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.
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 than 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.

![Medication Possession Ratio (MPR)](image)

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

### 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 2002</th>
<th>Pinikahana et al., 2002</th>
<th>Llorca a (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sociodemographic characteristics</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>+</td>
<td></td>
<td>3 (0)</td>
</tr>
<tr>
<td>Gender</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>3 (0)</td>
</tr>
<tr>
<td>Level of education</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Premorbid functioning</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>4 (3)</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>4 (3)</td>
</tr>
<tr>
<td>Income</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>Marital status</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>2 (0)</td>
</tr>
<tr>
<td>Overall intelligence</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Stability of living arrangements</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Illness-related characteristics</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>+</td>
<td></td>
<td>4 (3)</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>3 (1)</td>
</tr>
<tr>
<td>Symptomatology (positive symptoms, disorganization)</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>1 (0)</td>
</tr>
<tr>
<td>Number of prior hospitalizations</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Insight and attitudes</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>+/-</td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Medication-related factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication characteristics</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></td>
<td>4 (1)</td>
</tr>
<tr>
<td>Complexity of medication regimen</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>3 (1)</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 et al., 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>
</tbody>
</table>

+ associated with adherence/non-adherence, according to the reviewers. +/- 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.
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.

Figure 2. Number of effectiveness studies of interventions for improving adherence published annually between 1980 and 2008.
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.
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.


