Medication adherence in patients with schizophrenia: a means to an end
Kikkert, M.J.

Citation for published version (APA):
Kikkert, M. J. (2010). Medication adherence in patients with schizophrenia: a means to an end

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Medication adherence in patients with schizophrenia: a means to an end

Martijn Kikkert
Medication adherence in patients with schizophrenia: a means to an end

Martijn Johan Kikkert
Medication adherence in patients with schizophrenia: a means to an end.

Copyright © 2010, MJ Kikkert.
All rights reserved. No part of this thesis may be reproduced or transmitted, in any form or by any means, without the prior premission of the author.

Most of the studies in this thesis were funded by a grant from the European Union; Quality of Life and Management of Living Resources Programme (QLG4-CT-2001-01734). One study was financially supported by a grant from AstraZeneca BV.

The printing of this thesis was financially supported by: Arkin Amsterdam, Universeit van Amsterdam, AstraZeneca BV., Eli Lilly Nederland BV., and Lundbeck BV.

Layout: Legatron Electronic Publishing, Rotterdam, The Netherlands
Cover: Network Osaka (www.networkosaka.com)
Printed by: Ipskamp BV, Enschede, The Netherlands
Medication adherence in patients with schizophrenia: a means to an end

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus prof.dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op donderdag 11 maart 2010, te 12:00 uur

door

Martijn Johan Kikkert

geboren te Den Helder
Promotiecommissie

Promotor: Prof.dr. A.H. Schene
Co-promotor: Dr. M.W.J. Koeter
Overige leden: Dr. L. de Haan
Prof.dr. J.C.J.M. de Haes
Prof.dr. P.P.G. Hodiamont
Prof.dr. C.L. Mulder
Prof.dr. G.M. Schippers

Faculteit der Geneeskunde
Aan Ruth, Hana en Jin

in een nieuw werk m kikkert
## Contents

**Chapter 1**  
Introduction 9  
1.1 Chronic Conditions 10  
1.2 Schizophrenia 11  
1.3 Antipsychotic Medication 13  
1.4 Defining adherence 14  
1.5 Prevalence and characteristics of non-adherence 15  
1.6 Consequences of non-adherence 17  
1.7 Determinants of non-adherence 19  
1.8 Interventions for improving adherence 20  
1.9 Resolved and unresolved issues 24  
1.10 The present thesis 25  
1.11 References 29  

**Chapter 2**  
Adherence Therapy for People with Schizophrenia. European Multicentre Randomised Controlled Trial 37  

**Chapter 3**  
Medication Adherence in Schizophrenia: Exploring Patients’, Carers’ and Professionals’ views 55  

**Chapter 4**  
Assessment of Medication Adherence in Patients with Schizophrenia. The Achilles Heel of Adherence Research 75  

**Chapter 5**  
The Predictive Validity of Subjective Adherence Measures in Patients with Schizophrenia 95  

**Chapter 6**  
The Inventory of Medication Intake (IMI): Validation of an Instrument for Assessing Adherence to Antipsychotic Medication 113  

**Chapter 7**  
General Discussion 133  
7.1 Main findings and methodological issues 134  
7.2 Clinical implications and future research 142  
7.3 General conclusions 160  
7.4 References 162
Summary 171
Samenvatting 173
Curriculum Vitae 175
List of publications 176
Dankwoord 178
Chapter 1

Introduction
1.1 Chronic Conditions

The World Health Organization defines chronic conditions as conditions requiring ongoing management over a period of years or decades. They include a wide range of health problems, and estimates of the numbers of people in the European Union with chronic conditions vary from 20% to over 40% of the population (TNS Opinion & Social 2007). The personal impact of these conditions varies. Some are highly disabling, others less so. In a comparison of chronic conditions, psychiatric disorders were found to have most impact on health-related quality of life after musculoskeletal disorders (Saarni et al., 2006). At the patient level, the impact of a chronic condition on quality of life is not constant, and the adverse effect usually lessens later in life. In comparison with other chronic conditions, patients with a chronic psychiatric disorder have the lowest health-related quality of life between the ages of 30 and 44 (Melse et al., 2000; Saarni et al., 2007a; Stouthard et al., 2000; Ustün et al., 1999).

The prevalence of chronicity varies according to the definition used. Studies in the nineties found that, in the Netherlands, 75,000 to 100,000 people suffered from a chronic psychiatric condition (Kroon et al., 1998; Schene, 1995). Changes in mental health care and the definition of chronic psychiatric conditions have resulted in an increase of 32% in the past decade. In 2009, the national mental health organisation, GGZ Nederland, calculated that there were 160,000 people (0.66% of the Dutch population) receiving mental health care in 2006 who were suffering from a severe, long-term psychiatric disorder. Approximately one-third of these people were diagnosed with schizophrenia (Kroon et al., 1998; Schene, 1995).

It has been acknowledged that one of the major problems in the treatment of patients with schizophrenia, and chronic conditions in general, is treatment non-adherence. In particular medication non-adherence poses a threat to patient’s mental health. In this thesis we will focus on medication adherence in patients with schizophrenia.

It has been acknowledged that one of the major problems in the treatment of patients with schizophrenia, and chronic conditions in general, is non-adherence to treatment. In particular, medication non-adherence poses a threat to patients’ mental health. This thesis focuses on medication adherence in patients with schizophrenia.

This first chapter provides a brief outline of schizophrenia and antipsychotic medication. It also explores different aspects of medication adherence in patients with schizophrenia and concludes with a presentation of the research questions this thesis will address.
1.2 Schizophrenia

Schizophrenia is one of the major psychiatric disorders or cluster of disorders. The lifetime prevalence of schizophrenia varies from 0.55% to 0.70%, with point prevalence being approximately 0.34% to 0.45% (Goldner et al., 2002; Tandon et al., 2008). The age of onset is typically between 20 and 28 years in men, and between 26 and 32 years in women (Castle et al., 1991). Schizophrenia is characterised by positive symptoms such as hallucinations, delusions, and thought disorders. Most patients also have negative symptoms such as apathy, anhedonia, alogia, and avolition. In addition, patients can suffer from disorganised speech, thought and behaviour (Cohen & Docherty, 2004; Sims, 2002).

Approximately 20% of patients who meet the criteria for schizophrenia will recover from their first episode. These are patients who, in general, will not need maintenance treatment (Riecher-Rossler & Rossler, 1998) and are therefore not part of the long-term population cared for by mental health care institutes. This favourable outcome in one-fifth of patients shows that schizophrenia is not necessarily a chronic condition. A 15-year follow-up study of 82 patients diagnosed with schizophrenia in the Netherlands showed that approximately 11% will have chronic unremitting psychotic symptoms despite adequate treatment, while 22% will have no more than one psychotic episode, followed by either complete remission, or partial remission with symptoms of anxiety and depression or negative symptoms (Wiersma et al., 1998). In the majority of patients (55%) the disease has an episodic course with two or more psychotic episodes. In 15% of patients these episodes are followed by periods of complete remission, and in 40% of patients they are followed by periods with negative symptoms or anxiety and depression (Wiersma et al., 1998). Harrison et al. (2001) found similar results in a follow-up study of 644 patients with schizophrenia, using a modified version of Bleuler’s course typologies.

Schizophrenia has a major impact on patients’ social and professional functioning, and is considered to be one of the most impairing disorders (Melse et al., 2000; Saarni et al., 2007; Stouthard et al., 2000; Ustün et al., 1999). This is underlined by the fact that approximately 10% of patients commit suicide (Brown, 1997; Brown et al., 2000). The majority of patients are not able to maintain long-term relationships. Approximately 67% of patients with schizophrenia are single, and only 15% are married (Hanssens et al., 2007). Only a minority of patients (15%) have paid employment (Hanssens et al., 2007). Comorbid disorders are common. It is estimated that between one-quarter and one-third of patients with schizophrenia misuse alcohol or drugs (Giffen et al., 2007;
Theunissen et al., 2008; Weaver et al., 2003; Ziedonis et al., 2005). Other common psychiatric comorbidities are depression (50%), posttraumatic stress disorder (29%), obsessive-compulsive disorder (23%), and panic disorder (15%) (Buckley et al., 2009; Sim et al., 2006).

In general, the physical health of patients with schizophrenia requires attention. Approximately half of them suffer from a comorbid somatic disorder (Goldman, 1999; Theunissen et al., 2008). Studies indicate that patients with schizophrenia are more vulnerable to diseases such as diabetes, coronary heart disease, gastro-intestinal diseases, hypertension, circulatory disorders, pharyngeal cancer, lung cancer, emphysema and HIV (Baillargeon et al., 2003; Cournos et al., 1994; Gray et al., 2002; Hausswolff-Juhlin et al., 2009; Lichtermann et al., 2001; Marder et al., 2004; Mitchell & Malone, 2006). Average life expectancy is 10 to 12 years less, even when suicide is not taken into account (Brown, 1997; Brown et al., 2000; Harris & Barraclough 1998; Loonen, 2003; Phelan et al., 2001).

In mental health care for patients with schizophrenia, treatment focuses on enhancing functional status, minimising symptoms, and enhancing quality of life (Grumbach 2003). Antipsychotic medication is considered to be the primary treatment due to its efficacy in the acute phases and the prevention of relapse over time (Dunayevich et al., 2007; Janicak et al., 1993; Hunter et al., 2003; Soares et al., 2002; Waraich et al., 2002). Nevertheless, it should be noted that, although the efficacy of antipsychotic medication has been repeatedly demonstrated, its average effect size is only medium. On the basis of a meta-analysis of 38 trials, Leucht et al. (2009) concluded that the pooled effect size for overall symptoms of second-generation antipsychotic medication was 0.51 compared with placebo.

In addition to pharmaceutical treatment, psychological and psychosocial interventions such as social skills training, family interventions, psycho-education, social cognitive training and cognitive remediation have been developed. During the late 1980s, cognitive behavioural therapy (CBT) for patients with schizophrenia was introduced. CBT focuses on helping patients to relabel and interpret the contents of their delusions or hallucinations (van der Gaag, 2008). As a complement to pharmaceutical treatment, this may be particularly useful since medication reduces the intensity of positive symptoms but does not alter the faulty appraisal of these experiences (Kern et al., 2009). Studies have shown that CBT is effective (Kern et al., 2009; van der Gaag, 2008) and it is now recommended in the Dutch multidisciplinary Guideline for the treatment of schizophrenia. In a recent meta-analysis (Wykes et al., 2008) of randomised controlled trials comparing CBT with a
control group in patients with schizophrenia, the weighted mean effect size for CBT was 0.37 for positive symptoms, and 0.44 for negative symptoms. Although these are small to medium effects, they do demonstrate that CBT is effective at reducing the burden of positive and negative symptoms (Kern et al., 2009).

1.3 Antipsychotic Medication

The first antipsychotic medicine, chlorpromazine, was introduced in the fifties. It was discovered during the production of a histamine antagonist. Psychotic patients who were given chlorpromazine became calm and apathetic, while their intellect and consciousness remained intact. Unfortunately, some patients also experienced disturbing functional and social side effects such as extrapyramidal symptoms (Moleman, 2009). The development of new drugs continued and haloperidol was introduced in 1960, followed by clozapine in 1962. Since then, several new antipsychotic drugs have been developed. In 2007, the number of outpatients receiving antipsychotic medication in the Netherlands was 255,040. The associated annual costs amounted to 12.1 million euros (GIP/College voor zorgverzekeringen), which is only a small portion of the total health care costs for schizophrenia patients. There is no data available about antipsychotic medication dispensed in inpatient settings.

Antipsychotic medicines are often broken down into typical and atypical medication. These categories have more recently been labelled 'first-generation' and 'second-generation' antipsychotics. However, there is no clear rationale or criterion for this classification other than the side-effect patterns. First-generation antipsychotics are associated with a wide range of side effects such as lethargy, sedation, weight gain and sexual dysfunction. Side effects such as parkinsonism, akathisia, dystonia, and tardive dyskinesia are also common and can be disabling or result in severe social impairment (Barnes & Kielger, 1978; Kane et al., 1985). Second-generation antipsychotics seem to cause fewer of these side effects but they induce other adverse side effects such as weight gain and other metabolic problems that may exacerbate the risk of type-2 diabetes and cardiovascular disease (American Diabetes Association, 2004; Lindenmayer et al., 2003; Mackin et al., 2007; Nasrallah, 2003, 2008; Suvisaari, 2007). It has been demonstrated that there is no difference in the efficacy of classical and atypical medicines (Jones et al., 2006; Leucht et al., 2009; Lieberman et al., 2005; Tandon et al., 2008). However, in refractory schizophrenia, clozapine is more effective (Lewis et al., 2006; McEvoy et al., 2006).
Antipsychotic medication has a favourable effect on positive symptoms but little or no effect on primary negative symptoms (Darbá et al., 2009; Kopelowicz et al., 2000; Möller, 1993; Peralta et al., 2000). In high dosages, it may even induce or exacerbate negative symptoms. Patients who are severely psychotic or who suffer from severe negative symptoms often benefit less from this medication, and it is estimated that approximately one-third of patients with schizophrenia are considered to be treatment-resistant (Conley & Kelly, 2001; Kane, 1996; Kane, 1999). Treatment-resistant patients may suffer from persistent disabling symptoms despite at least two drug trials with chlorpromazine or an equivalent (Conley & Kelly, 2001; Kane, 1996; Kane, 1999). Obviously, medication adherence may be affected by treatment resistance and subjective side effects. This issue will be addressed later in this thesis.

1.4 Defining adherence

Ever since physicians have prescribed medicines, it has been known that patients do not always follow their instructions. This is true not only of schizophrenia patients but also of patients suffering from other conditions, and even of physicians themselves (Corda et al., 2000). Several reports indicate that, in everyday practice, approximately half of all patients do not use their medication as prescribed. This is a consistent finding for both somatic and psychiatric conditions (Cramer & Rosenheck, 1998; DiMatteo, 2004; Sluijs et al., 2006; WHO, 2003). The problem becomes more pressing with long-term medication.

Over the years, many papers have been published about this topic using different terms such as compliance, concordance, adherence and pharmionics. Although some of these terms seem interchangeable, they have different meanings and connotations. Compliance is medically centred and refers to the extent to which a patient follows treatment prescriptions (Lutfey et al., 1999; Sackett & Haynes, 1976). Concordance refers to the collaboration and shared decision-making process between patient and provider (Rittenhouse, 1996; Roth, 1987; Schmier & Leidy, 1998). A third term, adherence, is patient-centred. It reflects the autonomy of patients and the extent to which they choose to follow treatment prescriptions (Rand & Wise, 1994). Finally, pharmionics, a more recent term, relates to what patients do with their medication. It focuses exclusively on measuring and describing the characteristics of medication-taking behaviour such as timing and dosage. Unlike the other terms, then, it is less concerned with the relationship
between behaviour and the prescribed regimen (Urquhart, 2002, 2005). In concordance with most, especially western European literature, in this thesis the term 'adherence' will be used since it reflects patient autonomy. Adherence is defined as the extent to which a person’s behaviour corresponds to medical advice (Adam & Howe, 1993; Szeto & Giles, 1997; Urquhart, 1994).

1.5 Prevalence and characteristics of non-adherence

As mentioned above, medication non-adherence is as old as the use of medication itself. Nearly half a century ago, Parkes et al. (1962) and Renton et al. (1963) established that 45% of patients with schizophrenia failed to take their medication as instructed. Recent studies have shown that the level of non-adherence is still the same today. Recent systematic reviews have found an average prevalence for non-adherence of between 40% and 55% (Cramer & Rosenheck, 1998; Fenton et al., 1997; Lacro et al., 2002; Young et al., 1986).

Reported adherence rates vary considerably (Fenton et al., 1997). This may be due to aggregating studies that use different assessment methods, sub-standard instruments, and different follow-up periods. To obtain a more detailed and valid description of the level of non-adherence among patients with schizophrenia, this thesis will focus exclusively on studies that use the methods we consider to be most valid. The grounds for the selection will be given later in this thesis.

An interesting study in this respect is the one performed by Valenstein et al. (2002) of 47,632 outpatients with schizophrenia. The adherence rates in this study are based on pharmacy data over a one-year period and they are defined as the ratio of received and prescribed medication: the “medication possession ratio” (MPR). This study found that 41% of patients were non-adherent (MPR < 80%). Interestingly, 9% of patients collected more medication then prescribed (MPR > 110%) and the remaining 51% had an MPR of between 80% and 110%. Non-adherent patients had an average MPR of 47%. (See Figure 1.) The average MPR for the entire study population was 78%. These rates are, however, averages over a one-year period, which is one of the disadvantages of pharmacy-based adherence rates since they do not provide information on inconsistent or fluctuating intake behaviour over time. Finally, it should be noted that, although a relation between MPR and rates of admission has been demonstrated (Valenstein et al.,
2002; Weiden et al., 2004), it remains unknown to what extent MPR is related to actual medication intake.

Electronic medication monitoring devices are interesting for studying adherence over shorter time periods. These devices record exactly when a medication container is opened. This method is considered a valid indicator of medication intake (Byerly et al., 2007; Cramer, 1995; Diaz et al., 2001; Nakonezny et al., 2008; Nichol et al., 1999; Osterberg & Blaschke, 2005), but it has been used only in relatively few studies. We examined all studies reporting adherence rates over a one-month period, and found an average monthly medication adherence of 68.4% (Byerly et al., 2005a, 2005b, 2008; Diaz et al., 2001; Nakonezny et al., 2006; Remington et al., 2007). This represents the ratio of medication container openings to the prescribed medication regimen.

It would be even more interesting to examine temporal adherence patterns, but information about adherence over time is scarce. Diaz et al. (2001) reported monthly individual adherence rates over a follow-up period of 6 months for a very small sample of five patients. Although this sample is too small to draw any conclusions, it did demonstrate that the adherence of individual patients can vary considerably over time. In the case of one patient, adherence changed dramatically from 92% in one month to 16% in the next. The change in another patient was from 34% to 61%. Using annual average MPRs for 34,128 patients with schizophrenia, Valenstein et al. (2006) examined yearly adherence rates over four years. In this study, non-adherence was defined as an MPR below 80%. In two consecutive years, 11% of patients shifted from being adherent in one year to non-adherent in the following year, while another 11% shifted from non-adherent to adherent. The average adherence rates for the entire sample were therefore stable during the two years of the study.

Over time, the number of patients who were non-adherent at some point gradually increased. Only 39% of patients remained consistently adherent over an entire four-year period. In the Netherlands a similar study based on the pharmacy data for approximately 2% of the Dutch population was performed, focusing on time to discontinuation of antipsychotic medication (Herings et al., 1992). This study found that 57% of outpatients with schizophrenia stopped taking their medication within one year, 17% did so temporarily for at least 30 days and 26% took their medication consistently. A survival curve indicated that the number of patients who discontinue their medication is highest in the first 120 days after treatment onset, after which the number slowly decreases over time (Pharmo rapport, 2002).
On the basis of this information, we conclude that, at any given time, approximately half of all patients with schizophrenia are in one way or another non-adherent. Non-adherent patients use approximately half of the medication prescribed to them; this results in an average adherence rate for all patients of between 70% and 80%. Adherence is not stable over time and the majority of patients will, at some point, be non-adherent or partially adherent.

![Figure 1. Average Medication Possession Ratio over a one-year period (N=47,632)](image)

### 1.6 Consequences of non-adherence

With the exception of patients who receive compulsory treatment, patients have the right, and the autonomy, to alter medication intake to their liking. However, this becomes a problem when non-adherence reaches a level where medication is no longer sufficiently effective (Weiden, 2007). Sub-therapeutic intake of antipsychotic medication may result in an exacerbation of psychotic symptoms, increased aggression and a worsening of symptomatic prognosis, and it is the most important determinant of relapse (Ayuso-Gutierrez et al., 1997; Fenton, 1997; Kahn et al., 2008; Keith et al., 2003; Lieberman et al., 2005; Lieberman et al., 1998; Malla et al., 2006; Morken et al., 2008; Robinson et al., 1999; Weiden and Zygmunt, 1997; Wyatt, 1991).

When a relapse occurs, there is an increased risk of hospitalisation. Admission, however, does depend on more factors than mental health alone. It may be influenced by patient characteristics (e.g. patient preference), social characteristics (e.g. family or social
support and living conditions) and health care factors (e.g. number of beds available, policy, outpatient treatment facilities). Nevertheless, even though not all relapsed patients will be admitted, several studies have shown that non-adherence is associated with higher admission rates (Eaddy et al., 2005; Diaz et al., 2001; Gilmer et al., 2004; Law et al., 2008; Valenstein et al., 2002; Weiden et al., 2004). On the basis of seven studies examining the relationship between non-adherence and hospitalisation, Fenton et al. (1997) concluded that, compared with adherent patients, non-adherent patients were 3.7 times more at risk of rehospitalisation over a 6-month to 24-month period.

Relapse and admission to a psychiatric ward can be very distressing for patients. However, these events can also be highly burdensome for their partners, family, friends or neighbours (Awad & Voruganti, 2008; Bosch et al., 1999; Magliano et al., 1998, 2000; Schene & van Wijngaarden 1993; van Wijngaarden et al., 2009). Furthermore, relapse can also have other far-reaching consequences. Patients may, for instance, lose their jobs, partners or homes, or get into financial problems or difficulties with the law.

Non-adherence has considerable economic implications, requiring extra work from mental health professionals, hospital admissions, productivity losses, judicial costs, etc. Estimates of these costs are not available for the Netherlands. Although the results of analyses in the US and UK may not be representative for the situation in the Netherlands, they do give some idea of the magnitude of the costs. An older study by Weiden and Olfson (1995) stated that non-adherence accounts for approximately 40% of rehospitalisation costs for patients with schizophrenia in the two years after their discharge from inpatient treatment. Reviewing the literature, Sun et al. (2007) estimated national rehospitalisation costs related to antipsychotic non-adherence in schizophrenia patients at $1479 million in the US in 2005. Knapp et al. (2004) concluded that non-adherence is one of the most significant factors in pushing up external service costs in the UK. For each patient, the annual inpatient service costs related to non-adherence were estimated at approximately £2500, with the costs of total service use being estimated at over £5000.

Although the above focuses on patient’s psychiatric disorder, it is known that a substantial proportion of schizophrenia patients have a comorbid somatic disorder (Goldman, 1999; Theunissen et al., 2008). For these patients, non-adherence to treatment recommendations may therefore not only affect their psychiatric, but also their physical health.
1.7 Determinants of non-adherence

Many studies have been performed to find factors associated with, or predictors of, non-adherence in patients with schizophrenia. The most thorough review of these studies was published in 2002 by Lacro et al. This was a systematic review of 39 studies published after 1980. The authors concluded that non-adherence was influenced by several patient-related factors such as poor insight, a negative attitude towards medication, subjective response to medication, previous non-adherence, and short illness duration. The only medication-related factor consistently associated with non-adherence was higher antipsychotic dosage. Environmental factors associated with non-adherence were: poor alliance with the therapist or clinician, infrequent outpatient contact, inadequate discharge planning or poor aftercare environment. Lacro et al. found no association with non-adherence for other factors such as age, gender, ethnicity, marital status or level of education. Interestingly, they could not arrive at any conclusions about nearly half of all the variables included in the review because the study results were too inconsistent or conflicting.

To see whether they reached similar conclusions, we examined five other reviews published between 1997 and 2008 that included a systematic literature search (Fenton et al., 1997; Lacro et al., 2002; Llorca et al., 2008; Oehl et al., 2000; Perkins 2002; Pinikahana et al., 2002). A summary of the results of these reviews is shown in Table 1. Perkins (2002) and Llorca et al. (2008) only report factors which are clearly associated with non-adherence, the other reviewers concluded, in accordance with Lacro et al., that study results are inconsistent for several variables.

Even amongst reviewers there seems to be some disagreement about which factors are predictors of non-adherence. In general there is agreement that substance abuse, rates of positive symptoms, disorganization, and symptoms severity are higher in non-adherent patients. Adherence is better if patients have insight, positive attitudes towards medication, and belief or experience that medication is effective. A good therapeutical alliance is also consistently associated with medication adherence. Finally, patients who do not receive support from their relatives, live alone and who’s intake is not supervised are in general more non-adherent.
1.8 Interventions for improving adherence

To date, several interventions have been developed to improve medication adherence in patients with schizophrenia. The number of studies exploring the effectiveness of adherence interventions published between 1980 and 2008 is shown in Figure 2. A total of 69 studies were published in that period, mostly (84%) randomised controlled trials. These interventions are based on a variety of strategies such as psycho-education, behavioural modifications, cognitive interventions, group therapy and family interventions.

The aim of psycho-education is to improve patients’ knowledge and understanding of their illness and medication. Prior to 2000, this was often considered an effective way of enhancing adherence. In the eighties and nineties, approximately half of all studies used some form of psycho-education, making it one of the most frequently employed strategies. Behavioural interventions aim to shape behavioural patterns or simplify the practical aspects of medication intake. They may use reward and punishment, reinforcement, cues or reminders, and the promotion of self-management. Between 1980 and 2000 approximately a fifth of all studies evaluated this approach. Cognitive interventions gained some popularity during the nineties. These interventions encourage patients to examine factors that may affect their medication adherence and target patients’ attitudes and beliefs with respect to medication. Cognition-oriented interventions also often include some form of psycho-education. Group therapy emphasises the importance of peer support and recognition, while family therapy aims to improve support and understanding from family members. The involvement of family members, often in combination with other strategies such as patient education, was already frequent during the eighties. The popularity of this strategy increased in the nineties and, during this period, approximately one in three studies looked at interventions involving family members.

Figure 2 shows that the number of intervention studies slowly increased during the eighties and nineties, reaching a peak in 1995 and 1996. This was followed by a sharp decline in the number of studies and the time to evaluate the results seemed to have arrived. Six reviews were published between 2000 and 2003 (Gray et al., 2002; Dolder et al., 2003; McDonald et al., 2002; Merinder et al., 2000; Nose et al., 2003; Zygmunt et al., 2002). The conclusions of these reviews were fairly consistent. Psycho-educational programmes were successful in improving patients’ insight and knowledge with respect to their illness and treatment, but had little or no real effect on medication adherence (Gray et al., 2002; Dolder et al., 2003; McDonald et al., 2002; Merinder, 2000; Zygmunt et al.,
2002). These conclusions resulted in a dramatic decline in studies of psycho-educational interventions. We know now from more recent studies, as well as studies performed in patients suffering from other chronic diseases, that psycho-education tends to be more effective if family members are also involved (Byerly et al., 2007; Lincoln et al., 2007). Although the study results were inconsistent, behavioural interventions, interventions with behavioural elements, and cognitive interventions were found to be more successful on average in promoting adherence (Gray et al., 2002; Dolder et al., 2003; Merinder et al., 2000; Zygmunt et al., 2002). Overall, interventions of longer duration and intensity, and those involving family members, proved to be more effective (Byerly et al., 2007; Dolder et al., 2003; Merinder et al., 2000), but the most promising results were achieved with combined interventions and with community care approaches such as assertive community treatment (Dolder et al., 2003; McDonald et al., 2002; Zygmunt et al., 2002). The conclusions of these reviews clearly had an impact, and strategies with disappointing results were abandoned.

Several reviewers (Gray et al., 2002; McDonald et al., 2002; Zygmunt et al., 2002) found that one of the most promising interventions was the ‘adherence therapy’ developed during the early nineties by Kemp and colleagues in London (Kemp et al., 1996). Although the label ‘adherence therapy’ is rather generic, this is a protocolised cognitive behavioural intervention based on motivational interviewing techniques, as described by Kemp et al. (1996). This thesis follows the literature and uses the term ‘adherence therapy’ to refer to this intervention only. In two randomised controlled trials, adherence therapy was effective in improving adherence, drug attitudes, insight, overall psychopathology, functioning and rehospitalisation rates (Kemp et al., 1996, 1998). In the light of these findings, several new studies were initiated, including the QUATRO study which will be discussed below (Byerly et al., 2005; Gray et al., 2004, 2006; Maneesekorn et al., 2007; O'Donnel et al., 2003). Indeed, 6 out of the 12 studies published between 2003 and 2008 focused on adherence therapy. The QUATRO trial was designed to corroborate the effects found by Kemp et al. (1996, 1998) in a larger European trial.
Table 1. Summary of systematic reviews of risk factors of non-adherence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Fenton et al., 1997</th>
<th>Oehl et al., 2000</th>
<th>Lacro et al., 2002</th>
<th>Perkins et al., 2002</th>
<th>Pinikahana et al., 2002</th>
<th>Llorca et al., 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sociodemographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>3 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>3 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid functioning</td>
<td>-</td>
<td></td>
<td>+</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td></td>
<td>+/-</td>
<td>2 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall intelligence</td>
<td>-</td>
<td></td>
<td></td>
<td>1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability of living arrangements</td>
<td>+/-</td>
<td></td>
<td>-</td>
<td>- 1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Illness-related characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current past substance abuse</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+ 4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom severity</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>3 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatology (positive symptoms, disorganization)</td>
<td>+/-</td>
<td></td>
<td>+</td>
<td>+ 3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>+/-</td>
<td></td>
<td></td>
<td>+ 2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient status</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>-</td>
<td></td>
<td></td>
<td>1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>+/-</td>
<td></td>
<td></td>
<td>1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prior hospitalizations</td>
<td>+</td>
<td></td>
<td></td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insight and attitude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insight</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>5 (4)</td>
</tr>
<tr>
<td>Attitude towards medication</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>3 (3)</td>
</tr>
<tr>
<td>Belief that medication works</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td>2 (2)</td>
</tr>
<tr>
<td>Feeling susceptibility to relapse</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Previous non-adherence</td>
<td>-</td>
<td></td>
<td></td>
<td>+ 2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication-related factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral medication</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>Complexity of medication regimen</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
<td>2 (0)</td>
</tr>
<tr>
<td>Typical vs atypical</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (0)</td>
</tr>
</tbody>
</table>
Introduction

<table>
<thead>
<tr>
<th>Factor</th>
<th>Fenton et al., 1997</th>
<th>Oehl et al., 2000</th>
<th>Lacro et al., 2002</th>
<th>Perkins 2002</th>
<th>Pinikahana et al., 2002</th>
<th>Llorca a (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication-related factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Perceived efficacy / benefit</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Practical-related issues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial situation</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>2 (2)</td>
</tr>
<tr>
<td>Environment-related factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alliance with clinician</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Clinician's attitude towards medication</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>2 (2)</td>
</tr>
<tr>
<td>Providing information about medication</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>2 (2)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of outpatient contact</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Poor aftercare, inadequate discharge planning</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Social aspects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family or social support and involvement</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Living alone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>4 (4)</td>
</tr>
<tr>
<td>Medication supervision</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Attitude towards medication of relatives and friends</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stigma of illness</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* +/- inconclusive or conflicting evidence concerning the association with adherence/non-adherence according to the reviewers. - not associated with adherence/non-adherence according to the reviewers.

a number of reviews which mentioned this factor. b number of reviews which concluded that this factor is associated with adherence/non-adherence.
Figure 2. Number of effectiveness studies of interventions for improving adherence published annually between 1980 and 2008.

1.9 Resolved and unresolved issues

We have already discussed several resolved and unresolved issues relating to medication adherence. A short summary of these issues will be given here.

Schizophrenia is a severe mental disorder, for which medication is considered to be the most effective treatment. Nevertheless, half of all patients fail to take their medication as prescribed. This means that, despite all the research efforts, the development of interventions and new medication, we have not been able to improve adherence behaviour in the last half century. Although extensive research has improved our knowledge, much is still unknown and breakthroughs have not been achieved. We do know that non-adherence results in an increased risk of relapse and hospitalisation, and that it is associated with high economic costs. Unfortunately, a clear solution to this problem is not yet in sight.

The use of different definitions, assessment methods and units of measurement makes it difficult to give a valid and adequate description of patients’ adherence behaviour. The prevalence rates for non-adherence therefore vary widely between studies. In addition, information about individual adherence patterns is scarce, and the same applies to the actual risks associated with these patterns.
Research into risk factors has resulted in a list of variables associated with non-adherence. However, the relation between many variables and adherence is unclear due to the inconsistency of the findings. Although we know that some factors are consistently associated with non-adherence, few attempts have been made to explain how they relate to patients’ decision-making processes. As a consequence, our understanding of the mechanisms underlying non-adherence is scanty (Sluijs et al., 2006). For instance, we still do not know how often non-adherence is unintentional as a result of cognitive deficits such as forgetfulness, or how often it is deliberate because of side effects or negative attitudes toward medication.

All this may have had an impact on the development of interventions for improving adherence. Despite the large amounts of work done in the last decades, it is still not clear which strategy should be pursued. Interventions use a variety of strategies, and it remains uncertain to what extent they address the mechanisms causing non-adherence. Results from trials are sometimes disappointing or, as in the case of adherence therapy, inconsistent.

It has been argued that the relatively disappointing and inconsistent study results for risk factors and interventions are, at least partly, due to methodological problems (Dixon et al., 1997; Nichol et al., 1999; Owen et al., 1996). Different methods are used to measure adherence, and there is a lack of consensus about the definition, criteria and cut-off levels of adherence (Cramer & Rosenheck 1998; Gray et al., 2002; Lacro 2002; Nichol et al., 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006). If patients who are considered adherent in one study are labelled non-adherent in another, results for adherence-related factors will be inconsistent and efforts to understand and improve non-adherence are likely to remain unsuccessful.

1.10 The present thesis

The findings of Kemp et al. (1996, 1998) resulted in high expectations for adherence therapy. In 2005, the European Union gave a grant for a large European trial to study the effectiveness of adherence therapy. Four European sites – Leipzig, London, Verona and Amsterdam – participated in this project. Chapter 2 presents the main findings of the QUATRO study (Quality of life following adherence therapy for people disabled by schizophrenia and their carers).
As the researcher responsible for the Amsterdam site, the author became intrigued by patients’ reasons to stop taking medication. In interviews with patients, it was possible to ask them in more detail how they felt about their medication and how they used them. Most stories were unique and all patients dealt with medication in their own ways. One of the most interesting findings was that adherence was often understandable and rational once one accepts the pros and cons the patient attribute to medication use.

It also became clear that, from the patient’s perspective, it is very difficult to adhere to a medication regimen for a long period of time. The literature includes numerous studies that focus on risk factors but the results were often not satisfactory. In addition to the problem of inconsistent or conflicting results, no attempts were made to look at the issue from the patient’s perspective. Most studies seemed to see patients as a black box and the discussions the author had with patients were seldom reflected in these papers. Pending the results of the QUATRO study, it was decided to initiate a qualitative study to improve our understanding of non-adherence. The study evaluated patients’ possible reasons for taking their prescribed medication or not. The results are presented in chapter 3.

It was obvious from the scientific literature that the quality of many adherence studies was poor. One of the most important issues was the lack of a good adherence assessment instrument, a vital tool in adherence studies. During the drafting of the grant proposal, and after studying the literature, the principal investigators from the QUATRO study group deliberately opted for three validated and well-described adherence instruments as one of the outcome variables in the QUATRO study. When using these instruments, the question arose of whether this was the most appropriate way to measure medication adherence. Based on what patients tolled about their medication adherence, it became obvious that this was not always captured by the questionnaires. As a result, some patients who tolled they were not adherent scored as adherent on the instruments or vice versa. Chapters 4 and 5 focus on the validity of these three instruments.

The results of these studies, as well as personal conversations with patients and colleagues, led to the construction of a new instrument based on a different approach. Chapter 6 presents the validation study for this new adherence instrument, the Inventory of Medication Intake.

In one sense, this thesis was written in reverse order. Our primary aim was to explore the effectiveness of adherence therapy, hoping this would help resolve non-adherence in patients. In time, however, the focus narrowed towards understanding patients’ adherence behaviour, and finally towards methodological issues related to measuring medication adherence.
Introduction

The questions addressed in this thesis are:

1. **Is adherence therapy effective in reducing non-adherence in a European sample of patients with schizophrenia?**

   This study looks at the effectiveness of adherence therapy as developed by Kemp et al. (1996), exploring the issue in a European multisite randomised controlled trial. The effectiveness of adherence therapy was evaluated in terms of the quality of life in a sample of inpatients and outpatients with schizophrenia after a follow-up period of 12 months. Medication adherence and psychopathology were also evaluated to explore the effects of adherence therapy. The results are presented in chapter 2.

2. **What reasons do patients with schizophrenia have to use, or not use their antipsychotic medication?**

   To address this question we set up a concept mapping study. This is a qualitative approach. In addition to patients, we also recruited carers and professionals dealing with schizophrenia patients. The study was performed in the four European countries that participated in the QUATRO study. We explored factors that affect medication adherence in patients with schizophrenia, their underlying relations and relative importance. The results are presented in chapter 3.

3. **What is the concurrent validity of the adherence assessments used in the QUATRO study?**

   In order to examine the validity of subjective adherence instruments we compared the three adherence measures used in the QUATRO study. The patient-rated and clinician-rated adherence instruments were the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS). These are all well described and widely used, and they represent the most frequently used types of adherence instruments in adherence studies. We explored the extent to which these instruments match in terms of labelling patients as non-adherent, to what extent these instruments measure the same concept, and how they are related to established risk factors for non-adherence. The results are presented in chapter 4.

4. **What is the predictive validity of adherence assessments as used in the QUATRO study?**

   On the basis of the results of the previous study, we further explored the validity of the three adherence instruments by examining their predictive validity. To do so, we used weekly clinical course data relating to relapse and admission from the follow-up period of one year. The results are presented in chapter 5.
5. What is the validity of the Inventory of Medication Intake (IMI)?

We constructed a new adherence assessment method and, in this study, we examined its validity by comparing the results of the IMI with the Medication Event Monitoring System (MEMS). In addition, we also administered the three adherence instruments that had been the focus of the previous two studies. This study was performed in a sample of outpatients with schizophrenia in Amsterdam. The results are presented in chapter 6.

Chapter 7 (General discussion) will look at the results and implications of these different aspects of medication adherence, and make appropriate recommendations.
1.11 References


Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. Pharmacoeconomics, 26: 149-62.


GIP/College voor zorgverzekeringen. Available at: http://www.gipdatabank.nl/ (accessed may 2009).


Introduction


Valenstein M, Copeland LA, Blow FC, et al. (2002). Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Medical Care, 40: 630-639.


Chapter 2

Adherence Therapy for People with Schizophrenia.
European Multicentre Randomised Controlled Trial

Richard Gray
Morven Leese
Jonathan Bindman
Thomas Becker
Lorenzo Burti
Anthony David
Kevin Gournay
Martijn Kikkert
Maarten Koeter
Bernd Puschner
Aart Schene
Graham Thornicroft
Michelle Tansella

Abstract

**Background:** There is equivocal evidence of the effectiveness of adherence therapy in improving treatment adherence and clinical outcomes for people with schizophrenia.

**Aims:** To evaluate the effectiveness of adherence therapy in improving quality of life for people with schizophrenia.

**Method:** A 52-week, single-blind, multicentre randomised controlled trial of the effectiveness of adherence therapy. Participants were individually randomised to receive eight sessions of adherence therapy or health education. Assessments were undertaken at baseline and at 52-week follow-up.

**Results:** Adherence therapy was no more effective than health education in improving quality of life.

**Conclusions:** This effectiveness trial provides evidence for the lack of effect of adherence therapy in people with schizophrenia with recent clinical instability, treated in ordinary clinical settings.
Introduction

It has been estimated that non-adherence rates for prescribed antipsychotic medications are about 50% (Nose et al., 2003a). Relapse rates have been shown to be five times higher in people with schizophrenia who are non-adherent to medication compared with adherent people, resulting in a significant social and economic burden (Robinson et al., 1999).

Zygmunt et al. (2002) reviewed randomised controlled trials of adherence interventions in schizophrenia. They showed that only one-third of these studies reported significant treatment effects, but that interventions based upon the principles of motivational interviewing were 'promising'. A subsequent meta-analysis concluded that psychiatric services could use effective clinical interventions for reducing patient non-adherence, but that the benefit of these interventions would be more evident in the short-term than in the long term (Nose et al., 2003b). A recent randomised controlled trial of in-patients compared adherence therapy with non-specific counselling over 1 year, and found no clear advantage (O’Donnell et al., 2003).

Method

The main aim of this study was to compare the effectiveness of adherence therapy with a health education control intervention (which allows for therapist time and relationship), in improving health-related quality of life for people with schizophrenia receiving treatment from general adult mental health services in four European cities. The primary a priori hypothesis was that adherence therapy would result in improved quality of life for people with schizophrenia, compared with health education. Secondary a priori hypotheses were that, compared with health education, adherence therapy would improve medication adherence and symptoms.

The study design was a two-arm randomised controlled trial, with masking of assessors to the status of the participants. The interventions were delivered in routine general adult psychiatric settings, to maximise the generalisability of the results of this effectiveness trial (Tunis et al., 2003).
Study participants
Participants were recruited from June 2002 to October 2003 from people under the care of psychiatric services. A researcher approached senior treating clinicians at a range of locally typical general adult psychiatric in-patient and community settings, serving catchment areas in each of the four study sites: Amsterdam (The Netherlands), Leipzig (Germany), London (England) and Verona (Italy).

There were three inclusion criteria. First, a clinical diagnosis of schizophrenia should be confirmed by a research diagnosis of schizophrenia, established using the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990) when applied to case notes, using International Classification of Disease criteria (ICD–10; World Health Organization, 1992). Second, patients should need continuing antipsychotic medication for at least the year following baseline assessment, in the judgement of the responsible treating senior psychiatrist. Third, there should be evidence of clinical instability in the year before baseline, defined by one or more of the following: at least one hospital admission on mental health grounds, a change in type or dose of antipsychotic medication, planned or actual increased frequency of contact with mental health services, and indications of clinical instability reported by relatives, carers or the clinical team.

Exclusion criteria were: presence of moderate or severe mental handicap (learning disability); organic brain disorders; current treatment by forensic psychiatric services; alcohol or drug dependence; inability to speak the language of host country to a sufficient standard to receive the intervention; or assessment by the treating clinician as lacking capacity to give valid consent to participate.

Study procedures
Individuals participated only if they gave written, informed consent. All study sites gained full approval for the study from the appropriate local research ethics committee (institutional review board). Once participants had given consent, they underwent baseline interviews and then received a unique identification number. This was sent to an independent clinical trials unit, where allocation was carried out by permuted blocks of random size, stratified by centre. The allocation was notified to the therapist, who arranged directly with the participant for the allocated treatment to be given. The researcher who conducted the baseline interview and the follow-up assessment remained masked to allocation throughout the study, to minimise bias. Participants were not masked to whether they were receiving adherence therapy or health education, and consequently
this cannot be considered a double-blind trial. However, participants were informed that they would receive one of two interventions but were not told which was regarded by the investigators as the experimental intervention, and remained masked to the exact aims of the study.

**Study interventions**

The experimental intervention, adherence therapy, is a brief individual cognitive–behavioural approach (Gray et al., 2004; Kemp et al., 1996, 1998). The adherence therapy manual (http://www.adherencetherapy.com) describes a collaborative, patient centred phased approach to promoting treatment adherence in people with schizophrenia. There are six elements that form the core of the therapy: assessment; medication problem-solving; a medication timeline; exploring ambivalence; discussing beliefs and concerns about medication; and using medication in the future. Key therapy skills that therapists use include exchanging information, developing discrepancy between the patient’s thoughts and behaviours about medication, and working with resistance to discussing psychiatric medication and treatment. The aim of the therapy process is to achieve a joint decision about medication between the individual and therapist. A central tenet of the therapy is that where patients and therapists make choices about treatment together, adherence to that regimen will be enhanced.

Previous trials of adherence interventions have used a non-specific counselling intervention or standard care as the control intervention (Zygmunt et al., 2002). We offered participants a control intervention that would be acceptable and was not expected to enhance medication adherence, but which did control for the time spent with the therapist (Roth & Fonagy, 1996). We chose didactic health education rather than standard care alone as the control condition, to control for therapist time and other non-specific aspects of the intervention. The eight individual sessions of the health education package included presentations on health education-related topics such as diet and healthy lifestyle. Therapists presented information in a didactic way, and were trained not to use any adherence therapy skills or techniques.

For both experimental and control conditions, participants were offered a maximum of eight weekly sessions of adherence therapy or health education, each lasting on average between 30 and 50 min. Completion of treatment was defined as having attended at least five of the eight sessions over a maximum 5-month period. Both interventions were provided by one of nine therapists (four psychologists, three psychiatrists and two mental health nurses), all of whom had a background in delivering clinical interventions to people with schizophrenia. Treatment fidelity was assured as follows:
a. Both adherence therapy and health education interventions were described in detail in manuals.
b. The English language manuals were translated and back-translated into the appropriate languages (Dutch, German and Italian).
c. All therapists met for 7 days to receive intensive training, using videomodelling and role-play rehearsal of key skills.
d. Randomly selected therapy sessions (37) were audiotaped and independently rated using the Adherence Therapy Checklist (ATC; Vallis et al., 1986).
e. Throughout the 18 months of the intervention period, therapists attended monthly group telephone clinical supervision, focusing on case presentations, the resolution of clinical problems, and adherence to therapy manuals. Both adherence therapy and health education were offered at each site in addition to treatment-as-usual, which consisted of regular contact with psychiatrists and case managers, pharmacological therapy and the availability of day care, social support and acute hospital admission as required (Becker et al., 2002).

Outcome measures
Assessments took place at baseline and at 1 year after randomisation. The assessment scales included measures of sociodemographic characteristics, quality of life, adherence and psychopathology. The key results for the following scales are reported.

Medical Outcome Study (MOS) 36-Item
Short Form Health Survey (SF-36) The SF-36 is a self-report multidimensional survey measure of health-related quality of life and well-being (Ware & Sherbourn, 1992). The scales of the SF-36 address eight health domains, and two summary measures are provided: a physical component summary score (PCS) and a mental component summary score (MCS). The MCS was selected as the main quality of life (QoL) outcome measure, as it has been shown to have good sensitivity to change, which is uncommon among QoL measures (Rood et al., 2000). Further, in people with severe mental illness, the SF-36 has been found to have well-established psychometric properties (test-retest reliability and internal consistency) (Russo et al., 1998; Tunis et al., 1999).

Schedule for the Assessment of Insight – Expanded Version (SAI-E)
From this semi-structured interview, we used the keyworker rating of adherence, referred to as the SAI-C, on a scale ranging from 1 (complete refusal) to 7 (active participation in treatment) (David, 1990).
Medication Adherence Questionnaire (MAQ)
The MAQ addresses how patients may fail to take their medication as prescribed, for example because of forgetfulness, carelessness, stopping the drug when they feel better, or stopping the drug because they believe it makes them feel worse. The scale has good levels of validity and reliability (Morisky et al., 1986).

Brief Psychiatric Rating Scale – Expanded (BPRS-E)
The BPRS-E consists of 24 items measuring psychiatric symptoms (Lukoff et al., 1986; Ventura et al., 1993). It measures four different dimensions: positive symptoms, negative symptoms, depression and anxiety and manic excitement or disorganisation.

Sample size
A sample size of 300 participants was sought (150 in the treatment and 150 in the control group). This was sufficient to detect an overall difference between intervention and control of six points in the SF-36 MCS scale, based upon previous studies using such a magnitude of clinical change (Ware & Kosinski, 2003a) and equivalent to a medium standard effect size, with over 99% power. The calculation assumes that the analysis would adjust for baseline values, that the pre-post correlation would be 0.5, and a standard deviation of the MCS of about 12, as found in MOS patients (adults in various settings with depression in the USA) (Ware & Kosinski, 2003b). With an estimated 25% attrition rate, this required the recruitment of 400 participants (100 per site on average) at baseline.

Statistical methods
The effect of the intervention on the outcomes was assessed by comparing the mean values for intervention and control at follow-up using analysis of covariance (Mickey et al., 2004) to control for baseline value and site. The analyses were completed on an intention-to-treat basis. Double-sided critical levels for significance tests were used. Pro-rating dealt with missing items in the computation of sub-scales for each participant, so long as there were fewer than 20% missing items for that person; otherwise, the scale was set to missing. This rule was overridden where there were specific instructions for the scale (as in the case of the SF-36). If participants had an observation at neither time point, they were excluded. Where only one value was present, imputation was used for sensitivity analyses but not in results tables or primary analyses. Mean (within-site) imputation was involved for missing continuous covariates at baseline, such as the baseline values of the outcomes, and analyses were weighted if necessary (White & Thompson, 2005). Follow-
up values were also imputed from baseline values, and any other relevant variables at follow-up, if available. As a further sensitivity analysis, the MAQ and SAI-C scales, which were short scales with non-normally distributed data, were analysed using ordered logistic regression. Microsoft Access databases and SPSS version 11 for Windows were used for initial data acquisition and checking, and Stata version 8.2 for the analyses.

**Results**

**Socio-demographic characteristics**
The randomisation produced no substantial differences between the control and treatment groups at baseline (Table 1). As is common in treated prevalence studies of schizophrenia, the mean age of the sample was in the early forties, the slight majority were male, and relatively few were married or cohabiting. Three-quarters of the participants were White, and almost half lived alone, usually in owned or rented accommodation; only about 15% were in paid employment.

**Clinical characteristics**
At baseline there were no substantial clinical differences between the control and treatment groups (Table 1). Participants in both groups had spent about 1 month in the year before baseline as in-patients, and had been treated with antipsychotic medication for about 12 years. Between sites there were some differences in the profiles of symptoms and disability, but the variations in patterns of service use were more marked and reflected different service configurations in each of the four areas studied (Table 2) (Chisholm & Knapp, 2002).

**Participant flow**
Figure 1 shows the flow of participants through the study in the CONSORT format. Of the 1218 people screened, 917 were eligible to participate in the study. Of these, 366 (39.9%) refused to participate, 142 (15.5%) could not be randomised for other reasons, so a total of 409 (44.6%) were randomised. The three most common reasons for refusing to participate in the study were that potential participants did not have enough time, were not interested in the study or did not want to participate in research.
Table 1. Socio-demographic and clinical characteristics of the sample at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adherence therapy n=204</th>
<th>Health education n=205</th>
<th>Overall n=409</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>40.9 (11.7)</td>
<td>42.1 (11.4)</td>
<td>41.5 (11.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>122 (60)</td>
<td>123 (60)</td>
<td>245 (60)</td>
</tr>
<tr>
<td>Married or cohabiting, n (%)</td>
<td>25 (12)</td>
<td>22 (11)</td>
<td>47 (11.5)</td>
</tr>
<tr>
<td>White European, n (%)</td>
<td>151 (74)</td>
<td>159 (78)</td>
<td>310 (76)</td>
</tr>
<tr>
<td>Primary/secondary education only, n (%)</td>
<td>136 (67)</td>
<td>135 (67)</td>
<td>271 (67)</td>
</tr>
<tr>
<td>Living alone, n (%)</td>
<td>84 (41)</td>
<td>81 (40)</td>
<td>165 (40)</td>
</tr>
<tr>
<td>Living with partner, n (%)</td>
<td>31 (53)</td>
<td>28 (48)</td>
<td>59 (14.5)</td>
</tr>
<tr>
<td>Living with family, n (%)</td>
<td>45 (49)</td>
<td>47 (51)</td>
<td>92 (22.5)</td>
</tr>
<tr>
<td>Living with others (e.g. hostel), n (%)</td>
<td>43 (47)</td>
<td>49 (53)</td>
<td>92 (22.5)</td>
</tr>
<tr>
<td>Accommodation: owned or rented, n (%)</td>
<td>155 (76)</td>
<td>159 (78)</td>
<td>314 (77)</td>
</tr>
<tr>
<td>Employment: paid or self-employed, n (%)</td>
<td>29 (14)</td>
<td>30 (15)</td>
<td>59 (14.5)</td>
</tr>
<tr>
<td>Psychiatric in-patient days in past year, mean (s.d.)</td>
<td>28.1 (57.4)</td>
<td>27.8 (63.4)</td>
<td>27.9 (60.4)</td>
</tr>
<tr>
<td>Anypsychiatric admission in past year, n (%)</td>
<td>82 (40)</td>
<td>77 (38)</td>
<td>159 (39)</td>
</tr>
<tr>
<td>Years from first antipsychotic treatment to interview, mean (s.d.)</td>
<td>13.0 (9.4)</td>
<td>14.3 (10.3)</td>
<td>13.6 (9.9)</td>
</tr>
<tr>
<td>MAQ total score, mean (s.d.)</td>
<td>2.96 (1.25)</td>
<td>2.98 (1.19)</td>
<td>2.97 (1.21)</td>
</tr>
<tr>
<td>BPRS-E total score, mean (s.d.)</td>
<td>46.1 (13.4)</td>
<td>44.3 (12.5)</td>
<td>45.2 (13.0)</td>
</tr>
<tr>
<td>SF-36 MCS, mean (s.d.)</td>
<td>38.4 (11.2)</td>
<td>40.1 (12.1)</td>
<td>39.2 (11.7)</td>
</tr>
</tbody>
</table>

MAQ, Medical Adherence Questionnaire; BPRS, Brief Psychiatric Rating Scale; MCS, mental component summary of Medical Outcomes Study SF-36.

Study completion and attribution rates

Baseline and follow-up data for the core outcome measures were collected for 349 (85.3%) participants: 184 (90%) in the health education group and 165 (81%) in the adherence therapy group, a difference in follow-up rate that was statistically significant (p=0.01).

Table 3 shows that, overall, people who dropped out of the trial tended to have had more in-patient days (p=0.022), but in other respects were similar to those who completed the interviews, and the drop-outs were similar in the two arms.
Uptake of interventions and fidelity

The mean number of sessions of adherence therapy was 7 (s.d.=1.96) and the mean duration of each session was 36 min (s.d.=12.10). The mean number of sessions of health education was 7 (s.d.=2.49) and the mean duration of each session was 30 min (s.d.=9.92). In all, 54 participants did not complete treatment (attended fewer than 5 sessions in a 5-month period), split evenly between the two groups.

Table 2. Key baseline characteristics of participants, compared by site

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amsterdam</td>
</tr>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>40.0 (10.2)</td>
</tr>
<tr>
<td>Years of medication, mean (s.d.)</td>
<td>12.7 (9.2)</td>
</tr>
<tr>
<td>In-patient days in past year, mean (s.d.)</td>
<td>46.3 (90.7)</td>
</tr>
<tr>
<td>BPRS score, mean (s.d.)</td>
<td>37.5 (10.2)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>73 (73)</td>
</tr>
<tr>
<td>White European, n (%)</td>
<td>44 (44)</td>
</tr>
<tr>
<td>Antipsychiatric admission in past year, n (%)</td>
<td>40 (40)</td>
</tr>
</tbody>
</table>

BPRS, Brief Psychiatric Rating Scale.
1. n=366 for years of medication; for other variables, n=406-409.

Independent evaluation of 20 audiotapes of health education and 17 of adherence therapy, using the ATC, revealed that the adherence therapy was delivered in a way that was highly consistent with the adherence therapy manual. Participants receiving health education did not receive any of elements of adherence therapy.

Outcomes of intervention

Quality of life

There were no significant differences in quality of life between the two intervention groups at baseline or at follow-up (Table 4). Sensitivity analyses confirmed this finding.

Medication adherence

There was no significant difference between adherence therapy and health education at follow-up. This indicates that interventions were essentially equivalent. Sensitivity analyses did not reveal any major difference in these findings.
We conducted an exploratory post-hoc analysis to examine the effect of adherence therapy in a subgroup of the less treatment adherent participants (defined as a score of 2 or lower on the MAQ). Although such an analysis was not planned a priori, it was considered informative to explore any possible effect of adherence therapy in a sample of non-adherent individuals. Just under a third of the sample (n=120, 30%) met this criterion. There was no significant difference in medication adherence between the groups at follow-up.

Figure 1. CONSORT diagram. ICG, ItemGroup Checklist of the Schedule for Clinical assessment in Neuropsychiatry
Table 3. Comparison of participant trial completers and drop-outs and those lost to follow-up (baseline scores)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adherence therapy</th>
<th>Health education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completers</td>
<td>Non-completers</td>
</tr>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>42.1 (11.2)</td>
<td>41.9 (13.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>105 (60)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Married/cohabiting, n (%)</td>
<td>20 (10)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>White European, n (%)</td>
<td>149 (78)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>No education beyond secondary level, n (%)</td>
<td>126 (66)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Living alone, n (%)</td>
<td>79 (41)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Psychiatric in-patient days in past year, mean (s.d.)</td>
<td>26.9 (62.5)</td>
<td>41.2 (77.1)</td>
</tr>
<tr>
<td>MAQ total score, mean (s.d.)</td>
<td>2.96 (1.20)</td>
<td>3.23 (1.01)</td>
</tr>
<tr>
<td>BPRS total score, mean (s.d.)</td>
<td>44.3 (12.8)</td>
<td>44.3 (12.6)</td>
</tr>
<tr>
<td>SF-36MCS, mean (s.d.)</td>
<td>40.1 (12.2)</td>
<td>40.0 (10.9)</td>
</tr>
</tbody>
</table>

MAQ, Medical Adherence Questionnaire; BPRS, Brief Psychiatric Rating Scale; MCS, mental component summary of medical outcome study SF-36.

Psychopathology

The experimental and control groups did not differ significantly at baseline or at follow-up in terms of psychopathology.
Table 4. Outcomes measures at baseline and follow-up according to treatment group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adherence therapy</th>
<th>Health education</th>
<th>Difference 1 at follow-up (all available cases)</th>
<th>Difference 1 at follow-up (complete cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Baseline mean score (s.d.)</td>
<td>Follow-up mean score (s.d.)</td>
<td>n</td>
</tr>
<tr>
<td>Quality of life (SF-36 MCS)</td>
<td>175</td>
<td>58.34 (10.89)</td>
<td>40.24 (11.97)</td>
<td>192</td>
</tr>
<tr>
<td>Adherence (MAQ)</td>
<td>172</td>
<td>2.98 (1.24)</td>
<td>3.20 (1.07)</td>
<td>194</td>
</tr>
<tr>
<td>Adherence (SAI-C)</td>
<td>173</td>
<td>5.04 (1.39)</td>
<td>5.22 (1.57)</td>
<td>189</td>
</tr>
<tr>
<td>Symptoms (BPRS)</td>
<td>175</td>
<td>45.96 (13.23)</td>
<td>38.11 (11.33)</td>
<td>196</td>
</tr>
</tbody>
</table>

MCS, mental component summary of Medical Outcome Study; MAQ, Medication Adherence Questions are; SAI-C, Schedule for the Assessment of Insight - Compliance item; BPRS, Brief Psychiatric Rating Scale.

1. Difference between adherence therapy and health education groups.
2. Adjusted for site and baseline level.
3. Range is 0-4, higher scores indicating greater treatment adherence.
4. Range is 1-7, higher scores indicating greater treatment adherence.
Discussion

This study showed that adherence therapy had no clear benefit in terms of treatment adherence, psychopathology or quality of life when compared with health education, for people with generally chronic schizophrenia, in general adult mental health services, who showed recent clinical instability.

The study is the largest trial of adherence therapy to be conducted to date, and the sample size allows adequate statistical power to give a clear answer to the research question. High levels of treatment fidelity were achieved for both interventions. The intervention and control interventions were delivered by trained and clinically experienced therapists, and given over an average of seven sessions each which was realistic clinically (Kemp et al., 1998; O’Donnell et al., 2003). The SF-36 MCS is a well-established measure of direct clinical relevance, which has been used in studies of people with schizophrenia (Meijer et al., 2002). Research ratings were conducted in a masked fashion, and high rates of follow-up were achieved.

We shall discuss the interpretation of our findings in terms of the patients referred to and included in the trial, the intervention, the therapists and the timing of assessments.

Over two-thirds of the patients referred to this trial as meeting the inclusion criteria were excluded and not randomised. Almost a third of the patients referred to the study refused to participate, and a further 142 were excluded for other reasons (e.g. they initially agreed to participate and then withdrew, or the research worker was unable to make contact with them). It is possible that this may have biased our sample towards a subsample of more cooperative and adherent people who were unlikely to benefit from adherence therapy.

The sample selection meant that we recruited people who, despite the inclusion criterion of evidence of clinical instability in the previous year, had levels of self-reported treatment adherence which were only moderately impaired (Breen & Thornhill, 1998; Lacro et al., 2002; Nose et al., 2003b). It is therefore possible that a ceiling effect was operating, in which there was little room for further adherence improvement. The subgroup analysis of participants with low treatment adherence, however, suggests there was no beneficial effect of adherence therapy even for the least adherent individuals, compared with health education. In addition, there were low rates of agreement between patient-rated and staff-rated scores of treatment adherence. This confirms previous views that non-invasive measures of treatment adherence are poorly validated, whereas studies using biological assays, such as hair, urine or blood specimens, may be more
valid. However, the latter raise their own problems such as low rates of consent among poorly treatment-adherent patients, and may themselves intervene to change adherence for as long as they take place (Cummings et al., 1984; Matsui et al., 1994; World Health Organization, 2003).

The interventions were offered in a single course of therapy over 5 months or less, with no booster sessions. Although the number of hours of intervention offered was as much as most services in these countries could implement routinely, it is possible that this was an insufficient dose of treatment to be effective, although our data do not suggest even a modest treatment effect of adherence therapy compared with health education as delivered. Effectiveness might have been reduced by the use of therapists not previously known to the participant. This approach is clinically realistic, as it is usual in service studies for structured psychological interventions to be given by therapists not previously known to the patient.

The study extends previous work in this field in several respects. The results are applicable to patients with schizophrenia in a range of general adult treatment settings, rather than the in-patient samples used in previous studies (Kemp et al., 1998; O’Donnell et al., 2003). The results were consistent across all four study sites in different countries, despite some marked differences in patterns of service provision. Our results challenge the conclusions of previous reviews (Nose et al., 2003a; Zygmunt et al., 2002), which have indicated that such forms of adherence therapy show therapeutic promise. Our study also generates hypotheses for future studies, for example that adherence therapy might be effective when delivered by staff who are already members of a multidisciplinary clinical team, or that it might be selectively effective only in those patients who are least treatment adherent. This study therefore provides evidence of a lack of effect for adherence therapy in improving treatment adherence, psychopathology or quality of life of people with schizophrenia. The important challenge of how best to assist people with schizophrenia, who are unwilling or unable to adhere to treatment recommendations, therefore remains unresolved.

Declaration of interest
None. Funding detailed in Acknowledgements.

Acknowledgements
We acknowledge the contributions of the patients, carers and staff who have taken part in the study. The study was funded by a grant from the Quality of Life and Management of Living Resources Programme of the European Union (QLG4-CT- 2001-01734).
References


Adherence therapy for people with schizophrenia


Chapter 3

Medication Adherence in Schizophrenia: Exploring Patients’, Carers’ and Professionals’ views

Martijn J. Kikkert
Aart H. Schene
Maarten W. J. Koeter
Debbie Robson
Anja Born
Hedda Helm
Michela Nose
Claudia Goss
Graham Thornicroft
Richard J. Gray

Published in: Schizophrenia Bulletin vol. 32 no. 4 pp. 786–794, 2006
Abstract

One of the major clinical problems in the treatment of people with schizophrenia is suboptimal medication adherence. Most research focusing on determinants of non-adherence use quantitative research methods. These studies have some important limitations in exploring the decision making process of patients concerning medication. In this study we explore factors influencing medication adherence behavior in people with schizophrenia using concept mapping. Concept mapping is a structured qualitative method and was performed in 4 European countries. Participants were 27 patients with schizophrenia, 29 carers, and 28 professionals of patients with schizophrenia. Five clinically relevant themes were identified that affect adherence: medication efficacy, external factors (such as patient support and therapeutic alliance), insight, side effects, and attitudes toward medication. Importance ratings of these factors differed significantly between professionals and carers and patients. Professionals, carers, and patients do not have a shared understanding of which factors are important in patients’ medication adherence behavior. Adherence may be positively influenced if professionals focus on the positive aspects of medication, on enhancing insight, and on fostering a positive therapeutic relationship with patients and carers.
Introduction

Treatment non-adherence limits the clinical effectiveness of prescribed medication (Haynes et al., 2002). Studies often report that about 50% of patients are treatment non-adherent across a range of disorders (Sabaté, 2003). Different authors, often using a quantitative approach, generally present a range of factors that influence treatment adherence with medication in patients with schizophrenia (Fenton et al., 1997; Hughes et al., 1997; Lacro et al., 2002; Lindstrom & Bingeors, 2000; Oehl et al., 2000). Consistently reported factors include insight, beliefs about treatment, medication side effects, and treatment efficacy (Lacro et al., 2002). Although research has improved our knowledge, adherence rates do not seem to have changed in the last 4 decades (Parkes et al., 1962; Renton et al., 1963).

More recently, interventions focused on non-adherence were developed. Several researchers have proposed that these adherence interventions should focus more on patients’ decision making process (Fenton et al., 1997; Gray et al., 2002). For this, quantitative studies have some, but limited, value because they fail to adequately explain the complexity of medication-taking behavior and are only able to explore a limited number of variables.

Other more qualitative studies have tried to describe adherence behavior by focusing on the subjective responses or experiences of patients with antipsychotic medications and their decision making process in relation to starting, continuing, or stopping medication. Conclusions regarding which factors influence adherence behavior are often based on either patients (Carder et al., 2003; Carrick et al., 2004; Holzinger et al., 2002; Rogers et al., 1998), or professionals’ views (Weiden et al., 1994). These views might differ as we know from research in other fields. Fischer et al. (2002) for instance, showed that patients’, carers’, and professionals’ views concerning outcome and service priorities vary widely. Similar conclusions were drawn by Pope and Scott (2003) studying main reasons to stop medication treatment in patients receiving lithium for an affective disorder. To increase our understanding of medication adherence, we should make use of the valuable expertise and experience of different stakeholder groups. Relying solely on one of these groups might give limited and unsatisfactory results.

The aim of this article is to learn more about (non)adherence in patients with schizophrenia. For this, we will use concept mapping, an established qualitative methodology, to explore factors that influence adherence behavior in patients with schizophrenia. We will include the opinions of patients, carers, and professionals from 4 countries.
Materials and Methods

Setting
This study was conducted in 4 European Union countries: England, Germany, Italy and the Netherlands. It was part of the quality of life following adherence therapy for people disabled by schizophrenia and their carers (QUATRO) study, an international multisite randomized controlled trial assessing the effectiveness of adherence therapy in people with schizophrenia. All study sites gained full approval for the study from the appropriate local research ethics committee.

Participants
Participants were purposively selected out of the 3 stakeholder groups. Patients were meeting International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criterion for schizophrenia. Carers and professionals were, respectively, caring for and working with patients with schizophrenia. All participants needed to be familiar with positive and negative consequences of antipsychotic medication. Therefore, patients needed to have had antipsychotic medication prescribed to them for at least 1 year. Carers and professionals needed to care for or work with patients with schizophrenia for a period of at least 2 years. Participants should have experience with non-adherence. Although the majority of patients and, consequently, their carers go through a non-adherent period during the course of their illness (Fenton et al., 1997; Lieberman et al., 2005), patients were only included if they had been clinically instable in the previous year. This was defined by one or more of the following: at least one hospital admission on clinical (mental health) grounds, a change in antipsychotic medication, increased frequency of planned or actual contact, and indications of clinical instability from relatives, carers, or clinical team. These criteria were considered indicative of non-adherence. Carers were included if they were caring for patients fulfilling inclusion criteria. All participants were further expected to be able to adequately verbalize ideas and thoughts concerning medication adherence and perform the required tasks. A high-quality systematic review indicated that other sociodemographic characteristics have no influence on medication adherence and were therefore not assessed in this study. In order to increase variability of generated statements and generalizability of our results, stakeholder groups were unrelated. All participants gave written informed consent.
Exploring patients’, carers’ and professionals’ views

Procedure
To study variables or factors that (positively or negatively) influence patients, medication adherence behavior concept mapping was used. This method uses group discussions with patients, carers, and professionals to explore factors related to medication adherence. In contrast to other qualitative methods it also comprises a clustering and a prioritizing task. The clustering task allows for the participants to determine which factors or clusters emerge from the data and to what extent these clusters are related to each other. Therefore, compared with other qualitative research methods, the interpretation of the qualitative data might be less susceptible to the hypothesis that researchers may have. The prioritizing task enables, using a quantitative methodology, a comparison of the relative importance stakeholder groups address to the different factors or clusters (Southern et al., 1998; Trochim, 1989).

The procedure was administered by a trained facilitator and cofacilitator in each country. Concept mapping consists of 4 stages. For each stage, a written protocol was provided to make sure all sites followed the same procedure. A copy of the manual can be requested from the first author.

During the first stage, brainstorming sessions were held separately for patients, carers, and professionals in each of the 4 sites. According to Concept Mapping protocol (Severens, 1995), each of these 12 sessions were attended by 6-9 participants and took approximately 1.5 hours. Due to having 12 sessions, our study sample exceeded that of typical concept-mapping studies in which it is between 10 and 20 (Southern et al., 1998). Patients were invited to generate statements focusing on “all factors that influence whether you take or not take antipsychotic medication.” Carers and professionals were asked to generate statements on “all factors influencing the start and continued use of antipsychotic medication.” If patients were inhibited to verbalize their thoughts, they were invited to submit statements in writing or on a one-to-one basis after the session finished.

In the second stage, the number of generated statements had to be reduced to below 100 in order to control the complexity of the following steps. After translation into English, 5 researchers (not involved in the brainstorming sessions) independently reviewed all generated statements. Statements that were not understandable, not singular, too specific, or too abstract were removed. Next, repetitive or overlapping statements were combined into single statements. Finally, in each country, the remaining statements were reviewed and rated by researchers according to how well each related to the topic of medication adherence on a 3-point scale. Those rated least relevant were excluded, leaving...
a final list of statements. These were back-translated into German, Italian, and Dutch. Translations were conducted according to WHO guidelines (Sartorius & Kuyken, 1994).

Finally, in the third and fourth stage of the concept mapping procedure, statements had to be clustered and prioritized. Groups were reconvened, and participants were asked to individually perform the remaining tasks. First, participants had to organize the statements they thought belonged to the same category into clusters (stage three). Clustering could be done in any way the participant thought was logical. Each cluster had to contain between 5 and 40 statements. In addition, individual participants were asked to prioritize the statements (stage four) by sorting them into 5 equal piles, ranging from least to most important. Patients were asked how important each aspect was for their decision to take or not take antipsychotic medication, and carers and professionals were asked to rate how important they thought each aspect was for patients.

Data Analysis
The “Ariadne” software package was used to perform 2 types of analysis (Severens, 1995). The first, a principal component analysis, positions the statements on a concept map. Here the distance between statements represents how often they have been sorted together. Secondly, a cluster analysis grouped statements in clusters. This analysis produced between 2 and 18 clusters. Three researchers independently reviewed each of these 17 computer-generated cluster solutions starting with the simplest (ie, 2 clusters) and ending with the most complex (ie, 18 clusters). The cluster solution that was most understandable and meaningful was selected.

Finally, the relative importance of each cluster was calculated using the prioritizing data. For each participant, the percentage of statements, in each cluster, rated 4 or 5 (important) was calculated. Differences in means were tested using analysis of variance.

Results
Brainstorming sessions were attended by 91 participants (41% male) and the prioritizing and clustering sessions by 89 participants (44% male), approximately equally divided over the 4 sites (Table 1). Results of 4 patients and 1 carer across 3 sites were removed from the data set. These participants indicated they found the clustering and/or prioritizing task too complicated. They also did not profit from support, and their results clearly
demonstrated their lack of understanding (e.g. statements clustered according to card number instead of contents).

On average, patients (n=27; 59% male) had been prescribed antipsychotic medication for a period of 8.6 years (SD=8.2). Carers (n=29; 28% male) had been caring for someone with schizophrenia for an average of 12.6 (SD=7.4) years, and professionals (n=28; 46% male) had been working with patients with schizophrenia for an average of 11.4 (SD=11.1) years.

**Brainstorming**

The 12 brainstorming sessions produced a total of 769 statements relating to factors influencing medication adherence for patients with schizophrenia. Generated statements confirmed that participants were familiar with both positive and negative aspects of antipsychotic medication. Out of all the statements generated by patients, carers, and professionals, respectively, 48%, 42%, and 51% were negative aspects of medication use. Following translation, researchers reached consensus on the elimination of 141 statements not meeting the criteria and combined 424 statements with other statements because they were repetitive or overlapping. The amount of overlap indicated issues reaching a point of saturation. The remaining 204 statements were rated, resulting in a final set of 82 statements, of which approximately equal numbers of statements were found to be produced by the 3 stakeholder groups (56% of statements were mentioned by patients, 56% by carers, and 66% by professionals) and across the 4 sites.

**Clustering**

All statements are presented as dots on the concept map in Figure 1. Their spatial position is based on the clustering results. Statements that the participants sorted together more frequently are positioned closer to each other on the concept map. Consequently, the distances between the statements in Figure 1 indicate to what extent, according to the participants, statements and, consequently, clusters are related to each other. On the basis of these interstatement distances, clusters are defined. A 10-cluster solution was considered to be most understandable and meaningful. A cluster solution with fewer clusters resulted in the loss of clinically relevant clusters.
### Table 1. Participants in Brainstorming Session (BS) and Clustering and Prioritizing Tasks (CP)

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
<th>Professionals</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
<th>BS</th>
<th>CP</th>
<th>BS</th>
<th>CP</th>
<th>BS</th>
<th>CP</th>
<th>BS</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
<td>BS</td>
<td>CP</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>20</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leipzig</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>22</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>24</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verona</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>25</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>27</td>
<td>29</td>
<td>29</td>
<td>32</td>
<td>28</td>
<td>91</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cluster solutions with more clusters were difficult to interpret and resulted in clusters that were considered less meaningful. Clusters that were located close to each other referred to distinct but clinically related topics. Clusters on the map were numbered from left to right and labeled. Examples of statements are shown in Table 2.

![Figure 1. Concept map of factors influencing medication adherence for patients with schizophrenia.](image_url)

The map displays the 82 statements as dots, the 10 clusters, and 5 clinical themes; medication efficacy (m), external factors (e), insight (i), side effects (s), and medication attitudes (a). Distance between statements indicates how often they have been sorted together.
Exploring patients', carers' and professionals' views

Table 2. Cluster number, cluster label and examples of statements

<table>
<thead>
<tr>
<th>Cluster number and label</th>
<th>Examples of statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Professional and non-professional support</td>
<td>“being accurately informed about the potential side effects of the medication”</td>
</tr>
<tr>
<td></td>
<td>“the doctor asking you how you feel, being understanding and</td>
</tr>
<tr>
<td></td>
<td>listening to your concerns”</td>
</tr>
<tr>
<td></td>
<td>“family, friends remind you to take your medication”</td>
</tr>
<tr>
<td></td>
<td>“accessibility of the medication (getting the prescription and</td>
</tr>
<tr>
<td></td>
<td>medication on time)”</td>
</tr>
<tr>
<td>2 Information and involvement</td>
<td>“being given the choice whether or not to take medication”</td>
</tr>
<tr>
<td></td>
<td>“listening to other patients experiences of taking medication”</td>
</tr>
<tr>
<td></td>
<td>“not being told what your diagnosis is”</td>
</tr>
<tr>
<td></td>
<td>“having an understanding of the illness”</td>
</tr>
<tr>
<td>3 Side effect self management</td>
<td>“knowing how to manage the side effects”</td>
</tr>
<tr>
<td>4 Efficacy of medication</td>
<td>“being able to function better due to the medication”</td>
</tr>
<tr>
<td></td>
<td>“the medication is effective in reducing the hallucinations”</td>
</tr>
<tr>
<td></td>
<td>“the medication keeps you from feeling ill/ relapsing”</td>
</tr>
<tr>
<td>5 Insight</td>
<td>“having insight into the illness”</td>
</tr>
<tr>
<td></td>
<td>“accepting that medication is needed”</td>
</tr>
<tr>
<td></td>
<td>“your cultural beliefs fit in with medical advice”</td>
</tr>
<tr>
<td>6 Positive medication attitudes and</td>
<td>“having faith that the medication is effective”</td>
</tr>
<tr>
<td>expectations</td>
<td>“taking medication to avoid going back into hospital”</td>
</tr>
<tr>
<td></td>
<td>“good previous experiences with medication”</td>
</tr>
<tr>
<td>7 Negative medication attitudes</td>
<td>“feeling suspicious about the medication”</td>
</tr>
<tr>
<td></td>
<td>“believe that the medication will harm you”</td>
</tr>
<tr>
<td></td>
<td>“the voices telling you not to take the medication”</td>
</tr>
<tr>
<td></td>
<td>“believe that taking medication is unnatural”</td>
</tr>
<tr>
<td>8 Negative expectations</td>
<td>“feeling better when you stop taking it”</td>
</tr>
<tr>
<td></td>
<td>“a traumatic experience the first time you were given medication”</td>
</tr>
<tr>
<td></td>
<td>“preferring the symptoms to the side effects”</td>
</tr>
<tr>
<td>9 Social aspects of extrapyramidal side effects</td>
<td>“being embarrassed about movement disorders because people can see it”</td>
</tr>
<tr>
<td>10 Side effects</td>
<td>“obesity / weight gain due to the medication”</td>
</tr>
<tr>
<td></td>
<td>“sexual problems due to the medication”</td>
</tr>
<tr>
<td></td>
<td>“feeling tired due to the medication”</td>
</tr>
</tbody>
</table>
Table 3. Mean Percentage of Items Per Cluster Rated 4 or 5 (important), Stratified by Patients (Pa), Carers (Ca) and Professionals (Pr)

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Number of statements</th>
<th>Patients (n=27) (Pa)</th>
<th>Carers (n=29) (Ca)</th>
<th>Professionals (n=28) (Pr)</th>
<th>(p&lt;0.05)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Efficacy of medication</td>
<td>9</td>
<td>54 (20)</td>
<td>64 (23)</td>
<td>40 (21)</td>
<td>5</td>
</tr>
<tr>
<td>3 Side effect self management</td>
<td>1</td>
<td>48 (51)</td>
<td>34 (48)</td>
<td>39 (50)</td>
<td>6/7</td>
</tr>
<tr>
<td>5 Insight</td>
<td>4</td>
<td>44 (19)</td>
<td>54 (21)</td>
<td>52 (23)</td>
<td>1</td>
</tr>
<tr>
<td>1 Professional and non-professional support</td>
<td>21</td>
<td>42 (12)</td>
<td>52 (16)</td>
<td>37 (15)</td>
<td>8/9</td>
</tr>
<tr>
<td>6 Positive medication attitudes and expectations</td>
<td>12</td>
<td>42 (14)</td>
<td>36 (14)</td>
<td>36 (12)</td>
<td>10</td>
</tr>
<tr>
<td>10 Side effects</td>
<td>12</td>
<td>40 (21)</td>
<td>28 (19)</td>
<td>46 (24)</td>
<td>2</td>
</tr>
<tr>
<td>2 Information and involvement</td>
<td>4</td>
<td>39 (22)</td>
<td>36 (21)</td>
<td>37 (24)</td>
<td>8/9</td>
</tr>
<tr>
<td>8 Negative expectations</td>
<td>5</td>
<td>36 (22)</td>
<td>32 (18)</td>
<td>43 (22)</td>
<td>3</td>
</tr>
<tr>
<td>7 Negative medication attitudes</td>
<td>13</td>
<td>30 (13)</td>
<td>25 (16)</td>
<td>42 (14)</td>
<td>4</td>
</tr>
<tr>
<td>9 Social aspects of extrapyramidal side effects</td>
<td>1</td>
<td>22 (42)</td>
<td>28 (45)</td>
<td>39 (50)</td>
<td>6/7</td>
</tr>
</tbody>
</table>

¹ For each participant the percentage of statements rated 4 or 5 (important) in each cluster was calculated. The mean percentages over raters are reported in the table (e.g. patients rated on average 54% of the 9 statements in Cluster 4 as important).
² Rank order of clusters based on mean percentage.
³ ANOVA multiple comparisons (Tukey HSD).
Prioritizing

Table 3 shows the average percentages of statements in each cluster which were rated as important by patients, carers, and professionals. There was general agreement between patient and carer ratings of the relative importance of each cluster. However, there were a number of significant differences between patient and/or carer and professional ratings. The latter rated the efficacy of medication (cluster 4) as significantly less important and negative medication attitudes and beliefs (cluster 7) as more important cluster than carers and patients. The professional and nonprofessional support cluster (cluster 1) was rated as less important and the side effect cluster (cluster 10) as more important by professionals compared with carers.

Discussion

In this study, we used concept mapping to explore “all factors influencing the start and continued use of antipsychotic medication” comprehensively by including 3 different and independent groups of stakeholders, all familiar with schizophrenia for many years, from 4 different countries. In this discussion, we will interpret our results and describe its clinical and research implications.

Content and spatial location of the clusters are used to interpret the concept map and identify clinically relevant themes (figure 1). Statements, except those in clusters 1, 2, and 5, referred to perceived advantages or disadvantages of medication use and were divided into 3 themes; right in the middle we identified medication efficacy (cluster 4), surrounded clockwise by issues related to side effects (clusters 3, 9, and 10) and attitudes (clusters 6, 7, and 8). Although closely located, due to the content of the statements, insight (cluster 5) is considered a separate theme in this concept map. The remaining clusters 1 and 2, both distant from the other clusters, referred to external factors.

Efficacy

Cluster 4 represents the subjective efficacy of medication due to a relief of symptoms. Patients and carers both rated this cluster as the most important for medication adherence. This is in line with authors showing that the beneficial effects of medication on well-being have a major influence on adherence behavior (Adams & Howe, 1993; Freudenreich et al., 2004; Rettenbacher et al., 2004; Rogers et al., 1998). Accordingly, studies showed that patients who have the experience of their medications having no benefit, not being
helpful, or being ineffective and unnecessary more often do not comply (Gasquet et al., 2005; Hertz & Melville, 1980; Lieberman et al., 2005; Nelson et al., 1975; Ruscher & Mazmanian, 1997).

Professionals in our study surprisingly rated efficacy significantly less important than patients and carers. Professionals should (re)value efficacy as more important and are advised to closely monitor and discuss medication efficacy, from the patients perspective, as well as the perceived degree (or absence) of adverse symptoms, in order to understand and manage medication adherence.

External Factors
Clusters 1 (professional and nonprofessional support) and 2 (information and involvement) contain statements that refer to factors which contribute to establishing favorable conditions for adherence behavior by different means, such as increasing patients understanding, alliance, or trust with clinician; social support; and reduction of practical medication barriers. These factors can be labeled as external because they refer to influences from outside by important others, not directly under the control of the patient. Both clusters adjoin but are distant from the other clusters in the concept map, suggesting that they are not strongly related to the other clusters.

Nonprofessional (or professional) support, information, and involvement have been studied as important predictors of treatment adherence in people with schizophrenia (Agarwal et al., 1998; Frank & Gunderson, 1990; Kelly et al., 1990; Olfson et al., 2000; Sullivan et al., 1995). Some psychological approaches enhancing treatment adherence have placed them at the heart of the intervention (Gray et al., 2002; Nose et al., 2003), which is in accordance with our finding that patients and, in particular, carers rated support, information, and involvement as rather important. So far, compliance interventions focused on education and in- formation have not been found to be effective in improving adherence (Gray et al., 2002). This might explain why professionals rate these issues as less important (Paccaloni et al., 2004).

Insight
The map shows that insight (cluster 5) is closely related to positive expectations and attitudes toward the use of antipsychotic medication (cluster 6). All groups rated the insight cluster as important, which is in line with studies describing insight as a strong predictor of medication adherence (Bartko et al., 1988; Kampman et al., 2002; Lacro et al., 2002; Marder et al., 1983). This effect of insight has been addressed to an improvement
in understanding illness and medication consequences. The spatial locations of clusters 4 and 5 show that a clear relation with medication efficacy (cluster 4) is, however, lacking. Insight seems less important for appreciating subjective symptom relief due to medication than for indirect treatment benefit such as hospitalization or coercion. A patient who uses his or her medication because it improves well-being does not necessarily need to have insight into the disorder. This might also explain why Nageotte et al. (1997) found that 38% of patients were compliant despite the fact that they did not believe themselves to be ill.

**Side Effects**

Statements related to side effects that referred to objective perceived side effects of medication (cluster 10), the social aspects of side effects (in particular, movement disorders) (cluster 9), and self-management of side effects (cluster 3). The latter cluster referred to a positive characteristic, which patients rated as very important.

Medication side effects have often been associated with non-adherence (Rettenbacher et al., 2004; Fleischhacker et al., 1994; Weiden et al., 1986), although a consistent correlation between the presence or severity of these and the degree of adherence could not be found in a recent systematic review (Lacro et al., 2002). Side effects might not be the most important factor in determining adherence behavior (Adams & Howe, 1993; Fleischhacker et al., 1994; Marder et al., 1983; Mutsatsa et al., 2003; Nageotte et al., 1997; Weiden et al., 1986) and may have less impact than the efficacy of medication (Buchanan, 1992; Kampman et al., 1999; Linden, 1987) or expressed beliefs concerning susceptibility to relapse (Nelson et al. 1975). Our results confirm this and show that patients and carers prioritized side effects relatively low compared with positive medication aspects. In comparison, professionals prioritized side effects as the second most important cluster and, consequently, seem to overestimate the relative importance of side effects on adherence behavior. Although discussing side effects is essential during treatment because it is the most important disadvantage of medication use for patients, professionals might, however, understand the relative importance better in relation to other factors such as perceived advantages of medication, and coping strategies are taken into account.

**Medication Attitudes**

Finally, the clusters 6, 7, and 8 represent not only beliefs and attitudes concerning medication but also previous experiences with these agents. Statements of cluster 6 represent positive aspects or benefits of medication (e.g. reducing adverse consequences of
being ill such as hospitalization or coercion). Clusters 7 and 8 refer to negative attitudes and beliefs concerning medication and feeling better without medication. Different authors have stressed that both attitudes to medication and side effects have to be openly discussed with patients (Adams & Howe, 1993; Chan, 1984).

**Prioritizing**

Patients were instructed to rate the importance of statements based on their own experiences. Carers and professionals rated statements based on their observations of, and experiences with, patients. Two points are of interest. First, professionals, in general, rated negative aspects (side effects and negative medication attitudes) as more important than patients and carers, while patients and carers, more than professionals, stressed the positive aspects (efficacy and support). Secondly, the fact that carers and patients in our study prioritized clusters in a similar way indicates that carers can be well aware of patients' considerations concerning medication. Our results underline that professionals need to carefully assess patients' beliefs and experiences of treatment with antipsychotic medication in order to understand patients' perspectives. They also, if possible, should involve carers in treatment planning and evaluation. Not only will it improve patients' support, which was found to be an important issue, but also carers might be able to provide professionals with valuable information.

**Models for Understanding Adherence**

Our results correspond with the Health Belief Model, often used to explain adherence behavior (Becker & Maiman, 1975). According to this model, individuals' readiness to take action depends on their “perceived seriousness and susceptibility of illness” (such as belief in the accuracy of the diagnosis and subjective vulnerability to relapse) and “perceived benefits and barriers of medication use.” This is reflected in the themes insight, efficacy of medication, side effects, and medication attitudes. These themes demonstrate patients' considerations concerning advantages and disadvantages of medication use. Contrary to the Health Belief Model, we did not find perceived illness severity and medication benefit to be separate themes (e.g. “the medication is effective in reducing the hallucinations”).

We argue that patients are most motivated to use medication if they experience direct beneficial effects such as a reduction of adverse symptoms and/or because they realize it has indirect, long-term benefits such as preventing relapse. Although illness insight is not clearly positioned in the Health Belief Model, our results seem to indicate that insight
is particularly important for patients to understand and appreciate the indirect benefit of medication. Therefore, patients who experience no direct subjective benefit from medication are most likely to benefit from psychoeducation or brief cognitive behavioral therapy to enhance insight (Turkington & Kingdon, 2000). The external factors show us that there are a number of factors which are not under patient control, but which might affect adherent behavior. These factors include the alliance between carers and their key worker, the information given to patients, actively involving patients in treatment, and practical medication barriers. These factors are similar to “cues to action” in the Health Belief Model. Clinicians should therefore make every effort to inform patients concerning their illness and medication, increase patients understanding, their alliance with their patient, the provision of social support, and reduction of practical medication barriers.

Results of this study might be useful in screening patients with schizophrenia. Discussing the topics that were found in this study should help professionals to detect patients likely to be non-adherent.

Limitations
This study has some limitations. First, it should be noted that results are limited to issues which were involved in the decision making process of patients. Therefore, factors which have been found to correlate with adherent behavior such as sociodemographic characteristics and previous non-adherence are not reported in this study. Patient reports are limited to issues they are aware of and they are prepared to mention.

We included a heterogeneous sample of 91 participants. Although this is in accordance with the concept map protocol, this number is relatively low for analysis of between-group differences. However, differences were significant even with this low numbers per group.

Patients were selected if they had been clinically instable for some period of time within the previous year. This inclusion criterion might have influenced our results because these patients may have stressed the importance of factors that negatively influence medication adherence.

Conclusion
In conclusion, this study has learned that concept mapping is a useful tool in exploring relevant issues for patients' decision to use or not use prescribed antipsychotic medication.
The findings suggest that patients, carers, and professionals were able to identify and weigh up the factors that influence treatment adherence. Our findings provide a comprehensive overview of all relevant issues and how they relate to one another. Clusters could be organized into 5 clinically relevant themes: efficacy of medication, external factors, insight, side effects, and medication attitudes.

The discrepancies between patients’ and professionals’ views on the importance of clusters should be further explored in future research. Professionals need to be aware of patients’ considerations concerning their antipsychotic medication, in particular positive aspects of medication use, in order to provide effective support and guidance. Consequently, strengthening mutual understanding and alliance could improve adherence or make it easier to come to agreements on individually tailored medication regimens. Therefore, closing the gap between patients’ and professionals’ views on the importance of medication-related aspects seems vital.

Acknowledgments

The QUATRO study is a multicentre collaboration between the Health Services Research Department, Institute of Psychiatry, King’s College London; the Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy; the Department of Psychiatry, Leipzig University, the Department of Psychiatry II, Ulm University, Germany, and the Department of Psychiatry, Academic Medical Center, University of Amsterdam, the Netherlands. The study was funded by a grant from the Quality of Life and Management of Living Resources Programme of the European Union (QLG4-CT-2001-01734). The views expressed in this article are those of the authors and not necessarily those of the funders. We also wish to acknowledge the contributions of the patients, carers, and staff who have taken part in this study. We would like to acknowledge the contributions to this study of the following colleagues—Amsterdam site: Aart Schene, Annemarie Fouwels, Martijn Kikkert, Maarten Koeter, and Carin Meijer; Leipzig/Ulm site: Thomas Becker, Matthias Angermeyer, Anja Born, Anne Gießler, Hedda Helm, and Bernd Puschner; London site: Jonathan Bindman, Jayne Camara, Anthony David, Kevin Gournay, Richard Gray, Martin Knapp, Morven Leese, Paul McCrone, Mauricio Moreno, Anita Patel, Debbie Robson, Graham Thornicroft, and Ian White; and Verona site: Michele Tansella, Francesco Amaddeo, Corrado Barbui, Lorenzo Burri, Daniela Celani, Doriana Cristofaro, Claudia Goss, Antonio Lasalvia, Giovanna Marrelli, Mariangela Mazzi, Michela Nose’, Mirella Ruggeri, and Marta Solfa. We also like to thank Carin Meijer, Emile Barkhof, and Udo Nabitz for their contributions to this article.
Exploring patients’, carers’ and professionals’ views

References


Exploring patients’, carers’ and professionals’ views


Chapter 4

Assessment of Medication Adherence in Patients with Schizophrenia. The Achilles Heel of Adherence Research

Martijn J. Kikkert
Corrado Barbui
Maarten W. J. Koeter
Anthony S. David
Morven Leese
Michele Tansella
Anne Gießler
Bernd Puschner
Aart H. Schene

Published in: Journal of Nervous and Mental Disease 2008;196: 274–281.
Abstract

Measuring medication adherence in patients with schizophrenia is difficult and lacks a gold standard. Consequently, a great number of different methods and instruments have been proposed. Although it has been assumed that they all measure medication adherence, this study demonstrates that instruments differ significantly. Using data from an international multisite study (N=329), we found that 3 questionnaires, designed to measure medication adherence and typical for instruments used in studies in patients with schizophrenia, do not agree in labeling patients as non-adherent. Further, they seem not to measure the same trait, are related to different established risk factors of non-adherence, and are only weakly related to these established risk factors of non-adherence. If these results are representative of the validity of other measures used in adherence research, this may have serious consequences for the interpretation of and explanations for discrepancies found in the literature. Researchers should be aware of this problem and continue to combine objective and subjective methods in the hope of increasing the reliability and validity of measures of adherence.
Introduction

Non-adherence or poor adherence is a major concern in the treatment of chronic conditions such as schizophrenia. It places patients at risk for exacerbation of symptoms, care needs, and hospitalization with major social and economic consequences (Ayuso-Gutierrez & del Rio Vega, 1997; Weiden & Olfson, 1995). Although this has been known for several decades and studied extensively, clinicians still face a large number of non-adherent patients and do not make consistent use of evidence based adherence interventions (Ostenberg & Blaschke, 2005).

A vast literature has been published on this topic and a wide variety of instruments and methods are used to measure medication adherence (Velligan et al., 2006). It is unknown how these different measures of adherence affect study results. They at least make comparisons between studies problematic. This is particularly relevant in studies that try to determine (non)adherence rates, detect risk factors for non-adherence, and establish efficacy of adherence interventions. Not surprisingly non-adherence rates reported in studies vary considerably. Cramer and Rosenheck (1998) found non-adherence rates ranging from 24% to 90%. Lacro et al. (2002) in their systematic review found non-adherence rates ranging from 4% to 72% while others concluded that a mean of 40% to 60% of patients with schizophrenia are believed to not adhere to their prescribed medication regimen (Nose et al., 2003; Young et al., 1986).

Systematic reviews on risk factors for non-adherence in patients with schizophrenia show a consistent influence of certain variables (insight and therapeutical alliance, for example), while study results for other variables such as age, gender, marital status, duration of illness, etc., are too inconsistent to draw a conclusion regarding their influence on adherence behavior (Lacro et al., 2002; Oehl et al., 2000; Perkins, 2002; Pinikahana et al., 2002). Although it is unknown what causes these discrepancies, it has been argued that they might be attributed to different methods and instruments used to measure adherence, a problem which is not restricted to adherence measurements in schizophrenia (Nichol et al., 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006).

Although the concept of medication adherence, defined as the degree to which medication is taken as prescribed, is relatively simple, measuring adherence behavior clearly is not. Adherence assessments can be divided in objective and subjective measures. Objective measures are blood, urine or hair concentrations, pharmacy records and electronic pill counts. Subjective measures rely on assessments made by the patient or a closely involved person such as a clinician, nurse, or relative using questionnaires or
interviews. In self-reports, patients are asked to rate their own adherence behavior or
answer questions directly or indirectly related to medication use.

Reports from others usually rely on observed behavior such as clinical response,
medication refusal, missed doses, regularity of visits, etc. Some studies combine a number
of these methods to assess adherence rates. Lam et al. (2003) compared 3 different
measures of adherence in patients with schizophrenia (plasma levels, pill count, and self-
report) and found a remarkable poor agreement ranging from 0.17 to 0.28. In this study
we will focus on the agreement of 3 adherence measures which are more similar in their
approach.

In schizophrenia research approximately 75% of all studies rely on subjective measure
(Velligan et al., 2006). Objective measures are often too complex, invasive, costly, or
time-consuming. These subjective measures are, however, often poorly described, not
validated, and are susceptible to error, misinterpretation, or distortion (Kane, 1983;
Nicol et al., 1999; Nose et al., 2003; Otterberg & Blaschke, 2005; Velligan et al., 2006).
Consequently, for the majority of instruments it is not known how validly they measure
medication adherence. In the literature study, results are nevertheless interpreted as if
they measured the same concept. If, however, the different instruments measure different
concepts, this would partly explain between-study variability in findings and conclusions.

In this article, we will explore 3 subjective adherence instruments (1 clinician rated
and 2 patient rated) frequently used in adherence studies in schizophrenia. We will
examine: (a) to what extent these instruments agree in labeling patients as non-adherent,
(b) to what extent these instruments measure the same concept, and (c) how they are
related to established risk factors for non-adherence.

Methods

Study Design
This study uses baseline data from the Quality of Life Following Adherence Therapy for
People Disabled by Schizophrenia and their Carers (QUATRO) study, an international
randomized controlled trial assessing the efficacy of Adherence Therapy in patients with
schizophrenia.

All patients that fulfilled the inclusion criteria and gave written informed consent
completed a number of questionnaires and were interviewed before randomization and
start of the adherence intervention (Gray et al., 2006).
Participants
Patients were recruited in 4 European cities: London (United Kingdom), Verona (Italy), Leipzig (Germany), and Amsterdam (The Netherlands). Inclusion criteria were (a) clinical diagnosis of schizophrenia according to ICD-10 criteria, confirmed by a research diagnosis of schizophrenia using the Item Group checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (Wing et al., 1990), (b) in need of maintenance antipsychotic treatment for at least one year after entry into the study, and (c) evidence of clinical instability in the previous year, defined by one or more of the following: at least one hospital admission on clinical (mental health) grounds, a change in antipsychotic medication, increased frequency of planned or actual contact, indications of clinical instability from relatives, carers or clinical team. Exclusion criteria were (a) moderate or severe learning disabilities, (b) organic brain disorders, and (c) treatment by forensic psychiatric services.

Adherence Instruments
Subjective measures differ greatly among studies. Often unspecified and ad hoc measures are used (Velligan et al., 2006). Only a limited number of standardized and established instruments are available. None of them is considered a (gold) standard. We selected 3 of these instruments for which some methodological evidence for the validity of these measures exists. The measures are typical for instruments used in studies in patients with schizophrenia and represent the way adherence is often operationalized: a self-report questionnaire (Medication Adherence Questionnaire, MAQ) (Morisky et al., 1986), a clinician rating of adherence (the Compliance Rating Scale, CRS) (Kemp & David, 1996), and a selfreport questionnaire on drug attitudes (Drug Attitude Inventory, DAI) (Hogan et al., 1983).

The MAQ consists of 4 yes/no questions and addresses ways in which patients may fail to take their prescribed medication: forgetting, carelessness, stopping the drug when they feel better, and/or stopping the drug because they believe it makes them feel worse (Morisky et al., 1986). A higher score on the MAQ indicates less problems with medicine taking and good adherence behavior. The MAQ is applied to medical conditions including treatment for high blood pressure. Good internal consistency (α=0.61) have been demonstrated in a sample of 400 randomly selected patients who had been tested for high blood pressure. A factor analysis confirmed the unidimensionality of the scale. In a 5-year follow-up a significant positive correlation of 0.58 was found between the level of compliance measured by the MAQ and blood pressure control indicating good
validity of the MAQ (Morisky et al., 1986). In a study by Thompson et al. (2000) serum concentrations of a mood stabilizing drug (N=17) correlated 0.36 with the MAQ. George et al. (2000) compared the MAQ with the Medication Event Monitoring System (MEMS) in patients using tricyclic antidepressants and found sensitivity scores ranging from 72% to 84% and specificity scores ranging from 55% to 74%, depending on MEMS cut off level. Shalansky et al. (2004) concluded that the MAQ was a reasonable instrument in detecting non-adherent patients after comparing the MAQ with prescription refill data in patients using chronic cardiovascular medications (Shalansky et al., 2004).

The CRS is used to rate medication adherence on a 7-point scale. The CRS is scored by key workers. Complete refusal is scored 1, patients who partially refuse score 2, patients who reluctantly or passively accept treatment score 3, 4, or 5, and patients who moderately or actively accept treatment score 6 or 7. For each score a brief description of adherence behavior is provided in the questionnaire. Kemp et al. (1998) who described this instrument first, found a strong correlation between the CRS and self-reported measures of attitudes to drug treatment (DAI) (r=0.68). Byerly et al. (2005) however concluded that the clinicians’ ratings dramatically underestimated antipsychotic non-adherence. None of the patients who were determined as non-adherent according to MEMS data were detected by the CRS.

The DAI is a self-report measure comprising 10 yes/no statements reflecting patients’ experiences, attitudes, and beliefs about medication. Patients are asked to decide whether statements apply to them. Higher scores indicate a more positive attitude toward, and more positive experiences with medication. Hogan et al. (1983) validated the original 30-item DAI questionnaire on ratings made by the therapists about patients’ medication-taking behavior. Ten items were selected as having maximal group discrimination and classified 68% of the patients correctly as adherent or non-adherent compared with therapist’s ratings. Thompson et al. (2000) reported a correlation of 0.65 with serum concentrations of a mood stabilizing drug (N=17) and the DAI.

Risk Factors

We selected variables that have been identified as risk factors of non-adherence in at least 3 of 5 systematic reviews published between 1997 and 2002 (Fenton et al., 1997; Lacro et al., 2002; Oehl et al., 2000; Perkins, 2002; Pinikahana et al., 2002), and for which data were available. Given the attention they received in previous studies and their relevance for this topic, we decided to include side effects and medication characteristics in the analysis as well, although reports on their influence on adherence behavior are equivocal.
Assessment of medication adherence

Included risk factors cover the following domains: (a) patient-related factors, (b) perceived beneficial medication effects, (c) psychopathology and functioning, (d) illness insight, (e) medication side effects, (f) medication type and dose, and (g) complexity of medication regimen.

Patient-Related Factors
Living situation was assessed with the European version of the Client Sociodemographic and Service Receipt Inventory (CSSRI-EU) (Chisholm et al., 2000). As an indicator of medication supervision and degree of family involvement, items of the Involvement Evaluation Questionnaire (IEQ-EU) were used (Schene et al., 1998; van Wijngaarden et al., 2000), assessing respectively how often the family ensured that the required medicine was taken, and their average weekly telephone or personal contact with the patient over the past 4 weeks. The IEQ-EU was completed by 166 carers, identified by patients. Remaining patients either did not consent to use carers information or could not identify a carer.

Perceived Beneficial Medication Effects
The sum score of 4 DAI items was used as an indicator of perceived beneficial effects. Selected items reflect feeling more relaxed, more normal, and having clearer thoughts when using medication and the feeling that medication can prevent one from getting sick.

Psychopathology and Level of Functioning
Level of psychopathology was assessed using the expanded Brief Psychiatric Rating Scale (BPRS-E). The BPRS-E consists of 24 items measuring the following dimensions: positive symptoms, negative symptoms, depression/ anxiety, and disorganization (Ruggeri et al., 2005). A higher score indicates more and more severe symptoms. Depression was assessed using the Calgary Depression Scale (CDS). The CDS is specifically developed for assessing depression in patients with schizophrenia by a 9-item structured interview (Addington et al., 1992). A high summary score on the CDS indicates depression. Level of functioning was assessed using the Global Assessment of Functioning (GAF) (Jones et al., 1995). A low score on the GAF indicates poor functioning. Two items from the Involvement Evaluation Questionnaire (IEQ-EU) were used as an indicator of substance abuse (van Wijngaarden et al., 2000). On these items carers indicated how often, during the past 4 weeks, they guarded the patient from using too much alcohol, and illegal drugs.
Insight
Insight was assessed with the expanded version of the Schedule for Assessment of Insight (SAI-E). The SAI-E is a semistructured interview measuring 3 dimensions of insight: awareness of illness, relabeling of psychotic symptoms, and treatment compliance (David, 1990; Kemp et al., 1998). Awareness of illness and relabeling of psychotic symptoms are based on self-report items. The subscale “treatment compliance” comprises 1 self-report item and 2 items in which the clinician rates the extent to which the patient accepts treatment and whether the patient unprompted asks for treatment. These clinician rated items were, however, excluded because they overlap with the concept of adherence. The remaining self-report item, in which the patient is asked whether he thinks his condition, or the problem resulting from it, warrants treatment is used as an indicator of awareness of need for treatment. Higher scores indicate a higher level of insight.

Medication Side Effects
The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) was used to measure side effects consisting of 51 items (Day et al., 1995). Day et al. (1995) validated the LUNSERS and found that it had a good test-retest reliability (r=0.811, p<0.001) and concurrent validity against the UKU side effect rating scale for psychotropic drugs (UKU) (r=0.828, p<0.001).

Medication Type and Dose
Information on type and dosage of prescribed antipsychotic medication was provided by the patient’s clinician. The prescribed daily dosage (PDD) was expressed as the proportion of the Defined Daily Dose (DDD) which is the international unit of drug utilization approved by the World Health Organization (WHO, 2003).

Complexity of Medication Regimen
Total number of psychotropic drugs prescribed to a patient and how often they needed to be taken each day were used as an index of the complexity of the medication regimen.

Data Analysis
Criteria to label patients as either adherent or non-adherent were derived from the literature. For the MAQ, patients with a score ≤3 are defined as non-adherent (George et al., 2000; Morisky et al., 1986; Roth & Ivey, 2005). For the CRS, patients with a score ≤4 are considered non-adherent (Byerly et al., 2005; Kemp & David, 1996; Kemp et al.,...
Assessment of medication adherence

1998; Mutsatsa et al., 2003). For the DAI, the sum of the negative items is subtracted from the sum of the positive items. If the resulting score is less than or equal to 0, patients are considered to be non-adherent (Hogan et al., 1983).

In the remaining analysis we used continuous adherence scores to increase statistical power. Associations between interval and dichotomous variables were assessed with Pearson product moment correlation. For ordinal variables a Spearman rank correlation was used. Correlations of subjectively rated variables were calculated using residual scores corrected for site differences. In Table 3 the level is set at 0.05. To partly correct for the increased family wise error in Table 4 as a result of multiple testing, we set the level at 0.005.

Potential risk factors for non-adherence were categorized into domains. For each domain the relation between each risk factor and the 3 adherence instruments was presented. The overall variance in adherence scores explained by all risk factors within each domain, and the overall variance explained by all risk factors that were significant at p≤0.005, were calculated and reported as the $R^2$ of a linear regression model.

**Results**

In the QUATRO study sample (N=409) eighty patients (20%) were in an inpatient setting (psychiatric or medical ward or in a 24-hour staffed overnight facility). These patients are excluded for further analysis to improve uniformity of our sample and to eliminate the effect of staff supervision on medication intake, which is often common practice in inpatient settings. Social and demographic characteristics are given in Table 1. Our sample (N=329) was predominantly middle aged, single, unemployed, male, and chronic, which is typical for patients under the care of community mental health teams.

Of 284 patients, for which a score on all 3 instruments was available, overall non-adherence rates for the MAQ, CRS, and DAI are 54.9%, 20.4%, and 14.1% respectively. Full consensus among the 3 instruments in labeling patients non-adherent is reached in approximately 4% of the patients. For the remaining 96% of the patients the 3 instruments give different outcomes, 117 patients (41.2%) are non-adherent according to only 1, and 52 patients (18.3%) are non-adherent according to 2 of the 3 instruments (Table 2).
Table 1. Sociodemographic, clinical, and adherence characteristics of patients (n=329)

<table>
<thead>
<tr>
<th>Sociodemographic characteristics</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.3</td>
<td>11.6</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>185</td>
<td>56</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity Caucasian</td>
<td>254</td>
<td>77</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single / unmarried</td>
<td>285</td>
<td>87</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid or self employed</td>
<td>56</td>
<td>17</td>
<td>325</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (with/without children)</td>
<td>156</td>
<td>47</td>
<td>328</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years antipsychotic(s) prescribed</td>
<td>13.6</td>
<td>9.9</td>
<td>301</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Characteristics

| BPRS; positive symptom subscale | 12.2| 5.5 | 327  |     |     |
| BPRS; negative symptom subscale| 10.7| 4.0 | 327  |     |     |
| BPRS; depression/anxiety subscale| 13.1| 5.5 | 327  |     |     |
| BPRS; disorganization subscale  | 12.5| 3.7 | 327  |     |     |

Adherence

| MAQ sum score (0-4) | 2.89| 1.23| 319  |     |     |
| CRS (1-7)           | 5.37| 1.34| 304  |     |     |
| DAI sum score (0-10) | 6.71| 2.21| 312  |     |     |

Although all 3 instruments were developed and used to detect non-adherent patients, Table 2 and Figure 1 demonstrate the limited overlap in patients identified as non-adherent and show the differences in non-adherence rates. It is possible that this is due to using dichotomous scores that are based on different cut off criteria or interpretations of non-adherence. We therefore performed a Pearson product moment correlation to examine the relation between the total scores on the instruments (Table 3).

Again we found a poor overlap between the 3 instruments. The highest correlation coefficient was found between the CRS and the DAI (r=0.30; p<0.05), which is approximately equivalent to 9% explained variance. The low correlations do not exclude the possibility that one of these instruments is a valid measure of adherence behavior. In this case this instrument should, however, be related to established risk factors for medication non-adherence (Table 4).

All correlation coefficients of the 3 instruments with established risk factors were relatively low. Risk factors for which we found a statistically significant (though modest)
Assessment of medication adherence

correlation were perceiving little or few positive effects of the medication, severity of depressive/anxiety symptoms, lower level of functioning, and poor insight.

Table 2. Patients labeled non-adherent according to the MAQ, CRS, DAI, or a combination of these instruments (n=284)

<table>
<thead>
<tr>
<th>Non-adherent according to</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>one instrument</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>97</td>
<td>34.2</td>
</tr>
<tr>
<td>CRS</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>DAI</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>two instruments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ – CRS</td>
<td>33</td>
<td>11.6</td>
</tr>
<tr>
<td>MAQ – DAI</td>
<td>15</td>
<td>5.3</td>
</tr>
<tr>
<td>CRS – DAI</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>three instruments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ – CRS – DAI</td>
<td>6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Figure 1. Venn diagram representing the proportional overlap of the instruments in labeling patients non-adherent according to the MAQ, CRS, and DAI. Numbers present the size of each area in percentages (in contrast to Table 2 the denominator of the percentages in this diagram are the 180 patients labeled by at least one of the instruments as non-adherent).
Table 3. Correlation coefficients\(^1\) for adherence measures (n=329)

<table>
<thead>
<tr>
<th></th>
<th>MAQ n</th>
<th>CRS n</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAQ</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CRS</td>
<td>0.25</td>
<td>295</td>
</tr>
<tr>
<td>DAI</td>
<td>0.21</td>
<td>304</td>
</tr>
</tbody>
</table>

\(^1\) Boldface indicates p<0.05

Table 4. Correlation coefficients of risk factors with adherence measures\(^a\) and explained variance (R\(^2\)) for each domain and significant related variables (n=329)

<table>
<thead>
<tr>
<th></th>
<th>MAQ n</th>
<th>CRS n</th>
<th>DAI n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living situation (alone / with others)</td>
<td>-0.10</td>
<td>-0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Medication supervision by carer (IEQ-EU)</td>
<td>-0.06</td>
<td>-0.19</td>
<td>0.15</td>
</tr>
<tr>
<td>Family involvement (IEQ-EU)</td>
<td>0.17</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>R(^2) for patient-related factors(^b)</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Perceived beneficial medication effect(^c)</td>
<td>0.11</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>R(^2) for perceived beneficial medication effect</td>
<td>0.01</td>
<td>0.05</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Psychopathology and functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; positive symptom subscale</td>
<td>-0.13</td>
<td>-0.08</td>
<td>-0.12</td>
</tr>
<tr>
<td>BPRS; negative symptom subscale</td>
<td>-0.02</td>
<td>-0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>BPRS; depression/anxiety subscale</td>
<td>-0.16</td>
<td>-0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>BPRS; disorganization subscale</td>
<td>-0.02</td>
<td>-0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>GAF</td>
<td>0.13</td>
<td>0.24</td>
<td>0.00</td>
</tr>
<tr>
<td>Substance abuse (IEQ-EU)</td>
<td>-0.12</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>R(^2) for psychopathology and functioning(^d)</td>
<td>0.04</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Illness insight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAL-E; symptom relabelling and hypothetical contradiction</td>
<td>0.05</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>SAL-E; illness awareness</td>
<td>0.05</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>SAL-E; awareness of need for treatment</td>
<td>0.19</td>
<td>0.33</td>
<td>0.32</td>
</tr>
<tr>
<td>R(^2) for illness insight</td>
<td>0.03</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Medication side effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLUNSER; total score</td>
<td>0.03</td>
<td>-0.02</td>
<td>-0.16</td>
</tr>
<tr>
<td>R(^2) for medication side effects</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Assessment of medication adherence

Table 4. Continued

<table>
<thead>
<tr>
<th>Medication type and dose</th>
<th>MAQ n</th>
<th>CRS n</th>
<th>DAI n</th>
</tr>
</thead>
<tbody>
<tr>
<td>type of antipsychotic (atypical/classic)</td>
<td>-0.08</td>
<td>292</td>
<td>0.03</td>
</tr>
<tr>
<td>dose (PDD/DDD ratio)</td>
<td>-0.04</td>
<td>279</td>
<td>-0.11</td>
</tr>
<tr>
<td>depot (yes/no)</td>
<td>0.10</td>
<td>319</td>
<td>-0.07</td>
</tr>
<tr>
<td>$R^2$ for medication type and dose</td>
<td>0.01</td>
<td>279</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Complexity of medication regimen

| number of prescribed psychotropic agents | 0.00 | 292 | -0.04 | 281 | -0.04 | 286 |
| times a day patient needs to take medication | 0.11 | 286 | 0.04 | 275 | 0.12 | 280 |
| $R^2$ for complexity of medication regimen | 0.02 | 265 | 0.01 | 257 | 0.02 | 260 |

For each domain, we assessed in a separate regression analysis the overall relationship between the risk factors pertaining to this domain and the 3 questionnaires. For all instruments explained variance was relatively low for all domains. An additional regression analysis was performed for each instrument incorporating only significantly correlated risk factors over all domains. This resulted in an $R^2$ of 0.06 for the MAQ, a $R^2$ of 0.13 for the CRS, and a $R^2$ of 0.16 for the DAI.

Discussion

To date a wide variety of instruments and methods are used to measure adherence. The aim of this article was to examine the extent to which 3 subjective instruments (1 clinician rated and 2 patient rated), frequently used to measure adherence in schizophrenia,
identify the same patients as non-adherent, measure the same concept, and how they
relate to established risk factors for non-adherence. We found that there was little
agreement among the instruments in labeling patients non-adherent, and they did not
seem to measure the same concept. None of the instruments showed a clear relationship
with established risk factors of non-adherence. Therefore, it is difficult to decide which
one, if any, is an appropriate measure of adherence.

Our findings are highly relevant for studies that depend on a valid measure of
medication adherence. Many different methods and instruments have been used in
studies and it has been assumed that they all measure the same trait. We demonstrate
that it may not be justified to assume this. We found poor overlap in 3 representative and
frequently used measures. Although our results can not be generalized to other measures,
it seems justified to question the validity of other, often not validated, instruments. Still
most research uses one of these, or similar instruments. If adherence measures are not
informative about actual medication intake, study conclusions are likely to be distorted
and comparison with other studies is not possible. Given the importance of increasing
our knowledge and evidence-based skills in adherence interventions, we should critically
reconsider the use of inferior measures.

This study clearly indicates that conclusions regarding non-adherence rates or
predictive factors of non-adherence can differ considerably if they are based on any of these
3 instruments alone. Therefore we conclude that the discrepancies found in literature are
at least partly due to the heterogeneous methodology to measure medication adherence.

Although most variables used in this study have often been associated with adherence
behavior, we were surprised by the weak relation with the adherence scales. Relatively
few variables were significantly correlated with the adherence scales but more important,
the correlation coefficients were rather low. We were not able to explain more than 20%
of variance in adherence scores, a result that is not uncommon in this type of research.
Such effect sizes are too small to be clinically relevant for the prediction or explanation of
adherence behavior.

In this study we assumed that the adherence rates represent the degree of medication
adherence and we expected at least some relation with established determinants of non-
adherence. Given our results, we wonder if it is justified to assume a linear relation between
medication intake and adherence rates on these instruments. Possibly these instruments
are sensitive to deviant adherence behavior or negative medication attitudes. Using cutoff
criteria might therefore be useful in identifying patients who are likely, or at risk for
being non-adherent. We do, however, not know which patients are completely non-
Assessment of medication adherence

adherent, skip a dose once a while, or "only" have ambivalent thoughts about medication. In research these instruments might therefore have limited value.

Concerning the low correlations between the adherence rates and risk factors in our study, there are 3 other issues we would like to raise. First, it has been argued that a patient's subjective perception of the effect of medication greatly influences adherence behavior (Adams & Scott, 2000; Marder 2005; Naber et al., 2005; Perkins et al., 2006). Although it is equally likely that established negative attitudes heighten sensitivity to adverse effects. Many variables, however, are based on clinician assessments. It might be more informative to focus on the patient's subjective ratings of perceived burden, family support, complexity of medication schedule, etc. (Ritsner et al., 2002). The LUNSERS for instance asks patients to rate how much they experienced a specific side effect instead of how much it bothered them. Second, other studies demonstrate that some patients attribute benefits to their medication that are not directly related to their illness (Adams & Howe, 1993; Chan, 1984). Patients might, for instance, fear that their children will be placed into care, financial consequences because of losing paid work, or loss of social support if they do not take their medication as prescribed. Although we appreciate that it is difficult in quantitative studies to incorporate such specific risk factors, they might be nonetheless important in understanding patients' behavior (Adams & Howe, 1993; Kikkert et al., 2006). Third, besides choosing relevant risk factors and a relevant perspective to measure them, one needs to consider what type of relation is expected. The statistical methods used in most studies assume linear relations. For some variables, however, it might be more appropriate to consider more complex relations or 2 directional relations. For example, adverse side effects might inhibit medication intake but are also likely to decline if medication intake is low, making it difficult, particularly in cross-sectional designs, to demonstrate a relation. This could perhaps also apply to other variables such as positive symptoms and quality of life, which might have a causal as well as a dependent relation with adherence.

According to a general accepted definition, patients are non-adherent if they do not fully follow medication prescription. This ignores a relevant distinction between completely and partly non-adherent patients. Skipping or forgetting a dose once every week is not the same as not taking medication at all. Grouping these patients together is likely to distort study results. Researchers should be more aware of the difference between measuring adherence behavior (degree of medication intake in reference to their prescription) and detecting non-adherent patients (identifying patients that do not fully comply with medication regimen or are at risk for being non-adherent).
We would like to argue that methods used to measure medication adherence should indicate the actual proportion of used medication, and if the patient uses more than one agent, refers to the agent of interest. This will increase comparability among studies. It will also allow researchers to define patients as non-adherent based on a pharmacological effective threshold; a minimum dose that will produce a clinically meaningful reduction of symptomatology. This may have more clinical relevance than the definition of non-adherence used up to date and may result in more valid study conclusions.

Although objective measures seem most appropriate to do this, they each have their limitations. Serum levels are invasive, costly, and require knowledge of individual pharmacokinetic characteristics. Pharmacy records can be informative but require an accurate administration system and only provide average adherence rates over longer periods of time (Rijcken et al., 2004). In other fields electronic devices which record openings of a pill bottle container (MEMS) has been suggested as a new gold standard and seem to be a reliable indicator of medication adherence (Nichol et al., 1999; Osterberg & Blaschke, 2005), practical in use in patients with schizophrenia (Diaz et al., 2001; Nakonezny & Byerly, 2006). MEMS is, however, relatively expensive and is sensitive to patient errors (Arnet and Haefeli, 2000; Bova et al., 2005). Researchers who are limited to using questionnaires might consider asking patients to report their own intake behavior over a limited period of time and combine this with information gathered from other sources such as a carer and/or key worker. Self-reports might, however, be susceptible to error and distortion. One of the main concerns is that patients might find it difficult to be frank about their medication intake. Creating a confidential, understanding, and non-judgmental atmosphere is therefore important.

This study has limitations. Recruited patients met inclusion criteria including clinical instability in the previous 12 months. Although patient-related characteristics were representative for a population of patients with schizophrenia, this criterion might have affected our sample. Variables and adherence indexes used in this study were restricted by those used in the QUATRO study. For several variables we could not use appropriate measures but used proxies instead.

This study demonstrates that if we want to improve our understanding of adherence behavior in patients with schizophrenia, validated instruments are necessary that measure the degree of actual medication intake, as well as agreement among researchers to use them.
Acknowledgements

The QUATRO study is a multicenter collaboration between the Health Services Research Department, Institute of Psychiatry, King’s College London; the Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology; University of Verona, Italy; the Department of Psychiatry, Leipzig University, the Department of Psychiatry II, Ulm University, Germany, and the Department of Psychiatry, Academic Medical Center, University of Amsterdam, Netherlands.

The authors acknowledge the contributions of the patients, carers, and staff who have taken part in this study. The authors also acknowledge the contributions to this study of the following colleagues: Amsterdam Site (Aart Schene, Annemarie Fouwels, Martijn Kikkert, Maarten Koeter, Karin Meijer), Leipzig/Ulm Site (Thomas Becker, Matthias Angermeyer, Anja Born, Anne Gießler, Hedda Helm, Bernd Puschner); London Site (Jonathan Bindman, Jayne Camara, Anthony David, Kevin Gournay, Richard Gray, Martin Knapp, Morven Leese, Paul McCrone, Mauricio Moreno, Anita Patel, Debbie Robson, Graham Thornicroft, Ian White); and Verona Site (Michele Tansella, Francesco Amaddeo, Corrado Barbui, Lorenzo Burti, Daniela Celani, Dorian Cristofalo, Claudia Goss, Antonio Lasalvia, Giovanna Marrella, Mariangela Mazzi, Michela Nosè, Mirella Ruggeri, Marta Solfa).
References


Assessment of medication adherence


Chapter 5

The Predictive Validity of Subjective Adherence Measures in Patients with Schizophrenia

Martijn J. Kikkert
Maarten W.J. Koeter
Jack J.M. Dekker
Lorenzo Burti
Debbie Robson
Bernd Puschner
Aart H. Schene

Accepted for publication in: The International Journal of Methods in Psychiatric Research
Abstract

Despite frequent use of subjective adherence measures in patients with schizophrenia as well as other chronic conditions, there are several reports that question the validity of these instruments. Three well known, representative subjective measures are the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS). In this study we explored the predictive validity of these instruments in a European sample of 119 stabilized outpatients with schizophrenia. Clinical outcome variables were relapse and admission to a psychiatric hospital during a follow up period of 12 months. Results indicate that the predictive validity of all three measures was poor. The MAQ was the least problematic predictor for relapse (Nagelkerke $R^2=0.09$), and time to relapse ($R^2=0.07$) and had the best sensitivity for relapse (63.6%) as well as admission (87.5%). The MAQ and CRS were both moderate predictive for admission (Nagelkerke $R^2=0.21$, and $R^2=0.29$). We conclude that the validity of the instruments studied here is questionable and have limited clinical relevance. Given the feasibility and ease of most subjective instruments, researchers may be tempted to use them but should be aware of the serious drawbacks of these instruments.
The predictive validity of subjective adherence measures

Introduction

Studies have shown that medication use in patients with chronic conditions is generally poor (Sabaté et al., 2003). This is found for physical conditions such as cardiovascular diseases and HIV, but also in patients suffering from chronic mental health diseases such as psychotic disorders. This undermines the potential therapeutic effect of antipsychotic medication resulting in increased burden for patients, family, and professionals, as well as major economical costs.

Our knowledge concerning prevalence, efficacy of adherence interventions, and determinants of non-adherence is based on studies performed in the last decades. These studies have one thing in common; their outcomes rely on a valid assessment of medication adherence. Several methods are available to measure medication adherence but the majority of adherence studies in schizophrenia, resort to subjective instruments, such as questionnaires or interviews that rely on self report or on assessments made by others (Velligan et al., 2006). An advantage of these instruments is that they are cheap, easy to use and non intrusive. Unfortunately the instruments are often not validated, are susceptible to error, misinterpretation or distortion, and the quality of their description varies but is often poor (Kane, 1983; Nichol et al., 1999; Nose et al., 2003; Osterberg & Blaschke, 2005; Velligan et al., 2006).

In a previous article (Kikkert et al., 2008) we examined concurrent validity of three frequently used, subjective adherence measures; the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS) (Hogan et al., 1983; Kemp et al., 1998; Morisky et al., 1986). Although all instruments claim to assess the degree of medication adherence, our results indicated that the instruments did not seem to measure the same concept. Also the overlap of patients labelled as non-adherent by the three instruments was limited. Based on these results we concluded that the concurrent validity was low and that it is very unlikely that all three validly assess adherence. This did however not preclude the possibility that one of these instruments is a valid measure of adherence.

Since these, and similar type of adherence measures, are so commonly used, this may have had an impact on the results of many studies. In this study we will further explore the validity of these instruments using the possible consequences of non-adherence; clinical deterioration and consequently psychiatric hospitalization as criterion. So far there is overwhelming evidence for the efficacy of antipsychotic medication (Ayuso-Gutierrez et al., 1997; Kahn et al., 2008; Keith et al., 2003; Lieberman et al., 2005; Morken et al.,
Sub therapeutic intake of medication is related to exacerbation of symptoms and relapse (Fenton, 1997; Robinson et al., 1999; Weiden & Zygmunt, 1997), and is the most important determinant for relapse in first episode psychosis patients (Malla et al., 2006).

A secondary, clinically relevant effect of adherence might be (Law et al., 2008). In comparison to relapse, the effect of non-adherence on admission is influenced by circumstantial factors such as patient characteristics (e.g. patient preference), social characteristics (e.g. family support and living conditions) and (mental) health care characteristics (e.g. number of beds available, policy, outpatient treatment facilities). Therefore not all patients that relapse will also be admitted to a psychiatric hospital. Nevertheless, several large scale studies using pharmacy data or electronic medication monitoring as an indicator of medication adherence showed that non-adherent patients had higher admission rates (Diaz et al., 2001; Eaddy et al., 2005; Gilmer et al., 2004; Valenstein et al., 2002; Weiden et al., 2004).

Some studies evaluated relapse or admission as outcome variable, in this study we are able to evaluate relapse, as well as admission of 119 stabilized outpatients with schizophrenia over a 12 month follow up period. The aim of this study is to determine the predictive validity of three often used measures of adherence, the MAQ, DAI and CRS. Clinical outcome will be defined in our study as a. risk of relapse and admission, and b. time to relapse and admission.

Methods

Study design
Data used in this study was collected during the QUATRO study (Quality of life following adherence therapy for people disabled by schizophrenia and their carers), an international randomised controlled trial assessing the efficacy of Adherence Therapy in patients with schizophrenia (Gray et al., 2006). The study was approved by all four local institutional medical ethical committees. During this study assessments were conducted at baseline and after 12 months. Ratings assessed at baseline were used in this study together with data on relapse and hospitalisation during the 12 month follow up period.
The predictive validity of subjective adherence measures

Participants

Patients were recruited in four European cities: London (UK), Verona (Italy), Leipzig (Germany) and Amsterdam (the Netherlands). Inclusion criteria were: 1) clinical diagnosis of schizophrenia according to ICD-10 criteria, confirmed by a research diagnosis of schizophrenia using the Item Group checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (Wing et al., 1990), 2) in need of maintenance anti-psychotic treatment for at least one year after entry into the study, and 3) evidence of clinical instability in the previous year (at least one hospital admission on clinical, mental health grounds, a change in anti-psychotic medication, increased frequency of planned or actual contact, indications of clinical instability from relatives, carers or clinical team). Exclusion criteria were: 1) moderate or severe learning disabilities, 2) organic brain disorders and 3) treatment by forensic psychiatric services.

Approximately one third of patients are treatment resistant (Conley & Kelly, 2001; Kane 1996, 1999), ranging from persistent disabling symptoms despite adequate trials of medication, up to the absence of any medication benefit. For treatment resistant patients the assumed causal relation between medication adherence and relapse does not apply. In this study only outpatients, free of positive symptoms during the time of assessment were included for analysis. This ruled out the inclusion of treatment resistant patients. It also enabled us to examine the risk of relapse and psychiatric admission. The effect of antipsychotic medication on negative symptoms is limited and was therefore not incorporated as selection criterion or outcome variable. In the QUATRO study, there were no differences found between the treatment and control group on any of the outcome variables such as: the score on the MAQ, DAI and CRS, the risk for relapse or hospitalisation, psychopathology as measured with the Expanded Brief Psychiatric Rating Scale (BPRS-E), or insight as measured with the expanded version of the Schedule for Assessment of Insight (Gray et al., 2006). All patients were therefore considered eligible for this study and treatment arm was not incorporated as a confounder.

After screening, 917 patients from four European countries were found eligible for the QUATRO study. Approximately a third of these patients (N=366) refused to participate, and 142 patients could not be included for other reasons (Gray et al., 2006). Out of the 409 included patients in the QUATRO study, analysis in this study were based on 119 stabilized outpatients with schizophrenia who gave written informed consent. At baseline, 80 patients stayed in an inpatient setting or psychiatric hospital, and 148 outpatients were psychotic. A patient was rated psychotic if moderate to extremely severe positive symptoms, according to the BPRS-E, were present for at least one week. This was
rated by the clinician. Finally, 62 patients were excluded for analysis because their clinical course data was incomplete (covered <90% of the follow up period).

**Instruments**

All instruments were administered once at baseline. Starting at baseline, clinical course was recorded during the follow up period of 12 months.

**Clinical course rating**

Although there are no clear criteria for relapse, in accordance with Johnstone’s (1992) definition, we defined relapse in this paper as reappearance of positive symptoms. For this purpose we used an instrument which was constructed to identify clinical course patterns of patients (Burti et al., 2008). Clinicians were asked to rate if a patient was psychotic for each quarter of a month. Clinical course ratings were given for the entire follow up period of twelve months. As described above, patients were rated psychotic if moderate to extremely severe positive symptoms, according to the BPRS-E, were present for at least one week. Psychotic episodes were considered separate if they were interrupted by a non psychotic period of at least one month. Admissions to a psychiatric hospital were scored similarly on this instrument. Hospital admissions were considered separate if the time between two admissions was at least half a month (Burti et al., 2008).

**Adherence instruments**

For each patient adherence was assessed with two self report scales, the MAQ and the DAI, and one clinician rated adherence scale, the CRS.

The MAQ consists of four yes/no questions and addresses ways in which patients may fail to take their prescribed medication: forgetting, carelessness, stopping the drug when they feel better and or stopping the drug because they believe it makes them feel worse (Morisky et al., 1986). A higher score on the MAQ indicates less problems with medicine taking and better adherence behaviour.

The DAI is a self report measure comprising ten yes/no statements reflecting patients’ experiences, attitudes and beliefs about medication. This 10-items version of the DAI was designed to assess medication adherence in patients with schizophrenia. Based on a validation study, 10 items were selected from the original 30 DAI-items as having maximal group discrimination of adherent and non-adherent patients (Hogan et al., 1983). Patients are asked to decide whether statements apply to them. Higher scores indicate a more positive attitude towards medication, and better adherence behaviour.
The predictive validity of subjective adherence measures

The CRS is used to rate medication adherence on a 7-point scale. The CRS is scored by key workers. Complete refusal is rated 1, patients who partially refuse score 2, patients who reluctantly or passively accept treatment score 3, 4 or 5 and patients who moderately or actively accept treatment score 6 or 7. For each score a brief description of adherence behaviour is provided in the questionnaire. A detailed description of statistical characteristics of these instruments is given in Kikkert et al. (2008).

For some analysis we classified patients as adherent or non-adherent using standard cut off criteria if available. For the MAQ, patients with a score ≤3 are defined as non-adherent (George et al., 2000; Morisky et al., 1986; Roth & Ivey, 2005). For the CRS, patients with a score ≤4 are considered non-adherent (Byerly et al., 2005; Kemp & David, 1996; Kemp et al., 1998; Mutsatsa et al., 2003). For the DAI, the sum of the negative items are subtracted from the sum of the positive items. If the resulting score is less than or equal to zero, patients are considered to be non-adherent (Hogan et al., 1983).

Other instruments
Other instruments used in this study were:

- the Expanded Brief Psychiatric Rating Scale (BPRS-E): this instrument consists of 24 items measuring the following dimensions; positive symptoms, negative symptoms, depression/anxiety and disorganization (Ruggeri et al., 2005).
- the expanded version of the Schedule for Assessment of Insight (SAI-E): this is a semi-structured interview measuring three dimensions of insight: awareness of illness, relabelling of psychotic symptoms and treatment compliance (David, 1990; Kemp et al., 1998). Finally, information on type and dosage of prescribed antipsychotic medication was provided by the patient’s clinician.

Analysis
We explored sensitivity and specificity of the three instruments for relapse and psychiatric admission. Logistic regression analyses were used to study the relation between the continuous adherence ratings at baseline and psychotic relapse, and psychiatric admission during the follow up period. We used a Cox Regression analysis to explore time to relapse and time to admission. Before Cox Regressions were performed we formally tested the proportional hazard assumption by adding an intervention by time interaction term to the regression model (Kleinbaum, 1990). None of the regression coefficients of this
interaction term were statistically significant. Consequently, the proportional hazard assumption was met. To correct for multiple testing alpha was set at 0.017.

In the regression analyses a number of potential confounders were included as covariates. These confounders were all variables determined as risk factor for non-adherence based on literature reviews. For a detailed description see our previous paper (Kikkert et al., 2008). Potential confounders were: living situation, medication efficacy, psychopathology, functioning, illness insight, medication side effects, type of antipsychotic (first or second generation, and depot), antipsychotic dose and frequency, and number of prescribed psychotropic agents. Based on the change-in-estimate strategy (Maldonado & Greenland, 1993; Rothman & Greenland, 1998; Sonis, 1998), confounders were included in the analysis if, when added to the Cox regression model, the odds ratio for any of the adherence instruments changed more than 10%. Positive symptoms (measured with the BPRS-E) fulfilled this criterion but was not included as a confounder because we considered it part of the causal pathway between adherence and outcome. The following confounders were included: negative symptoms (subscale negative symptoms of the BPRS-E), insight; symptom relabelling and hypothetical contradiction (factor 1 of the SAI-E), insight; illness awareness (factor 2 of the SAI-E), and depot medication.

Results

Social-demographic characteristics and clinical outcomes for all included patients are shown in Table 1. Patients were middle aged, a slight majority was male, and relatively few were employed or married. On average patient’s had been prescribed antipsychotic medication for approximately 13 years. The sample in this study showed no differences compared to the remaining outpatients in the QUATRO study on any of the socio-demographic characteristics, except for ethnicity. In our sample we had less Caucasians (63.0%) compared to the remaining outpatients in the QUATRO sample (85.2%). We also found that our sample had less severe psychiatric symptoms (mean BPRS-E total score of 38.4 compared with 48.4) which is probably due to excluding patients who were psychotic at baseline. Compared with the characteristics of more then 8000 outpatients with schizophrenia in two other European multicenter studies; the SOHO study (Haro et al., 2006) and the EPSILON study (Ruggeri et al., 2005), characteristics of our sample showed no differences. We therefore conclude that patients in this study form a
The predictive validity of subjective adherence measures

representative sample of stabilized western European outpatients with schizophrenia who had been clinically unstable in the previous year.

During the 12-month follow up period, 57 (48%) patients experienced psychotic symptoms severe enough to define it a relapse. On average, the monthly relapse rate was 5.3%. Each quarter 15 patients (13%) relapsed, except for the last quarter in which 12 patients relapsed (10%). Most patients (79%) who experienced a psychotic period had only one episode, and 18% had two episodes. Two patients had respectively 3 and 5 separate psychotic episodes. Out of the 57 patients with a relapse, 16 (28%) patients were admitted to a psychiatric hospital. The average monthly admission rate in our sample was 1.2%. Each quarter between 3 and 5 patients were admitted. Two patients (13%) were admitted twice and one patient (6%) had three separate admissions. Most admitted patients (81%) were admitted once.

Logistic regression analysis shows that the risk for relapse decreases with increasing adherence rates. This relation was found for all three adherence measures but was only significant for the MAQ (see Table 2). Besides a slight increase in risk of relapse, time to relapse is shorter for patients with lower adherence rates. Again this was only significant for the MAQ (see Table 3). For both analyses the explained variation ranges from 0.05 to 0.09, which in terms of Cohen's effect size criteria for $R^2$, is an indication for a low to medium effect (Cohen, 1988).

The risk for admission also decreases with increasing adherence rates. Although this relation was found for all three adherence instruments, it was only significant for the MAQ and CRS (see Table 2). Time to admission is shorter for non-adherent patients but this was only significant for the CRS (see Table 3). Explained variation for chance of, and time to admission ranges from 0.10 to 0.29, which in terms of Cohen's effect size criteria for $R^2$, an indication for a medium to strong effect (Cohen, 1988).
Table 1. Characteristics of sample (n=119)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>40.7 (11.66)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>68 (57.1%)</td>
</tr>
<tr>
<td>Ethnicity, Caucasian, N (%)</td>
<td>75 (63.0%)</td>
</tr>
<tr>
<td>Single / unmarried, N (%)</td>
<td>107 (89.9%)</td>
</tr>
<tr>
<td>Paid or self employed, N (%)</td>
<td>20 (16.8%)</td>
</tr>
<tr>
<td>Living alone, with/without children, N (%)</td>
<td>68 (54.0%)</td>
</tr>
<tr>
<td>Years antipsychotic(s) prescribed, mean (SD)</td>
<td>13.17 (9.92)</td>
</tr>
<tr>
<td>Highest completed level of education, N (%)</td>
<td></td>
</tr>
<tr>
<td>Primary education or less</td>
<td>20 (16.9%)</td>
</tr>
<tr>
<td>Secondary education</td>
<td>58 (49.2%)</td>
</tr>
<tr>
<td>Tertiary/further education</td>
<td>40 (33.9%)</td>
</tr>
<tr>
<td>BPRS-E total score, mean (SD)</td>
<td>38.36 (12.04)</td>
</tr>
<tr>
<td>Psychotic relapse during follow up, N (%)</td>
<td>57 (47.9%)</td>
</tr>
<tr>
<td>Number of separate psychotic episodes, mean (SD) (N=57)</td>
<td>1.28 (0.67)</td>
</tr>
<tr>
<td>Duration between baseline and (first) episode in months, mean (SD) (N=57)</td>
<td>6.10 (3.26)</td>
</tr>
<tr>
<td>Duration of (first) psychotic episode in months, mean (SD) (N=57)</td>
<td>2.05 (1.81)</td>
</tr>
<tr>
<td>Hospitalized during follow up, N (%)</td>
<td>16 (13.4%)</td>
</tr>
<tr>
<td>Number of admissions, mean (SD) (N=16)</td>
<td>1.25 (0.58)</td>
</tr>
<tr>
<td>Duration between baseline and (first) admission in months, mean (SD) (N=16)</td>
<td>6.08 (3.29)</td>
</tr>
<tr>
<td>Duration of (first) admission in months, mean (SD) (N=16)</td>
<td>3.24 (2.60)</td>
</tr>
</tbody>
</table>
Table 2. Prediction of relapse and admission

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% CI</th>
<th>Nagel-kerke^2</th>
<th>N</th>
<th>-2 log likelyhood^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>relapse^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>-0.613</td>
<td>0.231</td>
<td>7.054</td>
<td>0.008</td>
<td>0.542</td>
<td>0.345-0.852</td>
<td>0.092</td>
<td>93</td>
<td>109.000</td>
</tr>
<tr>
<td>DAI</td>
<td>-0.120</td>
<td>0.106</td>
<td>1.296</td>
<td>0.255</td>
<td>0.887</td>
<td>0.721-1.091</td>
<td>0.059</td>
<td>92</td>
<td>111.178</td>
</tr>
<tr>
<td>CRS</td>
<td>-0.345</td>
<td>0.173</td>
<td>3.962</td>
<td>0.047</td>
<td>0.708</td>
<td>0.505-0.995</td>
<td>0.072</td>
<td>88</td>
<td>110.321</td>
</tr>
<tr>
<td>admission^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>-0.671</td>
<td>0.274</td>
<td>6.010</td>
<td>0.014</td>
<td>0.511</td>
<td>0.299-0.874</td>
<td>0.213</td>
<td>93</td>
<td>58.015</td>
</tr>
<tr>
<td>DAI</td>
<td>-0.292</td>
<td>0.136</td>
<td>4.584</td>
<td>0.032</td>
<td>0.747</td>
<td>0.572-0.976</td>
<td>0.241</td>
<td>92</td>
<td>56.509</td>
</tr>
<tr>
<td>CRS</td>
<td>-0.739</td>
<td>0.277</td>
<td>7.101</td>
<td>0.008</td>
<td>0.477</td>
<td>0.277-0.822</td>
<td>0.293</td>
<td>88</td>
<td>53.660</td>
</tr>
</tbody>
</table>

^1 Logistic regression. Dependent variable is relapse, or admission (yes/no); covariates are: negative symptoms (BPRS neg), symptom relabelling and hypothetical contradiction (SAIf1), illness awareness (SAIf2), depot medication (yes/no).

^2 Analyses performed on 83 patients who had a rating on each adherence instrument.

Table 3. Prediction of time to relapse and admission

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>Rp^2</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>relapse^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>-0.378</td>
<td>0.124</td>
<td>9.256</td>
<td>0.002</td>
<td>0.685</td>
<td>0.537-0.874</td>
<td>0.068</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>DAI</td>
<td>-0.096</td>
<td>0.066</td>
<td>2.121</td>
<td>0.145</td>
<td>0.908</td>
<td>0.798-1.034</td>
<td>0.052</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>-0.219</td>
<td>0.101</td>
<td>4.683</td>
<td>0.030</td>
<td>0.803</td>
<td>0.659-0.980</td>
<td>0.048</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>admission^1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>-0.433</td>
<td>0.195</td>
<td>4.936</td>
<td>0.026</td>
<td>0.649</td>
<td>0.443-0.950</td>
<td>0.101</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>DAI</td>
<td>-0.228</td>
<td>0.110</td>
<td>4.339</td>
<td>0.037</td>
<td>0.796</td>
<td>0.642-0.987</td>
<td>0.120</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>-0.463</td>
<td>0.150</td>
<td>9.475</td>
<td>0.002</td>
<td>0.630</td>
<td>0.469-0.845</td>
<td>0.144</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

^1 Cox regression; covariates are: negative symptoms (BPRS neg), symptom relabelling and hypothetical contradiction (SAIf1), illness awareness (SAIf2), depot medication (yes/no). Hazard rates were proportional.

^2 Explained variation ($R^2$) (Hosmer & Lemeshow, Applied Survival Analysis. Regression Modeling of Time to Event Data.) Analyses performed on 83 patients who had a rating on each adherence instrument.

Table 4 shows the sensitivity and specificity of the three instruments to detect non-adherence. Both the DAI and CRS label most patients as adherent (respectively 86% and 79%) and therefore sensitivity is low while specificity is high. Compared to the DAI and CRS, the MAQ has better sensitivity and specificity.
Table 4. Sensitivity and specificity for relapse and admission (n=119)

<table>
<thead>
<tr>
<th></th>
<th>relapse</th>
<th>admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sensitivity (%)</td>
<td>specificity (%)</td>
</tr>
<tr>
<td>MAQ</td>
<td>63.6</td>
<td>59.7</td>
</tr>
<tr>
<td>DAI</td>
<td>18.2</td>
<td>90.0</td>
</tr>
<tr>
<td>CRS</td>
<td>34.0</td>
<td>90.3</td>
</tr>
</tbody>
</table>

Discussion

In our previous study (Kikkert et al., 2008) we concluded that concurrent validity of the MAQ, DAI and CRS was low. However this did not rule out the possibility that one of them is a good index of medication adherence. To explore this possibility, we evaluated the predictive validity of these three measures in this study.

There is significant evidence for the efficacy of antipsychotic medication. Therefore, in a sample of responsive stabilized outpatients, it seems reasonable to assume a relationship between medication intake behaviour and clinical outcome. In this study we found that the MAQ was predictive for relapse and for time to relapse. The MAQ and CRS were both predictive for hospital admission. The CRS was also predictive for time to hospital admission. The clinical relevance of these effects is however limited. Adherence rates on any of the three measures could only explain a relatively small proportion of the variation. Although non-adherent patients in general had higher relapse and admission rates, sensitivity shows that out of all patients who relapsed or got admitted, the proportion labelled as non-adherent was very low. Although sensitivity and specificity of the MAQ was better, 42% of patients who were non-adherent according to the MAQ still did not relapse, and 35% of adherent patients did relapse.

Out of the two self report instruments, the DAI had the worst predictive validity. The DAI focuses on patient’s attitudes towards medication whereas the MAQ items directly relate to medication intake behaviour. The latter seemed to be a slight better approach in measuring adherence, although Karow et al. (2007) found that subjective well being may also be useful in predicting adherence.

Other studies demonstrated that clinician ratings of adherence have poor validity (Byerly et al., 2005, 2007; Remington et al., 2007). Our results confirm this finding. Clinicians performed relatively better at estimating adherence behaviour of patients with
poorer outcome defined as admission to hospital. In addition to more severe symptoms, patients who get admitted often have less social support and live alone. These are also associated with non-adherence (Fenton, 1997; Pinikahana et al., 2002; Perkins 2002) which may help explain why patients with high risk profiles for non-adherence are more easily detected by clinicians.

This study, however, also has its limitations. In a cohort study, Valenstein et al., (2006) examined adherence behaviour in two consecutive years and found that 83% of adherent patients, and 70% of non-adherent patients remained respectively adherent and non-adherent the following year. This may indicate that adherence is relatively stable for the majority of patients over two consecutive years. Nevertheless, in our study we only measured adherence at baseline and are unaware of any changes later in time. Patients may have changed their adherence behaviour after the baseline measurement. Patients who suffered mild or no symptoms may be more tempted to stop using their medication. On the other hand, patients who experienced exacerbation of symptoms due to non-adherence may have avoided relapse or hospitalization by increasing their medication intake in time. To reduce the influence of possible changes in adherence behaviour in time, we repeated our logistic regression analysis focusing only on relapses that occurred within the first 3, and 6 months. This did not change our results, none of the instruments were predictive for relapse in the first 3 or 6 months.

If a clinician was not sure about the patients condition over a certain period of time, the information on the clinical course rating was left blank. Nevertheless, the validity of the clinical course rating is not known and information regarding psychotic relapse can be affected by misinterpretation. This is not the case for admission data, which are therefore less likely to be inaccurate.

It is possible that a psychosis was induced by other causes such as life events or drug abuse. Although this would have strengthened our design, this information was not available for our sample. We do know from other studies that the increased risk for psychosis in drug abusers is at least partly due to non-adherence (Ascher-Svanum 2006; Perkins et al., 2008).

Relapse could also have been caused if inadequate doses of antipsychotic medication were prescribed. In our analysis, the daily dosage, expressed as the proportion of the defined daily doses of antipsychotic medication (WHO, 2003), turned out to have no influence on chance of, or time to relapse or admission. Therefore we conclude that patients in our sample received appropriate doses of medication.
Up to date subjective self report tests are the most frequently used methods to measure adherence. Although there is a wide variety of measures available, most of them are similar to either the MAQ, DAI or CRS. In a previous paper (Kikkert et al., 2008) we demonstrated that the MAQ, CRS and DAI do not measure the same trait. In this article we were able to determine the predictive validity in a European sample of treated stabilized outpatients with schizophrenia based on two significant clinical outcomes; relapse and admission. We found that none of the three instruments were able to clearly distinguish patients who are likely to relapse or get admitted to hospital in the following 12 months. Given the results of this study and our previous study (Kikkert et al., 2008) we conclude that the MAQ, CRS and DAI do not validly measure adherence and their use for scientific purposes is questionable. Unfortunately, the majority of adherence studies in patients with schizophrenia use these, or similar type of instruments. Researchers should be aware of the poor validity of subjective instruments and the impact it may have on study results. Given the convenience of subjective instruments, researchers should continue to strive for the development of valid, and easy to use adherence measures. Until these are available, objective instruments such as electronic medication monitoring, pill count or pharmacy based measures may be more preferable.

Acknowledgements

The QUATRO study is a multi-centre collaboration between the Health Services Research Department, Institute of Psychiatry, King’s College London; the Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology: University of Verona, Italy; the Department of Psychiatry, Leipzig University, and the Department of Psychiatry II, Ulm University, Germany, and the Department of Psychiatry, Academic Medical Center, University of Amsterdam, Netherlands. The study was funded by a grant from the Quality of Life and Management of Living Resources Programme of the European Union (QLG4-CT-2001-01734). The views expressed in this publication are those of the authors and not necessarily those of the funders. We also wish to acknowledge the contributions of the patients, carers, and staff who have taken part in this study. We would like to acknowledge the contributions to this study of the following colleagues: Amsterdam Site (Aart Schene, Annemarie Fouwels, Martijn Kikkert, Maarten Koeter, Karin Meijer). Leipzig/Ulm Site (Thomas Becker, Matthias Angermeyer, Anja Born, Anne Gießler, Hedda Helm, Bernd Puschner). London Site (Jonathan Bindman, Jayne Camara, Anthony David, Kevin Gournay, Richard Gray, Martin Knapp, Morven Leese, Paul McCrone, Mauricio Moreno, Anita Patel, Debbie Robson, Graham Thornicroft, Ian
The predictive validity of subjective adherence measures

White). Verona Site (Michele Tansella, Francesco Amaddeo, Corrado Barbui, Lorenzo Burri, Daniela Celani, Doriana Cristofalo, Claudia Goss, Antonio Lasalvia, Giovanna Marrella, Mariangela Mazzi, Michela Nosè, Mirella Ruggeri, Marta Solfa).

Declaration of Interests
The authors have no competing interests.
References


The predictive validity of subjective adherence measures


Valenstein M, Copeland LA, Blow FC, et al. (2002). Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Medical Care, 40: 630-639.


Chapter 6

The Inventory of Medication Intake (IMI): Validation of an Instrument for Assessing Adherence to Antipsychotic Medication

Martijn J. Kikkert
Jack J.M. Dekker
Maarten W.J. Koeter
Aart H. Schene

Submitted for publication in: Medical Care
Abstract

Background: It remains difficult to make a valid assessment of medication adherence in patients with schizophrenia. Several objective instruments are available but limited resources often mean that subjective instruments are used. Unfortunately, the validity of most of the available subjective instruments is poor or unknown.

Objective: To validate a new self-report instrument, the Inventory of Medication Intake (IMI). The IMI is a brief interview and relies on self-reporting about the number of missed doses of antipsychotic medication during a three-week period.

Methods: We evaluated the IMI in a sample of 51 patients with schizophrenia using the Medication Event Monitoring System (MEMS) as a reference. The feasibility, sensitivity, specificity, positive and negative likelihood ratios of the IMI were compared with other subjective instruments, namely the Medication Adherence Rating Scale (MARS), the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), the Compliance Rating Scale (CRS) and a 100-point clinician estimate of medication adherence.

Results: IMI scores were significantly related to MEMS adherence rates (r=0.445, p=0.001) but the IMI overestimates adherence (sensitivity=36.4; specificity=97.5). Patients detected by the IMI as adherent or non-adherent were in most cases labelled correctly (the positive and negative predictive values were 80.0 and 84.8, and the positive likelihood ratio was 14.6). Adherence among the patients in our sample was high, and this may have affected our results.

Conclusions: The IMI is easy to use and it performed better than other self-report measures. It suffers, however, from poor sensitivity, which limits its usefulness as an instrument for identifying non-adhering patients.
Introduction

Full adherence to antipsychotic medication regimens in schizophrenia patients continues to be a problem for approximately 61% of patients at some time (Valenstein et al., 2006). Over the years, many studies have been performed to understand or cope with non-adherence better. Some of these studies have tried to establish risk factors for non-adherence, while others evaluate the effectiveness of adherence interventions. The measurement of adherence is a crucial issue in these studies.

Several researchers have already found that measuring levels of adherence to a medication regimen is not easy (DiMatteo, 2004; Farmer, 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006). To date, a wide variety of methods have been used. They can be broken down into objective and subjective instruments. Objective methods are blood or urine samples, tracers, pharmacy-based measures, electronic pill monitoring or pill counts. Subjective measures are self-reports, clinician reports or significant-other reports.

Although objective methods are often considered to be more reliable and valid than subjective methods, they too suffer from weaknesses. In general, they are more expensive, complicated, and burdensome, and they also suffer from methodological and validity problems. Concentrations in blood or urine samples and biological markers are not valid indicators of adherence because of interindividual differences in metabolism (Farmer, 1999; Velligan et al., 2006; Cochran & Gitlin, 1988; George et al., 2000). Refill rates and prescription records can be affected by the use of old pills. This approach also requires a closed pharmacy system and it is not useful when monitoring adherence over a short period of time (Osterberg & Blaschke, 2005; Velligan et al., 2006; Rijcken et al., 2004). Pill counts may overestimate adherence and can also be affected by the use of old pills (Osterberg & Blaschke, 2005; Velligan et al., 2006; Wright, 1993). Finally, electronic monitoring is based on the assumption that patients take their medication (and the right dose) when they open a bottle of pills. Nevertheless it is generally accepted that electronic monitoring is the best available measure of adherence (Osterberg & Blaschke, 2005; Wright, 1993; Byerly et al., 2007; Cramer, 2001; Diaz et al., 2001; Nakonezny et al., 2008; Nichol et al., 1999), and that it can be used in patients with severe mental illness (Diaz et al., 2001).

Velligan et al. (2006) reviewed adherence measures in 161 studies of adherence to oral antipsychotics between 1970 and 2006 and concluded that subjective methods are used in 75% of studies. This is no surprise since subjective instruments are cheap and easy to use. Previous studies have indicated, however, that the validity of these instruments
is generally poor. Assessments made by significant others depend on the degree of involvement with the patient and may be based largely on observed clinical outcome. Several studies consistently showed that clinician reports are not good indicators of medication adherence (Byerly et al., 2005, 2007; Remington et al., 2007).

Self-report instruments have also often been found to be invalid (Velligan et al., 2006; Kikkert et al., 2008; Lam et al., 2003). This may be caused by several weaknesses: patients may not understand questions, or they may give socially desirable or untruthful responses (Osterberg & Blaschke, 2005). Responses may be influenced by interviewer skills. In addition, adherence instruments do not usually specify the agent they focus on but rather give an overall adherence score. The possible false assumption here is that patient adherence is the same for all prescribed agents. However, patients may, for instance, adhere to a benzodiazepine regimen but not to an antipsychotic regimen (Piette et al., 2007). Several self-report instruments do not inquire about the amount of consumed medication and focus on related issues such as medication attitudes and present or previous experience. As a result, the relation between subjective adherence rates, often reported on 3 to 7-point Likert-type scales (Velligan et al., 2006), and the actual amount of medication consumed is obscure, making it difficult to compare study results. If questions are more straightforward, patients usually have to rate their adherence on a 0-100 scale, which also leads to poor validity (Byerly et al., 2007; Remington et al., 2007). The validity of self-reporting seems, however, to improve if another approach is used: instead of asking patients to mark their adherence behaviour, Haynes et al. (1980) asked hypertension patients to report the average number of pills missed per day, week and month. The answers were closely correlated to pill counts. Stewart (1987) asked patients who visited their family physician how many doses they had missed in 10 days. The sensitivity and specificity of this question was good compared with pill counting. In a study of patients with hypertension, Choo et al. (1999) found that, the only one of a number of self-report items that correlated with electronic medication monitoring was the self-reported number of forgotten medication doses during one week. These studies indicate that asking patients to recall specific events when medication intake does not correspond with their prescription during a time frame may be an interesting approach for measuring adherence.

Recently, Byerly et al. (2008) reported on a new instrument: the Brief Adherence Rating Scale (BARS). This instrument is used to assess patients’ knowledge of their medication regimen, and patients are asked to report the number of days on which they fail to take some or all of their medication.
Validation of the inventory of medication intake

At the same time, and independently of the development of the BARS, our research group developed a new adherence instrument: the Inventory of Medication Intake (IMI). Although developed independently, the BARS and the IMI share the same basic principles. The IMI was constructed to assess the intake of medication based on a brief interview with the patient, overcoming some of the problems mentioned above. The key principle of this instrument is that patients are asked directly about their medication intake over a specified period of time.

The aim of this study is to validate the IMI in chronic outpatients with schizophrenia or a psychotic disorder. The results will be compared with four other frequently used subjective adherence measures: the Medication Adherence Rating Scale (MARS), the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), the Compliance Rating Scale (CRS) and a simple 100-point clinician estimate of medication adherence. The electronic Medication Event Monitoring System (MEMS) will be used as the gold standard to validate all the other measures. We will calculate the correlation with the MEMS for all measures, as well as sensitivity and specificity, and positive and negative predictive values.

Methods

Patients
Patients were recruited in community mental health care teams. The inclusion criteria were a diagnosis of schizophrenia, at least two years of continuous psychiatric care, sufficient command of the Dutch language, outpatient and prescribed oral atypical antipsychotic medication for at least the following 6 months. The study was approved by the Medical Ethics Committee and all patients gave informed consent.

Procedure
We selected three community mental health care teams serving a total of 600 outpatients. On the basis of case files, we selected patients who met the inclusion criteria. Treating clinicians were informed and asked for their approval to approach clients. Patients for whom approval was received were invited in alphabetical order to participate in our study. A research assistant visited the patients once they had given written informed consent. During the first visit, the IMI was completed and patients were instructed to use the MEMS container for the next three weeks. After three weeks, during the second visit,
the MEMS container was collected and the IMI was completed, together with two other self-report adherence instruments, and an exit interview was conducted. Mental health nurses were asked to complete a short questionnaire about their patients’ adherence to antipsychotic medication. Records of actual medication prescriptions were obtained from case files. The patients, the research assistant and the mental health nurses were not aware of MEMS-generated results.

Instruments

The Inventory of Medication Intake (IMI)
The IMI is based on self-reporting and is administered as a structured interview which takes approximately 7 minutes and does not require special training or knowledge. Some experience in interviewing patients with schizophrenia is, however, recommended. In a previous study, we assessed the efficacy of adherence therapy based on motivational interviewing techniques in patients with schizophrenia (Gray et al., 2006). We found that if an understanding, open-minded atmosphere was created, patients were usually frank about how they used their medication. Assessments were therefore preceded by a compulsory introduction aimed at promoting a non-judgemental and understanding atmosphere with a view to reducing patients’ hesitancy to be frank. During this introduction, the patients were told that, for anyone who is prescribed medication for a longer period of time, it is quite common to deviate from their prescription because people may feel more comfortable using more or less medication. It was explained that it is understandable for medication to be forgotten sometimes or for a mistake to be made. We also told patients that, if they told us that they had deliberately used more or less medication, they would not have to explain their reasons to us. Finally, we explained that any information we collected was confidential and would not be reported to their clinician or key worker.

After the introduction, patients were asked to report their medication regimen for all prescribed medication (see Appendix 1). Throughout the questionnaire, the number of pills was chosen as the unit of reference rather than the dose or the general expression ‘medication’. We expected this to be the easiest approach for patients and to generate the most accurate responses. Patients were then asked to report the number of days on which they had not taken that agent at all over the past three weeks. Three weeks was considered the maximum period for which most patients would be able to reconstruct their medication intake. Finally, they were asked to state the number of days on which their intake was more or less than prescribed, and how many pills they had taken on
the days they had not followed their prescription. Patients were asked whether their individual deviations from the prescription were intentional or accidental in each case. This was repeated for each prescribed psychotropic medication. The research assistant noted the answers.

Other self-report adherence instruments
The Medication Adherence Questionnaire (MAQ) consists of four yes/no questions and addresses ways in which patients may fail to take their prescribed medication (Morisky et al., 1986). Patients with a score ≤3 on the MAQ were considered non-adherent (George et al., 2000; et al., 1986; Rith & Ivey, 2005).

The Drug Attitude Inventory (DAI) asks patients to decide whether ten yes/no statements reflecting experiences, attitudes and beliefs about medication apply to them. Patients were labelled non-adherent if the sum of the negative items was greater or equal to the sum of the positive items (Hogan et al., 1983).

On the basis of the MAQ and six items from the DAI, it was possible to compute a third adherence scale: the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000). A higher score on the MAQ, DAI and MARS indicates better adherence.

Clinician reports
Although mental health nurses do not prescribe medication in our system, they have the most frequent contacts with patients. We therefore asked the nurses to estimate, for the antipsychotic medication only, the percentage of pills taken by the patient during the three-week period. They were also asked to indicate how confident they were about this estimate by choosing a range of 10%, 20% or 30% either way as a confidence interval.

Nurses were also asked to rate adherence behaviour using the 7-point Compliance Rating Scale (CRS). For each score, a brief description of adherence behaviour was provided, ranging from complete refusal to active participation in medication treatment (Kemp et al., 1998). Patients with a score ≤ 4 on the CRS were labelled non-adherent (Byerly et al., 2005; Kemp et al., 1998; Kemp & David, 1996; Mutsatsa et al., 2003).

MEMS
The Medication Event Monitoring System (MEMS) was used as the standard for validating all the other adherence instruments. The MEMS is an electronic device placed out of sight in the cap of a standard medication bottle. This cap registers the time and date of all openings of the medication bottle and is considered a valid indicator of medication intake.
(Byerly et al., 2007; Diaz et al., 2001; Nakonezny et al., 2008). The medication bottle contained only the primary oral antipsychotic medication.

The research assistant helped patients to place their medication in the medication bottle and told them that they should take all the antipsychotic medication they wanted to use from this bottle. It was emphasised that participation in the study should not interfere with medication intake. Patients were told about the MEMS device. Although the medical ethics committee approved withholding information from patients about the MEMS mechanism, we were concerned about potential damage to patient trust if they found out independently. In addition, during a pilot study, we had found it difficult to instruct patients without informing them.

Analysis

We defined medication adherence as the proportion of medication intake to prescribed medication during the three-week period. MEMS adherence rates were based on the total number of openings, regardless of the time of opening. To account for errors in MEMS data we asked patients during an exit interview (a) whether all the antipsychotic medication consumed was taken from the medication bottle, (b) whether the medication bottle had been opened without any pills being taken, (c) how often the medication bottle was opened for refilling, and finally (d) whether there had been any changes in the medication prescription. This information was used to correct the MEMS data. Bottle openings for refilling were, for instance, removed from the final MEMS data file.

IMI adherence rates were calculated using the self-reported medication intake based on questions 7, 9 and 10 of the IMI (see Appendix 1). Patients were considered adherent if their medication intake was between 80% and 110% of their prescribed antipsychotic medication. Patients using less than 20% of their prescribed medication were considered non-adherent. The remaining patients were classified as being partially adherent or, if they consumed more than 110%, as over-consumers.

A Pearson correlation was calculated between MEMS adherence rates and all other adherence instruments after we had checked whether the basic conditions had been met for this test. We also calculated univariate linear regression for the IMI. Specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for all adherence instruments. Test-retest reliability was calculated using a Pearson correlation.
Results

A total of 124 patients who met the inclusion criteria were selected for participation. Of these patients, 38 refused to cooperate, and the medical health nurses of 27 patients decided that participation would be too stressful, or too difficult for them. Eight of the patients who refused were reluctant to use the MEMS device, twelve preferred to continue using their pill box, and the remaining patients did not give a reason. A total of 59 patients agreed to participate in the study. The data of three patients were lost because the MEMS caps were lost. Another five patients did not understand the instructions and opened the MEMS container more often in order to ‘count’ medication as being taken. In all, the data of 51 patients (37 males and 14 females) were included in the analysis (see Table 1).

Correlation of IMI with MEMS

We first checked whether the medication regimen, as reported by the patient on the IMI, matched the actual prescription. In the case of nine patients, we found that the prescription reported by the patients on the IMI was different from the actual prescription. Seven patients were mistaken about the dosage (mg) of their prescribed medication. Another two patients were mistaken about the number of pills prescribed a day. Where there were differences between reported and actual medication prescription, the actual prescription was used to compute levels of adherence.

According to the MEMS, 25.5% of patients were not fully adherent during the measurement period. Average medication intake deviated 11.9% (SD=17.3) from medication prescription. According to the IMI, 7.8% of patients were not fully adherent and the average deviation was 3.9% (SD=10.4) (see Table 2).
Table 1. Characteristics of included patients (n=51)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>44.8</td>
<td>(9.3)</td>
</tr>
<tr>
<td>Sex, male, N (%)</td>
<td>37</td>
<td>(72.5)</td>
</tr>
<tr>
<td>Diagnosis, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>47</td>
<td>(92.2)</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>4</td>
<td>(7.8)</td>
</tr>
<tr>
<td>GAF score, mean (SD)</td>
<td>50.8</td>
<td>(10.7)</td>
</tr>
<tr>
<td>Level of education, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>6</td>
<td>(11.8)</td>
</tr>
<tr>
<td>High school</td>
<td>19</td>
<td>(37.3)</td>
</tr>
<tr>
<td>Higher education</td>
<td>6</td>
<td>(11.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
<td>(39.2)</td>
</tr>
<tr>
<td>Cultural background, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>32</td>
<td>(62.7)</td>
</tr>
<tr>
<td>African</td>
<td>5</td>
<td>(9.8)</td>
</tr>
<tr>
<td>Caribbean, Surinam</td>
<td>5</td>
<td>(9.8)</td>
</tr>
<tr>
<td>Other Europe</td>
<td>4</td>
<td>(7.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>(3.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>(5.9)</td>
</tr>
</tbody>
</table>

Table 2. Adherence rates according to the MEMS and the IMI (n=51)

<table>
<thead>
<tr>
<th>Adherence categories</th>
<th>MEMS N</th>
<th>%</th>
<th>IMI N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% – 20% (non-adherent)</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>21% – 80% (partial adherent)</td>
<td>11</td>
<td>21.6</td>
<td>4</td>
<td>7.8</td>
</tr>
<tr>
<td>81% – 110% (adherent)</td>
<td>38</td>
<td>74.5</td>
<td>47</td>
<td>92.2</td>
</tr>
<tr>
<td>110% – 140% (over-consumption)</td>
<td>2</td>
<td>3.9</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Intent or mistake**

Patients were asked to report, for each day they deviated from their medication prescription, whether they had done so deliberately or by mistake. A total of 13 patients said they had deviated on between 1 and 6 days from their prescription because they had forgotten their medication or made a mistake (e.g., accidentally taken an extra dose). One patient deliberately deviated from his prescription on 13 days.
Validation of the inventory of medication intake

Test-retest reliability
The correlation between reported adherence rates on the IMI at the first and second visits was 0.998, p=0.000. Assuming patients did not change their adherence behaviour, this indicates high test-retest reliability.

Correlation with IMI
Table 3 shows the mean adherence rates derived from the various adherence instruments and their correlation with MEMS. We checked for all instruments whether the basic assumptions for a Pearson correlation had been met. The correlation between the MEMS and IMI adherence rates was 0.445 (p=0.001). Correlation coefficients for the other instruments were lower and ranged from -0.067 to 0.169. We performed a linear regression with MEMS as the dependent variable and IMI as the independent variable and found an R² of 0.20, and a β of 0.81 (p=0.001).

Specificity and sensitivity
Using a cut-off point for the MEMS adherence rate of 80%, sensitivity and specificity were calculated for all adherence instruments (Table 3). This cut-off point of 80% is the most frequently used cut-off criterion in adherence research for patients with schizophrenia (Valenstein et al., 2002). Optimal sensitivity for the IMI was found with a cut-off point of 89.0. Sensitivity was 36.4 and specificity was 97.5, with an area under the curve of 59.5. The positive predictive value was 80.0, and the negative predictive value was 84.8. PPV and NPV were influenced by the prevalence of adherent and non-adherent patients in the sample and so we also present the PLR and NLR, which indicate that the IMI performs better than the other instruments.

To calculate sensitivity and specificity for the MAQ, DAI and CRS we used standard cut-off criteria derived from the literature. For the MARS and clinician estimates, we adopted cut-off points of 8.9 and 98.5 respectively, since this resulted in the best possible sensitivity with acceptable specificity. Sensitivity for the various instruments varied from 10.0 to 70.0, and specificity ranged from 38.9 to 97.5.

Nurse estimates of the proportion of taken medication on a range from 0% to 100% correlated poorly with actual adherence rates according to the MEMS data. When nurses were asked to state a confidence interval for their adherence estimates, the majority (81.8%) thought their estimates would not be more than 10% inaccurate in either direction. Accounting for this confidence interval, actual adherence rates fell in 75.0% of cases within this confidence interval. Adherence was overestimated in 22.7% of cases, and underestimated in 2.3% of cases.
Table 3. Means for adherence instruments, and the relationship with MEMS (n=51)

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Mean</th>
<th>SD</th>
<th>Correlation with MEMS</th>
<th>Sensitivity¹</th>
<th>Specificity²</th>
<th>AUC</th>
<th>PLR</th>
<th>NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI</td>
<td>0-100</td>
<td>96.1</td>
<td>10.4</td>
<td>0.445 0.001</td>
<td>36.4</td>
<td>97.5</td>
<td>59.5</td>
<td>14.56</td>
<td>0.65</td>
</tr>
<tr>
<td>MARS</td>
<td>0-10</td>
<td>7.8</td>
<td>1.7</td>
<td>0.169 0.261</td>
<td>70.0</td>
<td>38.9</td>
<td>53.1</td>
<td>1.15</td>
<td>0.77</td>
</tr>
<tr>
<td>MAQ</td>
<td>0-4</td>
<td>3.6</td>
<td>0.7</td>
<td>0.070 0.645</td>
<td>30.0</td>
<td>77.1</td>
<td>51.8</td>
<td>1.31</td>
<td>0.91</td>
</tr>
<tr>
<td>DAI</td>
<td>0-10</td>
<td>7.1</td>
<td>2.2</td>
<td>0.097 0.519</td>
<td>20.0</td>
<td>72.2</td>
<td>45.6</td>
<td>0.72</td>
<td>1.11</td>
</tr>
<tr>
<td>CRS</td>
<td>1-7</td>
<td>6.3</td>
<td>1.1</td>
<td>-0.067 0.659</td>
<td>10.0</td>
<td>94.4</td>
<td>38.3</td>
<td>1.79</td>
<td>0.95</td>
</tr>
<tr>
<td>Clinician estimate of adherence</td>
<td>0-100</td>
<td>95.5</td>
<td>7.2</td>
<td>0.083 0.594</td>
<td>50.0</td>
<td>67.6</td>
<td>56.5</td>
<td>1.54</td>
<td>0.74</td>
</tr>
</tbody>
</table>

¹ Probability that a non-adherent patient will be classified as non-adherent by the adherence instrument
² Probability that an adherent patient will be classified as adherent by the adherence instrument
³ Area under the curve
⁴ Positive likelihood ratio; ratio between the probability that a non-adherent patient will be classified as non-adherent by the adherence instrument, and the probability that a adherent patient will be classified as non-adherent by the adherence instrument [sensitivity/(1-specificity)]
⁵ Negative likelihood ratio; ratio between the probability that a non-adherent patient will be classified as adherent by the adherence instrument, and the probability that a adherent patient will be classified as adherent by the adherence instrument [(1-sensitivity)/specificity]

Discussion

In this study, we assessed the feasibility of the IMI and validated the IMI using the MEMS as the gold standard. IMI feasibility was good, and administration of the instrument was easy, taking approximately 7 minutes. Even though the mean GAF score in our sample was 51, no one found the questions difficult. We checked whether patients with lower GAF scores would make more errors in reconstructing their intake of medication and found no differences.

The adherence rates derived from the IMI refer exclusively to the proportion of consumed antipsychotic medication during the past three weeks. This makes the interpretation of the IMI straightforward and improves comparability, as recommended by Velligan et al. (2006).

With the IMI, we tried to improve on all existing subjective instruments by a) using a direct simple approach asking patients to report deviations from prescription, b) using
Validation of the Inventory of Medication Intake

pills as a reference, c) focusing on one type of medication, d) creating a non-judgemental environment. The resulting IMI is, in our view, the best possible subjective instrument for assessing adherence. The IMI outperforms the other subjective adherence instruments in our study in terms of sensitivity, specificity, NPV, PPV, and PLR and NR. Even so, using 80% adherence on the MEMS as a cut off point for non-adherence, the IMI misses two-thirds of all non-adherent patients, resulting in a sensitivity of 36.4. This makes its validity questionable and raises the question whether subjective methods are an appropriate way of identifying non-adherent patients.

A few questions had been added to the IMI to gain some insight into patient adherence. Two patients were non-adherent because they erred in their interpretation of their medication prescription. We also found that most non-adherence is unintentional, although we must bear in mind that patients may not easily admit to deliberate non-adherence. However, if forgetting about medication is a major reason for non-adherence, it is likely that many deviations are not accounted for on the IMI, resulting in higher adherence rates. Finally, we found that 20.8% of all patients did not know or understand what their prescribed antipsychotic medication was for, or only took it because it was prescribed to them.

This study has limitations. In some respects, our patients may not have been representative for the entire population. They had, on average, high adherence rates. Valenstein et al. (2006) found that, at any one time, adherence was poor in 37% of patients (< 0.8). In our sample, this was 22%. This may be caused by self-selection bias. Approximately half of all the selected patients were excluded. Furthermore, included patients were informed that their medication intake would be monitored. Although we stressed that this should not influence their behaviour and that they should use their medication as desired, we cannot exclude the possibility that patients were more aware of, or even compensated for, missed doses. We do not know how this affected our results. We can speculate that adherent patients are more forthcoming about their medication intake than non-adherent patients. If so, this may have had a positive impact on our results. We checked for this possibility and found no differences in correlation coefficients between the MEMS and the IMI for adherent and non-adherent patients. This may indicate that self-reports of non-adherent patients on the IMI are as valid as those from adherent patients.

In this study, patients were aware that information was confidential and not available to their treating clinicians. Depending on the therapeutic relationship, patients may be more or less hesitant to admit to deviations from their prescription. Although
administering the IMI in a clinical setting may be a good starting point for the discussion of medication use, further research will be needed to determine the validity of the IMI in such settings.

Recently, Byerly et al. (2008) reported on the BARS, an instrument quite similar to the IMI which was also administered by research assistants. Byerly et al. found a correlation coefficient with electronic medication monitoring (r=0.59) that was similar to our study, but they found higher sensitivity (73.1) and lower specificity (74.3) in sample of 61 patients with schizophrenia and schizoaffective disorder. Their study used a cut-off point of 70%. With the same cut-off point, the sensitivity and specificity of the IMI are 50.0 and 97.8 respectively. There are, however, some differences. Firstly, the BARS combines self-reporting with a clinician rating. The research associates estimated adherence rates on a visual analogue scale on the basis of information given by the patient. In the IMI, the self-reported information was used to compute the adherence rate in conjunction with the actual prescription. Secondly, Byerly et al. assessed patients more often and over a longer period of time. Finally, their sample included patients with schizoaffective disorders, more women, and fewer Caucasian patients. More importantly, however, the adherence rates in the sample of Byerly et al. were lower and more representative than in our sample.

Patients using atypical antipsychotics may be more adherent than users of conventional antipsychotics, but study results are not conclusive (Valenstein et al., 2004; Kahn et al., 2008; Lacro et al., 2002; Lieberman et al., 2005). Although there is no evidence to justify the assumption that the type of medication would have affected our results, we ensured that all patients in this study used atypical antipsychotic medication in order to improve the homogeneity of our sample.

Approximately one quarter of all adherence studies use non-validated adherence measures (Nichol et al., 1999). Nichol's study, as well as other studies, has shown that many measures, even though they are apparently valid, are poor indicators of medication adherence. Several studies, for instance, consistently showed that clinician reports are not valid. Nevertheless, this is the second most frequently used method in adherence research (Velligan et al., 2006). We advise researchers to refer exclusively to well described and validated instruments.

The use of the MEMS device has some drawbacks, as described by other researchers. It is not possible to check whether the right number of pills are taken each time the medication bottle is opened, and some of the MEMS caps were lost. In addition, we also found that the MEMS is quite difficult to use for some patients. Patients with
paranoid features were particularly reluctant to use the MEMS device. Others found it too confusing and, for instance, thought they had to press the counting device in the cap manually to count each pill taken.

The IMI is a feasible instrument but suffers from poor sensitivity. Depending on the cut-off point for the MEMS adherence rate, only 36% to 50% of non-adherent patients were detected by the IMI. Those who were labelled as non-adherent by the IMI were, however, labelled correctly in the majority of cases (80%) according to the MEMS.

In this study, IMI was superior to other, frequently-used, subjective measures of adherence. The IMI has a better correlation coefficient with MEMS and better positive predictive value. We therefore conclude that, if a quick, easy and cheap measure is required, the IMI should be used in combination with an objective measure such as electronic monitoring, pill counting, or refill rates and prescription records. Bearing in mind the more acceptable sensitivity and specificity characteristics found by Byerly et al. (2008) we conclude that further research into the validity of this method is necessary.

Researchers should continue to strive for better adherence measures. In this study, we hope to have demonstrated that sympathising with the difficult task of taking medication each and every day, and simply listening to patients, constitute an alternative way of acquiring valuable information.

Acknowledgements
This study was supported by AstraZeneca. We wish to acknowledge the contributions of the patients and staff who took part in this study.
References


Validation of the inventory of medication intake


Appendix 1: Inventory of Medication Intake (IMI)

Instructions

This questionnaire should be administered in an interview with the patient.

Answers are noted on the form by the interviewer.

The questionnaire assumes that the medication prescription dictates daily intake. If medication has to be taken with a lower frequency, please note the timeframe (e.g. week or month) the dose refers to.

The following introduction must be used before each interview.

Introduction

“In the following questions I would like to ask you about the use of medication. Although medication is prescribed by clinicians, it is up to the patient to decide whether or not they want to use them.

We know from other patients that it is difficult to comply with a medication prescription and it is quite common to deviate. Patients may sometimes feel more comfortable when they use more or less medication than is prescribed to them. And it is also obvious that medication may sometimes be forgotten or that other mistakes may be made.

I am interested in how much medicine you have taken in the past three weeks. If you have taken more or less of the medicine than was prescribed to you, you do not need to explain to me why. Please try to remember how you managed your medicine in the past three weeks.”
Validation of the inventory of medication intake

Questions
1. Are you being prescribed medication at the moment?  
   | yes | No (end interview) |
2. How many different drugs have been prescribed to you?  
   | ……. |
3. Can you tell me the names of these drugs?  
   | note in table below |

Pursue only the agents of interest in the remainder of the questionnaire. Ask questions 4 to 11 for each agent separately. Note the answers to the following questions in the table below:

4. Can you tell me what [agent] is for?
5. According to your prescription, do you know how many pills of [agent] you need to take each day?
6. Do you know the dose of one pill?

7. In the past three weeks, on how many days have you not taken [agent] at all?
8. If so, had you forgotten your medicine or did you choose to not take it?

9. In the past three weeks, how many days did you take more or fewer pills than was prescribed to you in the past three weeks?
10. If so, how many pills of [agent] did you take on average on these days?
11. Was this by mistake or deliberate?

Continue with question 4 for the next agent
<table>
<thead>
<tr>
<th></th>
<th>3. agent</th>
<th>4. purpose</th>
<th>5. number of prescribed pills (pills/day)</th>
<th>6. dose (mg/pill)</th>
<th>7. number of days pills were not taken at all (days)</th>
<th>8. forgotten or deliberate (forgotten)</th>
<th>9. number of days a deviating dose was taken (days)</th>
<th>10. average number of pills on deviating days (pills/day)</th>
<th>11. mistake or deliberate (mistake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 7

General Discussion
This thesis looked at several aspects of medication adherence in patients with schizophrenia. The QUATRO study (Quality of life following adherence therapy for people disabled by schizophrenia and their carers) examined the effect of adherence therapy, an intervention for improving adherence based on motivational interviewing techniques. Next, we explored the concept of medication adherence, and factors involved in patients’ decision-making about taking their medication. We then focused on a methodological area: the quality of adherence instruments. We first explored the overlap and validity of three adherence measures used in the QUATRO study. Subsequently, we tried to improve the assessment of medication adherence by developing a new adherence instrument – the Inventory of Medication Intake (IMI) – before, finally, determining the validity and feasibility of this new instrument. This chapter discusses the main results, as well as the methodological strengths and weaknesses, of these studies. Finally, we will discuss the implications of our findings, make recommendations, and give directions for future research.

7.1 Main findings and methodological issues

7.1.1 The effect of adherence therapy on non-adherence in a European sample of schizophrenia patients?

The aim of the QUATRO study was to assess the effectiveness of adherence therapy as developed by Kemp et al. (1996) in schizophrenia patients with recent clinical instability. In a single-blind, multicentre, international randomised controlled trial, 409 patients were allocated to either an experimental or control condition. The experimental condition included eight sessions of individual adherence therapy. Patients in the control condition received a placebo intervention consisting of eight sessions of health education. Both interventions were provided by therapists with a background in delivering clinical interventions to people with schizophrenia. Patients in both conditions also received standard psychiatric care from their regular care provider. Assessments took place at baseline and 12 months later.

The QUATRO study clearly demonstrated that adherence therapy was no more effective than health education in improving quality of life, medication adherence, or psychopathology. After 12 months, the addition of adherence therapy to regular psychiatric treatment, had no effect on any outcome variable. This contradicts the results found by Kemp et al. (1996; 1998). Given these inconsistent results, it remains uncertain whether this approach should be discarded.
Methodological considerations

There are some methodological considerations relating to the study sample, intervention, and outcome assessment which will be discussed here.

a. Study sample

An advantage of the QUATRO study is that patients were recruited in four cities in different European countries. This enhances the potential for the generalisation of the results. Furthermore, this was the largest adherence therapy trial yet conducted, enabling sufficient statistical power. After the study performed by Kelly and Scott (1990), it was also the second largest trial ever conducted to study the effects of an intervention for improving adherence.

By selecting patients who had been clinically instable in the previous year, we hoped to include patients who were more likely to have problems with medication adherence. Nevertheless, adherence in our sample was only moderately impaired. It is therefore possible that relatively few patients were in a position to benefit from adherence therapy.

b. Intervention

In accordance with the adherence therapy manual of Kemp et al. (1996), adherence therapy was given in addition to care as usual in a limited number of sessions. On average, patients attended 7 weekly sessions with a mean duration of 36 minutes each. It is possible that the duration or total number of adherence therapy sessions in our study was too limited to instil an effect that persisted after one year. Most researchers agree that interventions focusing on behavioural changes, especially in patients with mental disorders, may have a better long-term effect if they are repeated more often, over longer periods, and if booster sessions are used (Burke 2003; Zygmunt et al., 2002).

Another consideration with respect to the intervention is that the therapists providing the adherence therapy were not the patients’ usual key workers. This allowed the therapists to focus exclusively on adherence issues, and made it easier to follow the principles of adherence therapy. However, this also meant that the therapists, at least at the outset, were not familiar with the patient and vice-versa, and had fewer opportunities to establish a good therapeutic alliance. A study by Frank and Gunderson (1990) showed that it is difficult and time-consuming to establish a good therapeutic alliance, especially in patients with psychosis. In a sample of 143 patients with schizophrenia, only 14% of patients had a good therapeutic alliance after one month of individual psychotherapy. After three months, by which time adherence therapy would have ended in our study, the
alliance was good in only 21% of patients, and fair in 41%. Our study did not measure therapeutic alliance but it seems fair to assume that seven sessions will not have been enough to establish a good therapeutic alliance. This may have affected our results given the overwhelming evidence indicating that patients who have a good relationship with their therapist have more favourable outcomes and better adherence (Day et al., 2005; Frank & Gunderson, 1990; Hewitt & Coffey, 2005; Llorca, 2008; Martin et al., 2000).

c. Outcome assessment

It was hypothesised that poor adherence would have an adverse effect on clinical outcome and functioning, and consequently impair health-related quality of life. The mental component summary scale (MCS) of the 36-item version of the Short Form Health Survey (SF-36) was therefore chosen as the primary outcome variable in the QUATRO study. The SF-36 MCS has good psychometric properties and is a well-established measure of clinical relevance in patients with schizophrenia (Leese et al., 2008; Meijer et al., 2002; Rood et al., 2000; Russo et al., 1998; Tunis et al., 1999). The SF-36 MCS focuses on the direct consequences of health and functioning, and less on life satisfaction (Meijer et al., 2002). This makes it useful for the evaluation of the effects of adherence therapy since it is less sensitive to other factors such as social support, unemployment, housing situation, financial problems, etc.

However, there are studies indicating that the MCS is strongly influenced by mood symptoms in particular (Kaiser et al., 1997; Priebe et al., 2000; Scialfa et al., 2003), cognitive disorders, negative symptoms (Galletly et al., 1999; Ho et al., 1998; Packer et al., 1997) and side effects (Mäkinen et al., 2008). Positive symptoms may not have such a strong influence on subjective well-being (Pinikahana et al., 2002; Puschner et al., 2006, 2009). Antipsychotic medication, however, primarily affects positive symptoms, has little or no impact on affective and negative symptoms, and has a reverse impact on side effects. The effect of adherence on health-related quality of life as measured with the SF-36 MCS may therefore be limited. It should, however, be noted that although the SF-36 MCS may have had some limitations, this does not affect the main conclusions from our study. Results for all other outcome variables such as adherence and psychopathology clearly indicated that adherence therapy had no impact at follow-up.

Finally, the follow-up assessment was performed 12 months after the start of the intervention. A meta-analysis of 72 clinical trials evaluating motivational interviewing (Hetterman et al., 2005) showed its impact declines over time. The average short-term effect size of motivational interviewing is 0.77 at 0 to 1 month after treatment but 0.3 within
General discussion

6 to 12 months. Follow-up longer than 12 months has shown a reduction in the average effect to 0.11. It is possible that the effects in our study had disappeared by the time of the follow-up assessment.

7.1.2 The reasons for adherence and non-adherence to antipsychotic medication in schizophrenia patients

To enhance our understanding of medication adherence, we explored factors that may influence decision-making relating to the use of antipsychotic medication in schizophrenia patients. We used concept mapping, a structured qualitative method, for this purpose. In group sessions, we discussed and explored all factors that may influence the decision to take antipsychotic medication in schizophrenia patients in four European countries. Three separate sessions were held in each country for patients, carers and professionals respectively, resulting in a total of 12 sessions. During these sessions, the participants generated statements which they believed were a reflection of factors influencing medication adherence. After the statements had been collected, the participants were asked individually to cluster statements that belong to the same category, and to indicate the relative importance of each statement in the decision-making process.

Statements were generated by 91 participants, and clustered and rated by 84 participants from the three stakeholder groups. Based on a statistical analysis of the data, 10 clusters of statements were found to influence medication adherence. In a further interpretation of these clusters we identified five clinically relevant themes: medication efficacy, external factors (such as patient support, and therapeutic alliance), insight, side effects, and attitudes toward medication. The ratings of the importance of the statements indicated that there was no consensus among professionals, carers and patients about which factors are most important in medication adherence. Professionals believed that insight and the negative aspects of medication such as side effects and negative medication attitudes had most effect on patients’ adherence decisions. Patients also thought that insight was important but, in contrast to the professionals, both patients and carers found that the efficacy of medication was most important.

Methodological considerations

Concept mapping is a novel approach to the exploration of medication adherence in schizophrenia patients. Most studies exploring risk factors for non-adherence have, until now, used a quantitative approach. By comparison with quantitative methods, concept mapping has some advantages and drawbacks.
a. Advantages
A severe limitation of quantitative methods is that the results are limited to areas selected beforehand by the researchers. Quantitative studies are therefore unlikely to provide a comprehensive overview of all the relevant factors affecting adherence. Furthermore, quantitative studies depend on the validity of the instruments used. As already discussed here, measuring levels of non-adherence is difficult and this poses a serious problem for the validity of the results. Concept mapping does not have these drawbacks. Participants can state all the factors they think affect adherence, without any limitations. Another advantage of our study was that the results represent the perspectives of three different stakeholder groups from four European countries. This means that our results provide a comprehensive and representative overview of all relevant issues affecting patients’ decision-making processes relating to adherence.

b. Drawbacks
Concept mapping is a feasible way of assessing participants’ thoughts and ideas. In our analysis, we assumed that the thoughts and ideas that emerged were a valid reflection of the actual factors affecting adherence and the importance of those factors, but we were unable to confirm this. Patient reports may, for instance, omit factors they are not aware of or do not want to disclose. We therefore examined the scientific literature on this topic, and found evidence justifying our main conclusions.

Another drawback of concept mapping is that, at two stages of the procedure, subjective decisions need to be made by the researchers. Firstly, the number of statements generated by the focus groups was too large to be clustered and prioritised and paring-down was therefore necessary. This process of combining and discarding statements was performed in two stages on the basis of the consensus of five and, in the second stage, three independent researchers. This procedure ensured a balanced set of statements, even though we cannot rule out the possibility that some information may have been lost. Secondly, subjective decisions were involved in determining the final concept map, and in the interpretation and labelling of its clusters. The final concept map can have any number of clusters varying from 2 to 20. It is up to the researcher to select the most understandable and meaningful solution. In our study, after carefully exploring several options, we chose a concept map with 10 clusters. We considered this to be the minimum number of clusters for ensuring that clinically relevant information is not lost. Although it is apparent that, at some stages, the researchers have had some influence on the final concept map, we believe that this has not affected our main conclusions. In particular, the
clusters that were given high priority ratings were also present in solutions with more or fewer clusters.

7.1.3 The concurrent and predictive validity of adherence assessments as used in the QUATRO study?

In chapter 4 we explored the concurrent validity of three subjective adherence instruments used in the QUATRO study – the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI) and the Compliance Rating Scale (CRS) – using data from the QUATRO trial. All these three instruments are still in frequent use in adherence studies. They all claim to assess adherence behaviour, but use different approaches. We examined the extent to which they matched in terms of labelling patients as non-adherent, measure the same concept, and how they were related to established risk factors for non-adherence. In chapter 5, we examined the predictive validity of these instruments using data for stabilised schizophrenia outpatients who participated in the QUATRO study. The outcome criteria were relapse and admission during the 12-month follow-up period.

On the basis of data for 329 schizophrenia outpatients, we found that agreement between the three subjective measures for all these areas was poor. We concluded that the three instruments did not measure the same concept. This was most clearly reflected in the poor overlap of patients labelled as non-adherent by these instruments. In addition, all three instruments were only weakly related to the factors which are consistently associated with non-adherence in the literature.

The results in Chapter 5, which are based on the data for 119 stabilised outpatients with schizophrenia, showed that the predictive validity of all three adherence instruments was also poor. Although relapse, admission, and time to relapse were related to the MAQ, and the CRS was related to admission and time to admission, the strength of these relations was limited, especially from a clinical point of view. The DAI and CRS labelled most patients as adherent, resulting in low sensitivity and high specificity. Sensitivity and specificity were better in the MAQ but none of the instruments clearly identified patients who suffered a relapse or who were hospitalised during the 12-month follow-up period.

Methodological considerations

There are two main methodological considerations which will be discussed here. These concern the potential for the generalisation of the results of chapters 4 and 5, and the assumption made in chapter 5 that adherence was stable during follow-up.
a. Generalisation
In this analysis we were only able to explore the validity of three subjective instruments. Without further research we do not know to what extent our results are applicable to other subjective instruments. We do know, however, that the instruments in this study were chosen by the QUATRO study group because they were specifically designed to measure adherence and had been used frequently in the past. Furthermore, methodological evidence was also available about the validity of the instruments. These are criteria that are not met by a considerable number of other subjective adherence instruments (Velligan et al., 2006).

b. Stability of adherence
In chapter 5, we assume that patient adherence, as measured at baseline, remains stable during follow-up, allowing us to examine the predictive validity of the three instruments. Although Valenstein et al. (2006) state that this assumption is justified for the majority of patients, other studies have suggested that fluctuating adherence may be more common (Herings et al., 1992). Unfortunately, we were unaware of any changes that may have occurred in patient's adherence after the baseline assessment in our study. We performed an additional analysis to examine predictive validity for shorter follow-up periods of 3 and 6 months. Although this reduced the impact of possible changes in adherence behaviour over time, the results were the same. Nevertheless, we cannot exclude the possibility that adherence in some patients fluctuated during follow-up.

7.1.4 What is the validity of the IMI?
Our next step was to devise the Inventory of Medication Intake (IMI) in order to address some of the shortcomings of most subjective instruments used to date. To explore the validity of the IMI, we assessed medication adherence in 51 outpatients with schizophrenia using the Medication Event Monitoring System (MEMS) over a period of approximately three weeks. At baseline and follow-up, we administered the IMI and several other adherence instruments. Using MEMS as the standard, we computed the sensitivity, specificity, positive and negative likelihood ratios for the IMI and several other instruments.

The results of this study do not justify promoting the use of the IMI. Although the IMI was significantly related to MEMS adherence rates, and although it outperformed the other subjective adherence instruments in terms of sensitivity, specificity, positive
and negative likelihood ratios, it overestimated adherence and missed two thirds of non-adherent patients. The resulting poor sensitivity is a serious drawback of this instrument.

**Methodological considerations**

A few methodological considerations with respect to the study sample and the limitations of self-reporting will now be discussed.

a. **Study sample**

In our study 21% of selected patients were not eligible to participate, and 39% of remaining patients refused to participate. In addition, the data of 14% of included patients could not be used because MEMS caps were lost or because the instructions were not properly understood. This indicates that our sample may have been biased towards patients who were capable of, and willing to, follow study instructions. Our MEMS data seem to corroborate this: 75% of the patients included were adherent and this figure is higher than expected given the literature. It is possible that this has affected our results. Patients in our sample, compared with average schizophrenia patients, may have been more able and prepared to report their medication intake over a three-week period accurately. This would have benefited the validity of the IMI. On the other hand, only 11 patients in our sample were partially adherent or non-adherent (defined as using less than 80% of the prescribed medication). It is disputable whether this number is enough for a valid appraisal of the sensitivity of the IMI.

b. **Self-reporting**

It is known that self-report instruments can be flawed because of the misinterpretation of questions, recall bias, socially desirable answers, or misinformation (Brooks et al., 1994; Cox et al., 1994; Hays & DiMatteo, 1987; Kimberlin & Winterstein, 2008; Osterberg & Blaschke, 2005; Svarstad et al., 1999; Tourangeau & Yan, 2007). In our study, we tried to create an understanding atmosphere, and we stressed the confidentiality of the information in order to reduce socially desirable answers. Nevertheless, some patients who claimed to be adherent were non-adherent according to the MEMS. Other measures should possibly have been taken to ensure more accurate responses, such as shortening the recall period, including less threatening questions, or self-administration of the questionnaire (Gagné & Godin, 2005).
Chapter 7

7.2 Clinical implications and future research

This thesis looked at the three main aspects of medication adherence: an intervention for improving adherence, determinants of adherence, and the assessment of adherence. This section elaborates our results further against the background of the literature on adherence. Implications for clinical practice and directions for future research will be discussed.

7.2.1 Interventions for improving adherence

To date, several interventions have been developed to enhance adherence. Unfortunately, there is no single approach underpinned by convincing evidence that it is effective (Byerly et al., 2007; van Dulmen et al., 2007). As a result, professionals remain deprived of proper interventions, guidelines or recommendations. The Dutch Multidisciplinary Guideline for the treatment of schizophrenia (2005) notes that cognitive behavioural therapy and family interventions may be effective in improving medication adherence. However, it does not provide specific recommendations about how to cope with non-adherence.

Adherence therapy

As mentioned in the introduction, according to several reviews published between 2000 and 2003 one of the most promising interventions for promoting adherence in schizophrenia patients was adherence therapy based on motivational interviewing. That is why, after the initial two studies by Kemp et al. (1996, 1998), several other studies were conducted to determine the effectiveness of adherence therapy. We systematically searched the literature, and found in total 8 studies of adherence therapy in patients with psychotic disorders. Table 1 gives an overview of these studies. Three studies, including the QUATRO study, found that adherence therapy had no effect (Byerly et al., 2005a, Gray et al., 2006; O’Donnel et al., 2003). The other five studies did find an effect (Gray et al., 2004; Kemp et al., 1996, 1998; Manesakorn et al., 2007; Tay, 2007).

If we compare the characteristics listed in Table 1 of trials which found that adherence therapy was effective (for the sake of convenience, we refer to these trials as ‘successful’) with those of the trials that did not, we find that:

a. Diagnosis

The original studies of Kemp et al. (1996, 1998) used a heterogeneous sample of patients with psychotic and affective disorders admitted with an acute psychosis. It has been argued that patients with affective disorders may have been more responsive than patients with
psychotic disorders and that this may help to explain the differences between successful and unsuccessful studies (Byerly et al., 2005a). However, two other studies found positive effects of adherence therapy in samples consisting solely of schizophrenia patients (Gray et al., 2004; Maneesakorn et al., 2007).

b. Setting
Trials focusing on either inpatient or outpatient settings were both successful and not successful. Most successful trials were in acute psychiatric wards in patients who were recovering from psychosis. Patients were followed-up after discharge. It can be hypothesised that a substantial proportion of admitted patients had been non-adherent in the preceding period. These patients may be more receptive to adherence therapy: their potential for improvement may be greater than that of outpatients, explaining the larger effect.

c. Adherence therapy
The main characteristics of adherence therapy do not seem to be different in successful and unsuccessful trials. Adherence therapy in all trials was based on the intervention described by Kemp et al. (1996, 1998). The number of sessions varied between 4 and 7 weekly, or twice-weekly, individual sessions lasting between 20 and 60 minutes. Kemp et al., however, provided booster sessions at 3, 6 and 12 months (Kemp et al., 1996, 1998). In the study by Tay (2007), 68% of patients received group sessions, sometimes in combination with individual sessions. Another exception is the study performed by Gray et al. (2004). In their study, adherence therapy was integrated in the usual outpatient care and was therefore not limited in time. These studies may indicate that repeatedly applying adherence therapy through booster sessions or integration in standard care may enhance its effects.

d. Control intervention
The type of control intervention does not seem to have an impact on the effects of adherence therapy. Patients in the control condition received treatment as usual in two successful trials. Controlled trials which added non-specific or supportive counselling to the control for time spent with the therapist, as well as other non-specific factors, were both successful and unsuccessful.
e. Follow-up

The duration of the follow-up period (i.e. the interval between the last adherence therapy session and the follow-up assessment) seems to have some effect on outcome. Two successful studies (Maneesakorn et al., 2007; Tay, 2007) performed the follow-up assessment immediately after the adherence therapy. In the study by Gray et al. (2004), adherence therapy was not limited in time or duration. Assuming that their study used elements of adherence therapy, when appropriate, throughout the course of treatment implies that there is no time gap between adherence therapy and the follow-up measurement. In the studies by Kemp et al. (1996, 1998) the effects of adherence therapy were found up to 18 months after the start of the intervention. However, in this study, booster sessions were given at 3, 6, and 12 months. Two out of three unsuccessful trials (Gray et al., 2006; O’Donnel et al., 2003) had a follow-up period of approximately 10 months. In the third unsuccessful trial (Byerly et al., 2005a) the follow-up period was also relatively short at 3 to 4 months. It seems that studies with shorter follow-up periods tend to find effects of adherence therapy.

We conclude that several studies demonstrate that adherence therapy can be effective in improving adherence in patients with schizophrenia. Studies by Maneesakorn et al. (2007), and Tay (1997) indicate that adherence therapy may have an effect immediately after the intervention. These effects, however, seem to diminish over time. After 5 to 12 months, effects were not found when only 4 to 7 sessions of adherence therapy had been given. When booster sessions were given, or when adherence therapy was integrated in regular psychiatric treatment, long-term effects were found. This corroborates other findings (Burke, 2003; Hertema et al., 2005; Zygmunt et al., 2002). Finally, patients with a recent acute psychosis may be more responsive to adherence therapy. Future studies should focus on patient- or intervention-related conditions which are favourable for adherence therapy.

Improving adherence in other conditions

On the basis of the studies performed by Kemp et al. (1996, 1998), adherence therapy was thought to be a promising intervention. However, the results of adherence therapy trials performed later were inconsistent and disappointing, and it remains unclear which strategy or intervention is most effective in improving medication adherence in patients with schizophrenia. We will therefore broaden our focus and examine adherence interventions in patients with other conditions (Haynes et al., 2005, 2008; McDonald et al., 2002; van Dulmen et al., 2007). Although some of the findings and interventions
in schizophrenia patients and patients with other conditions are similar, there are also differences. There is evidence that behavioural interventions such as memory aids, reminders and feedback are effective in improving adherence. Another behaviour-oriented strategy, contingency management, has been found to be effective in other conditions such as tuberculosis, hypertension, and addiction (Giuffrida & Torgerson, 1997), but the effect in schizophrenia patients is not yet clear (Claassen et al., 2007; Szmukler, 2009).

Simplifying the medication regimen (e.g. by reducing the number of daily doses) is known to improve adherence in several disorders, including schizophrenia (Bangalore et al., 2007). One possible approach is depot medication (Bhanji et al., 2004; Donohoe et al., 2001; McEvoy, 2006; Patel et al., 2008; West et al., 2008). We do not know whether other successful interventions using more technical approaches – such as calendar and electronic blister packaging (Santschi et al., 2007; Schneider et al., 2008), fixed dose combination pills (Connor et al., 2004; ), or short messaging service (SMS) reminders (Cocosila et al., 2009) – are feasible or effective in patients with schizophrenia.

On the basis of a meta-analysis of 122 studies, DiMatteo (2004) concluded that various aspects of social support, but in particular practical support, were effective in improving medication adherence. Psychiatric disorders, however, were excluded from this review. In the fields of schizophrenia research, we found only four published studies since 2003 involving family members in interventions to improve adherence (Bressi et al., 2008; Chan et al., 2009; Li & Arthur, 2005; Pitschel-Walz et al., 2006). Most of these interventions were psycho-educational, and did not involve elements of practical support.

Finally, by contrast with the inconsistent results of adherence therapy in patients with schizophrenia, there is a strong evidence base for the efficacy of interventions based on motivational interviewing in other conditions (Hettema, 2005; Burke, 2003; Martins et al., 2009).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Diagnoses</th>
<th>Setting</th>
<th>Adherence therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemp et al., 1996</td>
<td>RCT</td>
<td>47</td>
<td>psychotic and affective disorders, admitted with acute psychosis</td>
<td>UK, inpatients in acute psychiatric ward (at baseline)</td>
<td>5.1 twice weekly sessions, 20-60min. each; booster sessions at 3, 6 months</td>
</tr>
<tr>
<td>Kemp et al., 1998</td>
<td>RCT (18 months follow-up of extended sample of 1996 study)</td>
<td>74</td>
<td>psychotic disorders, admitted with acute psychosis</td>
<td>UK, inpatients in acute psychiatric ward (at baseline)</td>
<td>4.7 twice weekly sessions, 20-60min each; booster sessions at 3, 6, 12 months</td>
</tr>
<tr>
<td>O'Donnell et al., 2003</td>
<td>RCT</td>
<td>56</td>
<td>schizophrenia</td>
<td>Ireland, inpatients ward</td>
<td>5 sessions, 30-60min. each</td>
</tr>
<tr>
<td>Gray et al., 2004</td>
<td>RCT (randomisation of 60 CMHNs)</td>
<td>72</td>
<td>schizophrenia</td>
<td>UK, outpatients, community mental health</td>
<td>AT integrated in regular care; 80 hours AT training to CMHNs</td>
</tr>
<tr>
<td>Byerly et al., 2005</td>
<td>uncontrolled trial</td>
<td>30</td>
<td>schizophrenia, schizoaffective disorder</td>
<td>US, urban outpatient clinics</td>
<td>4-6 sessions, 30-60min. each</td>
</tr>
<tr>
<td>Gray et al., 2006</td>
<td>RCT</td>
<td>409</td>
<td>schizophrenia</td>
<td>Europe, in- and outpatients</td>
<td>7 weekly sessions, 36 min. each</td>
</tr>
<tr>
<td>Maneesakorn et al., 2007</td>
<td>RCT</td>
<td>32</td>
<td>schizophrenia</td>
<td>Thailand, inpatients at start, and during trial discharged during the trial</td>
<td>7.5 weekly sessions, 43 min. each</td>
</tr>
<tr>
<td>Tay et al., 2007</td>
<td>uncontrolled trial</td>
<td>69</td>
<td>psychotic and affective disorders</td>
<td>Singapore; acute admission ward</td>
<td>1-5 group or individual sessions</td>
</tr>
</tbody>
</table>
### Control intervention Follow-up Instruments Results

<table>
<thead>
<tr>
<th>Control intervention</th>
<th>Follow-up</th>
<th>Instruments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9 supportive counselling sessions; booster sessions at 3, 6 months</td>
<td>baseline; after the intervention; at 3, 6 months</td>
<td>BPRS, GAF, DAI, attitude to treatment, SAI, CRS</td>
<td>effect at 6 months on the DAI-10, SAI, CRS</td>
</tr>
<tr>
<td>4.5 supportive counselling sessions; booster sessions at 3, 6, 12 months</td>
<td>baseline; after the intervention; at 3, 6, 12, 18 months</td>
<td>BPRS, GAE, DAI, SAI, CRS, attitude to medication, National adult reading test, impson-Angus scale for EPD SE.</td>
<td>effect at 18 months on the SAI, CRS, attitude to treatment, GAF, readmission rate</td>
</tr>
<tr>
<td>5 non-specific counselling sessions, 30-60min. each</td>
<td>baseline; at 12 months</td>
<td>Compliance, DAI, PANSS, SAI, GAF, QoL, National adult reading test</td>
<td>no effect</td>
</tr>
<tr>
<td>treatment as usual</td>
<td>baseline; at 6 months</td>
<td>PANSS, DAI-30, CRS, LUNSERs</td>
<td>effect at 6 months on the PANSS(tot), DAI-30, CRS</td>
</tr>
<tr>
<td>no control intervention</td>
<td>3, 2, 1 months prior baseline; baseline; at 5 months</td>
<td>MEMS, CRS, MARS, PANSS, SAI, DAI, LUNSERs</td>
<td>no effect</td>
</tr>
<tr>
<td>7 weekly health education sessions, 30 min. each</td>
<td>baseline; at 12 months</td>
<td>SF-36, BPRS, MAQ, etc</td>
<td>no effect</td>
</tr>
<tr>
<td>treatment as usual</td>
<td>baseline; at 9 weeks</td>
<td>PANSS, GAE, DAI-30, SWAM, LUNSERs</td>
<td>effect at 9 weeks on the PANSS(tot), DAI-30, SWAM. Geen effect op: GAE, LUNSERs</td>
</tr>
<tr>
<td>no control intervention</td>
<td>baseline; after last session</td>
<td>DAI-10, CRS</td>
<td>effect on the DAI-10</td>
</tr>
</tbody>
</table>
Conclusion
A wide variety of adherence interventions have been developed for both schizophrenia and other conditions, all of them targeting different aspects of medication non-adherence. Some focus more on behavioural or practical aspects of medication intake, others on social, affective or cognitive areas. The value of some approaches such as contingency management, technical approaches such as blister packaging, fixed dose combination pills, SMS reminders, and support from family still needs to be examined for schizophrenia patients. Although the literature is not always consistent, there is some evidence for many approaches indicating that they have an effect on medication adherence. However, no single intervention stands out clearly.

We have seen that conclusions with respect to the effectiveness of adherence therapy in schizophrenia patients, even in this restricted research area, are inconsistent. Looking at the eight trials in this area as a whole, we conclude that the efficacy of adherence therapy can be enhanced if it is given repeatedly and over longer periods of time. This may also be true for any other type of intervention for improving adherence. Furthermore, we argue that some patients are more receptive to adherence interventions than others.

Obviously, many patients have no problems adhering to their medication regimens, and adherence interventions are unlikely to have any effect in these cases. It would therefore be advisable to make an individual assessment of the need to take action with respect to medication adherence. Furthermore, if intervention is indicated, a careful assessment may identify the most suitable type of intervention. The next section will discuss the variety of causes underlying non-adherence. Patients may find side effects intolerable, lack insight, or forget to take the medication. As a result, the effectiveness of any intervention will depend on how well it fits in with patients’ needs, ideas and expectations. Some strategies may not be effective for all patients, but only for a small subsample. Daily SMS reminders will only be effective in patients who want to use their medication but find it difficult to do so regularly. Given this differentiation, it is unlikely that any single intervention will be effective for the vast majority of patients (Marland & Cash, 2005). A good example is a study by Hudson et al. (2008), which showed that patient-tailored strategies to address individual medication adherence barriers were more effective in improving adherence than a basic implementation strategy. This also supports the conclusion of several reviewers who found that complex combinations of strategies are most effective in improving adherence (Dolder et al., 2003; Haynes et al., 2008; McDonald et al., 2002; Roter et al., 1998).
7.2.2 Determinants of adherence

Knowing why patients stop using their medication is a first and indispensable step in finding solutions that really work. Unfortunately, our understanding of the underlying mechanisms of non-adherence is poor (Fenton et al., 1997, Gray et al., 2002, Sluijs et al., 2006). The absence of a model that stands up and explains the role of all major determinants of non-adherence is one of the main problems in adherence research. Table 1 in chapter 1 presented a summary of determinants of adherence in schizophrenia patients. These results, which are based on quantitative studies, generally corroborate the results of our concept mapping study in which we focused on the patients’ decision-making process. Although the concept map did not produce any new adherence determinants, it conveniently arranged the wide variety of factors into clinically meaningful clusters, provided indications about relative importance and showed how clusters relate to one another.

Decision-making model for medication adherence

To increase our understanding of adherence, it is useful to resort to the different psychological models that have been developed to explain how people make decisions (Spruyt-Metz, 1996). Despite the extensive psychological literature on this topic, there have been few attempts to apply the models to patient decisions about medication use. An exception is the Health Belief Model (HBM), which has been used by researchers to explain patient behaviour (Adams & Scott, 2000; Brawley & Culos-Reed, 2000; Corrigan, 2002; Lacro et al., 2002). The HBM is a psychological model which was initially developed to explain the reluctance of people to use a health programme. It was developed by Becker and colleagues in the seventies and eighties, and is based upon the value expectancy theory (Becker & Maiman, 1975). This theory states that patient behaviour depends both on the subjective importance of an outcome, and the subjective expectation that a particular behaviour will achieve that outcome.

Taking these basic principles into account, we propose a patient-centred framework for the key factors related to patient decision-making (see Figure 1). In this model, as in the HBM, patients weigh the outcomes of two options: taking their prescribed medication, or not. Each of these two options has benefits and drawbacks. Depending on patients’ individual perceptions of the benefits of medication, the gravity of, and susceptibility to, their illness, they will be more or less inclined to be adherent. The pros and cons of using medication (or not) incorporated in the model stem from the concept map and from scientific literature. It shows that, basically, patients can take their medication for
two reasons: to feel better or to stay better. Feeling better generally refers to the short-
term effects of medication on subjective well-being. Studies indicated that this is closely
related to the striatal D2 receptor occupancy (de Haan et al., 2000; 2003; 2004), but may
depend not only on the direct effects of medication on psychopathology, and physical and
psychological well-being, but also on indirect consequences such as social or professional
functioning, feelings of autonomy, the burden of using them, etc (Staring et al., 2009).

Staying better refers to the anticipated preventive effects of medication in the long-run.
This is a factor that is closely related to insight. If patients use their medication to prevent
a relapse or hospitalisation, they must, at least to some extent, acknowledge that they
are not well, and that treatment is needed to reduce the risk of relapse. This is the core
concept of insight (Amador et al., 1993; David, 1990; Trauer & Sacks, 2000), and several
studies have indeed confirmed that insight is an important determinant of medication
adherence (Lacro et al., 2002).

The model shows that some of the negative consequences of the illness and
medication efficacy are closely related. If patients do not perceive any unpleasant
symptoms or consequences of their illness, the medication has no potential short-term
benefit. Medication also becomes less appealing if patients’ past experience or any other
reason leads them to believe that the medication will not provide relief from disturbing
symptoms. In all these circumstance, patients may use their medication only to prevent
relapse.

The proposed model can be thought of as a simplified framework containing the
main issues involved in patient decision-making. It assumes that, for patients, medication
is a means to achieve the best possible outcome. The subjective efficacy of medication
is therefore one of the most important determinants of medication adherence. This
assumption is supported by overwhelming evidence from a wide variety of studies,
including our concept mapping study, and reviews (Adams & Howe, 1993; Freudenreich
et al., 2004; Gasquet et al., 2005; Jónsdóttir et al., 2009; Lieberman et al., 2005; Liu-
Seifert et al., 2005; Rettenbacher et al., 2004; Rogers et al., 1998; Ruscher et al., 1997;
Tarrier et al. 1998; van Dongen, 1997).

The model describes the decision-making process for the consequences of using
medication or not. However, whether the result of this assessment is reflected in patients’
actual behaviour depends on other factors. We know from our concept map study, as
well as from other studies, that patients’ ultimate behaviour can be affected by practical
barriers (accessibility of the medication, medication costs), self-efficacy, forgetting to
take medication, the support and attitudes of family members, and finally patients’
understanding of the prescription. The outcome of the decision-making process should therefore be seen as a tendency, or an attitude towards medication use.

Our concept mapping study demonstrated that qualitative research can be an interesting and complementary source of information about adherence in schizophrenia patients. In a literature search, we found only two other qualitative studies. One study, performed by Marland and Cash (2005), used the grounded theory method to explore decisions about taking medicine in schizophrenia patients. Interestingly, their description of an explanatory typology is analogous to the model described above. Another qualitative study was performed by Carrick et al. (2004), looking at patients taking antipsychotic medication. On the basis of their results, and concurring with our results, these authors emphasised the importance of subjective well-being in patients’ treatment decisions. It seems that, despite their potential value, qualitative studies are seldom performed to explore medication adherence in schizophrenia patients. The studies that have been conducted have generated similar results, and provide information that may be particularly valuable in enhancing our understanding of adherence from a patient perspective.

**Figure 1.** Decision-making model for medication adherence
Communication

The proposed model may be useful in clinical practice when discussing medication adherence issues with patients. It can help clinicians to target their questions and to ensure that all the main factors involved in patient decision-making are discussed. This implies that clinicians should explore patient expectations about the consequences of taking or not taking their medication. Discussing these issues may help to understand patient behaviour, to generate an insight into their perception of the extra value of medication, and help to identify obstacles to medication use or patient misconceptions. In addition, showing an interest in patient thinking and concerns is likely to further the therapeutic relationship, which is associated with successful outcome (Bambling & King, 2001; de Haan et al., 2007; Hewitt & Coffey, 2005; Martin et al., 2000; Ong et al., 1995). Finally, the next logical step is not only to listen to patients, but to involve them actively in treatment decisions. There is substantial evidence that shared decision-making is effective in improving adherence in chronic illnesses, including psychiatric conditions (Joosten et al., 2008; Makoul & Clayman, 2006; Malm et al., 2003).

Although the importance of discussing the subjective perception of symptoms and medication effects seems common sense and has been recommended for many years, the Dutch Multidisciplinary Guideline for the treatment of schizophrenia (2005) suggests that it is not common practice among clinicians. However, valid information about the actual quality and frequency of communication between clinicians and patients concerning medication is scarce. Rethink, the British severe mental illness charity, conducted a survey of 357 patients with schizophrenia and schizoaffective disorder. They found that there was some discussion about at least one aspect of medication with 88% of patients. This related most frequently to the medication type or the dose, or the time of intake. A discussion about potential side effects or about how the medication works took place in only 49% and 30% of patients respectively. No more than 36% of patients were given a choice about the type of medication, while ‘having their concerns taken seriously’ was ranked as top priority by patients (Borneo, 2008). Finally, another indication of the limited quality of the dialogue about medication comes from studies demonstrating that treating clinicians are, on average, not good at estimating the degree of adherence (Byerly et al., 2005b, 2007; Remington et al., 2007; Valenstein et al., 1998).

Symptoms and efficacy

As stated above, we assume that patients who experience no uncomfortable symptoms or those who do not experience any beneficial effects with medication will be more tempted...
to be non-adherent. If this is true, two factors may help to explain the high reported prevalence of non-adherence:

**Remission**

Firstly, in 55% of patients, psychotic episodes are followed by periods of remission in which psychotic symptoms are absent. Some of these patients undergo partial remission and have negative symptoms, anxiety or depression (Wiersma et al., 1998). Since antipsychotic medication primarily affects positive symptoms, non-adherence in these periods of remission may have few direct clinical consequences, or none at all. This was demonstrated by a study of 65 remitted patients with schizophrenia (Wunderink et al., 2007). In this study, guided discontinuation of antipsychotic medication after a first psychotic episode was successful in 22% of patients in an average follow-up period of 13.2 months. In 32% of patients, medication was discontinued for an average of 5.0 months, after which medication was restarted because of relapse or mild recurrent symptoms. In this study, discontinuation was not feasible in 46% due to the exacerbation of symptoms during the tapering of the dosage. Whether or not guided discontinuation is an appropriate strategy is an issue beyond the scope of this thesis. The results of Wunderink’s study do, however, show that 54% of patients could have been fully non-adherent without any consequences for several months up to more than one year. However, in the long run, non-adherence in remitted patients does exacerbate the risk of relapse.

**Therapy resistance**

Secondly, once medication is taken by the patient, pharmacokinetic factors may cause problems with the absorption or metabolism of the medication, resulting in suboptimal concentrations of the drug in plasma. Furthermore, at the drug receptor level, pharmacodynamic factors may cause suboptimal drug reception. Both pharmacokinetic and pharmacodynamic factors can interfere with the desired therapeutic effects of medication, resulting in non-optimal or suboptimal treatment response. Studies have found this phenomenon in approximately one-third of patients with schizophrenia (Conley & Kelly, 2001; Kane 1996, 1999). In a recent survey of 205 in- and outpatients with schizophrenia in Amsterdam, 27% of patients reported that the reduction of symptoms through medication was unsatisfactory, and 51% reported persistent symptoms (Theunisen et al., 2008). Clearly, in these patients, the potential benefit of medication – the reduction of adverse symptoms – is not achieved either fully or partially.
Based on the assumption that, at any given moment, 50% of patients are in remission, and 30% are resistant to drug treatment, it can be calculated that the proportion of patients who do not experience short-term, beneficial effects with their medication is approximately 65%. Although this scenario may not fully reflect the complex reality, it indicates that a considerable number of patients are potentially at risk of being non-adherent.

**Conclusion**

Understanding patient motives for taking prescribed medication or not is an important first step in finding the right solutions. On the basis of our results, as well as those from other qualitative and quantitative studies, we argue that patients’ primary motives for taking medication are a subjective improvement in well-being and the reduced risk of relapse. These factors are offset against the negative consequences of using medication, such as side effects, loss of autonomy, etc. For patients, adherence is a means to an end. If medication reduces well-being, which is likely in some cases, patients are more prone to becoming non-adherent. Additional research is warranted to further our understanding of the underlying mechanisms of adherence, and to explore patient perspectives. To achieve this goal, qualitative studies would seem to be useful to supplement the existing literature and quantitative studies. Future research should also examine the quality of the dialogue patients have with their clinician about medication related thoughts and concerns. Taking the time to explore these areas in clinical practice will not only enable clinicians to tailor adherence interventions; this approach is also likely to improve adherence by enhancing the therapeutic alliance. Putting this into practice will not always be easy but, as became evident from the Rethink survey, it will address one of patients’ top priorities.

### 7.2.3 Adherence assessments

The way patients use their medication varies from patient to patient and can be a complex and dynamic process. Some patients may consume more medication than prescribed, while others refuse to take any medication at all. Furthermore, their behaviour may change over time. Some patients skip a dose once in a while, take a drug holiday, or gradually vary their dose. For a comprehensive understanding of adherence behaviour, it is important to describe this complex and dynamic phenomenon accurately (Urquhart & Vrijens, 2005).
Defining and describing adherence

The most common definition of adherence – 'the extent to which a person's behaviour coincides with medical advice' – has, however, two important limitations: it does not specify a time frame or acknowledge the dynamic character of adherence. Consequently, reported adherence rates refer to follow-up periods varying from the moment of assessment to one year after. At best, adherence rates give an average of the medication taken or the time to discontinuation. Often, they fail to give a comprehensive description of the intake pattern and dose during periods of medication use, and also neglect the duration of periods in which no medication is taken at all.

Given the diversity of adherence patterns, it is even more challenging to define non-adherence. Theoretically, any pattern of medication intake which is below a therapeutically effective dose can be considered to be clinically relevant non-adherence. However, we do not know exactly what the individual minimum effective dose is. Patients are often classified as non-adherent if they do not take their medication as prescribed, or if their adherence rate is below 70% or 80% of prescribed medication. Although this is believed to be an average minimum effective dosage for antipsychotic medication, the available evidence for these cut-off points is thin. The minimum dosage which is therapeutically effective depends not only on a patient's clinical state, but also on the specific agent and its administration, as well as on individual pharmacokinetic and pharmacodynamic characteristics (Urquhart, 2002; Velligan et al., 2006).

As with adherence, non-adherence should be described in relation to a specific time frame. Occasionally skipping a dose while being adherent for the rest of the time may not be as hazardous as taking a drug holiday for one month, or taking 70% of the prescribed dosage for a longer period of time. This means that, although assigning patients to adherent and non-adherent categories may simplify the interpretation of study results, it does no justice to actual medication intake behaviour (Hughes et al., 1997).

Another problem with describing adherence behaviour is that there is no standard unit of measurement. The degree of adherence is often reported as a percentage of prescribed medication on Likert-type scales, or using descriptive categories such as 'always' and 'most of the time'. It is evident that it is difficult to compare and interpret results which use different units of measurement.

Finally, in all units of measurement, the degree of adherence is defined in relation to the prescribed dose. As will be discussed in more detail below, a valid assessment of the degree of adherence is difficult and prone to error. It should, however, be noted that the denominator, the prescribed dose, may also be prone to a certain level of error.
Any medication prescription depends on a valid diagnosis, proper guidelines and clinical experience. However, the large inter-individual variation in effective doses may mean that prescribed doses are not always appropriate. Although adherence is defined as the degree to which patient intake corresponds to the prescription, it may be useful to take this factor into account when interpreting results.

Assessment instruments
Several methods are available for measuring medication adherence. Unfortunately, all of them have drawbacks (DiMatteo, 2004; Farmer, 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006). Assessment instruments can be broken down into subjective and objective instruments. Subjective instruments such as self-reports, clinician reports or significant-other reports are inexpensive and easy to use. In this thesis we explored the validity of three well-known, typical subjective instruments and found their validity to be poor. Without further research, we cannot say to what extent our results can be generalised to other subjective instruments, since many of them are not validated and many are poorly described (Nichol et al., 1999; Nose et al., 2003; Osterberg & Blaschke, 2005; Velligan et al., 2006). It is, however, likely that other subjective instruments also suffer from poor validity because they use similar approaches to measure adherence.

There is consistent evidence for the poor validity of self-report instruments (Craig, 1985; Gordis et al., 1969; Grymonpre et al., 1998; Inui et al., 1981; Straka et al., 1997; Velligan et al., 2007) and clinician assessments of adherence (Byerly et al., 2005b, 2007; Remington et al., 2007; Valenstein et al., 1998; Velligan et al., 2007). The validity of self-reports may be affected by unintentional errors such as recall error and the misinterpretation of questions (Brooks et al., 1994; Hays & DiMatteo, 1987; Osterberg & Blaschke, 2005; Svarstad et al., 1999) or by patients’ tendency to give socially desirable answers (Cox et al., 1994; Kimberlin & Winterstein, 2008; Osterberg & Blaschke, 2005; Svarstad et al., 1999; Tourangeau & Yan, 2007). Finally, inadvertent non-adherence (due to forgetting, for example) is not likely to be reported on self-report scales. Clinician reports may be affected by the fact that clinicians’ main source of information – observed behaviour and symptoms – may not always be a good indicator of medication intake, as discussed in chapter 7.2.2.

Recently, Byerly et al. (2008) introduced a new self-report instrument, the Brief Adherence Rating Scale (BARS). The BARS is similar to the IMI we developed and asks patients to report their history of medication intake in recent weeks. Over a 6-month follow-up period, the sensitivity of the BARS was 73.1, with a specificity of 74.3,
compared with electronic monitoring in a sample of 61 patients with schizophrenia and schizoaffective disorder. Given these results, the BARS would seem to be a promising instrument and further research is warranted to confirm its validity.

Despite their limitations, 77% of adherence studies in patients with schizophrenia rely solely on subjective measures (Velligan et al., 2006). Alternatives to subjective instruments are objective instruments such as blood or urine samples, tracers, pharmacy-based measures, electronic pill monitoring and pill counts. Most of these instruments are expensive and more complex than subjective instruments. However, they may also have their limitations.

Plasma levels of antipsychotic medication for example are not useful indicators of the quantity of consumed medication, because of the major variations in individual absorption and metabolism patterns (Cochran & Gitlin, 1983; Farmer, 1999; George et al., 2000; Velligan et al., 2007). A study of 52 schizophrenia outpatients compared several assessment methods, such as self-reporting, physician report, pill counts, electronic monitoring, and blood plasma concentrations. Plasma concentrations were not correlated with any other measures of adherence (Velligan et al., 2007).

Some studies rely on pharmacy data to calculate proxies of medication adherence, such as the medication possession ratio (the ratio of received and prescribed medication), the cumulative mean gap ratio (the proportion of days that medication was unavailable), or the compliant refill rate (the proportion of medication fills that occurred at time-appropriate intervals) (Dolder et al., 2002; Valenstein et al., 2002). An advantage of this approach is that it enables medication monitoring without any interference from the clinician or patient, and will not suffer from high refusal or drop-out rates. It does, however, require a closed pharmacy system, and cannot verify how much medication is actually consumed by the patient (Osterberg & Blaschke, 2005; Rijcken et al., 2004; Velligan et al., 2006; Wright, 1993).

Counting pills is a simple way of measuring adherence. Like most other methods, it does not assess actual intake. Nor does it generate information about the pattern or timing of intake. Pill counting, and other approaches based on pharmacy data, can be flawed if patients use pills which are not accounted for. It is therefore important to register all the medication in a patient’s possession at the beginning of the study (Osterberg & Blaschke, 2005; Velligan et al., 2006; Wright, 1993). Several studies have found that pill counting is a good indicator of medication adherence. Pill counts correlate well with electronic monitoring, which is generally considered the best available measure (Remington et al., 2007; Velligan et al., 2007).
Electronic monitoring is performed using a technical device built into a pill box which records the time and date every time the pill box is opened. This method assumes that patients take their medication when they open their pill box. Like other methods, then, it does not assess actual intake. The most frequently used electronic monitoring device is the Medication Event Monitoring System (MEMS). This is an improvement on other instruments in that it provides detailed information about adherence patterns over time. It is often considered to be the best available measure of adherence (the ‘gold standard’) (Byerly et al., 2007; Cramer, 1995; Díaz et al., 2001; Nakonezny et al., 2008; Nichol et al., 1999; Osterberg & Blaschke, 2005; Wright, 1993). Nevertheless, electronic monitoring is an expensive method and the acceptability and feasibility of these devices may be limited in schizophrenia patients (Díaz et al., 2001). New electronic monitoring devices continue to be developed such as the Intelligent Drug Administration System (IDAS), which records electronically when the foil of a blister pack is ruptured (Santschi et al., 2007). Future research should explore whether these novel devices are useful in schizophrenia patients.

Assessing adherence: recommendations

Several recommendations will be described below which may help to overcome some of the methodological pitfalls associated with the assessment of medication adherence.

1. Instruments should have good psychometric characteristics. Although this seems self-evident, researchers often underestimate the complexity of adherence assessment and use non-validated instruments, as was mentioned above (Nichol et al., 1999; Nose et al., 2003; Osterberg & Blaschke, 2005; Velligan et al., 2006).

2. Instruments should measure the quantity of medication taken (in number of pills or mg, for example) (Velligan et al., 2006). Medication attitudes or reasons for non-adherence, which are the focus of some subjective instruments, may not be good indicators of actual medication intake, and are difficult to interpret and to compare.

3. Any description of adherence behaviour should include a specification of timing and duration. Instruments should therefore at least refer to a specific time frame. Indeed it is preferable to record the exact timing and duration of any deviance in medication intake, as is possible with electronic monitoring devices.

4. Studies have shown that, if a patient needs to take more than one drug, adherence can vary for different drugs (Piette et al., 2007; Rudd et al., 1989). It is therefore important to state explicitly which drug is being studied.
5. It is advisable to verify patients’ understanding of their medication prescription. Studies have found that misinterpretation or misunderstanding of medication prescriptions is a potential factor affecting adherence (Fletcher et al., 1979; Hulka et al., 1975; Isaac & Tamblyn, 1993; Kravitz et al., 1993; Mehta et al., 1997; Shrank & Avorn, 2007). Patients who fail to understand their regimen may report being adherent on a self-report questionnaire when in fact they are not.

6. The assessment of adherence, or participation in a study, is in itself likely to affect adherence behaviour. Patients may, due to their awareness of being monitored, display so-called ‘white coat compliance’, more social desirable behaviour, or perform better because they are more focused (Deschamps et al., 2006, 2008; Nieuwkerk, 2004; Podsadecki et al., 2008; Roese, 1993). In addition, many patients refuse to participate in adherence studies, do not understand research instruments, or are not able to fulfil the tasks required in some studies. Our knowledge is therefore based on the patients who are willing and able to participate in studies. Assessment methods which are unobtrusive or do not require any efforts from patients (assessments based on pharmacy records, for example) are therefore preferable.

Conclusion
In adherence research, medication intake is a key outcome variable. Studies in which instruments with poor validity are used may produce erroneous results. Given the costs and importance of adherence research, it seems unwise to economise on the assessment of adherence. All adherence measure have drawbacks and none assess actual medication intake. Nevertheless, this does not justify using substandard or non-validated instruments.

If researchers prefer to use a subjective instrument, the BARS seems the best available instrument to date but further research to confirm its psychometric properties is needed. In chapter 7.2.2 we emphasised the importance of discussing subjective responses to symptoms and medication effects with patients. Simply asking patients to report on their medication intake fits in with this approach. If researchers want to use objective instruments, counting pills, pharmacy records or electronic monitoring are the best options as long as the drawbacks of each measure are taken into account.

Measuring medication adherence remains difficult and complex. Given the importance of, and efforts invested in, adherence research, it is important for the development of high-quality adherence instruments to be given higher priority.
7.3 General conclusions

According to the literature, approximately half of all patients with schizophrenia are non-adherent (Cramer & Rosenheck, 1998; Fenton et al., 1997; Lacro et al., 2002; Young et al., 1986). As has become apparent, interpreting these rates and their consequences is not straightforward. First of all, prevalence rates themselves are prone to error due to the methodological complexity of assessing non-adherence. All the available measures of adherence have drawbacks and none assess actual medication intake. Adherence instruments used in studies may not have been valid, and definitions and cut-off criteria may be inconsistent or inappropriate. Finally, prevalence rates for non-adherence are mainly based on a subsample of patients who are willing and able to participate in studies (Haapea et al., 2008; Haro et al., 2006; Miettunen et al., 2007). Any of these factors can result in error, which is reflected in the discrepancies in reported adherence rates, and the poor overlap found between adherence instruments by ourselves and other researchers (Cramer & Rosenheck, 1998; Kikkert et al., 2008; Lam et al., 2003; Velligan et al., 2007).

Despite the methodological problems which are associated with the assessment of adherence, the numerous studies make it clear that a substantial proportion of patients are not adherent. We know that these patients are at increased risk of deteriorating psychotic symptoms, relapse, and more unfavourable prognosis (Ayuso-Gutierrez et al., 1997; Fenton, 1997; Kahn et al., 2008; Keith et al., 2003; Lieberman et al., 2005, 1998; Malla et al., 2006; Morren et al., 2008; Robinson et al., 1999; Tiihonen et al., 2009; Wyatt, 1991; Weiden and Zygmunt, 1997). This underlines the importance of addressing non-adherence in clinical practice. Nevertheless, the absolute risk of psychiatric admission amongst non-adherent patients is 23%, compared with 10% in adherent patients (Valenstein et al., 2002). Apparently, then, the majority of non-adherent patients do not relapse. This may be due to several factors. Patients who are non-adherent during assessment can, over time, increase their medication intake; some patients will be in remission, and some patients may have been prescribed doses that are too high. On the other hand, approximately one-third of admitted patients are adherent. In these cases, the medication may not have been sufficiently effective, or relapse may have been caused by external stressors or substance abuse (Conley & Kelly, 2001; Swofford et al., 1996; Tessner et al., 2009).

The duration, timing and pattern of non-adherence are likely to determine the actual risks of non-adherence, as are individual characteristics and the underlying mechanisms.
causing non-adherence. As we have seen, several causes of non-adherence can be identified. In this thesis, we focused on patient decision-making, and proposed a simplified model of adherence decision-making. More research is needed to extend our understanding of patients’ medication intake behaviour. We argued that patient decision-making is mainly influenced by anticipated outcomes with respect to well-being. Affective mechanisms (e.g. therapeutic alliance, family support), and behavioural mechanisms (e.g. practical barriers, forgetting) are, however, also important factors affecting adherence, even though they were not explored further in this thesis.

Adherence interventions are more likely to be effective if they target patients who are non-adherent, and if they fit in with the mechanism underlying non-adherence. This implies the necessity of careful individual assessment, and the monitoring of subjective experiences. So far, a wide variety of interventions have been developed and each may include effective components for tackling the different causes of non-adherence.

We conclude that adherence research may progress if researchers are more aware of the limitations and validity of adherence instruments, and if they select the most appropriate instrument for their purpose. Secondly, we recommend future research to focus on exploring and defining different typologies of non-adherence, and use this to develop tailored interventions.
7.4 References


General discussion


Summary

Schizophrenia is a severe mental disorder. In general patients have to use medication long term. Studies showed, however, that approximately half of all patients do not use their medication according to their prescription. As a consequence, these patients have an increased risk for relapse and psychiatric admission. This thesis explores three aspects of medication adherence in schizophrenia patients; an adherence improving intervention, determinants of medication adherence, and finally, assessment instruments will be studied.

Chapter 2 presents the results of the QUATRO study. This randomized controlled trial studies the effectiveness of ‘adherence therapy’. Adherence therapy is based on motivational interviewing techniques and aims to improve medication adherence. Equally divided over four European cities, 409 patients with schizophrenia were included. In the experimental condition, an average of seven sessions of adherence therapy were administered in addition to the regular psychiatric treatment. Compared with the control condition one year after the start of the intervention, there were no effects of the adherence therapy on any of the outcome variables.

Chapter 3 described a study exploring factors that may influence decision-making related to the use of antipsychotic medication. ‘Concept mapping’, a structured qualitative method, was used to assess patients, carers and professionals views on this topic, which could be reduced to ten factors. Next, these factors were clustered in five clinically relevant themes: medication efficacy, external factors, insight, side effects, and attitudes toward medication. We explored how these factors relate to one another, and their relative importance according to the different stakeholder groups. Results showed that patients rated the efficacy of medication as most important factor for medication adherence.

Chapter 4 explores to what extent three adherence measures, the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS) correspond with each other. Results indicated that the correlation between these instruments, although all three were designed to measure medication adherence, was low. There was little agreement among the instruments in labelling patients non-adherent. Finally, none of the instruments showed a clear relationship with established risk factors of non-adherence. It was concluded that there was little agreement among the instruments, and that they do not measure the same concept.

Despite the results from chapter 4, the validity of each of the three instruments remains unknown. Therefore, in chapter 5, the validity of the instruments is further
explored using clinical outcome data during the 12-month follow-up period for patients who participated in the QUATRO study. The results showed that the predictive validity of all three adherence instruments was poor. None of the instruments predicted the risk of, or time to relapse or admission.

Based on literature and the results described above, we constructed a new adherence instrument, the Inventory of Medication Intake (IMI). Chapter 6 presents the validation study for this new instrument. Medication adherence was assessed in patients with schizophrenia over a period of three weeks using an electronic monitoring system. This is considered one of the most valid methods to assess medication adherence. A comparison with the results from the IMI showed that the IMI was not a valid instrument to measure medication adherence.

Chapter 7 summarizes the results from the previous chapters and the most important methodological aspects of the studies. Furthermore, results from other studies who explored adherence improving interventions are discussed. Among these are not only studies who focus on adherence therapy, but also studies who explore other interventions among patients with psychotic disorders or other conditions. It is apparent that several types of interventions can be effective but results are not yet conclusive. Interventions which are recurrent and prolonged, as well as interventions who fit in with patients’ needs and circumstances are more likely to be effective.

Based on literature and the results from chapter 3 we propose a decision-making model for medication adherence. In this model medication is a means to achieve the best possible outcome for patients, not an end. Patient’s decisions will be based on the short-term or long-term anticipated effects. Understanding patient’s considerations will help clinicians in dealing with medication adherence in their daily clinical practice.

Finally, we discuss defining and measuring medication adherence. Different assessment methods are available and it is important that researchers are aware of the limitations of each adherence instruments.
Samenvatting

Schizofrenie is een ernstige psychiatrische aandoening. Patiënten moeten over het algemeen langdurig medicatie gebruiken. Onderzoek toont echter aan dat ongeveer de helft van alle patiënten hun medicatie niet volgens voorschrift gebruikt. Hierdoor hebben ze een verhoogd risico op terugval en psychiatrische opname. In dit proefschrift zijn drie aspecten van medicatietrouw bij mensen met schizofrenie onderzocht; een interventie om medicatietrouw te verbeteren, onderliggende redenen voor medicatietrouw, en tot slot zijn meetinstrumenten, waarmee de mate van medicatietrouw kan worden gemeten, bestudeerd.

In hoofdstuk 2 zijn de resultaten van de QUATRO studie gepresenteerd. In deze gerandomiseerde gecontroleerde studie is de effectiviteit van ‘adherence therapie’ onderzocht. Adherence therapie is gebaseerd op motiverende gesprekstechnieken en is gericht op het verbeteren van medicatietrouw. Verdeeld over vier Europese steden zijn 409 patiënten met schizofrenie geïncludeerd. Naast de reguliere behandeling werd in de experimentele groep gemiddeld zeven sessies adherence therapie gegeven. Een jaar na de start van de interventie werd, in vergelijking met een controle conditie, op geen van de uitkomstmaten een effect van adherence therapie gevonden.

Hoofdstuk 3 beschrijft een studie naar factoren die van invloed zijn op de beslissing van patiënten om voorgeschreven medicatie wel of niet te gebruiken. Middels ‘concept mapping’, een kwalitatieve onderzoeks methode, zijn de meningen van zowel patiënten, hulpverleners als betrokkenen van patiënten geïnventariseerd. Deze meningen konden worden herleid tot 10 factoren, die vervolgens zijn samengevat in vijf klinisch relevante thema’s namelijk: werkzaamheid, externe factoren, ziekte inzicht, bijwerkingen, en houding ten opzichte van medicatie. Daarnaast is onderzocht in hoeverre deze factoren aan elkaar gerelateerd zijn en het relatieve gewicht dat aan ze wordt toegekend. Hieruit bleek dat voor patiënten de positieve effecten van medicatie de grootste invloed had op hun beslissing om medicatie te gebruiken.

In hoeverre de resultaten van drie meetinstrumenten, de Medication Adherence Questionnaire (MAQ), de Drug Attitude Inventory (DAI) en de Compliance Rating Scale (CRS) overeenstemmen, is onderzocht in hoofdstuk 4. Uit de gegevens van de QUATRO studie bleek dat de instrumenten, alle drie ontwikkeld om de mate van medicatietrouw te meten, weinig met elkaar correleren. Ook is er tussen de instrumenten weinig overeenstemming in welke patiënten als medicatietrouw worden aangemerkt. Tot slot bleek dat de instrumenten slechts matig correleren met bekende risico factoren van
medicatietrouw. De conclusie van dit onderzoek is dat de drie instrumenten weinig overeenstemmen en niet hetzelfde concept meten.

In hoeverre de drie instrumenten een valide indicatie geven van de mate van medicatietrouw is op basis van de gegevens in hoofdstuk 4 niet te achterhalen. Daarom is in hoofdstuk 5 de validiteit van de drie instrumenten verder onderzocht. Hiervoor is gebruik gemaakt van de gegevens van het klinisch beloop van patiënten tijdens de QUATRO follow-up periode. Hieruit bleek dat de predictieve validiteit van de instrumenten laag is. Geen van de instrumenten was een goede voorspeller van de kans op, of de tijd tot, terugval of psychiatrische opname.

Op basis van zowel literatuur en eigen bevindingen is een nieuw instrument gemaakt, de Inventory of Medication Intake (IMI). In hoofdstuk 6 zijn de bevindingen van een validatiestudie van de IMI gepresenteerd. Bij een groep patiënten met schizofrenie is gedurende een periode van drie weken medicatiegebruik gemeten met een electronisch monitoring systeem. Dit wordt beschouwd als één van de meest valide methoden om medicatietrouw te meten. Deze gegevens zijn vergeleken met de informatie verkregen met de IMI. Daaruit bleek dat de IMI geen valide instrument is om medicatietrouw mee te meten.

In hoofdstuk 7 zijn alle resultaten uit de voorgaande hoofdstukken samengevat en zijn de belangrijkste methodologische aspecten van de studies besproken. Daarnaast zijn resultaten van andere studies naar therapietrouw bevorderende interventies besproken. Hieronder zijn niet alleen studies naar het effect van adherence therapie, maar ook andere interventies bij zowel mensen met een psychotische stoornis als ook andere stoornissen. Hieruit valt op te maken dat verschillende vormen van interventies effectief kunnen zijn maar dat resultaten vaak nog niet optimaal of consistent zijn. Mogelijk is het herhaald, en langdurig aanbieden zinvol, en moeten interventies zorgvuldig worden afgestemd op de behoeften en omstandigheden van de patiënt.

Op basis van de bevindingen uit hoofdstuk 3 en andere studies is een model opgesteld van het beslisproces met betrekking tot het gebruik van medicatie. Uitgangspunt hierbij is dat medicatie voor patiënten een middel is om de best mogelijke uitkomst te behalen. Het is vaak geen doel op zich. Patiënten baseren hun beslissing voornamelijk op geanticipeerde effecten op korte, of lange termijn. In de klinische praktijk is het van belang om inzicht te krijgen in de overwegingen van de patiënt zodat de behandelaar hier adequaat op kan inspelen.

Tot slot is stilgestaan bij het definieren en meten van medicatietrouw. Verschillende meetmethoden zijn beschikbaar en het is van groot belang om rekening te houden met de beperkingen van ieder instrument.
Curriculum Vitae

Martijn Kikkert was born in Den Helder on August 11, 1970. Interested in many things besides schoolwork, he pursued a more practical career after he graduated from the MAVO. In 1986 he went to the intermediate technical school (MTS) to learn mechanical engineering. Eventually, he became motivated to study Industrial Design at the Technical University in Delft. In order to be admitted in Delft he successfully completed the first three years of the MTS, and the first year of mechanical engineering at the Technical College (HTS) in Alkmaar. In 1990 he started his study Industrial Design at the Technical University in Delft. Although he obtained his first year exam, he found his study disappointing and switched to Psychology. Between 1991 and 1997 he studied Clinical Psychobiology and Neuropsychology at the University of Amsterdam.

From 1997 till 1998 he worked on a PhD project concerning the modulation of the jaw-jerk reflex at the department of Oral-Maxillofacial Surgery, Prosthodontics and Special Dental Care at the University Medical Center Utrecht. In 1998 he performed neuropsychological assessments at Duin en Bosch, Mental Health Care Institute in Castricum. In the same year he was offered a position at the department of Psychiatry of the Academic Medical Centre (AMC) in Amsterdam to study the effectiveness of adjuvant occupational therapy for work-related major depression in a randomised trial. In 2002 he became involved in the QUATRO study, which most of this thesis is based on. In 2005 he started working for the Mentrum research department, recently transformed into the Arkin Academy, where he is involved in several research projects.

In 2002 Martijn married Ruth Willems. In 2003 their daughter Hana is born, and three years later, in 2007, they receive a son Jin.
List of publications

Kikkert MJ, Dekker JJM, Koeter MWJ, Schene AH. The Inventory of Medication Intake (IMI): validation of an instrument for assessing adherence to antipsychotic medication. Medical Care, submitted for publication.


Dankwoord

De afgelopen jaren heb ik tijdens het schrijven van dit proefschrift veel morele en praktische steun gekregen. Een aantal mensen wil ik hiervoor in het bijzonder bedanken. Ten eerste mijn promotor Aart Schene. Beste Aart, bijna een jaar na de afronding van het LISV project belde je me om te vragen of ik geïnteresseerd was in een nieuw onderzoeksproject. Samen met jou, Maarten en Carin zouden we deelnemen aan een Europese studie naar medicatie trouw bij mensen met schizofrenie. Om het extra aantrekkelijk te maken noemde je de reisjes naar het buitenland en, wie weet, de mogelijkheid om te promoveren. Ik nam je aanbod aan en begon me al snel in het onderwerp te verdiepen. Langzaam kreeg een promotietraject vorm alhoewel een echte startdatum achteraf niet makkelijk te geven is. Een eerste lijst met mogelijk te schrijven artikelen dateert van februari 2004. Van dat lijstje zijn nog veel versies gemaakt omdat verschillende ideeën het uiteindelijk niet haalden. Veel deadlines trouwens ook niet. Beste Aart, ik ben blij dat je het aandurfde om met mij dit project aan te gaan. Ik heb veel van je geleerd en hopelijk kunnen we ook in de toekomst samen leuke projecten blijven doen.

Maarten Koeter, samen met Aart vormde je mijn vaste klankbord. Ik kon altijd rekenen op een snelle terugkeer van mijn teksten met de nodige opmerkingen en suggesties. Daarbij was er altijd ruimte voor discussie en eenmaal op dreef kon je enthousiast filosoferen over vraagstukken en problemen. Van jou heb ik geleerd om resultaten kritisch te beoordelen en objectief op te schrijven, ook al vielen ze soms wat tegen. Maarten ik heb het erg leuk gevonden om dit bijzondere project samen met je te doen.

Jack Dekker, tijdens het schrijven van mijn artikelen was ik op zoek naar een baan en kwam bij jou terecht. Een betere plek had ik niet kunnen treffen. Niet alleen is het prettig om met je te werken, we hebben ook samen de IMI-studie opgezet die in dit proefschrift terecht is gekomen. Alhoewel mijn promotie een AMC aangelegenheid was, heb je me altijd veel ondersteuning en ruimte gegeven om het af te maken. Zonder jou had het ongetwijfeld nog veel langer geduurd. Ik ben je daarvoor zeer dankbaar.

Dear QUATRO colleagues, most of this thesis is based on QUATRO data, the results of our combined efforts. It was a great pleasure to work with so many experienced researchers. I have in particular good memories of our times in Gatton Manor. Besides our writing sessions, we had interesting discussions about our work, as well as many other more personal subjects. I wish you all the very best.
Dankwoord

Dit onderzoek had niet plaats kunnen vinden zonder de medewerking van vele patiënten die het gesprek met me aangingen en bereid waren om mee te werken aan onderzoek. Ik waardeer hun inzet zeer. Daarnaast ben ik ook veel collega’s dank verschuldigd voor hun hulp bij dit onderzoek. Zij brachten mij in contact met patiënten en hebben geholpen met het verzamelen van de gegevens.

Tijdens het schrijven van dit proefschrift heb ik verschillende mensen gesproken die me door hun expertise op dit vakgebied weer verder konden helpen. In eerste instantie waren dat mijn collega’s en co-auteurs van de QUATRO studie, maar ook dichter bij huis waren er mensen van wie ik het nodige heb geleerd. Beste Emile Barkhof, ik wens je veel succes met het afronden van jouw studie en ik ben zeer benieuwd naar de uitkomsten. Pythia Nieuwkerk, wat leuk om binnen het AMC iemand tegen te komen met zoveel kennis over meetmethoden van medicatietrouw. Na ons gesprek ging ik met een hoofd vol ideeën, en een tas vol literatuur naar huis. Ik heb er veel aan gehad. Rob van Heerden, je was zo ontzettend vriendelijk om al mijn vragen te beantwoorden en om mijn manuscript te lezen. Het was eerlijk gezegd een opluchting dat het je goedkeuring kreeg.

In de afgelopen jaren was het hartverwarmend om te merken hoe mijn collega’s bij het AMC en Arkin met me mee leefde. Ik ben blij dat ik nu eindelijk tegen jullie kan zeggen dat het klaar is. Bedankt voor al jullie steun.

Een collega die ik in het bijzonder wil bedanken is Marianne Haages. Marianne, vanaf mijn eerste werkdag heb je me door de bureaucratie van het AMC geloodst en ook tijdens het afronden van het proefschrift kon ik altijd op je rekenen. Heel erg bedankt voor al je hulp.

Carin, ruim tien jaar geleden begonnen we tegelijk onze onderzoekers loopbaan op het AMC. Toen nog op andere projecten maar de QUATRO studie hebben we samen gedaan. Dat je straks als paranimf naast me staat is de enige passende afsluiting daarvan. Ik wens jou en Maarten veel geluk toe, in het bijzonder in de komende periode.

Marco, samen hebben we al een hele weg afgelegd. Ik ben ontzettend blij dat je ook nu weer naast me staat.

Lieve vrienden, bedankt voor al jullie steun, motivatie en interesse in mijn werk. We zien elkaar snel weer!
Mijn lieve ouders, dat ik ging studeren was niet vanzelfsprekend maar jullie stonden altijd voor de volle honderd procent achter me. Met jullie als vangnet heb ik me kunnen ontwikkelen tot waar ik nu ben. Ik prijs me gelukkig met zulke fantastische ouders. Lieve Judith, Pieter en Jorik bedankt dat jullie er altijd voor mij zijn.

Liege Hana en Jin, wat is het een feest dat jullie er zijn! Hana, je kan al lezen en soms van die filosofische dingen zeggen. Daarnaast ben je een ontzettend lief meisje en een lekkere knuffelkont. Het is een wonder om je te zien ontwikkelen. Kom nog maar vaak even bij ons in bed liggen. Jin, jij hebt een vrolijk makende levenslust en heel veel energie. Maar je kan soms ook zomaar lekker tegen me aan gaan liggen en in slaap vallen. Je kan je niet voorstellen hoe ik daarvan geniet. Jullie hebben me gelukkig vaak van mijn werk gehouden, maar waren ook de grootste motivatie om het snel af te maken.

Lieve Ruth, het is klaar! Dit proefschrift is geschreven in een periode waarin veel op ons af kwam en ik realiseer me dat het jou minstens zoveel inspanning heeft gekost als mij. We waren net overweldigd door de geboorte van Hana toen ik hier aan begon. In die eerste periode ging dat nog tijdens werktijden maar al snel begon het mijn, en daarmee ook jouw vrij tijd in beslag te nemen. De laatste jaren waren het zwaarst en soms was het moeilijk om de balans te vinden. Mijn contract op het AMC was afgelopen en ik moest voornamelijk in mijn vrije tijd de laatste artikelen en hoofdstukken schrijven. In de tussentijd werd Jin geboren, moesten we ons nieuwe huis verbouwen en verhuisden we naar IJburg. Bovendien was het voor jou ook een hele drukke periode. Je hebt je eigen bedrijf opgezet en publiceerde ook nog eens twee boeken. Het is aan jouw organisatietalent te danken dat we dit allemaal konden doen. Lieve Ruth, het is fantastisch om zoveel moois met je te mogen delen. Ik hoop dat we dat nog vele jaren met elkaar zullen blijven doen.