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 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; Scollie 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 (Hettema 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
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).
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; Maneesakorn 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 (Maneessakorn 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; Hettema 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 affect 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, 2005; Martins et al., 2009).
Table 1. Adherence therapy trails

<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'Donnel 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>Meanenakorn 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>
<tr>
<td>Control intervention</td>
<td>Follow-up</td>
<td>Instruments</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<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, DAL, attitude to treatment, SAI, CRS</td>
<td>effect at 6 months on the DAL, SAI, CRS</td>
<td></td>
<td></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, GAF, DAL, SAI, CRS, attitude to medication, National adult reading test, impon-Angus scale for EPD SE.</td>
<td>effect at 18 months on the SAI, CRS, attitude to treatment, GAF, readmission rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 non-specific counselling sessions, 30-60min. each</td>
<td>baseline; at 12 months</td>
<td>Compliance, DAL, PANSS, SAI, GAF, QoL, National adult reading test</td>
<td>no effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment as usual</td>
<td>baseline; at 6 months</td>
<td>PANSS, DAL-30, CRS, LUNSERs</td>
<td>effect at 6 months on the PANSS(tot), DAL CRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no control intervention 3, 2, 1 months prior baseline;</td>
<td>baseline; at 5 months</td>
<td>MEMS, CRS, MARS, PANSS, SAI, DAL</td>
<td>no effect</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment as usual</td>
<td>baseline; at 9 weeks</td>
<td>PANSS, GAE, DAL-30, SWAM, LUNSERs</td>
<td>effect at 9 weeks on the PANSS(tot), DAL-30, SWAM. Goo effect op: GAE, LUNSERs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no control intervention</td>
<td>baseline; after last session</td>
<td>DAL-10, CRS</td>
<td>effect on the DAL-10</td>
<td></td>
<td></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 circumstances, 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 (Theunissen 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 schizo-affective 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; Crанer, 1995; Diaz 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 (Diaz 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; Morken et al., 2008; Robinson et al., 1999; Tiitinen 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


McDonald HP, Garg AX, Haynes RB (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA, 288: 2868-2879.


General discussion


Chapters


