Adherence to treatment in patients with psychosis

Anton BP Staring
COLOFON

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Adherence to Treatment in Patients with Psychosis

Therapietrouw bij patiënten met psychose

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Overige leden: Prof.dr. S. Kushner
                Prof.dr. M.W. Hengeveld
                Prof.dr. A.H. Schene
“Graig walked away, his shoulders slumped, once again troubled that his life had no narrative to it. He was back to being “Graig: The Guy Who Merely Existed.” ”

Douglas Coupland – Generation A, p220

“We have evolved to tell ourselves interesting and useful little lies about monsters and gods and tooth faries, as a kind of prelude to creating really big lies, like ‘Truth’ and ‘Justice.’ ”

Terry Pratchett – The science of discworld II; the globe, p340
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CHAPTER 1

General introduction

A.B.P. Staring
Halfway during the 20th century, the development of antipsychotic medications revolutionised the care for patients with psychosis. Yet today, efficacy of antipsychotic medications is still far from perfect. Positive symptoms may persist despite antipsychotic treatment, the effects on cognitive and negative symptoms are small, and side-effects are often burdensome (Leucht et al., 2009a). Therefore, putting means and efforts into developing more efficacious medication, if possible with fewer side-effects, is to be applauded. However, effect-sizes of the second-generation antipsychotic medications on primary symptoms, in comparison to placebo, currently lie around .51 (Leucht et al., 2009b). Note that this effect-size is the result of a meta-analysis of controlled trials where medication intake was strictly monitored and adherence was probably high. However, in the average patient population, non-adherence is common in more than half of the patients (Perkins, 2002), and it is associated with poor outcome and high costs. In the UK for example, non-adherence to antipsychotic medication predicted an excess annual cost of more than 5,000 pound of service use per patient (Knapp et al., 2004), due to factors such as crisis interventions and readmissions. It is therefore plausible, considering that no recent development has improved the effects of antipsychotic medications substantially, that current intervention and research efforts are most likely to successfully improve outcome if they target the non-adherence problem. Medications, no matter how effective, are not helpful when patients do not use them. Given the fact that a mere 58% of the prescribed antipsychotic medications is actually taken by patients (Cramer & Rosenheck, 1998), solving the problem of non-adherence could theoretically almost double the efficacy of antipsychotic treatment in everyday practice.

Research on interventions to improve adherence has been accumulating over the past fifteen years, but the results are disappointing. It has become clear that non-adherence is no easy target for change. Patient education for example, i.e. teaching about the biomedical model of schizophrenia and the necessity of medication to control symptoms, does not increase adherence. Other interventions have produced mixed results. Looking at the scientific literature on predictors of non-adherence, it seems that poor insight, denial, the experience of stigma, and cognitive dysfunction each are of some relevance. However, although these factors are often specifically present in patients with psychosis, it is known that non-adherence is also a huge problem across other medical and psychiatric disorders. Non-adherence is certainly not confined to the field of psychosis. Therefore, non-psychopathological processes probably explain the largest part of the non-adherence problem in psychosis. These factors, found
in adherence studies in other illnesses, include a natural tendency to quit treatment when symptoms have receded, side-effects, a too complex medication regime, not wanting to think about being ill, forgetfulness, a poor alliance with the clinician, or maybe a general kind of anti-medication attitude (e.g. Jackson et al., 2009; Lingam & Scott, 2002).

In conclusion, treatment non-adherence in psychotic disorders is a big problem and we are presently in need of viable theoretical models and effective interventions to deal with it.

**RESEARCH QUESTIONS**

The first aim of this study was to develop an intervention that would have a good chance of improving adherence. For this, we conducted a literature-review to develop an empirical-theoretical model as the foundation of *Treatment Adherence Therapy* (TAT; Chapter 2).

The main objective of our research was to find out whether TAT is effective. To investigate this, we conducted a multi-centre randomised controlled trial (RCT) (Chapter 3). An RCT is to-date the best scientific method available for testing the effectiveness of interventions in health care.

We also examined research questions that would contribute to our understanding of the expected mechanisms of TAT. One is that adherence to antipsychotic medication may have diverging effects on patients’ quality of life, as good adherence is likely to result in symptom-reduction as well as more side-effects (Chapter 4). This would mean that structural monitoring of symptoms and side-effects is useful for finding an optimal balance for each patient with the best chance of improving quality of life, and possibly adherence.

Another issue is that insight into illness may not always be relevant for good adherence, but rather in only those patients who have sufficient cognitive abilities to act according to their convictions and beliefs (Chapter 6). If supported, this hypothesis would imply that the best strategies for improving adherence may be different per patient. Enhancing insight into illness would only be useful for some. However, insight may have negative consequences for self-esteem and quality of life, which raises the following dilemma: will improved insight into illness produce more benefits than drawbacks? We hypothesized that the detrimental effects of insight would depend on the amount of stigma that patients attach to the illness (Chapter 5). If supported, this could mean that
reducing self-stigmatization may be helpful in achieving positive consequences of insight into illness, while avoiding the detrimental ones.

Another research question was how it might be explained that the patients of ethnic minorities often adhere less to treatment than native patients. We hypothesized that immigrant patients are more likely to use a ‘sealing-over’ recovery style, a factor that is related to lower self-esteem (Chapter 7). Also, as a patient’s recovery style may significantly influence the manner in which they deal with and think about psychotic episodes as well as how they participate and benefit from treatment, we wanted to test if an ‘integrating’ recovery style was able to predict the remission of a psychotic disorder, and to compare its effects with those of insight into illness and the therapeutic alliance (Chapter 8).

During the execution of the randomised controlled study on TAT, we were soon confronted with the problem that some of the most non-engaging patients refused participation with the study. Of them, some were either very non-adherent to antipsychotic treatment or completely refusing medication, while at the same time repeatedly experiencing relapses and re-admissions. For them, we came up with the idea of using financial incentives to promote adherence to depot antipsychotic treatment. A research pilot evaluating this method was conducted (Chapter 9).
CHAPTER 2

Understanding and improving treatment adherence in patients with psychotic disorders: a review and a proposed intervention.

A.B.P. Staring
C.L. Mulder
M. van der Gaag
J.P. Selten
A.J.M. Loonen
M.W. Hengeveld

Current Psychiatry Reviews, 2006, 2, 487-494
ABSTRACT

Non-adherence to treatment in patients with psychotic disorders is related to higher rates of relapse, hospitalization, and suicide. Important predictors of non-adherence include poor social structure, cognitive deficits, negative medication attitude, side effects, depression, a sealing-over recovery style, feelings of stigmatization, denial of treatment need, and lack of insight. Attempts to improve adherence have shown that psycho-education alone is not fully effective, and that motivational interviewing, behavioural strategies, and linking a patient’s personal goals to treatment may increase adherence. Based on the empirical data reviewed, we formed four clusters of possible causes of non-adherence, each of which can be targeted by a specific module of our developed Treatment Adherence Therapy (TAT). These four modules are: self-enhancement, motivational interviewing, medication optimization, and behavioural training. An individual patient may benefit from one or more of these modules; and thus the contents of TAT vary in accordance with individual causes of non-adherence. Basically, TAT aims to help patients work out what they want regarding treatment and then support them in following this through.
2.1 INTRODUCTION

2.1.1 Definition

Although the term compliance is widely used in the medical literature on psychotic disorders, it has been criticized as implying that the patient is expected to passively obey the advice of the clinician (Bebbington, 1995). Indeed, this criticism is consistent with definitions of compliance: “the extent to which a person’s behaviour coincides with the medical advice he/she has received” (Kampman & Lethinen, 1999), or “the extent to which the patient’s behaviour, in terms of taking medications, following diets, executing life style changes, coincide with the clinical prescription” (Haynhes, Taylor & Sachett, 1979).

A definition that stresses the agreement reached between doctor and patient would seem more desirable (Zweben & Zuckoff, 2002; Kemp et al., 1998). The term concordance has been suggested, but then the problem arises that agreements with the patient are a necessity for someone to possibly become non-adherent. If no agreements are made, one cannot be non-adherent. This is not practical as especially those patients with whom no agreements can be made should be regarded non-adherent. We will therefore use the term adherence, based on the above mentioned compliance definition of Kampman and Lethinen (1999), and simultaneously realise that adherence is not necessarily desirable in all cases. As McDonald et al. (2002) put it: “The term adherence is intended to be non-judgmental, a statement of fact rather than of blame of the prescriber, patient or treatment.”

There are many measures of adherence, most of which concentrate on medication adherence, as measured by patient self-report and physician assessment. Both consistently overestimate adherence (Byerly et al., 2007; Churchill, 1985). Other methods to assess medication adherence include urine and blood assays or pill counts, but the first are subject to individual variations in pharmacokinetics, and with the latter it is unfortunately not possible to tell whether the patient has actually taken the medication or thrown it away. Extending the concept of adherence to also include a person’s availability for appointments, collaboration, and help-seeking behaviour, Tait et al. (2002) introduced the term service engagement. We consider this to be a more appropriate operational definition of treatment adherence because it encompasses several domains (Zweben & Zuckoff, 2002). However, many of the studies reviewed here were concerned with medication compliance and not the other aspects covered by the term service engagement.
2.1.2 Prevalence of non-adherence
The prevalence-numbers of non-adherence, as found in various studies, depend on the definition of adherence used and the cut-off scores to distinguish between adherent and non-adherent behaviour. It is therefore not surprising that a systematic review of 103 studies found estimates of failure to adhere to treatment programs to range from 24% to 90% (Nosé, Berbui & Tasella, 2003). Cramer and Rosenheck (1998) found that patients who were prescribed antipsychotics took on average 58% of the recommended amount of medication. They also concluded that adherence might be lower in patients with psychiatric disorders than in those with physical disorders. Perkins (2002), in her review of predictors of non-adherence, concluded that at least 50% of all patients with chronic psychotic disorders do not fully comply with treatment. Other studies not included in Perkins’ review reported that at least 50% and 75% of patients were non-adherent to antipsychotic drug treatment after 1 and 2 years, respectively (Bebbington, 1995; Weiden et al., 1991; Weiden, Aquila & Standard, 1996). It would thus seem that non-adherence is the norm rather than the exception.

2.1.3 Consequences of non-adherence
Non-adherence obviously prevents treatment from achieving its intended effect. Many authors claim that antipsychotic medication is effective for reducing (mainly the positive) symptoms in schizophrenic patients (Davis & Andruikaitis, 1986), but others make a case against it, arguing that the long-term natural course of schizophrenia has never thoroughly been investigated, making us unable to clearly determine the long term effects of antipsychotic medication (Whitaker, 2003). However, empirical studies have shown that the risk of relapse is three to five times higher after discontinuation of neuroleptic treatment (Fenton, Blyer & Heinssen, 1997; Dixon & Lehman, 1995; Robinson et al., 2002; Ucok et al., 2006; Weiden et al., 2004). The consequences of non-adherence are not only worsening of a person’s mental health, but also homelessness, imprisonment, violence, and suicide (Torrey & Zdanowicz, 2001). The risk of suicide is about 3.75 times higher in patients with schizophrenia who are poorly adherent than in those who adhere to treatment (Hawton et al., 2005). Zweben and Zuckoff (2002) summarized evidence for a relationship between treatment adherence and better outcome. Furthermore, they reported that clinicians could become frustrated and demoralized by patients who inconsistently attend therapeutic activities, and that patients who occupy available slots without fully utilizing the offered treatment prevent other, possibly more cooperative, patients from
accessing treatment. These last aspects underline the importance of a more broadly defined treatment adherence.

2.2 ATTEMPTS TO IMPROVE ADHERENCE IN PATIENTS WITH PSYCHOTIC DISORDERS

Given the prevalence and consequences of non-adherence, it is important to try to prevent and/or change this behaviour. Although psycho-education may seem appropriate, reviews conclude that it is not fully effective (Zygmunt et al., 2002; Dolder et al., 2003), because while education increases knowledge, it does not increase motivation to adhere to treatment (Kemp & David, 1995). For this reason other interventions have been developed and tested, the most frequently cited of which is Compliance Therapy (Kemp et al., 1998), which consists of four to six sessions dedicated to producing medication cognitions by means of cognitive behavioural techniques and motivational interviewing. The differences between regular psycho-education and compliance therapy mainly consist in that the latter searches for individual motives for (non-)compliance and uses specific psychological techniques and metaphors to work from – and add to – the patient’s perspective when providing information and correcting misconceptions. A randomised controlled trial in patients with psychotic disorders, comparing compliance therapy with supportive counselling, showed positive effects on insight, attitudes to treatment, and observer-rated compliance (Kemp et al., 1998). However, the trial had methodological shortcomings, such as attrition (only 48 of 75 patients remained after 18 months of follow-up) and compliance was estimated using only one item. O’Donnel et al. (2003) tried to replicate this study and compared compliance therapy with non-specific counselling in a group of 56 patients with schizophrenia. They used blind estimates of compliance but failed to detect an effect. They explained the difference in results by arguing that patients with schizophrenia may benefit less from compliance therapy than patients with other psychotic disorders.

Byerly et al. (2005a) investigated compliance therapy in 30 patients with either schizophrenia or schizoaffective disorder, but found no improvement in clinician and patient ratings of adherence. They concluded that patients with psychotic disorders might not benefit from this treatment. However, their sample was relatively adherent at study entry (an average of 72% medication adherence) which may have contributed to a ‘ceiling’ effect (Byerly et al., 2005a). This limitation emphasizes that non-adherent patients are the most suitable targets
for adherence promoting interventions. Moreover, the study did not include a control group, and therefore it was not possible to determine whether the intervention prevented the patients from sliding into non-adherence. It is also possible that more sessions are needed for a measurable and enduring effect. In a large European randomised controlled trial (QUATRO), Gray et al. (2006) did not find Adherence Therapy – based on compliance therapy – to be better than non-specific counselling in admitted patients with psychotic disorders. Again, however, also their patient sample was relatively adherent at study entry.

Cramer and Rosenheck (1999) reported that providing patients with visual feedback of their medication adherence rates, based on an electronic monitoring system, had positive effects in a 7-month controlled trial. However, about half of their respondents had mood disorders and the effects were different in different diagnostic subgroups. Kozuki et al. (2005) tried a similar intervention – Visual Feedback Therapy – in 23 patients with psychotic disorders but did not find an effect on adherence.

In their review of interventions to improve medication adherence in schizophrenia, Zygmunt et al. (2002) reached four conclusions: (1) one third of the 39 included studies reported significant effects; (2) psycho-education by itself was not effective; (3) concrete problem solving and motivational techniques that link medication adherence to personal goals were common features of successful programs; and (4) making adherence a specific target seemed to increase the chance of success. The authors emphasized the need for further theoretical development. Nosé et al. (2003) conducted a meta-analysis with similar goals, including 24 studies (the control condition was ‘care as usual’ in 63%). The odds ratio for dichotomous outcomes was 2.59 (95% CI 2.21-3.03) and the pooled standardized mean difference for continuous outcomes was 0.36 (95% CI 0.06-0.66), thus showing a significant general effect of such interventions. Contrasting their findings with the less positive conclusions of Zygmunt and others, the authors mentioned differences in study selection. For example, the review of Nosé et al. (2003) included studies that measured appointment (not solely medication) adherence and they excluded studies that did not measure adherence as the primary outcome. The latter selection criterion seems to be in line with the conclusion of Zygmunt et al. (2002), that interventions that specifically target adherence are more likely to be successful. In their meta-regression analysis, Nosé et al. (2003) found two factors to be associated with greater effect: a short follow-up period – which perhaps means that booster sessions are useful – and a diagnosis of schizophrenia. The latter is in conflict with the tentative conclusion of O’Donnel et al. (2003).
2.3 COMING TO A NEW MODEL FOR IMPROVING ADHERENCE:
TREATMENT ADHERENCE THERAPY

Given that theoretical models for improving treatment adherence have so far not proved satisfactory (Kemp & David, 1995), and that interventions yield at most only moderate effects (Puschner et al., 2005), we sought to develop a rationale for a new intervention, based on existing empirical literature on predictors and interventions.

Table I summarizes (a) three reviews of predictors of non-adherence in patients with psychotic disorders that include studies up until 2002, and (b) empirical studies reported in the literature from 2003 onward.

Unfortunately, some of the predictors of non-adherence are not easy to change. Age, ethnicity, and gender are beyond the control of practitioners. Although a small social network is a predictor of non-adherence, such networks cannot easily be expanded. Similarly, although failure to establish a working alliance between practitioner and patient is a predictor, it is not always possible to form such an alliance despite the best efforts of practitioners – and many continuing education programs already include training of the relevant skills.

We developed an intervention model – Treatment Adherence Therapy – that consists of four broad techniques (termed ‘modules’), each targeting one of four clusters of remaining predictors of non-adherence. The four clusters are as follows:

Cluster A
- cognitive deficits (e.g. forgetfulness, impaired executive function)
- poor social / daily structure

Cluster B
- medication side effects
- negative medication attitude

Cluster C
- a ‘sealing-over’ recovery style
- expecting only few benefits (low hope)
- depression

1 A ‘sealing-over’ recovery style is a way of coping by minimizing the significance of symptoms and the impact of psychosis and showing a lack of curiosity about the experience, thereby not integrating the illness into one’s self-identity.
### Table I
Studies on predictors of treatment adherence in patients with psychotic disorders

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<tr>
<th>Authors (year)</th>
<th>Patient sample (N)</th>
<th>Determinants investigated</th>
<th>Indicators of treatment adherence</th>
<th>Findings</th>
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</thead>
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<tr>
<td>Lacro et al. (2002)</td>
<td>1980-2000 review of risk factors for medication non-adherence in schizophrenia: 39 studies</td>
<td>Various</td>
<td>Medication adherence: various</td>
<td>Factors most consistently associated with non-adherence were: poor insight, negative attitude or subjective response toward medication, substance abuse, short illness duration, inadequate discharge planning or aftercare environment, and poor therapeutic alliance.</td>
</tr>
<tr>
<td>Perkins (2002)</td>
<td>1980-2002 review of predictors of adherence in schizophrenia</td>
<td>Various</td>
<td>Various</td>
<td>Beliefs about illness (e.g. poor insight and low perceived benefit of medication), perceived costs of treatment (e.g. side effects), and barriers to treatment (e.g. low family support) were all found to be predictive of non-adherence. (HBM)</td>
</tr>
<tr>
<td>Hudson et al. (2004)</td>
<td>Schizophrenia (150)</td>
<td>Patients reported barriers to medication adherence</td>
<td>None</td>
<td>Most reported barriers were: stigmatization, adverse drug reactions forgettingfulness, and lack of social support. Low insight was related to low medication adherence.</td>
</tr>
<tr>
<td>Kozuki et al. (2005)</td>
<td>Patients with psychotic disorders (23)</td>
<td>Insight (SUMD)</td>
<td>Medication adherence by electronic monitoring</td>
<td>Non-adherence was associated with lower GAF-scores, more compulsory treatment, and impaired insight into illness.</td>
</tr>
<tr>
<td>Rittmannsberger et al. (2004)</td>
<td>Patients with psychotic disorders (95)</td>
<td>GAF, CGI, and the insight-item of the PANNS</td>
<td>Medication adherence by self report and multiple informants</td>
<td>Non-adherence was associated with lower GAF-scores, more compulsory treatment, and impaired insight into illness.</td>
</tr>
<tr>
<td>Robinson et al. (2002)</td>
<td>Outpatient first-episode patients with psychotic disorders (112)</td>
<td>Symptoms, side effects, cognitive functioning, and attitude of family members</td>
<td>Medication discontinuation of at least one week (reports by any source)</td>
<td>Predictive of discontinuation were: poor premorbid cognitive function and Parkinsonian side-effects. Better executive functioning predicted better adherence.</td>
</tr>
</tbody>
</table>
Lambert et al. (2004) Schizophrenia (213) Antipsychotic side effects (UKU), self-efficacy, and attitude toward antipsychotics. Findings: Non-adherence was mainly predicted by negative general and efficacy attitudes toward antipsychotics and experience of side effects. Of the side effects, sexual dysfunction, extrapyramidal symptoms and psychic effects were more distressing than sedation or vegetative side effects.

Opolka et al. (2003) Patients with psychotic disorders (3,583) Ethnicity and type of medication. Covariates included comorbid conditions and demographics. Findings: White patients were more adherent than non-whites (African-Americans and Mexican-Americans). Olanzopine was better for adherence than risperdone, which was better than haloperidol.

Valenstein et al. (2004) Patients with schizophrenia or schizo-affective disorder (63,203) Type of medication and demographics. Findings: African-Americans and younger patients were more likely to be poorly adherent. Also, patients on atypical agents were more likely to be poorly adherent.

Droulout et al. (2004) Patients with psychotic disorders (42) Drug attitude (DAI) and insight (SUMD). Findings: Poor insight was related to discontinuation of medication, to lower scores on the scale for adherence, and to negative perception of treatment (DAI). These findings were independent from demographic and clinical characteristics.

Yen et al. (2005) Schizophrenia (74) Insight (SAI). Findings: Insight and adherence correlated positively at baseline, but insight did not predict adherence at one year follow-up.

<table>
<thead>
<tr>
<th>Authors (year)</th>
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<th>Indicators of treatment adherence</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tait et al. (2003)</td>
<td>Schizophrenia (50)</td>
<td>Recovery style (RSQ), insight (IS), and symptoms (PANSS)</td>
<td>Service Engagement Scale (SES)</td>
<td>Integrating recovery style contributed to adherence. Insight and symptoms did not.</td>
</tr>
<tr>
<td>Elbogen et al. (2005)</td>
<td>Schizophrenia and related disorders (528)</td>
<td>Substance abuse (DALI), depressive symptoms self-report, social demographics</td>
<td>Self-report medication adherence</td>
<td>Depressive symptoms, substance abuse, and living instability each contributed to medication non-adherence.</td>
</tr>
<tr>
<td>Perkins et al. (2006)</td>
<td>First episode schizophrenia and related disorders (254)</td>
<td>Beliefs about need for treatment, benefits of medication, negative aspects of medication; and external support (from ROMI &amp; ITAQ)</td>
<td>Pill counts; non-adherence defined as at least 7 days no medication</td>
<td>Low belief in need for treatment and in medication benefit both predicted non-adherence.</td>
</tr>
<tr>
<td>Yamada et al. (2006)</td>
<td>Outpatients with schizophrenia (90)</td>
<td>Symptoms (BPRS), side effects (UKU), and beliefs / attitudes (ROMI-J)</td>
<td>Interview at 2 year follow-up: non-adherence defined as at least 7 days no medication.</td>
<td>Most frequent reason for non-adherence was ‘distressed by side effects’ and for adherence was ‘relapse prevention’. Also, patients with at baseline higher agitation and no perceived daily benefit were more likely to become non-adherent. Follow-up adherent patients scored higher on baseline ‘fulfilment of life goals’.</td>
</tr>
<tr>
<td>Startup et al. (2006)</td>
<td>Patients with psychosis in cognitive behavioural therapy (20)</td>
<td>Recovery style and therapeutic alliance, as observed from session recordings</td>
<td>Dropping out of treatment prematurely (10 patients).</td>
<td>Patients who dropped out were less engaged in treatment, showed less agreement with their therapists, and had a sealing-over recovery style. No influence of therapeutic bond was found.</td>
</tr>
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Cluster D

- feelings of stigmatization
- negative, distrusting attitude
- denial of treatment need
- poor insight

With respect to cluster A, forgetfulness, poor executive function, poor attention, and chaotic thought can cause non-adherence because of difficulties with integrating structural treatment procedures into daily life (also depression may affect adherence this way because depressed individuals are often forgetful (Elbogen et al., 2005)). Although these factors are hard to alter, behavioural training can help the individual to cope with them (Boczkowski, Zeichner & DeSanto, 1985). Behavioural training, which has proven effective in studies of patients with schizophrenia (Zygmunt et al., 2002), consists of specific instructions and problem-solving strategies, such as reminders, self-monitoring tools, cues, family or partner support, reinforcement, and linking medication-use to highly frequent behaviours. We included this module in our Treatment Adherence Therapy, but it is only implemented when other barriers to treatment (clusters B, C, and D) have been ‘removed’.

Considering cluster B, when it has been established that these causes for non-adherence are present, we start with medication optimization. A rather high dosage will be prescribed of a (possibly yet untried) antipsychotic medication, and then we structurally build down while the patient, the practitioner, and a family member each monitor side effects and psychotic symptoms in the patient. Every six weeks, the dosage decreases another step. If necessary, this procedure can be repeated for up to three different antipsychotic medications. The patient finally decides as to which medication and in what dosage he prefers, and to aid in his decision he can make usage of the registered symptoms and side effects tables. Before start, the procedure of this module is explained in detail to the patient, personal choice is emphasized, and some safety arrangements are discussed.

We’ve tested these medication optimization in about seven patients, and subjectively found that they responded quite positive. One 46-year old woman (diagnosis is schizophrenia, paranoid type; she lives alone; and has an affair with a man who is also a psychiatric patient) had paranoid delusions of being watched and controlled by her neighbours’ machines. She was terrified by this and, even while the delusional ideas remained, using antipsychotic medication seemed to ‘protect’ her from this fear. However, medication also made her feel
less energetic. During her 20-year course of illness she had repeatedly ceased to take medication because of this reason. Problems came and went, and she had been hospitalized three times in a state of severe decompensation. Now, we proposed to her an experiment to search for her optimal dosage. She started with 10 mg of olanzopine, then 5 mg, then 3.5, then 2.5, and then 1 mg. These steps each lasted six weeks, and she was asked to record her experience of fear and energy every day. At 1 mg olanzopine, the fears came back. She was given 10 mg for one week and then returned to the dosage tried last that still worked well enough: 2.5 mg. Currently for two years at this same dosage, she hasn’t been afraid nor experienced side-effects. Furthermore, she has discovered this herself and now seems to require a lot less persuasion to keep using her medication. In one other patient, we used his mother to register symptomatic behaviour during the medication dosage module. This also worked well, seemingly because she now had more objective data in hands to show to her son the dose-response relationship between the antipsychotic medication and his behaviour.

With regard to cluster C, we hypothesized that many patients have not consciously thought about the pros and cons of treatment, about their current goals in life, the means to reach them, and about how this relates to their illness and its treatment. This is in line with data on recovery styles (McGlashan et al., 1975), as these ideas partially overlap: the non-integration (sealing-over) of psychotic illness into patients’ lives and self-image is predictive of non-adherence (Tait, Birchwood & Trower, 2003). Furthermore, Zygmunt et al. (2002) pointed out that linking medication adherence to personal goals was a common feature of successful interventions to improve adherence. We use motivational interviewing (Barkhof et al., 2006) to achieve this, a technique that has previously been used successfully to deal with the problem of non-adherence (Barkhof et al., 2006; Possidente, Bucci & McClain, 2005). This technique consists of developing discrepancy; expressing empathy; believing in the patient’s abilities; rolling with resistance; avoiding arguments; letting the patient sum up his perceived pros and cons; reflection; trying to let patients base their decisions on information instead of expectations; recalling goals of treatment that have already been reached; emphasizing freedom of choice; and other aspects (Miller & Rollnick, 2002). We included depression in this cluster of predictors because depression may cause non-adherence partially due to a general lack of motivation (Elbogen et al., 2005), an aspect amenable to motivational interviewing.
And finally for cluster D, we hypothesize that some patients are not ready to figure out what they want (by the strategy outlined for cluster C), as they ‘fool’ themselves with coping strategies that function to maintain some feelings of self-esteem. This is needed because their self-esteem is under threat by the possible acknowledgment that they have a chronic and stigmatized illness, that they may require treatment for a long time, that they will need to adapt their lifestyle, and that their current life situation is not as they would like it. Evidence for this mechanism comes from the finding that the above-mentioned sealing-over recovery style is linked to insecure adult attachment, negative self-evaluative beliefs, and insecure identity (Tait, Birchwood & Trower, 2003), and thus seems to be linked to threatened self-esteem. Self-esteem is known to be particularly vulnerable in the face of a chronic psychotic illness (Roe, 2003; Tarrier, 2001). Furthermore, patients with schizophrenia, more so than patients with other mental disorders (Corrigan, 2004) or diabetes (Lee, 2005), experience stigma from family, partners, friends, and colleagues, which has been linked to more illness concealment (Lee, 2005), avoidance of help-seeking (Dinos et al., 2004), and less positive attitudes toward treatment (Mann & Himelein, 2004). Feelings of stigmatization by significant others strongly affects self-esteem (Link et al., 2001), and avoidant coping styles – e.g. denial of treatment need or sealing-over – presumably protect the patient’s feelings. Indeed, it has been found that an integrating recovery style is associated with higher levels of discomfort (Bell & Zito, 2005), that insight into illness is associated with more feelings of depression (Trauer & Sacks, 2000; Lysaker et al., 2003), and that having doubt in a delusion instead of completely accepting it as the truth is associated with lower self-esteem (Feeman et al., 2004). In our model, lack of insight is assumed to especially influence adherence when it is caused by denial (for a differentiation in the etiology of poor insight into denial and cognitive impairment, see Lysaker et al. (2005) or for a review: Cooke et al. (2005)), which is in line with the finding that psycho-education by itself is not effective (Zygmunt et al., 2002; Dolder et al., 2003) – a lack of information is probably not the problem.

It is, in short, quite understandable that patients diagnosed with a psychotic disorder tend to use avoidant coping styles that coincide with lead to non-adherence. Our model includes a number of strategies to work on this: positive labelling; illness normalization; emphasizing the patient’s own wishes and ideas; using metaphors of integration; believing in the patient’s abilities; discussing famous people with psychosis; enhancing self-efficacy; and rolling with resistance. Some of these strategies are already included in motivational interviewing
(Miller & Rollnick, 2002); the others we refer to as *self-enhancement* strategies, because their goal is to lessen the perceived threat to the patient’s self-esteem.

The model of treatment adherence therapy is summarized in Figure I. A manual was written (in Dutch) by which the practitioner can get familiar with the intervention protocol, and we also propose that practitioners receive a training in the relevant techniques. During the first one or two sessions of treatment adherence therapy the practitioner estimates which of the four clusters mostly cause(s) non-adherence in the patient he/she is facing. The next step will be to apply the corresponding module(s, commencing with the one placed highest in figure I). Together, treatment adherence therapy probably takes up around ten sessions, but the actual number of sessions depends on the modules that need to be applied. Also, we propose two booster sessions to strengthen any pattern of achieved behavioural changes.

**Figure I** A model for improving adherence: Treatment Adherence Therapy
Since two of the proposed modules of treatment adherence therapy (behavioural training and motivational interviewing) have already separately been investigated by other researchers, and since another module (medication optimization) seemed effective during our pilot, we estimate that our intervention has a good chance of improving adherence. Furthermore, we expect that using an individualized mix of modules may add significantly to this effect. The effects of our proposed add-on intervention will be tested in a multi-centre randomised controlled trial, comparing treatment adherence therapy with treatment as usual. It should be noted as a limitation, however, that extremely low-adherent patients are probably not suitable for this type of intervention, as attendance of the sessions is a necessary element. For that group, more assertive interventions are called for, such as Assertive Community Treatment (ACT).

2.4 THE MORAL POSITION OF TREATMENT ADHERENCE THERAPY

Given the undesirable consequences of non-adherence on one hand and the apparent fact that some patients do not want any treatment for their disorder on the other, the question arises whether it is ethical to ‘psychologically’ intervene so as to influence patients’ perception and motivation. If we consciously try to make patients do something other than their own expressed preference, are we then knowingly acting against their will? Miller and Rollnick, in their motivational interviewing book, have devoted a chapter on this delicate topic in which they struggle with the morally questionable notion that, by using motivational interviewing, the patient may be changed in what he wants (Miller & Rollnick, 2002; p161). In our view, however, what is changed are the patient’s beliefs about what he wants. More specifically: we hope that these beliefs become more accurate. A philosophical analysis of this approach is more thoroughly explained in an article by Voerman (2006). Applied to treatment adherence therapy, it comes down to the following:

We consider that because the aim of treatment adherence therapy is to help patients understand what they want in terms of treatment, the ethical problem described above is at least partially solved. Treatment adherence therapy is not in conflict with what patients want nor changes what they want, because its underlying tenet is that some patients may not know what they want. The goal is exactly to help them discover this, by means of making them conscious of the pros and cons, asking them to weigh their options, getting them to create an integrating picture of their adherence behaviour and personal future goals,
and by trying not to evoke resistance while doing so. While patients afterwards may still decide they do not want treatment, they will at least have consciously thought about relevant aspects; they have been prompted to investigate what they really want and hopefully have made an informed decision. The practitioner should then accept a decision of non-adherence in our view, unless there is a question of danger and involuntary admission and treatment are called for. It is also important to recall that the known consequences of non-adherence consist in general patterns in group data, and adherence is not wisely applied as an absolute norm for each individual patient. But we do believe that most patients wish to function well and that if, after sorting out their feelings about the diagnosis and treatment, patients decide they want treatment, they are more likely to adhere to that treatment.
CHAPTER 3

Treatment Adherence Therapy in patients with a psychotic disorder: randomised controlled trial.

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ABSTRACT

Background
Interventions to improve adherence to treatment in patients with psychotic disorders have produced inconclusive results. We developed a new treatment, Treatment Adherence Therapy (TAT), whose intervention modules are tailored to the reasons for an individual patient's non-adherence.

Aim
To examine the effectiveness of TAT with regard to service engagement and medication compliance in outpatients with psychotic disorders who engage poorly.

Method
Randomised controlled study of treatment as usual (TAU) versus TAU + TAT in 109 outpatients. Most measurements were performed by masked assessors. We used intention-to-treat multivariate analyses. (Dutch Trial Registry; NTR1159)

Results
TAU + TAT vs. TAU significantly benefited service engagement (Cohen's d=.48) and medication compliance (Cohen's d=.43). Results remained significant at six-month follow-up for medication compliance. Near-significant effects were also found regarding involuntary re-admissions (1.9% vs. 11.8%; p=.053). Symptoms and quality of life did not improve.

Conclusions
Treatment Adherence Therapy helps improve engagement and compliance, and may prevent involuntary admission.
3.1 INTRODUCTION

Non-compliance with medication is prevalent in over fifty percent of patients with psychotic disorders (Cramer and Rosenheck, 1998; Keith and Kane, 2003; Bebbington, 1995; Thomas, 2007; Weiden et al., 1996; Weiden et al., 1991). If a patient stops using antipsychotic medication, the risk of relapse increases three to fivefold (Dixon and Lehman, 1995; Fenton et al., 1997; Robinson et al., 2002; Ucok et al., 2006; Weiden et al., 2004). Also, the risk of suicide has been found to be 3.75 times higher in non-compliant patients with schizophrenia than in compliant patients (Hawton et al., 2005).

Despite such detrimental consequences, dealing with this problem has proven difficult. Psycho-education, for example, is not effective in improving adherence (Zygmunt et al., 2002; Dolder et al., 2003; Lincoln et al., 2007). On the other hand, there is some evidence that cognitive behavioural therapy is effective if it specifically targets non-compliance (Lecompte & Pelc, 1996), and a meta-analysis has shown that effective strategies include practical problem-solving, and motivational techniques that link adherence to personal goals (Zygmunt et al., 2002). But while versions of Compliance Therapy and Adherence Therapy, both including these strategies, were shown to be effective in some studies (Kemp et al., 1998; Gray et al., 2004; Maneesakorn et al., 2007), they did not prove their usefulness in others (O’Donnel et al., 2003; Byerly, et al., 2005a; Gray et al., 2006). Research may have failed to detect effects because of a small study sample (Byerly et al., 2005a), relative effectiveness of the ‘comparator’ intervention (Gray et al., 2006), or because short term positive effects may have been lost where only one year outcomes were reported (O’Donnel et al., 2003). Based on current knowledge, the updated guidelines of National Institute for Health and Clinical Excellence (NICe, 2009) recommend that adherence interventions should not be used in patients with schizophrenia.

Adherence interventions may be more effective when they take the large variations in causes of non-adherence into account. This randomized controlled trial therefore measured the effectiveness of Treatment Adherence Therapy (TAT; Staring et al., 2006), in which strategies for improving adherence are tailored to patients’ individual situations.
3.2 METHOD

3.2.1 Design and hypotheses
This rater-blind randomized controlled trial compared a combination of Treatment Adherence Therapy (TAT) with Treatment As Usual (TAU). Our primary hypothesis was that TAT would more successfully improve service engagement and medication compliance. Our secondary hypotheses were that TAT would be more successful not only in preventing voluntary and involuntary re-admission, but also in reducing symptoms and improving quality of life. We hypothesized that these effects would have four mediators: a reduction in the experience of stigma, better therapeutic alliance, increased insight, and a more integrative recovery style.

3.2.2 Procedure
Inclusion criteria were (1) a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, (2) receiving outpatient treatment, (3) mastery of the Dutch language, (4) at least some problems with service engagement, as defined by an average item-score of 1.25 or higher on at least two subscales of the Service Engagement Scale (SES; see primary outcomes). Patients were referred when the clinician believed them to meet the criteria. In order to classify patients according to DSM-IV (APA, 1994), they were interviewed using the lifetime Composite International Diagnostic Interview, version 2.1 Auto (WHO, 1997). We then used the SES to determine whether a patient met the fourth criterion. If the patient did meet it, a research assistant asked them to participate and to give written informed consent.

At baseline (T0), at the end of the six-month treatment (T1), and at six-month follow-up (T2), all respondents and their mental-health professionals participated in a structured interview. These were conducted by psychology and medicine students who were blind to the patients’ treatment allocations. The students had received a two-day training that consisted of interview role-play and of scoring of the instruments. After co-rating a live interview conducted by the main researcher (AS), they conducted two interviews under supervision. When their ratings were sufficiently consistent with those of the experienced researcher, the students conducted interviews independently, but still under supervision every other week.

Within a week of baseline assessment, participants were randomly assigned to one of the treatment conditions. This was done according to a lottery system, executed by the main researcher. Allocation was not concealed from the participants, therapists or researchers. Only the raters were blind to the treatment
allocation. Because the risk existed that patients would tell to which group they had been allocated, raters were instructed to specifically ask the patient at the beginning of the interview to not say this. This was successful; patients did not report their allocation.

Patients were paid EUR 20 for each of the three interviews. The study design was approved by the Medical Ethics Committee of Erasmus MC University Medical Center.

### 3.2.3 Treatment Adherence Therapy

Treatment Adherence Therapy is an intervention based on an empirical-theoretical model described earlier (Staring et al., 2006), in which patient-determinants of non-adherence are clustered into three groups. The first group of determinants is characterized by a patient who denies or seals over his illness and has not integrated illness and treatment into life. The second is characterized by a patient who is not satisfied with his medication due its side-effects or low efficacy. The third is characterized by a patient who lacks the cognitive skills or daily structure to participate effectively in the treatment. According to the TAT-model, every non-adherent patient will have at least one of these clusters present, explaining the non-adherent behaviour.

The first cluster of causes of non-adherence mentioned here – the patient denies or seals over his illness and has not integrated illness and treatment into life – still consisted of two separate clusters in Chapter 2 of this thesis. When re-writing the treatment manual after that publication, based on a small pilot, two modules were combined in order to simplify the approach.

The first part of the TAT manual describes the procedure for one or two initial sessions which assess individual determinants of non-adherence. According to the clusters of determinants they detected, and after discussion with their supervisor, the therapists then filled out a decision-form and chose from the three modules available. These are listed here.

(1) The first module was an adapted form of *Motivational Interviewing*, which is intended to explore a patient’s perspective and goals, developing discrepancy between current behaviour and future goals, and to help him or her with the process of placing the illness and treatment into a coherent life-narrative, while avoiding resistance and emphasizing freedom of choice and the patient’s own responsibility. To this we added strategies for reducing self-stigmatization, such as the provision of a continuum-perspective on the illness, and discussion not only of the stress-vulnerability model, but also of famous people who have struggled with psychosis.
(2) The second module was *Medication Optimization*. Here, a normal dosage was prescribed of an antipsychotic medication, and was then optimally tailored (which sometimes meant that a dosage was reduced) while the patient, the TAT-therapist, and a family member each monitored any side-effects and psychotic symptoms in the patient. The dosage was adjusted every six weeks. If necessary, this procedure was repeated for various antipsychotics until an optimal medical treatment was reached. The patient clearly stated which medication he preferred, and in which dosage. To aid his decision, he used the log he had kept on his symptoms and side-effects. Before the start of this module, the procedure was explained to the patient in detail. The options for personal choice were emphasized, and some safety arrangements were discussed.

(3) The third option was *Behavioural Training*, which was provided to help individuals to cope with the problems caused by forgetfulness, poor executive function, poor attention, and chaotic thought, all of which can cause non-adherence due to difficulties with integrating structural treatment procedures into daily life. Training consisted of specific instructions and problem-solving strategies, such as reminders, cues, reinforcement, self-monitoring tools, family or partner support, and linking medication-use to highly frequent behaviours.

The structure of these three modules was hierarchical. Thus, if more than one cluster of problems was present in an individual patient, motivational interviewing was conducted first, followed by medication optimization, and then by behavioural training. The duration and number of sessions therefore varied according to the needs of the patient. In general, it took no more than six months.

Most of the TAT-therapists were psychiatric nurses. They were not the patients’ own mental health professional, and gave TAT in addition to TAU. They received a full week of training and an hour’s supervision every two weeks thereafter. To ensure treatment fidelity, all sessions were recorded and used in supervision. Although treatment fidelity was not rated with instruments, each executed session was discussed and therapeutic instructions were always given for the upcoming session. Tapes were often used to check and maintain the relevant therapeutic skills. No significant problems were encountered and the therapists were found to be compliant with the instructions given.

### 3.2.4 Treatment As Usual

Treatment as usual generally consisted of sessions with a psychiatric nurse and a psychiatrist when indicated. The sessions varied in frequency and duration, but mostly consisted of one or two sessions per month. The contents reflected
overall problems the patient might encounter, such as symptoms, social participation, work, daily activities, and medication issues. Some patients received psycho-education individually or in group sessions. This was recorded.

### 3.2.5 Primary outcomes: service engagement and medication compliance

#### Service engagement

We used the Service Engagement Scale (SES), a 14-item rating scale in which the service engagement observed is rated by the clinician most familiar with the patient. It has four subscales: (1) availability, (2) collaboration, (3) help-seeking, and (4) medication compliance. As well as having good face validity and content validity, it is user-friendly, and has been shown to have good test-retest reliability in patients with psychotic disorders (Tait et al., 2002). The total scale scores were used minus the subscale of medication compliance, because this subscale was included in our compiled measure of medication compliance (see medication compliance, below).

#### Medication compliance

We administered a semi-structured interview with the patient to assess medication compliance by the independent rater. The rater normalized non-compliance as well as possible reasons for it, stressed that the obtained information would be treated confidentially and not be passed on to the patient’s clinician, and inquired about the number of missed doses in the past days and weeks. Such an interviewing style has been found to produce a more valid measurement of adherence than some of the questionnaires that are used in adherence research, such as the Medication Adherence Rating Scale, the Medication Adherence Questionnaire, the Drug Attitude Inventory, and the Compliance Rating Scale (Kikkert et al., 2010). The score ranged from 0 to 4, with higher scores indicating more problematic compliance. The scoring method was modelled after the Health of the Nation Outcome Scales (Wing et al., 1998).

In this way, we used two different measures of medication compliance: one clinician-based (SES subscale) and one rater-based. These two measures were standardized, summed, and reversed, thereby creating a compiled measure of compliance, in which null scores indicated the average compliance in our study, and high scores indicated good compliance. Composite measures of medication compliance help reduce the underestimation of compliance that is associated with any individual source of information (Kikkert et al., 2008).
In our baseline data, this compiled measure of medication compliance correlated with the positive syndrome of the PANSS ($r = -0.23$) and with side-effects of neuroleptics ($r = 0.23$) (Staring et al., 2009a). Although relatively small, these associations provide some support for the measure’s validity.

### 3.2.6 Secondary outcomes

#### Admissions
We documented whether, at the time the study was conducted, patients had been readmitted to a psychiatric hospital, and, if so, whether this had been voluntary or involuntary.

#### Symptoms
The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a 30-item rating scale which is completed by the trained raters. It has three subscales: (1) positive syndrome, (2) negative syndrome, and (3) general psychopathology.

#### Quality of life
We used the self-report EQ-5D, which has been validated in patients with schizophrenia (Prieto et al. 2003). On the basis of a Dutch validation study (Lamers et al., 2005), the items were linearly transformed into a score ranging from -0.33 to 1.00. High scores reflect good quality of life.

### 3.2.7 Mediators

#### Insight
We used the self-report 8-item Insight Scale (IS) of Birchwood et al. (1994), whose total scores range from 0 to 12. The scale is reliable and valid, and is easy to use within this group of patients. To have some indication of the veracity of the patients’ response on this scale in our study, we’ve calculated the Pearson correlation between this scale and the insight item of the PANSS (A12) in our baseline data. It was $-0.514$ ($p<0.001$), indicating an important overlap between the two.

#### Recovery Style
Recovery style was measured using the Recovery Style Questionnaire (RSQ; Drayton et al., 1998), a 39-item self-report measure. Total scores range from 1 to 6, low scores reflecting integration and high scores reflecting sealing-over. Broadly defined, a sealing-over patient prefers not to think about his psychotic experience
during recovery, while an integrator is interested in the psychotic experience and desires to put it into some coherent perspective. The RSQ is reliable and correlates highly with McGlashan’s interview-based measure (Drayton et al., 1998).

**Stigma**

We used the 12-item ‘perceived devaluation and discrimination’ part of the self-report Stigma Scale (SS) (Link et al., 2002). The items cover the patient’s perception of common opinions about psychiatric patients, such as ‘Most people believe that entering a mental hospital is a sign of personal failure.’ Total scores range from 1 to 4, with higher scores indicating greater perceived stigmatization.

**Therapeutic alliance**

The 36-item Working Alliance Inventory (WAI) was used to measure the alliance factor of the therapeutic relationship as it is experienced by the patient (Horvath & Greenberg, 1989, 1994; Vervaeke & Vertommen, 1996).

**3.2.8 Statistical analyses**

Logistic regression analysis was used, with treatment allocation as the dependent variable, and with baseline demographics and instrument scores as independent variables to test whether the randomization process was conducted successfully. Next, we performed an intention-to-treat multivariate analysis (MANCOVA), in which primary outcomes were entered as dependent variables, treatment allocation as a fixed factor, and baseline SES and compliance scores as covariates. The analysis included the effects of the TAT intervention directly after it had ended (T1) and after six months of follow-up (T2). Significant outcomes were expressed in effect-sizes (Cohen’s d) by dividing the difference in mean scores of the two treatment allocations by their pooled standard deviation. For secondary outcomes and mediators, similar analyses were used as well as Fisher’s exact tests.

On the basis of the variances, error estimates, and observed effects of the first 58 patients who had completed T1, we calculated the minimum sample size necessary to achieving a power of .80 for our analyses. For this, we did a univariate two-group repeated-measures analysis of variance using the Greenhouse-Geisser correction to nominal degrees of freedom. It was concluded that at least 46 participants were needed in each treatment allocation to reliably detect an effect on the primary outcome measure.
3.3 RESULTS

3.3.1 Participants
We screened 391 people, 195 of whom were identified as meeting the inclusion criteria. Seventy-nine refused to participate, and 116 (59%) decided to participate. The 79 patients who declined participation were found to engage less with services than those who decided to participate; their respective SES total scores were 23.31 versus 20.89 (p<.05; independent samples t-test). Age or gender differences were not found.

Table I portrays the characteristics of the 109 patients who were randomized. Figure I shows progression through the trial. Because attrition was so small, we have performed the analyses with only the data actually gathered, rather than imputing scores for the few patients who died or refused further participation.

Table I Respondents characteristics

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| Sex | 77 patients (71%): male  
32 patients (29%): female |
| Average age at T0 | 39.0 years (SD=11.6) |
| Average age of the first contact with a mental health institution | 26.2 years (SD=9.9) |
| Employment | 91 patients (84%): unemployed  
18 patients (16%): employed |
| Ethnicity | 49 patients (45%): Dutch  
21 patients (19%): second-generation immigrants  
39 patients (36%): first-generation immigrants |
| Diagnoses | 76 patients (70%): schizophrenia  
- 57 paranoid type  
- 11 disorganized type  
- 7 catatonic type  
- 1 undifferentiated type  
33 patients (30%): schizoaffective disorder  
- 21 depressive type  
- 12 bipolar type |
| Antipsychotic treatment | 20 patients: no antipsychotic agent (completely non-compliant)  
14 patients: first-generation oral antipsychotic (mostly zuclopentixol and penfluridol)  
37 patients: second-generation oral antipsychotic (mostly risperid and olanzapine)  
13 patients: first-generation injectable antipsychotic (mostly zuclopentixol)  
7 patients: second-generation injectable antipsychotic (mostly risperid)  
18 patients: two antipsychotic agents combined |
Figure I Progression through the trial
3.3.2 Randomization
Results of the logistic regression analysis showed that the randomization procedure was successful; treatment allocation was not significantly predicted by any demographic variable, treatment characteristic, or outcome variable at baseline. Importantly, the subscriptions of oral and injectable antipsychotic agents were evenly distributed between the two treatment allocations. Independent samples t-tests produced similar results.

3.3.3 Therapy participation
Seven of the 54 patients who had been allocated to the TAT intervention dropped out after one or two sessions, and one had quit the study entirely. While another six patients did not complete the intervention, the remaining 40 patients (74%) did. Given the basic selection of non-adherent patients, this drop-out rate was not surprising. Those dropping out of TAT, did go on to receive treatment as usual. Data on the primary outcome measures was gathered successfully for all 54 patients but one. These data were used for the intention-to-treat analyses.

Forty of the 46 patients who participated in the TAT intervention were given the motivational interviewing module. Six of these forty patients also received the medication optimization module, and seven behavioural training. Of the remaining six patients, four received behavioural training, one the medication optimization module, and one both. The mean number of TAT sessions for the 46 participating patients was 9.89 (st-dev=2.72). This process took about six months.

3.3.4 Primary outcomes: service engagement and medication compliance
At baseline, the distributions of the outcome variables were approximately normal. As Table II shows, when we controlled for baseline levels in the multivariate analysis, there were significant differences in service engagement and medication compliance between the two treatment conditions at the end of the TAT intervention (T1). Cohen’s d was .48 for service engagement and .43 for medication adherence. These effect-sizes indicate clinical significance and can be regarded as medium effects (33). Six months later (T2), Cohen’s d was .39 for service engagement and .30 for medication adherence, indicating that after six months of follow-up, the effects had reduced somewhat, and now fell within the small to medium range. Despite the smaller effect-size, only the MANCOVA effects on medication adherence were still statistically significant, and not those on service engagement, which is due to differences at baseline.
3.3.5 Secondary outcomes

Admissions
At baseline, all respondents were in outpatient treatment. Of those allocated to the TAT intervention group, four patients (10%) had been re-admitted to a psychiatric hospital before T1, and they did not complete the intervention. By T2, a total of nine patients had at least once been re-admitted (17%). One of these patients (1.9%) had been admitted involuntarily. Of those allocated to the control group, more had been re-admitted: nine patients (18%) before T1; and by T2, this increased to fourteen patients (28%), six of whom (11.8%) had been admitted involuntarily. Fisher’s exact test showed that the difference in re-admissions at any time before T2 was not significant (p=.159; 1-sided), and that the difference in involuntary admissions tended to significance: 1.9% in the TAT group versus 11.8% in the control group (p=.053; 1-sided).

Symptoms and quality of life
The analyses showed no effects on symptoms or quality of life (Table III).

3.3.6 Mediators
The analyses showed no effects of TAT + TAU on insight, stigma, recovery style, or therapeutic alliance (Table III).
3.4 Discussion

3.4.1 TAT: observed effects and participation

The present study compared the outcomes of two treatment conditions – TAT versus TAU – and found that TAT enhanced service engagement and medication compliance more successfully than TAU did. The effects were smaller at six months follow-up, yet still statistically significant for medication compliance.

There was a trend that the patients within the TAT condition were less often involuntarily admitted to a hospital (1.9% versus 11.8%) – a difference that was almost significant. This can mean that patients in the TAT group were more likely to cooperate with their admission and inpatient treatment, whereas those in the TAU group tended to be more unwilling to comply with the recommended
treatment, and to be more likely to meet the dangerousness criteria that qualified them for an involuntary admission. This is undesirable, as compulsory admission is often an if-all-else-fails measure. Even though it may have positive effects, some patients also report negative ones, such as those on therapeutic alliance, family relationships, and employment prospects (O’Donoghue et al., 2009).

The majority of patients found TAT acceptable. In our view, the dropout rates from therapy were low (26%), especially when we take account of the targeted patients, who are often very difficult to engage in psychological treatment. On the basis of the frequent use of motivational interviewing, we also conclude that the most common reason therapists judged a patient to be engaging poorly with services was due, not to cognitive impairments, but to factors such as stigma, denial, and low insight.

3.4.2 Symptoms and quality of life

The absence of an effect on symptoms was unexpected, although other intervention studies have reported similar results (Valenstein et al., 2009). It may be that our sample size was too small to detect an effect on symptoms. Also, it may be that the duration and/or intensity of TAT was not enough to cause changes in symptoms and quality of life, and that we need longer or more intensive treatments. Alternatively, it may be that patients in our sample were in fact poorly adherent at baseline as a consequence of poor response to antipsychotic medication. Better adherence would then not result in large symptomatic improvements.

Although adherence improved, this also did not lead to better subjective quality of life. Apparently, improving adherence per se did not lead to less symptoms or increases in subjective well being in our study.

3.4.3 Mediators

Despite the effects of TAT on service engagement and medication compliance, it is not clear what the main mechanisms of change were. Surprisingly, insight into illness, therapeutic alliance, recovery style, and the experience of stigma were all unrelated to the effects of TAT. As the baseline means of these variables allowed for improvement, given the scale ranges, a ceiling-effect was ruled out. One possibility is that our sample size was too small to detect significant effects, for example on insight, which did correlate with compliance at baseline. Another possibility is that although patients’ views of treatment were changed and although patients were trained effectively in adherent behaviour, these factors were not covered by our mediator measurements.
In our study design, TAT was an add-on intervention administered by a therapist other than the patient’s own clinician. This has some drawbacks and benefits. A drawback may be that TAT did not result in a better therapeutic alliance with the patient’s own clinician. As we consider the approach to be patient-oriented and respectful of patients’ views, TAT may be more effective when it is administered by the patient’s own clinician: it might strengthen the alliance in the regular therapeutic relationship, a factor known to positively influence outcome (Hewitt & Coffey, 2005). On the other hand, a benefit of this choice in design may be that the therapist providing TAT was not confronted with other demanding topics that the patient would need help with, nor was the therapist impeded by requests to change or reduce medication, which may have interfered with the adherence work.

Because good insight has been associated with depressive symptoms, low self-esteem and lower quality of life (Staring et al., 2009a), improved adherence, if obtained by enhanced insight, may carry the risk of deteriorating quality of life and increasing depression (Rathod et al., 2005). It is therefore noteworthy that, although we could not detect any effect of TAT on quality of life, neither did we observe a deterioration. While TAT improved service engagement and compliance, it seems somehow to have ‘bypassed’ insight. Indeed, the primary focus of TAT is not on psycho-education: instead, because it stimulates the patient to develop an individual narrative into which treatment can somehow be integrated, individual motives for engagement or compliance may sometimes turn out to be different from what clinicians would find appropriate. For example, one patient realized that being adherent to treatment could help to avoid arguments with his partner, and this motivated him. However, he did not recognize that his symptoms and agitation increased whenever he stopped his medication, which is what caused the arguments with her.

### 3.4.4 Limitations and strengths

Seven limitations should be considered. First, the sample size was not large, which may have limited the power to detect treatment effects on secondary outcomes and mediators. For example, assuming that the observed difference in hospitalization rates were non-random and would hold in a larger study, about 120 patients would be needed in each group for a difference of 18% versus 28% to become statistically significant.

Second, our inclusion of many outcome variables may have increased the chances of finding a significant result.
Third, the patients who refused to participate in the study were engaging less with services than those included. An implication is that interventions such as TAT may not be acceptable for patients with very low treatment adherence. These may benefit more from assertive treatments and direct incentives to motivate them (Claassen et al., 2007; Staring et al., 2010a).

Fourth, our study design distributed attention unevenly between the two treatment allocations, which may have produced a bias. TAU mostly consisted of one or two sessions per month. Patients receiving TAT were given an average of 9.9 sessions on top of this during the course of six months. Thus, patients receiving TAT were given about twice the amount of sessions of those receiving TAU. Although one study on enhancing adherence did not produce results that were more significant than those produced in a control group that received less attention (Byerly et al., 2005), another found results indicating that patients improved in both the intervention and control group (Gray et al., 2006). It is therefore still unclear whether attention by itself can increase adherence, and we can not rule out that our results were in part due to an attention bias rather than the contents of TAT.

The fifth limitation is that our measure of compliance consisted of the SES plus a one-item rating scale. This latter measure has not been validated in other studies, and may not be the best available. However, measuring compliance is difficult, and a gold standard is certainly lacking (Kikkert et al., 2008). As well as self-report and interview measures, methods of measuring compliance include pill counts, electronic methods, prescription monitoring, and saliva, plasma and urine assay tests (Patel & David, 2007). Each has its advantages and disadvantages. Pill counts, for example, are not only time-consuming, but also have great potential for inaccuracy. And not only are saliva, plasma, and urine tests not possible for all drugs, they are expensive and invasive, and may also overestimate adherence for drugs that have a long half-life (Fenton et al., 1997; Zygmunt et al., 2002). However, future studies may use such alternative methods to verify our results. Hopefully, our study overcame some of the difficulties, not only because patients were asked about their compliance by interviewers who were not involved in the treatment, but also because it was made clear that the answers would be used solely for the purpose of this study and would not be communicated with care-givers. We are therefore reasonably confident that patients felt free to give honest answers on their medication compliance.

Sixth, we did not look at whether conducting the trial had an effect on what happened within TAU. The patients’ treatment allocations were known to their clinicians. As a result, clinicians may have been more aware of adherence issues
and have given the topic more attention, perhaps especially with patients in the control group. This may have influenced our results by for example increasing the effectiveness of TAU.

The seventh limitation is that, although assessors were blind to the patient’s treatment allocation, their clinicians were not. Therefore, the information clinicians gave on the service engagement scale was not blinded from the treatment allocation, and possible bias in this measure can not be ruled out.

Despite these limitations, the study also had at least four strengths:
(a) it had a well-defined treatment protocol that was based on an empirical-theoretical model in which strategies were tailored to the patient’s individual causes of non-adherence;
(b) it involved an intervention that was applied in routine settings by therapists who worked within the institutions;
(c) it used masked, independent assessors of outcome; and
(d) it had relatively high inclusion and follow-up rates of patients with poor service engagement.

These are important outcomes, particularly for patients who are non-adherent to treatment, and therefore risk future relapse and re-admission. The positive findings of TAT are promising and suggest optimism for further exploration. An important contributor to the effects may be that, after a patient’s individual situation has been assessed, TAT provides various intervention modules.
CHAPTER 4

Fewer symptoms vs. more side effects? Opposing pathways between antipsychotic medication compliance and quality of life.

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ABSTRACT

Background
Non-compliance with medication often has long-term detrimental effects in patients with schizophrenia. However, when patients are compliant, it is not certain whether they experience short-term improved quality of life. By simultaneously reducing symptoms and increasing side-effects, compliance with antipsychotics may have opposing effects on a patient’s perceived quality of life.

Aim
This study aimed to identify any clinical-empirical evidence for two pathways between compliance and quality of life.

Method
To evaluate various pathways between compliance (Service Engagement Scale plus a one-item rating), psychotic symptoms (Positive and Negative Syndromes Scale), adverse medication effects (Subjective Wellbeing under Neuroleptics scale), and quality of life (EQ-5D), we used Structural Equation Modeling on cross-sectional data of 114 patients with a psychotic disorder.

Results
Compliance was not directly related to quality of life (r=.004). The best-fitting model ($\chi^2=1.08; \text{df}=1$) indicated that high compliance was associated with fewer psychotic symptoms ($\beta=-.23$) and more adverse medication effects ($\beta=.22$). Symptoms ($\beta=-.17$) and adverse medication effects ($\beta=-.48$) were both related to lower quality of life.

Discussion
Our results suggest that compliance with antipsychotics has two opposing pathways towards quality of life, albeit indirect ones. While compliance was associated with less severe psychotic symptoms, and was thus related to higher quality of life, it was also associated with more adverse medication effects, and was thus related to lower quality of life. However, due to our study design, we cannot draw firm conclusions on causality. Two possible clinical implications of the results for compliance and interventions are discussed.
4.1 INTRODUCTION

Many patients with either a somatic or a psychiatric disorder do not comply with medication. Based on a review, Cramer and Rosenheck (1998) estimate that, on average, patients who have been prescribed somatic medicine use only 76% of the pills. This percentage is lower in the case of antipsychotics, where only 58% of the prescribed medication is estimated to be actually taken. Keith and Kane (2003) aptly conclude their review by observing that while compliance with medication is difficult for everyone – for example in the field of diabetes, high blood pressure, asthma, or birth control – it is particularly difficult for people with schizophrenia. Four studies have shown that 50% to 75% of patients on antipsychotic medication become non-compliant after one to two years of treatment (Bebbington, 1995; Thomas, 2007; Weiden et al., 1996; Weiden et al., 1991). Obviously, non-compliance makes it difficult to achieve the effects intended for treatment. When a patient stops using antipsychotics, the risk of relapse and admission or readmission increases three to five-fold (Dixon & Lehman, 1995; Fenton et al., 1997; Robinson et al., 2002; Ucok et al., 2006; Weiden et al., 2004). It should be mentioned, however, that in some cases non-compliance may follow clinical deterioration, which can be due to resistance in therapy, making causal attributions on the relationship between non-compliance and relapse difficult. In the same way, the risk of suicide may be 3.75 times higher in noncompliant patients with schizophrenia than it is in those who are compliant (Hawton et al., 2005), though here it is important to realise that depression increases the risk of non-compliance (Elbogan et al., 2005) as well as of suicide.

Although the long-term consequences of non-compliance are often detrimental to patients with schizophrenia, it is less obvious whether those who are compliant experience any short-term improvement in their quality of life. While three studies have found that people suffering from schizophrenia experienced substantially lower quality of life than healthy subjects (Carlsson et al., 2002; Reine et al., 2003; Zissi et al., 1998), few studies have investigated how experienced quality of life was affected by compliance with antipsychotics. One study reported an association between compliance and quality of life in first-episode patients (Coldham et al., 2002). Another initially found a small positive association that however was not borne out by subsequent statistical modelling (Puschner et al., 2006).

Arguably, by reducing symptoms on the one hand and increasing side-effects on the other, compliance with medication involves two mechanisms, each affecting a
patient’s perceived quality of life in a different direction. Although Puschner et al. (2006) did indeed find that better compliance and higher perceived quality of life were mediated by a reduction in psychopathology, they did not find that better compliance and lower quality of life were mediated by an increase in medication side-effects. This may be because they used the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS, Day et al., 1995) – a good self-report scale of side-effects that nonetheless does not make it possible to quantify their overall burden on a patient. It has been found in other studies, however, that side-effects of antipsychotics are associated with a reduced perceived quality of life (Angermeyer and Matschinger, 2000; Yen et al., 2008), and that they are sometimes a reason for discontinuing medication (Lambert et al., 2004; Robinson et al., 2002).

The objective of this study was to test the hypothesis that medication compliance has two opposing and indirect associations with a patient’s perceived quality of life: (1) that, by reducing psychotic symptoms, better compliance is associated with increased quality of life; and (2) that, by increasing adverse medication effects, better compliance is associated with poorer quality of life.

### 4.2 Method

#### 4.2.1 Study population

Participants were respondents in a multi-centre randomised controlled trial that took place in the Dutch city of Rotterdam and investigates the effects of Treatment Adherence Therapy (TAT). TAT is a tailored intervention in which, depending on a patient’s individual reasons or causes of non-compliance, four different intervention modules can be applied, for example behavioural interventions or an adapted form of motivational interviewing. For a more detailed description, see Staring et al. (2006). Inclusion criteria were: (1) schizophrenia spectrum disorder, (2) receiving outpatient treatment, (3) speaking the Dutch language, and (4) at least some problems with service engagement, as defined by an average item-score of 1.5 or higher on at least two subscales of the Service Engagement Scale (SES; see Measurements, below).

#### 4.2.2 Design and procedure

The study design was approved by the Medical Ethics Committee at Erasmus University Medical Centre. Participants had to give written informed consent before start. Patients were referred by their clinician; their participation was...
Two opposing pathways between compliance and quality of life

requested by a research assistant. In baseline assessment before randomization, all respondents and their clinicians participated in a structured interview. This was conducted by psychology and medicine students who received a sixteen hours training that mostly consisted of interview role playing and scoring of the instruments. After co-rating a live interview by the main researcher, they performed two interviews under supervision. When ratings were sufficiently in line with those of the experienced researcher, the students did interviews by themselves, while receiving bi-weekly supervision. Among others, we used the lifetime Composite International Diagnostic Interview, version 2.1 Auto (WHO CIDI, 1997) to assess mental disorders according to the definitions and criteria of DSM-IV (APA, 1994). Respondents were paid EUR 20 for participating in the interview. These baseline assessments provided the data for this article.

4.2.3 Measurements

Medication compliance

The Service Engagement Scale (SES) (Tait et al., 2002) is a 14-item rating scale in which observed service engagement is rated by the caregiver most familiar with the patient. The scale has four subscales: (1) availability, (2) collaboration, (3) help-seeking, and (4) medication compliance. The scale has good face validity and content validity, is user-friendly, and had good test-retest reliability in patients with psychotic disorders (Tait et al., 2002). In this study, only the fourth subscale was used as a measure of medication compliance. A high score indicates problematic compliance.

As well as the SES, we also assessed compliance in a semi-structured interview with the patient. This score ranges from 0 to 4, with higher scores indicating more problematic compliance. The method was modeled after the Health of the Nation Outcome Scales (HoNOS) (Wing et al., 1998; Mulder et al., 2004).

Thus, we used two different measures of medication compliance, one caregiver-based and one patient-based. Both measures were standardized, summed, and reversed, thereby creating a compiled measure of compliance, with high scores indicating good compliance. This compiled measure based on dual assessment warrants against biased measurements (Kikkert et al., 2008).

Quality of life

To measure quality of life we used the self-report EQ-5D, which has been validated in patients with schizophrenia (Prieto et al. 2003). The patient uses the EQ-5D to rate health-related quality of life on five dimensions: mobility, self-care,
usual activities, pain/discomfort, and anxiety/depression. On the basis of a Dutch validation study (Lamers et al., 2005), the items were linearly transformed into a score ranging from -0.33 to 1.00. A higher score stands for better quality of life.

Psychopathology

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a 30-item rating scale completed by the trained research staff at the conclusion of a semi-structured interview. For this study, we used only the positive syndrome scale as a measure of psychotic symptoms.

Adverse effects and wellbeing under neuroleptics

To measure the effects of antipsychotics experienced by our patients, we used the 20-item version of the Subjective Wellbeing Scale under Neuroleptics (SWN) (Naber et al., 2001; De Haan et al., 2002). The scale consists of five subscales: (1) physical functioning, (2) social integration, (3) mental functioning, (4) self-control, and (5) emotional regulation. The SWN covers adverse side-effects (Karow et al., 2007), and encompasses patients’ overall experience of the effects of antipsychotics. It is important to note that patients are kept unaware of the fact that the measurement is concerned with effects of antipsychotics. This makes it unlikely that a patient’s general attitude towards medication will play a role in the answers. For the purpose of this study, we reversed the total score, which ranges from 0 to 100: high scores thus indicate a high level of subjectively experienced adverse effects of antipsychotics.

4.2.4 Statistical analyses

Performance parameters of various pathway models were produced and compared using Structural Equation Modeling (SEM). We examined four competing models: (1) the model of the hypothesis (Figure I), in which the direct effect of compliance on quality of life was fixed at 0.00; (2) a model in which this effect was not fixed at 0.00, but the effect of psychotic symptoms on quality of life was; (3) a model in which the effects of compliance and psychotic symptoms on quality of life were both fixed at 0.00, and (4) a model in which the effect of compliance on quality of life was not fixed at 0.00, yet the effect of adverse medication effects was. By comparing these models, SEM makes it possible to identify and estimate the relevance of the various pathways. In all four competing models, psychotic symptoms were allowed to be correlated with adverse medication effects.
Two opposing pathways between compliance and quality of life

4.3 RESULTS

4.3.1 Patient characteristics

A total of 195 patients were asked to participate in the randomised controlled trial described above. Seventy-nine of them declined to participate. Of the remainder, two were too disorganized in thought and speech to be able to complete the questionnaires. The remaining 114 completed the baseline assessments. Lifetime diagnoses: 79 of these patients (69%) met the criteria of schizophrenia (60 paranoid type, 11 disorganized type, 7 catatonic type, and 1 undifferentiated type), and 35 (31%) met the criteria of schizoaffective disorder (22 depressive type and 13 bipolar type). Eighty-one patients (71%)
were male, and 33 (29%) female. Fifty-one patients (45%) were native to the Netherlands, 42 (37%) were first-generation immigrants, and 21 (18%) were second-generation immigrants. Most of the first-generation immigrants were from Suriname (24 patients), and the Dutch Antilles (six patients). As the Dutch language is spoken throughout both Suriname and the Dutch Antilles, performing the interviews with these immigrants did not produce problems. The remaining twelve first-generation immigrants also spoke Dutch, as this was a requirement for participation in the study. However, no specific measures were taken to ensure that the instruments were culture-sensitive.

One-hundred-and-two patients (90%) were not married or living with a partner. The majority were unemployed (95 patients; 83%). Mean age at first contact with a mental health institution was 25.8 years (SD=9.3); mean age at baseline assessment was 38.3 years (SD=11.5). Although following outpatient treatment, 21 patients were not, despite medical advice, taking antipsychotic medication (18%), and were thus totally non-compliant. Thirty-four patients (28%) were being treated with first-generation antipsychotics, and 61 (54%) with second-generation antipsychotics. Nineteen patients (17%) were using two different antipsychotics simultaneously. Average scores on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) were as follows: positive symptoms 13.7 (SD=5.40), negative symptoms 14.0 (SD=5.72), and general psychopathology 30.4 (SD=9.65).

4.3.2 Results concerning the hypothesis

As expected, significant correlations show that compliance was not only negatively associated with psychotic symptoms, but also positively associated with the perceived adverse effects of neuroleptics (Table I). Compliance was not significantly correlated with quality of life. Both psychotic symptoms and adverse medication effects had significant negative associations with perceived quality of life (Table I).

<table>
<thead>
<tr>
<th>Pearson correlations</th>
<th>Medication Compliance</th>
<th>Psychotic symptoms</th>
<th>Adverse medication effects</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic symptoms</td>
<td>-.23*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse medication effects</td>
<td>.23*</td>
<td>.27**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>.004</td>
<td>-.30**</td>
<td>-.53**</td>
<td></td>
</tr>
</tbody>
</table>

** Mean 0.00 13.74 33.26 0.71
SD 1.72 5.40 15.32 0.26

** Correlation is significant at the .01 level (two-sided)
* Correlation is significant at the .05 level (two-sided)
In models 2, 3, and 4, the $\chi^2 / df$ parameter was higher than 1.5, indicating a lack of fit with the data (Table II). Considering the p-value, model 4 should be rejected. Model 3, too, was nearly rejected, as the p-value was slightly above 0.05.

In terms of the highest scores on the relevant parameters, the hypothesis model—model 1—had the best performance. The details of this model, presented in Table III and in Figure II, suggest that compliance has two indirect pathways towards quality of life. High compliance was associated with fewer psychotic symptoms ($\beta=-.23$) and more adverse medication effects ($\beta=.22$). Symptoms and adverse medication effects were both related to quality of life ($\beta=-.17$ and $\beta=-.48$, respectively).

4.4 DISCUSSION

4.4.1 Compliance and quality of life

Our results suggest that compliance with antipsychotics in patients with a psychotic disorder involves two different and indirect pathways towards quality of life. While compliance seems to reduce psychotic symptoms—which may increase quality of life—compliance also seems to increase adverse medication effects—which may reduce quality of life. This finding is largely in line with an earlier study which found not only (1) that compliance with antipsychotics had no direct effect on quality of life, but also (2) clinical-empirical evidence for an indirect effect through a reduction of psychotic symptoms (Puschner et al., 2006). However, in their study, Puschner et al. (2006) did not find that an increase in medication side-effects mediated between better compliance and lower quality of life. This may be attributed to the fact that their side-effects measure (LUNSERS) did not cover the overall burden of adverse antipsychotics effects. Our measure, on the other hand, emphasized subjective wellbeing, which is important from the patients’ perspective (Naber et al., 2001; De Haan et al., 2002). The results of our study are also in line with findings in which the side-effects of antipsychotics were associated with a lower perceived quality of life (Yen et al., 2008; Angermeyer & Matschinger, 2000).

As well as the associations we had expected, we found psychotic symptoms to be significantly associated with adverse effects of antipsychotics. One possible explanation is that patients with severe psychotic symptoms are prescribed
### Table II Performance parameters of possible models

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p</th>
<th>$\chi^2$/df</th>
<th>CFI</th>
<th>TLI</th>
<th>RSMEA</th>
<th>SRMR</th>
<th>AIC</th>
<th>BIC</th>
<th>SBIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The hypothesis model, without a direct effect of compliance on QOL</td>
<td>1.08</td>
<td>1</td>
<td>0.30</td>
<td>1.08</td>
<td>1.00</td>
<td>0.99</td>
<td>0.03</td>
<td>0.02</td>
<td>2047.15</td>
<td>2077.15</td>
<td>2042.39</td>
</tr>
<tr>
<td>2</td>
<td>Model with a direct effect of compliance on QOL, but no effect of symptoms on QOL</td>
<td>2.88</td>
<td>1</td>
<td>0.09</td>
<td>2.88</td>
<td>0.97</td>
<td>0.82</td>
<td>0.13</td>
<td>0.03</td>
<td>2048.95</td>
<td>2078.96</td>
<td>2044.19</td>
</tr>
<tr>
<td>3</td>
<td>Model without a direct effect of compliance on QOL, and no effect of symptoms on QOL</td>
<td>5.47</td>
<td>2</td>
<td>0.06</td>
<td>2.74</td>
<td>0.94</td>
<td>0.83</td>
<td>0.12</td>
<td>0.05</td>
<td>2049.55</td>
<td>2076.82</td>
<td>2045.22</td>
</tr>
<tr>
<td>4</td>
<td>Model with a direct effect of compliance on QOL, but no effect of adverse medication effects on QOL</td>
<td>30.78</td>
<td>1</td>
<td>0.00</td>
<td>30.78</td>
<td>0.52</td>
<td>Could not properly be estimated</td>
<td>0.51</td>
<td>0.11</td>
<td>2076.86</td>
<td>2106.86</td>
<td>2072.09</td>
</tr>
</tbody>
</table>

A non-significant p-value (p>0.05) and the ratio of $\chi^2$/df < 1.5 represent a good model fit. Also, for good model fit, the Comparative Fit Index (CFI) should be higher than .95, the Tucker-Lewis Index (TLI) higher than 0.95, the Root Mean Square Error of Approximation (RMSEA) lower than 0.05, and the Standardised Root Mean Square Residual (SRMR) lower than 0.05. With regard to the last three parameters in the table (AIC, BIC, ABIC): the smaller, the better.
Two opposing pathways between compliance and quality of life

higher doses of antipsychotics, which in turn exacerbates adverse medication effects. A second possible explanation is that patients with severe psychotic symptoms are more likely to report feeling distressed, which is then reflected in their answers on the scale for adverse medication effects. A similar relationship was found in the study by Puschner et al. (2006), though the authors themselves did not comment on it.

4.4.2 Limitations
Our study had three main limitations. The first is our restricted sample size with mainly male participants (71%), in addition to which we excluded patients with very high service engagement—an exclusion criterion in the multi-centre randomised controlled trial addressing patients with moderate compliance. Neither is it likely that we included patients with very poor service engagement, who may have refused to participate or who may not have been in outpatient

<table>
<thead>
<tr>
<th>Table III SEM results of the hypothesis model tested</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of compliance on:</strong></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
</tr>
<tr>
<td>Adverse medication effects</td>
</tr>
<tr>
<td><strong>Effects of psychotic symptoms on:</strong></td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
<tr>
<td><strong>Effects of adverse medication effects on:</strong></td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
<tr>
<td><strong>Psychotic symptoms’ association with:</strong></td>
</tr>
<tr>
<td>Adverse medication effects</td>
</tr>
</tbody>
</table>

1) unstandardized regression coefficient
2) standard error of the unstandardized regression coefficient
3) standardized regression coefficient

Figure II Results of the best fitting model (model 1) of the SEM analyses, presenting the standardized regression coefficients
treatment. For these reasons, the service engagement of respondents in this study probably lay in the middle range. This makes it difficult to generalize our findings to patients with very high or very low compliance and future studies on the topic may try to include these patient groups, by for example including inpatients.

The second limitation is that our measure of compliance consisted of the SES plus a one-item rating scale. This latter measure has not been validated, and may not be the best available. However, measuring compliance is difficult, and a gold standard is certainly lacking (Kikkert et al., 2008). As well as self-report and interview measures, methods of measuring compliance include pill counts, electronic methods, prescription monitoring, and saliva, plasma and urine assay tests (Patel & David, 2007). Each has its advantages and disadvantages. Pill counts, for example, are not only time-consuming, but also have great potential for inaccuracy. And not only are saliva, plasma, and urine tests not possible for all drugs, they are expensive and invasive, and may also overestimate adherence for drugs that have a long half-life (Fenton et al., 1997; Zygmunt et al., 2002). However, future studies may use such alternative methods to verify our results. Hopefully, our study overcame some of the difficulties, not only because patients were asked about their compliance by interviewers who were not involved in the treatment, but also because it was made clear that the answers would be used solely for the purpose of this study and would not be communicated with care-givers. We are therefore reasonable confident that patients felt free to give honest answers on their medication compliance.

Finally, because our study used cross-sectional data, we cannot draw firm conclusions about the directions of causality. The causal interrelationships of the relevant variables would almost certainly be identified in longitudinal and intervention studies. However, to our knowledge, no studies have experimentally increased compliance and examined its effects on quality of life.

4.4.3 Clinical implications
Overall, our results may have two implications for clinical practice. The first is that, with regard to the effects of medication, the balance between symptom reduction and adverse effects is associated with the benefit a patient perceives in terms of improved quality of life. Generally, however, when evaluating the antipsychotic medication with which they have been prescribed, patients do not balance side-effects and symptoms as separate issues. Instead, they describe
Two opposing pathways between compliance and quality of life

Two opposing pathways between compliance and quality of life (Carrick et al., 2004). In clinical practice, it may therefore be useful to measure psychotic symptoms and side-effects repeatedly, to communicate about the measurements with the patient, and to work together with each individual patient to establish which antipsychotic (and dosage) is the most suitable. Such repeated measurements may enhance compliance, simultaneously helping the patient to distinguish between the ways in which medication not only reduces symptoms but also creates adverse effects. This method has been described elsewhere as part of an intervention for improving compliance (Staring et al., 2006).

The second implication is that outpatients who are compliant with the antipsychotics prescribed may not gain any improvement in perceived short-term quality of life. This means that their motives for compliance may not lie in the perception of short-term experienced benefits. They may have several other motives for being compliant—to gain partner or family support (Patel & David, 2007), to achieve a good relationship with the clinician (Fenton et al., 1997, Lacro et al., 2002), or possibly because they acknowledge the long-term consequences of non-compliance, such as the risk of relapse and admission or readmission. Interventions for improving compliance should try to focus on those motives, for example by helping patients to reflect on the long-term consequences of non-compliance. Examples of such interventions are compliance therapy and motivational interviewing, though there is no conclusive evidence on their effectiveness in this field as yet (Barkhof et al., 2006; Rusch and Corrigan, 2002). It may be that, despite the efforts of clinicians, some patients with severe cognitive deficits are unable to reflect on the more distant consequences of non-compliance, or to behave in accordance with them. A possible strategy for improving compliance in such patients is by applying a form of contingency management, a method intended to gradually transform compliance into a rewarding behaviour by providing patients with an incentive immediately after they have taken their medication. This method has been used to enhance compliance with medications whose effects are not immediately rewarding (Rounsaville et al., 2008); our results suggest that antipsychotics fit this category of medicine. We should add that, in assertive outreach involving people with severe mental illness, money has been used as an incentive to improve compliance, and the results of an empirical exploration were promising (Claassen et al., 2007).
Chapter 5

Stigma moderates the associations of insight with depressed mood, low self-esteem, and low quality of life in patients with psychosis.

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Schizophrenia Research, 2009, 115, 363-369
ABSTRACT

Background
Good insight into illness in patients with schizophrenia is related not only to medication compliance and high service engagement, but also to depression, low self-esteem, and low quality of life. The detrimental effects of insight pose a problem for treatment.

Aim
To investigate whether the negative associations of good insight are moderated by perceived stigma.

Method
Respondents were 114 patients with schizophrenia spectrum disorders. We used Analyses of Variance (ANOVA) and Structural Equation Modeling (SEM) to test moderation.

Results
Good insight was associated with high service engagement and high compliance. Also, good insight was associated with depressed mood, low quality of life, and negative self-esteem. This association was strong when stigma was high and weak when stigma was low. SEM showed that the constrained model performed significantly worse than the unconstrained model, in which detrimental associations of insight were free to vary across stigma groups ($\chi^2 = 19.082$ | df = 3 | p<.001).

Conclusions
Our results suggest that the associations of insight with depression, low quality of life, and negative self-esteem are moderated by stigma. Patients with good insight who do not perceive much stigmatization seem to be best off across various outcome parameters. Those with poor insight have problems with service engagement and medication compliance. Patients with good insight accompanied by stigmatizing beliefs have the highest risk of experiencing low quality of life, negative self-esteem, and depressed mood. A clinical implication is that when it is attempted to increase insight, perceived stigma should also be addressed.
5.1 INTRODUCTION

In patients with schizophrenia, insight into illness is associated with fewer symptoms, better psychosocial functioning, and better compliance with antipsychotic medication (Francis and Penn, 2001; Kuzoki et al. 2005; Lacro et al. 2002; Lysaker et al., 1998, 2002; Mohamed et al., 2009; Perkins 2002; Rittmannsberger et al. 2004). Insight has been regarded as a necessary condition for anticipating needs, developing realistic goals (Lysaker et al., 2001; Young and Ensign, 1999) and promoting positive social and health outcomes (McEvoy, 1998; McGorry and McConville, 1999). However, there appears to be a downside. Recent studies show that insight is both cross-sectionally and longitudinally related to depression, hopelessness, lower self-esteem (Cooke et al., 2007; Karow and Pajonk, 2006; Lincoln et al., 2007a; Mohamed et al., 2008) and lower quality of life (Hasson-Ohayon et al., 2006; Kravetz et al., 2000; Pyne et al., 2001; Schwartz, 2001). These opposing effects of insight are reflected by diagnosed individuals who express the belief that they have two choices: either to accept their diagnosis and life as a “chronic case,” or to reject the diagnosis and retain some semblance of control (Barham and Hayward, 1998).

If insight leads to an impoverished sense of self, worse quality of life, and pessimism about the future, should attempts be made to increase it? More understanding is needed of the psychological processes at work. To a greater extent than those with other mental disorders, patients with schizophrenia experience stigma from family, partners, friends, and colleagues (Corrigan, 2004; Lee, 2005). Lysaker et al. (2006) argued that negative outcome of insight depends on the internalization of stigmatic beliefs, on the meaning that patients attach to their illness. While some patients believe that they no longer have the ability to achieve valued social roles, others disagree, remain hopeful and engage in active coping (Lysaker et al., 2005). A similar idea was published by Williams (2008), who based a description of post-diagnostic identities for patients with schizophrenia on two dimensions: (1) the amount of identification with the community of people with severe mental illness, and (2) the amount of stigma that is internalized in the self-narrative. Patients with high identification but low internalized stigma are assumed to be socially active and not experience diminished self-esteem. The hypothesis that good insight is related to negative outcome only when it is accompanied by stigmatizing beliefs was recently supported (Lysaker et al. 2006).
To the best of our knowledge, the study by Lysaker et al. (2006) is the only one to have tested this hypothesis. Although it was well conducted, specific elements of its design limit the extent to which its findings can be generalized. For instance, their sample was relatively small (n=75), and its estimate of insight was based solely on a single item of the Positive and Negative Syndrome Scale. Also, a subscale of the Quality of Life Scale was used to reflect social functioning, but general quality of life was not included. And although its analyses included a scale of hopelessness, no measure of general depressive mood was used.

We investigated the same hypothesis as Lysaker et al. (2006), though using a larger sample, different outcome variables, other instruments, and more advanced statistical analyses. We hypothesized that service engagement and medication compliance are high in patients with good insight, independently of stigmatic beliefs. However, we also expected that stigma moderates the detrimental effects of insight.

5.2 METHOD

5.2.1 Study population
Participants were respondents in an ongoing multi-centre randomised controlled trial that investigates the effects of an intervention targeting service engagement in the Dutch city of Rotterdam (Staring et al., 2006). Inclusion criteria were: (1) schizophrenia spectrum disorder, (2) outpatient treatment, and (3) some problems with service engagement, as defined by an average item-score of 1.5 or higher on at least two subscales of the Service Engagement Scale (see measurements section).

5.2.2 Design and procedure
We used a cross-sectional design. The study design was approved by the Medical Ethics Committee at Erasmus University Medical Centre. Patients were referred by their clinician, and asked by a research assistant to participate. Participants had to give written informed consent. The inclusion period lasted from March 2005 until September 2008. Respondents were assessed on the basis of a structured interview, conducted by trained and supervised psychology and medicine students. To assess mental disorders according to the definitions of DSM-IV (APA, 1994), the lifetime Composite International Diagnostic Interview, version 2.1 Auto (WHO, 1997) was used. Respondents were paid EUR 20 for participating in the interview.
5.2.3 Measurements

**Insight**

The self-report 8-item Insight Scale (IS) of Birchwood et al. (1994) was used. There are three subscales: (1) awareness of illness, (2) re-labeling symptoms to illness, and (3) need for treatment. Total scores range from 0 to 12. The scale is reliable and valid, and is easy to use within this group of patients (Birchwood et al., 1994).

**Stigma**

We used the 12-item “perceived devaluation and discrimination” part of the self-report Stigma Scale (SS) by Link et al. (2002). The items cover the patient’s perception of common opinions about psychiatric patients, such as “Most people believe that entering a mental hospital is a sign of personal failure.” Total scores range from 1 to 4, with higher scores indicating more perceived stigmatization. Other parts of the Stigma Scale were not used, as they measure behavioural reactions on perceived stigma, such as secrecy or withdrawal.

**Service engagement and medication compliance**

The Service Engagement Scale (SES) (Tait et al., 2002) has 14 items on which the caregiver who is most familiar with the patient rates the observed service engagement. It has four subscales: (1) availability, (2) collaboration, (3) help-seeking, and (4) medication compliance. The scale has good face validity and content validity, is user-friendly, and had good test-retest reliability in patients with psychotic disorders (Tait et al., 2002). Total scores range from 0 to 42, high scores indicating problematic service engagement. In this study, the total score was used to reflect service engagement, and the fourth subscale was used to reflect medication compliance.

On the basis of a semi-structured interview with the patient, we also used a one-item rating scale to assess medication compliance. This item ranged from 0 to 4, high scores indicating problematic compliance.

In other words, because measuring compliance is difficult (Kikkert et al., 2008), we used two measures of compliance, one caregiver-based and one patient-based, hoping that this would provide a valid indication.

**Quality of life**

The self-report Euro-QOL with five dimensions (EQ-5D) was used, which has been validated in patients with schizophrenia (Prieto et al., 2003). Five
dimensions are rated: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Items are calculated into a weighed total score that ranges from -0.33 to 1.00, based on a Dutch validation study (Lamers et al., 2005). Higher scores represent better quality of life.

**Self-esteem**
We used the 20-item Self-Esteem Rating Scale-Short Form (SERS-SF) (Lecomte et al., 2006). This self-report scale has two subscales, supported by factor analysis: positive and negative self-esteem. Each subscale ranges from 10 to 70; high scores indicate high positive or high negative self-esteem. The scale has good internal consistency, good test-retest reliability, and adequate convergent validity in patients with schizophrenia (Lecomte et al., 2006).

**Depressed mood**
The depressed mood item of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used. PANSS is a 30-item rating scale completed by trained research staff at the conclusion of a semi-structured interview. The depressed mood item provides a rating from 1 to 7, higher scores reflecting higher levels of depressed mood.

**5.2.4 Statistical analyses**
We conducted an Analysis of Variance (ANOVA) to gain a view of our data. Then we used Structural Equation Modeling (SEM) in a multiple-group approach that would allow us to test the moderator hypothesis.

For the ANOVA, we constructed three groups, the first consisting of patients with poor insight, the second of patients with good insight and low stigma, and the third of patients with good insight and high stigma. A score of eight or higher on the Insight Scale (IS) was taken to reflect good insight, and all scores below this point to reflect poor insight. A score of 2.70 or higher on the Stigma Scale (SS) was seen as an indication that a patient perceived a lot of stigma. The groups were compared for outcome variables using one-way analyses of variance (ANOVA) with post-hoc Bonferroni, using SPSS 15.0. Bonferroni’s correction was used to correct for multiple testing.

Next, we used Structural Equation Modeling (SEM) to compare two models, both in which the continuous measure of insight was used to predict service engagement, compliance, depressed mood, quality of life, and self-esteem. Stigma was dichotomized using the same cut-off score as with the ANOVA, dividing the participants into two groups: those with low and those
with high stigma. An unconstrained model and a constrained model were then analyzed. In the latter, the effects of insight on depressed mood, quality of life and self-esteem were constrained to be equal across both stigma groups. In the unconstrained model, these effects were free to differ across the stigma groups. If the constrained model significantly worsened the model fit in comparison to the unconstrained model, this would be evidence of different relationships between insight and detrimental measures across the two stigma groups (Frazier et al., 2004). In other words, it would be evidence that the detrimental effects of insight depend on whether patients perceive much stigma or not. We compared the models using a chi-square test, in which the degrees of freedom are equal to the difference in degrees of freedom for the test statistics of the two models.

As measures of model performance, we used the $\chi^2$ test (Jöreskog, 1993) to determine the adequacy of the model-fit. A non-significant $p$-value ($p>0.05$) and the ratio of $\chi^2/df < 1.5$ would represent an adequate model fit. To provide for reliable evaluations of the model, we used the Comparative Fit Index (CFI>0.95; Bentler, 1990), Tucker-Lewis Index (TLI>0.95; 1973), Root Mean Square Error of Approximation (RMSEA≈0.05; Steiger, 1990), and Standardised Root Mean Square Residual (SRMR<0.05; Jöreskog, 1971). We used the M-Plus 5.0 program.

5.3 RESULTS

5.3.1 Patient characteristics
A total of 195 patients were asked to participate. Seventy-nine refused. As no data was available on those who refused, it was not possible to analyze biases due to selective participation. Two patients of those willing to participate were too disorganized to be able to complete the questionnaires. The remaining 114 completed the baseline assessments (Table I).

5.3.2 Effects of insight
The ANOVA results (Table III) showed that Bonferroni’s correction should be used for a maximum of three dimensions, which means that our alpha-criterion for each test was divided by three, resulting in an alpha of .017. Results indicated that service engagement and medication compliance were significantly more problematic in patients with poor insight than in those with good insight. The effect was independent of stigma for service engagement and caregiver-based compliance. On patient-based compliance, the post-hoc analysis clustered
patients with good insight and high stigma together with those who were low compliant and those who were high compliant. In short, mostly irrespective of the level of stigma, the ANOVA supported the hypothesized associations of insight with service engagement and compliance.

As to the detrimental associations, ANOVA showed that the group with good insight and high stigma scored significantly worse than both other groups on negative self-esteem (F = 14.52; p<.001) and quality of life (F = 7.52; p<.01); and this group also scored significantly worse on depressed mood than the group with poor insight (F = 5.93; p<.01). The group with good insight and low stigma scored significantly better on negative self-esteem and quality of life than the group with good insight and high stigma. Finally, the poor insight group scored significantly better on depressed mood, negative self-esteem and quality of life than the group with good insight and high stigma, though not better than the group with good insight and low stigma. There were no significant differences with regard to positive self-esteem. We therefore did not include positive self-esteem in subsequent analyses.

Table I Respondents characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>81 patients (71%): male</td>
</tr>
<tr>
<td></td>
<td>33 patients (29%): female</td>
</tr>
<tr>
<td>Average age</td>
<td>38.3 years (SD=11.5)</td>
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<tr>
<td>Average age of the first contact with a mental health institution</td>
<td>25.8 years (SD=9.3)</td>
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<tr>
<td>Employment</td>
<td>95 patients (83%): unemployed</td>
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<td></td>
<td>19 patients (17%): employed</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>51 patients (45%): Dutch</td>
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<td></td>
<td>42 patients (37%): first-generation immigrants</td>
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<tr>
<td></td>
<td>21 patients (18%): second-generation immigrants</td>
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<tr>
<td>Diagnoses</td>
<td>79 patients (69%): schizophrenia</td>
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<tr>
<td></td>
<td>- 60 paranoid type</td>
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<tr>
<td></td>
<td>- 11 disorganized type</td>
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<td></td>
<td>- 7 catatonic type</td>
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<tr>
<td></td>
<td>- 1 undifferentiated type</td>
</tr>
<tr>
<td></td>
<td>35 patients (31%): schizoaffective disorder</td>
</tr>
<tr>
<td></td>
<td>- 22 depressive type</td>
</tr>
<tr>
<td></td>
<td>- 13 bipolar type</td>
</tr>
<tr>
<td>Average PANSS positive syndrome score</td>
<td>13.7 (SD=5.4)</td>
</tr>
<tr>
<td>Average PANSS negative syndrome score</td>
<td>14.0 (SD=5.7)</td>
</tr>
<tr>
<td>Average PANSS general psychopathology score</td>
<td>30.4 (SD=9.7)</td>
</tr>
</tbody>
</table>
Table II Pearson correlations of the study variables

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Stigma (SS)</td>
<td></td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Problematic service</td>
<td>-.34**</td>
<td>- .01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>engagement (SES)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problematic medication compliance (SES-4)</td>
<td>-.37**</td>
<td>.13</td>
<td>.67**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problematic medication compliance (one item)</td>
<td>-.21*</td>
<td>.19*</td>
<td>.23*</td>
<td>.48**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood (PANSS G6)</td>
<td>.28**</td>
<td>.18</td>
<td>-.22*</td>
<td>-.15</td>
<td>.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life (EQ-5D)</td>
<td>-.21*</td>
<td>-.32**</td>
<td>.05</td>
<td>.03</td>
<td>-.04</td>
<td>-.50**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive self-esteem (SERS-SF)</td>
<td>-.08</td>
<td>-.18</td>
<td>.08</td>
<td>-.07</td>
<td>-.08</td>
<td>-.20*</td>
<td>.28*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative self-esteem (SERS-SF)</td>
<td>.32**</td>
<td>.32**</td>
<td>-.02</td>
<td>.00</td>
<td>-.01</td>
<td>.45**</td>
<td>-.48**</td>
<td>-.53**</td>
<td></td>
</tr>
</tbody>
</table>

**. Correlation is significant at the .01 level (2-tailed)
*. Correlation is significant at the .05 level (2-tailed)
In the SEM, we included insight as the predictor, and service engagement, compliance (both measures), depressed mood, quality of life, and negative self-esteem as outcome variables. Although the parameters discussed in the methods section show that the constrained model did not fit the data well (Table IV), the

### Table III ANOVA results comparing patients with (1) poor insight, (2) good insight and low stigma, and (3) good insight and high stigma

<table>
<thead>
<tr>
<th></th>
<th>(1) Poor Insight (n=50)</th>
<th>(2) Good insight and low stigma (n=37)</th>
<th>(3) Good insight and high stigma (n=27)</th>
<th>ANOVA Comparisons (Bonferroni)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problematic service engagement (SES)</td>
<td>22.9 (SD=6.18)</td>
<td>19.1 (SD=5.56)</td>
<td>18.4 (SD=6.05)</td>
<td>6.88** 1 &gt; 2,3</td>
</tr>
<tr>
<td>Problematic medication compliance (SES-4)</td>
<td>6.32 (SD=3.21)</td>
<td>3.84 (SD=2.76)</td>
<td>4.19 (SD=2.90)</td>
<td>8.62*** 1 &gt; 2,3</td>
</tr>
<tr>
<td>Problematic medication compliance (one item)</td>
<td>1.84 (SD=1.73)</td>
<td>1.00 (SD=0.97)</td>
<td>1.11 (SD=0.93)</td>
<td>4.87** 1 &gt; 2</td>
</tr>
<tr>
<td>Depressed mood (PANSS G6)</td>
<td>1.90 (SD=1.20)</td>
<td>2.51 (SD=1.52)</td>
<td>3.07 (SD=1.77)</td>
<td>5.93** 1 &lt; 3</td>
</tr>
<tr>
<td>Quality of life (EQ-5D)</td>
<td>0.76 (SD=0.23)</td>
<td>0.75 (SD=0.20)</td>
<td>0.55 (SD=0.30)</td>
<td>7.52** 1,2 &gt; 3</td>
</tr>
<tr>
<td>Positive self-esteem (SERS-SF)</td>
<td>52.1 (SD=9.99)</td>
<td>51.3 (SD=11.84)</td>
<td>47.7 (SD=9.58)</td>
<td>1.62 ns</td>
</tr>
<tr>
<td>Negative self-esteem (SERS-SF)</td>
<td>26.7 (SD=9.90)</td>
<td>30.9 (SD=14.69)</td>
<td>42.5 (SD=12.92)</td>
<td>14.52*** 1,2 &lt; 3</td>
</tr>
</tbody>
</table>

*** P < .001
** P < .01
* P < .017 (the alpha-criterion for each test due to Bonferroni’s correction)

### Table IV SEM fit to the data parameters of both the unconstrained and the constrained model

<table>
<thead>
<tr>
<th>Model description</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p</th>
<th>$\chi^2$/df</th>
<th>CFI</th>
<th>TLI</th>
<th>RMSEA</th>
<th>SRMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconstrained model: all effects of insight are unconstrained across both stigma groups</td>
<td>7.73</td>
<td>6</td>
<td>0.26</td>
<td>1.29</td>
<td>0.99</td>
<td>0.93</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Constrained model: the effects of insight on depression, quality of life, and negative self-esteem are constrained as equal across the stigma groups</td>
<td>26.81</td>
<td>9</td>
<td>0.002</td>
<td>2.98</td>
<td>0.90</td>
<td>0.54</td>
<td>0.19</td>
<td>0.11</td>
</tr>
</tbody>
</table>

A non-significant p-value (p>0.05) and the ratio of $\chi^2$/ df < 1.5 represent adequate model fit. For good model fit, the Comparative Fit Index (CFI) should also be higher than .95, the Tucker-Lewis Index (TLI) higher than 0.95, the Root Mean Square Error of Approximation (RMSEA) around 0.05, and ideally, the Standardised Root Mean Square Residual (SRMR) should be lower than 0.05.
unconstrained model had a very good fit. The constrained model was significantly worse than the unconstrained model ($\chi^2 = 19.082; \text{df} = 3; p<.001$), indicating that the associations of insight with depressed mood, quality of life, and negative self-esteem were unequal between the two stigma groups. The results of the unconstrained model are presented in Table V. The detrimental associations of insight with depression, quality of life, and negative self-esteem were more pronounced in the patients with high stigma than in those with low stigma.

We also explored the observed results of insight on a subscale level, comparing the same type of models as before, though using the subscales as three independent variables: (1) awareness of illness, (2) re-labeling symptoms to illness, and (3) need for treatment. Results showed that the constrained model significantly worsened the fit to the data ($\chi^2 = 27.59; \text{df} = 9; p<.01$), indicating that stigma moderates the detrimental effects of the insight subscales. When stigma was low, no large effect of any insight subscale was found on either depressed mood, quality of life, or negative self-esteem. When stigma was high, the subscale ‘need for treatment’ had the largest detrimental effects on depressed mood and quality of life, and the subscale ‘awareness of illness’ had the largest effect on negative self-esteem.
5.4 DISCUSSION

5.4.1 Effects of insight

Our results support the hypothesis that insight is associated with medication compliance and service engagement. This is consistent with earlier studies (Mohamed et al., 2008; Perkins 2002; Rittmannsberger et al. 2004). Our results also support the hypothesis that good insight is associated with low quality of life, depressed mood, and negative self-esteem, mainly when it is accompanied by stigmatizing beliefs. In patients who had good insight yet did not have many stigmatizing beliefs, these negative associations were either not observed or were smaller. The results therefore show that perceived stigma is a moderator of the detrimental associations of insight in patients with a psychotic disorder.

The results indicate that the patients, who have good insight into their illness and do not perceive much stigmatization, are best off. Those with poor insight have problems with service engagement and compliance, and are unable to optimally benefit from treatment. On the other hand, those with good insight and many stigmatizing beliefs about psychiatry, despite their engagement with services and compliance with medication, have the highest risk of experiencing low quality of life, negative self-esteem, and depressed mood.

Our findings are in line with those of Lysaker et al. (2006) and with the post-diagnostic identities as formulated by Williams (2008). Patients, when realizing that they have a psychotic disorder may or may not internalize the stigma and stereotypes which hold that people diagnosed with schizophrenia are damaged and deserving of low status. Those who internalize stigma may think that they are unable to achieve valued social roles. This reaction has been described as an engulfed post-diagnostic identity (Williams, 2008).

5.4.2 Clinical implications

Our findings support the notion that it is desirable to enhance insight as long as self-stigmatization is also addressed. If psycho-educational programs included a focus on aspects of stigma and illness-normalization, and if physicians were more alert to such questions, it might be possible to improve insight without risking a deterioration in mood, self-esteem, and quality of life. The effects of psycho-educational programs on insight nonetheless remain unclear. Although a meta-analysis showed that psycho-education increases knowledge about schizophrenia (Lincoln et al., 2007b), it is not clear whether patients apply the knowledge to themselves (Kemp and David, 1995; Sevy et al., 2004). Unfortunately, very little literature describes other attempts to enhance insight.
Henry and Ghaemi (2004) showed that atypical antipsychotic medication has a small positive effect on insight. Cognitive behavioural therapy addresses insight—though not explicitly—by re-labeling voices as harmless symptoms of the disease, or by restructuring paranoid thought content (Turkington et al., 2002).

It seems equally difficult to reduce self-stigmatization. Link et al. (2002) tested a 16-session group intervention in which patients who were instructed on the effects of social stigma were provided both with an outlet to discuss personal experiences, and with behavioural strategies for dealing with the social consequences of stigma. However, this produced no effect on stigma, self-esteem, or depressive symptoms (Link et al., 2002). Another study examined the effects of group therapy that focused on reducing engulfment, perceived stigma, and symptoms. Although the results were promising, this produced no significant improvement, possibly due to a lack of statistical power (McCay et al., 2006; McCay et al., 2007). New approaches for supporting patients that struggle with their post-diagnostic identities are being discussed (Williams, 2008).

5.4.3 Limitations

The first of the four limitations of this study is that the sample composition limited the possibilities for generalizing the results. Not only were most of the participants men (71%), patients with very high service engagement were not in this study, as this was an exclusion criterion of the randomised controlled trial. It is also probable that patients with a very low service engagement were not included in the study, either because they had refused to participate, or because they were not in outpatient treatment.

The second limitation is that we used only a single PANSS item to measure depressed mood, and made no detailed measurement of the symptoms distinctive of a depressive episode.

The third limitation is that our study used cross-sectional data, which makes it impossible to draw conclusions on directions of causality. It may be, for example, that negative self-evaluating beliefs cause patients to be more vulnerable to stigma, rather than the other way around. Longitudinal or intervention studies should tell us more about causal relationships.

The final limitation is that not all relevant variables were included in this study. Some cognitive dysfunctions, for example, are known to be related to insight (Simon et al., 2009) and may affect outcome, such as compliance, global functioning, and quality of life.
CHAPTER 6

Why do schizophrenia patients with poor insight still take antipsychotics? Memory deficits as a moderator between adherence belief and behaviour.

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H. Duivenvoorden
P. Weiden
C.L. Mulder

Submitted
ABSTRACT

Background
While lack of insight is often a strong predictor of antipsychotic non-adherence, there is considerable inconsistency in the literature that has not been adequately explained. We hypothesized that verbal memory deficits may be an important moderator in the association between insight and adherence.

Method
Based on cross-sectional data, outpatients treated with antipsychotics for a psychotic disorder were divided into those with (n=59) and without (n=53) severe verbal memory deficits.

Results
Poor insight was only associated with medication non-adherence in the patient group with relatively good memory (r=.43; p<.01). There was no relationship between poor insight and non-adherence in patients with severe memory deficits (r=.08; ns). Structural Equation Modelling analysis revealed significant moderation (χ²=4.72; df=1; p<.05).

Conclusions
The association between poor insight and poor adherence was only present in patients with intact memory. There may be two groups with low insight: patients with cognitive deficits, who do not understand their illness, and patients who use denial as coping. The latter group may oppose treatment because it conflicts with their beliefs. The first group, however, may reflect less critically and be more willing to comply with medical advice. When these patients are non-adherent, other risk factors than insight may be more relevant.
6.1 INTRODUCTION

Non-adherence with medication is highly prevalent in patients with psychotic disorders (Cramer and Rosenheck, 1998; Keith and Kane, 2003; Bebbington, 1995; Thomas, 2007; Weiden et al., 1996; Weiden et al., 1991). When a patient stops using antipsychotic medication, the risk of relapse increases three to five-fold (Dixon and Lehman, 1995; Fenton et al., 1997; Robinson et al., 2002; Ucok et al., 2006; Weiden et al., 2004). Similarly, the risk of suicide has been found to be 3.75 times higher in non-adherent patients with schizophrenia than in adherent patients (Hawton et al., 2005), though it should be noted that depression increases the risk of non-adherence (Elbogan et al., 2005) as well as of suicide. Despite the detrimental consequences of non-adherence, no interventions have dealt very successfully with this problem (Staring et al., 2006).

‘Lack of insight’ refers to a common observation that many patients with schizophrenia do not acknowledge the existence of a mental health problem or recognize the need for treatment. Although there are many theories about the underlying reasons for this finding, ranging from psychological defences against stigma to neurologic impairments analogous to anosognosia, there is a general agreement that poor insight is a major risk factor for poor medication adherence. However, there is a great deal of variability in the research literature about the magnitude of this association (Acosta et al., 2008; Kuzoki et al. 2005; Lacro et al. 2002; Mohamed et al., 2008; Perkins 2002; Rittmannsberger et al. 2004), and some studies have not found any association whatsoever (McCann et al., 2008; Tait et al., 2003; Yen et al., 2005). While this is perhaps not surprising given differences in setting, methods, and definition of insight and adherence, another possible explanation is that certain kinds of cognitive deficits might disrupt any association between attitude about the illness (insight) and behavioural outcomes that are influenced by such an attitude (medication adherence).

It has been suggested that there are two groups of patients with low insight: those with severe neurologic impairments, who do not really understand their illness or overview its symptoms and consequences, and those with psychologic defences against stigma, who may deny being ill at all (Lysaker et al., 2003; Startup, 1996). It is plausible that the latter group refuses treatment, as that would mean accepting the illness, and thus these patients may be very non-adherent. Patients in the first group, however, despite having low insight, may be more willing to comply with their clinician’s advice, as doing so does not really interfere with their own ideas. They may reflect less critically, accept their clinician’s judgement, and comply with medical treatment as well as they can.
Thus, lack of insight may be more predictive of low adherence in those patients who use denial as coping, than in patients with severe cognitive impairments.

Other research of interest is that on metacognition in schizophrenia. A range of studies have suggested that cognitive impairment is related to difficulties in thinking about thinking, which may play a major role in making it difficult for patients with schizophrenia to construct a meaningful picture of their own mental illness (Wiffen & David, 2009). Again, in such a group it is less that illness is denied and more that things about one’s own thinking are difficult to consider and as such may be less linked to behaviour. Non-adherence as a deliberate behaviour may therefore occur less in this group.

Because of these reasons, and although cognitive impairments have often been investigated as potential determinants of poor insight (e.g. Aleman et al., 2006), it may be useful to look at cognitive deficits in a new role: as a moderator of the association between insight and adherence. In this light, a relevant neurocognitive measure appears to be verbal memory, which has repeatedly been associated with different types of functional outcome in schizophrenic patients, for example adherence (Donohoe et al., 2001; Green, 1997; Heinrichs et al., 2007; Kim et al., 2006). Acquisition—the first stage of memory processing—is often particularly impaired (Toulopoulou and Murray, 2004). Because acquisition deficits underlie an impaired ability to organize and store information in a useful manner, they may affect patients’ actions due to a limited ability to transform insight into beneficial treatment behaviours such as adherence.

We wished to establish whether insight is associated with adherence in patients with severely impaired verbal memory (acquisition) in the same way as in patients without severely impaired verbal memory. In other words, we tested the hypothesis that verbal memory deficits moderate the association between insight and adherence in patients with a psychotic disorder. We expected that in patients with poor verbal memory, the link between insight and adherence would be less prominent than in patients with relatively intact verbal memory.

### 6.2 MATERIAL AND METHODS

#### 6.2.1 Study population

Participants were those who enrolled in a multi-centre randomised controlled trial that took place in the Dutch city of Rotterdam and investigated the effects
of an intervention targeting service engagement (Staring et al., 2006). Inclusion criteria were: (1) receiving outpatient treatment, (2) a diagnosis of schizophrenia or a related psychotic disorder, and (3) at least some problems with service engagement as defined by an average item-score of 1.5 or higher on at least two subscales of the Service Engagement Scale (SES; see Measurements, below). The only exclusion criteria was not speaking the Dutch language. Patients with severe cognitive deficits were not excluded.

6.2.2 Design and procedure
The study design was approved by the Medical Ethics Committee at Erasmus University Medical Centre. Patients were referred by their clinician; their participation was requested by a research assistant. Participants had to give written informed consent. In baseline assessment all respondents and their clinicians participated in a structured interview. This was conducted by trained and supervised psychology and medicine students, who used the lifetime Composite International Diagnostic Interview (CIDI), version 2.1 Auto (WHO, 1997) to assess mental disorders according to the definitions and criteria of DSM-IV (APA, 1994) as well as the Positive and Negative Syndrome Scale (PANSS; Key et al., 1987). Respondents were paid 20 Euros for participating in this interview. Baseline assessments provided the data for this article.

6.2.3 Measurements
The patients’ demographics were collected. Using a method based on Hollingshead (1975), socioeconomic status was measured by converting education and profession into a single score (range: 1-6), with high scores indicating high socioeconomic status.

Insight
To measure insight into illness and treatment, we used the self-report Insight Scale (IS) of Birchwood et al. (1994), which consists of eight items that are filled out by the patient. It has three subscales: (1) awareness of illness, (2) re-labeling symptoms to illness, and (3) need for treatment. The total score ranges from 0 to 12, high scores indicating good insight. The scale is sufficiently reliable and valid, and is easy to use within this group of patients (Birchwood et al., 1994). To have some indication of the veracity of the patients’ response on this scale in our study, we’ve calculated the Pearson correlation between this scale and the insight item of the PANSS (A12) in our data. It was -.514 (p<.001), indicating an important overlap between the two.
**Verbal memory**
Learning and memory deficits were measured using a Dutch version of the Auditory Verbal Learning Test (AVLT) (Saan and Deelman, 1986; Rey, 1964). It consists of five successive presentations by the researcher of a list of 15 words followed by the participant’s free recall on each trial. After interference tasks have been performed during 15 to 20 minutes, retention of the list is measured. We calculated (1) the total number of words immediately recalled over five trials (Adjusted Acquisition Score [AAS]), and (2) the number of words recalled after the 15 to 20 minute delay (Adjusted Delayed Recall Score [ADRS]), and corrected them for age, sex, and level of education. For the reasons specified in our introduction (above), we used the AAS as a measure of verbal memory (acquisition learning).

**Medication adherence**
Medication adherence was assessed with two different measures of medication adherence, one caregiver-based and one patient-based.

The caregiver assessment is derived Service Engagement Scale (SES) (Tait et al., 2002), which is a 14-item rating scale in which observed service engagement is rated by the caregiver most familiar with the patient. The scale has good face validity and content validity, is user-friendly, and had good test-retest reliability in patients with psychotic disorders (Tait et al., 2002). The SES has four subscales: (1) availability, (2) collaboration, (3) help-seeking, and (4) medication adherence. In this study, the fourth subscale was used as a measure of medication adherence. The range is 0 to 12, with higher scores indicating poorer medication adherence.

We also administered a semi-structured interview with the patient to assess medication compliance by the independent rater. The rater normalized non-compliance as well as possible reasons for it, stressed that the obtained information would be treated confidentially and not be passed on to the patient’s clinician, and inquired about the number of missed doses in the past days and weeks. Such an interviewing style has been found to produce a more valid measurement of adherence than some of the questionnaires that are used in adherence research, such as the Medication Adherence Rating Scale, the Medication Adherence Questionnaire, the Drug Attitude Inventory, and the Compliance Rating Scale (Kikert et al., 2010). The score ranged from 0 to 4, with higher scores indicating more problematic compliance. The scoring method was modelled after the Health of the Nation Outcome Scales (Wing et al., 1998).
Both measures were standardized, summed, and reversed, thereby creating a compiled measure of adherence, with high scores indicating good adherence. Composite measures of medication adherence help reduce the underestimation of adherence that is associated with any individual source of information (Kikkert et al., 2008). Our two independent adherence scores had a correlation of .540 (p<.001), indicating important overlap.

Symptoms
The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a 30-item rating scale which is completed by the trained raters. It has three subscales: (1) positive syndrome, (2) negative syndrome, and (3) general psychopathology.

6.2.4 Statistical analyses
First, we split the participants into better and worse memory based on the average value (-9.11) of the AAS, where low scores reflect a severe impairment in verbal memory (acquisition learning). Splitting the respondents this way produces two groups of about equal size and allows for testing the moderator hypothesis with Structural Equation Modelling (SEM) (Frazier et al., 2004). Using independent samples t-tests and Pearson correlations, the groups were compared for current levels of insight into illness and need for treatment and cross-sectional (current) medication adherence. The main moderator hypothesis was tested with a multiple-group approach with SEM (Frazier et al., 2004). With this method, the continuous measure of insight was used to predict adherence, and an unconstrained model was compared to a constrained model. In the latter, the association of insight with adherence was constrained to be equal across both memory groups. If the constrained model significantly worsened the model fit, this would be evidence of moderation, i.e. different relations between insight and adherence across the two verbal memory groups (Frazier et al., 2004). As measures of model performance, we used χ² tests (Jöreskog, 1993) to determine the extent of the model fit. Sufficient model fit is indicated by a non-significant p-value (p>0.05) and a χ² / df ratio of < 1.5. To obtain reliable indices of the model fit, we also used the Comparative Fit Index (CFI>0.95; Bentler, 1990), the Tucker-Lewis Index (TLI>0.95; 1973), the Root Mean Square Error of Approximation (RMSEA≈0.05; Steiger, 1990) and the Standardised Root Mean Square Residual (SRMR<0.05; Jöreskog, 1971). For these analyses, the M-Plus 5.0 program was used.
6.3 RESULTS

6.3.1 Patient characteristics
Between January 2006 and September 2008, a total of 195 patients met our inclusion criteria for the study. Of the 195, 116 (59%) agreed to participate and 112 completed the study procedures.

Lifetime diagnoses with the CIDI were as follows: 77 patients (69%) met the criteria of schizophrenia and 35 (31%) met the criteria of schizoaffective disorder. Seventy-nine (71%) were male, 33 (29%) female. One-hundred-and-one patients (90%) were not married or living with a partner; 11 (10%) were. The majority (93, 83%) were unemployed. The mean age of first contact with a mental health institution was 25.8 years old (SD=9.3). The mean age at baseline assessment was 38.4 years old (SD=11.6).

The medication status at the time of the assessment was as follows: 27 (23%) patients were prescribed first-generation antipsychotics, 49 (42%) were prescribed second-generation antipsychotics, 19 patients (16%) were prescribed both, and 21 patients (18%) were refusing all medication. The average scores on the Positive and Negative Syndrome Scale (PANSS) were total symptoms 58.2 (SD=17.1), positive symptoms 13.7 (SD=5.38), negative symptoms 14.0 (SD=5.73), and general psychopathology 30.3 (SD=9.71).

6.3.2 Associations between insight and adherence
The two groups split into better and worse memory were compared on demographic and symptom measures. The primary between-group symptom difference was that the worse memory group had significantly greater negative symptoms on the PANSS than the better memory group (15.3 versus 12.6; t = 2.58; p < .05).

Average insight and adherence differed between the two memory groups (see Table I). Patients in the worse memory group had higher (better) total insight scores (t = 2.51; p < .05). The group difference was greatest for the ‘need for treatment’ subscale (t = 3.51; p < .01). The patients in the worse memory group were also more adherent with their antipsychotic medication (t = 3.20; p < .01). However, this group did not show any significant correlation between insight and adherence (see Table II).

In the group with better memory, insight was significantly and positively related to adherence (r = .43; p < .01). Figure I shows that when insight was good, adherence scores were roughly equal between patients with better memory and those with worse memory. Patients with better memory whose insight was
Table I Adherence and insight scores in (1) patients with worse memory and in (2) patients with better memory

<table>
<thead>
<tr>
<th></th>
<th>Group 1: patients with worse memory (n=59)</th>
<th>Group 2: patients with better memory (n=53)</th>
<th>Independent samples t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence ¹</td>
<td>0.46 (SD=1.35)</td>
<td>-0.54 (SD=1.95)</td>
<td>t = 3.20**</td>
</tr>
<tr>
<td>Insight Scale total score ²</td>
<td>8.3 (SD=3.1)</td>
<td>6.7 (SD=3.7)</td>
<td>t = 2.51*</td>
</tr>
<tr>
<td>Insight subscale 1: illness awareness</td>
<td>2.5 (SD=1.5)</td>
<td>2.1 (SD=1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Insight subscale 2: symptom awareness</td>
<td>2.7 (SD=1.5)</td>
<td>2.4 (SD=1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Insight subscale 3: need for treatment</td>
<td>3.1 (SD=1.1)</td>
<td>2.3 (SD=1.4)</td>
<td>t = 3.51**</td>
</tr>
</tbody>
</table>

¹) The average of this compiled measure is zero. Higher scores indicate better adherence.
²) This scale ranges from 0 to 12, with higher scores indicating better insight.
* Significant at the .05 level (2-tailed)
** Significant at the .01 level (2-tailed)

good were significantly more adherent than those with better memory and poor insight (t = 3.86; p < .001). However, the adherence of those who combined worse memory with good insight was not significantly different from that of their peers with poor insight.

The SEM analysis included adherence as outcome variable, and the continuous total insight score as predictor. The unconstrained and the constrained models were both analyzed on their goodness of fit to the data. The results showed that

Table II Correlations of insight and adherence in (1) patients with worse memory and (2) patients with better memory

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Patients with worse memory (n=59)</th>
<th>Group 2: Patients with better memory (n=53)</th>
<th>Equality test for the correlations of the two groups, using Fischer’s Z transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total insight score with adherence</td>
<td>.08</td>
<td>.43**</td>
<td>Z = -1.95; p &lt; .05</td>
</tr>
<tr>
<td>Subscale (1) illness awareness with adherence</td>
<td>.18</td>
<td>.52****</td>
<td>Z = -2.03; p &lt; .05</td>
</tr>
<tr>
<td>Subscale (2) symptom awareness with adherence</td>
<td>-.14</td>
<td>.12</td>
<td>Z = -1.34; ns</td>
</tr>
<tr>
<td>Subscale (3) need for treatment with adherence</td>
<td>.16</td>
<td>.39**</td>
<td>Z = -1.29; ns</td>
</tr>
</tbody>
</table>

** Significant at the .01 level (2-tailed)
*** Significant at the .001 level (2-tailed)
the unconstrained model had a good fit – because it had zero degrees of freedom, no parameters needed to be estimated. The effect of insight on adherence in the second model was constrained to be equal across the two memory groups. Applying this constraint significantly reduced the fit of the model: $\chi^2=4.72$; df=1; p<.05 (see Table III). This meant that the effect of insight on adherence was not equal across the two groups, thus providing evidence for a moderator effect of memory impairments on the association between insight and adherence.

Table IV summarizes the results of the unconstrained model. It shows a pattern similar to that in Table II: insight in patients with better memory was associated with adherence, which was not the case in patients with worse memory.

**Table III** Structural Equation Modelling fit to the data parameters for the unconstrained and the constrained models

<table>
<thead>
<tr>
<th>Model description</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p</th>
<th>$\chi^2$/df</th>
<th>CFI</th>
<th>TLI</th>
<th>RSMEA</th>
<th>SRMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconstrained model: the effect of insight on adherence is unconstrained</td>
<td>0.00</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>(i.e. allowed to differ) across both memory groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constrained model: the effect of insight on adherence is constrained as equal</td>
<td>4.72</td>
<td>1</td>
<td>.030</td>
<td>4.72</td>
<td>0.59</td>
<td>0.18</td>
<td>0.26</td>
<td>0.10</td>
</tr>
<tr>
<td>across both memory groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sufficient model fit is represented by a non-significant $p$-value ($p>0.05$) and the ratio of $\chi^2$/df $< 1.5$. Also, for good model fit, the Comparative Fit Index (CFI) should be higher than .95, the Tucker-Lewis Index (TLI) should be higher than 0.95, the Root Mean Square Error of Approximation (RMSEA) should be lower than 0.05, and the Standardised Root Mean Square Residual (SRMR) should be lower than 0.05.
When both adherence measures were looked at separately, similar results were found. That is, in the group with worse memory no significant correlations were found between insight and either adherence measure, while in patients with better memory the correlations between insight and both patient-based adherence ($r=.33; p<.05$) and caregiver-based adherence ($r=.43; p<.01$) were significant.

6.4 DISCUSSION

6.4.1 Insight, memory, and adherence

Our results support the hypothesis that severe verbal-memory deficits moderate the association between poor insight and non-adherence in patients with a psychotic disorder. Although poor insight was clearly associated with non-adherence in patients with relatively intact verbal memory, this was not the case in patients with severely impaired verbal memory.

Memory is an essential link needed to change intent to action. In this study, the action is antipsychotic non-adherence. The lack of relationship between lack of insight and medication non-adherence in the poor memory group only is consistent with our hypothesis. An alternate explanation is that the greater severity of negative symptoms in the poor memory group is such that motivation for non-adherence is diminished.

In contrast, the relationship between poor insight and poor medication adherence was clearly present in the better memory group. Therefore, the combination of intact memory and poor insight is a strong predictor of medication non-adherence.

Paradoxically, a higher number of patients with deficits in verbal memory acknowledged the need for treatment, and also seemed to be more adherent than those without such deficits. This was not expected, as three other studies have found the opposite direction with greater cognitive deficits being associated...
with worse adherence (Donohoe et al., 2001; Heinrichs et al., 2007; Kim et al., 2006). Differences in the patient samples may explain this. Despite reasonable similarities on most characteristics of patient samples in all four studies—such as average age, duration of illness, and male/female ratio—our own patients, all of whom were outpatients, seemed to have fewer current psychotic symptoms than those in the three other studies, some of whom were still in the clinic. While the average PANSS positive scale in our study scored a mere 13.7, those in the other studies were 20.1 (Heinrichs et al., 2007), 15.5 (Donohoe et al., 2001), and 18.6 (Kim et al., 2006).

We therefore speculate that, when psychotic symptoms are prominent, a deficit in verbal memory will increase confusion and disorganisation, which will impair adherent behaviour. But when psychotic symptoms are more or less under control, patients with such a deficit may fail to reflect on their condition; they may accept the clinician’s judgement without much resistance, and subsequently improve on acknowledging need for treatment and on adherent behaviour. In contrast, patients without such deficits may become more conscious of the past and future consequences of their disorder; they may resist the diagnosis, denying the need for treatment and thus collaborating poorly. Denial has been proposed as a cause of lack of insight and there is evidence that, as a coping style, it is characteristic of patients without cognitive impairments (Lysaker et al., 2003).

If this indeed explains our results, it may provide an alternative explanation for the strong association between adherence and insight in patients without cognitive deficits. If insight is low due to denial, adherence may suffer as a result, whereas if insight is not affected by denial, adherence may largely be independent of insight. In other words: denial of illness and denial of need for treatment may lead to poor adherence, while—as we have observed in our patients—other causes of a lack of insight, such as cognitive deficits, may not lessen a patient’s readiness to comply with treatment.

Finally, patients with memory deficits had high scores on negative symptoms. It may be that, independently of their insight into illness, they were aware of their poor functioning, and therefore scored high on their acknowledgement of the need for treatment, and also on adherence.

6.4.2 Limitations
The first group of limitations concerns the possibility that the sample composition restricted the scope for generalizing our results. First, the sample was a
relatively small and most participants were men. Second, patients with very high service engagement were excluded, as this was an exclusion criterion of the multi-centre randomised controlled trial whose baseline measurements we used. Third, patients with very poor service engagement are unlikely to have been included either, as they may have refused to participate or may not have been in outpatient treatment. As a result, the level of service engagement of most respondents probably lay in the middle range.

The next limitation is that we based a distinction in the patient sample on the average of verbal memory scores. This was quite arbitrary, and was done for the lack of a better cut-off. It did not seem useful to base a cut-off on scoring below or above the average norm of the AVLT, as most patients scored below this point. Neither did this seem desirable, as mild impairments may not greatly affect the ability to benefit from insight. However, it does imply that another choice may yield slightly different results.

Another limitation is that, as no neurocognitive parameters other than verbal memory were measured, we were unable to regard the relevance of verbal memory’s effects in comparison to other possibly important neurocognitive parameters. It may for example well be that our findings reflect the relevance of general cognitive impairments rather than verbal memory deficits persé.

Finally, our study was performed with cross-sectional data, which makes it impossible to draw conclusions on the directions of causality. Longitudinal and intervention studies should be able to tell us more about the causal relationships at work.

6.4.3 Clinical implications

Our results suggest that patients with an impaired ability to organize and store information may derive little benefit from good insight. But neither, when it comes to adherence with antipsychotics, do they seem to be greatly hampered by a lack of insight. If adherence is poor in these patients, behavioural interventions are probably enough to overcome it. Various interventions are possible: reminders, the simplification of dosing frequency and polypharmacy use, the involvement of family members in treatment, or the use of types of contingency management such as financial incentives. For a more detailed description of such interventions, see Patel and David (2007), Velligan et al. (2007), and Masand and Narasimhan (2006).

Patients with relatively intact memory may be more likely to respond to interventions that address problems with medication attitudes or insight. Examples include cognitive therapy and other approaches based on principles
of motivational interviewing. These interventions comprise various elements: information on the illness and treatment is provided, symptoms are re-labelled, adherence is linked to the patient’s personal goals, the pros and cons of antipsychotic medication are discussed, and resistance is avoided as much as possible. For a more detailed description, see publications such as Rathod et al. (2005), Patel and David (2007), and Possidente et al. (2005).

Using different approaches for increasing adherence, based on patient characteristics such as cognitive ability and insight, may increase the effectiveness of these interventions.
CHAPTER 7

Recovery style and service engagement in psychosis – their relationship with ethnicity.

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C.L. Mulder

Submitted
ABSTRACT

Background
Surinamese, Antillean, and Moroccan immigrants in the Netherlands have a higher risk of developing schizophrenia. Subsequently, they engage less with services and have poorer outcome, which may be due, among others, to poor psychological adjustment (recovery style). We tested three hypotheses: (1) recovery style predicts service engagement; (2) immigrants with schizophrenia tend to use a sealing-over recovery style more than natives do; and (3) lower self-esteem may help explain more sealing-over in immigrants.

Methods
We used a cross-sectional design to analyze the data of 172 patients on recovery style, service engagement, and self-esteem.

Results
Sealing-over was associated with low service engagement ($r=.279; p<.01$), but not with low self-esteem. First-generation (not second-generation) immigrant patients had lower service engagement (ANOVA; $F=3.082; p<.05$), but they did not differ from natives with regard to recovery style or self-esteem.

Conclusions
Sealing-over predicted low service engagement. However, lower service engagement in immigrant patients than in natives was not attributable to sealing-over or low self-esteem. Based on earlier research, low self-esteem may contribute to the development of schizophrenia in a relatively high number of immigrants, but after onset, it may be equally common in native patients, and not lead to more sealing-over in immigrants.
7.1 INTRODUCTION

In the early 1980s the Netherlands started seeing itself as a country of immigration, with substantial numbers of immigrants who were likely to stay rather than return to their home countries. Categories of migrants were minorities from the former Dutch colonies, as well as low-skilled labour migrants and their family members from Turkey, Morocco, and various other countries. In the year 2009, 20% of the Dutch population consisted of migrants, and this percentage is rising (Statistics Netherlands). The largest groups currently consist of people coming from Surinam, the Dutch Antilles, Morocco, and Turkey. They have mostly settled in the urban areas of the Netherlands, where their numbers frequently concentrate in a specific neighbourhood (NISR, 2009a).

Similar to what has been observed in other Western countries (Harrison et al., 1997; Schier et al., 2001; Cantor-Graae & Selten, 2005), immigrants to the Netherlands from Surinam, the Dutch Antilles, and Morocco have an increased risk for developing schizophrenia (Selten et al., 2001). Risk factors may include discrimination, childhood adversity, insecure identity, and low self-esteem (Veling et al., 2007a, 2008a, 2008b; Cantor-Graae, 2007), which are related to immigrant status in the Netherlands in various ways. For example, unemployment and crime rates are higher in non-Western immigrants, and housing perspectives can be limited (Statistics Netherlands; NISR, 2009a). Also, participation in education and achievements are often lower in immigrants, due to low socio-economic status, language problems, and high percentage of single-parent families (NISR, 2009b), although large variations exist. Furthermore, non-Western immigrants may be the subject of discrimination based on their ethnic background, race, and skin colour. This may come in many forms, such as interpersonal experiences of racist insults or violence, but also in structural discrimination by institutions, as in employment policies or access to education or housing facilities.

Some specific issues include for example that the Moroccans have a very different culture, language and religion than the Dutch, giving rise to difficulties, e.g. on the topic of women's rights and social participation. And while the Surinamese and Antilleans all speak Dutch in their countries of origin, facilitating their integration in the Netherlands, they have a cultural history that is entwined with slavery, which may have had an impact on their cultural self-esteem and perception of Dutch natives.
When people of ethnic minorities develop schizophrenia, they are generally less compliant with medication and tend to engage less with mental health services than native patients (Cuffe et al., 1995; Emsley et al., 2002; Opolka et al., 2003; Valenstein et al., 2006), with adverse consequences (Staring et al., 2006). This pattern may be due to the socio-economic disadvantages and discrimination issues described earlier. Another possibility is that active engagement with mental health services is prevented by cultural taboo or culture-specific conceptions of illness and treatment – for example: ‘Djinn’ (spirits), ‘l’ayn’ (evil eye), and Islamic healings for Moroccans; ‘Brua’ (magic) for Antilleans; and ‘Winti’ for Surinamese Hindus. Moreover, language difficulties may complicate contacts with clinicians for Moroccans.

Alternatively, the factors that are thought to contribute to the high incidence of schizophrenia in immigrants may also play a role in their low service engagement. In other words, after onset of the illness, disadvantages that have contributed to their higher risk of developing schizophrenia may continue to weaken their ability to use coping skills and to benefit from treatment. One field of research indeed points in that direction: some of the risk factors (e.g. low self-esteem, insecure identity, childhood adversity) are related to the concept of a sealing-over recovery style rather than to an integrating one (McGlashan et al., 1975, 1976). ‘Integrators’ are patients who are more likely to see their psychotic experience as something that is part of them, has arisen from their life context, which they are responsible for, and may be used as a source of information about themselves, conflicts, relationships and behaviour (McGlashan, 1987). In contrast, individuals who seal over tend to distance themselves from their psychotic experiences, viewing them as causally independent, globally negative, interruptions to their lives. It has been found that a sealing-over style predicts poor service engagement (Startup et al., 2006; Tait et al., 2003) and that an integrating style is predictive of better outcome and functioning at long-term follow-up (McGlashan, 1987; Thompson et al., 2003).

A sealing-over style has been associated with more adverse childhood experiences (Drayton et al., 1998; Tait et al., 2004), suggesting that recovery style may arise out of individual’s life context rather than their psychotic experience. Integration allows for investment in relationships, affect tolerance, and acknowledgment of symptoms (Bell & Zito, 2005), while patients who seal over make more negative self-evaluations and have a more insecure identity than an integrator (Drayton et al., 1998; Tait et al., 2004). As anticipating loss and experiencing shame predict later depression, sealing-over may be motivated by defending against these emotions (Iqbal et al., 2000).
Immigrant patients with schizophrenia may be at specific risk for sealing-over styles due to the possibly disruptive migration process, adverse circumstances in their countries of origin, cultural taboo and shame, single-parent families and attachment difficulties, various forms of discrimination, lower socio-economic status in the Netherlands, language problems, insecure cultural identities, and lower self-esteem. A high prevalence of the sealing-over style may therefore explain part of the observed problem that immigrants portray low service engagement.

This study tested three hypotheses: (1) that recovery style predicts service engagement, (2) that immigrants with a schizophrenia-spectrum disorder tend to use a sealing-over recovery style more than native patients do, and (3) that lower self-esteem may help explain part of the greater sealing-over in immigrant patients.

7.2 METHOD

7.2.1 Study population

For testing the second hypothesis, we used the combined data of two separate study populations (study A and B), each of which included a measurement of recovery style. The other hypotheses were tested only in study A, since this study included measures of service engagement and self-esteem.

Study A

Patients in study A were the respondents in a multi-centre randomized controlled trial in Rotterdam, the Netherlands. The trial investigated the effects of an intervention promoting treatment adherence (Staring et al., 2006). The highly urbanized Rotterdam is home to many people from ethnic minorities, most of them originating from Surinam, the Dutch Antilles, and Morocco. Inclusion criteria were (1) having schizophrenia or schizoaffective disorder, (2) outpatient treatment, (3) being able to speak Dutch, and (4) having some problems with service engagement, as defined by at least two subscales of the SES (see instruments, below) having an average item-score of 1.25 or higher.

Study B

Patients in study B were the respondents in MATCH, a multi-centre randomized controlled trial in Amsterdam and Haarlem, the Netherlands, that investigated the effect of Motivational Interviewing (Miller & Rollnick, 2002) on adherence to antipsychotic medication in patients with schizophrenia and schizoaffective
disorders. As with study A, these cities are home to many people from ethnic minorities, especially Surinamese and Antilleans. Inpatients and outpatients were included. Inclusion criteria were (1) the presence of schizophrenia or schizoaffective disorder, (2) recent clinical deterioration due to medication non-adherence, (3) ability to speak Dutch, and (4) some improvement (CGI-I > 2) after restarting the medication.

7.2.2 Design and procedure

We used a cross-sectional design. Our definition of “immigrant” was the same as that used by Statistics Netherlands, a first-generation immigrant being someone born abroad, and a second-generation immigrant being someone whose mother or father was born abroad (one parent being enough). The country of origin is then the mother’s place of birth, unless she was born in The Netherlands, in which case it is the father’s.

Study A was approved by the Medical Ethics Committee at Erasmus University Medical Centre. Patients were referred by their clinician, and asked by a research assistant to participate. Participants had to give written informed consent. Respondents were assessed on the basis of a structured interview conducted by trained and supervised psychology and medicine students. To assess mental disorders according to the definitions of DSM-IV (APA, 1994), we used the lifetime Composite International Diagnostic Interview, version 2.1 Auto (WHO, 1997). Respondents were paid EUR 20 for participating in the interview. Baseline assessments provide the data for this article.

Study B was approved by the Medical Ethics Committee at Amsterdam University Medical Centre. Participants had to give written informed consent. To assess mental disorders, baseline assessments included the Structured Clinical Interview for DSM-IV Diagnoses (SCID). Assessments were performed by trained psychiatrists, psychologists, and supervised psychology students. Respondents were paid for travel expenses. The RSQ (see instruments, below) was included only in the one-year follow-up assessments, which were used for the purpose of this article.

7.2.3 Instruments

Recovery Style

In study A and B, recovery style was measured on the basis of the Recovery Style Questionnaire (RSQ; Drayton et al., 1998), a 39-item self-report measure designed to reflect categories consistent with those developed by McGlashan et
al. (1975). It produces six classifications: (1) integration, (2) towards integrating, (3) mixed picture in which integration dominates, (4) mixed picture in which sealing-over dominates, (5) towards sealing-over, and (6) sealing-over. The RSQ is reliable, and correlates highly with McGlashan’s interview-based measure (Drayton et al., 1998).

**Service engagement**

In study A, the Service Engagement Scale (SES) (Tait et al., 2002) was used. This 14-item rating scale is used by the clinician or therapist most familiar with the patient to rate the service engagement they observe. There are four subscales: (1) availability, (2) collaboration, (3) help seeking, and (4) medication adherence. The scale has good face value and content validity, is user-friendly, and had good test-retest reliability within a group of patients with psychotic disorders (Tait et al., 2002). Higher scores indicate more problems with service engagement.

**Self-esteem**

In study A, we used the 20-item Self-Esteem Rating Scale–Short Form (SERS-SF) (Lecomte et al., 2006), a self-report scale with two subscales supported by factor analysis: positive and negative self-esteem. Each subscale ranges from 10 to 70, high scores indicating high positive or high negative self-esteem. The scale has good internal consistency, good test-retest reliability, and sufficient convergence validity in patients with schizophrenia (Lecomte et al., 2006).

**7.2.4 Statistical analyses**

All data were analyzed with SPSS 15.0. To compare native patients with first and second-generation immigrant patients, we used analysis of variance (ANOVA) with post-hoc Turkey HSD. To test the associations between recovery style, service engagement, and self-esteem, we calculated Spearman’s Rho correlations.

**7.3 RESULTS**

**7.3.1 Patient characteristics**

Of the total of 195 patients who were asked to participate in study A, 79 refused and 116 decided to participate. Two patients were too disorganized in thought and speech to be able to answer the questionnaires, and one refused to be tested. A total of 113 completed the baseline assessments.
Of the 218 patients who were asked to participate in study B, 61 refused and 39 were excluded for other reasons, such as low IQ (<70) or new information on not meeting the inclusion criteria. A total of 118 patients decided to participate. During the intervention period, 16 patients dropped out. At one year follow-up – when RSQ data were collected – 72 patients completed the assessments. However, as the RSQ data of 13 patients were incomplete, 59 cases were included in the analyses.

Table I shows the patient characteristics. Most of the first-generation immigrants were from Suriname (37) and the Dutch Antilles (9). As Dutch is

<table>
<thead>
<tr>
<th>Study sample</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>113</td>
<td>59</td>
</tr>
<tr>
<td>Sex</td>
<td>80 patients (71%): male</td>
<td>49 patients (83%): male</td>
</tr>
<tr>
<td></td>
<td>33 patients (29%): female</td>
<td>10 patients (17%): female</td>
</tr>
<tr>
<td>Average age</td>
<td>38.2 years (SD=11.5)</td>
<td>35.5 (SD=9.5)</td>
</tr>
<tr>
<td>Average age at first contact with a mental health institution</td>
<td>25.8 years (SD=9.3)</td>
<td>27.6 years (SD=7.7)</td>
</tr>
<tr>
<td>Employment</td>
<td>94 patients (83%): unemployed</td>
<td>46 patients (78%): unemployed</td>
</tr>
<tr>
<td></td>
<td>19 patients (17%): employed</td>
<td>13 patients (22%): employed</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>50 patients (45%): Dutch</td>
<td>26 patients (44%): Dutch</td>
</tr>
<tr>
<td></td>
<td>42 patients (37%): first-generation immigrants</td>
<td>25 patients (42%): first-generation immigrants</td>
</tr>
<tr>
<td></td>
<td>- 24 Surinamese</td>
<td>- 13 Surinamese</td>
</tr>
<tr>
<td></td>
<td>- 6 Antillean</td>
<td>- 3 Antillean</td>
</tr>
<tr>
<td></td>
<td>- 2 Moroccan</td>
<td>- 3 Moroccan</td>
</tr>
<tr>
<td></td>
<td>- 10 other</td>
<td>- 6 other</td>
</tr>
<tr>
<td></td>
<td>21 patients (18%): second-generation immigrants</td>
<td>8 patients (14%): second-generation immigrants</td>
</tr>
<tr>
<td></td>
<td>- 8 Surinamese</td>
<td>- 7 Surinamese</td>
</tr>
<tr>
<td></td>
<td>- 3 Cape Verdean</td>
<td>- 1 Turkish</td>
</tr>
<tr>
<td></td>
<td>- 10 other</td>
<td></td>
</tr>
<tr>
<td>Diagnoses</td>
<td>79 patients (69%): schizophrenia</td>
<td>46 patients (78%): schizophrenia</td>
</tr>
<tr>
<td></td>
<td>- 60 paranoid type</td>
<td>- 33 paranoid type</td>
</tr>
<tr>
<td></td>
<td>- 10 disorganized type</td>
<td>- 4 disorganized type</td>
</tr>
<tr>
<td></td>
<td>- 7 catatonic type</td>
<td>- 2 catatonic type</td>
</tr>
<tr>
<td></td>
<td>- 1 undifferentiated type</td>
<td>- 5 undifferentiated type</td>
</tr>
<tr>
<td></td>
<td>35 patients (31%): schizoaffective disorder</td>
<td>13 patients (22%): schizoaffective disorder</td>
</tr>
<tr>
<td></td>
<td>- 2 residual type</td>
<td></td>
</tr>
<tr>
<td>Clinical status</td>
<td>113 patients (100%): outpatients</td>
<td>13 patients (22%): schizoaffective disorder</td>
</tr>
<tr>
<td>PANSS positive syndrome</td>
<td>13.6 (SD=5.3)</td>
<td>14.2 (SD=5.6)</td>
</tr>
<tr>
<td>PANSS negative syndrome</td>
<td>13.9 (SD=5.7)</td>
<td>15.8 (SD=6.6)</td>
</tr>
<tr>
<td>PANSS general psychopathology</td>
<td>30.3 (SD=9.6)</td>
<td>31.1 (SD=10.0)</td>
</tr>
</tbody>
</table>
spoken throughout these countries, there were no problems in performing the interviews with them. Although the remaining first-generation immigrants also spoke Dutch, as this was a requirement for participation in the studies, no specific measures were taken to ensure that the instruments were culture-sensitive.

As only three of all the immigrants were from Western countries, the rest, by definition, were from non-Western countries. Separate analyses conducted with the three Western immigrants and without them did not produce different findings. Below are the results of the analyses including all immigrants.

7.3.2 Recovery style, service engagement, and self-esteem

Although first-generation immigrants tend slightly towards a sealing-over recovery style (Figure I), ANOVA did not reveal significant differences for recovery style or self-esteem between native and first and second-generation immigrant patients (Table II). However, it did show that native patients were engaging more with services (SES) than the first-generation immigrants (ANOVA; p<.05). At a subscale level, the difference in SES scores was caused mainly by the availability subscale (F = 7.282; p < .01), indicating that native patients (mean score 2.49) were more available for services than both the first-generation ones (3.98) and the second-generation immigrant ones (4.43).

![Figure I](image-url)  
**Figure I** Recovery styles in native patients and first and second-generation immigrant patients with a schizophrenia-spectrum disorder (study populations A and B combined; n=172)
As Table III shows, a more sealing-over recovery style was significantly associated with low service engagement, though not with positive or negative self-esteem. The correlation of recovery style with the SES total score was caused mainly by the correlations with the help-seeking subscale and the medication-adherence subscale.

As most immigrants were from Suriname, we conducted the ANOVA again, now using a distinction between native patients, patients from Suriname (first

<table>
<thead>
<tr>
<th>Mean scores</th>
<th>(1) Native patients</th>
<th>(2) First-generation immigrant patients</th>
<th>(3) Second-generation immigrant patients</th>
<th>ANOVA results</th>
<th>Group comparisons (Turkey HSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSQ total score (studies A and B)</td>
<td>2.80</td>
<td>3.09</td>
<td>2.59</td>
<td>F = 2.002</td>
<td>n.s.</td>
</tr>
<tr>
<td>SES total score (study A)</td>
<td>19.1</td>
<td>22.2</td>
<td>21.4</td>
<td>F = 3.082</td>
<td>1 &lt; 2</td>
</tr>
<tr>
<td>SES availability score (study A)</td>
<td>2.49</td>
<td>3.98</td>
<td>4.43</td>
<td>F = 7.282</td>
<td>1 &lt; 2,3</td>
</tr>
<tr>
<td>SES collaboration score (study A)</td>
<td>4.84</td>
<td>5.48</td>
<td>5.14</td>
<td>F = 1.249</td>
<td>n.s.</td>
</tr>
<tr>
<td>SES help-seeking score (study A)</td>
<td>6.55</td>
<td>7.69</td>
<td>7.19</td>
<td>F = 1.827</td>
<td>n.s.</td>
</tr>
<tr>
<td>SES medication-adherence score (study A)</td>
<td>5.24</td>
<td>5.07</td>
<td>4.67</td>
<td>F = .236</td>
<td>n.s.</td>
</tr>
<tr>
<td>SERS-SF positive score (study A)</td>
<td>50.5</td>
<td>51.1</td>
<td>51.2</td>
<td>F = .049</td>
<td>n.s.</td>
</tr>
<tr>
<td>SERS-SF negative score (study A)</td>
<td>29.0</td>
<td>34.1</td>
<td>33.0</td>
<td>F = 1.670</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

As Table III shows, a more sealing-over recovery style was significantly associated with low service engagement, though not with positive or negative self-esteem. The correlation of recovery style with the SES total score was caused mainly by the correlations with the help-seeking subscale and the medication-adherence subscale.

As most immigrants were from Suriname, we conducted the ANOVA again, now using a distinction between native patients, patients from Suriname (first

<table>
<thead>
<tr>
<th>Spearman’s Rho correlations</th>
<th>RSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES total score</td>
<td>.279**</td>
</tr>
<tr>
<td>SES availability score</td>
<td>.000</td>
</tr>
<tr>
<td>SES collaboration score</td>
<td>.178</td>
</tr>
<tr>
<td>SES help-seeking score</td>
<td>.220*</td>
</tr>
<tr>
<td>SES medication-adherence score</td>
<td>.203*</td>
</tr>
<tr>
<td>Positive SERS-SF</td>
<td>-.083</td>
</tr>
<tr>
<td>Negative SERS-SF</td>
<td>-.037</td>
</tr>
</tbody>
</table>

* p < .05
** p < .01
and second generations combined, n=52), and other immigrant patients. The results of the analyses were the same, producing no differences with regard to recovery style or self-esteem, although native patients scored best on the SES availability subscale.

7.4 DISCUSSION

7.4.1 Hypothesis one: recovery style predicts service engagement.
The results of this study replicated the clinically significant finding that a sealing-over recovery style is predictive of low service engagement in patients with psychotic disorders (Tait et al., 2003; Startup et al., 2006). Patients who employ this recovery style may be more avoidant and require extra attention to help them engage with treatment. Talking about psychotic experiences (McCabe et al., 2002) and urging patients to take an interest in them may be helpful.

7.4.2 Hypothesis two and three: immigrant patients tend to use a sealing-over recovery style more than native patients do, and lower self-esteem may help explain this.
As expected, immigrant patients with schizophrenia were observed to engage less with psychiatric services than native patients. This finding is consistent with other studies which found membership of an ethnic minority group to be associated with low medication compliance and service engagement (Emsley et al., 2002; Opolka et al., 2003; Valenstein et al., 2006). The greatest difference in our study – on the availability subscale – indicated that immigrant patients kept appointments with their mental health professional less often, as well as were more avoidant in making them.

However, the observed difference in service engagement between immigrant and native patients was not attributable to more sealing-over, as no significant differences with respect to recovery styles were found. Also, our results did not show any difference in either positive or negative self-esteem between native and immigrant patients with schizophrenia. This is an intriguing finding, since it has been found that discrimination may indirectly contribute to the increased incidence of schizophrenia in ethnic minorities, via lower self-esteem (Veling et al., 2008a). Low self-esteem has indeed been found as a risk-factor for developing paranoid delusions (Bentall et al., 2001) and maintaining psychotic symptoms (Garety et al., 2001). Possibly, migrants may more often develop schizophrenia due to general lower self-esteem in comparison to the native general population, but once the illness has developed, self-esteem may be equally low in both
native and immigrant patients and therefore does not explain subsequent lower service engagement.

As we could not produce evidence for more sealing-over in immigrant patients, other explanations are needed for their observed low service engagement. It may be related to their cultural backgrounds. For example, if an immigrant’s views of his illness are not consistent with Western medical concepts, he may sometimes stop short of seeking help from at a mental health institution whose treatment is based on those concepts. It is indeed known that immigrant patients with a psychotic disorder in the Netherlands often seek alternative treatments that are related to their cultures of origin – such as Islamic, Winti, or Hindu healings – (Hoffer, 2005). But it is unknown whether this leads to greater avoidance of mainstream mental health institutions. Another possibility is that it may be less common in some cultures as it is in the Netherlands to plan and keep appointments with professionals that are strictly timetabled by date and time. As well as causing misunderstanding and frustration, this may lead mental-health professionals to believe that such patients are not engaging properly with services.

Looking at other factors rather than cultural background, discrimination on the side of the treatment institutions may prevent migrants to properly access services. Also, practical obstacles can reduce immigrants’ chances to benefit from health services, such as low socio-economic status (e.g. not being able to pay for additional costs or make time for frequent service visits that may accompany the treatment of schizophrenia), the family-structure with often only a single parent to take care of income as well as the children, and language difficulties. In other fields of health care in the Netherlands, language competence and self-reported health status (need factor) were both shown to have large impacts on service use across various immigrant groups (Denktas et al., 2009). Similarly, Fassaert et al. (2009) reported that language ability is important for health care use among Moroccans and Turks in the Netherlands. They also found that acculturation was associated with service use, although there was heterogeneity across ethnic and gender groups.

Most of these explanations, however, are speculative for patients with schizophrenia and should be studied further. And as language difficulty is not present in Surinamese and Antillean patients with schizophrenia in the Netherlands, it does not explain their low service engagement. So despite the knowledge that ethnicity is a risk-factor for low medication adherence and low service engagement in schizophrenia, the reasons for this are yet to be empirically established.
7.4.3 Limitations

The first of the four limitations of this study is that the sample composition limited the possibilities for generalizing the results. Not only were 75% of the participants men, neither study included patients with very high service engagement: in study A, this was an exclusion criterion, while study B included patients who had experienced a recent clinical deterioration due to non-adherence. It is also likely that patients with a very low service engagement had not been included in either study population because they had refused to participate. To ensure that their samples represented everyday practice, however, both studies had made considerable efforts to ensure that all eligible patients would be included. As a result, there were few exclusion criteria, and even fairly psychotic or disorganised patients were included.

The second limitation is that the immigrant patients in our study samples originated from various countries. As there may be considerable differences between them, they should not be seen as having similar characteristics. Although we analyzed the patients from Surinam in a separate analysis, our sample size did not allow for reliable sub-analyses with other immigrant groups. It may be that our results were dominated by the characteristics of the patients from Surinam, and that this limited the generalizability of our findings.

The third limitation is that we took no specific measures to ensure that the instruments we used were culture-sensitive. This may have led some immigrant patients to understand concepts relating to the instruments differently than native patients. Similarly, although the ability to speak Dutch was an inclusion criterion, various immigrant patients may have had a poorer mastery of this, and thus have had problems filling out the questionnaires. However, this limitation may not be the most important, as most immigrants were from Surinam and the Dutch Antilles, where Dutch is spoken and written.

Finally, because our study used cross-sectional data, we cannot draw conclusions on the direction of causality. It is more likely that the causal interrelationships of the relevant variables will be identified in longitudinal and intervention studies.
Chapter 8

Recovery style predicts remission at one-year follow-up in outpatients with psychosis

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M. van der Gaag
C.L. Mulder

Submitted
ABSTRACT

Background
While people with schizophrenia often use avoidant strategies rather than active coping ones, it is largely unknown how their coping style contributes to remission of the illness. The concept of recovery style – either sealing-over or integrating – reflects an important distinction. Broadly defined, a sealing-over patient prefers not to think about psychotic experiences during recovery, while an integrator is interested in the psychotic experience and desires to place it into some coherent perspective.

Aim
To examine whether recovery style predicts remission at one-year follow-up.

Method
As part of a randomised controlled trial, data was collected at baseline with regard to recovery style (RSQ), insight (IS), therapeutic alliance (WAI), and symptoms (PANSS) in 103 patients with psychotic disorders. To measure remission status, symptoms were assessed at six and twelve months (PANSS). Logistic regression analyses were used to test whether recovery style predicted remission, and also to control for baseline symptom levels, insight, and alliance.

Results
The final model showed that an integrating recovery style increased the odds of remission 5.66-fold (95% C.I.: 1.65-19.40). Insight and therapeutic alliance were not predictive. While remission was also predicted by positive symptom levels at baseline, this did not influence the effect of recovery style.

Conclusions
Independently of symptom levels, insight or therapeutic alliance, an integrating recovery style strongly increased the odds of remission at one-year follow-up. These findings provide support for the development of interventions such as motivational interviewing and cognitive therapy, designed to promote psychological adjustment to psychosis.
8.1 Introduction

Over recent years, consensus-defined standards for clinical status and improvement in patients with schizophrenia have become increasingly common. Remission criteria for schizophrenia have been introduced with the intent to facilitate insight into the etiology and the course of disease, and to standardize comparisons across treatments (Andreasen et al., 2005; Van Os et al., 2006). The use of these criteria has underlain renewed efforts to identify predictors of remission, such as cognitive performance (Helldin et al., 2006); baseline-negative symptoms (Petersen et al., 2008); duration of untreated psychosis (Emsley et al., 2006; Petersen et al., 2008); early symptomatic improvement (Emsley et al., 2006; Jager et al., 2009); having intimate relations and being married (Bankole et al., 2008; Emsley et al., 2006); and lifetime traumatic events (Bankole et al., 2008).

While people with schizophrenia often use avoidant coping strategies rather than active coping strategies, the way in which their coping style contributes to remission of the illness is largely unknown (Tait et al., 2003). The concept of recovery style – either sealing-over or integrating – reflects an important distinction in coping with psychosis. Broadly defined, a sealing-over patient prefers not to think about his psychotic experience during recovery, while an integrator is interested in the psychotic experience and desires to place it into some coherent perspective (McGlashan, Docherty, Siris, 1976). Evidence also suggests that an integrating recovery style predicts higher service engagement (Tait, Birchwood, Trower, 2003), fewer symptoms at one-year follow-up (Thompson, McGorry & Harrigna, 2003), and better long-term functional outcome (McGlashan, 1987).

In this study, we used the recent remission criteria for schizophrenia (Andreasen et al., 2005) to test whether an integrating recovery style would predict remission at one-year follow-up. We also compared the effects of recovery style with those of the therapeutic alliance and insight into illness, to which it may be related, especially as insight and alliance are both known to influence the course of treatment and predict outcome (e.g. Emsley, Chiliza & Schoeman, 2008; Hewitt & Coffey, 2005).
8.2 METHOD

8.2.1 Study population
Participants were the respondents in a multi-centre randomised controlled trial conducted in the Dutch city of Rotterdam to investigate the effects of Treatment Adherence Therapy (TAT). This tailored intervention allows four different intervention modules – such as behavioural interventions or an adapted form of motivational interviewing – to be applied according to a patient’s individual reasons or causes of non-compliance. For a more detailed description, see Starling et al. (2006). The four inclusion criteria were (1) schizophrenia spectrum disorder (DSM-IV), (2) receiving outpatient treatment, (3) mastery of the Dutch language, and (4) at least some problems with service engagement, as defined by an average item-score of 1.5 or higher on at least two subscales of the Service Engagement Scale (Tait et al., 2002).

8.2.2 Design and procedure
Patients were referred by their clinician and asked by a research assistant to participate. Participants had to give written informed consent. All participants were assessed at baseline (To), six months (T1), and twelve months (T2). The assessments consisted of structured interviews with the respondent and his/her clinician. The assessment interviews were performed by students in psychology and medicine, who had received two days’ training in role play and in scoring of the measurement instruments. After co-rating a live interview by the main researcher, they performed two interviews under supervision. When their ratings were sufficiently consistent with those of the experienced researcher, the students did interviews independently, but still under supervision every other week.

To assess mental disorders according to the definitions and criteria of DSM-IV (APA, 1994) we used various interviews including the lifetime Composite International Diagnostic Interview, version 2.1 Auto (WHO CIDI, 1997). Respondents were paid EUR 20 each time they participated in an interview. The study design was approved by the Medical Ethics Committee at Erasmus University Medical Centre.

8.2.3 Measurements

Psychopathology and remission
The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is a 30-item rating scale which is completed by trained research staff at the
Recovery style predicts remission of schizophrenia

1. Conclusion of a semi-structured interview. There are three subscales: (1) positive syndrome, (2) negative syndrome, and (3) general psychopathology. Remission was defined as a score for both T1 and T2 of three or lower on the proposed eight PANSS-items (Andreasen et al., 2005; Van Os et al., 2006), as such scores would suggest that the relevant symptoms had been in remission for at least six months.

2. **Recovery Style**

   Recovery style was measured using the Recovery Style Questionnaire (RSQ; Drayton et al., 1998), a 39-item self-report measure designed to reflect categories consistently with the categories developed by McGlashan et al. (1975). It produces six classifications: (1) integration, (2) towards integrating, (3) a mixed picture in which integration dominates, (4) a mixed picture in which sealing-over dominates, (5) towards sealing-over, and (6) sealing-over. The RSQ is reliable, and correlates highly with McGlashan's interview-based measure (Drayton et al., 1998).

3. **Insight**

   We used the self-report 8-item Insight Scale (IS) of Birchwood et al. (1994), which has three subscales: (1) awareness of illness, (2) re-labeling symptoms to illness, and (3) recognition of need for treatment. We used total scores in the analyses, which range from 0 to 12. The scale is reliable and valid, and is easy to use within this group of patients (Birchwood et al., 1994).

4. **Therapeutic alliance**

   The 36-item Working Alliance Inventory (WAI) was used to measure the alliance factor of the therapeutic relationship as it is experienced by the patient (Horvath & Greenberg, 1989; Vervaeke & Vertommen, 1996). The WAI has two factors or subscales: the bond subscale or emotional component, and the contract subscale, which consists of agreements on tasks and goals. It has good validity and reliability (Horvath & Greenberg, 1994; Vervaeke & Vertommen, 1996).

5. **8.2.4 Statistical analyses**

   Logistic regression analysis was used, with one-year follow-up remission as the dependent variable. In the first block, baseline scores on the three PANSS subscales and the treatment allocation (in light of the RCT design) were entered into the model in order to control for them.
In the next block, recovery style was added to the model. On the basis of the sample's mean score, the recovery-style variable was dichotomized into sealing over (score 0) and integrating (score 1). This was done in order to facilitate clinical interpretations of the results. However, all analyses were also performed with the original RSQ total score.

In the third block, we added the IS and the WAI to the model in order to see whether they predicted remission, and whether this in any way influenced the predictive power of recovery style. By then, however, there would be seven independent variables in the equation, and the number of events (remission) per variable should not be lower than ten (Peduzzi et al., 1996). As it was unlikely that this criterion would be met, we performed a last analysis in which all non-significant variables were deleted in order to produce the final regression model for predicting remission, and also to see whether any significant observations would still hold. For all analyses, SPSS 15.0 was used.

**8.3 RESULTS**

**8.3.1 Patient characteristics**
A total of 195 patients were asked to participate. Seventy-nine refused. As no data was available on those who refused, the biases caused by selective participation could not be analyzed. Two patients in the group of patients who were willing to participate were too disorganized to be able to complete the questionnaires. The remaining 114 completed the baseline assessments. Eleven patients were subsequently lost to follow-up; one had died as a consequence of physical health problems, and ten refused to participate any further. The analyses for the present study were conducted on the remaining 103 patients (Table I).

**8.3.2 Predicting remission**
As Table II shows, an integrating recovery style was associated both with fewer negative symptoms and with better insight into illness. At one-year follow-up, 22 of the 103 patients (21.4%) had been in remission for at least six months.

In the first block of the logistic regression analysis, the proportion of explained variance (Nagelkerke R Square) was .289, and the only significant independent variable was the PANSS positive-syndrome subscale (Wald=9.89; Exp(B)=.748; p<.01). When recovery style was added in the second block, the explained variance increased to .385. Positive symptoms (Wald=7.88; Exp(B)=.766; p<.01) and recovery style (Wald=6.93; Exp(B)=5.391; p<.01)
Table I Respondents characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>103</th>
</tr>
</thead>
</table>
| Sex                | 72 patients (70%): male  
                        31 patients (30%): female |
| Average age at T0  | 39.0 years (SD=11.6) |
| Average age at first contact with a mental health institution | 26.0 years (SD=9.6) |
| Employment         | 86 patients (84%): unemployed  
                        17 patients (16%): employed |
| Ethnicity          | 45 patients (43%): Dutch  
                        19 patients (19%): second-generation immigrants  
                        39 patients (38%): first-generation immigrants |
| Diagnoses          | 74 patients (72%): schizophrenia  
                        - 57 paranoid type  
                        - 10 disorganized type  
                        - 6 catatonic type  
                        - 1 undifferentiated type  
                        29 patients (28%): schizoaffective disorder  
                        - 19 depressive type  
                        - 10 bipolar type |
| PANSS positive syndrome (mean and standard deviation) | 13.7 (SD=5.4) |
| PANSS negative syndrome (mean and standard deviation) | 14.0 (SD=5.7) |
| PANSS general psychopathology (mean and standard deviation) | 30.4 (SD=9.6) |

Table II Pearson correlations of the study variables at baseline

<table>
<thead>
<tr>
<th>Pearson correlations</th>
<th>PANSS positive syndrome</th>
<th>PANSS negative syndrome</th>
<th>PANSS general psychopathology</th>
<th>Recovery Style (RSQ) (high = sealing-over)</th>
<th>Insight (IS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS negative syndrome</td>
<td>.316**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS general psychopathology</td>
<td>.623***</td>
<td>.512***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery Style (RSQ) (high = sealing-over)</td>
<td>.172</td>
<td>.264**</td>
<td>.101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insight (IS)</td>
<td>.057</td>
<td>.054</td>
<td>.191</td>
<td>-.277**</td>
<td>.008</td>
</tr>
<tr>
<td>Therapeutic Alliance (WAI)</td>
<td>.100</td>
<td>.072</td>
<td>-.035</td>
<td>-.027</td>
<td>.008</td>
</tr>
</tbody>
</table>

*. Correlation is significant at the .05 level (2-tailed)  
**. Correlation is significant at the .01 level (2-tailed)  
***. Correlation is significant at the .001 level (2-tailed)
both significantly predicted remission. In the third block, insight and therapeutic alliance were added. Although the explained variance increased to .417, none of the new variables added significantly to the model.

In the final model, all non-significant variables were deleted, leaving only positive symptoms and recovery style. As there were 22 events of remission, the number of events per variable was higher than ten, and the results were thus expected to be reliable (Peduzzi et al., 1996). As Table III shows, positive symptoms and recovery style together predicted 35.6% of the variance of remission status at one-year follow-up. Recovery style had an Exp(B) of 5.66, which means that a patient’s use of an integrating recovery style was estimated to increase by a factor of 5.66 the odds that he or she would be in remission at one-year follow-up (95% C.I.: 1.65-19.40).

Table III Results of the final logistic-regression model, with remission at one-year follow-up as the dependent variable

<table>
<thead>
<tr>
<th>Variables in the equation</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I. of Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS positive syndrome</td>
<td>-.234</td>
<td>.080</td>
<td>8.508</td>
<td>.004</td>
<td>.791</td>
<td>.676 – .926</td>
</tr>
<tr>
<td>Recovery style</td>
<td>1.733</td>
<td>.629</td>
<td>7.591</td>
<td>.006</td>
<td>5.656</td>
<td>1.649 – 19.398</td>
</tr>
</tbody>
</table>

In order to test the stability of the results, all analyses were also performed with the RSQ total score, without dichotomizing it. The results were comparable (e.g. the final effect of recovery style was WALD=5.676; Exp(B)=.544; p<.05).

### 8.4 DISCUSSION

#### 8.4.1 Recovery style and remission

The most important finding of this study is that the use of an integrating recovery style by patients with schizophrenia or a schizoaffective disorder strongly increased their odds of being in remission at one-year follow-up. This was independent of symptom levels, insight into illness, and therapeutic alliance.

This finding is in line with other studies that have shown the bearing of a patient’s recovery style on their engagement with treatment and their recovery from psychosis (Tait, Birchwood, Trower, 2003; Thompson, McGorry & Harrigna, 2003; McGlashan, 1987). It seems that an integrating recovery style allows patients to invest in relationships, tolerate affective states, and acknowledge symptoms (Bell & Zito, 2005), and that this may be crucial for
engaging effectively with treatment, achieving sustainable symptom remission, and constructively adapting one’s life after a psychotic episode.

Some studies have found that remission in schizophrenia was predicted by a patient’s having intimate relations, being married (Bankole et al., 2008; Emsley et al., 2006) and lacking lifetime traumatic events (Bankole et al., 2008). It may be that the influence of these factors is mediated by recovery style. It is known, for example, that patients with a sealing-over recovery style perceive their parents to be less caring – suggesting that the roots of sealing-over may in part stem from insecure attachment in childhood (Drayton et al., 1998). Similarly, Tait et al. (2004) found sealing-over to be associated with negative early childhood experience, insecure adult attachment, negative self-evaluative beliefs, and insecure identity. They concluded that a sealing-over recovery style denotes a person’s low personal resilience in adapting to psychosis, and reflects a history of attachment difficulties that is still manifest in current adult relationships (Tait et al., 2004). The connection between sealing-over and lower social competence has also been supported by empirical evidence (Modestin et al., 2004). It may thus be that a patient’s recovery style mediates both the negative impact of traumatic lifetime events on the remission of schizophrenia and the positive effect of marriage and intimate relationships.

We did not find that insight into illness or therapeutic alliance were predictive of remission at one-year follow-up, despite the fact that other studies have shown these concepts to be of important clinical significance (e.g. Emsley, Chiliza & Schoeman, 2008; Hewitt & Coffey, 2005). It may be that our sample size was too small to detect their influence. On the other hand, other studies have supported the notion that recovery style is more predictive for the course of illness than insight is (Tait et al., 2003). From this point of view, it is important to note that although our study found an association between insight and recovery style, the two are not synonymous. It is possible for patients to seal-over with or without insight, e.g. ‘I know I am ill but it was just one of those things and I want to forget about it and move on.’ (Tait et al., 2003).

We did not find that negative symptom levels at baseline were predictive of remission, which contrasts with the findings of Petersen et al. (2008). However, because we also found negative symptoms to be associated with the use of a sealing-over recovery style, our statistical model may have pre-empted the effects of negative symptoms, allowing the results to be dominated by those of recovery style. Indeed, in the first block of the regression analysis,
negative symptoms almost had a significant effect on remission (Wald=2.919; Exp(B)=.890; Sig=.088).

8.4.2 Limitations
The main limitations of this study involve issues of sample-composition, which therefore limit the options for generalizing the results. For example, our sample size was not large, and the number of remissions at one-year follow-up was only 22. Similarly, most of the participants were men (70%). Also, due to an exclusion criterion of the randomised controlled trial, the study did not include patients with very high service engagement. And neither is it probable that patients with a very low service engagement were included in the study, either because they were not in outpatient treatment, or because they had refused to participate, a factor that is likely to be related to a sealing-over recovery style. Although the latter may have introduced a bias in our sample, we made considerable efforts – including offering financial incentives – to ensure that all eligible patients would be included and the sample would thus represent everyday practice. This means that there were few exclusion criteria and that even fairly disorganized or psychotic patients were included.

8.4.3 Strengths
As far as we know, this is the first study to use the recently defined criteria to examine the influence of recovery style on the remission of schizophrenia at follow-up. One important methodological strength is the low attrition rate (9.6%). Another is that by comparing the effects of recovery style with the effects of clinically related and important concepts, such as insight and therapeutic alliance, we have also helped disentangle the psychological processes that are most relevant to recovery from a psychotic episode.

8.4.4 Clinical implications
Our results indicate that long-term remission may be promoted by helping patients to use a more integrating recovery style, for example by talking with them about their psychotic experiences, and by urging them not only to take an interest in these experiences during recovery, but also to place them in a coherent perspective within the self-narrative.

Although it can be difficult to change a patient’s recovery style, empirical evidence shows that it is not solely a trait characteristic (Tait et al., 2003). Recovery styles may vary at different stages of the recovery process. During the acute phase, for example, patients may be integrating, attempting to cope
Recovery style predicts remission of schizophrenia

...constructively with the challenge of the new situation. But during the course of clinical recovery, when the opportunity for reflection begins, they may employ more sealing-over. This means that an effect may be achieved by interventions that focus on a constructive recovery style and on talking about psychotic experiences. One illustration of this is the finding that getting patients to write about the most stressful aspects of their psychotic episode (emotional disclosure) helps reduce psychosis-related post-traumatic stress symptoms (Bernard et al., 2006).

Because vulnerable self-esteem is related to greater sealing-over (Drayton et al., 1998), patients who employ sealing-over may be those who experience greater loss and shame in their psychosis. In order to help them achieve greater integration, it may therefore be useful to address self-stigmatization and self-esteem. Rather than providing neurobiological explanations and telling a patient only that he has an incurable brain disease, strategies for this might include normalizing psychotic experiences within the stress-vulnerability model and within the range of sub-clinical psychotic symptoms in the general population. Important contributions to altering recovery style and to achieving remission may also be made by interventions intended to improve a patient’s self-esteem (e.g. Tarrier, 2001).

In general, the findings of this study confirm that psychological adjustment to psychosis should be promoted through the development of interventions such as motivational interviewing and cognitive therapy.
CHAPTER 9

Financial incentives to improve adherence to medication in five patients with psychotic disorders.

A.B.P. Staring
C.L. Mulder
S. Priebe

Psychopharmacology Bulletin, in press
ABSTRACT

Objective
Non-adherence to antipsychotic medication is common and increases the risk of psychotic relapse. A promising intervention may be a strategy wherein financial incentives are offered.

Methods
In a pilot study in The Netherlands, five patients with schizophrenia were offered financial incentives for a duration of one year to improve adherence to medication. Adherence and hospital days were measured.

Results
The percentage of accepted depot injections increased from an average of 44% in the previous year to 100% in the year when financial incentives were offered. While patients had been hospitalised for an average of 100.2 days in the previous year, only one was re-admitted for 17 days during the year of the intervention.

Conclusions
The differences in adherence before and after the intervention were large and of clinical significance. However, randomised controlled trials are required to provide conclusive evidence on the effectiveness of offering financial incentives and potential consequences.
Financial incentives for adherence – a pilot

9.1 INTRODUCTION

Non-adherence to antipsychotic medication in schizophrenia is high (Weiden, 2007; Cramer & Rosenheck, 1998) and is associated with a three to five times increased risk of relapse (Fenton et al., 1997; Ucok et al., 2006; Weiden et al., 2004). Developing effective interventions for improving adherence is a major challenge to mental health care. In the UK, Claassen et al. (2007) used financial incentives to improve the adherence to antipsychotic maintenance medication in five formerly non-adherent patients. Results were promising, yet no other studies have since been published.

We conducted a pilot study to test the feasibility of using financial incentives to improve adherence and explore potential benefits for patients in an Assertive Community Treatment (ACT) team.

9.2 METHODS

9.2.1 Procedure
Patients were gathered in Rotterdam, The Netherlands. Written informed consent was obtained from all patients after providing them with a complete description of the study. The intervention was over a one year period and the study was conducted from July 2008 to October 2009. A Medical Ethics Committee (METIGG, The Netherlands) approved the study (ref-number: 8208; CCMO number: NL22014.097.08).

9.2.2 Intervention: financial incentives for adherence
Patients received ten to twenty Euro cash (fifteen to thirty US $) for each depot injection of antipsychotic medication. The amount of money depended on the frequency of the depot. Ten Euro were offered for a depot administered every two weeks, 15 Euro for a depot every three weeks, and 20 Euro for a depot every four weeks.

9.2.3 Respondents
Inclusion criteria were (1) a diagnosis of schizophrenia or schizoaffective disorder, (2) being treated in the ACT-team for a period of one year or more, (3) the prescription of depot antipsychotic medication, (4) non-adherence, as defined by either not accepting all depot injections or repeated resistance and discussion when accepting the medication, (5) having been admitted to a psychiatric
hospital in the past year as a consequence of non-adherence (as assessed by the responsible clinician).

Six patients were asked to participate out of which one refused and five decided to participate. Two patients were native to The Netherlands. The others were first-generation immigrants; one from Suriname, one from Turkey, and one from the Dutch Antilles. For more details, see Table I.

9.2.4 Measurements
For both the year before and the year during which the intervention was applied, the following data were collected from the patients’ files: (1) the number of administered depot injections as compared to the prescribed one; and (2) the number of days the patient spent in psychiatric in-patient treatment. Furthermore, we designed a short questionnaire to capture the views of patients, their relatives and clinicians (workers in the ACT-team) on the experiences with offering financial incentives.

9.3 RESULTS

9.3.1 Depot acceptance and hospital days
As Table I shows, all five patients accepted every depot injection of antipsychotic medication during the year of the intervention. During the year before the intervention, adherence was much lower. Patient B had previously always

<table>
<thead>
<tr>
<th>Patient (sex; age)</th>
<th>DSM-IV diagnosis</th>
<th>One year before the intervention</th>
<th></th>
<th></th>
<th>One year during the intervention</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A (male; 23 yrs)</td>
<td>Schizophrenia, paranoid subtype</td>
<td>76</td>
<td>45%</td>
<td>0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (male; 24 yrs)</td>
<td>Schizophrenia, paranoid subtype</td>
<td>260</td>
<td>0%</td>
<td>17</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (male; 21 yrs)</td>
<td>Schizophrenia, paranoid subtype</td>
<td>89</td>
<td>20%</td>
<td>0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (male; 43 yrs)</td>
<td>Schizophrenia, paranoid subtype</td>
<td>14</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (male; 34 yrs)</td>
<td>Schizophrenia, disorganised subtype</td>
<td>62</td>
<td>55%</td>
<td>0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This is the percentage of depot injections that were effectively given to the patient in comparison to what was officially prescribed, counting only the outpatient days.
declined a depot injection of antipsychotics, despite the fact that mental health professionals had often tried to motivate him because of his poor compliance with oral medication and his recurring and severe psychotic relapses.

The number of days patients spent in psychiatric in-patient care decreased during the intervention. Only one of the five patients was admitted whilst being offered financial incentives. However, the same patient (B), during the period of the intervention, had been in detention for 195 days for domestic violence while being in a psychotic state. Thus, the incentives improved adherence, but the medication did not sufficiently control his psychotic symptoms.

![Depots accepted graph](image1.png)

**Figure I** Depots accepted one year before and one year during the intervention

* This is the percentage of depot injections that were effectively given to the patient in comparison to what was officially prescribed, counting only the outpatient days.

![Hospital days graph](image2.png)

**Figure II** Hospital days one year before and one year during the intervention
9.3.2 Views of patients, relatives and clinicians

In the short questionnaire on the experiences with the intervention all five patients considered the intervention to be a good project. The reasons they gave were “I don’t like the injection, but money makes it better,” “Money keeps me motivated,” and “The depot injections keep me balanced.” When prompted, two patients said that they perceived financial incentives as a voluntary and non-coercive measure, two patients did not know what to think about this, and one indicated that he perceived financial incentives as a coercive measure, saying that “I have to take the medication anyway.” All patients said that they spent the money on food and on cigarettes, and one patient also bought household products. It was observed, however, that at least one patient had spent some of the money on cannabis. All five patients stated that the amount of money was too low. None of them, however, had asked for more money during the intervention. All five patients said that they preferred receiving cash to other systems of reward such as vouchers for food, sports activities, etc.

Three patients either had no relatives or did not allow us to interview them in this study. The two interviewed relatives – two mothers – indicated that they considered financial incentives to be a good measure, saying that “There can never be enough research” and “This project is in the best interest of both the patient and his parents.” They considered the amount of money to be sufficient, and they preferred the reward of money over vouchers.

During the intervention, two patients had repeatedly asked for their depot injections sooner than scheduled, which was always declined. Despite this, no clinician reported a negative impact on the therapeutic relationship. Two patients complained about side-effects, and one expressed concerns that the depot injection could kill him, after watching a TV program in which someone died as a result of medication.

No other patient in the care of the team complained about unequal treatment or demanded to be paid for taking their medication as well.

9.4 DISCUSSION

The pilot results are promising and seem to indicate that offering financial incentives can increase adherence with depot antipsychotic medications and, as a consequence, reduce the risk of relapse in patients with schizophrenia that are treated in an ACT-team. The difference in adherence and clinical outcomes
Financial incentives for adherence – a pilot

1. with the total prevention of further hospitalisations in four out of five patients is substantial. The benefits of such changes for the patients concerned and their relatives as well as the reduction of service costs appear to justify the intervention.

2. The positive results are consistent with findings of a previous study in the UK (Claassen et al., 2007). Unlike that previous study, we also assessed experiences of patients, relatives, and clinicians. Overall, experiences were positive, cash incentives were preferred to vouchers, other patients did not ask to be offered incentives as well, and no negative impacts on therapeutic relationships were noted. However, the reported experiences also indicated potential problems with offering incentives. Some patients felt they should receive more money and the issue of a coercive nature of the intervention was raised. Some of these issues are linked to ethical considerations about offering financial incentives to change health behaviour in general (Prendergast et al., 2006) and particularly for improving medication adherence in patients with schizophrenia which have been discussed elsewhere (Claassen, 2007; Claassen et al., 2007).

9.5 CONCLUSIONS

3. The differences in adherence before and after the beginning of the intervention were large and of clear clinical significance. However, randomised controlled trials are required to provide conclusive evidence on the effectiveness of offering financial incentives and potential consequences (Priebe et al., 2009). Such research should distinguish between an effect on adherence itself and a positive impact of the medication.
CHAPTER 10

General discussion, conclusions, and recommendations.

A.B.P. Staring
10.1 SHORT SUMMARY OF THE FINDINGS

The main objective of this study was to find ways to improve treatment adherence in patients with psychotic disorders. In Chapter 2, based on a literature-review, three clusters of possible causes of non-adherence are summarized, each of which can be targeted by a specific module of our developed *Treatment Adherence Therapy* (TAT). Our multi-centre randomised controlled trial showed that this intervention was effective in improving treatment adherence (Chapter 3).

It was also shown that adherence to antipsychotic medication has diverging effects on patients’ quality of life, as good adherence is associated with symptom-reduction as well as side-effects (Chapter 4). Also, insight into illness was not always relevant for good adherence, but rather in only those patients who have sufficient cognitive abilities (Chapter 6). Furthermore, the detrimental effects of insight depended on the amount of stigma that patients attach to the illness (Chapter 5).

We hypothesized that immigrant patients were more likely to use a sealing-over recovery style, which might explain their observed low service engagement, but this was not supported (Chapter 7). We did find, however, that an integrating recovery style strongly predicted the remission of a psychotic disorder (Chapter 8).

Finally, we did a pilot study on using financial incentives to promote adherence to depot antipsychotic medications. The results indicated that it may be a very effective method (Chapter 9).

10.2 MOTIVATIONS FOR ADHERENCE AND INTERVENTION STRATEGIES

The results that are reported in Chapters 3 and 4 indicate that good adherence to antipsychotic medication does not, on average, improve patients’ short-term quality of life. In other words, patients report that they do not feel much better or happier with their lives. We know that antipsychotic medications generally do not produce immediate pleasant effects, and this is unlike some other medications, for example benzodiazepines. Rather, the first thing that patients often experience is a range of unpleasant side-effects. Therefore, those who keep using their medication for a prolonged time, as prescribed, probably do so because they have some other short-term reason (e.g. to sleep better, avoid arguments, or reduce certain symptoms), or because they have insight in the long-term consequences of non-adherence, such as the increased odds of relapse and...
re-admission. Thus, in order to achieve adherence in non-adherent patients, it seems useful to create awareness of the short-term and long-term consequences that are of personal significance from a patient’s perspective. This is indeed what we have explored, and our intervention strategies in Treatment Adherence Therapy (TAT) are aimed at developing a personal narrative in which these consequences intrinsically motivate patients to adhere to treatment (Chapters 2 and 3).

However, some well motivated patients may still find it difficult to adhere to medication because of a lack of self-control. For them, the solution is rather straightforward: give them depot injections of the medication, or support them with various behavioural strategies to make it easier to use oral medication, such as reminders, cues, self-monitoring tools, family or partner support, and linking medication-use to highly frequent behaviours.

Other patients, even after talking about all relevant consequences, still consider medication as not helpful. Several causes can be imagined: Is this opinion based on a balance of pros and cons? Do they experience adverse effects? It seems best to start a period of testing medication types and dosages in order to examine what works best for an individual patient, and to develop his awareness of effects and side-effects. We have done so by the module medication optimization in TAT. Some of these patients may finally decide that there is no suitable antipsychotic medication with benefits outweighing the side-effects. Clinicians could probably best support this decision of non-adherence (except when danger is involved and involuntary measures are needed). This group of patients may actually be larger than is generally expected (Chapter 3). Many of the non-adherent patients may have decided to become non-adherent as a consequence of not responding well to antipsychotic medication, and this may have produced part of the frequently observed associations – mentioned throughout this thesis – between non-adherence and an increased risk of relapse and re-admission (Dixon & Lehman, 1995; Fenton et al., 1997; Robinson et al., 2002; Ucok et al., 2006; Weiden et al., 2004)

Other patients may change their opinions and acknowledge that antipsychotic medication helps them control symptoms and prevent social exclusion.

However, there may be patients who do not change their opinions and who are still frequently non-adherent despite the observed medication benefits and despite recurrent involuntary admissions. For them, it may be important to realise that cognitive dysfunction, positive symptoms, and perception biases may incapacitate them to judge their own situations well and to behave in accordance with beliefs (Chapter 6). In these cases, providing incentives for
adherence seems a good option. This might be a better option than the threat of involuntary admission in a psychiatric hospital ward. Providing incentives is probably more effective, less traumatic, and less expensive (Chapter 9).

The abovementioned vignettes of patient perspectives on the use of antipsychotic medication are helpful in developing a heuristic model for improving adherence behaviour, as is integrated in Treatment Adherence Therapy (TAT; Chapter 2).

**10.3 THE EFFECTS OF TREATMENT ADHERENCE THERAPY**

The multi-centre randomised controlled trial in this thesis has supported the hypothesis that *Treatment Adherence Therapy* (TAT) enhances service engagement and medication adherence in patients with psychotic disorders. The effect on medication adherence remained significant at six-month follow-up. Also, there was a trend that the patients receiving TAT were less often involuntarily admitted to a hospital. These results contrast with the lack of significant improvements in some of the other attempts to improve adherence (e.g. Gray et al., 2006), and may be due to the model of TAT in which intervention strategies are tailored to patients’ individual situations. However, we could not detect any effects of TAT on symptoms, quality of life, insight, recovery style, therapeutic alliance, or the experience of stigma.

The effects of TAT on adherence, although still significant, were somewhat reduced at six-month follow-up. This is in keeping with the findings of a meta-analysis (Nosé et al., 2003), where length of follow-up was negatively associated with treatment effect on adherence. Thus, the benefit of this type of intervention is less evident with increasing length of follow-up. Until more long-term data has become available, clinical interventions should be implemented in practice as short-term measures, and may need frequent and routine repetition for enduring effects.

Based on the frequent use of motivational interviewing, it can be concluded that the most common reason therapists judged a patient to be poorly engaging with services in the TAT study was related to factors such as stigma, denial, and low insight. Behavioural training and medication optimization were less often employed. This pattern may be the result of the way clinicians referred patients for the study. Clinicians may have primarily focussed on those patients who
would openly resist their diagnosis and treatment, and they may have failed to
detect non-adherence when it was a consequence of cognitive problems such
as forgetfulness, or in those instances where patients secretly disposed of the
medication because they believed it was not helpful or produced too many side-
effects. It is indeed known that clinicians often underestimate non-adherence
(Byerly et al., 2007). This mechanism may have produced a bias in our study
sample, limiting the possibility to generalize the findings.

In our study design, TAT was an add-on intervention administered by a thera-
pist other than the patient’s own clinician. As we consider the approach to be
patient-oriented and respectful of patients’ views, TAT may be more effective
when it is administered by the patient’s own clinician. Such an approach might
strengthen the alliance in the regular therapeutic relationship, a factor known
to positively influence outcome (Hewitt & Coffey, 2005).

10.4 WHY DID SYMPTOMS NOT IMPROVE?

Despite the effects of TAT on service engagement and medication adherence,
we did not detect symptomatic improvements. Interestingly, some other inter-
ventions have yielded similar results: adherence to antipsychotic medications
improved, yet psychiatric symptoms did not (Kemp et al., 1996; Velligan et al.,
2008; Valenstein et al., 2009). What’s going on?

One possibility is that the adherence-measurements used were not valid and
failed to reflect the true adherence of patients. This is unlikely, however, because
other outcome measures did in fact show some improvement, for example on
functioning (Kemp et al., 1996; Velligan et al., 2008), as well as a near signifi-
cant effect on involuntary admissions in the TAT study.

Another explanation for the lack of symptomatic improvement is that the
sample sizes were too small to detect a not very large effect. Maybe then, the
duration and intensity of the interventions were not enough to cause large
changes in symptoms, and that we need longer or more intensive treatments.

Alternatively, it may be the case that referred patients were actually poorly
adherent at baseline as a consequence of insufficient improvement with antipsy-
chotic medication. Non-adherent patients might have a more malignant course
of the illness, leading to both non-adherence and poor outcome. Somewhat
related to this explanation is the possibility that symptoms were relatively
under control at baseline and that, despite incomplete adherence, patients
may have had already gained the maximum benefit from their antipsychotic
treatment. In both these scenarios, creating better adherence would not have
improved symptoms. Arguably then, future interventions will produce simi-
larly disappointing results, and it is to be expected that improved adherence to
antipsychotic medications may simply not always do very much for reducing
psychotic symptoms. Possibly, it may influence emotion and behaviour rather
than psychotic symptoms persé, which may explain the observed benefits of
an improved adherence for functioning and involuntary admissions. Indeed,
there is evidence that antipsychotic medication, when regarding the various
dimensions of psychotic experiences, produces the largest effect on the behav-
ioral impact as well as somewhat smaller effects on cognitive preoccupation
and emotional involvement, but that it hardly influences the conviction and
external perspective of psychotic experiences (Mizrahi et al., 2006).

Most likely, the truth lies somewhere in the middle, and all these factors are
combined in explaining the results to a certain extent.

Adherence is not a sufficient treatment goal or clinical outcome by itself.
Interventions for improving adherence are only useful if they in the end help
patients feel or function better. Adherence is a tool to achieve goals (Weiden,
2007). Life goals, such as improved quality of life and achieving – or preventing
the loss of – valued relationships and social roles, are relevant outcomes for
patients. Obstacles in achieving these goals are useful treatment targets, which
may or may not include psychiatric symptoms, and adherence is only a useful
aim when viewed within this context.

10.5 CONSIDERATIONS

In Chapter 1, it was argued that a lot of effort is being put into developing
better antipsychotic medications, and that perhaps more effort should be made
to increase adherence. However, these two issues are related to each other in
various ways. For example, if a new antipsychotic agent would appear on the
market that produces direct pleasurable effects, the problem of non-adherence
might be less prominent. Also, if antipsychotic medications would reach a level
of effectiveness in which all of the symptoms – positive and negative – of schizo-
phrenia are very much reduced, without any side-effects, then being adherent
would produce a lot more benefit for patients. Alongside this, the amount of
stigma attached to schizophrenia would likely make a dramatic drop, because
patients would look and behave as all others when e.g. extrapyramidal side-effects would be absent. And without stigma, another reason for non-adherence disappears. Any improvement along these lines may have a significant influence on the issues of adherence in psychosis.

However, it is also known that adherence in other fields of health care is problematic just the same, e.g. hypertension and diabetes. More effectiveness and fewer side-effects, therefore, are unlikely to completely solve the problem of non-adherence in these patients.

As mentioned before, adherence to medication does not improve short-term quality of life. Besides the stated implications for the way in which patients may be motivated for adherence, this also means that being adherent to antipsychotic medication is not enough to achieve substantial improvements for desired goals and satisfaction in life. Also, better adherence may worsen somatic side-effects, reduce frontal grey matter in the brain, and increase mortality—consequences of long use of antipsychotic medication (Weinmann & Aderhold, 2010).

Considering this, a certain conclusion is becoming more and more discernible: achieving adherence to antipsychotic medication is not the holy grail in treating psychosis. We should always be aware that for some patients antipsychotic medication may not really be helpful, despite the possible presence of severe symptoms and high risk of re-admission. Also, even when the medication is helpful, severe adverse effects stress the need to minimize long-term use and doses, and other interventions and efforts are often needed to support patients to more fully recover from their psychosis and regain a desired level of functioning and quality of life. This highlights the need for strategies such as the involvement of family, cognitive behavioural therapy, rehabilitation strategies, treatment of co-morbid disorders, and other interventions that explore personal life meanings of psychotic experiences (Weinmann & Aderhold, 2010; Stainsby et al., 2010).

10.6 LIMITATIONS

Some important limitations of our study should be considered. First, the sample size was not large, which may have limited the power to detect effects of TAT on secondary outcomes and mediators.

Second, our research design distributed attention unevenly between the two treatment allocations, which may have produced a bias. The effects we
observed may have been caused simply by giving the patients in the TAT group more attention. We can therefore not confirm that the therapeutic contents of TAT were in fact the actual effective ingredients.

Third, our measure of compliance consisted of the SES plus a one-item rating scale. This latter measure has not been validated, and may not be the best available. However, measuring compliance is difficult, and a gold standard is certainly lacking (Kikkert et al., 2008). As well as self-report and interview measures, methods of measuring compliance include pill counts, electronic methods, prescription monitoring, and saliva, plasma and urine assay tests (Patel & David, 2007). Each has its advantages and disadvantages. Pill counts are not only time-consuming, but also have great potential for inaccuracy. And not only are saliva, plasma, and urine tests not possible for all drugs, they are expensive and invasive, and may also overestimate adherence for drugs that have a long half-life (Fenton et al., 1997; Zygmunt et al., 2002).

Fourth, patients were referred to our study when their clinicians believed they were not sufficiently adherent. They have probably not detected all cases of non-adherence, which may have produced a bias in the selection of our study sample.

10.7 CONCLUSIONS

Based on the findings in this thesis, I am positive that adherence with antipsychotic medication, as well as more general service engagement, can be positively affected by professionals’ attitudes and interventions. However, the updated guidelines of the National Institute for health and Clinical Excellence (NICE, 2009) recommend not to use any kind of adherence therapy in patients with psychosis. And most likely, the forthcoming update of the Dutch Multidisciplinary Guidelines for Schizophrenia (due 2010), will similarly advise against this type of intervention. I will not dispute these recommendations. They are correct in that inconclusive evidence exists for the various variations of adherence therapy. Also, other psychosocial interventions in psychosis, not aimed at adherence, have produced much more conclusive evidence supporting their merit over the years, such as cognitive behavioural therapy and family-based interventions. And as these treatments are not yet available in the every-day practice of many mental health institutions, implementing them deserves the highest priority.
However, this thesis shows that a comprehensive assessment of patient’s motives and capabilities can indicate what type of intervention may effectively support them in becoming more adherent. Treatment Adherence Therapy has produced significant effects (Chapter 3). And research on other strategies is currently underway, such as a CBT-type intervention by Peter Weiden et al., financial incentives by Stefan Priebe et al. (2009) as well as by Charlotte Audier et al., behavioural strategies in order to bypass cognitive deficits by Velligan et al. (2009), and an adherence coping skills therapy by Sarah Uzenoff et al. (2008). Combining the best strategies into an integrated approach, where each patient receives a tailored treatment to improve adherence, may eventually become an evidence-based guideline.

Adherence studies underline the need to strive to understand patients from their personal individual perspectives. This means giving them the opportunity to have their voices adequately heard. In doing so, it is hoped that the adverse clinical and economic impact of non-adherence may be further reduced.

10.8 RECOMMENDATIONS

It has become clear that non-adherence in patients with schizophrenia is a heterogeneous problem, and that intervention strategies should be tailored to patients their individual situations, ideas, and capabilities (Chapters 2, 4, & 6). Future research, then, can focus on the clearer assessment of patients’ individual reasons for non-adherence and its consequences, allowing intervention strategies to be applied with more accuracy. An implication of this realisation is that group formats for adherence interventions are unlikely to be successful.

Future research on TAT or a similar type of intervention may use the following recommendations: (1) to compare its effects with a control condition in which an equal amount of attention is given to the patients; (2) to use various adherence-measurements; (3) to let patients’ own clinicians execute the intervention; (4) longer or more intensive treatment; (5) longer-term follow-up; and (6) to distinguish between an effect on adherence itself and a positive impact of the medication.

Also, adherence to medications is one thing, but adherence to appointments and psychosocial treatments is similarly important for patients in order to achieve desired improvements. Also, when patients better adhere to appointments, it is easier to monitor adherence to medications.
It seems practical and can probably work as a preventive measure to use the TAT method of medication optimization as a standard practice whenever a patient is given a new antipsychotic medication and is not in a too psychotic state to be involved in this kind of strategy. Doing so would involve patients in structurally monitoring symptoms and side-effects, and it would take their view seriously. Also, it would do justice to the fact that we never know beforehand if a certain antipsychotic medication or dosage is suitable. The collaborative and structured empirical nature of this intervention is, in my view, a realistic and respectful approach, and consistent with the process of shared decision making that we need in adherence issues (Gray et al., 2010). If non-adherence rates are to decrease, it will ultimately be necessary to align the incentives of the treater and the treated.
CHAPTER 11

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### 11.2 Summary

#### 11.2.1 Treatment Adherence Therapy

The main objective of this research was to find ways in which to improve treatment adherence in patients with psychosis. **Chapters 1 and 2** constitute the introduction in which the literature on non-adherence in psychosis is reviewed. It was found that non-adherence to treatment in patients with psychotic disorders is common and related to relapse, hospitalization, and suicide. Important predictors of non-adherence include poor social structure, cognitive deficits, negative medication attitude, side effects, depression, a sealing-over recovery style, feelings of stigmatization, denial of treatment need, and lack of insight. Studies on interventions to improve adherence have shown that patient education is not fully effective, and that motivational interviewing, behavioural strategies, and linking a patient's personal goals to treatment may increase adherence. Intervention studies have produced inconclusive results, however.

Based on the empirical data reviewed, we formed three clusters of possible causes of non-adherence, each of which can be targeted by a specific module of our developed **Treatment Adherence Therapy** (TAT). These modules are: (1) adapted motivational interviewing, (2) medication optimization, and (3) behavioural training. An individual patient may benefit from one or more of these modules; and thus the contents of TAT vary in accordance with individual causes of non-adherence. Basically, TAT aims to help patients work out what they want regarding treatment and then support them in following this through.

In **Chapter 3**, we analyzed the effects of Treatment Adherence Therapy (TAT) with a single-blind randomised controlled study of treatment as usual (TAU) versus TAU + TAT in 109 outpatients. Measurements were performed by masked assessors at the end of treatment and at six-month follow-up. Significant benefits were shown on service engagement (Cohen's $d=.48$) and medication compliance (Cohen's $d=.43$). Results remained significant at follow-up for medication compliance. Also, near significant effects were found on involuntary re-admissions ($1.9\%$ vs. $11.8\%$; Sig=.053), but symptoms and quality of life did not improve. It was concluded that Treatment Adherence Therapy is effective for improving engagement and compliance, and that it may prevent involuntary admissions.

#### 11.2.2 Adherence, insight, and recovery styles

**Chapter 4** deals with the issue that, when patients adhere to their antipsychotic medication, it is not certain whether they experience short-term
improved quality of life. By simultaneously reducing symptoms and increasing side-effects, compliance with antipsychotics may have opposing effects on a patient’s perceived quality of life. Using Structural Equation Modeling (SEM), this hypothesis was tested in 114 outpatients with psychotic disorders, using the baseline data of the current randomised controlled trial. It was found that compliance was not directly related to quality of life. The best-fitting model indicated that high compliance was associated with fewer psychotic symptoms and more adverse medication effects. Symptoms and adverse medication effects were both related to lower quality of life. This means that, with regard to the effects of medication, the balance between symptom reduction and adverse effects is associated with the benefit a patient perceives in terms of improved quality of life. Also, as quality of life generally is not higher in those who are adherent, patients who keep using their pills for a prolonged time, probably do so because they have some other short-term reason (e.g. to sleep better, to avoid arguments, or to reduce certain symptoms), or because they have insight in the long-term consequences of non-adherence, such as increased odds of relapse and re-admission.

In Chapter 5, we looked at effects of insight in patients with psychosis, because it is known that good insight is related not only to medication compliance and high service engagement, but also to depression, low self-esteem, and low quality of life. We investigated the possibility that the negative effects of good insight are moderated by perceived stigma. Again, this was done by the method of SEM, using the baseline data of our study sample. We found that good insight was associated with high service engagement and high compliance. Also, insight was related to depressed mood, low quality of life, and negative self-esteem. These latter associations were strong when stigma was high and weak when stigma was low. SEM showed that the detrimental effects of insight are moderated by stigma. A clinical implication is that when attempting to increase insight, perceived stigma should also be addressed.

Another issue with insight is that while lack of insight into illness is often a strong predictor of antipsychotic non-adherence, there is considerable inconsistency in the literature that has not been adequately explained. In Chapter 6, we investigated the hypothesis that verbal memory deficits may be an important moderator in the association between insight and adherence, because memory is an essential link needed to change intent to action. Results showed that insight was associated with compliance in patients without, but not in patients with severe verbal memory deficits. Thus, in patients with verbal memory deficits, compliance is unaffected by the amount of insight. If compliance is poor in
these patients, behavioural interventions are probably enough to overcome it, such as reminders, the simplification of dosing frequency and polypharmacy use, the involvement of family members in treatment, or the use of contingency management such as financial incentives. Patients without memory impairments, whose insight is poor, may benefit not only from behavioural strategies, but also from insight-enhancing interventions such as cognitive therapy or motivational interviewing.

In Chapter 7, the hypothesis is tested that low service engagement in immigrant patients – frequently observed – is caused by more sealing-over recovery styles, and that this is related to low self-esteem. Broadly defined, the sealing-over patient prefers not to think about psychotic experiences during recovery, while the integrator, by contrast, is interested in the psychotic experience and desires to place it into some coherent perspective. Results showed that sealing-over was associated with low service engagement, but not with low self-esteem. However, although first-generation immigrant patients had lower service engagement, they did not differ from natives with regard to recovery style or self-esteem, and neither did second-generation immigrants. It was concluded that sealing-over predicted low service engagement, but that lower service engagement in immigrant patients than in natives was not attributable to sealing-over or low self-esteem. Low self-esteem may contribute to the development of schizophrenia in a relatively high number of immigrants, but after onset, it may be equally common in native patients, and not lead to more sealing-over in immigrants. Their low service engagement may be related to other factors, such as non-Western views or a different attitude towards the need to keep appointments.

Finally, we were interested in the way that patients’ recovery styles contributed to remission of schizophrenia. In Chapter 8, we used data of 103 patients on recovery style, insight, therapeutic alliance, and symptoms. At twelve months, remission status was assessed. Results showed that having an integrating recovery style increased the odds of remission 5.66-fold (95% C.I.: 1.65-19.40). Insight and therapeutic alliance were not predictive. While remission was also predicted by positive symptom levels at baseline, this did not influence the effect of recovery style. These findings provide support for the development of interventions such as motivational interviewing and cognitive therapy, designed to promote psychological adjustment to psychosis.
11.2.3 Financial incentives for improving adherence

In Chapter 9, we describe a pilot study in which five patients received financial incentives for a duration of one year to improve adherence to medication. Results showed that the percentage of accepted depot injections increased from an average of 44% in the previous year to 100% in the year when financial incentives were offered. And while patients had been hospitalised for an average of 100.2 days in the previous year, only one was re-admitted during the year of the intervention, which was for 17 days.

11.2.4 Conclusions and recommendations

In Chapter 10, the findings are discussed in the light of the literature and future directions. The guidelines of the National Institute for Health and Clinical Excellence (NICE, 2009) recommend not to use any kind of adherence therapy in patients with psychosis. And most likely, the forthcoming update of the Dutch Multidisciplinary Guidelines for Schizophrenia (due 2010), will similarly advise against this type of intervention. However, the findings of this thesis suggest that adherence with antipsychotic medication, as well as service engagement, can be positively affected by professionals’ attitudes and interventions. A thorough assessment of patient’s individual situations can indicate what type of intervention may effectively support them in becoming more adherent. Other research on specific strategies is currently underway in various countries. Combining the best strategies into an integrated approach, where each patient receives an individually tailored treatment to improve adherence, may turn out to be the most effective method. However, at this moment, there is still insufficient evidence that interventions aimed at improving adherence result in better treatment outcomes, and widely implementing such interventions in standard mental health care is not yet advisable.
11.3 SAMENVATTING

11.3.1 Treatment Adherence Therapy

Het belangrijkste doel van dit onderzoek was het ontwikkelen van manieren om de therapietrouw te verbeteren in patiënten met psychoses. *Hoofdstukken 1 en 2* vormen de introductie waarin de stand van zaken in de literatuur over therapie-ontrouw bij patiënten met psychoses wordt geschetst. Er is gevonden dat therapie-ontrouw veel voorkomt en gerelateerd is aan terugval, rehospitalisatie en suïcide. Predictoren voor therapie-ontrouw zijn weinig sociale structuur, cognitieve stoornissen, een negatieve houding ten opzichte van medicatie, bijwerkingen van de medicatie, depressie, een toedekkende copingstijl, gevoelens van stigmatisatie, ontkennings van de behandel noodzaak, en laag ziekte-inzicht. Studies naar interventies om therapietrouw te verbeteren laten zien dat psychoeducatie geen effect heeft, maar dat motiverende gespreksvoering, gedragsstrategieën en het koppelen van behandeling aan persoonlijke doelen van een patiënt, allemaal een effect kunnen hebben. Echter, de bestudeerde interventies hebben tot nu toe zeer wisselende successen laten zien.

Op basis van deze empirische gegevens hebben we drie clusters van mogelijke oorzaken van therapie-ontrouw vastgesteld, en voor ieder cluster is een specifieke module gemaakt. Deze therapie hebben we *Treatment Adherence Therapy* (TAT) genoemd. De modules zijn: (1) motiverende gespreksvoering, (2) medicatie optimalisatie en (3) gedragstraining. Een individuele patiënt kan baat hebben bij één of meer van deze modules, en de inhoud en duur van de totale interventie variëren dus afhankelijk van de individuele oorzaken van therapie-ontrouw. TAT helpt patiënten bij het uitzoeken van wat ze willen met betrekking tot behandeling, en steunt ze vervolgens bij het gevolg geven daaraan.

In *Hoofdstuk 3* hebben we de effecten geanalyseerd van Treatment Adherence Therapy (TAT) met een enkel-blind gerandomiseerde gecontroleerde studie waarbij in 109 ambulante patiënten treatment as usual (TAU) werd vergeleken met TAU + TAT. Metingen werden verricht direct na de interventie en na een follow-up van zes maanden. Er werden significante resultaten gevonden op behandelmedewerking (Cohen's d = .48) en medicatiertrouw (Cohen's d = .43). Deze resultaten bleven significant na de follow-up periode voor medicatiertrouw. Daarnaast werd een bijna significant effect gevonden op gedwongen opnames (11,8% versus 1,9%; Sig=.053). Echter, symptomen en kwaliteit van leven verbeterden niet. Treatment Adherence Therapy blijkt dus effectief te zijn in het verbeteren van de behandelmedewerking en de medicatiertrouw, en mogelijk voorkomt het gedwongen opnames.
11.3.2 Therapietrouw, inzicht en copingstijlen

Hoofdstuk 4 gaat over de kwestie dat indien patiënten trouw hun antipsychotische medicatie gebruiken, het niet duidelijk is of ze op korte termijn wel een betere kwaliteit van leven ervaren. Door het tegelijkertijd verminderen van symptomen en het veroorzaken van bijwerkingen, kan therapietrouw aan antipsychotica tegengestelde effecten hebben op de kwaliteit van leven. Met Structural Equation Modeling (SEM) is deze hypothese getoetst in 114 ambulante patiënten met een psychotische stoornis, waarbij gebruik is gemaakt van de baseline gegevens van de huidige studie omtrent TAT. We vonden dat therapietrouw niet direct gerelateerd was aan kwaliteit van leven. Het meest passende model liet zien dat goede therapietrouw samenhangend met minder psychotische symptomen en meer bijwerkingen van de medicatie. Symptomen en bijwerkingen hadden allebei een negatief effect op de kwaliteit van leven. Dit betekent dat met betrekking tot de effecten van antipsychotische medicatie, de balans tussen symptoomreductie en bijwerkingen geassocieerd is met de verbetering die een patiënt ervaart in diens kwaliteit van leven. Verder, aangezien de kwaliteit van leven in het algemeen niet hoger is in patiënten die therapietrouw zijn, zullen de persoonlijke redenen om medicatie langdurig te gebruiken waarschijnlijk op andere gebieden liggen dan een verhoogd welbevinden, zoals b.v. op korte termijn beter slapen, ruzies voorkomen, of bepaalde symptomen reduceren, of op lange termijn het verkleinen van de kans op terugval en heropname.

In Hoofdstuk 5 hebben we gekeken naar de effecten van ziekte-inzicht, aangezien het bekend is dat goed inzicht niet alleen gerelateerd is aan medicatie trouw en algemene medewerking aan behandeling, maar ook aan depressie, lage zelfwaardering en lage kwaliteit van leven. We hebben onderzocht of de negatieve effecten van ziekte-inzicht gemodereerd worden door ervaren stigma. Dit is wederom met SEM gedaan, op basis van de baseline gegevens. We vonden dat goed inzicht inderdaad gerelateerd is aan hogere behandelmedewerking en medicatie trouw. Echter, goed inzicht was ook gerelateerd aan depressieve stemming, lage kwaliteit van leven en negatieve zelfwaardering. Deze laatste verbanden waren sterk wanneer er stigma werd ervaren, en zwak wanneer er geen stigma werd ervaren. SEM liet zien dat de negatieve effecten van inzicht gemodereerd worden door de hoeveelheid stigma die wordt ervaren. Een klinische implicatie is dat, wanneer pogingen worden ondernomen om het ziekte-inzicht te verbeteren, er ook aandacht moet zijn voor het ervaren stigma of de zelf-stigmatisatie.

Een andere kwestie rondom het ziekte-inzicht is dat hoewel inzicht vaak een sterke voorspeller is van ontrouw aan antipsychotische behandeling, er
11.3 Samenvatting
toch aanzienlijke inconsistentie in de literatuur is die nog niet is verklaard. In Hoofdstuk 6 hebben we de hypothese onderzocht dat problemen in het verbale geheugen een belangrijke moderator zijn voor de relatie tussen inzicht and therapietrouw. Het geheugen is namelijk een essentiële link om van intentie te komen tot gedrag. De resultaten lieten zien dat inzicht sterk gerelateerd was aan therapietrouw in patiënten zonder ernstige problemen in het verbale geheugen, maar dat er geen verband was in de patiënten met dergelijke problemen. In patiënten met een slecht verbaal geheugen lijkt de mate van therapietrouw dus niet te worden beïnvloed door het ziekte-inzicht. Wanneer zij therapie-ontrouw zijn, zijn gedragstrategieën waarschijnlijk voldoende om er iets aan te doen, zoals bijvoorbeeld het aanbieden van herinneringen, simplificatie van pil-inname of het aantal medicaties, het betrekken van familieleden in de behandeling, of contingency management zoals het aanbieden van financiële beloningen. Voor patiënten zonder geheugenproblemen met een laag inzicht kunnen ook inzicht-verhogende interventies zinvol zijn, zoals cognitieve gedragstherapie en motiverende gespreksovering.

In Hoofdstuk 7 werd de hypothese getoetst dat weinig behandelmedewerking in allochtone patiënten – zoals vaak geobserveerd – veroorzaakt wordt door een toedekkende copingstijl. Breed gedefinieerd denkt de toedekkende patiënt liever niet na over diens psychotische ervaringen tijdens herstel, terwijl de integrerende patiënt, aan de andere kant, geïnteresseerd is in diens psychose en het wenst te plaatsen in een coherent narratief. Resultaten lieten zien dat toedekken gerelateerd is aan weinig behandelmedewerking, maar niet aan een lage zelfwaardering. Echter, hoewel de 1e generatie allochtone patiënten minder meewerken met behandeling, verschilden ze niet van autochtonen in hun copingstijl of zelfwaardering, en dat geldt ook voor de 2e generatie. Concluderend bleek dat een toedekkende copingstijl voorspellend is voor een matige therapietrouw, maar dat het feit dat de meeste allochtone patiënten minder met behandeling meewerken dan autochtone patiënten niet verklaard kan worden door meer toedekken of een lagere zelfwaardering. Een lage zelfwaardering draagt mogelijk bij aan de ontwikkeling van schizofrenie in een relatief groot aantal allochtonen, maar na start van de ziekte lijkt de zelfwaardering hetzelfde te zijn als bij autochtone patiënten en niet geassocieerd met meer toedekking bij allochtone patiënten. Hun lagere medewerking met behandeling heeft mogelijk met andere factoren te maken, zoals niet-Westere ideeën over de stoornis, of een andere houding ten opzichte van het maken en nakomen van afspraken.

We waren tenslotte geïnteresseerd in de manier waarop de copingstijl van patiënten zou bijdragen aan de remissie van schizofrenie. In Hoofdstuk 8
hebben we gegevens van 103 patiënten verzameld op de gebieden van coping-stijl, inzicht, therapeutische relatie, en symptomen. Twaalf maanden later is remissie vastgesteld. Resultaten lieten zien dat het toepassen van een integrerende copingstijl de kans op remissie met 5,66 keer vergrootte (95% B.I.: 1,65-19,40). Inzicht en therapeutische relatie voegden niets toe aan de voorspelling. Ook het baseline niveau van positieve symptomen voorspelde remissie, maar dit had geen invloed op het effect van copingstijl. Deze bevindingen bieden steun voor het ontwikkelen van interventies zoals motiverende gespreksvoering en cognitieve therapie, gericht op het stimuleren van psychologische aanpassing aan een psychose.

11.3.3 Financiële prikkels om therapietrouw te verhogen

In Hoofdstuk 9 beschrijven we een pilot-studie waarin vijf patiënten, gedurende een jaar, geldelijke beloningen hebben ontvangen voor het verhogen van de medicatietrouw aan depot medicatie. Resultaten lieten zien dat het percentage geaccepteerde depot-injecties van 44% in het voorafgaande jaar steeg naar 100% in het jaar tijdens de interventie. En terwijl de patiënten gemiddeld 100,2 dagen waren opgenomen in het voorafgaande jaar, is slechts één patiënt nogmaals opgenomen tijdens het jaar van de interventie, voor 17 dagen.

11.3.4 Conclusies en adviezen

De bevindingen worden besproken in Hoofdstuk 10. De richtlijnen van de National Institute for health and Clinical Excellence (NICE, 2009) adviseren om geen gebruik te maken van enige vorm van adherence therapy in patiënten met psychose. En waarschijnlijk zal het binnenkort te verschijnen document van de Multidisciplinaire Richtlijnen voor Schizofrenie (ergens in 2010) een vergelijkbaar advies formuleren. Echter, resultaten in dit proefschrift wijzen erop dat zowel medicatietrouw als een meer algemene behandelmedewerking positief te beïnvloeden zijn door extra interventies. Een uitvoerig onderzoek van een patiënt’s individuele situatie kan bepalen wat voor type interventie effectief kan zijn in het verbeteren van de therapietrouw. Er wordt momenteel onderzoek gedaan naar specifieke strategieën in verschillende landen. Het combineren van de best-werkende interventies in een geïntegreerde aanpak, waardoor iedere patiënt een op maat gesneden behandeling krijgt om de therapietrouw te verbeteren, zou uiteindelijk misschien het beste kunnen werken. Tot nu toe is er echter onvoldoende bewijs dat interventies gericht op het verbeteren van therapietrouw daadwerkelijk resulteren in een verbeterde behandeluitkomst, en is brede implementatie van deze interventies nog niet aan de orde.
11.4 Dankwoord

Mijn dank gaat uit naar de promotoren Niels Mulder en Mark van der Gaag. Beide zijn fijne en actieve begeleiders die altijd beschikbaar waren en het nooit te druk hadden om te antwoorden op mijn vragen of om steeds binnen korte tijd de geschreven stukken te lezen en te becommentariëren. Ze hebben me ontzettend veel geleerd en gestimuleerd, zowel in het onderzoek als in de patiëntenzorg. Het is dankzij hen en hun vertrouwen in mij dat ik me op professioneel gebied heb kunnen ontwikkelen tot waar ik nu ben.

♣


♣

Alle co-auteurs van de hoofdstukken van dit proefschrift hebben een belangrijke bijdrage geleverd aan het uiteindelijke geheel, waarvoor ik ze van harte bedank.

♣

Er hebben verscheidene instellingen aan het onderzoek meegewerkt. Dit waren het Erasmus Medisch Centrum, Bavo-Europoort, Riagg Rijnmond, Delta Psy-
chiatrisch Centrum, en De Grote Rivieren. Bedankt voor alle mogelijkheden en de medewerking die aan het onderzoek zijn geboden!

♣

Farrid Maagdelijn en Jiska van Espelo, bedankt voor het meedenken en ontwerpen van de omslag van dit proefschrift.

♣

Katja Korte, dank voor alle steun en liefde.

♣

Tot slot wil ik alle patiënten bedanken die aan het onderzoek hebben deelgenomen. Ze hebben eraan meegewerkt en de behandeling ondergaan die erbij hoort. Ze hebben privé-informatie beschikbaar gesteld en moeilijke kwesties met ons besproken. Veel dank!
11.5 OVER DE AUTEUR

11.6 PUBLICATIONS

International


Chapter 11

National
# 11.7 PhD Portfolio

**Summary of PhD-training and teaching**

<table>
<thead>
<tr>
<th>Name PhD student: A.B.P. Staring</th>
<th>PhD period: May 2005 – Aug 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erasmus MC Department: Psychiatry</td>
<td>Promotor 1: Prof.dr. C.L. Mulder</td>
</tr>
<tr>
<td>Research School: O3 Research Center</td>
<td>Promotor 2: Prof.dr. M. van der Gaag</td>
</tr>
</tbody>
</table>

## 1. PhD training

<table>
<thead>
<tr>
<th>General courses</th>
<th>Year</th>
<th>Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Psychiatric Epidemiology (NIHES)</td>
<td>2006</td>
<td>26</td>
</tr>
<tr>
<td>- English scientific writing (O3 Research Centre)</td>
<td>2006-2007</td>
<td>12</td>
</tr>
<tr>
<td>- Regression Analyses (NIHES)</td>
<td>2007</td>
<td>45</td>
</tr>
<tr>
<td>- Clinical Trials (NIHES)</td>
<td>2007</td>
<td>20</td>
</tr>
<tr>
<td>- Bridging science and clinical practice (ZonMW)</td>
<td>2008</td>
<td>21</td>
</tr>
</tbody>
</table>

### Specific courses (e.g. Research school, Medical Training)

| - WHO-CIDI training, DSM-IV en ICD-10 diagnoses | 2005 | 20 |
| - Motivational interviewing | 2005 | 40 |

### Seminars and workshops

| - Seminars at O3 Research Centre, Erasmus MC | 2005-2010 | 30 |
| - Seminars at the Platform Psychiatry and Philosophy, VvP | 2009-2010 | 20 |

### Presentations

| - Various presentations at research seminars and mental health institutions | 2005-2010 | 200 |

### (Inter)national conferences

| - The Schizophrenia International Research Society Congress, Florence, Italy | 2010 | 30 |
| - Schizofrenie Congres, Zwolle (oral presentation) | 2009 | 30 |
| - The International Congress for the Psychological Treatments of Schizophrenias and other Psychoses, Kopenhagen, Denmark (two oral presentations) | 2009 | 70 |
| - Werken met moeilijke mensen. Nieuwe interventies en instrumenten in de Openbare GGz, Poortugaal (oral presentation) | 2009 | 20 |
| - Najaarscongres van de Vereniging voor Gedragstherapie en Cognitieve therapie (VGCt), Veldhoven (oral presentation) | 2008 | 20 |
| - 36e Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie, Amsterdam (oral presentation) | 2008 | 20 |
| - (F)ACT bemoeizorg-congres, Amsterdam (oral presentation) | 2008 | 20 |
| - Schizofrenie Congres, Zwolle (poster presentation) | 2007 | 30 |
| - International Congress on Schizophrenia Research, Colorado Springs, USA | 2007 | 32 |
| - Doorbraakproject Schizofrenie, Zutphen (oral presentation) | 2006 | 20 |
| - Symposium Samenwerking in behandeling, Amsterdam (oral presentation) | 2005 | 20 |

## 2. Teaching

### Supervising Master’s theses (two theses)

<table>
<thead>
<tr>
<th>Year</th>
<th>Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2008</td>
<td>100</td>
</tr>
</tbody>
</table>

| - Consultation and training for the research team of Prof.dr. P.J. Weiden at the University of Illinois in Chicago (UIC), in light of the “Cognitive Behavioural Therapy Adherence Intervention Program,” financed by the National Institute of Mental Health (NIMH, R34 MH080978). | 2009 | 50 |
| - Various courses and workshops in motivational interviewing for mental health institutions, general practitioners, and the Radbout University Nijmegen. | 2007-2010 | 100 |

**TOTAL** | 996 hours