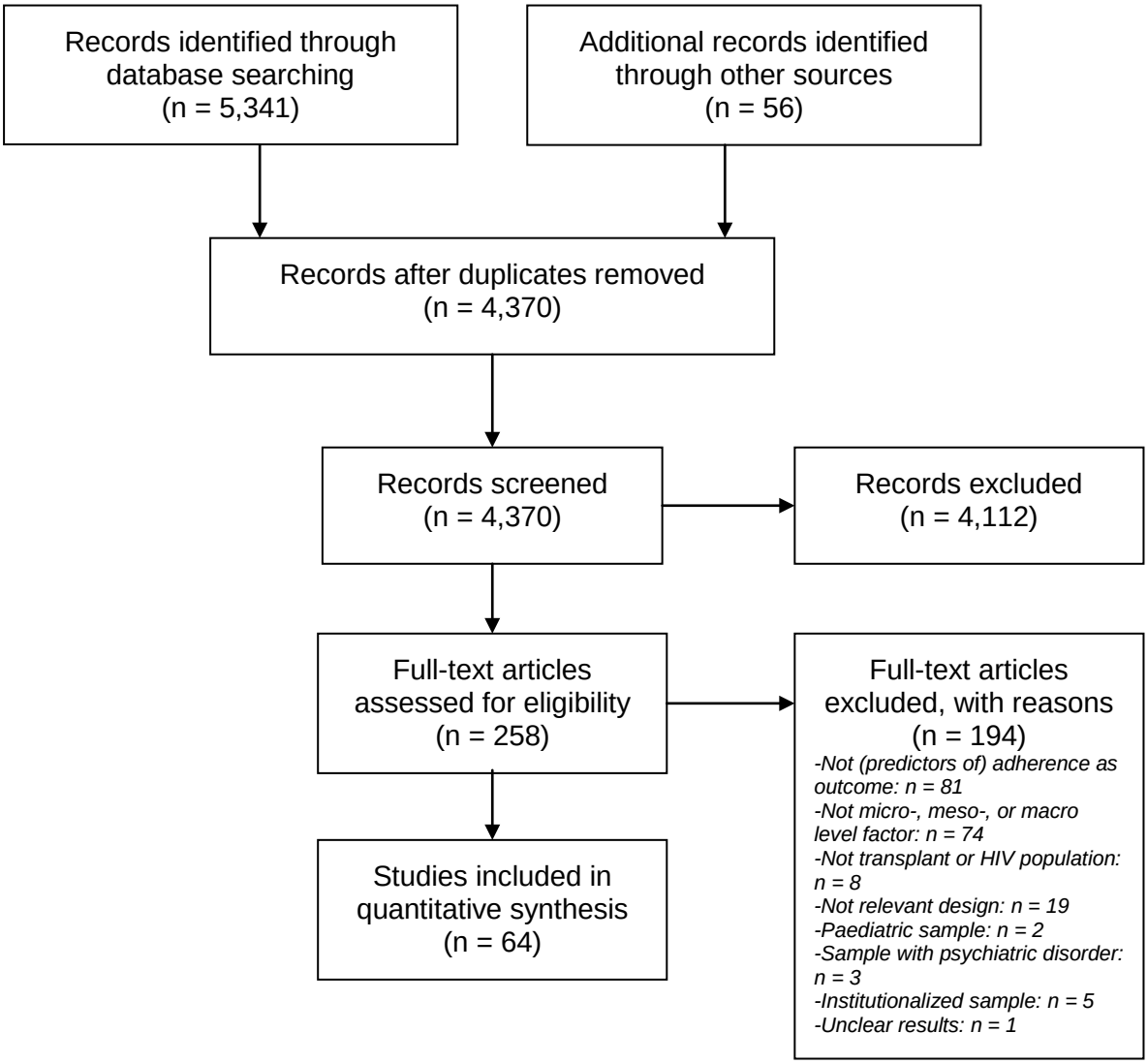

Table 2: Summary of characteristics of the studies

Study location	**HIV** (n= 57) **n (%)**	**Tx** (n= 7) **n (%)**	**Total** N= 64 **n (%)**
North-America	26 (45.6)	3 (42.9)	29 (45.3)
Europe	12 (21.1)	2 (28.6)	14 (21.9)
Africa	9 (15.8)	0	9 (14.1)
Asia	6 (10.5)	1 (14.3)	7 (10.9)
South-America	4 (7.0)	0	4 (6.3)
Combined (North-America & Europe)	0	1 (14.3)	1 (1.6)
Study design			
Cross-sectional/retrospective	45 (78.9)	4 (57.1)	49 (76.6)
Prospective	12 (21.1)	3 (42.9)	15 (23.4)
Method of adherence assessment			
Self-report	46 (80.7)	3 (42.9)	49 (76.6)
Pharmacy refill	4 (7.0)	0	4 (6.3)
Pill count	2 (3.5)	0	2 (3.1)
Electronic monitoring	1 (1.8)	2 (28.6)	3 (4.7)
Collateral report	0	1 (14.3)	1 (1.6)
Blood levels	0	1 (14.3)	1 (1.6)
Multiple	4 (7.0)	0	4 (6.3)
System level			
Micro	28 (49.1)	1 (14.3)	29 (45.3)
Meso	5 (8.8)	2 (28.6)	7 (11.0)
Macro	11 (19.3)	4 (57.1)	15 (23.4)
Micro and meso	7 (12.3)	0	7 (11.0)
Meso and macro	3 (5.3)	0	3 (4.7)
Micro and macro	1 (1.8)	0	1 (1.6)
Micro, meso and macro level	2 (3.5)	0	2 (3.1)

Figure 3: Quality appraisal of studies

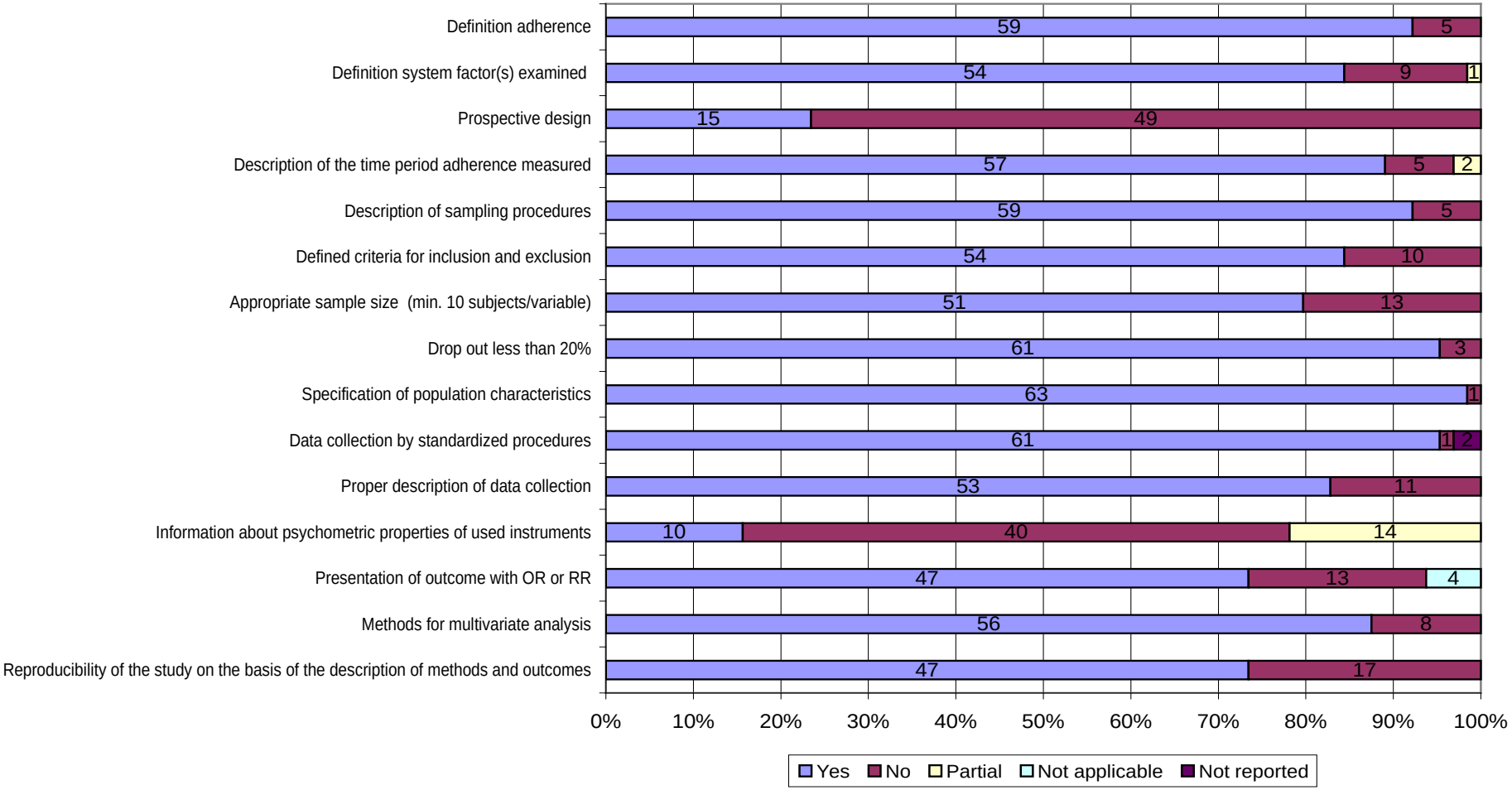

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Table 3: Studies Examining the Relationship between Micro Level Systems Factors and Adherence

Study/Patient Population	Design/Sample/ Definition of Adherence/Non-Adherence	Micro Level Factors	Results	Adherence Effect Size
Mulltivariate Analysis				
Beach, Keruly, & Moore, 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 1743 (38.8% women); duration of ART not reported **Non-adherence**= not missed 1 dose of medication during the past 3 days as measured by self-report Adherence rate= 74.9%	Quality of the patient-provider relationship	OR= 1.33 (95% CI 1.02, 1.72) p= 0.034	Multivariate OR: 1.33 (1.02, 1.72)
Bonolo Pde, Cesar, Acurcio, Ceccato, de Padua, Alvares et al., 2005 HIV/AIDS	**Design:** Prospective **Setting:** Brazil **Sample:** 306 (35% women); newly initiated ART **Non-adherence**= < 95% of prescribed number of doses taken during previous 3 days as measured by self-report Adherence rate= 63.1%	Counseling about ART	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate hazards ratio for non-adherence: 1.33 (95% CI 0.9, 1.97)	Unable to calculate
Carballo, Cadarso-Suarez, Carrera, Fraga, de la Fuente, Ocampo et al., 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** Spain **Sample:** 235 (28.5% women); on ART ≥ 3 months **Adherence**= ≥ 95% during the prior 3 months; measured by self-report Adherence rate= 55.7%	Satisfaction with health care provider	Intermediate to high satisfaction vs low: OR= 2.07 (95% CI 1.07, 3.98), p= 0.03	Multivariate OR: 2.07 (1.07, 3.98)
Catz, Heckman, Kochman, & DiMarco, 2001 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 84 (20% women); ≥ 45y older **Adherence**= no skipped doses in the past week as measured by self-report Adherence rate= 69%	Relationship with physician	OR= 2.18 (95% CI 1.19, 3.96), p= 0.01	Multivariate OR: 2.18 (1.19, 3.96)
Delgado, Heath, Yip, Marion,	**Design:** Prospective **Setting:** Canada	Physicians' HIV-related experience	OR= 1.27 (95% CI: 1.13, 1.42; p< 0.001)	Multivariate OR: 1.27 (1.13, 1.42)

Alfonso, Montaner et al., 2003 HIV/AIDS	**Sample:** 886 (13.5% women); ART naive at enrolment and followed for the first 12 months of therapy **Adherence**= > 95% of the time during the 1 year of therapy; measured by prescription refill rates Adherence rate= 55.9%	(per 100 HIV-positive patients treated)		
Durante, Bova, Fennie, Danvers, Holness, Burgess et al., 2003 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 63 women; duration of ART not reported **Adherence**= 100% adherence during the previous 3 days; measured by self-report Adherence rate= 67%	Trust in physician	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate analysis: Wilcoxin Z= -0.83, p= 0.41	Estimated bivariate OR=0.67 (0.26, 1.74)
Eholie, Tanon, Polneau, Ouiminga, Djadji, Kangah-Koffi et al., 2007 HIV/ADIS	**Design:** Cross-sectional **Setting:** Côte d'Ivoire **Sample:** 308 (53% women); on ART ≥ 1 month **Adherence**= < 90% over the previous 7 days measured by self-report Adherence rate= 24%	Previous counseling about ART	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate results no reported.	Unable to calculate
Gauchet, Tarquinio, & Fischer, 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** France **Sample:** 127 (22% women); duration of ART > 2 months **Adherence**= measured as a continuous variable measured by a self-report scale Adherence rate= not reported	Confidence in physician	B= 0.30; p= 0.02	Unable to calculate
Gremigni, Bacchi, Turrini, Cappelli, Albertazzi, & Bitti, 2007 Transplant Recipients	**Design:** Cross-sectional **Setting:** Italy **Sample:** 34 renal transplant recipients (62% women) ≥ 12 months post-transplant (mean= 6 yrs) **Adherence**= taking medications exactly as prescribed during the past month; measured by self-report. Adherence rate= 76%	Clarity of physician instructions Trust in health care provider	Both factors not significant related to adherence in multivariate analysis (p value not reported)	Unable to calculate Unable to calculate

Heckman, Catz, Heckman, Miller, & Kalichman, 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US, living in rural areas **Sample:** 329 (30% women); duration of ART not reported **Adherence**= 100% adherent during the previous week; measured by self-report Adherence rate= 50%	Relationship with physician (good vs poor)	OR= 1.82 (95% CI 0.79, 4.17), ns	Multivariate OR: 1.82 (0.79, 4.17)
Ingersoll & Heckman, 2005 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 120 (38% women); duration of ART not reported **Adherence**= always taking medication as prescribed, never running out of medication as measured by self-report and not having non-adherence noted in the medical records Adherence rates based on meeting all three criteria= 29%	Patient-physician relationship Physician communication	Being non-adherent (based on meeting one or fewer of the 3 criteria: OR= 0.97 (95% CI 0.94, 1.01) OR= 1.04 (95% CI 1.00, 1.09)	Multivariate OR: 1.03 (1.00, 1.06) 0.96 (0.92, 1.00)
Johnson, Chesney, Goldstein, Remien, Catz, Gore-Felton et al., 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 276 (26% women); mean duration of ART= 2.4 years **Adherence**= $\geq$ 90% adherence during the previous 3 days as measured by self-report Adherence rate= 68.25%	Patient-physician relationship	Not significantly related to non-adherence OR= 0.86 (95% CI 0.74, 1.01)	Multivariate OR: 1.16 (0.99, 1.36)
Kalichman, Ramachandran, & Catz, 1999 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 184 subjects on triple combination therapy (24% women); duration of ART not reported **Adherence**= 100% for the past 2 days; measured by self-report Adherence rate= 80%	Relationship with health care provider	OR= 1.1 (95% CI 0.6, 1.4), ns	Multivariate OR: 1.1 (0.6, 1.4)
McDonnell Holstad, Pace, De, & Ura, 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 120 (35% women); on ART $\geq$ 1 months (M=3.1 years) **Adherence**= measured as a continuous	Interpersonal aspects of care (i.e., communication, concern, trust)	Not significantly related to adherence multivariately; statistics not reported	Unable to calculate

	variable over the past 4 weeks by a self-report survey Mean adherence rate= 83.1%±15.7%			
Molassiotis, Morris, & Trueman, 2007 HIV/ADIS	**Design:** Cross-sectional **Setting:** UK **Sample:** 38 (21.1% women) (average 57 months on ART) **Adherence** > 2 doses missed in past week or > 2 days total non-adherence in past 3 months as measured by self-report Adherence rate= 63.2%	Level of trust in nurse	SE= 0.42 Beta= 0.52 p< 0.001	Unable to calculate
Moralejo, Ines, Marcos, Fuertes, & Luna, 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** Spain **Sample:** 143 (31% women); mean days on ART= 539.9 **Non-adherence**= any reported non-adherence by self-report ≥ 2 days during the previous 5 days or any reported non-adherence reported by pharmacy both measured by self-report Adherence rate= 67.13%	Patient-physician relationship Accessibility to physicians	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate OR= 2.08 (95% CI 0.28, 15.38) Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate OR= 0.88 (95% CI 0.31, 2.56)	Bivariate OR: 2.08 (0.28, 15.38) Bivariate OR: 0.88 (0.31, 2.56)
Murphy, Marelich, Hoffman, & Steers, 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 115 patients who were having problems with adherence; duration of ART not reported **Adherence**= ≥ 95% adherent during the past 3 days, past week and past month as measured by self-report Adherence rate= 58.3% during the previous 3 days, 34.8% during the past week and 26.1% during the previous month	Patient-provider relationship: Patient Information Index, Patient Communication Index Patient Affective Index	3 day adherence: Communication index: OR: 1.13, (95% CI: 1.01, 1.27), p< 0.05 Patient Information Index and Patient Affective Index not significant multivariately; no statistics reported 1 week adherence: None of the indexes were significant mutivariately; statistics not reported	Multivariate OR: 1.13 (1.01, 1.27) Unable to calculate Unable to calculate

			1 month adherence: None of the indexes were significant multivariately; statistics not reported	
Nilsson Schonnesson, Diamond, Ross, Williams, & Bratt, 2006 HIV/AIDS	**Design:** Prospective **Setting:** Sweden **Sample:** 144 (22% women); on ART ≥ 6 months **Adherence**= 100% adherent to ART dose and schedule over the past 4 days measured by self-report Mean adherence rate= 61% dose and 39% to schedule	Patient-provider relationship Perceived pressures for taking medication from medical staff	Dose adherence: no significant relationship; no statistics reported Schedule adherence: OR= 1.579, B= 0.457, SE= 0.453, p= 0.313 Dose adherence: no significant relationship; no statistics reported Schedule adherence: OR= 0.59, B= -0.533, SE= 0.262, p= 0.04	Bivariate OR: 1.08 (0.54, 2.16) Multivariate OR: 1.58 (0.85, 3.83) Multivariate OR: 0.92 (0.68, 1.25) Multivariate OR: 0.59 (0.34, 0.99)
Nilsson Schonnesson, Williams, Ross, Bratt, & Keel, 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** Sweden **Sample:** 193 (25% women); duration of ART ≥ 6 months (mean= 47 months) **Adherence** to dose instruction= ≥ 95%; adherence to schedule instructions= 100%; measured over the past 4 days by self-report Adherence rate= 88% to doses prescribed; 63% to dosing schedule	Patient-provider relationship	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate OR for non-adherence to dosing= 0.81 (95% CI 0.34, 1.96) Bivariate OR for scheduling non-adherence= 1.04 (0.58, 1.91)	Bivariate OR (dosing): 1.23 (0.51, 2.99) Bivariate OR (scheduling): 0.96 (0.53, 1.76)
Protopopescu, Raffi, Roux, Reynes, Dellamonica, Spire et al., 2009 HIV/AIDS	**Design:** Prospective **Setting:** France **Sample:** 1010 (21.5% women); median duration of ART= 0.6 years **Adherence**= 100% adherent during the previous 4 weeks; measured by self-report Adherence rate= not reported	Confidence in physicians	Not significantly related to adherence multivariately; statistics not reported	Unable to calculate
Reif, Whetten,	**Design:** Cross-sectional	Unmet needs for	OR= 0.32, p< .01	Multivariate OR: 0.32

Lowe, & Ostermann, 2006 HIV/AIDS	**Setting:** US **Sample:** 526 (36% women); duration of ART not reported **Adherence**= always took medication as prescribed during the past month; measured by self-report Adherence rate= 62%	counseling		(CI not reported: unable to calculate)
Remien, Bastos, Jnr, Raxach, Pinto, Parker et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** Brazil **Sample:** 200 (29% women); on ART ≥ 1 month **Adherence**= ≥ 90% over the previous 3 days measured for self-report Adherence rate= 86%	Positive patient-provider interactions	Not significantly related to adherence multivariately; statistics not reported	Unable to calculate
Schneider, Kaplan, Greenfield, Li, & Wilson, 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 554 (15.29% women); duration of ART not reported **Adherence**= measured ordinally: 0-60%; 61-90%; 91-99%; 100% over the prior 4 weeks; measured by self-report	<u>Perceptions about quality of physician relationship:</u> Communication HIV counseling Trust Participatory decision making Adherence counseling Overall satisfaction Willingness to recommend	 OR= 1.15 (95% CI 1.07, 1.23), p< .001 OR= 1.09 (95% CI 1.01 to 1.16), p= .02 OR= 1.10 (95% CI 1.01, 1.21), p= .03 OR= 1.07 (95% CI 0.99 to 1.15), p= .12 OR= 1.20 (95% CI 1.10, 1.30), p< .001 OR= 1.14 (95% CI 1.04, 1.25), p= .004 OR= 1.09 (95% CI 1.02, 1.15), p= .009	Multivariate OR: 1.15 (1.07, 1.23) 1.09 (1.01, 1.16) 1.10 (1.01, 1.21) 1.07 (0.99, 1.15) 1.20 (1.10, 1.30) 1.14 (1.04, 1.25) 1.09 (1.02, 1.15)
Shaahu, Lawoyin, & Sangowawa, 2008	**Design:** Cross-sectional **Setting:** Nigeria **Sample:** 428 (64.7% women); 74.3% had been on ART > 6 months	Perception of health care provider as non-judgmental	Not significantly related to adherence multivariately; Bivariate OR: 1.97 (1.25, 2.12)	Bivariate OR: 1.97 (1.25, 2.12)

HIV/AIDS	**Adherence:**= ≥ 95% adherent between the onset of treatment and the time of the study by self-report Adherence rate= 62.6%			
Shah, Walshe, Saple, Mehta, Ramnani, Kharkar et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** India **Sample:** 278 (27.2% women); on ART ≥ 3 months **Adherence**= ≥ 95% of the prescribed doses over the past 4 days measured by self-report Adherence rate= 73%	Number of elements addressed during pre-ART counseling	Not significantly related to adherence multivariately; no statistics reported	Unable to calculate
Sodergard, Halvarsson, Tully, Mindouri, Nordstrom, Lindback et al., 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** Sweden **Sample:** 659 (36.7% women); on ART ≥ 4 months **Adherence**= ≥ 95% of prescribed doses by self-report; time period not reported Adherence rate= 63%	Relationship with health care provider (very good vs less than very good)	OR for non-adherence= 0.59 (95% CI 0.37, 0.95); p= 0.031	Multivariate OR: 1.69 (1.06, 2.70)
Tadios & Davey, 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** Ethiopia **Sample:** 431 (49.9% women); duration of ART not reported **Adherence**= ≥ 95% during the previous 7 days as measured by self-report Adherence rate= 81.2%	Patient-provider relationship Physician judged capable and trustworthy	OR= 7.5 (95% CI 1.9, 28); p= 0.003 OR= 10.8 (95% CI 1.4, 86); p= 0.025	Multivariate OR: 7.50 (1.90, 28.00) 10.80 (1.40, 86.00)
van Servellen & Lombardi, 2005 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 85 Spanish speaking Latino's, with adherence problems documented in med record (10% women); duration of ART not reported **Adherence**= ≥ 90% adherence during the past 4 days; measured by self-report Adherence rate= not reported	Patient-provider communications and relationships	OR= 1.03 (95% CI 0.93, 1.15), p= 0.53	Multivariate OR: 1.03 (0.93, 1.15)
Vincke & Bolton, 2002 HIV/AIDS	**Design:** Cross-sectional **Setting:** Belgium **Sample:**86 (21.4% women); duration of ART	Satisfaction with relationship with health care provider	β= -0.04, ns	Unable to calculate CI

	not reported **Adherence**= measured as a continuous variable; self report SR: subjects reported that on average had not take ART as prescribed 1-2 days during past 4 weeks Sign others mean = 4.2± 0.5 on a 5 point scale (5 = excellent adherence)			
Wang, He, Li, Yang, Chen, Fennie et al., 2008 HIV/AIDS	**Design:** Cross-sectional **Setting:** China **Sample:** 308 (37.3% women); duration of ART ≥1 month (mean=17.7 months) **Adherence**= taking > 90% of ART during previous 7 days; measured by self-report Adherence rate= 79%	Satisfaction with health care provider	Not significantly related to adherence bivariately; not included in multivariate analysis Bivariate OR adherence: 0.81 (95% CI 0.29, 2.30)	Bivariate OR: 0.81 (0.29, 2.30)
Wang & Wu, 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** China **Sample:** 181 (59.7% women); 24.4% on ART < 6 months **Adherence**= ≥ 95% during the previous 3 days by self-report Adherence rate= 81.8%	Trust in physician	OR= 7.79 (95% CI 1.26, 48.95), p= 0.03	Multivariate OR: 7.79 (1.26, 48.95)
Bivariate analysis only				
Bakken, Holzemer, Brown, Powell-Cope, Turner, Inouye et al., 2000 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 707 (23% women); duration of ART not reported **Adherence**= measured as continuous variable by self report; time period no reported Adherence rate= not reported	Relationship with health care provider	r= 0.11, p= 0.005	Approximate bivariate OR: 1.49 (1.14, 1.96)
Bogart, Bird, Walt, Delahanty, & Figler, 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 110 (17% women); duration of ART not reported **Adherence**= 100% adherent during the last week and last 2 weeks as measured by self-	Negative physician traits	2 week adherence: r= -0.17, ns 1 week adherence: r= -0.16, ns	Approximate bivariate OR: 0.56 (0.27, 1.11) 0.53 (0.13, 1.06)

	report Adherence rate= not reported	Positive physician traits Positive feelings about physician	2 week adherence: r= 0.02, ns 1 week adherence: r= 0.05, ns 2 week adherence: r= 0.07, ns 1 week adherence: r= 0.05, ns	1.08 (0.54, 2.14) 1.20 (0.60, 2.39) 1.09 (0.60, 2.39) 1.29 (0.65, 2.57)
Deschamps, Graeve, van Wijngaerden, De Saar, Vandamme, van Vaerenbergh et al., 2004 HIV/AIDS	**Design:** Prospective **Setting:** Belgium **Sample:** 43 (12% women); on ART ≥ 1 month **Non-adherence**= taking adherence < 90%, or dose adherence < 75% and at least 1 drug holiday or a timing adherence < 80% and at least 1 drug holiday, or > 6 drug holidays per 100 days over the prior 3 to 4 months; measured by electronic monitoring Adherence rate= 60.5%	Satisfaction with health care provider	Not significantly related to adherence bivariately (p= 0.17)	Approximate bivariate OR: 2.21 (0.72, 6.76)
Dorz, Lazzarini, Cattelan, Meneghetti, Novara, Concia et al., 2003 HIV/AIDS	**Design:** Cross-sectional **Setting:** Italy **Sample:** 109 (19.3% women); duration of ART≥ 6 months **Adherence**= ≥ 80%= adherent during the previous week as measured by self-report Adherence rate= 88.1%	Physician-patient relationship	Quality of the relationship: Adherent M= 87.3±16.6 (n= 96); Non-adherent M= 87.3±12.4 (n= 13), ns Competence and communication about therapy: Adherent M= 82.6±17.7 (n= 96); Non-adherent M= 75.0±19.6 (n= 13), ns Availability of provider: Adherent M= 73.6±19.1 (n= 96); Non-adherent M= 70.7±19.6 (n= 13), ns	Approximate bivariate OR: 1.01 (0.35, 2.89) 2.02 (0.70, 5.79) 1.31 (0.70, 5.75)
Thorburn Bird, Bogart, & Delahanty, 2004	**Design:** Cross-sectional **Setting:** US **Sample:** 110 (17.3% women); duration of	Perceived discrimination in HIV treatment		

HIV/AIDS	ART not reported **Adherence**= 100% adherent during the past 2 weeks, past week and past 2 days; measured by self-report Adherence rate= not reported	during interactions health care providers: Race based Socioeconomic-based	 Past 2 weeks r= -0.12; ns Past week r= -0.14, ns Past 2 days r= -0.19, ns Past 2 weeks r= -0.29; p< 0.01 Past week r= -0.32; p< 0.01 Past 2 days r= -0.32; p< 0.01	Approximate bivariate OR: 0.64 (0.34, 34.99) 0.76 (0.29, 1.20) 0.49 (0.23, 1.00) 0.33 (0.16, 0.68) 0.29 (0.14, 0.60) 0.29 (0.14, 0.60)

Table 4: Studies Examining the Relationship between Meso Level Systems Factors and Adherence

Study/Patient Population	Design/Sample/Definition of Adherence/Non-Adherence	Meso Systems Factors	Results	Adherence Effect Size
Mulltivariate Analysis				
Bonolo Pde, Cesar, Acurcio et al., 2005 HIV/AIDS	**Design:** Prospective **Setting:** Brazil **Sample:** 306 (35% women); newly initiated ART **Non-adherence**= < 95% of prescribed number of doses taken during previous 3 days as measured by self-report Adherence rate= 63.1%	Center > 6 month interval between visits Difficulty finding HIV-specific services	Not significantly related to adherence bivariately [Relative Hazard= 1.42 (95% CI 0.82, 2.44)] not included in multivariate analysis Not significantly related to adherence bivariately [Relative Hazard= 0.99 (95% CI 0.60, 1.64)]: not included in multivariate analysis Not significantly related to adherence bivariately [Relative Hazard= 1.02 (95% CI 0.68, 1.51)]; not included in multivariate analysis	Unable to calculate Unable to calculate Unable to calculate
Denhaerynck, Steiger, Bock et al., 2007 Transplant recipients	**Design:** Prospective **Setting:** 2 centers in Switzerland **Sample:** 291 renal (43.4% women); ≥1 year post-transplant (mean= 8.5 yrs) **Non-adherence**= inter-dose interval that deviated more than 25% from the prescribed interval; measured for electronic monitoring for 2 months following a 35 day wash-out period Dosing adherence= 98%; timing adherence= 96%	Center	$OR_{\text{Center 1 vs. 2}}$ not significant bivariately after adjusting for multiple comparisons [OR= 0.51 (95% CI 0.27, 0.96)]; not included in multivariate analysis $OR_{\text{Center 1 vs. other centers}}$= not significant bivariately after adjusting for multiple comparisons [OR= 0.23	Bivariate OR: 0.51 Bivariate OR: 0.23

			(95% CI 0.06, 0.96)]; not included in multivariate analysis	
Ingersoll & Heckman, 2005 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 120 (38% women); duration of ART not reported **Adherence**= always taking medication as prescribed, never running out of medication as measured by self-report and not having non-adherence noted in the medical records Adherence rates based on meeting all three criteria= 29%	Organizational accessibility	Being non-adherent (based on meeting one or fewer of the 3 criteria: OR= 0.97 (95% CI 0.94, 1.01)	Multivariate OR: 1.03 (1.00, 1.06)
Kapadia, Vlahov, Wu, Cohen, Greenblatt, Howard et al., 2008 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 573 (100% women); median ART treatment= 38.7 months; median HAART= 18.5 months **Adherence**= $\geq$ 95% over the past 6 months based on self-report Adherence rate= 73%	Had a doctor's visit in last 6 months	No significant relationship bivariately (p= .59); not examined multivariately	Bilvariate OR=0.58 (0.33, 1.01)
Kleeberger, Phair, Strathdee, Detels, Kingsley, & Jacobson, 2001 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 539 (not women); duration of ART not reported **Adherence**= 100% adherent over the past 4 days; measured by self-report Adherence rate= 77.7%	Use of health care (no health care visits within the previous 6 to 12 months)	OR non-adherence= 3.6 (95%CI 1.5, 8.4)	Multivariate OR: 0.28 (0.12, 0.67)
Marcellin, Boyer, Protopopescu, Dia, Ongolo-Zogo, Koulla-Shiro et al., 2008 HIV/AIDS	**Design:** Cross-sectional **Setting:** Cameroon **Sample:** 533 (70.9 % Women) Mean time of ART= 13.9 m **Non-adherence**= Interruption > 2 days during the previous 4 weeks; measured by self report Adherence rate= 82.7%	Pharmacy stock shortages Difficulty obtaining a consultation with physician	Multivariate OR for non-adherence of 3.25 (1.78, 5.90), p< 0.0001 Not significant multivariately; no statistics reported	Multivariate OR: 0.31 (0.17, 0.56) Unable to calculate
Mellins, Chu,	**Design:** Prospective	Center	Not significantly related to	Unable to calculate

Malee, Allison, Smith, Harris et al., 2008 HIV/AIDS	**Setting:** US **Sample:** 309 women in 3th trimester of pregnancy, 220 at 6 months postpartum **Adherence**= no missed doses in the past month; measured by self-report Adherence rate= 61% during the 3rd trimester and 44% 6 months postpartum		adherence multivariately; no statistics reported	
Merenstein, Schneider, Cox, Schwartz, Weber, Robison et al., 2009 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 1419 (100% women); duration of ART not reported **Adherence**= ≥ 95% during the previous 6 months by self report Adherence rate= 76%	Seen by a social worker or case manager since last visit	OR= 1.06 (95% CI 0.95, 1.18)	Multivariate OR: 1.06 (0.95, 1.18)
Moralejo, Ines, Marcos et al., 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** Spain **Sample:** 143 (31% women); mean days on ART= 539.9 **Non-adherence**= any reported non-adherence by self-report ≥ 2 days during the previous 5 days or any reported non-adherence reported by pharmacy both measured by self-report Adherence rate= 67.13%	Accessibility to the pharmacy hospital to collect medication	Not significantly related to adherence bivariately [OR= 0.91 (95% CI 0.41, 2.26); not included in multivariate analysis	Bivariate OR: 0.91 (0.41, 2.26)
Muyingo, Walker, Reid, Munderi, Gibb, Ssali et al., 2008 HIV/AIDS	**Design:** Prospective **Setting:** Uganda and Zimbabwe **Sample:** 2957 (65% Women) ART naive at enrollment; followed for 52 weeks post-initiation **Adherence**= 100% over the prior 4 weeks by pill count 49% of subjects had good adherence (≥ 95%) across all treatment visits 100% adherence rate= 75%; 95% adherence rate= 93%	Center (2 centers in Uganda (1 with an additional satellite site) and 1 center in Zimbabwe)	Multivariate OR relative to Center A: Center B: 1.32 (1.20, 1.47) Center C: 1.89 (1.71, 2.10) Center D: 1.70 (1.42, 2.03) P< 0.001	Multivariate OR: 1.32 (1.20, 1.47) 1.89 (1.71, 2.10) 1.70 (1.42, 2.03)
Nemes, Carvalho, &	**Design:** Cross-sectional **Setting:** Brazil	Center (number of patients seen: ≤ 100	Non-adherence OR= 1.51 (95% CI 1.06, 2.15), p=0.02	Multivariate OR: 0.58 (0.38, 0.89)

Souza, 2004 HIV/AIDS	**Sample:** 1972 (38% women); on ART ≥2 months **Adherence**= > 95% of the prescribed ART for the past 3 days; measured by self-report Adherence rate= 75%	vs >500) Quality of care (best+, best, worst, worst-)	No significant relationship bivariately (Non-adherence: OR, 95% CI) Best vs. best+: 0.81 (0.60, 1.08) Worst vs. best+: 0.99 (0.69, 1.42) Worst- vs. best +: 0.87 (0.68, 1.12); not examined multivariately	Bivariate OR: Best vs. best+: 1.23 (0.91, 1.67) Worst vs. best+: 1.01 (0.70, 1.45) Worst- vs. best+: 1.15 (0.97, 1.47)
Reif, Whetten, Lowe et al., 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 526 (36% women); duration of ART not reported **Adherence**= always took medication as prescribed during the past month; measured by self-report Adherence rate= 62%	Use of HIV case management	OR= 1.23, ns (CI not reported)	Multivariate OR: 1.23 (CI not reported; unable to calculate)
Shaahu, Lawoyin, & Sangowawa, 2008 HIV/AIDS	**Design:** Cross-sectional **Setting:** Nigeria **Sample:** 428 (64.7% women); 74.3% had been on ART> 6 months **Adherence**= ≥ 95% adherent between the onset of treatment and the time of the study by self-report Adherence rate= 62.6%	ART always available at the clinic	OR= 5.2 (95% CI 3.1, 8.6), p< 0.001	Multivariate OR: 5.20 (3.10, 8.6)
Shah, Walshe, Saple et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** India **Sample:** 278 (27.2% women); on ART≥ 3 months **Adherence**= ≥ 95% of the prescribed doses over the past 4 days measured by self-report Adherence rate= 73%	Satisfaction with clinic	Not significantly related to adherence multivariately; no statistics reported	Unable to calculate
Sitta, Lert, Gueguen, Spire, & Dray-Spira,	**Design:** Cross-sectional **Setting:** France **Sample:** 699 (25% women); duration of ART	Center	Not significantly related to adherence multivariately; no statistics reported	Unable to calculate

2009 HIV/AIDS	not reported **Adherence**= scrupulously following treatment during the past 7 days by self-report Adherence rate= 63.3%			
Tadios & Davey, 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** Ethiopia **Sample:** 431 (49.9% women); duration of ART not reported **Adherence**= ≥ 95% during the previous 7 days as measured by self-report Adherence rate= 81.2%	Access to reliable pharmacy Having scheduled appointments	OR= 3.0 (95% CI 1.3, 6.9); p= 0.009 OR= 6.9 (95% CI 2.0, 22.9), p= 0.002	Multivariate OR: 3.00 (1.30, 6.90) 6.90 (2.00, 22.90)
Turner, Newschaffer, Zhang, Cosler, & Hauck, 2000 HIV/AIDS	**Design:** Retrospective **Setting:** US **Sample:** 549 HIV+ post-partum women prescribed ART during 1 post-partum year **Adherence**= ≥ 80% of days during the 1st year post-partum measured by prescription refill rate Adherence rate= 28%	HIV focused service Average number of physician/clinic visits per month	OR= 2.13 (95% CI 1.05, 4.30), p= 0.04 Not significantly related to adherence bivariately (p= 0.18); not included in multivariate analysis	Multivariate OR: 2.13 (1.05, 4.30) Unable to calculate
Weng, Israni, Joffe, Hoy, Gaughan, Newman et al., 2005 Transplant recipients	**Design:** Prospective **Setting:** 8 centers in Pennsylvania (US) **Sample:** 278 renal transplant recipients (38.8% female) Recruited at time of Tx and followed up to 12 months **Adherence**= Subjects categorized into 4 groups: 0-50%; > 50 to 80%; > 80-95%, and > 95 to 100% average daily % adherence for up to 12 months follow-up measured by electronic monitoring Adherence rates= 95%-100%= 41%; 80%-95%= 32.4%	Center	Significantly related to adherence: p< 0.001, ORs not reported	Approximate multivariate OR (based on p-value): 0.43 (0.28, 0.66)
Bivariate analysis only				
Castillo, Palepu, Beardsell, Akagi, Yip,	**Design:** Retrospective **Setting:** Canada **Sample:** 788 (proportion of women (varied	HAART dispensing site: AIDS care pharmacy (with	Adherence rates: AIDS pharmacy: 70.4% Off-site pharmacy: 59.2%	

Montaner et al., 2004 HIV/AIDS	from 13.7% in AIDS Pharmacies to 30.3% in physician offices); newly started on ART; followed for 1 year **Adherence**= > 90% during the first year of therapy; measured by pharmacy refill rates Adherence rate= pharmacy: 70.4% in AIDS pharmacies, 59.2% in off-site pharmacies and 55.7% in physician offices	regular medication counseling), outpatient pharmacy, or physician office	Physician office: 55.7% AIDS pharmacy vs off-site and physician office p= .0001); Off-site vs physician office (p= 0.52) AIDS pharmacy vs off-site AIDS pharmacy vs physician office Off-site vs physician office	 Bivariate OR: 1.64 (1.05, 2.56) 1.89 (1.34, 2.65) 1.15 (0.71, 1.88)
Gross, Zhang, & Grossberg, 2005 HIV/AIDS	**Design:** Retrospective **Setting:** US **Sample:** 110 veterans (2% women); on ART≥ 3 months **Adherence**= ≥ 85% during the past 3 months measured by refill rates Adherence rate= mail order 91; pick-up 80%; pill organizer 99%	Dispensing of drugs	Proportion of subjects with "good" adherence: 100% (n= 10) with pharmacy dispensed pill organizers vs. 39% (n= 23) who picked up refills at pharmacy (p= <.001) 61% (n= 25) who received refills via mail vs. 39% (n= 23) who picked up prescriptions (p= .03) 100% (n= 10) with pharmacy dispensed pill organizer vs.61% (n= 25) with mailed refills (p= .02)	32.62 (3.95, 269. 19) 2.45 (1.08, 5.54) 2.61 (1.60, 115.09)

Table 5: Studies Examining the Relationship between Macro Level Systems Factors and Adherence

Study/Patient Population	Design/Sample/ Definition of Adherence/Non-Adherence	Macro Level Factors	Results	Adherence Effect Size (OR, 95% CI)
Mulltivariate Analysis				
Arrivillaga, Ross, Useche, Alzate, & Correa, 2009 HIV/AIDS	**Design:** Cross-sectional **Setting:** Colombia **Sample:** 269 (100% women); duration of ART not reported **Adherence**= complying at least 64% of the "treatment requirements" as measured by self-report Adherence rate= 57%	Subsidized national health care plan or uninsured vs enrollment in a contributive plan	OR= 3.48 (95% CI 1.96, 6.18); p< 0.0001	Multivariate OR: 0.29 (0.16, 0.51)
Bonolo Pde, Cesar, Acurcio et al., 2005 HIV/AIDS	**Design:** Prospective **Setting:** Brazil **Sample:** 306 (35% women); newly initiated ART **Non-adherence**= < 95% of prescribed number of doses taken during previous 3 days as measured by self-report Adherence rate= 63.1%	Not having health insurance	No significant multivariate relationship; statistical results not reported	Unable to calculate
Byakika-Tusiime, Oyugi, Tumwikirize, Katabira, Mugyenyi, & Bangsberg, 2005 HIV/AIDS	**Design:** Cross-sectional **Setting:** Uganda **Sample:** 304 (53.3% women); duration of ART≥ 1 month **Adherence**= ≥ 95% during the previous 3 days; measured by self-report Adherence rate= 68%	Cost of drugs Distance from home to treatment	OR= 0.95 (95% CI 0.29, 3.15) OR= 1.01 (95% CI 0.45, 1.25)	Multivariate OR: 0.95 (0.29, 3.15) 1.01 (0.45, 1.25)
Carlucci, Kamanga, Sheneberger, Shepherd, Jenkins, Spurrier et al., 2008	**Design:** Prospective **Setting:** Zambia **Sample:** 424 (63% women); On ART ≥ 2 months **Adherence**= ≥ 95% scheduled doses taken since previous appointment measured by pill count	Travel duration Cost of transportation	OR= 1.0 (95%CI 0.91, 1.1), p= 0.9 OR= 0.7 (95% CI 0.35, 1.4), p= 0.3	Multivariate OR: 1.0 (0.91, 1.1) 0.70 (0.35, 1.4)

HIV/AIDS	Adherence rate= 83.7%			
Chisholm, Kwong, & Spivey, 2007 Transplant recipients	**Design:** Retrospective **Setting:** US **Sample:** 53,997 renal (40% women); up to 36 months post-transplant **Adherence**= no chart report of non-adherence during the first 36 months post transplant. Adherence rate= 94%	Primary insurance	Compared to those not on Medicare, Medicare recipients were significantly less likely to be non-adherent (OR: 0.61; 95% CI 0.54, 0.68; p< 0.001) Medicaid was not significantly related to non-adherence (OR= 1.13; 95% CI: 0.92, 1.39)	Multivariate OR: 1.64 (1.45, 1.85) 0.89 (0.72, 1.09)
Denhaerynck, Desmyttere, Dobbels et al., 2006 Transplant recipients	**Design:** Cross-sectional **Setting:** Subjects from 3 independent but similar studies conducted in the US and Western Europe (Belgium, the Netherlands & Switzerland) **Sample:** Renal transplantation: 1563 US and 614 European (EU) patients (Belgium: n= 187; the Netherlands: n= 85; Switzerland: n= 342); EU sample 39.5% female, US sample 51.2% female; Mean months since transplantation: EU sample: 64.2±67.25, US: 36.2±32.4 **Adherence**= taking 100% of medication as prescribed during the past 4 weeks; measured by self-report Adherence rate= 86.8% of EU and 80.7% of U.S.	Continent Country	U.S. compared to EU: odds of non-adherence: OR= 1.78 (1.10, 2.89) p=0.019 The Netherlands compared to Belgium: OR= 0.27 (09, 0.80), p=0.0186 Switzerland vs. Belgium: OR= 0.17 (0.07, 0.42), p< .001 Switzerland vs the Netherlands: OR= 0.61 (0.20,1.92), p= .40	Multivariate OR: 0.56 (0.35, 0.91) 3.70 (1.23, 11.11) 5.88 (2.42, 14.29) 1.64 (0.54, 5.00)
Dew, Dimartini, De Vito Dabbs, Zomak, De Geest, Dobbels et al., 2008 Transplant	**Design:** Prospective **Setting:** US **Sample:** 178 lung 126 heart transplant recipients (40.6% women); enrolled 2 months post-tx and followed until month 24 **Non-adherence**= missing primary	Insurance status	Transplant recipients relying on public health insurance were significantly more likely to be non-adherent than those who did not: OR= 2.60 (1.06,	Multivariate OR: 0.38 (0.16, 0.94)

recipients	immunosuppressant medication at least once/month measured by self-report Adherence rates decreased over in both transplant groups: Lung - from 90.4% at 2 months to 80.3% at 24 months; heart - from 88.9% at 2 months to 69.4% at 24 months		6.25), p< 0.05	
Halkitis, Kutnick, & Slater, 2005 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 300 HIV+ men-who-have-sex-with-men; mean duration of ART=1.63 years **Adherence**= ≥ 95% measured by electronic monitoring and self-report over the prior 2 weeks Adherence rate: electronic monitoring= 60.7%; self-report= 67.0%	Health care coverage	No significant multivariate relationship; statistical results not reported	Unable to calculate
Heckman, Catz, Heckman et al., 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US, living in rural areas **Sample:** 329 (30% women); duration of ART not reported **Adherence**= 100% adherent during the previous week; measured by self-report Adherence rate= 50%	Barriers to obtaining health care and social services (e.g. long distance to hospitals, lack of transportation)	OR= 1.08 (95% CI 0.76, 1.53), ns	Multivariate OR: 1.08 (0.76, 1.53)
Ingersoll & Heckman, 2005 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 120 (38% women); duration of ART not reported **Adherence**= always taking medication as prescribed, never running out of medication as measured by self-report and not having non-adherence noted in the medical records Adherence rates based on taking ≥ 95%= 69.6%; meeting all three criteria= 29%	Financial accessibility (defined as the fairness/value of the cost of care),	Non-adherence measured as taking < 95% of prescribed medications: OR= 0.91 (95%CI 0.84–1.00), p< .05	Multivariate OR: 1.10 (1.01, 1.19)
Kapadia, Vlahov, Wu et al., 2008 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 573 (100% women); median ART treatment= 38.7 months; median HAART= 18.5 months	Health insurance type (none, private, public)	No significant relationship bivariately (p= 0.16); not included in multivariate analysis	Bivariate OR: Private vs. none: 2.14 (0.97, 4.70) Public vs. none:

	Adherence= ≥ 95% over the past 6 months based on self-report Adherence rate= 73%			1.48 (0.84, 2.62) Private vs. public: 1.44 (0.77, 2.69)
Kleeberger, Phair, Strathdee et al., 2001 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 539 (not women); duration of ART not reported **Adherence**= 100% adherent over the past 4 days; measured by self-report Adherence rate= 77.7%	Insurance coverage	No significant relationship bivariately [adherence OR= 0.85 (95% CI 0.31, 2.30)], not included in multivariate analysis	Bivariate OR: 0.85 (0.31, 2.30)
Marcellin, Boyer, Protopopescu et al., 2008 HIV/AIDS	**Design:** Cross-sectional **Setting:** Cameroon **Sample:** 533 (70.9% Female); mean time of ART= 13.9 months **Non-adherence**= Interruption > 2 days during the previous 4 weeks; measured by self-report Adherence rate= 82.7	Previous month's total health expenditures Duration of transport to hospital	No significant bivariately [OR for nonadherence= 0.93 (95% CI 0.50, 1.72), p= 0.82]; not included in multivariate analysis No significant multivariately; no statistical results reported	Bivarviate OR: 1.08 (0.58, 2.00) Unable to calculate
Ramadhani, Thielman, Landman, Ndosi, Gao, Kirchherr et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** Tanzania **Sample:** 150 (63% women); on ART ≥ 6 months **Non-adherence**= < 100% from the start of treatment as measured by self-report Adherence rate= 84%	Walking time to clinic Proportion of months receiving self-funded treatment	Non-adherence: OR= 1.2 (95% CI 0.94-1.6), p= 0.14; Non-adherence: OR= 23.5 (95% CI 1.2, 444.4) p= 0.04	Bivariate OR: 0.83 (0.62, 1.11) 0.07 (0.00, 0.08)
Reif, Whetten, Lowe et al., 2006 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 526 (36% women); duration of ART not reported **Adherence**= always took medication as prescribed during the past month; measured by self-report Adherence rate= 62%	Unmet need for financial assistance including with obtaining medications	OR= 0.95 (CI not reported), ns	Multivariate OR: 0.95 (CI not reported)
Sarna, Pujari, Sengar et al.,	**Design:** Cross-sectional **Setting:** India	Cost of medications: free or paid out of	Multivariate OR for non-adherence when treatment	Multivariate OR: 0.25 (0.09, 0.70)

2008 HIV/AIDS	**Sample:** 310 (16% Women); duration of ART ≥ 30 days **Non-adherence**= < 90% over 4 day; measured by self-report Adherence rate= 84%	pocket	was free = 4.05 (1.42, 11.54) p= 0.009	
Shah, Walshe, Saple et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** India **Sample:** 278 (27.2% women); on ART≥ 3 months **Adherence**= ≥ 95% of the prescribed doses over the past 4 days measured by self-report Adherence rate= 73%	Cost of ART	Not significantly related to adherence multivariately; no statistics reported	Unable to calculate
Sharma, Singh, Laishram, Kumar, Nanao, Sharma et al., 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** India **Sample:** 226 (2.2% women); duration of ART not reported **Non-adherence**= ever missing a dose by self-report Adherence rate= 59%	ART provided for free or not	Not receiving free ART was sign related to non adherence (p= 0.001)	Approx multivariate OR=2.22 (based on reported p-values); unable to calculate 95% CI
Turner, Newschaffer, Zhang et al., 2000 HIV/AIDS	**Design:** Retrospective **Setting:** US **Sample:** 549 HIV+ post-partum women prescribed ART during 1 post-partum year **Adherence**= ≥ 80% of days during the 1st year post-partum measured by prescription refill rate Adherence rate= 28%	Medicaid eligible during the entire 1st post-partum year	OR= 0.33 (95% CI 0.14, 0.78), p= 0.01	Multivariate OR: 0.33 (0.14, 0.78)
Wagner, 2002 HIV/AIDS	**Design:** Prospective **Setting:** US **Sample:** 180 (18% women); duration of ART≥ 1 month **Adherence**= a continuous variable; measured by electronic monitoring (n= 61, medication diary (n= 60) and self report (n= 59); measured over the previous 4 weeks Adherence rates= 93.7% (self-report), 80.6% (electronic monitoring), and 92.6%	Having health insurance	Not significantly related to adherence multivariately; no statistics reported	Unable to calculate

	(medication diary)			
Weiser, Wolfe, Bangsberg, Thior, Gilbert, Makhema et al., 2003 HIV/AIDS	**Design:** Cross-sectional **Setting:** Botswana **Sample:** 109 (50% women); on ART ≥ 3 months **Adherence**= taking 95% of prescribed dose during the previous year; measure by self-report Adherence rate= 54%	Cost of ART	OR= 0.11 (95% CI 0.04, 0.3), p< 0.0001	Multivariate OR: 0.11 (0.04, 0.30)
Bivariate analysis only				
Deloria-Knoll, Chmiel, Moorman, Wood, Holmberg, & Palella, 2004 HIV/AIDS	**Design:** Cross-sectional **Setting:** US **Sample:** 255 (14% women): duration of ART= 4.7 ± 3.1 years in non-adherent subjects and 4.2±2.7 yrs in adherent subjects, ns **Adherence**= skipping ≥1 dose during the previous 3 days, measure by self-report Adherence rate= 67%	Insurance status	Adherent subjects: 62% private insurance, 25% government insurance Non-adherent subjects: 55% private insurance; 32% government insurance Calculate OR= 3.76 (95% CI 2.08, 6.78)	Bivariate OR: 3.76 (2.08, 6.78)
Liu & Zaki, 2004 Transplant recipients	**Design:** Cross-sectional **Setting:** Malaysia (Kuala Lumpur) **Sample:** 246 renal Tx recipients (41.5% women); ≥ 6 months post-tx **Adherence**= Cyclosporine / tracolimus blood level > 25 ng/ml; tacrolimus > 1 ng/ml Adherence rate= 90.7%	Cost of immunosuppressive medication (free vs paying for) Country (China, India, Kuala Lumpur, others)	(p= 0.87) Country (p= 0.27) China vs India China vs Kuala Lumpur India vs Kuala Lumpur	Approximate Bivariate OR: 1.21 (0.26, 5.62) 2.53 (0.69, 9.26) 1.10 (0.33, 3.66) 0.43 (0.15, 1.22)
Wanchu, Kaur, Bambery, & Singh, 2007 HIV/AIDS	**Design:** Cross-sectional **Setting:** North India **Sample:** 200 (31% women); on ART ≥ 1 month **Non-adherence**= Missed ≥ 1 dose during past 4 weeks as measured by self-report Adherence rate= 73%	Source of funding (self vs. state)	85.37% who the state paid for their medication were adherent compared to 65.25% of those who self-paid (difference reported as sign; p-value not reported)	Bivariate OR: 3.11 (1.51, 6.38)

When a study reported an OR (95% CI) for non-adherence, a OR (95%CI) was calculated for adherence using the following formula:

OR adherence=1/OR non-adherence

Lower limit (LL) OR adherence LL=Exponent (Ln(OR adherence)-(1.96*SE LnOR LL)).

Upper limit (UL) OR adherence LL=Exponent (Ln(OR adherence)+(1.96*SE LnOR LL))

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Chapter 4

Effect size calculation: methods and examples

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Introduction

It is standard practice in nursing research to examine whether a study's result is statistically significant. However, a common mistake in the interpretation of the results, is equating statistically significant results (i.e., a p-value of ≤ 0.05 or 0.01) with a clinically meaningful effect. A p-value is the probability of that the results are due to chance alone, or in other words, the probability of incorrectly rejecting the null hypothesis [1, 2]. It does not, however, provide any information about the practical importance of the findings. Furthermore, p-values are dependent on the sample size. This means that a small effect could be statistically significant if the sample size is very large and, conversely, there can be a large effect in a small sample size without the p-value being significant [1]. The advantage of effect size estimates is that they are independent of sample size and measure the extent of a treatment effect or strength of the association between variables. Mays and Melnyk (2009) define effect size as "a measure of the magnitude of the influence of an independent or predictor variable on a dependent or criteria variable" [3] (pg. 125). Effect size estimates information on both the magnitude and direction of influence. In addition to providing important information about the impact of a treatment on the outcome of interest, it also provides a common metric to compare the direction and strength of the relationship between variables across studies, which is key to conducting a meta-analysis. Meta-analysis is "a technique for quantitatively combining and integrating the results of multiple studies on a given topic" [2] (pg. 723). Meta-analyses are considered the highest level of evidence for clinical practice [2]. For meta-analysis it is crucial to define a common effect size metric which is capable of representing the quantitative findings of a set of research studies in a standardized form and permits meaningful numerical comparison and analysis across the studies [4]. Although guidelines such as the CONSORT statement, an evidence-based minimum set of recommendations for reporting randomized clinical trials [5], and the American Psychological Association manual [6] recommend reporting effect sizes even when results are not statistically significant, a number of research articles, even more recent ones, do not report effect sizes. The researcher conducting a meta-analysis must then rely on summary and test statistics reported in the article to calculate the effect size.

Because the sample in a research study rarely totally represents the characteristics of the target population for the study findings, effect size estimates are only

estimates of the true effect in the target population. The extent to which the estimated effect size accurately reflects the effect in the target population will vary. Therefore, when investigators report the effect size for their studies, they should also include a measure of its precision, i.e., a confidence interval [1]. The confidence interval is the range of values within which a population parameter is estimated to lie for a given probability [2]. The narrower the confidence interval, the more precise the estimated effect size is [1]. While the effect size is not influenced by the sample size, its precision, conveyed through the confidence interval, is. In general, the larger the sample size, the more precise the effect size estimate (as evidenced by a narrower confidence interval) will be.

This article will focus on effect size calculation based on data and statistics reported in published studies. We will provide the formulas utilized to directly calculate common effect sizes when researchers report summary data from their studies, as well as examples of methods utilized to indirectly estimate the effect size from summary statistics.

Methods to calculate effect sizes

The method utilized to calculate an effect size will vary with the results reported in the primary study. The effect size can be calculated directly when the published study results include certain basic information such as the mean and SD, exact correlation coefficient or the number events and non-events in two groups. Unfortunately, many published studies fail to report the summary statistics needed to directly calculate an effect size. While one can (and should) attempt to contact the author(s) to obtain the missing data, such attempts are often unsuccessful. When the basic information needed to directly calculate an effect size is not available, there may be methods available to estimate the effect size from less than optimal statistical information [7]. We will present and illustrate methods utilized to directly calculate an effect size and its 95% confidence interval based on reported (1) means and standard deviations, (2) correlation coefficients and (3) number of events and non-events in two groups. These summary statistics are utilized to calculate the most common effect size indices used in meta-analysis, the standardized mean difference (e.g., Cohen's d), correlation coefficient (r) and odds

ratio (OR) [8]. We will also present examples of methods utilized to indirectly estimate the effect size from summary statistics.

Effect size based on means and standard deviations

When studies compare continuous outcomes in two groups and report the mean (M) and standard deviation (SD) in both groups, the raw mean or standardized mean difference are the preferred effect sizes [9]. If the outcome of the studies was measured using a meaningful scale and all of the studies for which an effect size is being calculated used the same scale, the effect size can be calculated as the raw mean difference between the two groups:

Mean difference = $M_{group\ 1} - M_{group\ 2}$. In reality, however, is rare to have a set of studies that all measure the outcome of interest using the same scale. This is particularly true in behavioural research. More commonly, studies use different methods of measuring the outcome of interest. When this is the case, the most commonly used effect size calculation is the standardized mean difference which is calculated as the difference between the two group means divided by their pooled standard deviation. This effect size (ES), the standardized mean difference, is often referred to as Cohen's d or Hedge's g [7]. The standardized mean difference is calculated as [10]: $ES_{sm} = \frac{M_1 - M_2}{S_{pooled}}$ where $S_{pooled} = \sqrt{\frac{(n_1-1)s_1^2+(n_s-1)s_1^2}{n_1+n_2-2}}$.

ES_{sm}= effect size: standardized mean difference
M_1= mean of group 1
M_2 = mean of group 2
S_{pooled} = pooled standard deviation
s^2_1 = squared standard deviation in group 1
s^2_2 = squared 1standard deviation in group 2

Calculation of the confidence interval around the standardized mean differences requires calculation of the variance. The formula used to calculate the variance is [10]:

$V_{sm} = \frac{n_1+n_2}{n_1 n_2} + \frac{ES_{sm}^2}{2(n_1+n_2)}$.

V_{sm} = the variance of the standardized mean difference
ES_{sm}^2 = the squared effect size
n_1 = the sample size in group 1
n_2 = the sample size in group 2

The standard error of the standardized mean difference is the square root of its variance:

$SE_{sm} = \sqrt{V_{sm}}$ and the 95% confidence interval (95% CI) around the standardized mean differences is calculated as: 95% CI = ES_{sm} ± (1.96 x SE_{sm}).

Example

This fictitious study examined the impact of motivational interviewing on medication taking adherence to antihypertensive drugs in patients identified as poor adherers after baseline screening with electronic event monitoring (EM). Those whose adherence rate during the 6 weeks of baseline monitoring was less than 80% were eligible to participate in the intervention phase of the study. These subjects were randomly assigned to a motivation interviewing intervention or to a usual care group. The outcome was the percent change in adherence rates measured by EM at the end of the 8 week intervention compared to baseline. The mean taking adherence rate increased 10.54 (SD=2.11) percent in the intervention group (n=66) and 3.21 (SD=2.00) percent in the usual care control group (n=65; p<0.001). To calculate the effect size, we first need to calculate the pooled standard deviation:

$$S_{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} = \sqrt{\frac{(66 - 1)2.11^2 + (65 - 1)2.00^2}{66 + 65 - 2}} = \sqrt{\frac{545.39}{129}} = \sqrt{4.23} = 2.06$$

The pooled standard deviation is then is used to calculate the standardized mean difference: $ES_{sm} = \frac{M_1 - M_2}{S_{pooled}} = \frac{10.54 - 3.21}{2.06} = \frac{7.33}{2.06} = 3.55$.

Next, we need to calculate the variance of the standardized mean difference:

$$V_{sm} = \frac{n_1 + n_2}{n_1 n_2} + \frac{ES_{sm}^2}{2(n_1 + n_2)} = \frac{66 + 65}{66 \times 65} + \frac{3.55^2}{2(66 + 65)} = \frac{131}{4209} + \frac{12.60}{262} = 0.03 + 0.05 = 0.08$$

The standard deviation of the standardized mean difference effect size (SE_{sm}) is calculates as the square root of the variance V_{sm}: $SE_{sm} = \sqrt{V_{sm}} = \sqrt{0.08} = 0.28$ and the 95% confidence interval (CI) around the standardized mean difference is calculated as: $95\%\ CI = ES_{sm} \pm 1.96(SE_{sm}) = 3.55 \pm (1.96 \times 0.28) = 3.55 \pm 0.55 = 3.00, 4.10$.

In this example, the effect size and its 95% CI are 3.55 (3.00, 4.10).

Effect size based on correlation coefficients

When studies examine the associations between scores on two variables the correlation coefficient itself can serve as an effect size estimate: ES_r = r. In order to calculate the 95% CI around the correlation coefficient, its standard error needs to be calculated. Because simply using the correlation coefficient to calculate the standard error is problematic, correlations are generally transformed using Fisher's Zr transformation prior to calculating the effect size and its 95% CI [4, 10]. Fisher's Zr is calculated as:

$ES_{z_r} = 0.5 \times ln\left[\frac{1+r}{1-r}\right]$.

ES_{z_r} = Fisher transformed effect size for the correlation coefficient (r)
ln = the natural logarithm

To calculate the 95% CI, the standard error of Z_r (SE_{z_r}) needs to be calculated by first calculating the variance (V_{z_r}) and then its square root: $V_{z_r} = \frac{1}{n-3}$ and $SE_{z_r} = \sqrt{V_{z_r}}$.

The 95% CI can then be calculated as: $95\%\ CI = ES_{z_r} \pm 1.96 \times SE_{z_r}$. This is the confidence interval for the transformed effect size. While this will be used for meta-analysis, when reporting effect sizes and confidence intervals in a table or forest plot in a systematic review or meta-analysis you need to report the effect size for the original correlation coefficient (ES_r) and its corresponding 95% CI. To do this, you will need to transform the upper and lower bounds of the Z_r confidence interval back into the standard correlational form. The formula to transform the ES_{z_r} 95% CI back to a ES_r 95% CI is: $r = \frac{e^{2ES_{z_r}}-1}{e^{2ES_{z_r}}+1}$.

e = the base of the natural logarithm
ES_{z_r} = the effect size based on Fisher's z

This transformation needs to be done for both the lower and upper bound of the ES_r 95% CI.

Example

Papelbaum and colleagues (2010) examined the association between quality of life and the characteristics of subjects with type 2 diabetes (n=100) and reported that the univariate correlation between duration of diabetes and quality of life (measured by the Problem Areas of Diabetes scale) was r = 0.30 [11]. First, we need to transform r to Fisher's z (ES_{z_r}): $ES_{z_r} = 0.5 \times ln\left[\frac{1+r}{1-r}\right] = .05 \times ln\left[\frac{1+0.30}{1-0.30}\right] = 0.5 \times \ln(1.86) = 0.31$. Next, we need to calculate the variance $V_{z_r} = \frac{1}{n-3} = \frac{1}{100-3} = 0.01$ and the standard error:

$SE_{z_r} = \sqrt{V_{z_r}} = \sqrt{0.01} = 0.10$. Finally, we calculate the 95% CI: 95% $CI = ES_{z_r} \pm 1.96 \times SE_{z_r} = 0.31 \pm (1.96 \times 0.10) = 0.31 \pm 0.20 = 0.11, 0.51$. If you are doing meta-analysis, you will use the ES_{z_r}, but if you are reporting the effect size in the manuscript or table of studies, the r and its 95% CI are easier to interpret than the ES_{z_r} and its 95% CI. Thus, experts recommend converting the upper and lower bound of the ES_{z_r}CI back to the r metric [4]: $ES_{r_{lower\ bound}} = \frac{e^{2ES_{z_r}}-1}{e^{2ES_{z_r}}+1} = \frac{e^{2\times 0.11}-1}{e^{2\times 0.11}+1} = \frac{0.25}{2.25} = 0.11$ and $ES_{r_{upper\ bound}} = \frac{e^{2ES_{z_r}}-1}{e^{2ES_{z_r}}+1} = \frac{e^{1.02}-1}{e^{1.02}+1} = \frac{1.77}{3.77} = 0.47$.

In this example, the effect size and its 95% CI are 0.30 (0.11, 0.47).

Effect size based on the number of events and non-events in two groups

Studies often report dichotomous outcomes in two study groups, e.g., the number and proportion of subjects whose adherence improved in a treatment and control group or the number of patients who were and were readmitted after hospital discharge for heart failure. While there are several effect size indices that can be calculated to describe the direction and magnitude of the relationship between a dichotomous independent and dependent variable (e.g., relative risk, risk ratio, risk difference and odds ratio), odds ratio is probably the most commonly reported effect size. The odds ratio (OR) is based on a 2 x 2 contingency table such as the one below.

	Adherent	**Not Adherent**	
Treatment	A	B	n_1
Control	C	D	n_2

$$OR = \frac{AD}{BC}$$

The odds ratio is the odds of an outcome (e.g., being adherent) in one group (e.g., the treatment group) relative to its odds in the other group (e.g., the control group). To compensate for the fact that the odds ratio is centered around 1 (which indicates no relationship) rather than zero, all analyses are preformed on the natural log of the odds ratio (lnOR) [4]. First, the lnOR (ES_{lnOR}) and its standard error (SE_{lnOR}) are calculated:

$ES_{lnOR} = \ln(OR)$ and $SE_{lnOR} = \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}$ and used to calculate the 95% CI:

95% $CI = ES_{lnOR} \pm 1.96 \times SE_{lnOR}$. While the natural log values will be used during meta-analysis, they should be transformed back into the odds ratio and its 95% CI when reported in the text or tables of a manuscript or in a forest plot. The following formulas are used to calculate the lower and upper limits of the 95% CI around the OR: $Lower\ limit_{OR} = e^{(ES_{\ln OR} - 1.96 SE_{lnOR})}$ and $Upper\ limit_{OR} = e^{(ES_{lnOR} + 1.96 SE_{lnOR})}$.

Example

Beeckman et al. (2010) examined the effectiveness of the Pressure Ulcer Classification education tool in increasing nurses' ability to correctly classify photographs of pressure ulcers and incontinence-associated dermatitis (IAD) [12]. Following the educational intervention nurses in the intervention group correctly classified 70.2% of the photographs of IAD compared to 35.8% of photographs that were correctly classified by the control group.

	IAD Correctly Identified	
	Yes	**No**
Treatment	1360	577
Control	589	1058

$$OR = \frac{AD}{BC} = \frac{1360 \times 1058}{577 \times 587} = 4.23$$

After calculating the odds ratio, we need to calculate the natural log of the OR (ES_{lnOR}) and its standard error (SE_{lnOR}): $ES_{lnOR} = \ln(OR)$=ln(4.23)=1.44 and $SE_{ln} = \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} = \sqrt{\frac{1}{1360} + \frac{1}{577} + \frac{1}{587} + \frac{1}{1058}} = \sqrt{0.0051} = 0.07$.

These values are used to calculate the 95% CI for the natural log of the OR. 95% $CI = ES_{lnOR} \pm 1.96 \times SE_{lnOR} = 1.44 \pm (1.96 \times 0.07) = 1.44 \pm 0.14 = 1.3, 1.58$.

Finally, to present the effect size in a manuscript, we need to transform the lower and upper bound of the 95% CI for the natural log OR to a 95% for the OR: $Lower\ limit_{OR} = e^{(ES_{\ln OR} - 1.96 SE_{lnOR})} = e^{(1.44 - (1.96 \times 0.07))} = 3.67andUpper\ limit_{OR} =$

$e^{(ES_{lnOR}+1.96SE_{lnOR})} = e^{(1.44+(1.96\times0.07))} = 4.85$. In this example, the odds ratio effect size and its 95% CI are 4.23 (3.67, 4.85).

When using OR's as the ES measure in a systematic review or meta-analysis, you need to be sure that they all reflect the same outcome (e.g., that all reflect the odds of adherence). If you use the OR and 95% CI reported in studies, this may not be the case. For example, some studies report the OR/95% CI for adherence and others for non-adherence. To change the direction of a OR for the reported outcome to the desired outcome, e.g. from modeling non-adherence to modeling adherence, you need to compute the inverse of the OR: $Inverse\ OR = \frac{1}{OR}$. The standard error of the lower limit of the natural log odds ratios of the original 95% CI also needs to be calculated. The formula to do this is:

$SE_{LL_{OR}} = \frac{-(\ln[LL_{original\ OR}]-\ln[OR])}{1.96}$. This value is utilized to calculate the 95% CI for the inverse odds ratio:

$LL_{OR} = e^{(\ln[\text{Inverse OR}]-(1.96\times\text{SE}_{\text{LL}_{\ln[\text{OR}]}}))}$ and $UL_{OR} = e^{(\ln[\text{Inverse OR}]-(1.96\times\text{SE}_{\text{UL}_{\ln[\text{OR}]}}))}$.

Example

Ingersoll and Heckman (2005) examined the association between patients' perceptions of clinician's knowledge about them (*knowledge of patient)* and adherence to HIV medications [13]. They reported that the OR and 95% CI for knowledge or patient and non-adherence was 0.97 (0.94, 1.01). In our review, we want to report the effect sizes for adherence so we need to convert this OR and 95% CI for non-adherence to the odds of adherence and its 95% CI. First we need to convert the OR for non-adherence to the OR for adherence: $Inverse\ OR = \frac{1}{OR} = \frac{1}{0.97} =$ 1.03. Then, we need to calculate the standard error for the log odds ratio based on the lower limit of the original 95% CI:

$SE_{LL_{lnOR}} = \frac{-(ln_{LL\ OR}-ln_{OR})}{1.96} = \frac{-(\ln[0.94]-\ln[0.97])}{1.96} = 0.016$. The $SE_{LL_{lnOR}}$ is used to calculate the 95% CI for the inverse OR: $LL_{OR} = e^{(\ln[\text{Inverse OR}]-(1.96\times\text{SE}_{\text{LL}_{\ln[\text{OR}]}}))} = e^{\ln[1.03]-(1.96\times-0.016)} =$ 0.998 and $UL_{OR} = e^{(\ln[\text{Inverse OR}]+(1.96\times\text{SE}_{\text{LL}_{\ln[\text{OR}]}}))} = e^{\ln[1.03]+(1.96\times0.06)} = 1.063$. Thus, in this example, the OR and 95% CI for adherence is 1.03 (0.998, 1.063).

Indirect methods to calculate the effect size

As previously noted, published studies often fail to report the summary statistics needed to directly calculate an effect size. If one is unable to obtain the missing data from the author(s) of the manuscript, there may be methods available to estimate the effect size from less than optimal statistical information [7]. Readers are referred to the Lipsey and Wilson (2001) [4] or Rosenthal (1991) [14] books for procedures for calculating effect sizes from a variety of reported statistics.

One example of indirectly calculating the effect size when summary statistics (means and standard deviations) are not reported is calculating it from a reported t-statistic in a study comparing a continuous outcome in two independent groups (student's t-test). If the author(s) report(s) a t-statistic and the sample size for each of the two groups, a standardize mean effect size (ES_{sm}) can be calculated as[4]: $ES_{sm} = t\sqrt{\frac{n_1+n_2}{n_1 \times n_2}}$.

Example

A fictitious study examined the impact of an intervention on perceived barriers to regular exercise. They compared scores on a barrier scale in treatment (n=25) and control subjects (n=26). The test statistics reported were t=7.2, p<0.001. Using the formula above, we can calculate: $ES_{sm} = t\sqrt{\frac{n_1+n_2}{n_1 \times n_2}} = 7.2\sqrt{\frac{25+26}{25 \times 26}} = 2.017$. If only the total sample is reported, Rosenthal [14] suggests that the effect size can be calculated as: $ES_d = \frac{t}{\sqrt{\frac{df}{2}}}$. The estimated effect size will be a somewhat less precise than when using the Lipsey and Wilson formula [4].

In some studies, the only test statistic reported is a p-value. As long as an exact p-value and sample size are reported, an estimated effect size (ES) can be calculated. Calculation of ES requires *p*-value to be converted to a *Z* score (standard normal deviate). This can be done using a table of Z score. There are also websites that will convert p-values to z scores. One example is: http://sampson.byu.edu/courses/z2p2z-calculator.html. If the p is two tailed, convert it to a one-tailed (p divided by 2) before entering it into the program. Once you have the Z score, the following formula can be used to calculate an effect size

correlation (ES_r): $ES_r = \frac{Z}{\sqrt{n}}$ [14]. If you want to report standardized mean effect sizes rather than correlation effect sizes, ES_r can be converted to a Cohen's d (a standardized mean effect size measure): $ES_d = \frac{2r}{\sqrt{1-r^2}}$.

Example

If a study only reports that the p-value was 0.043 and the sample size is 150, we can estimate the effect size (ES_r). First, we need to find the Z score that corresponds to the reported p-value. If there is no reason to assume that a one tailed test was used (e.g., explicitly stated by the author(s) or the presence of a hypothesis that stated that a one-direction outcome was expected), it is probably best to assume that the study used a two-tailed test and divide the p-value by 2 prior to finding in the corresponding Z score. In our example, we assumed a 2-tailed test was used and divided out reported p-value (0.043) by two and used a p-value of 0.0215 to find the corresponding Z score of 2.024. Now we can calculate the effect size for r: $ES_r = \frac{Z}{\sqrt{n}} = \frac{2.024}{\sqrt{150}} = 0.17$ and use to compute Cohen's d: $ES_d = \frac{2r}{\sqrt{1-r^2}} \frac{2\times0.17}{\sqrt{1-0.17^2}} = 0.345$.

Unfortunately, it is not uncommon to find that in addition to not reported the summary statistics need to directly calculate an effect size or the test statistics need to indirectly calculate it, authors do not report an exact p-value which means that you cannot estimate the effect size with any degree of confidence. This is particularly problematic if you want to statistically combine the result of studies included in a review (perform meta-analysis) or to graphically display them in a forest plot. Not uncommonly when study findings are negative, the p-value is simply reported as not significant or p >0.05. Even when the study findings are positive (i.e., significant), the exact p-value may not be reported. Instead, authors may report p<0.05 or may include a table legend that indicates which p-values are less than pre-determined levels (e.g., *p<0.05, **p<0.001, ***p<0.0001).

The first approach when there is insufficient information to calculate an effect size is to contact the author(s) to request the needed information. Unfortunately, this is not always successful for a variety of reasons. Lipsey and Wilson (2001) discuss several other approaches to dealing with studies where an effect size cannot be calculated [4]. The first is to only include studies where an effect size can be calculated. This issue with this approach is that studies with negative findings are

generally less likely report the data needed to calculate an effect size. If these study findings are ignored, it is likely that the effect in the target population is overestimated. Another approach is to code all effect sizes for studies that reported that their findings were non-significant as zero. If studies report that the findings were significant without an exact p-value or simply report that p≤0.05, the effect size calculation can be based on the assumption that p=0.05. These approaches are, however, conservation and will result in downward bias in the mean effect size across studies and underestimate the population effect size. If the author(s) do not report an exact p-value for significant findings but instead report that p-values are less than several predetermined levels (e.g., p<0.05, p<0.01, p<0.001), it will be somewhat less conservative to use p-values that are half between the adjacent p-values when estimating the effect size. For example, we would assume (based on this example) that all effects noted to have a p-value less than 0.05 are half way between 0.05 and 0.01 and those noted to have a p-values <0.01 to have a value half way between 0.01 and 0.001.

Software to calculate effect sizes

Fortunately, there is software available to help with many effect size calculations. There are a number of freeware programs available on the web. One of sites that the authors have used and recommend was developed by David Wilson, co-author of the Lipsey and Wilson book on meta-analysis (2001) [4]. This website, *The Practical Meta-Analysis Effect Size Calculator* (http://gunston.gmu.edu/cebcp/EffectSizeCalculator/index.html), was recently updated and can be utilized to compute effect sizes and 95% CIs based on a variety of reported statistics. There are also a number of commercial software packages that calculate effect sizes such as *Effect Size Generator-Pro* (Melbourne, Australia) and *Comprehensive Meta-Analysis* (Biostat, Englewood NJ).

Interpreting effect size results

While Cohen (1988) suggested rules of thumb for interpreting effect sizes for Cohen's d (small= 0.20, medium= 0.50 and large= 0.80) and correlations (r:

small= 0.10, medium= 0.30 and large= 0.50) for the social sciences, the interpretation of effect sizes in terms of their magnitude and clinical significance varies with the area of scientific study [15]. More specifically, it varies with the how precisely the independent and dependent (or X and Y) variables are measured. In behavior research, there is generally a lot of noise in the measurement of variables, making them less precise than many physiologic measures. Consequently, effect sizes often need to be higher in physiologic than in behavioral research to be considered clinically significant.

Conclusions

Secondary to limitations of many traditional test statistics and the p-value in providing information about the clinical significance of research findings, most current research guidelines recommend that investigators also report the effect size for the interventions or association that they examined. Unfortunately, effect sizes are not included in publications of many research studies. In these situations, clinicians and researchers need to be able to calculate effect sizes and their 95% confidence interval in order to know if statistically significant findings are also clinically meaningful and are a precise representative of the effect in the target population.

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Chapter 5

Which interventions are used by health care professionals to enhance medication adherence in cardiovascular patients? A survey of current clinical practice

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Abstract

Background: Complex medication regimens are often required to manage cardiovascular diseases. As non-adherence, which can have severe negative outcomes, is common among cardiovascular patients, various interventions to improve adherence should be implemented in daily practice.

Aim: To assess which strategies cardiovascular nurses and allied health professionals utilize to (1) assess patients' adherence to medication regimen, and (2) enhance medication adherence via educational/cognitive, counseling/behavioral, and psychological/affective interventions.

Method: A 45-item questionnaire to assess adherence assessment and interventional strategies utilised by health care professionals in daily clinical practice was distributed to a convenience sample of attendants of the 10th Annual Spring Meeting of the European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions conference in Geneva (Switzerland) in March 2010. Respondents not in direct clinical practice were excluded. Descriptive statistics were used to describe practice patterns regarding adherence management.

Results: Of 276 distributed questionnaires, 171 (62%) were returned, of which 34 (20%) were excluded as respondents performed no direct patient care. Questioning patients about non-adherence during follow-up was the most frequently reported *assessment strategy* (56%). Educational/cognitive *adherence enhancing interventions* were used most frequently, followed by counselling/behavioural interventions. Psychological/affective interventions were less frequently used. The most frequent intervention used was providing reading materials (66%) followed by training patients regarding medication taking during inpatient recovery (48%). Slightly over two-thirds (69%) reported using a combination of interventions to improve patient's adherence.

Conclusion: Educational interventions are used most in clinical practice, although evidence shows they are less effective than behavioural interventions at enhancing medication adherence.

Background

Cardiovascular disease is the leading cause of death worldwide [1, 2], accounting for approximately 17.1 million deaths in 2004 [1]. In the UK alone, about 2.6 million people currently suffer from cardiovascular disease [3], while in the US a third of all people aged 18 and more live with one or more cardiovascular disease [4]. Managing a cardiovascular disease generally necessitates a complex regimen of medications to prevent and/or delay the disease's progression, control symptoms, decrease re-hospitalization and improve survival [5].

For a prescribed treatment to be effective, adherence to the medication regimen is essential. *Medication adherence* (also called compliance) can be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [6] (pg. 46). *Medication persistence*, on the other hand, is "the duration of time from initiation to discontinuation of therapy" [6] (pg. 46). Non-adherence to medication regimens in the cardiovascular patient population is common. A meta-analysis showed an average adherence among cardiovascular patients of 77% (CI: 73.4-79.8) [7]. In a group of 58,744 medication naive patients with a cardiovascular disease, 32% discontinued their medication treatment during the first 30 days of treatment [8]. Large variations in adherence rates among studies are observed, partly due to variations in measurement methods and operational definitions.

Medication non-adherence can have serious consequences, including poor clinical outcomes, higher (re)hospitalization rates, increased health care costs, and higher mortality [9-16]. Non-adherence is associated with a significantly elevated risk of recurrent myocardial infarction [9, 10, 12]. Examining the reasons for hospital readmission in heart failure patients, Annema et al. (2009) found that one-third of patients described improvement of adherence to their treatment regimens as the most important condition to prevent readmission [17].

The reasons for medication non-adherence in patients suffering from chronic diseases, including cardiovascular disease, are only partially understood [18]. However, associated factors have been identified and can be categorized in five dimensions: (1) patient-related factors (e.g., self-efficacy, knowledge, intentions), (2) therapy-related factors (e.g., dose frequency, duration of treatment), (3) socio-economic factors (e.g., social isolation, cost of treatment), (4) condition-related

factors (e.g., depression, number of co-morbidities), and (5) health care team- and system-related factors (e.g., quality of provider communication, trust in the health care worker) [18].

Adherence can be measured using different strategies (e.g., self-report, collateral report, pill count, electronic monitoring, pharmacy refill, observation, assay) [19-21]. Once an adherence issue is identified, a range of interventions can be implemented to target the patient, health care provider, health care organization or health care system [22]. Interventions focusing on the patient can be classified as educational/cognitive, counseling/behavioral, and psychological/affective interventions [23]. *Educational/cognitive interventions* present information individually or in a group setting, delivering it verbally, in written form, and/or audio-visually. *Counseling/behavioral interventions* shape and/or reinforce behavior, empowering patients to participate in their care, and building skills or routines. *Psychological/affective interventions* focus on the patient's feelings, emotions, relationships and social support [23].

Not all types of interventions are supported by evidence. A Cochrane review [24], focusing on the efficacy of adherence enhancing interventions and measuring both adherence and clinical outcomes, included 70 trials testing 83 interventions for long-term treatments. This review showed that for long-term treatments, only 36 of the 83 interventions showed significant associations with improvements in medication adherence [24], while only 25 led to improvement in at least one treatment outcome [24]. No simple and few complex interventions resulted in improvement of adherence and clinical outcomes. Conn et al. (2009), in a meta-analysis investigating the efficacy of interventions to improve medication adherence in older adults, showed that a number of interventions significantly improved medication adherence, but reported large differences in the effect size of different interventions on medication adherence [25]. In this meta-analysis, interventions also significantly improved knowledge and diastolic blood pressure; however, no significant effects were found for systolic blood pressure, other health outcomes or health services utilization [25].

In a recent study focusing on physicians of patients with chronic myeloid leukemia, it has been shown how widely perceptions of the utility and applicability of adherence enhancing interventions differed among physicians [26]. Although the importance of developing interventions to enhance patient adherence is recognized, little is known which interventions are implemented in routine cardiovascular care.

The aim of this study was therefore to assess the strategies cardiovascular nurses and allied health professionals utilize to (1) assess patients' adherence to their medication regimens, and (2) enhance their medication adherence (educational/cognitive, counseling/behavioral, or psychological/affective techniques).

Methods

Design, setting and sample

This study used survey methodology. All attendees of the 10th Annual Spring Meeting of the European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions (CCNAP) in Geneva (Switzerland) on March 12th & 13th, 2010, were invited to participate in this study. To be included in this study, participants had to have direct patient contact. This study was supported by the UNITE budget and by Eli Lilly.

Variables and measurement

A structured questionnaire in English assessed the following set of variables:
Demographic information: Demographic information was collected from all participants (Table 1).
Adherence Assessment and Intervention Strategies: The questionnaire presented 29 items to survey adherence assessment and interventions. Participants were asked to indicate on a 5-point Likert-type scale, ranging from never (1) to all the time (5), the frequency with which they utilized each of three strategies to assess medication adherence: (1) questioning patients about medication adherence during follow-up visits; (2) screening patients for risk factors for medication non-adherence during follow-up; and (3) using an electronic monitoring device to assess adherence/risk factors. Furthermore, participants were given a list of educational/cognitive (6 items), counseling/behavioral (11 items), and psychological/affective (9 items) interventions and asked to indicate on a 5-point Likert-type scale ranging from never (1) to all the time (5) the frequency with which they used each to increase patients' medication adherence.

The questionnaire was developed for this study. The interventions and assessment strategies in the list were derived from interventions found in the literature [18, 24, 27-29]. The draft questionnaire was discussed and adapted a number of times in the research group before being finalized. To evaluate the understandability and feasibility of this scale, it was piloted on 13 health care professionals working with patients post organ transplantation in the US and the UK. As findings showed highly skewed answer patterns for most items, responses to the Likert-scale questions were collapsed prior to analysis, into never= 0 ('never'), seldom= 1 ('occasionally' and 'sometimes'), and frequently= 2 ('frequently' and 'all the time').

Data collection

All delegates attending the 2010 Spring Meeting of the European Society of CCNAP were informed about the study at the time of registration and given a copy of the questionnaire. The study was also introduced at the opening session of the conference. Attendees were asked to put their completed questionnaires into the designated collection boxes. Questionnaires could be submitted during both conference days. The distribution process guaranteed that only one questionnaire was distributed per attendee. Research associates were available throughout the conference to provide information and support to the attendees on filling out their questionnaires as well as to motivate them to participate in the survey.

Data analysis

Data were analyzed using descriptive statistics: frequencies, percentages and, where appropriate, measures of central tendencies and variability. We calculated the mean proportion of interventions in each of the three categories (education/cognitive, cognitive/behavioural and psychological/affective) that participants reported using frequently or all of the time. Participants who reported that they frequently or always used one or more intervention from at least two of the categories were classified as frequently utilizing a combination of methods to enhance medication adherence. The statistical analyses were performed using SPSS 16 (SPSS Inc, Chicago, Il). Data were analyzed at the item level.

Human subject considerations

All conference attendees were informed twice regarding the aim of the study: once when the questionnaires were distributed at registration, and once during a short oral presentation at the beginning of the conference. Informed consent of the participants was implied by the completion of the questionnaire. No identifying data were collected from the participants assuring anonymity of the data.

Results

Demographic information

Of the 276 distributed questionnaires, 171 (62%) were completed and returned. Thirty-four respondents (20%) provided no direct patient care and were therefore excluded from further data analysis. The demographic characteristics of the final sample (Table 1), show that the majority of participants were women (83%) with a mean age of 41 years. Most (85%) worked with adult patients, and more than half (56%) worked in inpatient departments. Just over one-quarter (27%) reported receiving formal training in health behaviour modification.

Strategies to assess adherence

Figure 1 shows the findings regarding use of the different adherence assessment strategies. Questioning patients about non-adherence during follow-up was the strategy most often reported, used frequently by 56% of the participants. Next came screening for risk factors for non-adherence during follow up, which was used frequently by 40% of the respondents. Using an electronic monitoring device to assess non-adherence was rare: 86% never used this method.

Interventions to enhance adherence

Educational interventions were used most often, followed by behavioral and least often, affective interventions (Figure 2). More specifically, participants reported using a higher proportion of educational/cognitive interventions (mean= 36%, SD=

24) than counseling/behavioral (mean= 32%, SD= 26) or psychological/effective interventions (mean= 23%, SD= 25).

Examining the data at the intervention level, we found that providing reading materials about cardiovascular care was the most used adherence-enhancing intervention, with 66% of respondents using it frequently (Table 2). Almost half of the participants (48%) reported that they frequently trained patients about how to properly take their medications at home during their inpatient recovery. Nearly half of the clinicians (47%) frequently offered individual patient/family instructions about medication adherence.

Using electronic monitoring devices for feedback was the least commonly reported method of improving adherence. Establishing support groups or peer mentor programs to reinforce adherence were never used in daily practice by 66% and 62% of participants, respectively. The other intervention used infrequently was computer assisted educational programs: with nearly 60% never using this technology.

Furthermore, we examined the proportion of the sample reporting frequent use of a combination of methods. Ninety-five participants (69%) reported that they frequently combined at least two interventions from the educational/cognitive, counseling/behavioral and/or psychological/affective categories to enhance adherence in daily cardiovascular care.

Discussion

The high prevalence of non-adherence in the cardiovascular patient population and its links to poor clinical outcomes, high (re)hospitalization rates, increased health care costs and higher mortality [9-15] demand the implementation of adherence enhancing interventions in daily clinical practice. To our knowledge, this is the first study to examine the types of medication assessment strategies and adherence enhancing interventions used by cardiovascular nurses and allied health professionals in daily clinical practice.

Assessment strategies

The most frequently used medication adherence assessment method in our sample was questioning patients about medication adherence during follow-up visits. This

self-report method is a simple, inexpensive and feasible method to assess adherence in daily care, but is prone to recall and socially desirable response bias [19, 20]. However, no gold standard exists for assessing patients' adherence [19] and all methods have their strengths and weaknesses [19-21]. Osterberg & Blaschke state that a combination of different adherence measures is the best approach to maximize accuracy [19].

Educational/cognitive interventions

Although evidence shows that educational interventions do not effectively enhance medication adherence [25], educational approaches were used most often in this study. A recent meta-analysis showed that despite evidence showing variable associations between knowledge and adherence, many interventions in older adults are educational [25]. In our sample the most frequently utilized method was providing reading materials about cardiovascular care. Interesting to note is that the previously mentioned meta-analysis did not find significant differences in adherence improvement following interventions using written information about medication or disease with those that did not. The effect of this intervention on knowledge, however, was significant [25]. Furthermore, larger adherence effect sizes could be found in participants taking 3-5 medications [25]. In order for educational interventions to be effective, the information materials should incorporate simple text and pictograms [30]. Patient education is likely to have more impact on adherence when it is consistent over time, presented by health care providers and tailored to patient characteristics including cognitive, educational, developmental and intellectual capabilities [22]. Moreover, the WHO report 'Adherence to long-term therapies – evidence for action' states that, while adherence interventions at the patient level have usually focused on increasing knowledge by providing education, knowledge alone is not enough to establish and maintain good adherence behavior [18].

Counseling/behavioral interventions

The method used least frequently in practice was employing electronic monitoring devices as a feedback system. Electronic monitoring devices are pill bottles or

blister packets that continuously record the date and time of each opening, which presumably corresponds with medication intake [22]. Data can be uploaded to a computer and printouts of the device's data show the user's medication dynamics, which the patient and health care team can discuss to jointly establish adherence goals. In cases of improved adherence, patients received positive feedback, inducing mastery experiences [31]. Although electronic monitoring can offer a powerful tool to enhance patients' adherence, it is not often offered in daily practice. This could be because electronic monitoring devices are rather expensive, may be too complicated for some patients to use and may be too time-consuming for the health care provider.

Although computer based information packages for patients have been shown to have a positive effect on self-efficacy and on behavioral outcomes [32], assisted learning programs were not frequently used in our sample. Cardiovascular health care professionals may be reluctant to use computer assisted programs due to the typically older age of their patient population. To benefit from such programs, the patient requires access to a computer and, for some programs, internet access, as well as the skills necessary to use computer hardware and software effectively. These requirements may be barriers to utilization of this type of intervention in older patient populations. It has been shown, however, that older patients with chronic diseases can be trained to use a computer and computer programs effectively [33, 34].

Psychological/affective interventions

Neither support groups nor peer mentor programs were used by most of the participants in this study, although a recent systematic review reported mixed outcomes from the use of non-professional volunteers [35]. In the literature examining non-adherence, one study in three reports a significant effect from these interventions [35]. Regarding patients' experiences of peer support, a qualitative study in kidney patients found that they greatly valued peer support and that it helped them to adapt to their chronic illness by normalizing adherence to their demanding treatment regimens [36].

Limitations of this study

This study has several limitations, the foremost of which is that the questionnaire focuses only on adherence enhancing interventions at the patient level. Interventions at the micro level (strategies focusing on patient-provider interactions), the meso level (characteristics of the treatment center or hospital), and the macro level (interventions focusing on the health care system or on the society in which a patient lives) are also crucial to improving adherence [37]. A further limitation is the limited generalizability of the findings as conference attendees may not accurately represent the population of cardiovascular clinical practice nurses and allied professionals. Compared to surveys conducted in previous years (with response rates of 33% [38] and 48% respectively [39]), this conference's survey had a high response rate of 62%. Unfortunately, we do not have data on the non-responders so it is not possible to see if they had a different socio-demographic profile or if there were more or less nurses/allied professionals not directly working in clinical practice among the non-responders.

Recommendations

Health care professionals working with cardiovascular patients are strongly advised to implement adherence enhancing interventions in their daily practice. Moreover, they are advised to implement multi-dimensional interventions combining educational/cognitive, counseling/behavioral, and psychological/affective interventions. To enable health care workers to deliver interventions that optimize adherence, they need to receive training in health behavior modification strategies.
Further research should address which interventions at the micro-, meso-, and macro level are most effective to enhance patients' adherence to their medication regimens. Future studies are also needed to examine health care workers' perceptions of the effectiveness of the adherence enhancing interventions they utilize.

Conclusion

A variety of interventions are used in daily cardiovascular care to improve medication adherence. The most frequently used interventions in this sample were educational/cognitive interventions, although evidence shows these are less effective than behavioural interventions at enhancing medication adherence. For clinicians committed to positively influencing medication adherence, it would be more effective to focus on combining interventions, especially implementing alternatives to educational interventions.

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Table 1: Demographic information

Variable	N= 137
Gender	
Female, n (%)	114 (83)
Age years	
Mean ± SD	41.36 ± 8.98
Continent where department is located	
Europe, n (%)	129 (94)
North-America, n (%)	4 (3)
Asia, n (%)	2 (2)
Highest level of education	
Basic nursing training, n (%)	48 (35)
Bachelor, n (%)	40 (29)
Master, n (%)	39 (29)
PhD, n (%)	10 (7)
Current position	
Staff nurse, n (%)	46 (34)
Advanced Practice Nurse, n (%)	38 (28)
Head nurse/Nurse manager, n (%)	22 (16)
Other[1], n (%)	31 (23)
Case load	
Adult patients, n (%)	116 (85)
Paediatric patients, n (%)	1 (1)
Both, n (%)	18 (13)
Main specialty department (more than one answer possible)	27
Critical care (ICU/CCU), n	26
Interventional cardiology (e.g. cath lab), n	23
Cardiac rehabilitation, n	21
Outpatient clinic, n	20
Internal medicine, n	20
Cardiac surgery, n	20
Intermediate CCU, n	14
Diagnostic (e.g. EKG, Echo, Nuclear Stress), n	11
Emergency Room, n	8
Transplantation, n	4
Community health care, n	13

Other[2], n	
Type of hospital	
University teaching hospital, n (%)	86 (63)
Teaching hospital, n (%)	21 (15)
Regional or community hospital, n (%)	19 (14)
Clinic, n (%)	7 (5)
Community health care organization, n (%)	2 (2)
Advanced Practice Nurse working at the department	
Yes, n (%)	83 (61)
Years practicing	
Mean ± SD	18.16 ± 9.94
Years practicing in cardiovascular nursing	
Mean ± SD	12.46 ± 9.28
Years practicing in current department	
Mean ± SD	9.12 ± 8.01
Percentage of work	
Mean ± SD	87.59 ± 22.71
Received formal training in health behavior modification	37 (27)

[1]Other current positions including: Study nurse/nurse researcher, biomedical engineer, physiotherapist, medical doctor, nurse manager/care manager.
[2]Other main specialty departments including: Physical training centre, patient organization, vascular surgery ward, nursing ward.

Figure 1: Non-adherence (NA) assessment strategies

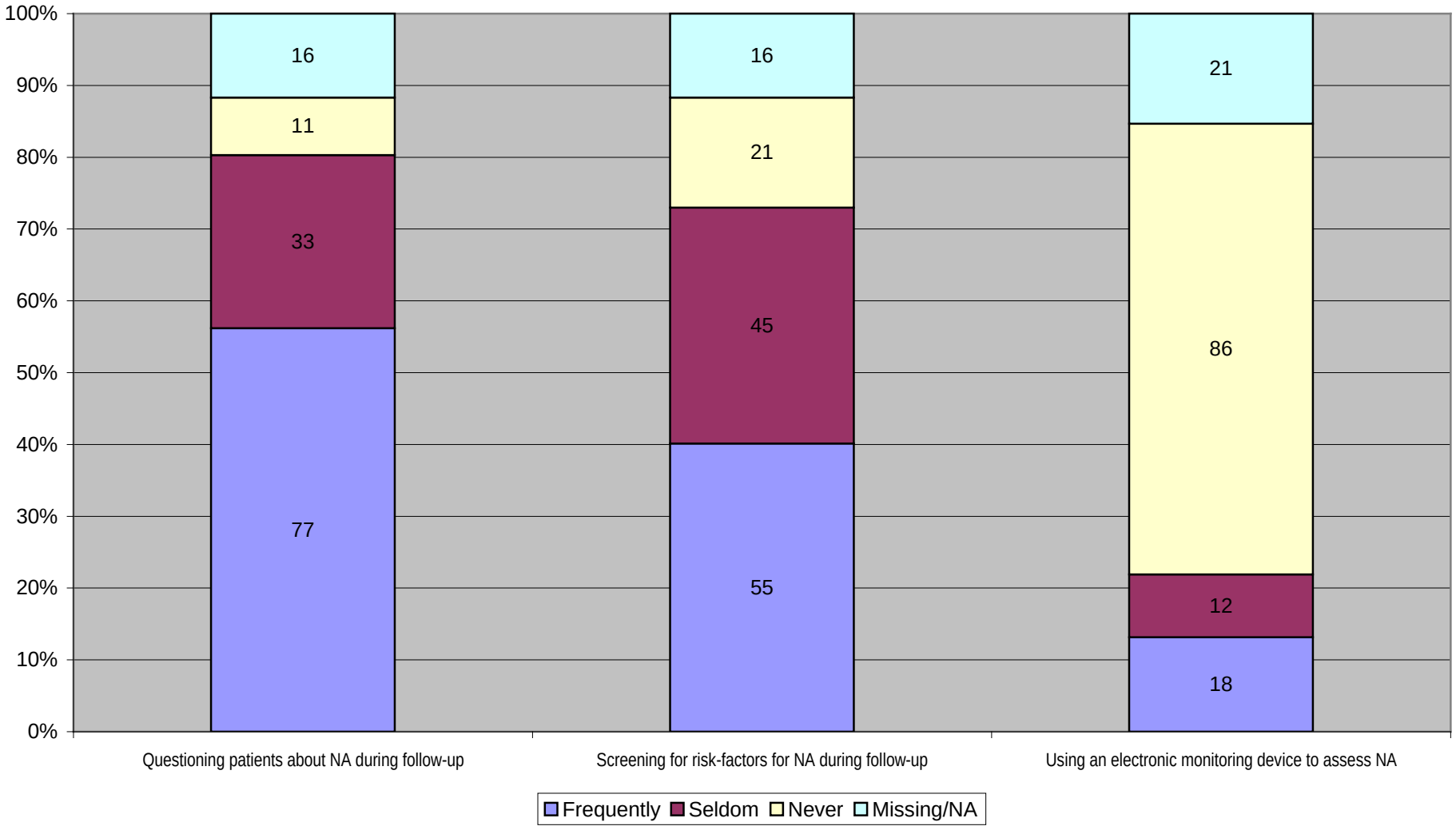

Figure 2: Number of participants reporting that they frequently used the intervention

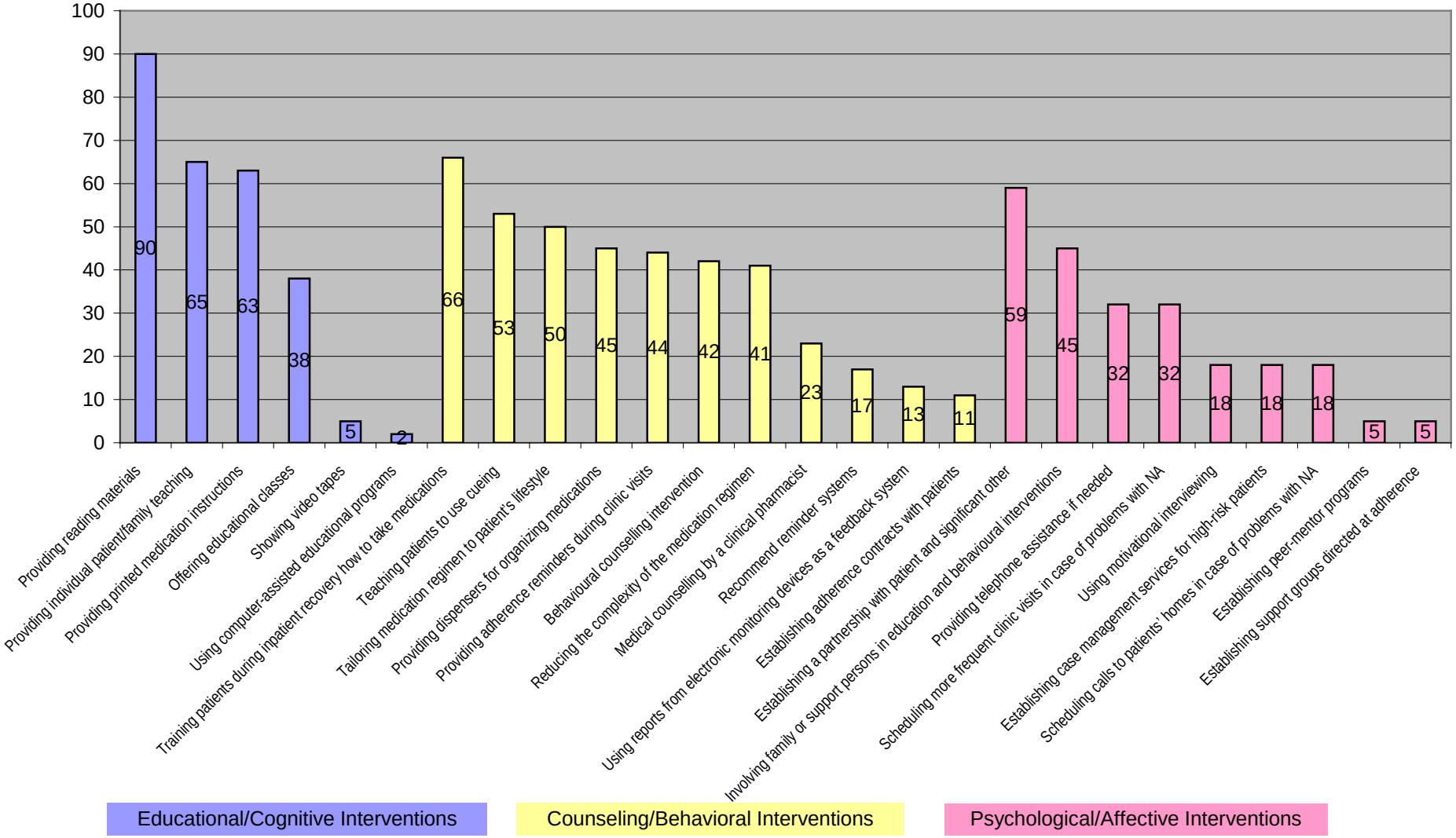

Table 2: Adherence enhancing intervention N =137

Variable	Frequently %	Seldom %	Never %
Educational/Cognitive interventions			
Providing reading materials	66	19	6
Providing individual patient/family teaching	47	24	18
Providing printed medication instructions	46	24	18
Offering educational classes	28	20	40
Showing video tapes	4	30	56
Using computer-assisted educational programs	2	31	58
Counselling/behavioural interventions			
Training patients during inpatient recovery how to take medications	48	22	16
Teaching patients to use cueing	39	25	21
Tailoring medication regimen to patient's lifestyle	37	26	26
Providing dispensers for organizing medications	33	22	31
Providing adherence reminders during clinic visits	32	20	28
Behavioural counselling intervention	31	28	22
Reducing the complexity of the medication regimen	30	33	21
Medical counselling by a clinical pharmacist	17	20	51
Recommend reminder systems	12	26	47
Using reports from electronic monitoring devices as a feedback system	10	5	69
Establishing adherence contracts with patients	8	24	53
Psychological/affective interventions			
Establishing a partnership with patient and significant other	43	26	15
Involving family or support persons in education and behavioural interventions	33	36	13
Providing telephone assistance if needed	23	39	21
Scheduling more frequent clinic visits in case of problems with NA	23	26	34
Using motivational interviewing	13	27	42
Establishing case management services for high-risk patients	13	23	46

Scheduling calls to patients' homes in case of problems with NA	13	21	49
Establishing peer-mentor programs	4	18	62
Establishing support groups directed at adherence	4	12	66

Chapter 6

Which interventions are used by health care professionals to enhance medication adherence in transplant patients? A survey of current clinical practice

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Abstract

Context: Although medication non-adherence is associated with severe complications including graft rejection and loss, its prevalence remains high among organ transplantation (Tx) recipients. Still, little information exists on clinical use of interventions to improve medication adherence (MA).

Objective: To identify Tx health care professionals' MA assessment methods, classify the used interventions, and measure those interventions' perceived effectiveness.

Design, Setting & Participants: A 46-item questionnaire on adherence assessment and interventions was distributed at the 2010 International Transplant Nurses Society symposium in Germany. Data were analyzed using descriptive statistics.

Results: Of 141 distributed questionnaires, 94 (67%) were returned. Respondents with no direct patient contact (9%, n= 8) were excluded. The most frequently used assessment strategy was patient self-reporting (61%, n= 52). On average, participants reported using 47% of the educational/cognitive and 42% of the counseling/behavioral interventions listed. Training patients to self-administer medications and providing printed adherence information were the most frequent interventions (79% each, n= 68), followed by providing printed medication instructions (69%, n= 59). Most respondents (90%, n= 77) reported combining interventions. The intervention perceived as most effective was medication self-administration training.

Conclusion: Although available alternatives are demonstrably more effective for MA enhancement, this sample relied significantly more on educational interventions.

Background

For solid organ recipients, maintaining graft health following transplantation (Tx) demands lifelong medication intake. Successful outcomes are linked closely to medication adherence (also called "compliance"), which the World Health Organization (WHO) defines as "the extent to which a person's behavior (e.g. taking medications) corresponds with the agreed recommendations of a health care provider " [1] (pg. 3).

Conversely, the effect of post-Tx non-adherence on short- and long-term outcomes – and associated health care costs – can be catastrophic: 15% to 60% of late acute rejections and 5% to 36% of graft losses are associated with non-adherence [2-6]. In a meta-analysis of renal transplantation data, Butler et al. showed that the odds of graft failure were seven times higher in non-adherent patients than in their adherent counterparts [5]. Even faced with such risks, a substantial proportion of solid organ recipients fail to take their medication as prescribed [2-4, 7-9]. A 2005 meta-analysis found that, among adult transplant (Tx) recipients, the magnitude of non-adherence to immunosuppressants was 22.6 cases per 100 patients per year across transplant groups [7].

A first step in tackling the major problem of non-adherence is measuring adherence during follow-up. This can be done using different strategies (e.g., self-reports, collateral reports, pill counts, electronic monitoring), each of which has its strengths and weaknesses [10-12]. The most accurate adherence data are gathered using a combination of measures [10] e.g., triangulation of electronic monitoring, self-reports and pill counts.

Once a patient's adherence rate is known, if necessary, interventions aiming to improve adherence can be implemented. These interventions can be classified as educational/cognitive, counseling/behavioral, or psychological/affective [13]. *Educational/cognitive interventions* present information individually or in a group setting, delivering it verbally, in written form, and/or audio-visually. *Counseling/behavioral interventions* shape and/or reinforce behavior, empowering patients to participate in their own care, while positively changing their skill levels or normal routines. *Psychological/affective interventions* focus on patients' feelings and emotions or social relationships and social support [13]. A systematic review examining medication adherence interventions after transplantation showed a serious shortage of intervention research in transplantation [13]. We recently

conducted a study assessing which strategies cardiovascular health care professionals use to assess patients' medication adherence and which interventions they apply to enhance medication adherence. In the sample surveyed, participants reported using a range of interventions to improve medication adherence [14]. Russell (2005) examined perception of 59 transplant health care providers regarding medication non-adherence [15]. Yet, both studies did not assess the health care professionals' perceptions of their chosen interventions' effectiveness. In another study, focusing on physicians of patients with chronic myeloid leukemia, Noens et al. showed how widely physicians' perceptions differed regarding the utility and applicability of adherence enhancing interventions [16]. This wide variation highlights the principle that, although medication adherence enhancing interventions are clearly necessary, little is known either of which ones health care professionals actually use for Tx recipients' routine care or of how they perceive the results.
This study therefore has three aims: (1) to identify which strategies Tx health care professionals utilize to assess their patients' medication adherence; (2) to classify the medication adherence enhancing interventions used (i.e., educational/cognitive, counseling/behavioral, or psychological/affective); and (3) to assess how these professionals perceive their chosen interventions' effectiveness.

Methods

Design, sample & setting

This study used survey methodology, replicating earlier research on health care professionals working with cardiovascular patients [17]. All participants attending the 2nd European International Transplant Nurses Society (ITNS) symposium in Berlin (Germany) (June 18th – 19th, 2010) were invited to participate. To be included, participants had to perform direct patient care. No other inclusion- or exclusion criteria were applied.

Variables and measurement

The questionnaire was originally developed for our earlier study in cardiovascular health care professionals [17] and adapted for transplantation. The listed interventions and assessment strategies were drawn from those described in the literature [18-22]. The draft questionnaire was discussed and adapted a number of

times in the research group before being finalized. To evaluate the understandability and feasibility of using the scale, we pilot-tested it with 13 Tx health care professionals who did not participate at the conference.

The structured questionnaire was available in two languages: English and German. Following Brislin's guidelines [23], it was first translated from German to English, then back-translated and compared to the original. After a number of items on participants' demographic characteristics, the remaining sets queried the participants on their medication adherence assessment strategies, the interventions they utilized to improve patients' medication adherence, and their perceptions regarding the effectiveness of the interventions they reported using.

Demographic information included*:* age in years; gender; highest level of education; current position (staff nurse, advanced practice nurse, Tx coordinator, head nurse/nurse manager, or other); the patient population they worked with; work setting (pre-Tx program, post-Tx program, or both); total years of clinical practice; years of clinical experience in Tx care; years worked in the current Tx program and percentage of working time spent in their Tx program; formal training in health behavior modification (yes/no); country (location) of the Tx center; what kind of transplants were performed in the Tx program; type of hospital where the Tx program was located; and whether there was an Advanced Practice Nurse working in the Tx program.

Adherence Assessment and Intervention Strategies: On a 5-point Likert scale, ranging from never to all the time, participants were asked to indicate the frequency with which they utilized three strategies to counter non-adherence (questioning patients about non-adherence during follow-up; screening for non-adherence risk factors during follow-up; and using electronic monitoring devices to assess non-adherence). Furthermore, given a list of educational/cognitive (6 items), counseling/behavioral (11 items), and psychological/affective (9 items) interventions, participants were asked to indicate on a similar scale the frequency with which they used each to increase patients' medication adherence. The intervention and assessment strategy lists were comprised of interventions found in the literature [18-22]. For any intervention they reported using (occasionally, sometimes, frequently or all the time) participants were asked to indicate on a three-point scale (not at all, somewhat or extremely) how effective they considered that intervention.

Data collection

All attendees of the 2nd European ITNS symposium were given the study questionnaire at the time of registration and informed about the study by two research assistants. The study was also introduced at the opening session of the conference. Attendees were asked to deposit their completed questionnaires into any of the designated collection boxes. Questionnaires could be submitted during both conference days. The distribution process guaranteed that only one questionnaire was distributed per attendee. Research associates were available throughout the conference to provide information and support in filling out the questionnaire as well as to motivate attendees to participate in the survey.

Data analysis

Data were analyzed using descriptive statistics: frequencies, percentages and, where appropriate, measures of central tendencies and variability were calculated. For each of the three intervention categories (education/cognitive, cognitive/behavioral and psychological/affective), we calculated the mean proportion of interventions that participants reported using frequently or always. Participants who reported frequently or always using one or more intervention from at least two of the categories were classified as frequently utilizing combinations of methods to enhance medication adherence. Prior to analysis, because of the highly skewed answer patterns for most items measuring medication adherence assessment strategies and adherence enhancing interventions, the Likert scale response data were assigned numerical values: never= 0 ('never'), seldom= 1 ('occasionally' and 'sometimes'), and frequently= 2 ('frequently' and 'all the time'). To analyze the perceived effectiveness of interventions, we ranked them by category, from the highest to the lowest proportion of respondents rating them extremely effective. Perceived effectiveness was only rated if the health care professional personally used the intervention to enhance medication adherence. We calculated descriptive statistics (mean, standard deviation and median) to describe the average ratings of effectiveness for each category of interventions. Statistical analyses were performed using SPSS 16 (SPSS Inc, Chicago, Il).

Human subject considerations

The questionnaire was reviewed and approved by ITNS. Informed consent of the participants was implied by completion of the questionnaire. Participants were free to decide whether they anted to complete the questionnaire or not. Data were collected anonymously (i.e., no identifying data were collected from the participants).

Results

Demographic information

Of the 141 questionnaires distributed, 94 (67%) were completed and returned. Eight respondents (9%) indicated not being involved in direct patient care and were therefore excluded from further data analysis. Table 1 shows the demographic characteristics of the final sample (N= 86). The majority (86%) of participants were female, with a mean age of 41 years (SD: 8.52). Most (76%) worked with adult patients; more than half (51%) were working in inpatient Tx departments.

Strategies to assess medication adherence

The assessment strategies used are shown in Figure 1. Questioning patients about non-adherence during follow-up was frequently used by the majority of the sample (61%). Screening for non-adherence risk factors was performed frequently by 43% of participants. Other methods participants reported using were monitoring blood levels (two participants (2.3%) reported using this strategy frequently), and using medication diaries (reported by one participant).

Interventions to enhance medication adherence

Figure 2 shows the percentage of participants who reported frequently using each intervention. On average, participants reported frequently using 47% of the educational/cognitive interventions, 44% of the counseling/behavioral interventions and 42% of the psychological/affective interventions listed.

The frequencies at which participants used interventions to promote medication adherence are shown in figures 3-5. The two interventions used most frequently were providing reading materials (educational/cognitive intervention) and training patients during inpatient recovery how to take medications (counseling/behavioral intervention). Seventy-nine percent of the sample reported using both interventions frequently. The next most commonly used intervention, used frequently by 69% of the participants, was providing printed medication instructions. Almost two-thirds of the sample (63%) reported teaching patients to use cueing to increase medication adherence.

The intervention employed least frequently was using reports from electronic monitoring devices to provide adherence feedback. Most participants (75%) reported never using such devices. Fifty-seven percent indicated never using counseling by a pharmacist to improve adherence. More than half (54%) never used computer assisted educational programs.

We also examined the proportion of the sample that reported frequently using a combination of methods. Of this group, 77 (90%) reported frequently combining at least two adherence enhancing interventions from the educational/cognitive, counseling/behavioral and/or psychological/affective categories in daily Tx patient care.

Perceived effectiveness of used medication adherence assessment strategies and MA enhancing interventions

The intervention perceived as most effective in increasing adherence to the prescribed medication treatment was training patients during inpatient recovery how to take medications (Figure 6). Of the 73 participants who rated its effectiveness, 57 (78%) considered it extremely effective. The second most effective intervention was providing medication organizer dispensers. Thirty-eight of the 60 participants (63%) using this intervention considered it extreme effective. Sixty percent of participants reported that establishing a partnership with patients and significant other(s) was extremely effective in promoting adherence. Comparing the effectiveness ratings per category, the average effectiveness ratings for the three categories of interventions were very similar [educational cognitive: mean= 2.52 (SD= 0.40), median= 2.60; counseling/behavioral: mean= 2.49 (SD= 0.32), median= 2.50; psychological/affective: mean= 2.51 (SD= 0.36), median= 2.59].

Discussion

As non-adherence after organ transplantation has a high prevalence [2-4, 8, 9] and is associated with poor clinical outcomes and increased health care costs [2-6, 24, 25], it is imperative that Tx health care professionals implement medication adherence promoting interventions in daily practice. To our knowledge, this is the first study examining the types and frequencies of Tx health care professionals' medication adherence assessment strategies and adherence to the medication regimen enhancing interventions.

Assessment strategies

Our sample's most frequently used adherence assessment method was questioning patients about their adherence during follow-up visits. As this strategy is simple, inexpensive and feasible for daily care, this result supports our earlier findings in cardiovascular health care professionals [14] and the findings by Russell in a small sample of transplant health care providers [15]. However, this assessment method is particularly prone to recall and socially desirable response bias [10, 11]. As no gold standard exists for assessing patients' medication adherence [10], i.e., all methods have significant weaknesses [10-12], Osterberg and Blaschke promote a combination of adherence measures as the most reliable and accurate approach [10]. An example of an optimal combination is the triangulation of self-report, assay and physician or nurse report.

Educational/cognitive interventions

The most frequently used method to promote medication adherence in this study was providing reading material on transplant care; providing printed medication instructions was ranked third. Overall, educational approaches to improve medication adherence were applied more than any other intervention type, despite compelling evidence that educational interventions have particularly limited effectiveness – a result consistent with our previous research in cardiovascular health care professionals [14]. These findings are consistent with findings of Hathaway and colleagues [26] who also found that health care providers reported that they would used primarily educational interventions to improve adherence. That

study, however, did not focus specifically on medication adherence but also included adherence to other aspects of the treatment regimen (e.g., diet, exercise and non-smoking).

The WHO report 'Adherence to long-term therapies – evidence for action' concludes that, while adherence interventions at the patient level have usually focused on increasing knowledge, i.e., patient education, knowledge alone is not enough to establish and maintain strong adherence behavior [22]. A recent meta-analysis showed that, although providing written medication or disease education improves knowledge, it is much less effective at translating that knowledge into more desirable behavior, i.e., improved adherence [27]. However, Mansoor and Dowse (2006) had earlier argued that the specific design of the printed material influenced its value, i.e., that in order for printed material to be effective at improving adherence, it should employ simple text and pictograms [28]. Earlier still, Turnbull (2003), posited that producing good patient information required a team effort between professionals and patients [29].

Although computer based information packages for patients have been shown to have positive effects on self-efficacy and behavioral outcomes [30], computer assisted learning programs were not frequently used in our sample. This result is not surprisingly, as only very limited computer assisted patient education programs are currently available in transplantation. A study evaluating the validity and usability of one computer-based training and assessment program developed for transplant recipients revealed that the program deviated significantly from current medical practice regarding content and language [31]. Furthermore, health care professionals may be reluctant to use such programs due to the increasing average age of their patient population in follow-up. Such programs require that the patient have both access to a computer (sometimes with internet access) and the skills necessary for effective computer hardware and software use – prerequisites that might deter many older patients from using this type of intervention. Responding to such concerns, Marziali (2009) showed that older patients with chronic diseases can be trained to use computers and software packages effectively [32]. The implementation of computer assisted learning programs in clinical practice could also save valuable health care professionals' time, as patient/users can receive considerable amounts of information from a program rather than a highly-trained professional, and can later address specific questions and concerns to their health care providers. Once issues such as these have been addressed, and well-designed, accurate computer-

assisted patient education packages become available, the savings they offer will make them difficult to ignore.

Counseling/behavioral interventions

The method least frequently used in practice was using reports from electronic monitoring devices as a feedback system. Electronic monitoring devices are pill bottles or blister packets that automatically record the date and time of each manipulation of the system that presumably corresponds with medication intake [33]. Data can be uploaded to a computer and printed out to show the user's medication dynamics, which can be discussed with the patient and used to establish adherence goals. In cases of improved adherence, patients receive positive feedback, inducing mastery experiences [34]. Yet, while this is a powerful intervention to enhance patient's medication adherence [34], it is not often offered in daily practice, possibly because electronic monitoring devices are rather expensive, may be complicated for some patients and may be time consuming for the health care provider to administer. However, in a study among older kidney transplant recipients, most participants gave positive responses regarding their experiences with the electronic monitoring device [35].

Another intervention our sample used infrequently to enhance adherence was medical counseling by a clinical pharmacist. This low usage rate of medical counseling by clinical pharmacists as an adherence-enhancing method may result from the general rarity of clinical pharmacists in European hospitals. Unlike a traditional pharmacist, a clinical pharmacist works directly with health care providers and patients, providing a broad range of specialized services [36]. A literature review evaluating the effects of interventions by clinical pharmacists on processes and outcomes of care in hospitalized adults showed that medication adherence, knowledge and appropriateness improved in 7 of the 11 studies reviewed [36]. Furthermore, the involvement of clinical pharmacists in Tx cases has been associated with decreased mortality, lower complication rates, lower hospital charges and reductions in preventable adverse drug events [37].

In our sample, a large majority of participants (90%) frequently combined two or more interventions from the educational/cognitive-, counseling/behavioral- and/or psychological/affective categories to enhance adherence in the daily care of Tx patients. This is much higher than in our cardiovascular health care professional

study, where 69% used multi-dimensional interventions [14]. Evidence clearly indicates that the most effective method of enhancing medication adherence was the use of multi-dimensional interventions, i.e., combining educational/cognitive, counseling/behavioral, and psychological/affective interventions [18-21, 38]. A Cochrane review of 70 trials, testing 83 interventions aiming to improve long-term adherence, showed that fewer than half (n= 36) of the interventions were significantly associated with improvements in medication adherence, while only 25 could be linked causally to improvement in at least one treatment outcome [20]. No simple and few complex interventions resulted in improvement of medication adherence and clinical outcomes [20]. The interventions most effective for long-term care included combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-ups, and supportive care [20]. In a recent meta-analysis of studies regarding older adults, Conn et al. (2009) showed that a number of interventions significantly improved medication adherence; however, they also reported large differences in the effect sizes of different interventions [27].

Perceived effectiveness of interventions

Of the medication adherence enhancing interventions listed on our questionnaire, training patients during inpatient recovery on medication self-administration was perceived as the most effective: 78% of participants who used it rated it as extremely effective. This method was also used most frequently. The other most frequently used intervention, providing reading materials, was perceived as extremely effective by fewer than half of the participants (45%) who used it in daily practice. As mentioned above, evidence shows that written medication and disease information has limited effect on adherence improvement [27]. Interestingly, while this intervention was used most often, it was not perceived as effective at medication adherence improvement.

At the bottom of the usage scale, the intervention least frequently employed in practice – using reports from electronic monitoring devices as a feedback system – was ranked second most often as extremely effective. As stated above, this is clearly an effective system of improving patients' adherence [34].

Limitations of this study

This study has several limitations, beginning with our questionnaire's focusing only on medication adherence enhancing interventions at the patient level. Interventions at the micro level (e.g., focusing on the patient-provider interaction or on the patient's social support system), the meso level (i.e., the treatment center or hospital), and the macro level (i.e., the patient's health care system or society) are also crucial in improving adherence [39]. A further limitation of this study is the limited generalizability of its findings, as the participants were conference attendees and may not have accurately represented the majority of health care professionals working in transplant clinical practice. Although we provided the questionnaire in two languages, language barriers may still have existed for participants fully fluent in neither. However, one notable strength of this study is its 67% response rate, which is high compared to many research studies conducted at conferences [40, 41].

Recommendations

Health care professionals working with transplant recipients are strongly recommended to implement evidence-supported medication adherence enhancing interventions in their daily practice. Moreover, they are advised to implement multi-dimensional interventions, i.e., to combine educational/cognitive, counseling/behavioral, and psychological/affective interventions. Further, enabling health care professionals to deliver effective interventions that optimize adherence will require training in health behavior modification strategies. Further research should also assess which interventions are utilized at the health care provider-, health care organization-, and health care system level to enhance transplant patients' medication adherence [33].

Conclusion

Tx health care professionals apply a variety of interventions to improve Tx recipients' medication adherence. Although evidence shows that educational/cognitive interventions are less effective than behavioral interventions, they were used most frequently by members of this sample. For clinicians

committed to enhancing medication adherence, it would be advisable to focus more on implementing alternatives to educational interventions.

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Table 1: Demographic information

Variable	N= 86
Gender	
Female, n (%)	73 (85.9)
Age years	
Mean ± SD	41.24 ± 8.52
Continent where department is located	
Europe, n (%)	80 (93.0)
North-America, n (%)	4 (4.7)
Australia, n (%)	2 (2.3)
Language questionnaire	
English, n (%)	36 (41.9)
German, n (%)	50 (58.1)
Highest level of education	
Basic nursing training, n (%)	55 (64.0)
Bachelor, n (%)	12 (14.0)
Master, n (%)	15 (17.2)
PhD, n (%)	2 (2.3)
Other (Medical Secretary), n (%)	1 (1.2)
Missing, n (%)	1 (1.2)
Current position	
Staff nurse, n (%)	56 (65.1)
Advanced Practice Nurse, n (%)	12 (14.0)
Transplant Coordinator, n (%)	8 (9.3)
Head nurse/Nurse manager, n (%)	3 (3.5)
Other[2], n (%)	6 (7.1)
Missing/Not applicable, n (%)	1 (1.2)
Type of transplant performed at transplant program	
Kidney, n (%)	9 (10.5)
Lung, Heart, Heart-Lung, n (%)	9 (10.5)
Kidney, Liver, Lung, Heart, Heart-Lung, Pancreas, Bone Marrow, n (%)	7 (8.1)
Heart, n (%)	6 (7.0)
Lung, n (%)	5 (5.8)
Liver, n (%)	3 (3.5)
Combined Organ Transplantation, n (%)	47 (54.6)
Case Load	
Adult Patients, n (%)	65 (75.6)

Pediatric Patients, n (%)	5 (5.8)
Both, n (%)	16 (18.6)
Pre/post transplant program	
Pre-transplant program, n (%)	3 (3.5)
Post-transplant program, n (%)	32 (37.2)
Both, n (%)	51 (59.3)
Primarily work in	
An inpatient transplant program, n (%)	44 (51.2)
An outpatient transplant program, n (%)	16 (18.6)
Both, n (%)	24 (27.9)
Other, n (%)	2 (2.3)
Advanced Practice Nurse working at the department	
Yes, n (%)	32 (37.2)
Years practicing	
Mean ± SD	18.96 ± 8.88
Years practicing in transplant nursing	
Mean ± SD	10.61 ± 7.21
Years practicing in current transplant program	
Mean ± SD	8.15 ± 7.36
Percentage of work	
Mean ± SD	83.07 ± 30.14

[1]Other countries including: Australia, Canada, Spain, and United States.

[2]Other current positions including: Staff Nurse & Education, Staff Nurse & Diabetes Assistant, Staff Nurse & Organ Donation Agent

[3]Other main specialty departments including: Rehabilitation, education.

Figure 1: Non-adherence (NA) assessment strategies

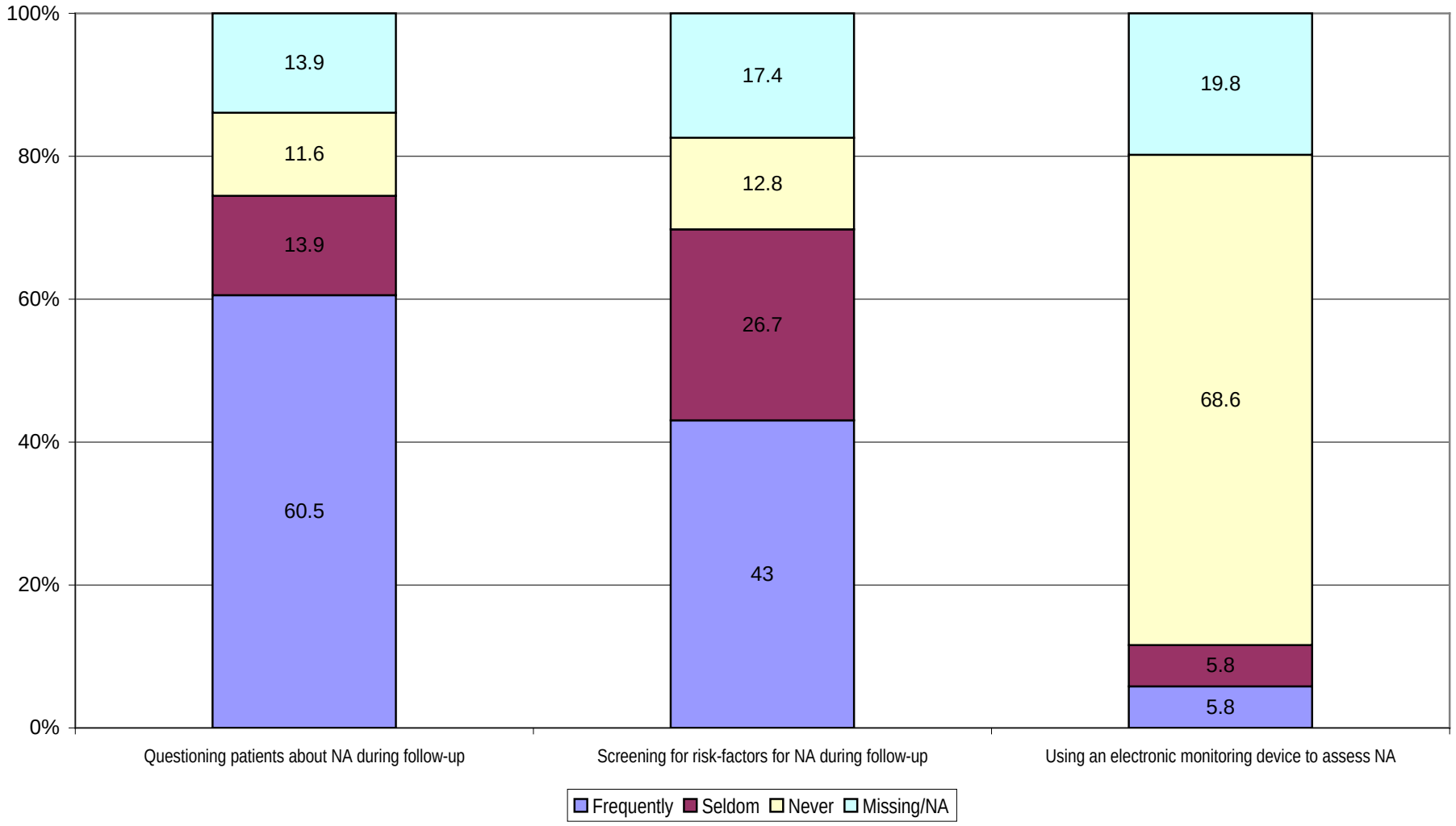


Figure 2: Percentage of participants reporting that they frequently used the intervention

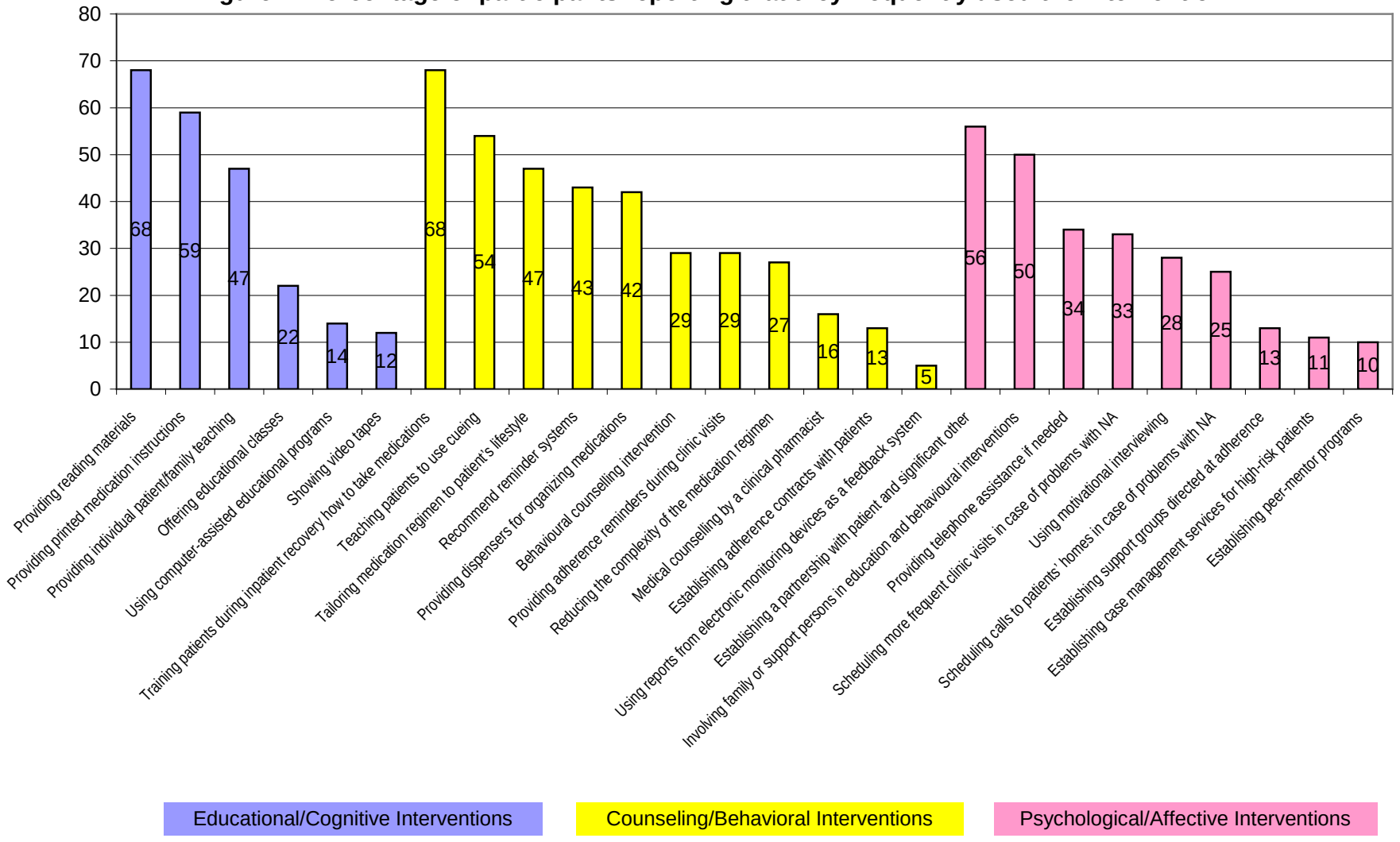


Figure 3: Educational/Cognitive interventions

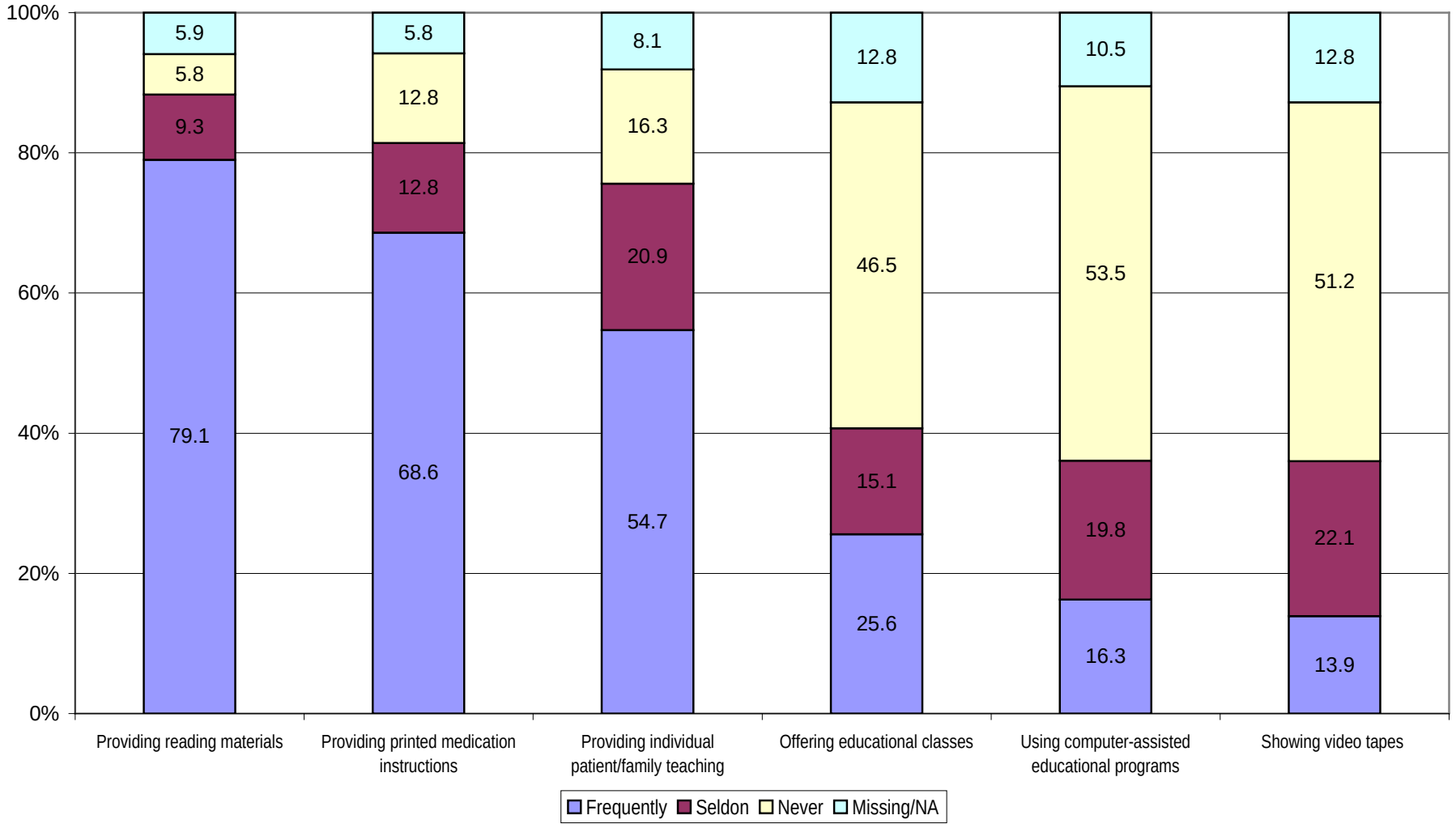


Figure 4: Counseling/Behavioral interventions

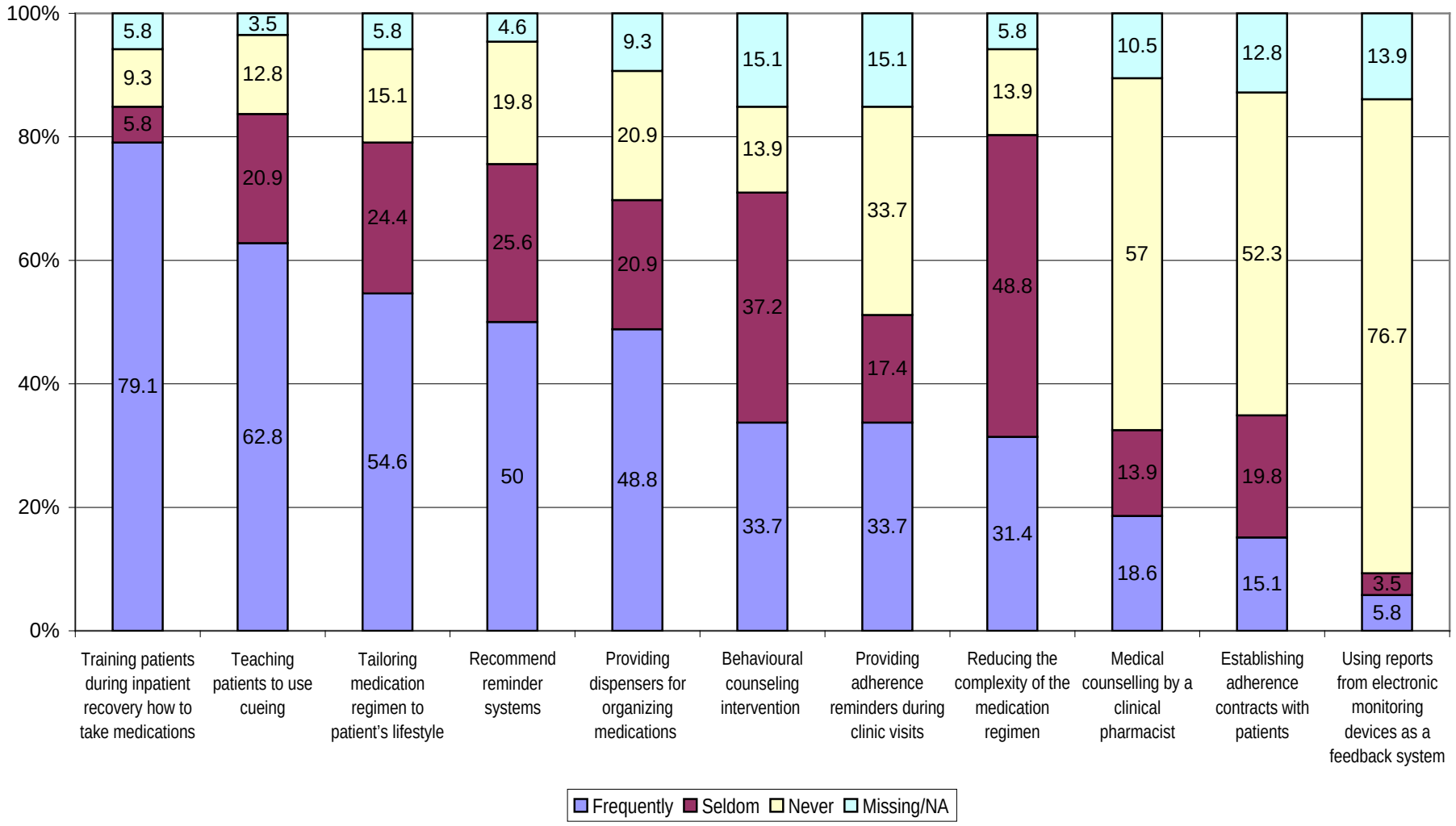


Figure 5: Psychological/Affective Interventions

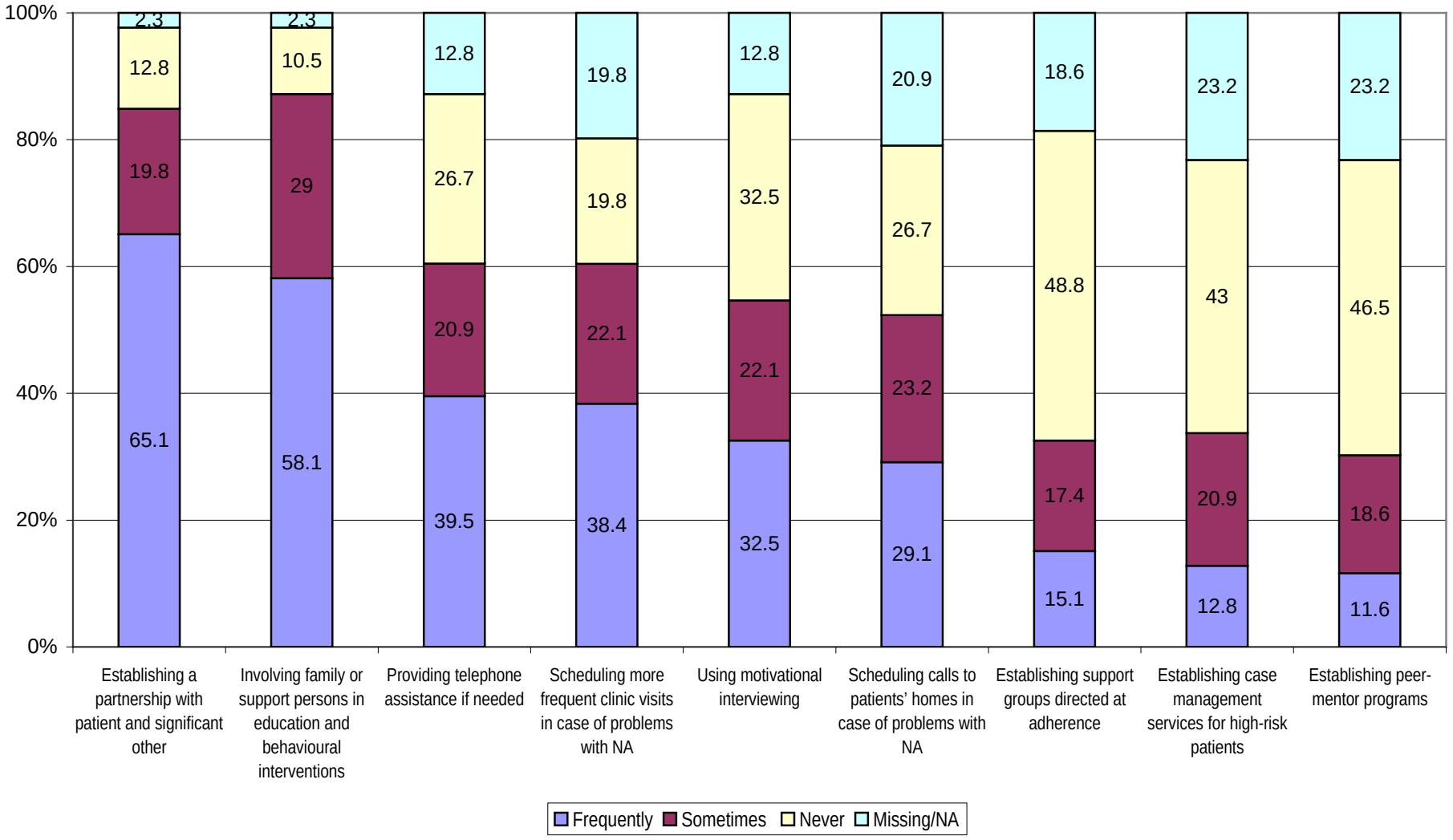
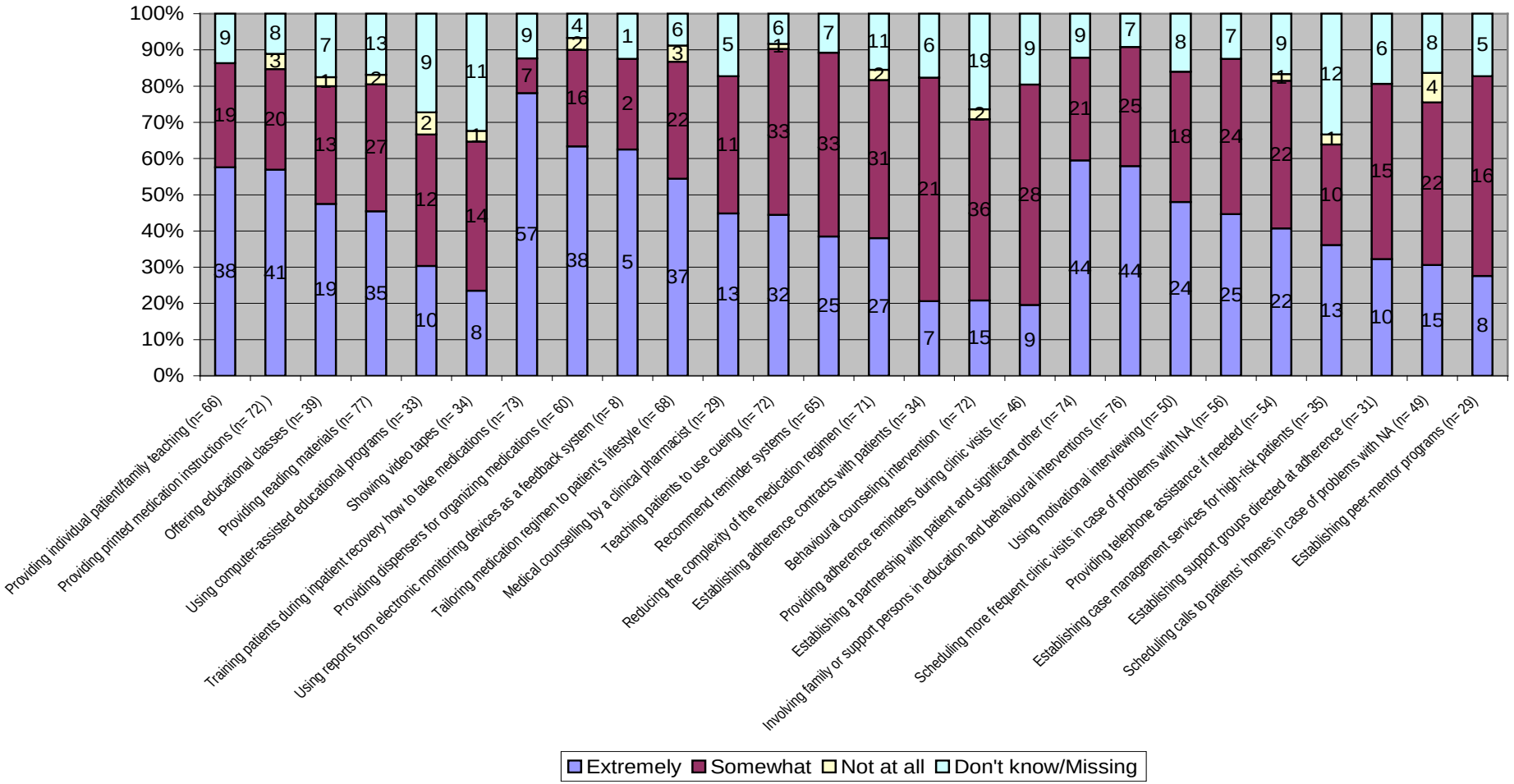


Figure 6: Perceived effectiveness of used interventions*



*Perceived effectiveness was only rated if the health care professional used the intervention to enhance medication adherence.

Chapter 7

Development, content validity and inter-rater reliability testing of the CIMI-BRIGHT: an instrument to assess the level of chronic illness management implemented in transplant programs

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Abstract

Background: We developed the Chronic Illness Management Implementation - Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument to assess the level of chronic illness management implemented in transplant centers.

Aim: The aim of this study is to describe the development of the CIMI-BRIGHT instrument and to assess initial content validity and inter-rater reliability.

Methods: To evaluate content validity, the relevance of each 'chronic illness management' construct item (N= 51) was rated on a 4-point Likert scale ranging from 1= not relevant to 4= highly relevant by 7 experts (3 from USA, 4 from Europe) in chronic illness management. Content validity indexes were calculated for each item and the instrument as a whole. To evaluate inter-rater reliability, we conducted a pilot study in one abdominal and one renal transplant program. Participant agreement by center for the total CIMI-BRIGHT instrument was compared by averaging the percent agreement on individual items.

Results: Of the 51 items, 42 had a good content validity. Two of the nine items with low content validity were deleted and the remaining seven were revised. The percentage agreement in the two transplant programs for the total instrument was 84.6% and 74.8% respectively, indicating good inter-rater reliability.

Conclusion: The results of this initial validation of the CIMI-BRIGHT instrument are promising, suggesting its value as a measure of the extent to which the chronic illness model is being implemented in transplant programs. Further validation is needed to fully evaluate the validity and reliability of this instrument.

Background

Over the past decades, patient as well as graft survival rates improved for solid organ transplant (Tx) recipients. This is mainly due to improvements in immunosuppressive management. One year patient survival rates for heart transplant patients, for instance, increased from 86.1% in 1998 to 89.2% in 2007, for renal transplant patients (deceased donor), this increase was from 94.9% in 1998 to 96.5% in 2007, and for heart lung transplant patients it even increased more from 7.2% in 1998 to 90.3% in 2007 [1]. However, survival gains are limited to the first 6 to 12 months after transplantation, with long-term survival rates remaining largely unchanged [2-5]. Improving long-term outcomes is considered a priority in transplantation [3, 4].

Receiving an organ transplant implies that recipients have to adopt a number of long-term health behaviors, including medication taking, self-monitoring for signs of rejection and infection, as well as regular follow-up visits to their physician. Based on these requirements, transplantation does not cure patients, and hence transplant recipients should be perceived as chronically ill patients. To-date, however, health care for Tx recipients has most common been organized around an acute, episodic model of care. In a care system designed to address acute health problems the purpose is to diagnose and to treat a patient's presenting complaint [6]. There is generally no need to follow the patient over time. Yet, this model of care does not meet the needs of Tx patients who are chronically ill [6-8]. Providing optimal care for the chronically ill implies a shift in the organization of care from an acute focus to a system where the principles of chronic care are integrated, namely continuity of care; partnership with patients, families and communities; support for patients in improving their self-management; attention to preventive measures; decision-making support; and the availability of clinical information systems [6, 7, 9-11]. Studies in asthma and diabetes, for instance have reported improved patient outcomes when care systems to manage chronically ill patients shift from an acute to a chronic care model [11-14].

The World Health Organization's (WHO) Innovative Care for Chronic Conditions (ICCC) framework (see Figure 1) presents a framework for health care systems to improve care for the chronically ill [6, 15, 16]. This framework can help decision makers or those who are working in the health care system to progressively create or redesign health care organizations and system to expand its capacity to manage long-term health problems [6, 16]. The framework is based on a set of guiding principles acting at three levels [7]. The micro level emphasizes the partnership between patients and families, and the health care professionals. The meso level refers to the health care organization and the community. The macro level refers to policy and financial contexts [6, 7, 16].

Within the health care organization or meso level, there are five essential building blocks that health care organizations need to focus on to improve the care of chronically ill patients (see Figure 1). First, they need to *promote continuity and coordination*, which refers to the need of chronically ill patients for services that are coordinated across levels of care (i.e., primary, secondary, and tertiary care) and across providers [6]. Second, they need to *encourage quality care through leadership and incentives;* senior and other influential leaders need to lend clear support and sponsorship for improving the care of chronic conditions in their health care organization. Third, they need to *organize and equip health care teams* by providing them with the skills and knowledge (e.g., effective communication abilities) to manage chronic conditions [6]. Forth, they need to *support self-management and prevention*; health care professionals need to be informed about self-management strategies and know how to educate patients and families about self-management [6]. Finally, the last building block, *the use of information systems*, means that health care organizations must provide timely information about individual patients and populations of patients. Information systems are needed to gather and organize data about epidemiology, treatment and health care outcomes. The goal is to use information systems to improve planning and the general standard of care [6].

Center effects, which can be defined as "differences in outcome among centers that cannot be explained by identifiable differences in patients treated or specific treatments applied" [17] (pg. 417), are presumed to result from differences in the ways health care is delivered. A number of studies demonstrated that variations in the practice patterns influence patient outcomes. A study in hematopoietic stem cell transplantation in the United States identified the following center factors to be associated with decreased 100-day mortality: the presence of physicians answering after hours calls and higher patient-per-physician ratio [18]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective, observational study among hemodialysis centers in seven different countries showed that center characteristics such as the size of the center and the percentage of highly trained staff and the country where the dialysis center was located were related to dialysis non-adherence rates [19, 20]. These center-specific differences regarding outcomes indicate that processes at the level of the health care organization are influential and should be further examined.

Assessment of level of chronic illness management

The level of chronic illness management implemented in a health care organizations can be assessed either from the patient perspective [21] or from the perspective of the health care provider [22]. The Patient Assessment of Chronic Illness Care (PACIC) questionnaire was developed by the MacColl Institute for Health care Innovation to assess the implementation of the CCM from the patient perspective [21]. To assess the level of chronic illness care through health care provider information, Bonomi et al. [22] developed the Assessment of Chronic Illness Care (ACIC) questionnaire. There were, however, poor correlations between ACIC scores and chronic disease experts' ratings of team performance ($r = 0.28$ to 0.52) [22]. Furthermore, the ACIC questionnaire was not specifically developed for transplant populations, identifying a clear gap in the literature on how to assess the level of chronic illness care from the meso level perspective.

The aims of this study therefore were:

1) to describe the development of the CIMI-BRIGHT instrument
2) to assess the content validity of the CIMI-BRIGHT instrument
3) to assess the inter-rater reliability of the CIMI-BRIGHT instrument

Methods

1) Development of CIMI-BRIGHT

The development of the CIMI-BRIGHT instrument was based on the previously described conceptual framework of ICCC, as well as on clinical expertise of the members of the research team. Based on this framework, we generated items to capture each building block of the health care organisation. To test the completeness of the instrument, the clarity of the items and the clarity of the answer scoring, a focus group interview with a group of 7 international nurses who work in transplantation was conducted. The feedback received during this interview was integrated in the instrument. After content validity testing (see content validity testing) the instrument was adopted (i.e., items deleted and items revised) resulting in the CIMI-BRIGHT instrument which was used for the pilot study (see inter-rater reliability testing).

2) Content validity testing

The framework used to validate this instrument was the Standards for Educational and Psychological testing proposed by the American Educational Research association, American psychological Association and the National Council on Measurement in Education [23]. The AERA defines validity as "the degree to which evidence and theory support the interpretations of test scores implied by the proposed uses of a test" [23] (pg. 9). In this study, we tested the content validity of our instrument empirically, in order to provide evidence on content area of the measurement [23, 24].

Sample and setting: An interdisciplinary group of international (Europe and US) experts in chronic illness management were selected by the research team. We defined an expert in chronic illness management as a person who was recognized in the chronic illness scholarly world as evidenced by at least two publications or presentations on chronic illness management. Two authors (LB & SE) searched on the World Wide Web for experts, a third author (SDG) approved the choices. The expert group was composed of nurses, physicians and health policy professionals.

Measurement: For each individual item, the content experts were asked to rate the relevance of the item on a 4-point Likert scale (1= not relevant, 2= somewhat relevant, 3= quite relevant, and 4= highly relevant) in relation to the construct 'chronic illness management' [25] on the Content Validity Form

Data collection: The identified chronic illness management experts were contacted by mail and asked to participate in this study. The CIMI-BRIGHT instrument and the Content Validity Form were mailed to those agreeing to participate. During a scheduled phone call, the background, aims and methodology were briefly described by the first author (LB), as well as information on the purpose and use of the Content Validity Form. Participating experts were asked to return the completed Content Validity Form by either electronic mail or regular mail. If the Content Validity Form was not returned within one month, the participants received a reminder mail to return the Content Validity Form. If they did not respond to the reminder, they were considered non-responders. Data were collected in Autumn 2009.

Data analysis: To evaluate the content validity of the CIMI-BRIGHT instrument, content validity indexes (CVI) were calculated. CVI's were calculated for each item (content validity for item, I-CVI) and the instrument as a whole (content validity index for scales, S-CVI). The I-CVI was computed as the number of experts giving a rating of either 3 (quite relevant) or 4 (highly relevant) divided by the total number of experts [25]. To evaluate the content validity on the scale level, we averaged the item-level CVI's. More specifically, the I-CVI's were summed and divided by the number of items [25]. An instrument is considered to

have excellent content validity if it is composed of items with a I-CVI of .78 or higher and the S-CVI is .90 or higher [25].

3) Inter-rater reliability testing

To be able to calculate inter-rater reliability of the CIMI-BRIGHT instrument, we conducted a pilot-study in two Tx programs. Reliability is defined as "the consistency of measurements when the testing procedure is repeated on a population of individuals or groups" [23] (pg 25). Reliability can be generated in terms of stability, equivalence or internal consistency [24]. For the purpose of this study we tested reliability as equivalence, more specifically inter-rater (or inter-observer) reliability, which represents the agreement among raters.

Sample and setting: The pilot study of the CIMI-BRIGHT study was conducted in one abdominal and one renal Tx program in the US. Health care professionals were eligible to participate if they were working in the Tx program for longer than six months, were employed 50% or more in clinical practice and had knowledge about the content of care provided in the outpatient Tx program. Student nurses, nursing assistants, and float pool nurses were excluded from the sample. The instrument was also completed by the medical Tx director of each center. All health care professionals who met the inclusion criteria were invited to complete the CIMI-BRIGHT instrument.

Data collection: The abdominal and kidney Tx programs were identified and contacted by a member of the research team. A contact person at each Tx program was identified. Data collection for the pilot study was conducted in the Tx programs between March and December 2010. Health care professionals were surveyed voluntarily and anonymously. The CIMI-BRIGHT instrument was distributed by the contact person at the respective Tx program and were collected in a secured box located at each of the participating Tx programs. The contact person of each Tx program mailed the completed instruments to the principal investigator.

Ethical considerations: Approval was obtained from each Tx program's ethical committee prior to data collection. Informed consent of health care professionals was implied by the completion and return of the CIMI-BRIGHT instruments.

Data analysis: The percent agreement between the different health care professionals in each Tx program was calculated for the total CIMI-BRIGHT instrument assessing the 5 building blocks of the ICCC framework. Due the small sample size and few participant selecting some of the response options, they were collapsed into 1) strongly disagree & disagree; 2) agree and strongly agree; 3) don't know, not applicable or missing. Percentage agreement for the instrument of > 60% was interpreted as indicating substantial inter-rater reliability, 80% or more as almost perfect agreement [26].

Results

1) Development of CIMI-BRIGHT

Examples of items included in the CIMI-BRIGHT instrument are shown in Table 1. The first version of the CIMI-BRIGHT instrument consisted of 51 items covering the five ICCC building blocks for the health care organization level: 1) promote continuity and coordination (14 items), 2) encourage quality through leadership and incentives (6 items), 3) organize and equip health care teams (7 items), 4) support self-management and prevention (19 items), and 5) use of information systems (5 items). After integrating the results of the content validity testing, the instrument was composed of 49 items, namely 14 items for promoting continuity and coordination, 5 items assessing encouragement of quality through leadership and incentives, 6 that assessed organization and equipping health care teams, 19 that measured supporting self-management and prevention, and 5 that inquired about the use of information systems.

2) Content validity testing

Demographic information

Eleven experts in chronic illness management (six from USA and five from Europe) were indentified and asked to participate in the content validity evaluation of the CIMI-BRIGHT. Seven agreed to participate (three from USA and four from Europe), a response rate of 64%. One of the seven experts only rated part of instrument.

Content Validity Index

The experts evaluated the 51 items of the first version of the CIMI-BRIGHT. Forty-two items were rated having good content validity with content validity indexes ranging from 0.83 (22 items) to 1.00 (15 items). Nine items had low content validity. Two of these were deleted (i.e., "we have a highly organized quality improvement process, whereby we focus on a small number of important problems or conditions over sufficient time to ensure improvements are implemented and sustained" and "innovations (e.g., virtual teams linked through information or communication technology) are used by the transplant team"), the remaining seven items were revised based on suggestions from the experts. The Scale Content Validity Index (S-CVI) was 0.83. With the deletion on the two items, the S-CVI was 0.86.

2) Inter-rater reliability

Demographic information

The characteristics of the participants are shown in Table 2. In total six health care professionals of the abdominal and five of the renal Tx program completed the CIMI-BRIGHT instrument. All participants in both groups were women. The percentage of work spent in transplant care in the abdominal Tx program ranged from 50% to 100%, in the renal Tx program all participants were working 100%. Most participants worked in the outpatient transplant unit. The median years working in the particular transplant program was 3 years (IQR:

0.9 – 6.5), for the abdominal Tx program this was 7 years (IQR: 5.5 – 12.5). In the renal Tx program, following transplantation all patients followed by the Tx program until the time of death. In the abdominal Tx program, liver and intestine Tx patients are followed by the Tx program until the time of death. Not all renal Tx patients in this abdominal Tx program are followed by the program, some of them were followed by their referring nephrologist after their transplant.

Percentage agreement

The percentage agreement over all participants included in the abdominal Tx program was 84.5%. Excluding the dietician from the calculation, the percentage agreement improved to 86.9%. For the renal Tx program, the overall percentage agreement was 74.8%.

Discussion

As practice patterns (i.e., the presence of physicians answering after hours calls and higher patient-per-physician ratio [18]) are observed, processes at the level of the health care organization should be further examined. We, for the first time, developed an instrument assessing the extent to which chronic illness management is implemented in the follow-up care of transplant patients. By developing the CIMI-BRIGHT instrument, we will be able to assess differences in practice patterns related to implementation of chronic illness management among transplant programs. In this study we conducted the initial validity and reliability testing of the instrument.

This instrument shows preliminary evidence of adequate content validity. While the item CVI was good for 42 of the original 51 items, two items with low I-CVI scores were excluded from the instrument based on recommendations from the expert reviewers. The scale CVI (S-CVI) was 0.86 with the two items removed. The I-CVI for seven additional items varied from 0.50 (one item) to 0.67 (six

items). Comment from the reviewers suggested that these items were too vague. We revised these items to clarify their meaning.

We measured inter-rater reliability within each of the two Tx programs where we pilot tested the instrument. In one of the Tx programs, the percentage agreement between the health care providers indicated near perfect agreement on the extent to which the chronic illness models, as measured by the CIMI-BRIGHT instrument, was being implemented in their Tx program. In the second Tx program, while the percent agreement was somewhat lower, there was still satisfactory agreement. A limitation of this study is that the pilot-testing was only conducted in US Tx program, excluding European Tx programs.

This early testing of the CIMI-BRIGHT instrument suggests that it has promise as a measure for the extent to which the chronic illness model is being implemented in transplant centers. Additional testing is, however, needed to fully evaluate the validity of the instrument and to confirm that its inter-rater reliability is acceptable in other transplant programs. If additional testing supports the validity and reliability of the CIMI-BRIGHT instrument it could be a valuable instrument in not only assessing the current level of chronic illness management, but in also evaluating the impact of interventions designed to improve the organization of care for chronically ill patients.

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Figure 1: Innovative Care for Chronic Conditions Framework [6]

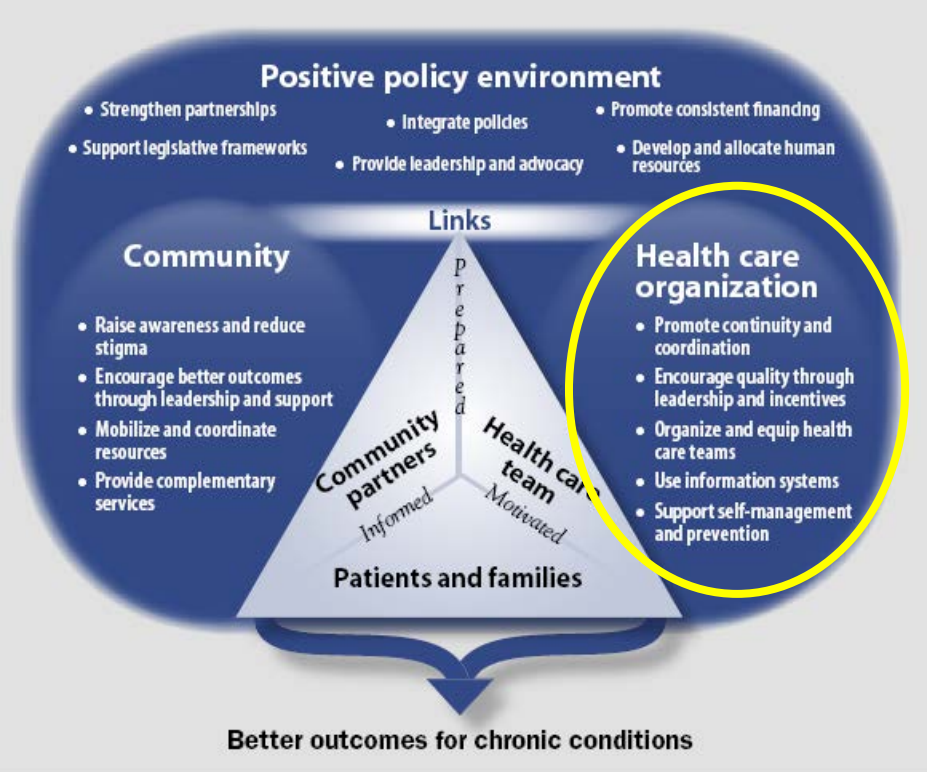

Table 1: Examples items CIMI-BRIGHT per building block

	Please circle the number that best represents the status of your transplant team and program	Strongly disagree	Disagree	Agree	Strongly agree	Not applicable	Don't know
Promote continuity and coordination	Inpatient and outpatient services are coordinated. For example, the outpatient transplant program can arrange examinations while the patient is in the inpatient clinic and vice versa	1	2	3	4	5	6
	Patients are strongly encouraged (but not forced) to see the same health care workers over time	1	2	3	4	5	6
	Patients who cancel their follow-up visits are contacted to reschedule the missed appointment	1	2	3	4	5	6
Encourage quality through leadership and	Patients are given incentives (e.g., recognition or financial awards) for effective self-management[1] and/or health outcomes	1	2	3	4	5	6
	The transplant program has a system for routinely monitoring the quality of care	1	2	3	4	5	6
	Senior and other influential leaders clearly help improve the quality of care in our transplant program	1	2	3	4	5	6
Organize and equip health care teams	Written guidelines for care are easily available	1	2	3	4	5	6
	Written guidelines for care are supported by education/courses	1	2	3	4	5	6
	The heart transplant program is based on a system of interdisciplinary team care (not run by physicians alone)	1	2	3	4	5	6
Support self-management and prevention	The heart transplant team routinely works with patients to identify clear, measurable and workable self-management[1] goals	1	2	3	4	5	6
	The heart transplant team lets patients decide on the self-management[1] goal(s) they consider best for them	1	2	3	4	5	6
	The heart transplant team gives each patient a copy of the agreed treatment plan, including information on self-management[1] and medication adherence[2]	1	2	3	4	5	6
Use of information systems	Care guidelines are built into the information system through computerized prompts/reminders or other support tools	1	2	3	4	5	6
	The heart transplant team's information system automatically gives health care workers specific guidance for individual patient care, such as reminders to schedule a follow-up visit or to perform a blood test	1	2	3	4	5	6
	The heart transplant team's information system automatically flags patients who are overdue for routine follow-up	1	2	3	4	5	6

[1]self-management refers to actions performed by patients for themselves in daily life to manage their illness and treatment, and to avoid health deterioration

[2]adherence deals with how well a person's behaviour (for example, taking medication) matches the recommendations of a health care provider

⇨ Adherence is a core concept of self-management

Table 2: Characteristics of participants

	Center 1: Abdominal Tx program (N= 6)	**Center 2: Kidney Tx program (N= 5)**
Age years Median (IQR)	33 (28.5 – 39.5)	42 (39 – 50)
Gender Female, n (%)	6 (100)	5 (100)
Current position in Tx program Tx coordinator, n (%) Advanced Practice Nurse, n (%) Physician assistant, n (%) Agency nurse, n (%)	 3 (50) 1 (16.7) 1 (16.7) 1 (16.7)	 5 (100) 0 0 0
If Tx coordinator Registered nurse Advanced Practice Nurse, n (%) Registered dietician, n (%)	 1 (33.3) 1 (33.3) 1 (33.3)	 5 (100) 0 0
Years practicing Median (IQR)	10.5 (6.3 – 18.5)	19 (17 – 28)
Years practicing in Tx Median (IQR)	4 (2.5 – 7.8)	7 (5.5 – 12.5)
Years in current Tx program Median (IQR)	3 (0.9 – 6.5)	7 (5.5 – 12.5)
Percentage working in Tx care Median (IQR)	100 (84 – 100)	100 (100 – 100)
Working primarily in Inpatient Tx unit, n (%) Outpatient Tx unit, n (%) Both, n (%)	 1 (16.7) 3 (50) 2 (33.3)	 0 3 (60) 2 (40)
Completed formal program in Tx care No, n (%)	 6 (100)	 6 (100)

Chapter 8

Synthesis, discussion and perspectives

Synthesis, Discussion and Perspectives

Chronically ill patients, a patient population which has increased dramatically world-wide and is expected to increase further, are bound to life-long health behavioral adaptations and the need to engage in a number of activities to insure their physical and psychosocial health [1]. One health behavior which is a crucial prerequisite for a treatment to be effective is patients' adherence to their medication regimen. Yet, the prevalence of medication non-adherence among chronically ill patients is high and associate with poor clinical and economic outcomes [2-4]. Non-adherence to a medication regimen can be defined as "the deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect" [5] (pg. 36). Current research has focused mainly on patient and treatment related factors to explain non-adherence. Yet, patient behavior is also influenced by factors from the patients' environment, i.e., system level factors. However, to-date there is only very limited research examining the impact of system factors on the health behaviors such as medication taking in chronically ill patients. This lack of focus on the broader system in which patients live as a possible explanation for non-adherence rates may explain why currently only a small part of the variability in non-adherence can be explained [6].

Until now, health care system factors have received relatively little attention as an explanation for patient behavior. This is in contrast to other disciplines, such as education where it has long been acknowledged that predicting achievements of students requires not only consideration of student-related variables such as intelligence, motivation or self-efficacy, but also variables on the level of the teacher, the school, and the educational system [7,8]. Health care system factors may impact patient behavior, e.g., adherence to their medication regimens, in much the same way as educational system variables affect student achievement.

Today, most health care systems are mainly build around an acute model of care. However, this model of care does not meet the needs of patients suffering of a chronic disease [1,9-12]. There are substantial differences between acute and

chronic diseases [13]. Acute diseases are episodic, and if the patient responds to treatment, his/her health returns to normal. There is generally no need to follow the patient over time. In contrast, chronic diseases are persistent, and there is generally no cure. Chronic conditions are associated with ongoing treatment and require behavioral changes to prevent worsening of the disease [13]. It is of extreme importance that care models are adapted to fit the special needs of patients suffering of one or more chronic conditions. This implies that there needs to a shift in the organization where care takes place [14-16] from an acute care focus with limited attention for aspects of self-management, prevention and continuity of care to a system where the principles of chronic illness management are integrated [1,10,14,17,18]. These principles of chronic illness management are continuity of care; partnership with patients, families and communities; support for patients in improving their self-management; attention to preventive measures; decision-making support; and the availability of clinical information systems [1,10,14,17,18]. Moreover, in providing high quality and effective care for the chronically ill, health care providers need to have the competencies to work in these new system of care and to support patients in their self management such as correct medication taking [19]. From this it can be inferred that the health care system in which the patient lives and receives care for their chronic condition(s) is of upmost importance to achieve favorable outcomes.

This dissertation took an innovative perspective as it explored the role of *system factors* in chronic illness management with a special focus on medication adherence in the chronically ill. An *ecological model* (McLeroy et al.) [20,21] and the World Health Organization's *Innovative Care for Chronic Conditions Framework* [11,12,14] served as the theoretical frameworks for the studies performed. The patient populations addressed in this dissertation were organ transplant recipients, persons living with HIV and patients suffering from cardiovascular diseases, all chronically ill patient populations were non-adherence to medication regimen is associated with poor clinical outcomes, higher (re-) hospitalizations rates and increased health care costs [2,22-30].

The findings of these studies strengthen the knowledge base on medication adherence as (1) they highlight the state of science about system factors related to adherence to medication regimens; (2) they provide insight into current practice patterns of health care professionals relative to the assessment and support of medication adherence; and (3) they present findings related to the development and preliminary psychometric testing of an instrument to assess the level of adherence-related chronic illness management implemented in transplant centers. These three contributions provide a solid basis to the further understanding of the role system related factors and adherence to medication regimens play and provide impetus for furthering the research in this field.

The manuscripts that are part of this dissertation are following:

1) A systematic review of quantitative studies addressing factors at the micro-, meso-, and macro levels of the health care system that are associated with adherence to medication regimens in individuals with HIV and organ transplant recipients (Chapter 3).
2) A methodological paper describing the most commonly effect size measures and how they are calculated (Chapter 4).
3) A study describing the strategies cardiovascular nurses and allied health professionals utilize to assess patients' adherence to their medication regimens, and the strategies they use to enhance adherence (i.e., educational/cognitive, counseling/behavioral, or psychological/affective techniques) (Chapter 5).
4) A study describing the strategies transplant health care professionals utilize to assess and promote medication adherence, as well as their perceptions regarding the effectiveness of the adherence prompting strategies they utilize (Chapter 6).
5) A study describing the development as well as the content validity and inter-rater reliability testing of the Chronic Illness Management Implementation - Building Research Initiative Group: Chronic Illness

Management and Adherence in Transplantation (CIMI-BRIGHT) instrument (Chapter 7).

We discuss the findings of this dissertation below taking a perspective that goes beyond the discussion of the individual manuscripts (Chapters 3 to 7). Implications for further research and suggestions for clinical practice will also be presented.

Synthesis and discussion of key findings

This discussion will focus on following key messages:

1) There remains a significant knowledge deficit in view of the influence of health care system factors on medication adherence calling for further research investment.
2) Nurses' practice patterns in view of adherence-related interventions call for a change in curricula. The health care workforce needs to be equipped with the required competencies for behavioral management. Moreover, practice development focused on integrating behavioral strategies to improve adherence management is needed.
3) The CIMI-BRIGHT instrument is the first and only tool developed to systematically assess the level of chronic illness management in transplant centers and thus provides a building block for further observational and intervention research in transplantation.

1) There remains a significant knowledge deficit in view of the influence of health care system factors on medication adherence calling for further research investment.

We performed the first systematic review that examined the relationship between multiple factors at the micro-, meso-, and macro levels of the health care system and adherence to medication regimens in individuals living with HIV and organ transplant recipients (Chapter 3). This systematic review

included published studies examining the association between characteristics at the *micro-* (i.e., quality of the patient-provider relationship, medication counseling, satisfaction with the health care provider, relationship with health care providers, health care providers' disease-specific experience, trust/confidence in the health care provider, clarity of health care providers' instructions about medications, accessibility to the health care providers, perceived pressure from the provider to take medications, and perceptions of non-judgmental attitudes of health care providers), *meso-* (i.e., center effects, frequency of health care visits, access to disease-specific services, access to medications, quality of care, and satisfaction with the health care setting) and *macro* (i.e., health insurance, drug costs, distance from and access to clinical site, and country/continent) levels of the health care system and medication adherence. Overall, the relationships between the factors examined and adherence varied across studies, making it difficult to reach firm conclusions in view of which system factors explained most of the variability observed in medication adherence. The two factors that were most consistently related to medication adherence were trust in the health care provider (a micro level factor) and access to medications (a meso level factor).

Trust in the health care provider can be defined as "the optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for the truster's interests" [31] (pg. 615). While trust/confidence in the health care provider was one of the system factors most consistently related to medication adherence, the relationship was only statistically significant in 62.5% of the eight studies that examined it. Methodological differences in study settings, sample characteristics, definitions and assessment of adherence and the methods used to measure trust in the health care provider may have contributed to these inconsistencies [32]. An increasing number of studies have examined trust in health care providers [33]. One of the factors contributing to this increased interest for trust in health care providers is the perceived threat that managed care systems might impose to the doctor-patient relationship [33]. In previous studies, trust in the health care provider was related to a number of clinically important outcomes including [34,35] lower blood glucose levels [36-41], earlier detection of the cancer [42], fewer post operative complications [43],

symptom improvement [44], better mental health related quality of life [45-47], higher acceptance of medications [47,48], higher satisfaction with the physician [47,48], higher general satisfaction with care [47,48] in addition to higher adherence to physicians' advice and recommendations [34,35].

Of the studies included in this review, only those focusing on adherence to HIV medications examined the relationship between trust and medication adherence. It was not examined in any of the transplant studies included in our review. Future studies examining predictors of medication adherence in the transplant population should examine the role of trust in the health care provider. We integrated therefore trust in the health care provider into the Swiss Transplant Cohort Study, the first and only nationwide cohort study in transplantation that embraced a biopsychosocial perspective assessing not only biomedical but also selected psychosocial and system related factors from pre-transplant to life-long post-transplant [49]. The finding that trust in the health care provider is significantly associated with non-adherence has also implications for clinical practice. As trust in the health care professional does not happen instantaneously but evolves over time [50], continuity of care is an important aspect of the care of chronically ill patients. Therefore, to the extent possible, patients should be followed by the same health care provider. Furthermore, as health care providers with good communication skills instill more trust, clinical practice settings need to focus on providing education and training to improve communication between providers and patients [33].

Drug access refers to the availability of drugs. In their report "The *World Medicines Situation*" (2004), the World Health Organization states that essential medicines should be continuously available for patients [51]. In our review, access to drugs was associated with better medication adherence. However, in the studies that examined the relationship between medication availability and adherence multivariately, the relationship was significant in developing countries but not in developed countries. This finding is not unexpected given the issues with drug access in many developing countries [51]. One reason why drug access in developing countries is often not guaranteed is the fluctuating production of essential drugs [52], which leads to stock shortages in hospitals or

pharmacies. This finding has implications for clinical practice sites but also implications for health policy and international aid for developing countries.

Unfortunately, methodological limitations of the studies included in the review, hamper firm conclusion regarding the role of individual system factors in promoting or inhibiting medication adherence. Major variability across the studies was observed in the definition of medication adherence. Different cut-offs were used to define adherence across the studies. This variability may, in part, explain the variability we found in the associations between the health care system factor(s) examined and adherence. In addition, there were variations in the adherence assessment time period (ranging from "ever" to "the previous two days") and the method used to assess adherence. Furthermore, variations in study designs (cross-sectional versus prospective designs), the system factors examined and how they were measured, the methods of analysis (bivariate versus multivariate analysis techniques), and incomplete reporting of statistical findings made the combination of study results (meta-analysis) inappropriate. Based on these limitations, we strongly recommend conducting a large multi-continental, multi-country, multi-center study to examine the associations between multiple factors at the micro-, meso-, and macro levels and non-adherence to medication regimens. To address this research gap, we designed the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study, an international multi-center cross-sectional study to explore the relation between selected patient level, health care system factors and non-adherence with immunosuppressive drugs in transplant recipients. Forty heart transplant programs (20 from North-America and 20 from Europe) will be included in this study. A further recommendation for future research evolving of this systematic review is that authors report the magnitude of the examined system factors' effect on adherence. Our methodological manuscript, which describes the most commonly used effect size measures and how they are calculated, will assist and encourage authors to provide this essential information in their manuscripts (Chapter 4).

Additionally, most of the studies included in this review did not base their factor selection on a theoretical framework such as the ecological model. Use of such a

framework will guide the selection of factors to be examined, ensure that all important factors are included and contribute to building scientific understanding related to the complex phenomena of medication adherence. It is only with this knowledge, that we can develop effective strategies to address this major public health issue. Future studies are strongly encouraged to use a theoretical framework to underpin the selection of the patient-related- as well as of the system-related variables included in their study.

2) Nurses' practice patterns in view of adherence-related interventions call for a change in curricula. The health care workforce needs to be equipped with the required competencies for behavioural management. Moreover, practice development focused on integrating behavioural strategies to improve adherence management is needed.

We examined practice patterns related to interventions used to promote patients' adherence to medications by performing two surveys of health care professionals, primarily nurses, working with cardiovascular and transplant patients, respectively. At two conferences we invited all participants to complete an instrument assessing the frequency with which they used 26 adherence enhancing interventions. The interventions were identified from the literature [2,53-56] and classified as educational/cognitive, counseling/behavioral and psychological/affective based on the classification proposed by De Bleser [57]. Educational/cognitive interventions present information individually or in a group setting delivering it verbally, in written form, and/or audio-visually. Counseling/behavioral interventions shape and/or reinforce behavior, empowering patients to participate in their own care, while positively changing their skill levels or normal routines. Psychological/affective interventions focus on patients' feelings and emotions or social relationships and social support [57].
In both samples, participants reported using a higher proportion of educational/cognitive interventions than of counseling/behavioral and psychological/affective interventions. In the study of transplant nurses, we also

asked the participants to rate the perceived effectiveness of the interventions used. Their average effectiveness ratings for the three groups of interventions were very similar. This is contrary to current evidence that indicates that educational interventions are not very effective in promoting adherence [2,56,58]. There are a number of possible explanations for this finding.

First, educational/cognitive interventions are relatively simple and inexpensive to implement and, therefore, feasible in most clinical settings. Evidence, however, indicates that counseling/behavioral and psychological/affective interventions are more effective in promoting long-term behavioral changes [59] such as ongoing medication adherence [60]. Yet, they are time consuming to implement, require more skills and require more follow-up to be successful. They necessitate continuity of care i.e., supervision of the chronically ill patient by the same health care professional(s) [61]. This may be a major barrier in their use as in many health care settings where care is still mainly built around an acute model of care which does not meet the specific needs of patients suffering of chronic illnesses [1,9-12].

However, like health care organizations, curricula in health science schools are often outdated and static resulting in graduates who are ill equipped to address the rapidly shifting balance between acute and chronic health problems [19,62,63]. In most education settings there is a serious mismatch between the development of professional competencies and existing and emerging patient and population needs such as the needs of the chronically ill. Indeed, the curricula in most health sciences colleges and universities focus much more on acute care than on chronic care [13,64-66]. While schools address some aspects of chronic care in their programs, it is rarely central to their curriculum [13]. This need has also been recognized by the Institute of Medicine which strongly recommend in their 2010 report *The Future of Nursing* that nursing curricula need to be reexamined, updated and adaptive to change as patients needs and advances in science and technology [63].

In response to concerns about the lack of emphasis on chronic care in the US, a curriculum task force was established to increase the proportion of schools of medicine, nursing and allied health whose basic curriculum includes the core competencies in health promotion and disease prevention [67]. The Task Force

published a *Clinical Prevention and Population Health Curriculum Framework*. One of the recommended domains in this curriculum is counseling for behavioral change. This domain includes approaches to behavior change that incorporate diverse patient perspectives (e.g., counseling skills training and motivational interviewing), clinician-patient communication (e.g., patient participation in decision making, informed consent, risk communication, advocacy, and health literacy), criteria for successful counseling (e.g., effectiveness, benefits and harms, cost, and acceptance by patient), and evidence-based recommendations [67]. Curricula also need to integrate interprofessional education. Interprofessional education occurs when two or more professions (e.g., doctors, nurses, physiotherapists, social workers) learn with, from and about each other to improve collaboration and the quality of care [68]. A growing body of evidence shows that interprofessional education leads to closer collaboration between health care professionals as well as between health care organizations. This improved collaboration can, in turn, improve the quality of care for patients [68].

Since the majority of practicing nurses do not have the educational foundation recommended in *The Future of Nursing* [63] report and the *Clinical Prevention and Population Health Curriculum Framework* [67], they often lack the training and competencies necessary to provide effective chronic illness care including skills needed to promote long term-changes in behavior such as medication adherence [69]. Therefore, it is essential that educational and organizational leaders support the preparation of nurses and other health care professionals with the required competencies by providing ongoing education and training. An example health care organizations could offer is training in motivational interviewing. Motivational interviewing is a client-centered, directive method for enhancing the intrinsic motivation to change one's behavior by exploring and resolving ambivalence [70,71]. Motivation interviewing has been shown to be an effective method to change patient behavior and improving clinical outcomes [72].

Efforts in curriculum reforms as well as the development of continuous education programs are urgently needed to enhance the competencies of nurses and other health care professionals in view of interventions to enhance adherence to medication regimens. Future studies should evaluate the extent to

which these investments 1) increase health care professionals' competencies in implementing counseling/behavioral and psychological/affective interventions and 2) improve long-term clinical outcomes for patients with chronic illnesses.

3) The CIMI-BRIGHT instrument is the first and only tool developed to systematically assess the level of chronic illness management in transplant centers and thus provides a building block for further observational and intervention research in transplantation.

Survival gains after transplantation have been limited to the first 6 to 12 months with long-term survival rates remaining unchanged [73-75]. Transplant outcomes are determined by the interplay of a number of factors including biomedical, behavioral, psychosocial, and socio-demographic as well as system factors (e.g., practice patterns in transplant centers) [76-79]. In the past, most research and clinical interest focused on biomedical factors.

Improving long-term outcomes is one of the most important future challenges. This need has also been recognized by the European Commission, that as part of the EU 7th Framework programs, recently launched a call for proposals addressing novel strategies to improve long-term outcomes after transplantation. Given the fact that transplant patients belong to the group of the chronically ill, which means that they are in need of continuity of care, support for self-management and preventive measures, it can be put forward that transplant care could be strengthened by adopting a care model that follows the principles of chronic illness care. Indeed, a shift in attention toward the long-term follow-up of transplant patients will have to occur to really make an impact on long-term outcomes [74,75]. We, for the first time, developed a tool assessing the extent to which chronic illness management is implemented in the follow-up care of transplant patients. The development of the Chronic Illness Management Implementation - Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument was based on the conceptual framework of WHO's *Innovative Care for Chronic Conditions* (ICCC) framework, as well as the clinical expertise of the

members of the research team. As part of this dissertation, we completed initial testing of its content validity and inter-rater reliability. The results suggest that the CIMI-BRIGHT instrument has promise as a measure of the extent to which the chronic illness model is being implemented in transplant centers.

The work we performed with the development of the CIMI-BRIGHT provides a building block for future studies designed to examine the extent to which transplant centers implement chronic illness management principles. Data from such studies will allow investigators to determine whether differences in chronic illness practice patterns impact patient outcomes. These differences may be related to the differences to "center effects" that have been observed in some studies [80-85]. Center effects refer to differences in outcome that cannot be explained by identifiable differences in the patients treated or specific treatments applied [80]. Center effects are presumed to result from differences in the ways health care is delivered. For instance, individual centers may have different long-term follow-up programs that could potentially influence outcomes [80]. A number of studies have demonstrated that variations in practice patterns influence patient outcomes. In a study in hematopoietic stem cell transplantation in the United States, two center factors, 'presence of physicians answering after hours calls' and a 'lower patient-per-physician ratio', were associated with decreased 100-day mortality rates: [81]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective, observational study among hemodialysis centers in seven different countries showed that center characteristics such as the size of the center and the percentage of highly trained staff, and the country where the dialysis center was located were related to dialysis non-adherence rates [82,83]. The Swiss HIV cohort study also found that the center where the patient is followed up accounted for significant variability in adherence rates [84]. An 11 country survey of primary care doctors by Schoen et al. (2009) found wide variations at a national level in practice systems, incentives, perceptions of access to care, use of health information technology and programs to improve quality [85]. The mere fact that center-specific differences regarding outcomes for chronically ill patients are observed indicates that processes at this level are influential and require to be scrutinized.

The first step in improving chronic illness management in transplant centers should be to design studies to explore the extent to which the principles of chronic illness care are implemented by transplant centers. The relationship between implementation of elements of the model and adherence-related outcomes should also be examined. This knowledge will provide the basis for developing interventions designed to improve implementation of the model. The CIMI-BRIGHT instrument, if further validation supports it use for these purposes, could also be relevant to assess the impact of these interventions on medication adherence.

Conclusion

As patient behavior, i.e., patient adherence, is prone to the influence of system factors it is of upmost importance to scrutinize these factors. Yet, there is limited research examining the impact of system factors on adherence. This dissertation contributes to the science of adherence by systematically examining current evidence related to the role of system factors in adherence and by identifying important gaps in nursing practice and knowledge related to adherence-promoting interventions. The findings of this dissertation emphasis the need for nurses and other health care providers to be prepared with a foundation in systems thinking and competencies to ensure the delivery of effective and high quality care. Furthermore, this dissertation points to the need for continuous efforts to improve outcomes in chronically ill patients. The evidence from this dissertation provides a strong foundation for future research.

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Personal data

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Education

Graduate

2008 to present:	PhD study program
	Institute of Nursing Science, University of Basel, Switzerland
2005 - 2007:	Master of Science in Nursing
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2004 – 2005:	Bachelor of Science in Nursing
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1998 – 2001:	Bachelor of Science in Nursing
	Katholieke Hoge School Limburg, Hasselt, Belgium

Professional Experience

2007 to present:	Research assistant
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2008-2009:	Research assistant
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2002- 2004:	Co head nurse
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Theses

MASTER'S THESIS:	*Institute of Nursing Science, University Basel, Switzerland:* Prevalence and correlates of influenza vaccination among renal transplant patients.
BACHELORS'S THESIS:	*Katholieke Hogeschool Limburg, Hasselt, Belgium:* Development of a clinical pathway: gastro intestinal bleedings

Publications

Articles in international literature

- De Bleser, L., Dobbels, F., **Berben, L.,** Vanhaecke, J., Verleden, G., Nevens, F., & De Geest, S. (In press). The spectrum of non-adherence with medication in heart, liver and lung transplant patients assessed in various ways. *Transpl Int.*
- **Berben, L.,** Bogert, L., Leventhal, M. E., Fridlund, B., Jaarsma, T., Norekval, T. M., Smith, K., Strömberg, A., Thompson, D.R., De Geest, S., on behalf of the UNITE research group (2011). Which interventions are used by health care professionals to enhance medication adherence in cardiovascular patients? A survey of current clinical practice. *Eur J Cardiovasc Nurs*, *10*(1), 14-21.
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- Dobbels, F., **Berben, L.**, De Geest, S., Drent, G., Lennerling, A., Whittaker, C., et al. (2010). The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. *Transplantation, 90*(2), 205-219.
- De Geest, S., Burkhalter, H., De Bleser, L., **Berben, L.**, Duerinckx, N., De Bondt, K., & Dobbels, F. (2010) Non-adherence to immunosuppressive drugs in transplantation: What can clinicians do? *Journal of Renal Nursing. 2*(2), 58-63.
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- **Berben, L.**, Denhaerynck, K., Schaub, S. & De Geest, S. (2009) Prevalence and correlates of influenza vaccination among renal transplant patients. *Transpl Int 22*(S2), 143.
- **Berben, L.**, Hill, M. & De Geest, S. (2007) Adherence enhancing interventions in hypertensive patients. *Eur J Cardiovasc Nurs 6*(suppl 1), 31.

Manuscripts submitted

- **Berben, L.**, Engberg, S., Sereika, S. M., Dobbels, F., Hill, M., & De Geest, S. (Submitted). System factors as correlates of medication adherence in HIV and transplant populations: a systematic review.
- Van de loock, K., **Berben, L.**, Denhaerynck, K., Schmid-Mohler, G., Dobbels, F., Martin, S., Ducci, J., De Simone, P., Wüthrich, R.P., Vanhaecke, J., Engberg, S., Sereika, S.M., & De Geest, S. (Submitted). Barriers for immunosuppressive medication-taking differ among adult renal, liver and heart transplant recipients.
- **Berben, L.**, Dobbels, F., Kugler, C., Russell, C., & De Geest, S. (submitted). Which interventions are used by health care professionals to enhance medication adherence in transplant patients? A survey of current clinical practice.
- Dobbels, F., De Geest, S., Lennerling, A., **Berben, L.**, Vandenbroeck, S., Kugler, C, & the Transplant360 Task Force Members (Submitted). The Transplant360 Task Force Members Which self-report instruments are most suitable to assess barriers to medication adherence in adult transplant patients? A systematic review.

Presentations

International

- De Geest, S., **Berben, L.,** De Bleser, L., & Dobbels, F. New interventions for adherence in organ failure. 31th Annual Meeting of the Interntational Society for Heart and Lung Transplantation. April 13-16 2011, San Diego (USA). Oral presentation.
- **Berben, L. "**Organization, policy and anti-hypertensive adherence". 11th Annual Spring Meeting on Cardiovascular Nursing. April 1-2 2011, Brussels (Belgium). Oral presentation.
- **Berben, L.,** Bogert, L., Leventhal, M.E., Fridlund, B., Jaarsma, T., Norekvål, T.M., Smith, K., Strömberg, A., Thompson, D.R., De Geest, S., on behalf of the UNITE research group. "Which interventions are used by health care professionals to enhance medication adherence in cardiovascular patients? A survey of current clinical practice". 11th Annual Spring Meeting on Cardiovascular Nursing. April 1-2 2011, Brussels (Belgium). Poster presentation.
- **Berben, L.**, Russell, C., Engberg, S., Dobbels, F., & De Geest, S. "Development and Content Validity Testing of the CIMI-BRIGHT questionnaire". ITNS European Symposium 2010 - Transplant Nursing: Improving Patients Outcomes. June 18-19 2010, Berlin (Germany). Poster presentation.
- Van de loock, K., **Berben, L.**, Denhaerynck, K., Schmid-Mohler, G., Dobbels, F., Martin, S., Ducci, J., De Simone, P., Wüthrich, R.P., Vanhaecke, J., Engberg, S., Sereika, S.M., De Geest, S. "Barriers for immunosuppressive medication-taking differ among adult renal, liver and heart transplant recipients". ITNS European Symposium 2010 - Transplant Nursing: Improving Patients Outcomes. June 18-19 2010, Berlin (Germany). Poster presentation.
- **Berben, L.**, Denhaerynck, K., Schaub, S. & De Geest, S. "Prevalence and correlates of influenza vaccination among renal transplant patients". 2nd Ethical, Legal, and Psychosocial Aspects Congress. April 17-20, 2010, Rotterdam (The Netherlands). Poster presentation.
- Van de loock, K., **Berben, L.**, Denhaerynck, K., Schmid-Mohler, G., Dobbels, F., Martin, S., Ducci, J., De Simone, P., Wüthrich, R.P., Vanhaecke, J., Engberg, S., Sereika, S.M., De Geest, S. "Barriers for immunosuppressive medication-taking differ among adult renal, liver and heart transplant recipients". 17th annual meeting of the Belgian Transplantation Society. March 18, 2010, Brussels (Belgium). Oral presentation.
- **Berben, L.**, Russell, C., Engberg, S., Dobbels, F., & De Geest, S. "Development and Content Validity Testing of the CIMI-BRIGHT questionnaire". 10th Annual Spring Meeting on Cardiovascular Nursing. March 12-13 2010, Geneva (Switzerland). Poster presentation.

- Van de loock, K., **Berben, L.,** Denhaerynck, K., Schmid-Mohler, G., Dobbels, F., Martin, S., Ducci, J., De Simone, P., Wüthrich, R.P., Vanhaecke, J., Engberg, S., Sereika, S.M., De Geest, S. "Barriers for immunosuppressive medication-taking differ among adult renal, liver and heart transplant recipients". Verpleegkundig congres: samen bouwen aan veilige zorg. February 5, 2010, Leuven (Belgium). Poster presentation.
- **Berben, L.**, Russell, C., Dobbels, F., & De Geest, S. "Chronic Illness Management Implementation - Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT). 18th annual International Transplant Nurses Society symposium. September 24-26, 2009, Montreal (Canada). Oral presentation.
- **Berben, L.**, Denhaerynck, K., Schaub, S. & De Geest, S. "Prevalence and correlates of influenza vaccination among renal transplant patients". 14th European Society for Organ Transplantation Congress. August 30 – September 2, 2009, Paris (France). Poster presentation.
- **Berben, L.** & De Geest, S. "Monitoring patient compliance: new methods". International Symposium: Transplant Nursing. June 18-19 2009, Florence (Italy). Oral presentation.
- **Berben, L.** "Influenza vaccination and the Need for Vaccination in Solid Organ Transplantation". 17th annual International Transplant Nurses Society symposium. September 24-26 2008, St. Louis (USA). Oral presentation.
- **Berben, L.**, Denhaerynck, K., Schaub, S. & De Geest, S. "Prevalence and correlates of influenza vaccination among renal transplant patients". 16th annual International Transplant Nurses Society symposium. October 4-6 2007, Denver (USA). Poster presentation.
- **Berben, L.**, Hill, M., De Geest, S. "Adherence enhancing interventions in hypertensive patients". 7th Annual Cardiovascular Nursing Spring Meeting. March 23-24 2007, Manchester (UK). Poster presentation.
- De Geest, S., Hill, M., **Berben, L**. "Adherence enhancing interventions in hypertensive patients". Call to Action - Task Force Meeting. May 20-21 2006, New York (USA). Oral presentation.

National

- **Berben, L.** "Which interventions are used by health care professionals to enhance medication adherence in cardiovascular patients? A survey of current clinical practice". Medizinische Universitäts-Poliklinik. February 23, 2011, Basel (CH). Oral presentation.
- **Berben, L.** "Transplant360. Eine interaktive Plattform zur Förderung der Adherenz". Eröffnungsveranstaltung Netzwerk Transplantationspflege. January 21, 2011, Zürich (CH). Oral presentation.
- **Berben, L.**, Denhaerynck, K., Schaub, S. & De Geest, S. "Prevalence and correlates of influenza vaccination among renal transplant patients". SBK Kongress. March 21-23, 2008, Basel (CH). Poster presentation.
- **Berben, L.** "Verbreitung und Wechselwirkung der Grippeimpfung bei Patienten mit einer Nierentransplantation". *(Prevalence and correlates of influenza vaccination among renal transplant patients).* Extra-Impulsveranstaltung, Institute of Nursing Sience and Department of Clinical Nursing Science. June 10, 2008, Basel (CH). Oral presentation.

Teaching activities

- Quantitative Research course. Lectures for bachelor students of the Institute of Nursing Science, University of Basel, Switzerland
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- Advanced Nursing Practice course. Lectures for bachelor students of the Institute of Nursing Science, University of Basel, Switzerland
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  2009-2010; 2010-2011
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