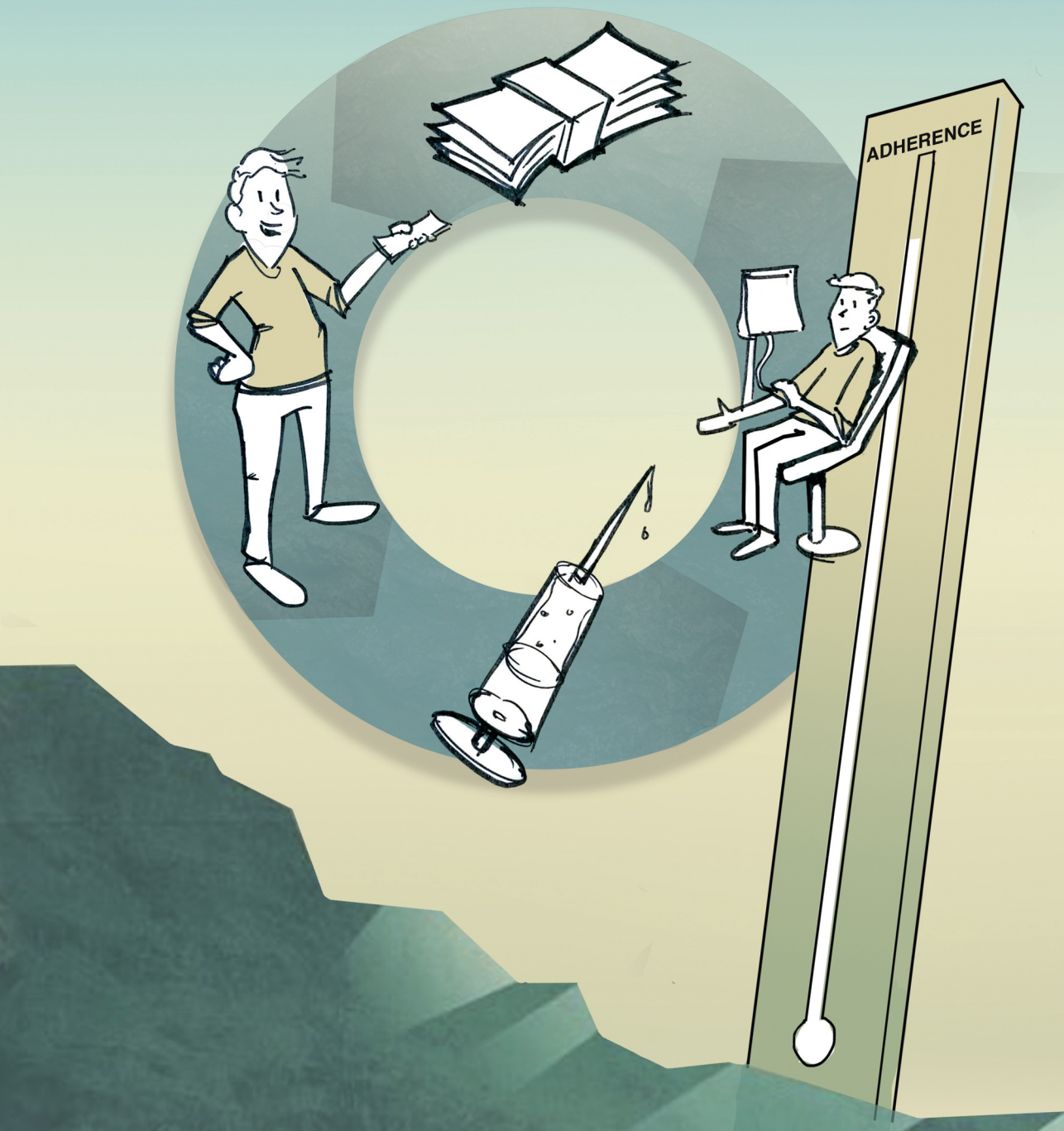
# MONEY FOR MEDICATION

## FINANCIAL INCENTIVES FOR IMPROVING ANTIPSYCHOTIC MEDICATION ADHERENCE IN PATIENTS WITH PSYCHOTIC DISORDERS




ERNST NOORDRAVEN

# Money for Medication

Financial incentives for improving antipsychotic medication adherence in patients with psychotic disorders

Ernst Leonard Noordraven

## Colofon


| | |
|---|---|
| ISBN | 978-94-6375-015-8 |
| Cover design | Mart Veeken (INK strategy) |
| Lay-out | Ilse Stronks, persoonlijkproefschrift.nl |
| Printing | Ridderprint BV \| www.ridderprint.nl |

**Money for Medication**

Financial incentives for improving antipsychotic medication adherence in patients with psychotic disorders

**Geld voor medicatie**

Financiële beloningen ter verbetering van antipsychotische medicatietrouw bij patiënten met psychotische stoornissen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

3 juli 2018 om 15.30 uur

door

Ernst Leonard Noordraven
geboren te Nijmegen

## Promotiecommissie

| | |
|---|---|
| **Promotor:** | Prof. dr. C.L. Mulder |
| **Overige leden:** | Prof. dr. S.A. Kushner<br>Prof. dr. M. van der Gaag<br>Prof. dr. I.H.A. Franken |
| **Copromotoren:** | Dr. A. I. Wierdsma<br>Dr. P. Blanken |

# Contents


| | | |
|---|---|---|
| **Chapter 1** | General introduction | 7 |
| **Chapter 2** | Study protocol "Money for Medication" | 43 |
| **Chapter 3** | Financial incentives for improving medication adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial | 65 |
| **Chapter 4** | Depot-medication compliance for patients with psychotic disorders: the importance of illness insight and treatment motivation | 87 |
| **Chapter 5** | The effect of financial incentives on patients' motivation for treatment: results of "Money for Medication", a randomised controlled trial | 101 |
| **Chapter 6** | Ethical acceptability of offering financial incentives for taking antipsychotic depot medication: patients' and clinicians' perspectives after a 12-month randomized controlled trial | 117 |
| **Chapter 7** | Medical and Social Costs after Using Financial Incentives to Improve Medication Adherence: Results of a One Year Randomised Controlled Trial | 135 |
| **Chapter 8** | General discussion and conclusions | 149 |
| **Appendices** | Summary | 166 |
| | Nederlandse samenvatting | 170 |
| | Curriculum Vitae | 175 |
| | PhD Portfolio | 176 |
| | List of publications | 179 |
| | Dankwoord | 180 |

# Chapter 1

General introduction

"All I want is compliance with my wishes, after reasonable discussion" [1].

### 1.1.1 Consequences of non-adherence

Many patients with psychotic disorders have difficulty adhering to their prescribed antipsychotic medication [2,3]. Clinicians often wish for improved medication adherence because complete or partial adherence is associated with adverse individual and societal outcomes such as inconsistent symptom control, more relapses [4–6], more (re)hospitalizations [7,8], and more suicide attempts [9,10]. In sum, patients' failure to adhere sufficiently to their prescribed medication severely reduces the effectiveness of the medical treatment of schizophrenia and interferes with therapeutic efforts [11]. This shows the need for better adherence. Reasonable discussions between patients and their clinicians are not always sufficient in order to improve adherence: there are various reasons for patients not to take their medication and interventions to improve compliance are not always effective or suitable for patients with schizophrenia.

### 1.1.2 Risk factors of non-adherence

Risk factors of non-adherence can be divided into patient-, treatment- and environmental-related factors [12]. Patient-related risk factors include poor illness insight, negative attitudes towards medication, a shorter duration of illness or comorbid substance use [13–15]. If patients experience distress by side effects from the antipsychotic medication, this is considered a treatment-related risk factor for non-adherence [16]. Environmental-related risk factors include stigma of taking medication, lack of support [17], financial problems, chaotic living situations and poor aftercare [17,18]. Together, these factors show the variety of reasons that contribute to non-adherence and illustrate why improving adherence and changing patients' behavior is often a complex and difficult task.

### 1.1.3 Interventions to improve medication adherence: a systematic review

Over the past 35 years, many interventions (e.g. adherence therapy, motivational interviewing, psychoeducation or contingency management) have been developed and tested for improving antipsychotic medication adherence among patients with psychotic disorders [19,20]. Some studies did not demonstrate efficacy in improving adherence [21–23], yet other studies did [24–26]. However, interventions that are effective in improving adherence do not always show positives effects on outcomes such as psychiatric symptoms or psychosocial functioning [22,27,28]. This is surprising, concerning the well-known correlational data on the associations between non-adherence and poor outcome [29].

Two large systematic reviews included intervention studies to improve antipsychotic medication adherence between 1980 and 2000. Zygmunt and colleagues [20] reviewed 39 studies and concluded that psychoeducational interventions without additional strategies (e.g. family therapy or behavioural management) were least effective in improving medication adherence. Integrated programs, however, which used various interventions to improve adherence found positive results. Similar results were found by Dolder and colleagues [19], who reviewed 21 studies and concluded that improvements in adherence were most effective after combinations of educational, behavioral and system-oriented interventions. Both reviews supported the idea of using an integrated treatment programme to improve adherence. The most recent review, by Barkhof and colleagues [30] included 15 randomized controlled trials conducted between 2000-2009. Their results showed that long lasting interventions with a focus on adherence were more successful at improving medication adherence than short term interventions. Adapted forms of motivational interviewing, such as compliance therapy did not show improvements in adherence rates. The authors also acknowledge the need for more individualized approaches due to the large variety of reasons associated with non-adherence.

Furthermore, a meta-analysis was done on adherence enhancing interventions in a wide range of other chronic illnesses than psychotic disorders [31]. These authors focused on studies that assessed medication adherence through electronically compiled drug dosing histories. In 79 studies it was found that patients randomized to an intervention group had an average combined adherence outcome of 74.3%, which was 14.1% higher in comparison to patients in the control group. Interestingly, however, among 57 studies measuring clinical outcomes, only eight reported a significant improvement in clinical outcome.

Finally, a recent review and meta-analysis focussed on improving adherence in patients with various disorders to various medications – not just antipsychotics – by using incentives [32]. This intervention, defined as Contingency Management (CM) [33], has demonstrated its effectiveness for improving adherence rates [34]. CM-interventions typically reinforce pre-set, well-defined and verifiable target behaviors (e.g., drug abstinence or medication intake), by providing external rewards.

In sum, recent reviews have focused mainly on which type of interventions are effective for improving medication adherence. It seems that integrated programs (combinations of educational, behavioral and system-oriented interventions) are most effective for improving adherence behavior, and that long lasting interventions are more effective than short-term interventions.

However, improving adherence is a means to an end: to achieve better patient outcomes. Knowing which interventions are more effective than others is an important first step, but

we also need to know when and how better medication adherence leads to better symptom control, improved functioning and quality of life.

### 1.1.5 Effects of interventions on adherence and clinical outcomes: a systematic review

We conducted a systematic review of randomized controlled trials (RCT's) aimed at improving adherence to antipsychotic medications and on clinical outcomes. First, we will review the effect of various psychosocial interventions on medication adherence. Second, we will focus on the effects of the interventions on clinical outcomes such as psychiatric symptoms, psychosocial functioning, and quality of life. Finally, this overview aims to explore reasons (i.e. methodological concerns) why studies find different results. All studies are described with regard to the large variety in methods used to assess adherence to antipsychotic medication, measurements of clinical outcomes, type of interventions and settings. Recommendations for future research are discussed in order to improve comparability between studies.

## 1.2 Selection methods

### 1.2.1 Eligibility criteria

To be included in the review the selection criteria were as follows: 1) a randomised controlled design was used, 2) the experimental treatment was specifically aimed at improving adherence with antipsychotic medications, 3) patients were diagnosed with a psychotic disorder for which antipsychotic medications were prescribed, 4) papers were published in a peer reviewed English written journal, and 5) only full papers (no conference abstracts) were selected.

### 1.2.2 Information resources

Literature searches were conducted using Embase.com (Medline and Embase), Medline (OvidSP), Web of science, PsycINFO, Cochrane, Pubmed publisher, and Google Scholar.

### 1.2.3 Search strategy

Literature searches were conducted using Embase.com (Medline and Embase), Medline (OvidSP), Web of science, PsycINFO, Cochrane, Pubmed publisher, and Google Scholar. The search strategies were designed by a biomedical information specialist and a psychologist. The basic search elements were medication adherence or compliance and anti-psychotic agents. These were combined with the Cochrane sensitive filter for Randomized Controlled Trials (RCTs). Each element was thoroughly translated in controlled vocabulary terms of the databases (Emtree for Embase, Medical Subject Headings for Medline and the Thesaurus of

Psychological Index Terms for PsycINFO) and in free text words in title and/or abstract. The mentioned information resources were searched from inception until September, 2017. The results were de-duplicated using the reference tool EndNote. Next, we searched within existing reviews for references that were not yet included.

### 1.2.4 Study selection

All papers were screened on titles and abstracts by two researchers (CM and AS). Those meeting the criteria were read with care (EN and AW). Differences in judgements were discussed in order to reach consensus.

## 1.3 Adherence intervention studies

### 1.3.1 Included studies

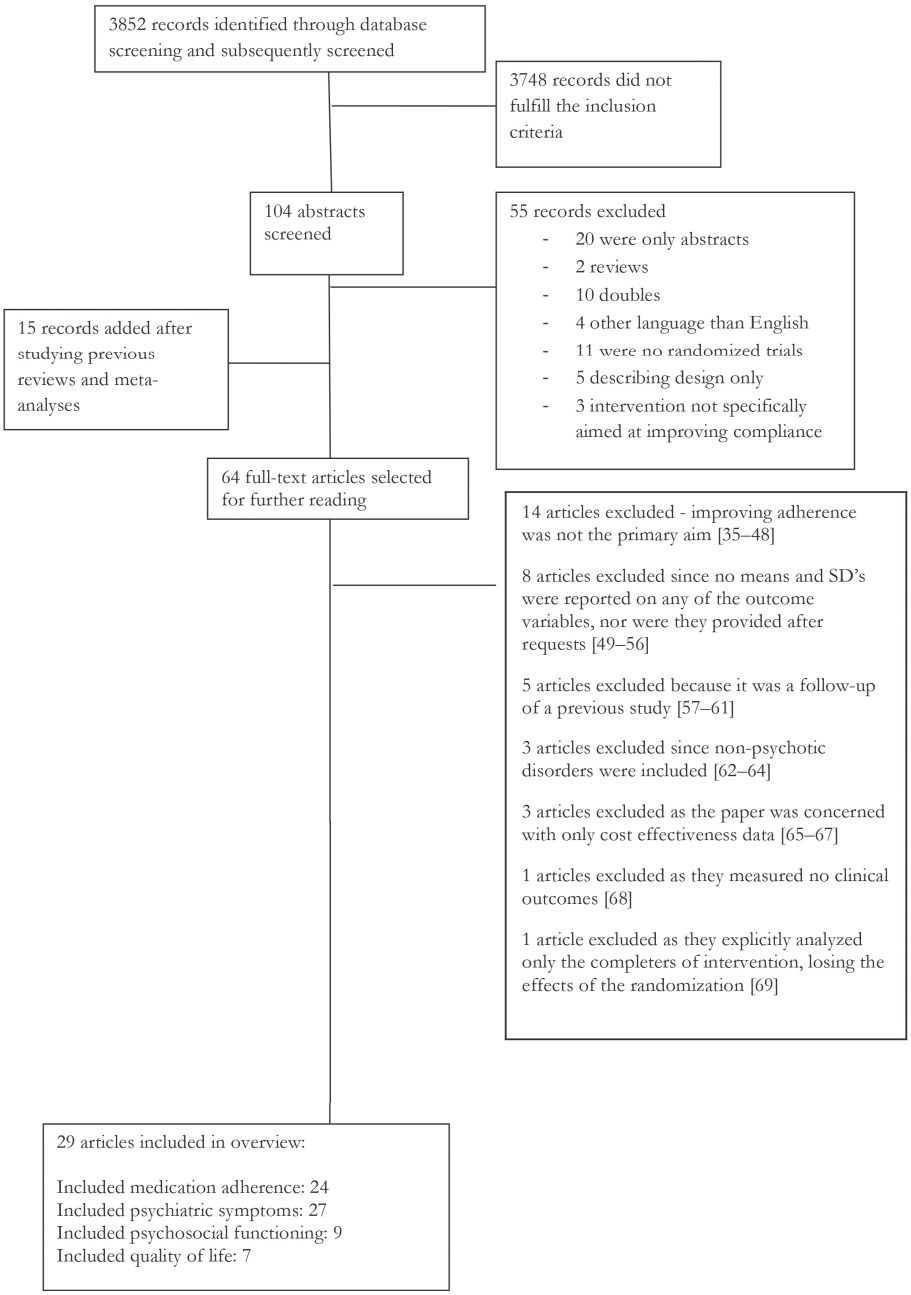
The search strategy resulted in 7116 titles: Embase.com (Medline and Embase) 2423 abstracts; Medline (OvidSP) 1669 abstracts; Web of science 1652); PsycINFO 934; Cochrane 226, Pubmed publisher 112; and Google Scholar 100. The papers were de-duplicated using the reference tool EndNote, leaving 3852 abstracts. Studies on interventions to improve adherence to antipsychotic medications were selected following the selection process as outlined in Figure 1. The selection criteria were as follows: 1) a randomised controlled design was used, 2) the experimental treatment was specifically aimed at improving adherence with antipsychotic medications, 3) patients were diagnosed with a psychotic disorder for which antipsychotic medications were prescribed, 4) papers were published in a peer reviewed English written journal, and 5) only full papers (no conference abstracts) were selected.

In total we included 29 studies, of which 24 studies were included with data on medication adherence. We verified if the study reported independent outcomes on psychiatric symptoms, psychosocial functioning and quality of life. We found that 27 studies measured psychiatric symptoms, 9 studies measured social functioning and 7 studies included quality of life.

### 1.3.2. Study characteristics

The main characteristics of the selected studies are summarized in Table 1. There is a large variety in study protocols regarding (a) type and duration of intervention, (b) methods to assess adherence to antipsychotic medication and clinical outcomes, and (c) setting and study design.

**Figure 1. Flow Chart of the selection of studies**



*Type and duration of interventions*

Some interventions are behaviour-oriented, focusing on stimuli such as financial incentives or reminders [27,70]. More complex interventions are individualized adherence therapies including or combining motivational interviewing, cognitive adaption training or psycho-education for the patient and/or family members. Such programs may have 5 to 12 sessions over a period of six to nine months. One study used a more personalized approach and offered various types of adherence therapy, depending on patients' individual situations and reasons for non-adherence [28]. Intervention periods ranged from 2 weeks [71] to 12 months [70,72,73], and follow-up periods varied from 2 months [25,74] to 2,5 years [72,75,76]. Overall, this shows that studies used relatively short-term follow-up periods.

*Assessments of adherence and clinical outcomes*

Medication adherence was assessed using patient self-reports and attitudes to medications, caregivers' reports, or more objective indicators such as blood levels, pill count, or service use records. Subjective measures included different methods, such as Medication Adherence Rating Scale (MARS) [25,77,78], Rating of Medication Compliance [79], or Register of Adherence to Treatment (RAT) [80]. Additionally, different semi-structured or structured interviews were used to assess medication compliance [28,72,73]. The Medication Adherence Questionnaire (MAQ) [81] was often used and labelled as the nearest to gold-standard [82]. Objective measures included pill counts [83], electronic monitoring [27], plasma drug levels [75], and the Medication Possession Ratio (MPR) [70,84,85].

Psychiatric symptoms were measured using either of three types of questionnaires: the Positive and Negative Syndrome Scales (PANSS) [86], the Brief Psychiatric rating Scale (BPRS) [87], and the Global Clinical Impression Scale (CGI) [88]. BPRS and PANSS scores are very different in number of items (16 versus 30), and use different methods for assessing positive and negative symptoms. In addition, relating absolute PANSS/BPRS scores to relative improvements on the CGI seems to be affected by patient- and methodological factors (i.e. illness severity at baseline and percentage cut-offs to define response in a trial) [29].

Few studies investigated other outcomes than psychiatric symptoms. Level of functioning was measured with questionnaires that used comparable scoring procedures, including the Global Assessment of Functioning (GAS) [73], the Social and Occupational Functioning Scale (SOFAS) [27,83], and the Global Assessment Scale (GAS) [75,89]. Lower scores (e.g. 0-10) indicate 'the need for constant supervision to prevent hurting self or others, and no attempts to maintain minimal personal hygiene' [90]. However, definitions of 'quality of life' varied across studies and were assessed using generic questionnaires. The Quality of Well-Being Scale (QWB) [91] consists of 71 items and measures health and wellbeing over the past three days on four

domains (i.e. physical activities, social activities, mobility, and symptoms). The EQ-5D [28,80] measures 5 domains (i.e. mobility, self-care, usual activities, pain, and anxiety or depression), which can be scored 1,2 or 3 (indicating 'no', 'mild' or 'severe' problems). Patients' health status is defined by a 5 digit number, potentially creating 243 different health states. In the general population, health state evaluations by the EQ-5D have shown good psychometric properties [92], and the instrument is brief and cognitively simple to conduct.

Furthermore, study settings varied with regard to patient population, sample size, and time of assessments. Patients admitted to psychiatric hospitals or clinics may be in higher need for care than outpatients, and can have acute psychotic episodes that might be caused by prolonged periods of non-adherence. Additionally, care-as-usual (control group) is assumed to be different for the in- and outpatient setting. Sample sizes ranged from less than 30 patients per treatment arm in nine studies [8,26,48,71,84,89,93] to 100 patients or more in five studies [21,75,76,79,80]. Finally, different follow-up periods make it difficult to compare outcomes. Adherence levels are sometimes measured immediately after the intervention period, even though interventions may need some processing time to be effective.

Thus, heterogeneity of the study population and heterogeneity of methods contribute to the large heterogeneity of results across studies.

### 1.3.3 Results on adherence and clinical outcomes

*Effects on adherence*

Of the 24 studies that assessed medication adherence, 13 studies (54%) reported a significant positive effect of the intervention and 11 studies (46%) found no significant differences. More specific, 5 of these studies (21%) found improvements in favour of the intervention group although effect sizes remained non significant [71,77,84,94,95] and 6 studies (25%) reported no differences between the intervention and control group [21–23,74,79,93]. All differences are described in Table 1 for each outcome measure.

For each study we summarized the results based on their effects on adherence (positive, negative or not assessed) in combination with the effects on psychiatric symptoms and social functioning or quality of life. Because only 2 studies assed both of these outcomes -and none of the studies showed positive outcomes for functioning and negatives result for quality of life or vice versa)- we combined the effects of these outcomes (Table 2).

*Effects of clinical outcomes*

Of the 13 intervention studies that improved medication adherence, 12 studies also assessed psychiatric symptoms. In total, only 4 of these studies (33%) significantly reduced psychotic symptoms, 4 studies showed improvements in the right direction although non-significant

**Table 1. Characteristics of the selected studies**

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh$^+$ | Symp$^+$ | Func$^+$ | QoL$^+$ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Anderson et al. (2010) [74] | 26 | Intervention group: Adherence Therapy Control group: TAU | PETIT, PANSS | 8 weekly sessions (between 20-60 minutes) | 8 weeks | - | - | x | x | Adherence Therapy=TAU. *Psychiatric symptoms showed no significant differences, but improved for both groups. The clinical level of positive symptoms for the PANSS changed for the AT group, decreasing 22% from baseline to follow up.* |
| Barkhof et al. (2013) [23] | 114 | Intervention group: Motivational Interviewing. Control group: Health Education | MAQ, PANSS, CGI | 26 weeks (5-8 sessions within 26 weeks, between 20-45 minutes) | 6 and 12 months | - | - | x | x | Motivational Interviewing=Health Education. *No differences on psychiatric symptoms (both groups showed improvements). Hospitalisation rates were n.s. lower in MI group (27% vs. 40%). Overall, 39% of the identified sample refused to participate.* |
| Beebe et al. (2016) [77] | 140 | Intervention group: Telephone reminders Control group: TAU | MARS, PANSS | 12 weeks (1 reminder per week) | 3 months | + | + | x | x | Medication adherence was higher and *psychiatric symptoms improved (both non-significant). Patients were recruited from one study site and showed high refusal rates.* |
| Bormann et al. (2015) [101] | 70 | Intervention group: Adherence Therapy Control group: TAU | PANSS, GAF | 8 weekly sessions (between 23-57 minutes) | 26 weeks | x | ++ | + | x | No measures of adherence. *Significant improvement on symptoms. AT fidelity was not measured and only administered by one therapist. Patients were included after acute exacerbation.* |
| Cavezza et al. (2013) [25] | 48 | Intervention group: Adherence Therapy Control group: Health Education | MARS, BPRS | 8 weekly sessions (between 30-50 minutes) | 2 months | ++ | + | x | x | Adherence Therapy>TAU *No effect on psychiatric symptoms (both groups showed improvements). Patients were recruited from a forensic psychiatric hospital.* |

**Table 1. Continued**

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh$^+$ | Symp$^+$ | Func$^+$ | QoL$^+$ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Chien et al. (2016) [78] | 134 | Intervention group: Adherence Therapy<br>Control group: TAU | ARS, PANSS, SLOF | 12 weeks (2-h sessions every 2 weeks) | 6 and 18 months | ++ | ++ | ++ | x | Adherence therapy>TAU *Significant improvements on psychiatric symptoms and functioning. Sign. reduction of duration of hospitalisations. Selective sampling and outcome measures were reported by patients.* |
| Farooq et al. (2011) [73] | 110 | Intervention group: Adherence via family members (STOP)<br>Control group: TAU | Adherence Interview (5-scale) PANSS, GAF | 12 months, continuous supervision and support during study period by appointed family member | 12 months | ++ | ++ | ++ | x | STOP>TAU *Significant improvement in psychiatric symptoms and functioning (LAMI country). Antipsychotics were freely distributed (high costs normally in Peshawar region and low social economic standards) and adherence was subjectively measured.* |
| Gray et al. (2004) [94] | 72 | Intervention group: Medication management training<br>Control group: TAU | Compliance Scale, PANSS | 10 weeks (day-release, 80 hours in total) | 6 months | + | ++ | x | x | Medication management training=TAU *Significant improvement in psychiatric symptoms. Incomplete outcome data for 26% of the patients.* |
| Gray et al. (2006) [21] | 371 | Intervention group: Adherence Therapy<br>Control group: Health education | MAQ, BPRS, SF36 | 8 weekly sessions (between 30-50 minutes) | 12 months | - | - | x | - | Adherence Therapy=Health Education *No effect on psychiatric symptoms or quality of life. A possible selection bias of patients being cooperative and already adherent. Therapist were not familiar with the included patients.* |
| Hamman et al. (2006) [97] | 107 | Intervention group: Shared decision making<br>Control group: TAU | Compliance Scale, PANSS, CGI, GAF | 1 session (30-60 minutes, working through the decision aid book) | 18 months | x | - | x | x | No measures of adherence. *No effect on psychiatric symptoms. Perceived involvement increased. Cluster randomized within state hospitals and broad inclusion criteria.* |

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh+ | Symp+ | Func+ | QoL+ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Kemp et al. (1996) [24] | 47 | Intervention group: Compliance Therapy Control group: non-specific counselling | Compliance Scale, BPRS, GAF | 3 weeks (4-6 sessions, twice per week, between 20-60 minutes) | 3 and 6 months | ++ | + | ++ | x | Compliance Therapy>Counselling *Significant improvement in psychiatric symptoms and global functioning. Possible observer bias, ratings on compliance and functioning were made by a research psychiatrist not blind to the intervention.* |
| Kopelowicz et al. (2012) [72] | 121 | Intervention group: Multifamily group-focussing (FMG-adherence) Control group: TAU | Treatment Compliance Interview, BPRS | 12 months (2 sessions per month, 90 minutes) | 12, 18, 24 months | ++ | + | x | x | FMG-adherence>TAU *No effect on psychiatric symptoms. Significant decrease in hospitalisation rates. Around 26% dropped out immediately after baseline assessment.* |
| Maneesakorn et al. (2007) [98] | 32 | Intervention group: Adherence Therapy Control group: TAU | PANSS, GAF | 8 weekly sessions (between 15-60 minutes) | 9 weeks | x | ++ | - | x | No measures of adherence. *Significant improvement in psychiatric symptoms, but not for global functioning. Only one therapist provided AT within a small sample size.* |
| Mittal et al. (2009) [84] | 40 | Intervention group: Antipsychotic adherence intervention (AAI) Control group: TAU | MPR, PANSS, GAF | 4 months (9 sessions; 3 daily sessions, 3 weekly sessions and 3 monthly telephone reminders) | 4 months | + | - | x | - | Antipsychotic Adherence intervention=TAU *No improvements psychiatric symptoms, quality of life. Veterans-only sample and inpatient recruitment and outpatient follow-up.* |
| Montes et al. (2010) [80] | 865 | Intervention group: Phone call reminders Control group: TAU | RAT, CGI-SCH, EQ-5D | 3 months (1 phone call per month) | 4 months | ++ | ++ | x | + | Phone call reminders>TAU *Significant improvement in psychiatric symptoms and and considerable improvement in quality of life. Large sample size, although design was not blind for assessing adherence.* |

**Table 1. Continued**

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh$^+$ | Symp$^+$ | Func$^+$ | QoL$^+$ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| O'Donnell et al. (2003) [93] | 56 | Intervention group: Compliance Therapy Control group: non-specific counselling | Clinical Interview, PANSS, GAF, Heinrichs Scale | 5 weekly sessions (between 30-60 minutes) | 12 months | + | - | - | - | Compliance Therapy=Control group *No effect on psychiatric symptoms, quality of life, global functioning, insight and attitudes to treatment (both groups improve). Baseline compliance was 35% (intervention) vs 19% (TAU) and increased to 43% and 54%.* |
| Omranifard (2012) [99] | 72 | Intervention group: Compliance therapy Control group: TAU | PANSS, GAF, Heincrichs Scale | 6 months (8 sessions; 30-60 minutes, first every 2 weeks, then monthly for 6 months) | 3 and 6 months | x | ++ | ++ | ++ | No measures of adherence. *Significant improvements on psychiatric symptoms, functioning and quality of life. For all outcome measures, the intervention group performed significantly better already at baseline.* |
| Pitschel-Walz et al. (2006) [75] | 160 | Intervention group: Psycho-education for the patient and family Control group: TAU | 4-point adherence scale, BPRS, GAF | 5 months (4 weekly and 4 monthly sessions psychoeducation with systematic family involvement) | 12 and 24 months | ++ | ++ | ++ | x | Psychoeducation>TAU *Significant reduction of hospitalisation rates, improved psychiatric symptoms and social functioning. Possible selection bias as few patients were included compared to screened and patients needed to have relatives caring for them* |
| Priebe et al. (2013) [70] | 131 | Intervention group: Financial incentives Control group: TAU | MPR, CGI, DIALOG | 12 months (Financial incentives for each depot injections taken) | 12 months | ++ | - | x | ++ | Financial; incentives>TAU *Significant improvement for QoL, no effect on psychiatric symptom and hospital admissions. Only non-adherent patients were selected on depot medication.* |

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh$^+$ | Symp$^+$ | Func$^+$ | QoL$^+$ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Ran et al. (2003) [79] | 229 | Intervention groups: Psycho-education for family members (FIG) or Drug Treatment. Control group: TAU | 3-point rating of adherence, General Psychiatric Interview | 9 months (9 sessions; 3 monthly family psychoeducation, between 1,5-3 hr and 3 family workshops every 3 months) | 9 months | ++ | x | x | x | Psychoeducation>TAU *Significant reduction of relapse rates between FI&MI and TAU. However, TAU provided no mental health care services.* |
| Schulz et al. (2013) [22] | 123 | Intervention group: Adherence Therapy Control group: TAU | CDR, PANSS, GAF | 2 months (8 weekly sessions) | 3 months | - | ++ | - | x | Adherence Therapy=TAU *Psychiatric symptoms improved significantly. No effects on treatment attitudes or functioning. About half of the patients assessed for eligibility refused to participate.* |
| Skarsholm (2014) [95] | 70 | Intervention group: system oriented therapy Reference group: individual compliance therapy | Compliance scale, PANSS, GAF | 6 weekly sessions and 3 booster sessions (between 30-45 minutes). | 6 months | + | + | - | x | System oriented approach=Compliance therapy. *Also, non-significant improvements for symptoms. Patients only received small amounts of individual compliance therapy. Potential bias due to unblinded treatment and differences in providing therapy due to level of experience.* |
| Staring et al. (2010) [28] | 105 | Intervention group: Treatment Adherence Therapy Control group: TAU | Combined measure of adherence, PANSS, EQ-5D | 6 months (between 1-2 sessions per month) | 6 and 12 months | ++ | - | x | - | Treatment Adherence Therapy>TAU *Significant improvement in service engagement. Psychiatric symptoms and quality of life did not improve. Clinicians were not blind to treatment allocation and attention was unevenly distributed between the groups.* |

**Table 1. Continued**

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh$^+$ | Symp$^+$ | Func$^+$ | QoL$^+$ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Tsang et al. (2005) [71] | 47 | Intervention group: Compliance Therapy Programme (CTP) Control group: TAU | Self-report drug compliance, BPRS | 2 weeks (5 group sessions; 2-3 times per week) | 6 months | + | + | x | x | Compliance therapy Programme=TAU *Both groups demonstrated improved adherence rates and symptom scores. Only male patients with schizophrenia were included.* |
| Uzenoff et al. (2008) [100] | 19 | Intervention group: Adherence Coping Education (ACE) Control group: TAU | Medication Adherence by patient report, PANSS, QLS | 6 months (14 sessions, between 30-45 minutes; 6 weekly and 8 biweekly sessions) | 6 months | x | ++ | x | - | Ceiling effect medication adherence for both groups, dropped from analyses. *Significant decrease in psychiatric symptoms and improvements in attitudes toward treatment. Small sample size and significant differences on baseline PANSS scores.* |
| Valenstein et al. (2011) [85] | 115 | Intervention group: Meds-Help Control group: TAU | MPR, PANSS, QWB | 12 months (continuous Meds-Help support during study period) | 6 and 12 months | ++ | - | x | - | Meds-Help>TAU *No significant differences in symptoms, quality of life and patient satisfaction. Only veterans were included and patients had lower levels of psychotic symptoms, as patients with borderline personality disorder were also included.* |
| Velligan et al. (2008) [96] | 58 | Intervention groups: Full-CAT or Pharm-CAT (cognitive adaption training) Control group: TAU | Pill counts, BPRS, SOFAS | 9 months Pharm-Cat (cognitive adaption training) | 6, 9, 12 and 15 months | ++ | - | + | x | Pharm-CAT>TAU, also during follow-up. *Full CAT improved patients' functional outcomes, but not during follow-up. Average illness duration around 10 years and high number of inpatients were not randomized.* |

| Study | N | Design | Outcome measures~ | Duration of intervention | Follow-up time (after baseline) | Adh+ | Symp+ | Func+ | QoL+ | Adherence outcome and comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Velligan et al. (2012) [27] | 71 | Intervention groups: Pharm-CAT (cognitive adaption training) or Med-E-Monitoring (MM) Control group: TAU | Electronic monitoring, BPRS, SOFAS | 9 months (Pharm-Cat, home visits once per week 30 minutes); (MM, every 3 days checking website by clinicians) | 3, 6 and 9 months | ++ | - | - | x | Pharm-CAT and MedE>TAU. *No improvements on clinical outcomes. Higher drop out of patients from the MM group than the Pharm-Cat.* |
| Zhou et al. (2015) | 201 | Intervention: Self management training Control group: TAU | MAQ | 6 months (weekly self management skills training) followed by monthly booster sessions for 24 months | 30 months | ++ | x | x | x | Self management training >TAU. *The intervention group showed significantly lower (1.9%) relapse rates than the control group (14.3%) over the 30 months follow-up.* |

~Abbreviations: MAQ (Medication Adherence Questionnaire); MARS (Medication Adherence Rating Scale); ARS (Adherence Rating Scale), MPR (Medication Possession Ratio); RAT (Register of Adherence to Treatment); PETIT (Personal Evaluation of Transitions in Treatment, CDR (Concentration to Dose Ratio); PANSS (Positive and Negative Syndrome Scale); BPRS (Brief Psychiatric Rating Scale); CGI (Clinical Global Impression Scale); GAF (Global Assessment of Functioning); SLOF (Specific Level of Functioning Questionnaire); SOFAS (Social and Occupational Functioning Scale); QLS (Quality of Life Scale)
+Adherence; Symptoms; Functioning; Quality of Life: ++ (significant difference) + (improvement in the right direction but non-significant); - (no significant difference); x (no measurement)

(33%), and 4 studies showed no differences between the intervention and control group (33%). Additionally, one study reported positive outcomes for psychotic symptoms [22], despite negative findings on medication adherence.

Furthermore, of the four studies that showed improved medication adherence in combination with reduced psychotic symptoms, three studies (75%) also reported better social functioning or improved Quality of Life [73,75,78]. Finally, two of the remaining eight studies -those with improved medication adherence without a significant effect on psychotic symptoms- showed improved functioning [89,96].

Although all studies aimed to improve medication adherence, five studies assessed clinical improvement instead, since patient recovery was regarded as primary concern [97–101]. Four of these studies (80%) reported a significant reduction of psychotic symptoms, although only one of these studies (25%) also reported improved social functioning and better quality of life.

**Table 2. Overview of possible 11 combinations of study results, grouped by effects on adherence[+]**

| | **Adherence** | **Symptoms** | **Functioning/QoL** | **Studies (N)** |
|---|---|---|---|---|
| **0** | - | NA | NA | 1 |
| **1** | - | - | NA | 5 |
| **2** | - | - | - | 4 |
| **3** | - | + | - | 1 |
| | | | | (**11** *subtotal*) |
| **4** | + | NA | NA | 1 |
| **5** | + | - | - | 3 |
| **6** | + | - | + | 1 |
| **7** | + | + | NA | 2 |
| **8** | + | + | + | 6 |
| | | | | (**13** *subtotal*) |
| **9** | NA | - | NA | 1 |
| **10** | NA | + | - | 3 |
| **11** | NA | + | + | 1 |
| | | | | (**5** *subtotal*) |

[+] (NA)=Not assessed; (-)=no effect (+)=improvement

## 1.4 Discussion

In total, 29 randomized controlled trials between 1996 and 2017 were included which primarily aimed to improve adherence. Out of the 24 studies that assessed medication adherence, 13 studies (54%) found that adherence levels improved for patients receiving psycho-, social-, or behavorial interventions. Psychiatric symptoms improved for only 33% of the studies that showed better medication adherence. Furthermore, few studies also assessed social functioning and quality of life. In these studies, better symptom control was accompanied by better functional outcomes and higher ratings on quality of life. Together, these results indicate that only some patients with psychotic disorders may benefit from better intake of their antipsychotic medication, as it can improve their psychiatric symptoms and could also lead to better social and role functioning, and quality of life.

However, when comparing all studies, excessive variation occurred on many levels regarding: the assessment of outcomes, adherence problems and symptom severity at baseline, patient settings, intervention types, and duration of intervention- and follow-up periods. This large heterogeneity makes it difficult to draw definite conclusions about the effectiveness of these studies and to interpret the relationships between adherence and clinical outcomes. Better understanding of this heterogeneity is needed to improve comparability between intervention studies and to develop better defined and more homogenous study protocols.

### 1.4.1 Effects on medication adherence

*1.4.1.1 Study design*

Three studies reported no effects of interventions aimed to improve medication adherence in patients with psychotic disorders [21–23], and two studies found within-patients improvements but no statistically significant differences between the intervention and control group [71,93]. There are several reasons why intervention studies sometimes show negative results.

One obvious reason is the challenge in conducting adherence trials to recruit non-adherent patients. Convenience sampling is often the only option in clinical trials in severely ill patients, but may lead to samples biased to treatment adherence. In the failed trials, rates of refusal ranged between 40% [21,30,93] and 80% [74]. Rates for loss to follow-up were around 15%.

In addition, some studies used health education [21,23] or non-specific counseling [93] instead of treatment as usual as active control, thus to some degree leveling the difference between the intervention and control group.

Finally, follow-up periods of 2-3 months may have been too short to detect a positive effect on adherence [22,74].

*1.4.1.2 Measurement of medication adherence*

Many different methods were used for assessing levels of adherence, both objective (i.e. pill counts, plasma levels, electronic monitoring, MPR) and subjective (i.e. MAQ, MARS, RAT, CRS, DAI). While each method has its own benefits, it remains impossible to compare blood levels with pill counts or patient rated compliance scales. Subjective measures seem to overestimate levels of adherence [102,103], whereas objective measures are often expensive or inaccurate; pills might be thrown away [104], individual differences occur when using plasma levels or patients might falsely be classified as adherent or non-adherent [105], and patients might be reluctant to repeatedly give blood samples [18] which only represent a temporary reflection of adherence behavior [106]. Clearly, there is no gold-standard for measuring adherence, although we would recommend using the Medication Possession Ratio (MPR) [107].

Compared with other subjective measures of adherence and following the 'Expert Consensus Guideline Series' [18] we would argue that the Medication Possession Ratio (MPR) seems a relatively accurate, reliable and efficient method to determine adherence levels in patients using depot medication. The MPR is an objective method -based on pharmacy records- which is not affected by subjective judgement, and has the benefit of assessing adherence behavior over time, instead of using one time point. It calculates a percentage within a time period, in which the amount of medication taken is divided by the total prescribed dosages. Patients can obtain an MPR between 0% and 100%, whereas the cut-off between adherence and non-adherence has been pre-defined at 80%. It has been argued, though, that the MPR cannot take into account the gap size in defining discontinuation of medication [108]. However, these outcomes can be calculated by the MPR, defined as 'time-to-discontinuation' or 'slippage' [70,109].

In sum, subjective measures of adherence and physician reports tend to overestimate adherence levels [110]. From the available objective measures, the MPR seems most suitable but ofcourse restricted to depot medication.

Of the 13 intervention studies that improved medication adherence, 12 studies also assessed psychiatric symptoms. In total, only 4 of these studies (33%) significantly reduced psychotic symptoms, 4 studies showed improvements in the right direction although non-significant (33%), and 4 studies showed no differences between the intervention and control group (33%). Additionally, one study reported positive outcomes for psychotic symptoms [22], despite negative findings on medication adherence.

### 1.4.3 Effects on psychiatric symptoms

In total, 12 studies improved medication adherence and also assessed psychiatric symptoms. Four of these studies (33%) significantly reduced psychotic symptoms [73,75,78,80], whereas the remaining 8 studies showed either improvements in the right direction (although non-significant) [25,70,72,89], or reported no differences between the intervention and control group [27,28,85,96]. For those studies without effects on adherence, only one study found improvements in psychiatric symptoms, although ceiling effects and selection bias were likely to have influenced these results [22]. Furthermore, five studies used psychiatric symptoms as their primary outcome instead of medication adherence. All of these studies aimed to improve medication adherence and 4 studies showed improved psychiatric symptoms (although it remains unclear whether improvements in adherence were actually obtained) [98–101].

### 1.4.4 Measurement of psychiatric symptoms

The most used symptom rating scales are the Brief Psychiatric Rating Scale (BPRS) [87], the Positive and Negative Syndrome Scale (PANSS) [86] and the Clinical Global Impression Scale (CGI) [88]. Each method has its own scoring procedures and uses various items for measuring the same outcome. This makes it difficult to draw conclusions on which questionnaire is preferred to use in clinical trials. In short, the BPRS is sensitive to detect symptom changes and has shown high interrater reliability [111], although the measurement of negative symptoms has been criticised as it uses few negative syndrome items [112].

The PANSS uses a more broad range of positive, negative and general psychopathology scales and shows consistency in individual patients' scores over time [113]. However, factor analyses revealed that some items load on more than one factor or syndrome scale (negative, positive, general scales) [114]. Although these questionnaires have been validated, the BPRS and PANSS scores are very different in number of items (16 vs. 30), and use different methods for assessing positive and negative symptoms. For example, the average patient with schizophrenia entering a clinical trial scores 33 when using the BPRS, and 91 with the PANSS [115].

The CGI for schizophrenia has shown strong validity and correlates well with scores on the PANSS or BPRS [116–118]. Also, it is brief and easy to administer for clinicians. However, it appears to lack high interrater reliability and relating absolute PANSS/BPRS scores to relative improvements on the CGI seems to be affected by patient- and methodological factors (i.e. illness severity at baseline and percentage cut-offs to define response in a trial) [117].

Furthermore, it has been found that patients with schizophrenia are more likely to judge smaller symptom changes as improvements, even though such differences may seem less important for trained interviewers [119]. In order to detect clinically meaningful changes,

researchers and clinicians must be aware why studies sometimes fail to find improvements in symptom severity.

### 1.4.5 Defining clinical response

First, the time needed to observe clinical benefits of improved adherence is unknown. It may be that follow-up periods have been too short in the RCT's included in the review (between 4 and 24 months) to detect clinical benefits of improved adherence.

Second, ratings on the BPRS or PANSS capture only a limited timeframe and might not be representative for the symptomatology over time. More frequent assessments could more adequately display the natural course of psychotic symptoms during intervention and follow-up periods. For instance, patients could provide information each week or month about their psychiatric symptoms by using mobile devices [120].

Third, it remains unclear how much of their prescribed antipsychotics patients need to take before their symptoms will improve. Being fully compliant might not have much added benefit for symptom control compared to taking 80% of prescribed medication. Additionally, responsiveness to antipsychotics varies greatly between patients and type of antipsychotics [116,121]. In practice, prescribing the right type and amount of antipsychotics takes time as clinicians may need to adjust their medication regimen if patients show no improvements. Together, it seems unclear what level of adherence is most beneficial for reducing psychiatric symptoms and individual variations influence the responsiveness on antipsychotic drug treatment.

Fourth, inpatient-recruitment and out-patient follow-up assessments [83,84] made it more difficult to detect differences between the intervention- and control groups. Going from an in-patient to outpatient setting inherently indicates better symptoms. If so, receiving an additional intervention (aiming to improve adherence) might not have more added benefit than the control group.

Fifth, symptom severity at baseline was relatively mild within the included patient samples, leaving few room for improvement (floor effect) [27,83]. Often, it is difficult to include patients who are suffering from severe psychotic symptoms or who are completely non-adherent. Moreover, patients showing poor adherence might not take their medications because they are not responding to antipsychotics.

Finally, relatively small sample sizes (between 40 and 120 patients), indicated lack of power to detect statistical differences. Importantly, symptoms did not get worse during any of the studies.

Together, these reasons provide better understanding why studies sometimes fail to improve symptoms and shows the need for clinicians and researchers to focus on in depth studies on the associations between (non-)adherence and clinical outcomes.

### 1.4.6 Functioning and quality of life

Although only 9 studies measured these outcomes, 4 studies found that improvements in psychiatric symptoms were accompanied by improvements in functioning [24,73,75,78]. These results seem to indicate that social functioning improves when symptoms get better. Only for one study, increased social and role functioning was achieved without showing better symptoms [96]. However, baseline symptoms were already low in this sample but did not worsen. This is important, since improved psychosocial functioning might increase stress for patients, which in return could worsen their psychiatric symptoms.

Two studies found that improved psychiatric symptoms was accompanied by improved ratings of quality of life [70,80]. In two other studies showing no improvements in psychiatric symptoms, also quality of life did not improve [28,85]. Only one study achieved better quality of life ratings without significantly improving symptoms [70]. It seems that improving quality of life is difficult to achieve when suffering from psychotic symptoms. However, definitions of 'quality of life' varied greatly across studies, and was assessed using generic questionnaires.

### 1.4.7 Measurement of functioning and quality of life

Levels of functioning were measured with the Global Assessment of Functioning (GAF) [73], the Social and Occupational Functioning Scale (SOFAS) [27,83], and the Global Assessment Scale (GAS) [24,75]. All patients scores ranged between 0 and 100, with higher scores (e.g. 91-100) reflecting 'no symptoms, superior functioning in a wide range of activities' and lower scores (e.g. 0-10) indicating 'the need for constant supervision to prevent hurting self or others, and no attempts to maintain minimal personal hygiene' [90]. Although these scores seem comparable, construct validity is often low as 'functioning' is a complex construct, domains that are addressed are not always the same, and assessments only occurred at one point in time.

Quality of life was measured with the EQ-5D and QWB. In the general population, health state evaluations by the EQ-5D have shown good psychometric properties [92], and the instrument is brief and cognitively simple to conduct. However, it has been found that the EQ-5D shows moderate ceiling effects in patients with psychotic disorders and has poor responsiveness to clinical changes in mental health [122,123]. Since the answering options are limited and somewhat non-specific (i.e. 3 options on 5 domains), more elaborate health states are difficult to obtain. Also, assessing general health states for the past year based on

information from only 1 time point remains limited, as this construct changes over time during the course of clinical treatment [124].

In addition, the Quality of Well-Being Scale (QWB) [91] consists of 71 items and measures health and wellbeing over the past three days on four domains (i.e. physical activities, social activities, mobility, and symptoms). The large number of items seem better capable of measuring a wide range of complaints than the EQ-5D. However, the type of domains are similar and scores correlate well with the EQ-5D [125]. Determining which domains should be included to assess quality of life in people with mental health problems is an ongoing debate, although recently [126] six domains were identified for this purpose: a feeling of being in control, autonomy and choice, self-perception, sense of belonging, engagement in activities, and hope or optimism.

Overall, it seems that better quality of life was only achieved after improving symptoms. It remains unclear whether this improvement can solely be attributed to better symptom control, since scores on these questionnaires reflect generic measures which may not be suitable for patient with psychotic disorders [127]. Also, there seem to be different opinions about the definition of quality of life and how they should be measured [128]. Some researchers focus on total life experiences, whereas others focus on the absence of disease or social wellbeing [129]. Furthermore, assessing general health states is affected by patients' affective mood when judging how satisfied they are with their lives [130]. This makes it difficult to reach consensus on a universal definition and assessment method of quality of life. A meta-analysis on quality of life in patients with schizophrenia revealed that a high level of psychopathology was the strongest contributor to poor quality of life [131] and that negative and positive symptoms are weakly correlated to quality of life in patients with a short duration of illness. Therefore, future studies should take into account the clinical setting (inpatient vs. outpatient), symptom severity during inclusion, and illness duration. Also, longitudinal studies with repeated measures seem preferable, since the concept of quality of life is complex, contains multiple domains and may change during various phases of clinical treatment.

## 1.5 Implications and pitfalls

Researchers must be aware of possible selection bias when designing clinical trials. Inclusion of severely ill patients is difficult for most intervention studies, often leaving little room for improvement. This can be affected by the type of study setting (in- or outpatient). If symptom severity at baseline is low or mild, it remains important to monitor that symptoms do not deteriorate, even when no improvements are observed. Assessing symptom change

or improvement is often done relative to baseline conditions and it has been shown that antipsychotics are effective for patient of all severity levels [132]. This is often done within randomized trials and appears to reflect a change over time, although studies often only have two assessments. This means that symptom development or progression over time cannot be adequately detected. Therefore, we would recommend assessing these questionnaires more frequently. Repeated measures could better display the natural course of psychotic symptoms during intervention and follow-up periods. This could benefit our judgment on whether improvements actually occurred, instead of focusing solely on statistical differences between two measures. For instance, clinicians could assess PANSS scores monthly, or use mobile devices where patients could give weekly feedback [120].

Additionally, defining clinical response remains difficult since responsiveness to antipsychotics varies greatly between patients and type of antipsychotics [116,121]. In practice, prescribing the right type and amount of antipsychotics takes time, as clinicians may need to adjust their medication regimen if patients show no improvements. For these reasons, and because patients often suffer from a chronicle illness, future studies should aim for longer follow-up periods (>2 years).

Finally, researchers and clinicians should be aware that interventions aiming to improve medication adherence may not influence complex outcomes such as functioning or quality of life. For example, it seems unlikely that monthly telephone calls aimed to improve medication adherence, by itself will help patients to take up social roles again or experience less psychosomatic problems in everyday life. Therefore, expectations about intervention studies should be clearly defined beforehand and not be overestimated. Improving complex outcomes may require multiple interventions focusing on various domains, and are unlikely to improve solely by simplistic and short term interventions which are primarily targeted to change adherence behavior.

## 1.6 Conclusions

About 50% of the intervention studies in this overview significantly improved medication adherence among patients with psychotic disorders. Only 33% of these studies seemed to obtain improved psychiatric symptoms as well. However, large heterogeneity remains an important limitation and there are several reasons why studies sometimes fail to find significant improvements (e.g. various assessment methods, short term intervention- and follow-up periods, small sample sizes, low baseline symptom severity, or individual variations in responsiveness to antipsychotic drug treatment). Comparability between studies could improve

if future studies strive for more homogenous measures of adherence. Furthermore, longer intervention- and follow-up periods are recommended in combination with more frequent assessments over time in order to capture a more accurate course of illness for patients with psychotic disorders. Finally, interventions primarily aimed to improve medication adherence seem insufficient to improve complex outcomes such as social functioning or quality of life.

## 1.7 Aims and outline of this thesis

The overall objective of the current thesis is to study the effectiveness of a behavorial intervention (i.e. financial incentives) which showed promising results for improving adherence to antipsychotic depot medication. In 2013, Priebe and colleagues [70] offered financial incentives to 141 non-adherent patients with psychotic disorders. After 12 months, mean adherence to antipsychotic depot medication was significantly better in patients receiving financial incentives than in those in the control group. It remains unclear what happens prospectively to patients' medication adherence when financial incentives are offered not only to non-adherent patients, but also to adherent patients and what happens after financial incentives are no longer offered. Within the Netherlands, the effectiveness of this intervention has only been studied for five patients with psychotic disorders. For these reasons, the randomized controlled trial "Money for Medication" was conducted.

The first aim was to provide an overview **(this chapter)** of randomized controlled trials (RCT's) aimed at improving adherence to antipsychotic medications. All studies are described with regard to the large variety in methods used to assess medication adherence and clinical outcomes, type of interventions and settings. Recommendations for future research are discussed in order to improve comparability between studies.

The second aim was to assess the effectiveness of providing financial incentives to improve adherence to maintenance treatment in patients with psychotic disorders. The details of the study protocol 'Money for Medication' are described in **Chapter 2**. The results of this randomized controlled trial are presented in **Chapter 3**, which shows the medication adherence rates and clinical outcomes for the intervention and control group after the 12 month intervention- and 18 month follow-up period.

The third aim was to gain more understanding about the role of motivation for treatment, given its impact on functional outcomes in schizophrenia [133]. Therefore, as described in **Chapter 4**, we explored the associations between patients' motivation for treatment, level of illness insight, and medication adherence. In **Chapter 5**, we described the effects of financial

incentives on patients' intrinsic and extrinsic motivation for treatment, after the intervention- and follow-up period.

Providing financial incentives to promote adherence to antipsychotic depot medication is controversial, with many ethical dilemmas. Therefore, the fourth aim of this thesis was to explore the ethical aspects of this intervention **(Chapter 6).** In this study, we compared several ethical concerns that patients and clinicians expressed after using this intervention in daily practice. These ethical concerns were based on the four principle approach by Beauchamp and Childress (2012) [134], and categorized into patient autonomy, beneficence, non-maleficence and justice.

Finally, we wanted to know whether providing financial incentives was a cost-effective intervention in our study **(Chapter 7)** and the thesis ends with a summary and discussion of the findings, strenghts and limitations, and implications for clinical practice (**Chapter 8**).

## References


1. Churchill WS. The Gathering Storm. Boston, USA: Houghton Mifflin Company; 1948.
2. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res [Internet]. 2010 Apr 30 [cited 2013 Aug 7];176(2–3):109–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20185182
3. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee T a, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry [Internet]. 2006 Oct;67(10):1542–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17107245
4. Llorca P-M. Partial compliance in schizophrenia and the impact on patient outcomes. Psychiatry Res [Internet]. 2008 Nov 30 [cited 2013 Aug 23];161(2):235–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18849080
5. Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. Eur Neuropsychopharmacol [Internet]. 2007 Mar [cited 2013 Aug 23];17(4):235–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17137759
6. Marder SR. Overview of Partial Compliance. J Clin Psychiatry. 2003;64(16):3–9.
7. Valenstein M, Copeland L a, Blow FC, McCarthy JF, Zeber JE, Gillon L, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care [Internet]. 2002 Aug [cited 2013 Aug 23];40(8):630–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12187177
8. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial Compliance and Risk of Rehospitalization Among California Medicaid Patients With Schizophrenia. Psychiatr Serv [Internet]. 2004;55(8):886–91. Available from: http://dx.doi.org/10.1176/appi.ps.55.8.886
9. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol [Internet]. 2010 Nov [cited 2013 Aug 20];24(4 Suppl):81–90. Available from: http://www.pubmedcentral.nih.gov/articlerender.cgi?artid=2951591&tool=pmcentrez&rendertype=abstract
10. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide : systematic review of risk factors. Br J Psychiatry. 2005;187:9–20.
11. Valenstein M, Blow FC, Copeland L a, McCarthy JF, Zeber JE, Gillon L, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophr Bull [Internet]. 2004 Jan;30(2):255–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15279044
12. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol [Internet]. 2013 Aug [cited 2014 Jan 21];3(4):200–18. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3805432&tool=pmcentrez&rendertype=abstract
13. Westermeyer J. Comorbid schizophrenia and substance abuse: a review of epidemiology and course. Am J Addict [Internet]. 2006 [cited 2013 Aug 16];15(5):345–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16966190
14. Ascher-svanum H, Ph D, Zhu B, Faries D, Lacro JP, Pharm D, et al. A Prospective Study of Risk Factors for Nonadherence With Antipsychotic Medication in the Treatment of Schizophrenia. J Clin Psychiatry. 2006;67(7):1114–23.
15. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. Schizophr Res [Internet]. 2009 Feb [cited 2014 Feb 10];107(2–3):213–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18849150

16. Löffler W, Kilian R, Toumi M, Angermeyer MC. Schizophrenic Patients' Subjective Reasons for Compliance and Noncompliance with Neuroleptic Treatment. Pharmacopsychiatry. 2003;36:105–12.
17. Hudson TJ, Owen RR, Thrush CR, Han X, Pyne JM, Thapa P, et al. A pilot study of barriers to medication adherence in schizophrenia. J Clin Psychiatry [Internet]. 2004 Feb;65(2):211–6. Available from: http://europepmc.org/abstract/MED/15003075
18. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The Expert Consensus Guideline Series: Adherence Problems in Patients with Serious and Persistent Mental Illness. J Clin Psychiatry. 2009;70(4):1–46.
19. Dolder CR, Lacro JP, Leckband S, Jeste D V. Interventions to improve antipsychotic medication adherence: review of recent literature. J Clin Psychopharmacol. 2003;23(4):389–99.
20. Annette Zygmunt PD, Mark Olfson MD, Carol A. Boyer PD, David Mechanic P. Interventions to Improve Medication Adherence in Schizophrenia. Am J Psychiatry. 2002;159(10):1653–64.
21. Gray R, Leese M, Bindman J, Becker T, Burti L, David A, et al. Adherence therapy for people with schizophrenia European multicentre randomised controlled trial. Br J Psychiatry. 2006;189(6):508–14.
22. Schulz M, Gray R, Spiekermann A, Abderhalden C, Behrens J, Driessen M. Adherence therapy following an acute episode of schizophrenia: a multi-centre randomised controlled trial. Schizophr Res [Internet]. 2013 May [cited 2014 Oct 20];146(1–3):59–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23452506
23. Barkhof E, Meijer CJ, de Sonneville LMJ, Linszen DH, de Haan L. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. Schizophr Bull [Internet]. 2013 Nov [cited 2014 Oct 20];39(6):1242–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24072808
24. Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients : Randomised controlled trial. Br Med J. 1996;312:345–9.
25. Cavezza C, Aurora M, Ogloff JRP. The effects of an adherence therapy approach in a secure forensic hospital : a randomised controlled trial. J Forens Psychiatry Psychol. 2013;24(4):458–78.
26. Gray R, Wykes T, Edmonds M, Leese M, Gournay K. Effect of a medication management training package for nurses on clinical outcomes for patients with schizophrenia: Cluster randomised controlled trial. Br J Psychiatry. 2004;185(AUG.):157–62.
27. Velligan D, Mintz J, Maples N, Xueying L, Gajewski S, Carr H, et al. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. Schizophr Bull [Internet]. 2012 Sep [cited 2014 Oct 15];39(5):999–1007. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3756784&tool=pmcentrez&rendertype=abstract
28. Staring ABP, Van der Gaag M, Koopmans GT, Selten JP, Van Beveren JM, Hengeveld MW, et al. Treatment adherence therapy in people with psychotic disorders: randomised controlled trial. Br J Psychiatry [Internet]. 2010 Dec [cited 2014 Oct 20];197(6):448–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21119150
29. Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. J Clin Psychiatry [Internet]. 2006;67 Suppl 5(5):3–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16822090
30. Barkhof E, Meijer CJ, de Sonneville LMJ, Linszen DH, de Haan L. Interventions to improve adherence to antipsychotic medication in patients with schizophrenia-A review of the past decade. Eur Psychiatry [Internet]. 2012;27(1):9–18. Available from: http://dx.doi.org/10.1016/j.eurpsy.2011.02.005
31. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: A systematic literature review and meta-analysis. Drugs. 2013;73(6):545–62.

32. DeFulio A, Silverman K. The use of incentives to reinforce medication adherence. Prev Med (Baltim) [Internet]. 2012 Nov [cited 2013 Aug 19];55 Suppl:S86-94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22580095
33. Petry NM. A comprehensive guide to the application of contingency management procedures in clinical settings. Drug Alcohol Depend [Internet]. 2000;58(1–2):9–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10669051
34. Petry NM, Rash CJ, Byrne S, Ashraf S, White WB. Financial reinforcers for improving medication adherence: Findings from a meta-analysis. Am J Med. 2012;125(9):888–96.
35. Atkinson JM, Coia DA, Gilmour WH, Harper JP. The impact of education groups for people with schizophrenia on social functioning and quality of life. Br J Psychiatry [Internet]. 1996;168(2):199–204. Available from: http://search.proquest.com/docview/78381345?accountid=14568%5Cnhttp://jabega.uma.es:4550/resserv?genre=article&issn=00071250&title=The+British+journal+of+psychiatry+%3A+the+journal+of+mental+science&volume=168&issue=2&date=1996-02-01&atitle=The+impact+of+
36. Buchkremer G, Klingberg S, Holle R, Schulze Mönking H, Hornung WP. Psychoeducational psychotherapy for schizophrenic patients and their key relatives or care-givers: results of a 2-year follow-up. Acta Psychiatr Scand [Internet]. 1997;96(6):483–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9421346
37. Fung KMT, Tsang HWH, Cheung W ming. Randomized controlled trial of the self-stigma reduction program among individuals with schizophrenia. Psychiatry Res [Internet]. 2011;189(2):208–14. Available from: http://dx.doi.org/10.1016/j.psychres.2011.02.013
38. Girón M, Fernández-Yañez A, Mañá-Alvarenga S, Molina-Habas A, Nolasco A, Gómez-Beneyto M. Efficacy and effectiveness of individual family intervention on social and clinical functioning and family burden in severe schizophrenia: a 2-year randomized controlled study. Psychol Med [Internet]. 2010;40(1):73–84. Available from: http://www.journals.cambridge.org/abstract_S0033291709006126
39. Leff JP, Berkowitz R, Shavit a, Strachan a, Glass I, Vaughn CE. A trial of family therapy versus relatives' groups for schizophrenia. Br J Psychiatry. 1989;154:58–66.
40. Merinder L, Viuff A, Laugesen H, Clemmensen K, Misfelt S, Espensen B. Patient and relative education in community psychiatry: a randomised controlled trial regarding its effectiveness. Soc Psychiatry Psychiatr Epidemiol. 1999;34(6):287–94.
41. Morken G, Grawe RW, Widen JH. Effects of Integrated Treatment on Antipsychotic Medication Adherence in a Randomized Trial in Recent-Onset Schizophrenia. J Clin Psychiatry [Internet]. 2007;68(4):566–71. Available from: http://article.psychiatrist.com/?ContentType=START&ID=10003013
42. Rathod S, Kingdon D, Smith P, Turkington D. Insight into schizophrenia: The effects of cognitive behavioural therapy on the components of insight and association with sociodemographics - Data on a previously published randomised controlled trial. Schizophr Res. 2005;74(2–3):211–9.
43. Tarrier N, Lewis S, Haddock G, Bentall R, Drake R, Kinderman P, et al. Cognitive-behavioural therapy in first-episode and early schizophrenia : 18-month follow-up of a randomised controlled trial Cognitive behavioural therapy in first-episode and early schizophrenia. Brit. 2004;184:231–9.
44. Telles C, Karno M, Mintz J, Paz G, Arias M, Tucker D, et al. Immigrant families coping with schizophrenia: behavioral family intervention versus case management with a low-income Spanish-speaking population. Br J Psychiatry. 1995;167:473–9.
45. VALENCIA M, RASCON ML, JUAREZ F, MUROW E. A psychosocial skills training approach in Mexican out-patients with schizophrenia. Psychol Med [Internet]. 2007;37(10):1393–402. Available from: http://www.journals.cambridge.org/abstract_S0033291707000657
46. Xiang M, Ran M, Li S. A controlled evaluation of psychoeducational family intervention in a rural Chinese community. Br J Psychiatry [Internet]. 1994;165(4):544–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7804673

47. Xiong W, Phillips MR, Hu X, Wang R, Dai Q, Kleinman J, et al. Family-based intervention for schizophrenic patients in China. A randomised controlled trial. Br J Psychiatry. 1994;165(2):239–47.
48. Lee S-H, Choi TK, Suh S, Kim YW, Kim B, Lee E, et al. Effectiveness of a psychosocial intervention for relapse prevention in patients with schizophrenia receiving risperidone via long-acting injection. Psychiatry Res [Internet]. 2010 Feb 28 [cited 2014 Oct 12];175(3):195–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20022120
49. Boczkowski JA, Zeichner A, DeSanto N. Neuroleptic compliance among chronic schizophrenic outpatients: An intervention outcome report. J Consult Clin Psychol [Internet]. 1985;53(5):666–71. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/0022-006X.53.5.666
50. Kozuki Y, Schepp KG. Visual-feedback therapy for antipsychotic medication adherence. Int Clin Psychopharmacol. 2006;21:57–61.
51. Kelly GR, Scott JE. Medication Compliance and Health Education among Outpatients with Chronic Mental Disorders. Med. 1990;28(12):1181–97.
52. Macpherson R, Jerrom B, Hughes A. Relationship between insight, educational background and cognition in schizophrenia. Br J Psychiatry. 1996;91(5):718–22.
53. Razali MS, Yahya H. Compliance with treatment in schizophrenia: a drug intervention program in a developing country. Acta Psychiatr Scand. 1995;91(5):331–5.
54. Streicker S, Amdur M, Dincin J. Educating patients about psychiatric medications: Failure to enhance compliance. Psychosoc Rehabil J. 1986;9(4):15–28.
55. Youssef FA. Adherence to therapy in psychiatric patients: an empirical investigation. Int J Nurs Stud. 1984;21(1):51–7.
56. Dahan S, Behrbalk P, Stolovy T, Greenberger C. Improving Adherence in Hospitalized Patients Diagnosed With Schizophrenia: An Integrative One-on-One Intervention. Arch Psychiatr Nurs [Internet]. 2016;30(6):660–5. Available from: http://dx.doi.org/10.1016/j.apnu.2016.03.002
57. Kemp R, Kirov G, Everitt B, Hayward P, David a. Randomised controlled trial of compliance therapy. 18-month follow-up. Br J Psychiatry [Internet]. 1998 May 1 [cited 2014 Oct 20];172(5):413–9. Available from: http://bjp.rcpsych.org/cgi/doi/10.1192/bjp.172.5.413
58. Hamann J, Cohen R, Ph D, Leucht S, Busch R, Math D, et al. Shared Decision Making and Long-Term Outcome in Schizophrenia Treatment. J Clin Psychiatry. 2007;68(July):993–8.
59. Hornung W, Schonauer K, Feldmann R, Monking H. Medication-related attitudes of chronic schizophrenic patients. A follow-up study after psycho-educational intervention. Psychiatr Prax. 1998;25(1):25–8.
60. Beebe LH, Smith K, Phillips C. Effect of a Telephone Intervention on Measures of Psychiatric and Nonpsychiatric Medication Adherence in Outpatients With Schizophrenia Spectrum Disorders. J Psychosoc Nurs Ment Health Serv [Internet]. 2017;55(1):29–36. Available from: http://www.healio.com/doiresolver?doi=10.3928/02793695-20170119-04
61. Chien WT, Mui JH, Cheung EF, Gray R. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomized controlled trial. Trials [Internet]. 2015;16(1):270. Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0785-z
62. Cramer JA, Rosenheck R. Enhancing medication compliance for people with serious mental illness. J Nerv Ment Dis. 1999;187(1):53–5.
63. Robinson GL, Gilbertson AD, Litwack L. The effects of a psychiatric patient education to medication program on post-discharge compliance. Psychiatr Q. 1986;58(2):113–8.
64. Seltzer A, Roncari I, Garfinkel P. Effect of Patient Education on Medication Compliance. Can J Psychiatry. 1980;25(8):638–45.
65. Gilden J, Staring a. BP, der Gaag M Van, Mulder CL. Does Treatment Adherence Therapy reduce expense of healthcare use in patients with psychotic disorders? Cost-minimization analysis in a randomized controlled trial. Schizophr Res [Internet]. 2011;133(1–3):47–53. Available from: http://dx.doi.org/10.1016/j.schres.2011.09.025

66. Healey A, Knapp M, Astin J, Beecham J, Kemp R, Kirov G, et al. Cost-effectiveness evaluation of compliance therapy for people with psychosis. Br J Psychiatry. 1998;172(5):420–4.
67. Patel A, McCrone P, Leese M, Amaddeo F, Tansella M, Kilian R, et al. Cost-effectiveness of adherence therapy versus health education for people with schizophrenia: randomised controlled trial in four European countries. Cost Eff Resour Alloc [Internet]. 2013;11(1):12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3668244&tool=pmcentrez&rendertype=abstract
68. Schirmer UB, Steinert T, Flammer E, Borbé R. Skills-based medication training program for patients with schizophrenic disorders : a rater-blind randomized controlled trial. Patient Prefer Adherence. 2015;1(9):541–9.
69. Hornung WP, Kieserg A, Feldmann R, Buchkremer G. Psychoeducational training for schizophrenic patients: Background, procedure and empirical findings. Patient Educ Couns. 1996;29(3):257–68.
70. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, et al. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics : cluster randomised controlled trial. BMJ [Internet]. 2013;345:f5847(347). Available from: http://dx.doi.org/doi:10.1136/bmj.f5847
71. Tsang HW, Wong TK. The effects of a compliance therapy programme on Chinese male patients with schizophrenia. Asian J Nurs Stud. 2005;8(2):47–61.
72. Kopelowicz A, Zarate R, Wallace CJ, Liberman RP, Lopez SR, Mintz J. The Ability of Multifamily Groups to Improve Treatment Adherence in Mexican Americans With Schizophrenia. Arch Gen Psychiatry. 2012;69(3):265–73.
73. Farooq S, Nazar Z, Irfan M, Akhter J, Gul E, Irfan U, et al. Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS). Br J Psychiatry [Internet]. 2011 Dec [cited 2014 Oct 20];199(6):467–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22130748
74. Anderson KH, Ford S, Robson D, Cassis J, Rodrigues C, Gray R. An exploratory, randomized controlled trial of adherence therapy for people with schizophrenia. Int J Ment Health Nurs [Internet]. 2010 Oct [cited 2014 Oct 20];19(5):340–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20887608
75. Pitschel-Walz G, Engel RR, Ph D, Wagner M, Kissling W. Psychoeducation and Compliance in the Treatment of Schizophrenia: Results of the Munich Psychosis Information Project Study. J Clin Psychiatry. 2006;67(3):443–52.
76. Zhou B, Gu Y. Effect of self-management training on adherence to medications among community residents with chronic schizophrenia : a single- blind randomized controlled trial in Shanghai , China. 2015;26(6):332–8.
77. Beebe LH, Smith K, Phillips C. Effect of a Telephone Intervention Upon Self-Reported Medication Adherence and Self-Efficacy in Outpatients With Schizophrenia Spectrum Disorders (SSDs). Issues Ment Health Nurs. 2016;37(10):708–14.
78. Chien WT, Mui J, Gray R, Cheung E. Adherence therapy versus routine psychiatric care for people with schizophrenia spectrum disorders: a randomised controlled trial. BMC Psychiatry [Internet]. 2016;16(1):42. Available from: http://www.biomedcentral.com/1471-244X/16/42
79. Ran M-S, Xiang M-Z, Chan CL-W, Leff J, Simpson P, Huang M-S, et al. Effectiveness of psychoeducational intervention for rural Chinese families experiencing schizophrenia--a randomised controlled trial. Soc Psychiatry Psychiatr Epidemiol [Internet]. 2003 Feb [cited 2014 Oct 20];38(2):69–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12563548
80. Montes JM, Maurino J, Diez T, Saiz-Ruiz J. Telephone-based nursing strategy to improve adherence to antipsychotic treatment in schizophrenia: A controlled trial. Int J Psychiatry Clin Pract [Internet]. 2010 Nov [cited 2014 Oct 20];14(4):274–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24917439

81. Morisky D, Green L, Levine D. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67–74.
82. Culig J, Leppee M. From Morisky to Hill-bone; self-reports scales for measuring adherence to medication. Coll Antropol. 2014;38(1):55–62.
83. Velligan DI, Diamond PM, Mintz J, Maples N, Li X, Zeber J, et al. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. Schizophr Bull [Internet]. 2008 May [cited 2014 Jan 27];34(3):483–93. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2632420&tool=pmcentrez&rendertype=abstract
84. Mittal D, Owen RR, Lacro JP, Landes RD, Edlund M, Valenstein M, et al. Antipsychotic Adherence Intervention for Veterans over Forty with Schizophrenia : Results of a Pilot Study. Clin Schizophr Relat Psychoses. 2009;4(1):317–25.
85. Valenstein M, Kavanagh J, Lee T, Reilly P, Dalack GW, Grabowski J, et al. Using a pharmacy-based intervention to improve antipsychotic adherence among patients with serious mental illness. Schizophr Bull [Internet]. 2011 Jul [cited 2014 Oct 11];37(4):727–36. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3122282&tool=pmcentrez&rendertype=abstract
86. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale ( PANSS ) for Schizophrenia. Schizophr Bull. 1987;13(2):261–72.
87. Overall J, Gorham D. The Brief Psychiatric Rating Scale. Psychol reports. 1962;10(3):799–812.
88. Guy W, Bonato R. Clinical Global Impression (CGI). Natl Inst Ment Heal. 1970;1(12):121–6.
89. Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients : randomised controlled trial. BMJ. 1996;312(February):345–9.
90. Endicott J, Robert L, Spitzer M. The Global Assessment Scale. Arch Gen Psychiatry. 1976;33(1):766–71.
91. Patterson TL, Kaplan RM, Grant I, Semple SJ, Moscona S, Koch WL, et al. Quality of well-being in late-life psychosis. Psychiatry Res. 1996;63(2–3):169–81.
92. Rabin R, Charro F. EQ-SD: a measure of health status from. Ann Med. 2001;33(5):337–43.
93. O'Donnell C, Donohoe G, Sharkey L, Owens N, Migone M, Harries R, et al. Compliance therapy: a randomised controlled trial in schizophrenia. BMJ. 2003;327(October):1–4.
94. Gray R, Wykes T, Edmonds M, Leese M, Gournay K. Effect of a medication management training package for nurses on clinical outcomes for patients with schizophrenia: cluster randomised controlled trial. Br J Psychiatry [Internet]. 2004 Aug [cited 2014 Oct 20];185:157–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15286068
95. Skarsholm H, Stoevring H, Nielsen B. Effect of a System-Oriented Intervention on Compliance Problems in Schizophrenia : A Pragmatic Controlled Trial. Schizophr Res Treatment. 2014;1:1–8.
96. Velligan DI, Diamond PM, Mintz J, Maples N, Li X, Zeber J, et al. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. Schizophr Bull [Internet]. 2008 May [cited 2014 Oct 16];34(3):483–93. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2632420&tool=pmcentrez&rendertype=abstract
97. Hamann J, Langer B, Winkler V, Busch R, Cohen R, Leucht S, et al. Shared decision making for in-patients with schizophrenia. Acta Psychiatr Scand [Internet]. 2006 Oct [cited 2014 Oct 20];114(4):265–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16968364
98. Maneesakorn S, Robson D, Gournay K, Gray R. An RCT of adherence therapy for people with schizophrenia in Chiang Mai, Thailand. J Clin Nurs [Internet]. 2007 Mar [cited 2014 Oct 20];16(7):1302–12. Available from: http://doi.wiley.com/10.1111/j.1365-2702.2006.01786.x
99. Omranifard V, Karahmadi M, Jannesari Z, Maracy M. Efficacy of modified compliance therapy for schizophrenia patients. J Res Med Sci. 2012;17(2):259–64.

100. Uzenoff SR, Perkins DO, Hamer RM, Wiesen CA, Penn DL. A preliminary trial of adherence-coping-education (ACE) therapy for early psychosis. J Nerv Ment Dis. 2008;196(7):572–5.
101. von Bormann S, Robson D, Gray R. Adherence therapy following acute exacerbation of schizophrenia: A randomised controlled trial in Thailand. Int J Soc Psychiatry [Internet]. 2015;61(1):3–9. Available from: http://journals.sagepub.com/doi/10.1177/0020764014529099
102. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. Strategies for addressing adherence problems in patients with serious and persistent mental illness: recommendations from the expert consensus guidelines. J Psychiatr Pract [Internet]. 2010 Sep [cited 2013 Aug 23];16(5):306–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20859108
103. Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, et al. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res. 2005;133(2–3):129–33.
104. Kane JM, Kishimoto T, Correll CU. DISORDERS : DETERMINANTS AND MANAGEMENT Non-adherence to medication in patients with psychotic disorders : epidemiology , contributing factors and management strategies. World Psychiatry. 2013;12(October):216–26.
105. Yalcin-Siedentopf N, Wartelsteiner F, Kaufmann A, Biedermann F, Edlinger M, Kemmler G, et al. Measuring adherence to medication in schizophrenia: The relationship between attitudes toward drug therapy and plasma levels of new-generation antipsychotics. Int J Neuropsychopharmacol. 2015;18(5):1–7.
106. Masand PS, Roca M, Turner MS, Kane JM. Partial adherence to antipsychotic medication impacts the course of illness in patients with schizophrenia: a review. Prim Care Companion J Clin Psychiatry [Internet]. 2009 Jan [cited 2013 Aug 23];11(4):147–54. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2736032&tool=pmcentrez&rendertype=abstract
107. Sclar DA, Pharm B, Chin A, Skaer TL, Okamoto MP, Nakahiro, Randall K, et al. Effect of Health Education in Promoting Prescription Refill Compliance Among Patients with Hypertension. Clin Ther. 1991;13(4):489–95.
108. Ren XS, Herz L, Qian S, Smith E, Kazis LE. Measurement of treatment adherence with antipsychotic agents in patients with schizophrenia. Neuropsychiatr Dis Treat. 2009;5(1):491–8.
109. Noordraven EL, Audier CH, Staring A, Wierdsma AI, Blanken P, van der Hoorn B, et al. Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. BMC Psychiatry [Internet]. 2014 Dec 2 [cited 2015 Feb 3];14(1):343. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4258939&tool=pmcentrez&rendertype=abstract
110. Stephenson JJ, Tuncelli O, Gu T, Eisenberg D, Panish J, Crivera C, et al. Adherence to oral second-generation antipsychotic medications in patients with schizophrenia and bipolar disorder: Physicians' perceptions of adherence vs. pharmacy claims. Int J Clin Pract. 2012;66(6):565–73.
111. Overall J, Gorham D. The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertaining and scaling. Psychopharmacol Bull. 1988;24(1):97–9.
112. Eckert SL, Diamond PM, Miller AL, Velligan DI, Funderburg LG, True JE. A comparison of instrument sensitivity to negative symptom change. Psychiatry Res. 1996;63(1):67–75.
113. Mortimer AM, Mortimer ANNM. Symptom rating scales and outcome in schizophrenia REVIEW ARTICLE AUTHOR ' S PROOF S ymptom rating scales and outcome in schizophrenia. 2012;1.
114. Van den Oord EJCG, Rujescu D, Robles JR, Giegling I, Birrell C, Bukszár J, et al. Factor structure and external validity of the PANSS revisited. Schizophr Res [Internet]. 2006 Feb 28 [cited 2013 Aug 23];82(2–3):213–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16229988

115. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ. 2000;321(7273):1371–6.
116. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry. 2006;163(4):743–5.
117. Leucht S, Kane JM, Etschel E, Kissling W, Hamann J, Engel RR. Linking the PANSS, BPRS, and CGI: clinical implications. Neuropsychopharmacology [Internet]. 2006 Oct [cited 2013 Aug 23];31(10):2318–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16823384
118. JM H, SA K, S O, D N, K R, A F, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand. 2003;416:16–23.
119. Hermes ED, Sokoloff DM, Scott Stroup T, Rosenheck RA. Minimum clinically important difference in the Positive and Negative Syndrome Scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). J Clin Psychiatry. 2012;73(4):526–32.
120. Ben-Zeev D, McHugo GJ, Xie H, Dobbins K, Young MA. Comparing retrospective reports to real-time/real-place mobile assessments in individuals with schizophrenia and a nonclinical comparison group. Schizophr Bull. 2012;38(3):396–404.
121. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Zhou W, et al. Early Response to Antipsychotic Drug Therapy as a Clinical Marker of Subsequent Response in the Treatment of Schizophrenia. Neuropsychopharmacology [Internet]. 2010;35(2):581–90. Available from: http://www.nature.com/doifinder/10.1038/npp.2009.164
122. Payakachat N, Ali M., Tilford JM. Can The EQ-5D Detect Meaningful Change? A Systematic Review. Pharmacoeconomics. 2015;33(11):95–121.
123. Brazier J. Is the EQ-5D fit for purpose in mental health? Br J Psychiatry. 2010;197(5):348–9.
124. Bernhard J, Lowy A, Mathys N, Herrmann R, Hurny C. Health related quality of life: a changing construct? Qual Life Res [Internet]. 2004;13(7):1187–97. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15473497%5Cnhttp://www.springerlink.com/content/q4rm6188282608w5/fulltext.pdf
125. Boonen A, van der Heijde D, Landewé R, van Tubergen A, Mielants H, Dougados M, et al. How do the EQ-5D, SF-6D and the well-being rating scale compare in patients with ankylosing spondylitis? Ann Rheum Dis. 2007;66(6):771–7.
126. Connell J, Brazier J, O'Cathain A, Lloyd-Jones M, Paisley S. Quality of life of people with mental health problems: a synthesis of qualitative research. Health Qual Life Outcomes [Internet]. 2012;10(1):138. Available from: http://hqlo.biomedcentral.com/articles/10.1186/1477-7525-10-138
127. Papaioannou D, Brazier J, Parry G. How valid and responsive are generic health status measures, such as EQ-5D and SF-36, in Schizophrenia? A systematic review. Value Heal [Internet]. 2011;14(6):907–20. Available from: http://dx.doi.org/10.1016/j.jval.2011.04.006
128. Katschnig H. Quality of life in mental disorders: challenges for research and clinical practice. World Psychiatry [Internet]. 2006;5(3):139–45. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1636133&tool=pmcentrez&rendertype=abstract
129. Bergner M, Bobbit R, Carter W, Gilson B. The Sickness Impact Profile: development and final revision of a health status measure. Med Care. 1981;19(8):787–805.
130. Pukrop R, Schlaak V, Möller-Leimkühler AM, Albus M, Czernik A, Klosterkötter J, et al. Reliability and validity of Quality of Life assessed by the Short-Form 36 and the Modular System for Quality of Life in patients with schizophrenia and patients with depression. Psychiatry Res. 2003;119(1–2):63–79.
131. Eack SM, Newhill CE. Psychiatric symptoms and quality of life in schizophrenia: A meta-analysis. Schizophr Bull. 2007;33(5):1225–37.

132. Furukawa TA, Levine SZ, Tanaka S, Goldberg Y, Samara M, Davis JM, et al. Initial severity of schizophrenia and efficacy of antipsychotics: Participant-level meta-analysis of 6 placebo-controlled studies. JAMA Psychiatry. 2015;72(1):14–21.
133. Medalia A, Brekke J. In search of a theoretical structure for understanding motivation in schizophrenia. Schizophr Bull [Internet]. 2010 Sep [cited 2015 Feb 6];36(5):912–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2930333&tool=pmcentrez&rendertype=abstract
134. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York, Oxford: Oxford University Press; 2012. 1-480 p.

# Chapter 2

## Study protocol for Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders

Ernst L Noordraven
Charlotte H Audier
Anton BP Staring
Andre I Wierdsma
Peter Blanken
Bas EA van der Hoorn
Leona Hakkaart-van Roijen
Cornelis L Mulder

*BMC Psychiatry 2014, 14:343.*

## Abstract

### Background

Non-adherence with antipsychotic medication is a frequently occurring problem, particularly among patients with psychotic disorders. Prior research has generally shown encouraging results for interventions based on 'Contingency Management' (CM), in which desirable behaviour is encouraged by providing rewards contingent upon the behaviour. However, little is known about the application of CM on medication adherence in patients with psychotic disorders. An earlier pilot-study by our study group showed promising results in reducing admission days and increasing adherence. The current study is a randomized controlled trial concerning the effectiveness of a CM procedure called 'Money for Medication' (M4M), aimed at improving adherence with antipsychotic depot medication in psychotic disorder patients.

### Methods/Design

Outpatients (n =168) with a psychotic disorder will be randomly assigned to either the experimental group (n =84), receiving a financial reward for each accepted antipsychotic medication depot, or the control group (n =84), receiving treatment as usual without financial rewards. Patients are included regardless of their previous adherence. The intervention has a duration of twelve months. During the subsequent six months follow-up, the effects of discontinuing the intervention on depot acceptance will be assessed.

The primary goal of this study is to assess the effectiveness of providing financial incentives for improving adherence with antipsychotic depot medication (during and after the intervention). The primary outcome measure is the percentage of accepted depots in comparison to prescription. Secondary, we will consider alternative measures of medication acceptance, i.e. the longest period of uninterrupted depot acceptance and the time expired before depot is taken. Additionally, the effectiveness of the experimental intervention will be assessed in terms of psychosocial functioning, substance use, medication side-effects, quality of life, motivation, cost-utility and patients' and clinicians' attitudes towards M4M.

### Discussion

This RCT assesses the effectiveness and side-effects of financial incentives in improving adherence with antipsychotic depot medication in patients with psychotic disorders. This study is designed to assess whether M4M is an effective intervention to improve patients' acceptance of their antipsychotic depot medication and to examine how this intervention contributes to patients' functioning and wellbeing.

## 2.1 Background

### 2.1.1 Consequences of non-adherence

Approximately 60% of patients with psychotic disorders experience difficulties being adherent over time or fail to take their medications as prescribed, with mean non-adherence rates around 50% [1-3]. Moreover, among patients who do not openly refuse to accept their antipsychotic medication, many are only partially adherent [4]. Failure to take the medication as prescribed is associated with a wide array of adverse individual and societal outcomes such as inconsistent symptom control, more relapses [5-7], more (re)hospitalizations [8,9], more suicide attempts [10,11] and more encounters with police and justice, either as a victim or as a perpetrator [12].

Clinical advantages of antipsychotic medication are often limited by patients' failure to adhere sufficiently to their prescribed medication. This partial compliance severely reduces the effectiveness of the medical treatment of schizophrenia and interferes with therapeutic efforts [13]. For example, relapses occur within one year for 50 to 75% of the patients with schizophrenia after discontinuing with their antipsychotics [14]. Missing antipsychotic medication has also been associated to double the risk for hospitalization [9]. Throughout this protocol alternative definitions such as 'acceptance' or 'compliance' relate to the concept of medication adherence.

### 2.1.2 Risk factors for non-adherence

Risk factors for non-adherence have been studied extensively and were systematically reviewed by Higashi and colleagues [15]. They distinguished (1) patient-, (2) treatment-, and (3) environmental-related factors to be associated with non-adherence.

(1) Patient-related factors included poor insight, negative attitudes towards medication, obesity, previous non-adherence and a shorter duration of illness. Furthermore, comorbid substance use disorders - particularly prevalent in patients with psychotic disorders (70–80%) [16] were also associated with increased non-adherence [9,17-19]. In addition, temperamental characteristics like sensation seeking and disinhibition predicted poor medication adherence in patients with psychotic or mood disorders [20]. From this perspective it is important to also study the (moderating) effects of impulsivity and substance use on the effectiveness of the M4M intervention because certain subgroups of patients could respond differently to the intervention (e.g. impulsive patients perhaps profit less from our intervention since they have more difficulties regulating their behavior). Therefore, this study investigates the role of impulsivity

and substance use disorders in patients with psychotic disorders and their associated medication adherence.

(2) Treatment-related risk factors for non-adherence included distress by side effects of the medication [21], higher antipsychotic doses and the use of classical antipsychotic medications [22,23].

(3) Environmental-related risk factors included stigma of taking medication, lack of support [24], poor therapeutic relationships, financial problems, chaotic living situations and poor aftercare [21,25].

### 2.1.3 Interventions to improve compliance

Unfortunately, most studies investigating interventions to improve adherence yield inconsistent results and do not always lead to less symptoms, better functioning or improved quality of life [26,27]. Therefore, a (combination) of innovative methods is needed to help patients take their antipsychotic medication as prescribed [28-30]. One such innovative intervention is contingency management.

Contingency Management (CM) interventions typically reinforce pre-set, well-defined and verifiable target behaviors (e.g., drug abstinence or medication intake), by providing financial incentives or vouchers. Interventions based on CM-principles have been applied in various settings targeting a variety of behaviors, and have shown robust effects in reducing drug use and increasing treatment compliance and medication adherence (for overviews see; [31,32]). Currently, no studies have investigated the effect of CM for non-depot medication adherence in patients with schizophrenia.

In reviewing studies using CM based interventions in patients with mental health problems, Priebe et al. [33] did not find any randomized controlled studies testing the effectiveness of financial incentives to improve depot medication adherence in patients with psychotic disorders. However, two pilot studies were conducted that showed promising results.

Claassen and colleagues [34] included five non-adherent patients of which four patients accepted financial incentives upon medication acceptance. This resulted in improved adherence rates and significantly decreased patients' hospital admissions during the intervention period. Staring et al. [35], also included five non-adherent patients with psychotic disorders in their pilot study. Results showed that the percentage of accepted depot injections increased from an average of 44% in the previous year to 100% in the year in which financial incentives were offered. While patients had been hospitalized for an average of 100 days in the preceding year, only one patient was re-admitted for 17 days during the intervention year. More recently, the first cluster randomized controlled trial tested the effectiveness of offering financial incentives to patients (n = 141) with psychotic disorders who were partially non-compliant to improve

their medication adherence [36]. Interestingly, although adherence to antipsychotic depot medication increased significantly in the CM group as compared to the control group (85% and 69% acceptance of depot after one year), this did not result in a significant difference on clinician rated clinical improvement. In sum, two pilot studies showed promising results and one RCT showed partial positive results of financial incentives upon acceptance of antipsychotic depot medication.

### 2.1.4 Study objectives

The goal of the current study is to assess the effectiveness of providing financial incentives upon depot acceptance in psychotic disorder patients. The primary objective of this study is to assess the effectiveness of M4M during the intervention in terms of acceptance of antipsychotic depot medication (the medication possession ratio; MPR). To assess how discontinuing the intervention affects depot acceptance, we will also compare the MPR during the follow-up period (six months), in which no CM takes place. In addition to the MPR, secondary objectives include the longest uninterrupted period of depot medication acceptance, the expired time before depot is taken and attitudes towards medication. Our third objective is to assess the effects of medication acceptance on patients psychosocial functioning, quality of life, cost-utility, substance use and side effects of the antipsychotic medication.

### 2.1.5 Hypotheses

The primary hypothesis is that M4M results in significantly more accepted depots than treatment as usual (TAU). Patients from both the TAU and M4M condition are prescribed antipsychotic depot medication. Secondary hypotheses are that M4M, compared to TAU, leads to (1) longer uninterrupted periods of depot acceptance and (2) less time expired before the depot is taken. From our tertiary measures, we expect M4M (compared to TAU) to result in (3) less severe symptoms and better psychosocial functioning, (4) improved quality of life, (5) less substance use, and (6) lower costs.

Using exploratory analyses we will look for patient characteristics (at baseline) – the stratification variables (gender, comorbid substance use, and medication adherence) and, other variables including impulsivity, motivation and attitudes towards antipsychotic medication and M4M – that could moderate the effects of M4M and might be used for future patient treatment matching. In addition, we will explore the role of potential mediating variables – e.g., medication side effects – in M4M's effectiveness. Finally, we will analyze self-reported data on patients' and clinicians' perceptions of M4M. This enables us to discuss the ethical considerations of M4M.

## 2.2 Methods

The contents of the study design, data collection, analyses, interpretation of data, writing of the manuscript and the decision to submit the manuscript for publication was not influenced by the funding body (Palier, department of Parnassia Psychiatric Institute).

### 2.2.1 Study design

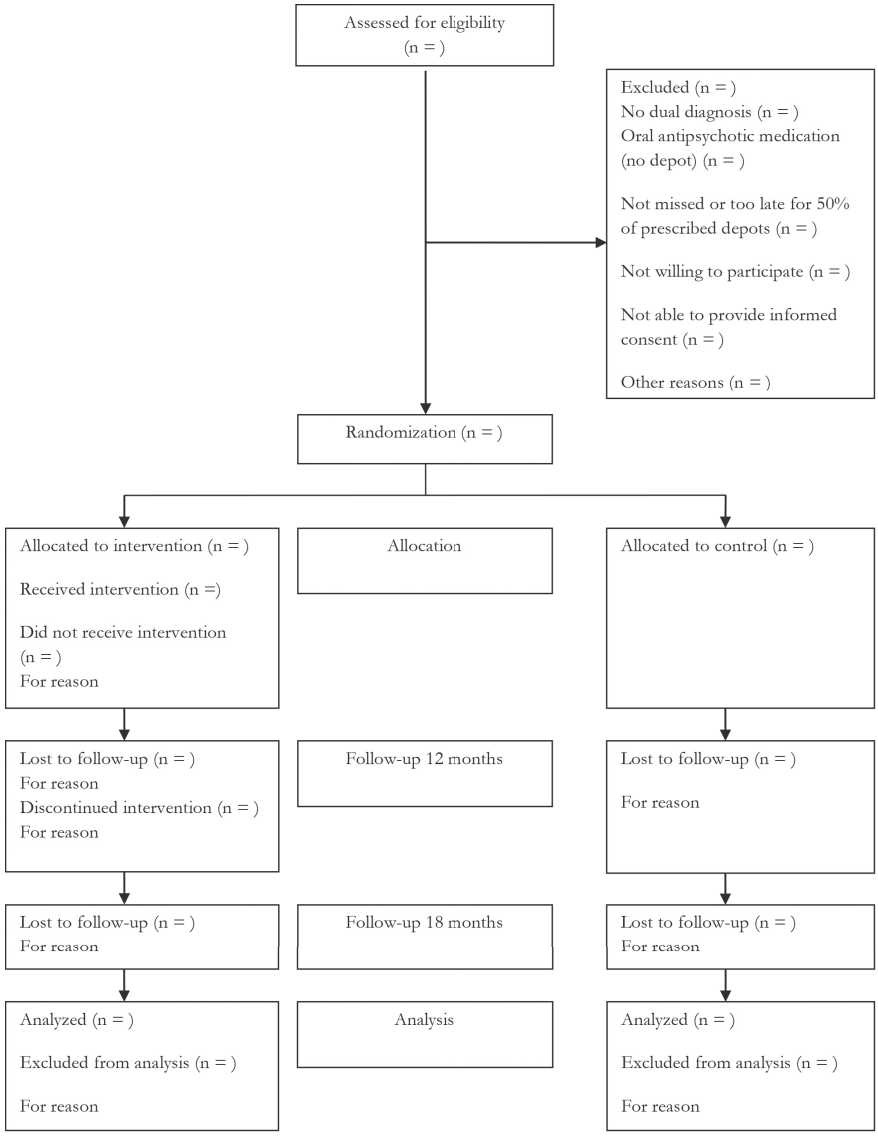
In a parallel-group randomized controlled trial, patients will be randomly assigned to the experimental condition (M4M), or to the treatment as usual (TAU) control condition. Note that during the recruitment phase of the study, only patients who are prescribed or have an indication for antipsychotic depot medication, and who have expressed their willingness to accept antipsychotic depot medication are eligible for inclusion and after providing written informed consent for randomization. Patients assigned to the experimental condition (M4M, n =84) will receive a financial incentive for each prescribed depot they accept, in addition to treatment as usual. Patients in the control condition (TAU, n =84) will receive treatment as usual only without financial incentives upon depot acceptance. After randomization, both patients in the TAU condition and patients in the M4M condition are prescribed depot medication. After the intervention period of 12 months, there will be a follow-up period of 6 months in which patients in both study groups receive TAU and no financial incentives for accepting their prescribed antipsychotic depot medication.

### 2.2.2 Participants/Setting

Patients will be 168 outpatients with a psychotic disorder from three mental health care institutions in the Netherlands: (1) Palier ('Dual Diagnosis Centre' (CDP)), (2) Parnassia and (3) BavoEuropoort. These organizations primarily treat patients with psychotic and other severe mental disorders, (often with comorbid substance use disorder), from the cities of Rotterdam and the Haque in the Netherlands. Per team around two hundred patients with a psychotic disorder are treated. Patients will be recruited based on the following inclusion criteria: age between 18 – 65 years, a psychotic disorder (including schizophrenia, schizoaffective disorder or other psychotic disorders), taking antipsychotic depot medication or an indication to start using depot medication, outpatient treatment (either starting outpatient treatment after discharge from a psychiatric hospital, or being in outpatient treatment for at least four months), and given informed consent. In concordance with their psychiatrist, patients who will start using antipsychotic depot medication are considered to have an indication for antipsychotic depot medication. These patients are - if they meet the other inclusion criteria- eligible to contact for our study. Exclusion criteria are the inability to participate due to cognitive

impairments and/or insufficient understanding of the Dutch language (clinical judgment). Refer to Figure 1 Participant flowchart for details.

**Figure 1. Participant flowchart**



### 2.2.3 Intervention

Patients assigned to the intervention group (M4M; Money for Medication) will receive treatment as usual (see below), plus a financial incentive for each time they accept their prescribed depot of antipsychotic medication during the 12 months experimental study phase. All patients in the M4M group will receive a maximum of 30 euro per month. The amount of money per accepted depot is dependent upon the frequency of depot administration. For example, a patient who receives one depot every two weeks will receive 15 euro per accepted depot. A patient who receives one depot every three weeks will receive 22.50 euro for each accepted depot, et cetera. Patients receiving oral penfluridol with a frequency of once a week will also be included in the study. Oral penfluridol is used when patients have problems taking antipsychotic medication on a daily basis, and when they do not accept intramuscular depot injections. They will receive 7.50 euro for each time they accept their weekly penfluridol oral tablet. The financial incentives will be given by the patients' treating nurses directly upon administration of the depot or penfluridol. They will receive their depot medication primarily at the clinic ('depot room') and sometimes at home during home visits. Patients will sign a proof of receipt.

Patients assigned to the control group will receive treatment as usual (TAU) during the 12 months experimental study phase and during the 6 months follow-up. TAU includes outpatient treatment provided by community mental health teams and flexible assertive community treatment teams [37]. All clinicians encourage continuing depot medication in case this is prescribed by the psychiatrist of the team. When needed, crisis services can be used or patients can be hospitalized (in)voluntarily. The type and dosage of the depot antipsychotic medication and other medications patients receive will be determined by the patients' psychiatrist together with the patient. The type, frequency and dosage will not be affected by participation in the study. Administration of the depots will be done by the psychiatric nurses working in the teams.

### 2.2.4 Procedure

Candidate participants will be selected from the caseloads, applying the in- and exclusion criteria. Patients who meet the criteria will be informed and asked to participate by their clinician. Patients who consider participation receive a take-home brochure with information about the study. The clinician asks the patient's permission to be contacted by a researcher. If the patient agrees, the researcher contacts the patient to schedule an appointment for the baseline interview. If a patient indicates that he or she does not want to participate, this will be registered anonymously together with their demographic and clinical characteristics (DSM

IV-TR diagnosis on axes I and II) to enable assessment of selection bias. If possible, the patient will be asked to explain why he or she does not want to participate.

With support of the management, all teams and their clinicians have expressed their willingness to co-operate with the conduct of our Money for Medication study. Clinicians of course can be resilient about the concept and intervention of our study. Therefore, we assess clinicans' attitudes towards M4M.

Prior to the baseline interview the researcher explains the design and purpose of the study, the research goals and the randomization procedure. After written informed consent is given, the baseline interview will take place and subsequently, participants will be randomized to the intervention (M4M) or control condition (TAU). Randomization will be stratified by site, gender, substance use disorder (absent vs. prevalent) and previous compliance with antipsychotic medication (compliance rate <50% vs. ≥50%). There will be three interviews at 0, 12 and 18 months (see Table 1). All participants will receive a remuneration of 20 euro for each interview. In the cases where the researchers cannot overcome certain practical obstacles (e.g. imprisonment, hospitalization), patients who can demonstrate that they have accepted their depot medication (for instance in the form a written statement by the treating prison or hospital medical doctor), receive their monetary reward as soon as possible, but with a delay. In case of discontinuation of depot intake, the monetary reward will stop and data of non-depot medication intake will be monitored in order to have a complete overview on the number of patients discontinuing depot medication and switching to non-depot.

Originally the start date for patient recruitment was May 21, 2010 and was planned to be completed by September 2012. Due to a change in personnel and organizational factors that caused logistical delays, patient recruitment was low and continued again in September 2013. Note that this is an ongoing study and that we expect to finish our complete data collection by April 2016. Therefore, we expect to submit the results of this study in 2016.

## 2.3 Instruments

**Baseline variables**

Demographic variables, DSM-IV diagnoses on Axis I and II, and psychiatric history (including hospitalizations during the last three years, current antipsychotic and concomitant medication, and antipsychotic depot acceptance 4 months before the study) will be collected in the first interview and from patients' records.

**Table 1. Measures and instruments and assessment times**

| Category | Outcome measure | Instrument | Assessment (month) | | |
|---|---|---|---|---|---|
| | | | 0 | 12 | 18 |
| **Demographics** | | Registration forms | X | | |
| **Medication acceptance** | - Percentage accepted depots (MPR) | Registration forms | Continuously | Continuously | Continuously |
| | - Longest uninterrupted period | Registration forms | Continuously | Continuously | Continuously |
| | - Time expired before depot is taken | Registration forms | Continuously | Continuously | Continuously |
| | - Attitudes towards medication | ROMI | X | X | X |
| **Psychosocial functioning** | - Psychiatric symptomatology | PANSS | X | X | X |
| | - Health, psychological and social functioning | HoNOS | X | X | X |
| | - Substance use | ASI | X | X | X |
| | | CIDI-SAM | X | | |
| | | Urine screens | X | X | X |
| | - Quality of Life | MANSA | X | X | X |
| | - Antipsychotic side-effects | ASC | X | X | X |
| | - Treatment Entry Questionnaire | TEQ | X | X | X |
| | - Dickman Impulsivity questionnaire | DII | X | X | X |
| **Cost-utility** | - Health-care consumption | TiC-P | X | X | X |
| | - Health-related quality of life | EQ-5D | X | X | X |
| | - Self-reported delinquent behaviour | SRD | X | X | X |
| | - Effort of clinicians | Registration forms | Continuously | Continuously | Continuously |
| **Ethical aspects** | - Attitudes towards M4M | Questionnaire constructed for the current study | X | X | X |

ROMI: Rating Of Medication Influences, PANSS: Positive And Negative Symptoms Scale, HoNOS: Health of the Nations Outcome Scales, ASI: Addiction Severity Index, CIDI-SAM: Composite International Diagnostic Interview – Substance Abuse Module, MANSA: Manchester Short Assessment of Quality of Life, ASC: Antipsychotic Side-effects Checklist, TEQ: Treatment Entry Questionnaire, TiC-P: Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness, EQ-5D: EuroQol-5D, Quality of Life, SRD: Self-Reported Delinquency questionnaire.

### 2.3.1 Outcome measures

1. *Primary outcome measure:* The primary outcome measure is medication acceptance, represented by the percentage of accepted depot injections. This is defined as the 'Medication Possession Ratio' (MPR) first reported by Sclar, Chin and Skaer [38]. The MPR is the number of accepted depots antipsychotic medication divided by the number of prescribed depots antipsychotic medication (the number of supplies needed for continuous use of antipsychotic medication).
2. *Secondary outcome measures:* The secondary outcome measures include additional measures of adherence, including the longest uninterrupted period of depot medication acceptance, the time expired before the depot is taken and patients attitudes towards medication.

a. *Longest uninterrupted period of depot medication acceptance:* Sometimes occasional missed doses are not regarded as 'non-adherence' [39]. However, as even partial adherence can severely undermine clinical improvement [9] it is important to strive for continuous medication adherence. Therefore, the longest uninterrupted period of medication acceptance will be assessed as well. In sum, this outcome measures the time period (number of days/ weeks) a patient takes the prescribed antipsychotic depot medication according to schedule, without missing or not taking a single depot prescription).

b. *Time expired before depot is taken:* Following Priebe et al. [33], we will monitor the time that has expired before the patient accepts the prescribed depot. Note that all patients receive depot medication (M4M and TAU) according to their own schedule (i.e., every 14 days). This variable (*time expired before depot is taken*) allows us to see whether patients are late for their prescribed depot. The time 'slippage' of taking depots is defined as the percentage of the prescribed time interval that has expired before the depot is taken.

c. *Attitudes towards medication:* To assess how patients attitudes towards medication relate to the effectiveness of M4M, the 'Rating of Medication Influences' (ROMI) scale [40] will be used. The ROMI measures attitudinal and behavioral factors influencing patient adherence with neuroleptic treatment. The ROMI consists of three subscales related to adherence (prevention, influence of others and medication affinity) and five subscales related to non-adherence (denial/dysphoria, logistical problems, rejection of label, family influence and negative therapeutic alliance). In sum, the ROMI asks questions about the reasons for taking medication and patients' general attitudes towards treatment. An example item: "Do you have a positive relation with the clinical staff?" Patients can answer yes/no and indicate to what extent this affects their medication intake (no/some/strong).

3. *Tertiary outcome measures:* The tertiary outcome measures include measures on the effects of medication acceptance on patients psychosocial functioning, substance use, quality of life and side-effects of the antipsychotic medication:

a. *Psychiatric symptomatology:* Psychiatric symptomatology will be assessed by trained interviewers with the Dutch version of the 'PANSS', the Positive and Negative Syndrome Scale, originally conceived by Kay, Fiszbein and Opler [41]. The PANNS consists of three subscales: positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items, including anxiety and depression). Items are scored on a scale from 1 (symptom absent) to 7 (symptom interferes with almost all aspects of daily functioning). Internal and external consistency of the PANNS has been found to be adequate [42-44].
b. *Health, psychological and social functioning:* To assess patients' health and psychosocial functioning, the Dutch translation of the Health of the Nations Outcome Scales ('HoNOS') [45,46] will be administered by trained interviewers. The HoNOS is a structured interview to quantify health and social functioning during the last two weeks on four subscales (behavioural problems, impairments, symptoms and social problems). Items are rated on a 5-point scale ranging from 0 (no problems) to 4 (severe to very severe problems).
c. To test for the potential modifying effect of impulsivity on the M4M intervention, we will assess impulsivity by means of the Dickman Impulsivity Inventory (DII) [47], which has been validated for the Dutch situation [48] and has good psychometric properties among substance users as well [49]. The DII consists of 24 dichotomous items, resulting in a "functional impulsivity" and a "dysfunctional impulsivity" score.
d. *Substance use:* Substance use will be assessed with the 'Alcohol and drug use' section of the European version of the 'Addiction Severity Index' ('EuropASI') [50] and the Substance Abuse Module of the International Diagnostic Interview [51]. The CIDI is a structured interview based on the criteria and definitions of the ICD-10 and DSM-IV with good psychometric properties [52]. Self-reported drug-use will be verified by urinanalysis sticks at baseline, 12 and 18 months (follow-up) for amphetamines, benzodiazepines, cocaine, morphine/heroin and cannabis.
e. *Subjective Quality of Life:* To assess patients' subjective quality of life we will use the third section of the 'Manchester Short Assessment of Quality of Life' ('MANSA') [53]. The MANSA assesses the patients subjective ratings of life in general and satisfaction with several more specific domains of quality of life, including work or education related issues, financial situation, social relations, leisure activities, accommodation, family situation, personal safety and physical and mental health. Items are rated on a seven-point scale ranging from 1 (could not be worse) to 7 (could not be better). The MANSA has good psychometric properties [53,54].

f. *Antipsychotic Side-effects:* To assess how medication affects patients' subjective wellbeing, we will use the 17-item Dutch translation of the 'Antipsychotic Side-effect Checklist' ('ASC') [55]. The ASC-C is a checklist designed for mental health clinicians to use as a brief interview to check for common problems (side-effects) associated with the use of antipsychotic medication during a regular therapeutic session. Items are rated as: symptom present or symptom absent.

g. *Cost-utility:* The cost-utility of M4M will be compared with treatment as usual. To estimate direct health care from a societal perspective, costs will be determined and calculated by multiplying resource use with official charge standards. Our focus will be on patients' health care consumption (admissions, contacts with clinicians, and efforts initiated to provide depots) and illegal activities. Measures will be collected from the patients file and the Trimbos/iMTA self-report questionnaire for Costs associated with Psychiatric Illness (TiC-P; [56]), a questionnaire for Self-Reported Delinquency (SRD, adapted from the INternational CAnnabis Need of Treatment (INCANT) study), and the depot acceptance registration forms.

h. *QALY's will be assessed using the EQ-5D:* The EQ-5D is a standardized instrument that scores health-related quality of life on five levels of health (mobility, self-care, daily activities, pain/discomfort and anxiety/depression), which generates a score for health-related quality of life that can be used as a weight to calculate Quality Adjusted Life Years or 'QALY's' [57], a weighted health-index. The EQ-5D has been shown to have good discriminative and construct validity and to be sensitive in detecting changes in QoL ratings in patients with substance use [58].

i. *Time spent by clinicians to provide depot:* To assess how M4M affects patients' willingness to accept their antipsychotic depot medications, the time and effort spent by the clinicians to provide the depot (e.g. calling, home visits, et cetera) will be monitored with standard registration forms designed for the current study.

j. *Attitudes towards M4M:* In addition to the outcome measures above, patients' and clinicians' attitudes towards M4M will be assessed with a short questionnaire constructed for the current study. Items address different attitudes towards M4M in terms of its advantages and disadvantages (e.g. effects on motivation, insight, wellbeing, depot acceptance, dependency, the relationship between the patient and the clinician, and moral, ethical and practical considerations). Items will be scored on a 5-point scale (1 = strongly disagree, 5 = strongly agree).

k. *Intrinsic and extrinsic motivation:* To measure patients" intrinsic and extrinsic motivation during the study, the Dutch version of the Treatment Entry Questionnaire (TEQ) is being used, which has good psychometric properties [59]. On 27 statements regarding motivation for the current intervention patients answer if they agree (1 = strongly disagree, 7 = strongly agree).

### 2.3.2 Ethical approval

The study protocol has been approved by the accredited Dutch Medical Ethical Trial Committee (METC) of the Erasmus University Medical Centre (registered under number NL31406.097.10 and file number P13.258). According to the Dutch Data Protection Act (DPA) data will be safely stored and anonymized and is only accessible for members of the research group or the Medical Ethical Committee. All patients will provide informed consent before entering the study.

### 2.3.3 Sample size/power

Following the CONSORT statement we calculated our power to the primary outcome measure of this study and not for the secondary or tertiary outcome measures. Based on previous findings and study protocols [33,60], we expect a difference of 65 to 85 percent (an absolute difference of 20%) of accepted depots between the control group and the money-for-medication condition. In terms of Cohen's h, this constitutes a medium effect size (h =0.5). With Type I error rate (alpha) set at 5%, power at 0.90 (1 – Type II Error rate; 1- β), and 20—25% drop-out, we will need 84 patients per arm to detect an absolute difference of 20% [61]. In total 168 patients will be included.

### 3.3.4 Statistical analyses

The primary outcome will be reported as accepted depots as percentage of planned depots, most often weekly, biweekly or monthly. The effects of the intervention on our outcome measures will be analysed using generalized linear models as appropriate to the outcome, with random effects for sites or treatment teams. Sensitivity analyses will be conducted to explore the impact of different strategies for handling missing data. A detailed analysis plan will be completed prior to analysis of baseline measurements.

## 2.4 Discussion

The aim of the current randomized controlled study is to assess the effectiveness of financial incentives (M4M), compared to treatment as usual, in improving the acceptance of antipsychotic depot medication in patients with psychotic disorders. Our primary outcome measure will be the MPR. Secondary outcome measures include patients' health, social and psychological functioning and subjective quality of life. Tertiary measures are used to assess the effects of medication acceptance on patients' psychosocial functioning, substance use, quality of life and side effects of the antipsychotic medication. This allows us to assess not only whether

M4M is an effective intervention to improve acceptance, but also to what extent medication acceptance contributes to patients' wellbeing We will also compare the MPR during the follow-up period (six months), in which no CM takes place.

### 2.4.1 The use of financial incentives in M4M

In the pilot study of Claassen et al. [34], M4M did not have a negative impact on the therapeutic relationship. Furthermore, they have not found that other patients who did not participate in the M4M study complained about unequal treatment or demanded to be paid for taking medication as well.

In the pilot study of Staring, Mulder, and Priebe [35], all five participants considered M4M to be a good project. The reasons they gave to participate in the pilot 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 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. Other patients did not ask to be offered incentives as well and no negative impacts on therapeutic relationships were noted. Some patients however felt that they should receive more money (they received 10 euro for every two weekly depot, 15 euro for every three-weekly depot and 20 euro for every four-weekly depot).

Although higher payments have been found to result in bigger effects [62,63], in the present study we have chosen a maximum of 30 euro's on average per month because (1) patients could get used to or become financially dependent on higher payments or even lose their social security benefits and (2) to strive for acceptable cost-utility of M4M. From a societal perspective it is important to focus on cost-effective interventions and given the results of prior research [35], it seems not necessary to use higher incentives.

### 2.4.2 Strengths and limitations

Our study started in 2010, prior to some of the recent findings as described above. The difference with the earlier RCT studying the effects of M4M [36] is that we will include both patients who are partially non-compliant, as well as patients who are compliant in taking depot medication. The rationale to also include compliant patients is the observation in several studies that around thirty percent of patients initiated on antipsychotic depot medication cease to accept their depot within one year [5,64,65]. In addition, when we eventually might want

to implement this intervention into daily clinical practice, it is more ethical as well as more practical to reward both compliant and non-compliant patients.

A possible limitation of this study are the different medication depots. Although most patients receive medication injections it is also allowed for patients to take oral penfluridol. The disadvantage of this oral antipsychotic medication is that it is more difficult to check if patients actually take their medication. However, penfluridol is also a depot and because we aim to test if our intervention is broadly applicable we decided to include both patients with oral penfluridol and injections.

Another limitation is that the clinicians cannot be blinded to the intervention condition, possibly resulting in a more stimulating attitude for accepting depot medication in the intervention group. Also, the interviewers are not blind to the patients' condition and therefore can rate patients' responses as more positive or negative.

Furthermore, the intervention effect can be influenced by different depot frequencies. For example, patients who receive money every week are rewarded four times as often compared to patients that receive depot every month. Receiving a small incentive more frequently can be more stimulating or motivating compared to receiving a bigger incentive only once a month. This can interfere with our intervention effect, even though the mean amount of money per month remains equal for all participants.

### 2.4.3 Ethical issues

Ethical concerns have been raised about paying patients to accept their medication and whether this is an acceptable means in the treatment of patients with psychotic disorders [66,67]. One of these concerns is that patients' intrinsic motivation to accept medication will disappear if money is involved. We will study this by assessing intrinsic motivation over time, as possible decreases in depot acceptance can occur during the 6 month follow-up without M4M. Another frequently raised ethical argument is that patients might buy drugs or alcohol from the money they receive. We will monitor alcohol and drug use by using assessment scales as well as obtaining urine samples.

Apart from these ethical concerns, we will also assess the intervention from a cost-utility perspective, because this is an important factor to consider from a societal point of view. In conclusion, we will test if M4M improves patients' MPR, reduces their psychotic symptoms and contributes to a clinical improvement.

## Acknowledgements

We would like to thank Palier, department of Parnassia Psychiatric Institute for funding the study.

## References


1. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC: Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry* 2006, 67:1542–1550.
2. Gilmer TP, Ph D, Dolder CR, Pharm D, Lacro JP, Folsom DP, Lindamer L, Garcia P, Ed D, Jeste DV: Adherence to treatment with antipsychotic medication and health care costs among medicaid beneficiaries with schizophrenia. *Am J Psychiatry* 2004, 161:692–699.
3. Velligan DI, Diamond PM, Mintz J, Maples N, Li X, Zeber J, Ereshefsky L, Lam Y-WF, Castillo D, Miller AL: The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. *Schizophr Bull* 2008, 34:483–493.
4. Llorca P-M: Partial compliance in schizophrenia and the impact on patient outcomes. *Psychiatry Res* 2008, 161:235–247.
5. Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D: Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *Eur Neuropsychopharmacol* 2007, 17:235–244.
6. Weiden PJ, Olfson M: Cost of relapse in schizophrenia. *Schizophr Bull* 1995, 21:419–429.
7. Marder SR: Overview of partial compliance. *J Clin Psychiatry* 2003, 64:3–9.
8. Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, Bingham CR, Stavenger T: Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care* 2002, 40:630–639.
9. Weiden PJ, Kozma C, Grogg A, Locklear J: Partial compliance and risk of rehospitalization among California medicaid patients with schizophrenia. *Psychiatr Serv* 2004, 55:886–891.
10. Hor K, Taylor M: Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 2010, 24(4 Suppl):81–90.
11. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ: Schizophrenia and suicide: systematic review of risk factors. *Br J Psychiatry* 2005, 187:9–20.
12. Ascher-Svanum H, Nyhuis AW, Faries DE, Ball DE, Kinon BJ: Involvement in the US criminal justice system and cost implications for persons treated for schizophrenia. *BMC Psychiatry* 2010, 10:11.
13. Giuffrida A, Torgerson DJ: Should we pay the patient? Review of financial incentives to enhance patient compliance. *BMJ* 1997, 315:703–707.
14. Valenstein M, Blow FC, Copeland L a, McCarthy JF, Zeber JE, Gillon L, Bingham CR, Stavenger T: Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophr Bull* 2004, 30:255–264.
15. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M: Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol* 2013, 70:1–46.
16. Westermeyer J: Comorbid schizophrenia and substance abuse: a review of epidemiology and course. *Am J Addict* 2006, 15:345–355.
17. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW: Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry* 2006, 67:453–460.
18. Olfson M, Mechanic D, Hansell S, Boyer C a, Walkup J, Weiden PJ: Predicting medication noncompliance after hospital discharge among patients with schizophrenia. *Psychiatr Serv Washingt DC* 2000, 47:853–858.
19. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T: Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. *Schizophr Res* 2009, 107:213–217.
20. Liraud F, Verdoux H: Association between temperamental characteristics and medication adherence in subjects presenting with psychotic or mood disorders. *Psychiatry Res* 2001, 102:91–95.

21. Löffler W, Kilian R, Toumi M, Angermeyer MC: Schizophrenic Patients' subjective reasons for compliance and noncompliance with neuroleptic treatment. *Pharmacopsychiatry* 2003, 36:105–112.
22. Janssen B, Gaebel W, Haerter M, Komaharadi F, Lindel B, Weinmann S: Evaluation of factors influencing medication compliance in inpatient treatment of psychotic disorders. *Psychopharmacology (Berl)* 2006, 187:229–236.
23. Lacro JP, Pharm D, Dunn LB, Dolder CR, Leckband SG, Ph R, Jeste DV: Prevalence of and risk factors for medication nonadherence in patients with schizphrenia: a comprehensive review of recent literature. *J Clin* 2002, 63:893–910.
24. Hudson TJ, Owen RR, Thrush CR, Han X, Pyne JM, Thapa P, Sullivan G: A pilot study of barriers to medication adherence in schizophrenia. *J Clin Psychiatry* 2004, 65:211–216.
25. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP: The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009, 70:1–46.
26. Staring ABP, Mulder CL, Der Van Gaag M, Selten J, Loonen AJM, Hengeveld MW: Understanding and improving treatment adherence in patients with psychotic disorders: a review and a proposed intervention. *Curr Psychiatry Rev* 2006, 2:487–494.
27. Staring ABP, Van der Gaag M, Mulder CL: Schizophrenia and antipsychotic medication - Better adherence, better outcomes? *Schizophr Res* 2013, 151:296–297.
28. Haynes RB, McDonald HP, Garg AX: Helping patients follow prescribed treatment: clinical applications. *JAMA* 2002, 288:2880–2883.
29. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM: Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res* 2010, 176:109–113.
30. Osterberg L, Blaschke T: Adherence to medication. *N Eng J Med* 2005, 353:487–497.
31. Prendergast M, Podus D, Finney J, Greenwell L, Roll J: Contingency management for treatment of substance use disorders: a meta-analysis. *Addiction* 2006, 101:1546–1560.
32. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST: A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction* 2006, 101:192–203.
33. Priebe S, Burton A, Ashby D, Ashcroft R, Burns T, David A, Eldridge S, Firn M, Knapp M, McCabe R: Financial incentives to improve adherence to anti-psychotic maintenance medication in non-adherent patients - a cluster randomised controlled trial (FIAT). *BMC Psychiatry* 2009, 9:61.
34. Claassen D, Fakhoury W, Ford R, Priebe S: Money for medication : financial incentives to improve medication adherence in assertive outreach. *Psychiatr Bull* 2007, 31:4–7.
35. Staring AB, Mulder CL, Priebe S: Financial incentives to improve adherence to medication in five patients with schizophrenia in the Netherlands. *Psychopharmacol Bull* 2010, 43:1–6.
36. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, David AS, O'Connell N, Forrest A, Burns T: Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomised controlled trial. *BMJ* 2013, 345:f5847.
37. Van Veldhuizen JR: FACT: a Dutch version of ACT. *Community Ment Health J* 2007, 43:421–433.
38. Sclar DA, Pharm B, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA: Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clin Ther* 1991, 13:489–495.
39. Perkins DO: Adherence to antipsychotic medications. *J Clin Psychiatry* 1999, 60(suppl 21):25–30.
40. Weiden PJ, Rapkin B, Mott T, Zygmunt A, Goldman D, Horvitz-lennon M, Frances A: Rating of medication influences (ROMI) scale in schizophrenia. *Schizophr Bull* 1994, 20:297–310.
41. Kay SR, Qpjer LA: The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull* 1987, 13:261–272.

42. Knegtering H, Bruggeman R: Meetinstrumenten bij psychotische stoornissen. *Tijdschr Psychiatr* 2004, 46:675–679.
43. Van den Oord EJCG, Rujescu D, Robles JR, Giegling I, Birrell C, Bukszár J, Murrelle L, Möller H-J, Middleton L, Muglia P: Factor structure and external validity of the PANSS revisited. *Schizophr Res* 2006, 82:213–223.
44. Wolthaus JE, Dingemans PM, Schene AH, Linszen DH, Knegtering H, Holthausen EA, Cahn W, Hijman R: Component structure of the positive and negative syndrome scale (PANSS) in patients with recent-onset schizophrenia and spectrum disorders. *Psychopharmacology (Berl)* 2000, 150:399–403.
45. Mulder CL, Staring ABP, Loos J, Buwalda VJA, Kuijpers S, Systema S, Wierdsma AI: De Health of the Nation Outcome Scales (honos) als instrument voor 'routine outcome assessment. *Tijdschr Psychiatr* 2004, 6:273–284.
46. Bebbington P, Brugha T, Hill T, Marsden L, Window S: Health of the Nation Outcome Scales (Ho NOS). *Br J Psychiatry* 1999, 174:389–394.
47. Dickman SJ: Functional and dysfunctional impulsivity : personality and cognitive correlates. *J Pers Soc Psychol* 1990, 58:95–102.
48. Claes L, Vertommen H, Braspenning N: Psychometric properties of the Dickman Impulsivity Inventory. *Pers Individ Dif* 2000, 29:27–35.
49. Pedrero Pérez EJ: Evaluación de la impulsividad funcional y disfuncional en adictos a sustancias mediante el Inventario de Dickman. *Psicothema* 2009, 21:585–591.
50. Kokkevi A, Hartgers C: EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *Eur Addict Res* 1995, 1:208–210.
51. Wittchen H-U: Reliability and validity studies of the WHO Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatric Res* 1994, 28:57–84.
52. Andrews G, Peters L: The psychometric properties of the composite international diagnostic interview. *Soc Psychiatry Psychiatr Epidemiol* 1998, 33:80–88.
53. Priebe S, Huxley P, Knight S, Evans S: Application and results of the Manchester short assessment of quality of life (Mansa). *Int J Soc Psychiatry* 1999, 45:7–12.
54. Björkmann T, Svensson B: Quality of life in people with severe mental illness. Reliability and validity of the Manchester Short Assessment of Quality of Life (MANSA). *Nord J Psychiatry* 2005, 59:302–306.
55. Weiden PJ, Miller AL: Which side effects really matter? Screening for common and distressing side effects of antipsychotic medications. *J Psychiatr Pract* 2001, 7(January):41–47.
56. van Hakkaart RL: Trimbos / iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P). *iMTA* 2002, 5:5–45.
57. König H-H, Roick C, Matthias A: Validity of the EQ-5D in assessing and valuing health status in patients with schizophrenic, schizotypal or delusional disorders. *Eur Psychiatry* 2007, 22:177–187.
58. Van der Zanden BP, Dijkgraaf MGW, Blanken P, de Borgie CA JM, van Ree JM, van den Brink W: Validity of the EQ-5D as a generic health outcome instrument in a heroin-dependent population. *Drug Alcohol Depend* 2006, 82:111–118.
59. Jochems EC, Mulder CL, Duivenvoorden HJ, van der Feltz-Cornelis CM, van Dam A: Measures of motivation for psychiatric treatment based on self-determination theory: psychometric properties in Dutch psychiatric outpatients. *Assessment* 2014, 21:1–17.
60. Remington G, Kwon J, Collins A, Laporte D, Mann S, Christensen B: The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. *Schizophr Res* 2007, 90:229–237.
61. Cohen J: *Statistical Power Analysis for the Behavioral Sciences.* 2nd edition. Hillsdale, NJ: Lawrence Erlbaum; 1988:407–537.
62. Festinger DS, Marlowe DB, Dugosh KL, Croft JR, Arabia PL: Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. *Drug Alcohol Depend* 2008, 96:128–135.
63. Higgins ST, Heil SH, Dantona R, Donham R, Matthews M, Badger GJ: Effects of varying the monetary value of voucher-based incentives on abstinence achieved during and following treatment among cocaine-dependent outpatients. *Addiction* 2007, 102:271–281.

64. Ciudad A, Haro JM, Alonso J, Bousoño M, Suárez D, Novick D, Gilaberte I: The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain. *Eur Psychiatry* 2008, 23:1–7.
65. Zhu B, Ph D, Ascher-svanum H, Faries D, Montgomery W, Pharm B, Marder SR: Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. *Psychiatr Serv* 2008, 59:315–317.
66. Shaw J, Burns T: Is it acceptable for people to be paid to adhere to medication? No. *BMJ* 2007, 335:233.
67. Priebe S, Sinclair J, Burton A, Marougka S, Larsen J, Firn M, Ashcroft R: Acceptability of offering financial incentives to achieve medication adherence in patients with severe mental illness: a focus group study. *J Med Ethics* 2010, 36:463–468.

# Chapter 3

## Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial

Ernst L Noordraven
Andre I Wierdsma
Peter Blanken
Anthony FT Bloemendaal
Anton BP Staring
Cornelis L Mulder

*Lancet Psychiatry 2017; 4:199-207.*

## Abstract

### Background

Provision of financial incentives is a promising intervention for improving adherence in patients taking antipsychotic medication. We aimed to assess the effectiveness of this intervention for improving adherence to antipsychotic depot medication in patients with psychotic disorders, irrespective of their previous compliance.

### Methods

We did this multicentre, open-label, randomised controlled trial at three mental health-care institutions in secondary psychiatric care services in the Netherlands. Eligible patients were aged 18–65 years, had been diagnosed with schizophrenia or another psychotic disorder, had been prescribed antipsychotic depot medication or had an indication to start using depot medication, and were participating in outpatient treatment. Patients were randomly assigned (1:1), via computer-generated randomisation with a block size of four, to receive 12 months of either treatment as usual plus a financial reward for each depot of medication received (€30 per month if fully compliant; intervention group) or treatment as usual alone (control group). Randomisation was stratified by treatment site and suspected prognostic factors: sex, comorbid substance-use disorder (absent *vs* present), and compliance with antipsychotic medication in the 4 months before baseline (<50% *vs* ≥50%). Patients, clinicians, interviewers, and research assistants were masked to group allocation before, but not after, group assignment. The primary outcome was the Medication Possession Ratio (MPR), defined as the number of depots of antipsychotic medication received divided by the total number of depots of antipsychotic medication prescribed during the 12 month intervention period. Patients were followed up for 6 months, during which time no monetary rewards were offered for taking antipsychotic medication. We did analysis by intention to treat. This trial is registered with the Nederlands Trial Register, number NTR2350.

### Findings

Between May 21, 2010, and Oct 15, 2014, we randomly assigned 169 patients to the intervention group (n=84) or the control group (n=85). Primary outcome data were available for 155 (92%) patients. At baseline, the mean MPR was 76·0% (SD 28·2%) in the intervention group versus 77·9% (28·5%) in the control group. At 12 months, the mean MPR was higher in the intervention group (94·3% [SD 11·3%]) than in the control group (80·3% [19·1%]), with an adjusted difference of 14·9% (95% CI 8·9–20·9%; p<0·0001). This difference was maintained throughout the 6 month follow-up period: mean MPR of 86·6% (SD 22·2%) in the intervention

group versus 76·0% (22·7%) in the control group (adjusted difference 6·5%, 95% CI 2·0–10·9; p=0·047).

**Interpretation**

Financial incentives are an effective way of improving adherence to antipsychotic depot medication among patients with psychotic disorders. Further research is needed to study the long-term effects of this intervention.

## 3.1 Introduction

Over time, many patients with psychotic disorders have difficulty adhering to their prescribed antipsychotic medication, or do not take their medication as prescribed [1,2]. Such partial compliance reduces the effectiveness of the medical treatment of schizophrenia [3]. Although use of antipsychotics can reduce relapses [4], hospital admissions [5], psychiatric symptoms [6], and violent crimes [7], non-adherence rates remain high.

Interventions to improve adherence, such as adherence therapy or psychoeducation, produce inconsistent results [8] and are not always effective for patients with schizophrenia [9,10]. One promising intervention is the provision of financial incentives to increase adherence in patients taking antipsychotic medication. This intervention was successful in two pilot studies [11,12] in which medication compliance rates were substantially improved in non-adherent patients with psychotic disorders. In 2013, Priebe and colleagues [13] reported findings from the first cluster randomised controlled trial (N=141) of financial incentives for improvement of adherence to maintenance treatment with antipsychotics in patients with poor adherence. At 12 months, mean adherence to anti-psychotic depot medication was significantly better in patients receiving financial incentives (85% [SD 15]) than in those in the control group (71% [22]); the adjusted estimated effect was 11·5% (95% CI 3·9–19·0; p=0·0003). A substantial part of this effect emerged within the first 3 months of the study [14]. Additionally, subjective quality of life improved significantly in the intervention group, although clinician-rated clinical improvement did not differ between groups. Thus, although the two pilot studies [11,12], which had small sample sizes, showed promising results, the first large trial showed positive results only for improving adherence to antipsychotics for non-adherent patients with psychotic disorders, but no differences in these patients' clinical outcomes.

Because these three studies targeted patients with poor medication adherence, the generalisability of the results is restricted; whether financial incentives can improve adherence to antipsychotic depot medication among patients with psychotic disorders, irrespective

of their previous compliance, remains unclear. The effectiveness of this intervention is particularly important to establish because adherence can change over time: an estimated 25–50% of adherent patients eventually stop using medication against clinical advice [15]. What will happen to patients' medication adherence when financial rewards are no longer offered likewise remains unclear.

We did the Money for Medication study to assess the effectiveness of provision of financial incentives in improving patients' adherence to antipsychotic depot medication, irrespective of their previous level of medication adherence. Here we report outcomes after the 12 month intervention period, as well as outcomes of the 6 month follow-up period, during which time patients were no longer offered monetary rewards for taking antipsychotic medication.

## 3.2 Methods

### 3.2.1 Study design and participants

We did this multicentre, open-label, randomised controlled trial at three mental health-care institutions in secondary psychiatric care services in the Netherlands: the Dual Diagnosis Center (CDP) Palier, Parnassia, and BavoEuropoort. These organisations treat patients primarily with psychotic and other severe mental disorders (often with comorbid substance use) from the cities of Rotterdam and The Hague. Eligible patients were aged 18–65 years, had a psychotic disorder classified by the DSM-IV (eg, schizophrenia, schizo-affective disorder, or another psychotic disorder), had been prescribed antipsychotic depot medication or had an indication to start using depot medication, and were participating in outpatient treatment. Exclusion criteria were an inability to participate because of cognitive impairments or insufficient understanding of the Dutch language. Patients who initially met the inclusion criteria were informed about the study by their clinicians and were asked to participate. If a patient declined to participate, this decision was registered anonymously to allow assessment of selection bias. The study was approved by the accredited Dutch Medical Ethical Trial Committee (registration number NL31406.097.10, file number P13.258) of the Erasmus University Medical Center. All patients provided written informed consent.

### 3.2.2 Randomisation and masking

After informed consent had been obtained and the baseline interview completed, patients were randomly assigned (1:1), via a computer-generated randomization [16] with a block size of four, to receive 12 months of either experimental treatment (money for medication) or treatment as usual (control group) [17]. Randomisation was stratified by treatment site and suspected

prognostic factors: sex, comorbid substance-use disorder (absent *vs* present), and compliance with antipsychotic medication in the 4 months before baseline (<50% *vs* ≥50%).

The principal investigator had no influence on the enrolment process. Patients, clinicians, interviewers, and research assistants were masked to group allocation before, but not after, assignment. Importantly, adherence to depot medication was an objective event, and was not biased by the absence of assessors' concealment to a patient's treatment allocation.

### 3.2.3 Intervention

Patients allocated to the control group received treatment as usual, during both the 12 month experimental study phase and the 6 month follow-up period. Treatment as usual comprised outpatient treatment provided by community mental health teams. During treatment as usual, clinicians encouraged patients to continue the antipsychotic depot medication they had been prescribed. Whenever necessary, crisis services were used or patients were admitted to hospital. The type and dose of the depot antipsychotic medication and any other medication was determined by a patient's psychiatrist together with the patient, and was not affected by participation in this study. In general, all patients received their depot medication mainly at the outpatient clinic, but occasionally during home visits. Depot antipsychotics were administered by the psychiatric nurses working in the teams.

Patients in the intervention group received the same treatment as usual, plus a financial reward every time they received their prescribed depot of antipsychotic medication during the 12 month experimental study phase. The maximum reward was €30 per month. The amount of money per received depot depended on the frequency with which the depot was administered, which ranged from between one and four times a month. For example, a patient who received one depot every 2 weeks received €15 per depot. Patients receiving oral penfluridol once a week received €7·50 a week. The rewards were paid by the patients' treating nurses directly after administration of the depot or penfluridol. After the 12 month intervention period, all patients entered the 6 month follow-up period in which treatment as usual was continued, but neither group received financial incentives for taking prescribed antipsychotic depot medication.

Medication adherence was registered continuously on depot registration lists by the medical staff providing the antipsychotic medication. Patients were interviewed at baseline and after months 12 and 18. To assess patients' attitudes to antipsychotic medication, we used the Rating of Medication Influences [18]. To monitor common side-effects associated with use of antipsychotic medication, we used the Antipsychotic Side-effect Checklist [19]. Psychiatric symptomatology was measured on the Positive and Negative Syndrome Scale [20]. We measured subjective quality of life with the Manchester Short Assessment of Quality

of Life (MANSA) [21], and health and psychosocial functioning with the Health of the Nation Outcomes Scale (HoNOS) [22]. We assessed substance-use severity and symptoms with the Addiction Severity Index [23] and the Substance Abuse Module of the Composite International Diagnostic Interview [24]. At each interview, we verified self-reported drug use with rapid urine tests and collected information from patients' medical records (e.g., type and dosage of antipsychotic medication, and hospital admissions). Interviews were done in person by trained research assistants (Master's-level psychologists). Participants received €20 remuneration per interview. All data were electronically stored by use of OpenClinica on a secure server at Erasmus Medical Center.

### 3.2.4 Outcomes

The prespecified primary outcome was the Medication Possession Ratio (MPR) [25], defined as the number of depots of antipsychotic medication received divided by the total number of depots of antipsychotic medication prescribed during the 12 month intervention. We calculated the MPR after the 12 month intervention and 6 month follow-up periods. Calculation of the MPR excluded periods of hospital admission; in such cases, the contextual factors in which patients took their depot medication (such as daily monitoring by nurses) differed from those in the outpatient situation. We defined treatment responders as patients with an MPR of at least 80% medication adherence [26]. Prespecified secondary outcome measures were the longest uninterrupted period during which depot medication was received, the time to first discontinuation of depot medication, the total number of days without depot medication, and the time between prescription date and the date the depot was actually received. If a patient received a depot after more than one time interval, this deposit was registered as not received. Furthermore, we assessed patients' attitudes towards medication, clinical symptoms, psychosocial functioning, substance use, quality of life, and side-effects of the antipsychotic medication. The secondary outcomes not reported in this paper—i.e., effort initiated by clinicians, impulsivity, attitudes towards the money for medication, and cost utility—will be reported elsewhere.

### 3.2.5 Statistical analysis

We calculated the sample size needed for assessment of the primary outcome measure. On the basis of previous findings and study protocols [13,27,28], we expected patients to take 65% of their prescribed depots in the control group and 85% in the intervention group (absolute difference 20%). In terms of Cohen's *h*, these estimates would constitute a medium effect size of 0·5. With a type 1 error rate ($\alpha$) of 5%, 0·90 power (1–type 2 error rate; 1–$\beta$), and 20–25%

**Table 1. Patient characteristics at baseline**

| Variable | Total (n=169) | Intervention group (n=84) | Control group (n=85) |
|---|---|---|---|
| Age mean (SD), years | 40.7 (9.8) | 40.6 (9.4) | 40.7 (10.2) |
| Gender, *N* (%) | | | |
| - Male | 127 (75) | 61 (73) | 66 (78) |
| Patients > 50% medication adherence, *N* (%) | 135 (79.9) | 68 (80.0) | 67 (79.8) |
| Location of treatment, *N* (%) | | | |
| - The Hague | 46 (27.2) | 18 (21.4) | 18 (21.2) |
| - Rotterdam | 123 (72.8) | 66 (78.6) | 67 (78.8) |
| Substance use disorder, *N* (%) | 94 (55.6) | 48 (57.1) | 46 (54.1) |
| Ethnicity, *N* (%) | | | |
| - Dutch | 64 (37.9) | 29 (34.5) | 35 (41.2) |
| - Surinamese | 39 (23.1) | 17 (20.2) | 22 (25.9) |
| - Other | 66 (39.0) | 38 (45.2) | 28 (32.9) |
| Outpatient commitment measures, *N* (%)† | 60 (35.5) | 31 (36.9) | 26 (30.6) |
| Diagnosis, *N* (%) | | | |
| - Schizophrenia paranoid type | 97 (57.4) | 46 (54.8) | 51 (60.0) |
| - Schizoaffective disorder | 18 (10.6) | 10 (11.9) | 8 (9.4) |
| - Psychotic disorder NOS | 18 (10.6) | 12 (14.3) | 6 (7.1) |
| - Schizophrenia disorganized type | 11 (6.5) | 4 (4.8) | 7 (8.2) |
| - Other schizophrenic disorders | 25 (14.8) | 12 (14.3) | 13 (15.3) |
| Duration of illness mean (SD), years | 12.2 (8.5) | 11.5 (7.3) | 12.9 (9.5) |
| Medication at baseline, *N* (%) | | | |
| - First-generation antipsychotics | 126 (74.5) | 61 (72.6) | 65 (76.5) |
| - Second-generation antipsychotics | 40 (23.7) | 22 (26.2) | 18 (21.2) |
| - Unknown | 3 (1.8) | 1 (1.2) | 2 (2.3) |
| Penfluridol antipsychotic medication (oral) | 25 (14.8) | 16 (19.0) | 11 (12.9) |
| No. of psych admissions,‡ median (interquartile range) | 1 (0-3) | 2 (0-4) | 1 (0-3) |
| Length of psych admission days,‡ median (interquartile range) | 44 (0-120) | 71 (0-161) | 18 (0-103) |
| Patients per admission frequency,‡ *N* (%) | 52 (30.8) | 23 (27.4) | 29 (34.1) |
| - 0 admission | 44 (26.0) | 19 (22.6) | 25 (29.4) |
| - 1 admission | 22 (13.0) | 12 (14.3) | 10 (11.8) |
| - 2 admissions | 51 (30.2) | 30 (35.7) | 21 (24.7) |
| - > 2 admissions | | | |

*†Mental health law for compulsory admissions and outpatient commitment in the Netherlands*
*‡3 years preceding the baseline interview*

drop-out, we needed 84 patients per group to reliably detect an absolute difference of 20%. Recruitment ended when 169 patients had been included.

We used generalised linear models with binomial errors and logit link to analyse differences in MPR. The denominator of the MPR was the number of prescribed depots, ranging from 12 to 52 during the intervention period (i.e., between one and four incentives per month). We also modelled the differences in the proportion of treatment responders with an MPR of at least 80%. We tested differences in the time to discontinuation of depot medication with Kaplan–Meier analysis and multivariate Cox regression. All models included the stratification variables sex, substance-use disorder, and compliance with antipsychotic medication in the 4 months before randomisation. Treatment sites were not included because of structural changes within the teams during the study.

Regression models were compared on the basis of the log-likelihood ratio test or Akaike's information criterion (values for non-nested models). We used error distributions appropriate to the outcome measure: binomial for MPR and other ratios, Poisson for counts, and Gaussian for sum or composite scores. For the final model, we assessed diagnostics graphically.

For sensitivity analyses we used a worst-case scenario. Patients from the control group with incomplete depot registrations were assumed to have 100% adherence and patients in the intervention group were assumed to have 0% adherence, thereby lowering the contrast between groups. Finally, we used different strategies for handling missing values for secondary outcomes (eg, simple mean and regression imputation). We did analysis by intention to treat. Analyses were done with SPSS (version 21.0). This trial is registered with the Nederlands Trial Register, number NTR2350.

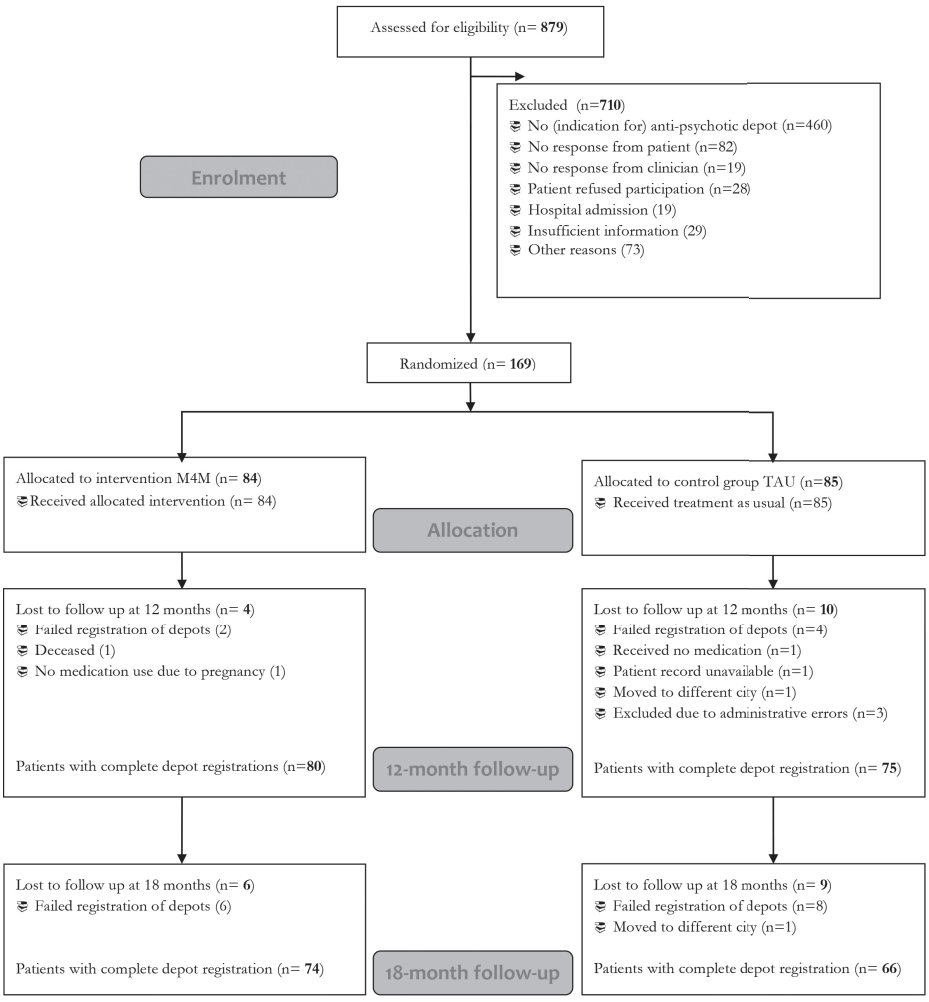
*Role of the funding source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## 3.3 Results

Between May 21, 2010, and Oct 15, 2014, we randomly assigned 169 patients to the intervention group (n=84) or the control group (n=85; figure 1). Baseline characteristics were similar between groups (table 1). Primary outcome data were available for 155 (92%) patients.

**Figure 1. Trial profile of Money for Medication**




### 3.3.1 Primary outcome

After 12 months, the estimated MPR was 92·7% (95% CI 89·6–94·9) in the intervention group and 77·0% (72·1–81·3) in the control group, with an adjusted difference of 14·9% (95% CI 8·9–20·9; p<0·0001; table 2). Dependent on the antipsychotic medication patients were prescribed, the MPR ranged between 85·2% (once per week) and 96·9% (once per month) in

**Table 2. Outcome measures after 12-month intervention period**

| | Intervention group | | Control group | | No of patients in multi-variable analysis | Adjusted effect estimate* (intervention vs. control) (95% CI) | |
|---|---|---|---|---|---|---|---|
| **Primary outcome** | **No of patients** | **Mean (SD)** | **No of patients** | **Mean (SD)** | | | **P value** |
| Medication Possession Ratio (MPR) | | | | | | | |
| - Baseline~ | 78 | 76% (28%) | 75 | 78% (28%) | | | |
| - End of study period | 80 | 93% (11%) | 75 | 77% (19%) | 155 | 14·9% (8·9% to 20·9%) | < 0·0001 |
| Patients with an MPR ≥ 80% | | | | | | | |
| - Baseline | 84 | 56% (4·5%) | 82 | 61% (4·5%) | | | |
| - End of study period | 80 | 95% (1·9%) | 75 | 59% (4·3%) | 155 | 33·1% (20·2% to 45·4%) | 0·031 |
| **Secondary outcomes** | | | | | | | |
| Longest uninterrupted time interval | | | | | | | |
| - End of study period | 80 | 273 (96) | 75 | 177 (109) | 155 | 96 (63·46 to 128·54) | < 0·0001 |
| Days between prescription date and the date the depot was taken - End of study period | 79 | 7·2 (9·6) | 75 | 10·9 (10·4) | 154 | 2·8 (1·77 to 3·94) | 0·049 |
| Days without medication | | | | | | | |
| - End of study period | 80 | 43 (59) | 75 | 112 (88) | 155 | 66·8 (43·16 to 90·44) | < 0·0001 |
| Attitude towards antipsychotic medication (ROMI; range: -20-18) | | | | | | | |
| - Baseline | 80 | 2·1 (6·1) | 81 | 4·0 (6·3) | | | |
| - End of study period | 66 | 3·1 (6·8) | 65 | 3·7 (6·6) | 131 | 0·19 (-0·72 to 0·35) | 0·87 |

| | Intervention group | | Control group | | No of patients in multi-variable analysis | Adjusted effect estimate* (intervention vs. control) (95% CI) | |
|---|---|---|---|---|---|---|---|
| **Clinical outcomes** | **Mean (SD)** | **No of patients** | **Mean (SD)** | | | **P value** | |
| PANSS total score (range: 30-210) | | | | | | | |
| - Baseline | 84 | 53·6 (16·2) | 81 | 49·9 (13·6) | | | |
| - End of study period | 68 | 55·7 (17·7) | 63 | 51·1 (15·3) | 131 | 3·93 (-1·47 to 9·34) | 0·32 |
| PANSS positive score (range: 7-49) | | | | | | | |
| - Baseline | 84 | 12·3 (5·1) | 81 | 11·8 (4·4) | | | |
| - End of study period | 68 | 12·3 (5·5) | 63 | 12·4 (5·4) | 131 | 0·25 (-2·05 to 1·56) | 0·85 |
| PANSS negative score (range: 7-49) | | | | | | | |
| - Baseline | 84 | 13·6 (5·8) | 81 | 11·6 (4·1) | | | |
| - End of study period | 68 | 14·9 (6·5) | 63 | 12·5 (4·8) | 131 | 2·32 (0·36 to 4·29) | 0·105 |
| Medication side effects (ASC; range: 0-17) | | | | | | | |
| - Baseline | 84 | 5·3 (4·0) | 81 | 4·3 (3·8) | | | |
| - End of study period | 68 | 5·1 (4·4) | 63 | 4·0 (3·9) | 131 | 0·20 (0·03 to 0·36) | 0·094 |
| No of patients admitted† | | | | | | | |
| - End of study period | 80 | 28% (4·4%) | 75 | 21% (4·1%) | 155 | 7·28% (-9·11% to 21·11%) | 0·406 |
| Length of admission (days) | | | | | | | |
| - End of study period | 22 | 52·2 (69·3) | 16 | 31·0 (59·7) | 38 | 24·59 (-17·14 to 66·34) | 0·29 |
| Patients with substance-use disorder (CIDI) | | | | | | | |
| - Baseline | 84 | 57% (4·5%) | 85 | 54% (4·6%) | | | |
| Alcohol problem score (ASI; range: 0-1) | | | | | | | |
| - Baseline | 84 | 0·05 (0·10) | 82 | 0·05 (0·12) | | | |
| - End of study period | 68 | 0·09 (0·20) | 66 | 0·06 (0·11) | 134 | 0·02 (-0·05 to 0·09) | 0·59 |
| Drug problem score (ASI; range: 0-1) | | | | | | | |
| - Baseline | 84 | 0·07 (0·13) | 82 | 0·08 (0·13) | | | |
| - End of study period | 68 | 0·12 (0·16) | 66 | 0·11 (0·13) | 134 | 0·01 (-0·08 to 0·10) | 0·78 |

**Table 2. Continued**

| | Intervention group | | Control group | | No of patients in multi-variable analysis | Adjusted effect estimate* (intervention vs. control) (95% CI) | |
|---|---|---|---|---|---|---|---|
| Quality of Life (MANSA; range: 13-91) | | | | | | | |
| - Baseline | 84 | 57·5 (12·8) | 81 | 62·0 (10·7) | | | |
| - End of study period | 68 | 58·2 (11·8) | 63 | 60·7 (10·4) | 131 | 2·5 (-1·29 to 6·32) | 0·36 |
| Psychosocial functioning (HoNOS total; range: 0-36) | | | | | | | |
| - Baseline | | | | | | | |
| - End of study period | 84 | 10·7 (5·2) | 81 | 9·5 (5·1) | | | |
| | 67 | 10·9 (5·2) | 66 | 9·3 (4·6) | 133 | 1·26 (-0·25 to 2·76) | 0·25 |

*Each model was adjusted for gender, medication compliance in the 4 months before baseline, and substance-use disorder. The reference category for the adjusted effect estimates included previous compliant men who were not diagnosed with substance use disorders. To test for differences between the conditions, Generalized Linear Models were used with different distributions appropriate to the outcomes.

˜Baseline adherence registrations were incomplete for some patients (6 intervention, 10 controls) and could only be assessed for the dichotomous MPR outcomes. †Frequency of admissions, median (interquartile range): M4M: 0 (0-1), TAU: 0 (0-0). To test for differences between the conditions, Generalized Linear Models were used with different distributions appropriate to the outcomes. ROMI=Rating of Medication Influences; PANSS=Positive and Negative Syndrome; Scale CIDI=Composite International Diagnostic Interview; ASI=Addiction Severity Index; ASC=Antipsychotic Side Effect Checklist; MANSA=Manchester Short Assessment of Quality of Life; HoNOS=Health of the Nations Outcome Scores.

the intervention group, and between 67·9% (once per week) and 89·9% (once per month) in the control group.

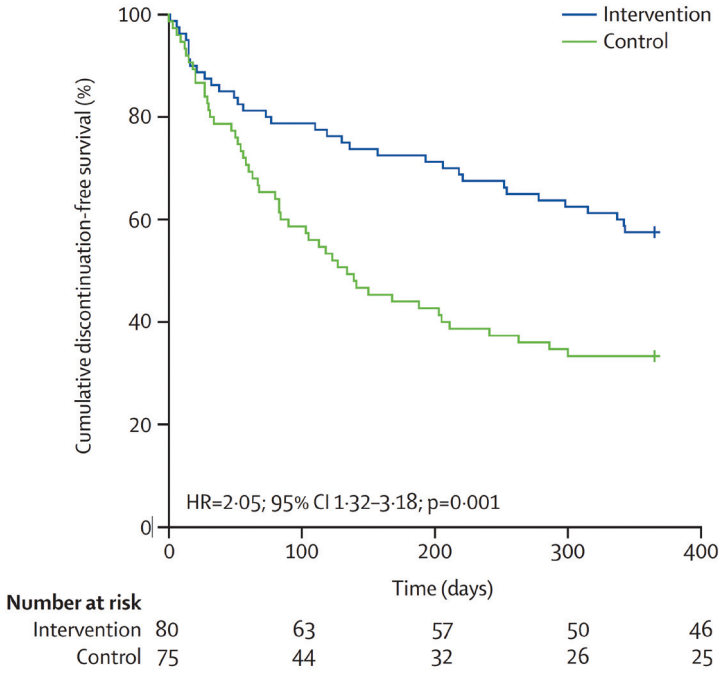
After dichotomisation of patients with an MPR of 80% or higher in the intervention (n=76) and control (n=44) groups, the adjusted difference in the proportion of patients achieving good adherence levels was 33·1% (95% CI 20·2–45·4; p=0·031) in favour of the intervention group (table 2). Overall improvement of the MPR in the intervention group was contributed mainly by patients with low adherence rates at baseline (from 52% to 91%), whereas rates in patients with good adherence at baseline remained high after 12 months (around 98%). By contrast, patients in the control group with high adherence rates at baseline (98%) had lower adherence after 12 months (81%).

### 3.3.2 Secondary outcomes

The longest uninterrupted period during which depots were received was almost 100 days longer for patients in the intervention group (table 2). Furthermore, time to discontinuation was significantly improved in patients in the intervention group (median 365 days [IQR 132–365]) compared with those in the control group (134 days [52–365]; log-rank test, $\chi^2$=10·57, 1 degree of freedom; p=0·001; figure 2). The mean time that expired before the prescribed depot was received was 2·8 days (95% CI 1·77–3·94) lower for patients receiving the intervention than for those receiving the control strategy (table 2). The total number of days without antipsychotic medication differed significantly in favour of the intervention group (table 2). Patients' attitudes towards medication at the end of the 12 month study period did not differ significantly from those at baseline (table 2).

There were no differences between groups in total psychiatric symptoms, positive symptoms, or negative symptoms (table 2). The number of side-effects of the antipsychotic depot medication did not differ significantly between patients in the intervention and control groups, and the number of patients who had the most prevalent side-effects (i.e., feeling sleepy, loss of energy, and muscle tension) was similar between groups (n=15 and n=17, respectively). Neither the number of patients who had been admitted to hospital, nor their lengths of hospital stay, differed significantly between groups (table 2). Composite scores for problematic alcohol and drug use did not differ between groups (table 2). No significant differences were recorded for subjective quality-of-life ratings assessed with the MANSA (table 2). Differences in psychosocial functioning assessed with HoNOS total scores were not significant between groups (table 2), nor were Bonferroni-corrected differences in terms of the HoNOS subscores of symptoms (β=0·23, 95% CI −0·38 to 0·83; p=0·467), behaviour (0·14, −0·25 to 0·52; p=0·494), and impairment (0·48, 0·03 to 0·93; p=0·038).

**Figure 2. Kaplan–Meier curves showing time to fi rst discontinuation of depot medication**
HR calculated with Cox regression analysis. Vertical lines represent patients censored. HR=hazard ratio.



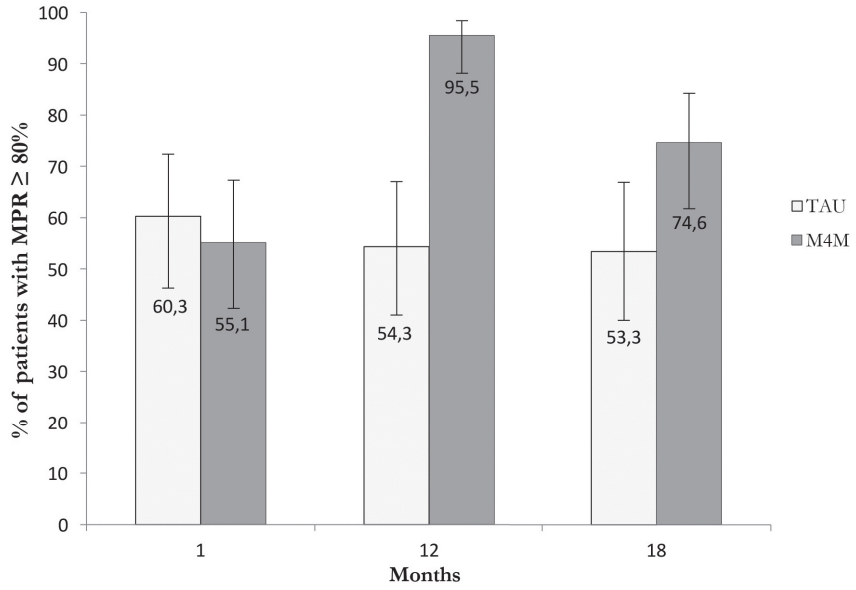

### 3.3.3 Follow-up period

After the 6 month follow-up period, during which time patients in the intervention group received treatment as usual, but no longer received monetary rewards, depot registrations were available for 140 patients (figure 1). The estimated MPR had decreased in the intervention group, from 92·7% (95% CI 89·6–94·9) to 83·4% (77·8–87·6), and remained stable in the control group, going from 77·0% (72·1–81·3) to 76·0 (69·3–81·7), with an adjusted difference of 6·5% (95% CI 2·0-10·9; p=0·047). The proportion of patients achieving good adherence (≥80% MPR) was substantially higher in the intervention group (74% [n=55]) than in the control group (55% [n=36]), with a significant adjusted difference of 22·1% (95% CI 4·2–39·8%; p=0·011; figure 3).

### 3.3.4 Sensitivity analyses

In sensitivity analyses, we first analysed data for all randomly assigned patients (N=169) and used a worst-case scenario to impute missing values for those without depot registration (n=4 in the intervention group and n=10 in the control group). The mean MPR difference remained in

**Figure 3. Patients achieving MPR ≥ 80% during 18-month study period**




favour of the money for medication intervention (11·9%, 95% CI 5·4–18·4; p<0·0001). Second, we calculated the MPR without correction for periods of hospital stay for the intervention group (92·1%) and the control group (75·6%), which produced an MPR difference of 15·2% (95% CI 9·1–21·2; p<0·0001). Third, we added outpatient commitment measures to our regression model, which produced an MPR difference of 15·1% (95% CI 8·7–21·5; p<0·0001) in favour of the intervention. Finally, we imputed values for the 6 month follow-up period by use of the worst-case scenario (n=10 in the intervention group and n=19 in the control group), resulting in an MPR difference of 5·4% (95% CI 1·0–9·9; p=0·21).

## 3.4 Discussion

Our findings show that financial incentives improved adherence to antipsychotic depot medication in patients with psychotic disorders. After 12 months, adherence was 14% higher in the intervention group than in the control group. Importantly, 95% of the patients in the intervention group achieved adherence levels of 80% or higher, compared with only 59% of patients in the control group. During the 6 month follow-up period, when the offer of financial incentives was discontinued, the positive effects on medication adherence decreased, but

adherence levels remained about 5–7% higher in the intervention group than in the control group. Moreover, 74% of patients in the intervention group achieved MPR rates of 80% or higher, compared with 54% of patients in the control group.

To our knowledge, this study is the first to include both adherent and non-adherent patients; therefore, the results are more generalisable than those of previous studies [12,13]. Although targeting of all patients with psychotic disorders led to inclusion of patients with relatively high adherence levels at baseline (77%), thereby leaving less opportunity for improvement, our use of financial incentives increased medication adherence by 17% for patients receiving the intervention, whereas adherence in the control group remained unchanged. Sensitivity analyses showed a robust intervention effect for all patients with psychotic disorders receiving depot medication, irrespective of their level of adherence at study entrance.

Limitations of our study include its open-label character. Although masking of patients to receipt of a financial reward was not possible, the outcomes might have been influenced by the absence of masking of the clinicians and interviewers. However, we minimised bias by collecting primary outcome data from patients' records. A second limitation is that this study did not succeed in recruitment of completely non-adherent patients, who refused any form of treatment contact.

The first randomised controlled trial by Priebe and colleagues [13] showed that financial incentives improved compliance with antipsychotic depot medication among psychotic disorder patients with poor adherence (11·5% difference between the experimental and control conditions). Our study supports those findings (14·9% difference between groups) and shows that the effectiveness of the intervention is not restricted to patients with poor adherence, but is generalisable to all patients with psychotic disorders, irrespective of their level of medication adherence. Our study is also the first to show that, during a 6 month follow-up period, the effects on medication adherence persist after monetary rewards are discontinued, albeit at a reduced level (14·9% *vs* 6·5%).

Although financial incentives successfully improved medication adherence for patients with psychotic disorders, what are the potential risks of applying this intervention? And to what extent is increased adherence related to clinical outcomes? Clinicians might argue against the use of financial incentives, claiming that such incentives give patients the opportunity to spend the money on, for instance, drugs or alcohol. However, in this study, we recorded no differences in the severity of substance abuse between patients in the intervention and control groups. Clinicians might also argue that the offer of financial incentives affects patients' (intrinsic) motivation for taking antipsychotic depot medication. Therefore, our finding that patients do not immediately refuse all depot medication when financial incentives are discontinued,

even though the positive effect on medication adherence does diminish somewhat over time, is important. Another potential risk factor is that improved medication adherence might increase medication side-effects, thereby restricting the benefits of treatment. However, in our study, patients with improved medication adherence did not report an increase in incidence of side-effects. Finally, higher intake of antipsychotics is often associated with increased negative symptoms (such as flattened affect, anhedonia, or apathy) that could negatively influence patients' clinical and functional outcomes [29]. In our study, negative symptoms did not increase, and remained low in both groups. We therefore believe that financial incentives can be used to improve antipsychotic depot medication adherence without increasing substance-use problems, medication side-effects, or negative symptoms.

Although these results are beneficial with regard to improvements in medication adherence, the idea of giving patients money for taking medication raises ethical issues [30]. One main ethical concern is the risk of reducing patients' autonomy, because people who are in financial difficulties might feel they need to take the medication to receive money, irrespective of whether or not they want to take the medication. There is a risk that if money is offered, the decision of a patient about whether to take medication is not based purely on a balance of risks and benefits of the medication. In addition to upholding ethical principles of respect for autonomy, clinicians also have a duty to work in a patient's best interests and not to harm patients, and clinicians might be concerned that offering money could seem as if they are bribing patients or that the side-effects and risks of treatment are assumed to be lower than they actually are; this could also harm the clinician–patient relationship.

Another concern when considering giving money to some patients and not others, or some groups of society and not others, is the principle of fairness and equality. If money is offered only to people who have low adherence to medication, people with better adherence might feel this is unfair or even change their adherence patterns in order to receive money [31]. If a health system allocates money for taking medication, this money might have to be withdrawn from treatment of another group of patients, or other groups might begin to expect money for taking medication or making health-related behavioural changes—e.g., for taking diabetes medications or for stopping smoking or losing weight. These and other ethical issues will be described in depth in a separate paper about patients' and clinicians' ethical considerations when offering financial incentives in clinical practice.

To offer patients equal treatment opportunities, we believe that this intervention should be available to all patients, irrespective of their previous level of adherence. Therefore, we would recommend those in clinical practice (e.g., physicians, psychologists, psychiatrists, social workers) to offer financial incentives to all patients, even though these findings cannot be fully concluded from this study.

Finally, adherence is a behaviour that changes dynamically, and often patients become non-adherent over time. Provision of incentives might help patients to take their medications for a longer, uninterrupted period. In the present study, the direct intervention costs were fairly low (on average €339 per patient per year). Further cost-utility analyses will be reported in a separate paper that compares the direct and indirect medical and societal costs between the intervention and control groups.

Although medication adherence improved, we recorded no differences in patients' subjective quality of life, psychiatric symptoms, and hospital admissions. Nonetheless, this absence of statistical significance does not confirm that there were no real differences in these outcomes. If we assume differences in clinical outcomes, why might they not have been identified here? The first reason might be that patients' subjective quality of life and psychosocial functioning were relatively high, leaving little room for improvement. However, patients' clinical functioning did not worsen during the intervention period. Second, improved medication adherence might not be sufficient to improve complex clinical outcomes, such as quality of life. Improved clinical outcomes might require additional interventions focusing on social factors [32]—e.g., active involvement of the social-support system, (volunteer) work, physical exercise, and the establishment of a structured daily schedule.

Because antipsychotics might have less effect on improving psychiatric symptoms after many years compared with early in the course of illness (the average illness duration is 12 years), a third possible reason is that patients who had been ill for a long time did not derive any added benefit from improved medication adherence. If this is the case, these patients might have symptoms that are not further reduced by improved adherence to antipsychotic depot medication. These reasons might explain why intervention studies often succeed in improving adherence levels, but do not show significant improvements in clinical outcomes. Conversely, what if our findings reflect a true lack of effect on clinical outcomes? Financial incentives would still serve a more practical purpose, such as encouraging patients to maintain regular contact with the clinic, and supporting clinicians' efforts to contact their patients. Precisely because these patients are ambiguous in their medication adherence and are often very difficult to contact, we would still recommend this intervention, because incentives facilitate the outreaching care of mental health-care teams.

Further research is needed to study the long-term effects of use of financial incentives, for example in a randomised controlled trial that compares the effectiveness of a 12 month versus a 24 month intervention period. These studies should also aim to improve clinical outcomes, such as psychiatric symptoms and quality of life.

## Acknowledgments

This study was funded by the Dual Diagnosis Center Palier. We thank the patients, research assistants, clinicians, and health-care facilities that participated in this study.

## References


1. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res* 2010; 176: 109–13.
2. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry* 2006; 67: 1542–50.
3. Llorca P-M. Partial compliance in schizophrenia and the impact on patient outcomes. *Psychiatry Res* 2008; 161: 235–47.
4. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res* 2011; 127: 83–92.
5. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev* 2012; 5: CD008016.
6. Suzuki T, Remington G, Arenovich T, et al. Time course of improvement with antipsychotic medication in treatment-resistant schizophrenia. *Br J Psychiatry* 2011; 199: 275–80.
7. Fazel S, Zetterqvist J, Larsson H, Langstrom N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet* 2014; 384: 1206–14.
8. Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: meta analysis. *Br J Psychiatry* 2003; 183: 197–206.
9. Gray R, Leese M, Bindman J, et al. Adherence therapy for people with schizophrenia. European multicentre randomised controlled trial. *Br J Psychiatry* 2006; 189: 508–14.
10. Staring ABP, Van der Gaag M, Mulder CL. Schizophrenia and antipsychotic medication—better adherence, better outcomes? *Schizophr Res* 2013; 151: 296–97.
11. Claassen D, Fakhoury W, Ford R, Priebe S. Money for medication: financial incentives to improve medication adherence in assertive outreach. *Psychiatr Bull* 2007; 31: 4–7.
12. Staring ABP, Mulder CL, Priebe S. Financial incentives to improve adherence to medication in five patients with schizophrenia in the Netherlands. *Psychopharmacol Bull* 2010; 43: 5–10.
13. Priebe S, Yeeles K, Bremner S, et al. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomised controlled trial. *BMJ* 2013; 345: f5847.
14. Pavlickova H, Bremner SA, Priebe S. The effect of financial incentives on adherence to antipsychotic depot medication: does it change over time? *J Clin Psychiatry* 2015; 76: e1029–34.
15. Denee TR, Geerts P, Sermon J, et al. Treatment continuation and treatment characteristics of four long acting antipsychotic medications (paliperidone palmitate, risperidone microspheres, olanzapine pamoate and haloperidol decanoate) in the Netherlands. *Value Health* 2015; 18: A335–766.
16. Urbaniak GC, Plous S. Research Randomizer (version 4.0). 2013. http://www.randomizer.org/ (accessed June 22, 2013).
17. Noordraven EL, Audier CH, Staring A, et al. Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. *BMC Psychiatry* 2014; 14: 343.
18. Weiden PJ, Rapkin B, Mott T, et al. Rating of Medication Influences (ROMI) scale in schizophrenia. *Schizophr Bull* 1994; 20: 297–310.
19. Weiden PJ, Miller AL. Which side effects really matter? Screening for common and distressing side effects of antipsychotic medications. *J Psychiatr Pract* 2001; 7: 41–47.
20. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13: 261–72.
21. Priebe S, Huxley P, Knight S, Evans S. Application and results of the Manchester Short Assessment of Quality of Life (MANSA). *Int J Soc Psychiatry* 1999; 45: 7–12.
22. Bebbington P, Brugha T, Hill T, Marsden L, Window S. Health of the Nation Outcome Scales (HoNOS). *Br J Psychiatry* 1999; 174: 389–94.

23. Kokkevi A, Hartgers C. EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *Eur Addict Res* 1995; 1: 208–10.
24. Wittchen HU. Reliability and validity studies of the WHO–Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994; 28: 57–84.
25. Sclar DA, Pharm B, Chin A, et al. Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clin Ther* 1991; 13: 489–95.
26. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009; 70: 1–46.
27. Priebe S, Burton A, Ashby D, et al. Financial incentives to improve adherence to antipsychotic maintenance medication in non-adherent patients—a cluster randomised controlled trial (FIAT). *BMC Psychiatry* 2009; 9: 16.
28. Remington G, Kwon J, Collins A, Laporte D, Mann S, Christensen B. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. *Schizophr Res* 2007; 90: 229–37.
29. Möller H-J. Clinical evaluation of negative symptoms in schizophrenia. *Eur Psychiatry* 2007; 22: 380–86.
30. Claassen D. Financial incentives for antipsychotic depot medication: ethical issues. *J Med Ethics* 2007; 33: 189–93.
31. Szmukler G. Financial incentives for patients in the treatment of psychosis. *J Med Ethics* 2009; 35: 224–28.
32. Yesufu-Udechuku A, Harrison B, Mayo-Wilson E, et al. Interventions to improve the experience of caring for people with severe mental illness: systematic review and meta-analysis *Br J Psychiatry* 2015; 206: 268–74.

# Chapter 4

## Depot-medication compliance for patients with psychotic disorders: the importance of illness insight and treatment motivation

Ernst L Noordraven
André I Wierdsma
Peter Blanken
Anthony F T Bloemendaal
Cornelis L Mulder

*Neuropsychiatric Disease and Treatment 2016, 12: 269–274*

## Abstract

### Background

Noncompliance is a major problem for patients with a psychotic disorder. Two important risk factors for noncompliance that have a severe negative impact on treatment outcomes are impaired illness insight and lack of motivation. Our cross-sectional study explored how they are related to each other and their compliance with depot medication.

### Methods

Interviews were conducted in 169 outpatients with a psychotic disorder taking depot medication. Four patient groups were defined based on low or high illness insight and on low or high motivation. The associations between depot-medication compliance, motivation, and insight were illustrated using generalized linear models.

### Results

Generalized linear model showed a significant interaction effect between motivation and insight. Patients with poor insight and high motivation for treatment were more compliant (94%) (95% confidence interval [CI]: 1.821, 3.489) with their depot medication than patients with poor insight and low motivation (61%) (95% CI: 0.288, 0.615). Patients with both insight and high motivation for treatment were less compliant (73%) (95% CI: 0.719, 1.315) than those with poor insight and high motivation.

### Conclusions

Motivation for treatment was more strongly associated with depot-medication compliance than with illness insight. Being motivated to take medication, whether to get better or for other reasons, may be a more important factor than having illness insight in terms of improving depot-medication compliance. Possible implications for clinical practice are discussed.

## 4.1 Introduction

Nonadherence to antipsychotic medication has been shown to be a major obstacle to achieving successful treatment outcomes in patients with psychotic disorders [1]. Approximately 60% of these patients have difficulty in being adherent over time, leading to problems such as inconsistent symptom control, more relapses, more hospitalizations, and more suicide attempts [2,3]. Patient, treatment, and environment-related risk factors have all been associated with nonadherence [4]. This article focuses on two important patient risk factors that appear to have a great impact on whether patients adhere to their prescribed medication regimen: illness insight and motivation for treatment.

Illness insight has been defined by David [5] as 1) the recognition that one has a mental illness, 2) the recognition of the need for treatment, and 3) the ability to relabel unusual mental events as pathological. Of patients with a psychotic disorder, approximately 50% to 75% have only a limited degree of illness insight, which often results in poorer treatment outcomes [6–8].

The relationship between insight and medication adherence is somewhat ambiguous [9]: while some studies showed a clear positive association [10–12], others either failed to find an association or showed that the effect of insight on medication adherence diminished over time [13,14]. In sum, illness insight is not enough to improve medication compliance. Neither is it a prerequisite for taking medication. Perhaps patients with poor insight who accept their medication are simply motivated to take medication, whether or not they completely understand or acknowledge their mental illness.

Motivation has been defined as "the probability that a per-son will enter into, continue, and adhere to a specific change strategy" [15]. Motivation for treatment among psychotic patients has been studied extensively in therapeutic settings, and is positively associated with effective treatment outcomes [16]. Often, however, motivation for treatment is lacking in patients with psychotic disorders such as schizophrenia [17]. As a result, these patients are less willing to adhere to antipsychotic medication prescriptions, to engage in treatment activities, or to show up for appointments. Neither are they likely to benefit from their treatment. As a negative symptom of schizophrenia disorder, lack of motivation is a common problem that is difficult for patients and clinicians to address.

To increase the benefits of treatment, patients can be prescribed antipsychotic depot medication, which is easier to monitor, has long-lasting effects, and reduces relapse rates more than oral medication [18]. However, since the effects of depot medication in different treatment settings are somewhat unclear [19], we decided to focus on the effects of antipsychotic depot medication among outpatients with a psychotic disorder.

Thus, impaired insight and lack of motivation can have a negative impact on medication compliance. It remains unclear, however, how these risk factors relate to each other and to medication compliance. This is important for developing intervention studies that might focus more on developing illness insight or increasing motivation for treatment. Therefore, in a cross-sectional study we explored the associations between illness insight, motivation for treatment, and adherence to antipsychotic depot medication.

## 4.2 Methods

### 4.2.1 Patients

Baseline data were obtained from 169 patients participating in Money for Medication, an ongoing randomized controlled trial on the effectiveness of financial incentives for improving adherence to depot medication (for protocol details, see Noordraven et al [20]). Patients were recruited from three mental health care institutions in the Netherlands that primarily treat patients with psychotic and other severe mental disorders (often with comorbid substance-use disorder). Patients met the following inclusion criteria: age between 18 and 65 years, having a psychotic disorder, taking antipsychotic depot medication or an indication to start using it, receiving outpatient treatment, and having given written informed consent on participating in a randomized controlled trial. There were two exclusion criteria: inability to participate due to cognitive impairments and inability to participate due to insufficient understanding of the Dutch language. The study was approved by the accredited Dutch Medical Ethical Trial Committee at Erasmus University Medical Center (Trial Registration NTR2350).

### 4.2.2 Procedure

Candidate participants were selected from the caseloads on the basis of the inclusion and exclusion criteria. The baseline interview was conducted after written informed consent had been given and before randomization. All interviews were conducted by psychologists who had received professional training in the Positive And Negative Syndrome Scale (PANSS) and Health of the Nation Outcome Scales (HoNOS) interview and its subsequent scoring procedures. Per interview, all participants received a remuneration of €20. Demographic variables, *DSM*-IV diagnoses on axis I and II, and psychiatric history were collected during the first interview and from patients' medical records. In the trial, randomization took place after the first interview, whereas for this study all patients were treated as one sample. For a more detailed protocol description, see Noordraven et al [20].

### 4.2.3 Measurements

*Medication compliance*

The medication possession ratio (MPR), first reported by Sclar et al. [21] was used as a measure for depot-medication compliance. MPR is defined as the number of accepted depots of antipsychotic medication divided by the number of depots of antipsychotic medication prescribed, that is, the number of supplies needed for continuous use of antipsychotic medication. Each patient's MPR at baseline was determined on the basis of the 4 months prior to the baseline interview.

*Illness insight*

Insight was measured using the Dutch version of the PANSS [22], a 30-item semistructured interview intended to determine the presence of positive and negative symptoms and general psychopathology. Illness insight was assessed on the basis of item A12 of the PANSS "Do you have a psychiatric disorder or mental health problem?" in which the patient is also asked to elaborate his answer. Specifically, this item describes a patient's ability to acknowledge his or her psychiatric disorder, need for treatment, and ability to make future plans. Items were scored on a scale from 1 (illness insight present) to 7 (active denial of having a psychiatric disorder). Response scores for insight (item A12) were dichotomized into patients having "poor insight" (scoring 3–7 on the insight item) and "high illness insight" (scoring 1–2).

*Motivation for treatment*

Motivation for treatment was assessed on the basis of an item added to the Dutch version of the HoNOS [23], which describes a patient's motivation in terms of cooperation, personal interest, and possible resistance to treatment: "How motivated are you for your current treatment?" As with the other items of the HoNOS, this item was rated on a 5-point scale ranging from 0 (no problems) to 4 (very severe problems). Patient scores were dichotomized into "high motivation for treatment" (scoring 0–1 on the motivation item) and "low motivation for treatment" (scoring 2–4).

### 4.2.4 Missing values

Due to administrative errors, data for the total sample lacked baseline data for three patients. Similarly, 13 values were missing for compliance rates, 2 for motivation, and 2 for insight. One patient had missing values for both motivation and insight. Therefore, in total, 19 patients were excluded from the analyses. Sensitivity analyses using imputed data on average values did not show different results.

### 4.2.5 Statistical analyses

We used generalized linear models to estimate the effect of motivation and insight on the number of depots accepted as a percentage of the number of depots prescribed. Because MPR values are proportion data, we assumed binomial error distribution and used the logit link function. Patients were grouped into four categories: 1) those with low motivation and poor insight (n=62); 2) those with high motivation but poor insight (n=17); 3) those with low motivation but a high degree of insight (n=17); and 4) those whose motivation and illness insight were high (n=54). All groups were entered as one categorical predictor variable. Since patients with low motivation and poor insight had the lowest compliance rate (65.8%), we used this category as our reference group. All statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

**Table 1. Baseline Characteristics of the study sample (*N* = 166)**

| Variable | Mean / N | SD / % |
|---|---|---|
| Age (years) | 40.7 | 10.2 |
| Gender (*N*) | | |
| - Male | 124 | 74.3 % |
| - Female | 42 | 25.1 % |
| Duration of illness (years) | 12.3 | 8.5 |
| Ethnicity | | |
| - Dutch | 64 | 38.3 % |
| - Surinamese | 39 | 23.4 % |
| - Other | 63 | 38.3 % |
| BOPZ measure, *N* (%)* | 60 | 36.7 % |
| Diagnosis, *N* (%) | | |
| - Schizophrenia paranoid type | 96 | 57.5 % |
| - Schizoaffective disorder | 18 | 10.8 % |
| - Psychotic disorder NOS | 18 | 10.8 % |
| - Schizophrenia disorganized type | 11 | 6.6 % |
| - Other schizophrenic disorders | 24 | 14.3 % |
| Medication at baseline, *N* (%) | | |
| - First-generation antipsychotics | 125 | 75.8 % |
| - Second-generation antipsychotics | 39 | 23.6 % |
| - Depot medication | 140 | 82.6 % |
| Motivation: median (IQR), min-max | 2 (2) | 0-4 |
| Illness insight: median (IQR), min-max | 3 (3) | 1-7 |
| No. of psych admissions,** median (IQR), min-max | 1 (3) | 0-17 |
| No. of admission days,** median (IQR), min-max | 44 (120) | 0-622 |

**Mental health law for compulsory admissions and outpatient commitment in the Netherlands*
*** 3 years preceding the baseline interview*

## 4.3 Results

### Patient characteristics

Table 1 presents the sociodemographic and clinical data of all patients at baseline. Data for motivation, insight, and medication compliance at baseline are presented in Table 2.

### 4.3.1 Relationship between insight and compliance

Insight was positively associated with MPR (β=1.471, 95% confidence interval [CI]: [0.468, 1.00], $P<0.001$), (Table 2). Patients with high illness insight were almost 10% more compliant with their prescribed antipsychotic depot medication than patients with poor insight.

### 4.3.2 Relationship between motivation and compliance

Motivation, too, was positively associated with MPR (β=1.133, 95% CI: [0.854, 1.413], $P<0.001$), (Table 2). Patients with a high motivation for treatment were 18% more compliant with the antipsychotic depot medication prescribed to them than patients with low motivation for treatment.

### 4.3.3 Insight, motivation, and their association with compliance

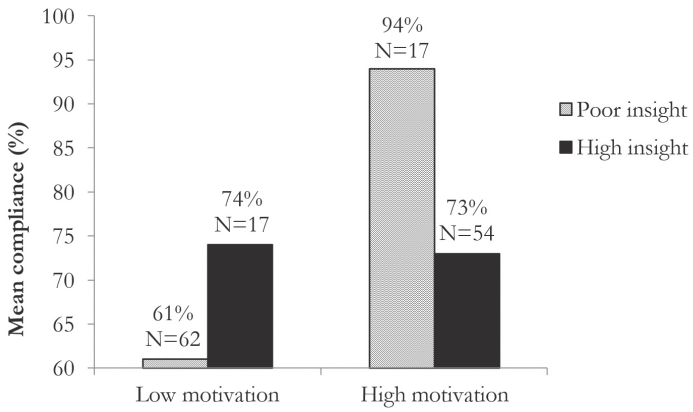
Our results showed a significant interaction effect between motivation and insight (Figure 1). Patients with poor insight but high motivation for treatment were more compliant with their medication (94%; β=2.655, 95% CI: [1.821, 3.489], $P<0.001$) than patients with poor insight and low motivation (61%; β=1.570, 95% CI: [0.288, 0.615], $P<0.001$). Patients with high insight and motivation (73%; β=1.017, 95% CI: [0.719, 1.315], $P<0.001$) and patients with high insight but low motivation (74%, β=1.028, 95% CI: [0.547, 1.510], $P<0.001$) were more compliant than patients with low motivation and poor insight (61%). Switching our reference category to patients with high motivation and insight (73%) allowed us to compare their medication compliance with patients with high insight and low motivation (74%), which showed no significant difference. However, patients with high motivation and poor insight

**Table 2. Mean MPR scores at baseline interview by motivation and insight**

| Variable | | Medication Possession Ratio | N |
|---|---|---|---|
| Insight | Poor | 71.9 % | 79 |
| | High | 81.6 % | 71 |
| Motivation | Low | 68.0 % | 79 |
| | High | 85.8 % | 71 |

(94%) were more compliant than those with high insight. This suggests that insight is not only less strongly associated with compliance than motivation, but also that the level of compliance in patients with high motivation may be reduced by insight.

**Figure 1. Interaction effect between patient categories**




## 4.4 Discussion

### 4.4.1 Insight, motivation and adherence

The main finding of our study was that motivation for treatment seems to be more important than illness insight for compliance with depot medication in psychotic dis-order patients. Specifically, we found that patients with a high motivation for treatment were most compliant with their medication, independent of insight. Unexpectedly, patients with high insight and high motivation showed less compliance as compared to patients with poor insight and high motivation.

It may seem contradictory that patients with poor illness insight were willing to accept their antipsychotic depot medication. From this perspective, one could argue that having illness insight is not a prerequisite for achieving compliance. In other words, it may be more important to be motivated to take medication – whether to get better, or for other reasons – than to have illness insight with regard to improving depot-medication compliance.

Our findings may have two important clinical consequences for increasing compliance with depot medication. First, we found that patients with poor insight who were highly motivated for treatment had over 30% more compliance. Therefore, it may be more important in patients with poor insight to improve motivation for treatment as a first step, for example,

by using motivational interviewing strategies [24], instead of immediately trying to enhance illness insight.

Second, when addressing illness insight, we have to be aware of possible negative consequences regarding compliance, since we found that a high degree of illness insight in highly motivated patients was accompanied by a level of compliance that was ~20% lower than that in patients with poor insight. This suggests that greater illness insight is not necessarily associated with higher compliance rates in patients who are highly motivated, but may sometimes be accompanied by lower medication acceptance. This is surprising, since it has always been assumed that it would be better to have good insight. Although our finding that greater illness insight does not lead to better compliance is counterintuitive, it may be that patients who are highly motivated and also have illness insight want to use other treatment options, such as oral medication and/or psychotherapy.

### 4.4.2 Limitations

Three important limitations of this study should be considered. First, our cross-sectional design makes it difficult to infer causality [25]. Longitudinal and experimental studies are needed to further study the associations between motivation, illness insight, and compliance.

The second limitation is that motivation and insight were both measured using a single item. In previous studies, however, the PANSS insight item showed high correlations with questionnaires assessing insight such as the Insight and Treatment Attitudes Questionnaire or the Schedule for the Assessment of Insight [26,27]. With respect to the HoNOS motivation item, earlier studies also found high and significant correlations with scales measuring the motivation construct, including the Treatment Entry Questionnaire and the Treatment Motivation Scale [28].

The third limitation is that only patients on depot medication participated in this study. Associations between illness insight and motivation may be different for patients on daily oral medication.

### 4.4.3 Conclusions

Motivation and illness insight both play an important role in a patient's acceptance of antipsychotic depots. Attempts to improve compliance should be made carefully, first by assessing their level of motivation and illness insight. The clinician can then make an informed decision on the extent of any interventions intended to improve compliance through improved motivation and/or insight. Our results suggest that it may be more important to improve compliance by improving motivation than by enhancing insight, especially in patients whose insight is already poor. It will be interesting to investigate whether this is also the case with

compliance with daily oral antipsychotic medications. Ultimately, different treatment protocols might be used for patients with different combinations of insight and motivation. In everyday practice, it may be best for clinicians not to focus on either insight or motivation, but to recognize that the most important factor in understanding compliance with antipsychotic medication lies in the combination of the two. Future research should establish whether these associations are valid over time and which interventions clinicians should use to improve motivation and illness insight among patients with a psychotic disorder.

## References


1. Gray R, Leese M, Bindman J, et al. Adherence therapy for people with schizophrenia European multicentre randomised controlled trial. Br J Psychiatry. 2006;189(6):508–514.
2. Llorca PM. Partial compliance in schizophrenia and the impact on patient outcomes. Psychiatry Res. 2008;161(2):235–247.
3. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California medicaid patients with schizophrenia. Psychiatr Serv. 2004;55(8):886–891.
4. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol. 2013;3(4):200–218.
5. David AS. Insight and psychosis. Br J Psychiatry. 1990;156(6): 798–808.
6. Buchy L, Torres IJ, Liddle PF, Woodward TS. Symptomatic determinants of insight in schizophrenia spectrum disorders. Compr Psychiatry. 2009;50(6):578–583.
7. Quee PJ, van der Meer L, Bruggeman R, et al. Insight in psychosis: relationship with neurocognition, social cognition and clinical symptoms depends on phase of illness. Schizophr Bull. 2011;37(1):29–37.
8. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70(4):1–46.
9. Lincoln TM, Lüllmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia. A systematic review. Schizophr Bull. 2007;33(6):1324–1342.
10. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. Schizophr Res. 2009;107(2–3):213–217.
11. Kozuki Y, Froelicher ES. Lack of awareness and nonadherence in schizophrenia. West J Nurs Res. 2003;25(1):57–74.
12. Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry. 2008;69(1):106–113.
13. McEvoy JP, Freter S, Everett G, et al. Insight and the clinical outcome of schizophrenic patients. J Nerv Ment Dis. 1989;177(1):48–51.
14. Yen CF, Chen CS, Ko CH, et al. Relationships between insight and medication adherence in outpatients with schizophrenia and bipolar disorder: prospective study. Psychiatry Clin Neurosci. 2005;59(4): 403–409.
15. Miller WR, Rollnick S. Motivational Interviewing: Preparing People to Change Addictive Behavior. New York: Guilford Press; 1991:1–300.
16. Yamada AM, Lee KK, Dinh TQ, Barrio C, Brekke JS. Intrinsic motivation as a mediator of relationships between symptoms and functioning among individuals with schizophrenia spectrum disorders in a diverse urban community. J Nerv Ment Dis. 2010;198(1):28- 34.
17. Choi J, Medalia A. Intrinsic motivation and learning in a schizophrenia spectrum sample. Schizophr Res. 2011;118(1–3):12–19.
18. Novick D, Haro JM, Bertsch J, Anand H, Jemiai N, Haddad PM. Comparison of treatment discontinuation and hospitalization among nonadherent patients initiating depot or oral typical antipsychotic medications. Int Clin Psychopharmacol. 2012;27(5):275–282.
19. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia – a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127(1–3):83–92.

20. Noordraven EL, Audier CH, Staring AB, et al. Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. BMC Psychiatry. 2014;14(1):343.
21. Sclar DA, Chin A, Skaer TL, Okamato MP, Nakahiro RK, Gill MA. Effect of health education in promoting prescription refill compliance among patients with hypertension Clin Ther. 1991;13(4):489–495.
22. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–272.
23. Kortrijk HE, Staring ABP, Van Baars AW, Mulder CL. Involuntary admission may support treatment outcome and motivation in patients receiving assertive community treatment. Soc Psychiatry Psychiatr Epidemiol. 2010;45:245–252.
24. Barkhof E, Meijer CJ, de Sonneville LM, Linszen DH, de Haan L. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. Schizophr Bull. 2013;39(6):1242–1251.
25. Flanders WD, Lin L, Pirkle JL, Caudill SP. Assessing the direction of causality in cross-sectional studies. Am J Epidemiol. 1992;135(8): 926–935.
26. Jørgensen R, Licht RW, Lysaker PH, et al. Effects on cognitive and clinical insight with the use of guided self-determination in outpatients with schizophrenia: a randomized open trial. Eur Psychiatry. 2015;30(5): 655–663.
27. Sanz M, Constable G, Lopez-Ibor I, Kemp R, David AS. A comparative study of insight scales and their relationship to psychopathological and clinical variables. Psychol Med. 1998;28:437–446.
28. Mulder CL, Jochems E, Kortrijk HE. The motivation paradox: higher psychosocial problem levels in severely mentally ill patients are associated with less motivation for treatment. Soc Psychiatry Psychiatr Epidemiol. 2014;49(4):541–548.

# Chapter 5

## The effect of financial incentives on patients' motivation for treatment: results of "Money for Medication", a randomised controlled trial

Ernst L Noordraven
André I Wierdsma
Peter Blanken
Anthony F T Bloemendaal
Cornelis L Mulder

*BMC Psychiatry, 2018 (accepted)*

## Abstract

### Background

Offering financial incentives is an effective intervention for improving adherence in patients taking antipsychotic depot medication. We assessed whether patients' motivation for treatment might be reduced after receiving financial rewards.

### Methods

This study was part of Money for Medication, a multicentre, open-label, randomised controlled trial, which demonstrated the positive effects of financial incentives on antipsychotic depot compliance. Three mental healthcare institutions in Dutch secondary psychiatric care services participated. Eligible patients were aged 18–65 years, had been diagnosed with schizophrenia or another psychotic disorder, had been prescribed antipsychotic depot medication or had an indication to start using depot medication, and were participating in outpatient treatment. For 12 months, patients were randomly assigned either to treatment as usual (control group) or to treatment as usual plus a financial reward for each depot of medication received (€30 per month if fully compliant; intervention group). They were followed up for 6 months, during which time no monetary rewards were offered for taking antipsychotic medication. To assess treatment motivation after 0, 12 and 18 months, interviews were conducted using a supplement to the Health of the Nation Outcome Scales (HoNOS) and the Treatment Entry Questionnaire (TEQ).

### Results

Patients were randomly assigned to the intervention (n=84) or the control group (n=85). After 12 months, HoNOS motivation scores were available for 131 patients (78%). Ninety-one percent of the patients had no or mild motivational problems for overall treatment; over time, there were no significant differences between the intervention and control groups. TEQ data was available for a subgroup of patients (n=61), and showed no significant differences over time between the intervention and control groups for external motivation (β=0.37 95% CI: -2.49 – 3.23, p=0.799); introjected motivation (β=-2.39 95% CI: -6.22 – 1.44, p=0.222); and identified motivation (β=-0.91 95% CI: -4.42 – 2.61, p=0.613). After the 6-month follow-up period, results for the HoNOS and TEQ scores remained comparable.

### Conclusions

Offering financial incentives for taking antipsychotic depot medication does not reduce patients' motivation for treatment.

## 5.1 Introduction

Non-adherence to antipsychotic medication remains a considerable problem in the treatment of patients with psychotic disorders [1,2]; it is associated with poor clinical outcomes such as increased psychiatric symptoms, hospital admissions, violent crimes and suicide rates [3–5]. Randomised controlled studies demonstrated that medication adherence improved when financial incentives were offered [6,7]. However, a systematic review by Deci and colleagues (1999) found that people who received performance-contingent rewards showed lower levels of intrinsic motivation than people who received no rewards [8]. This can arise if incentives are perceived as controlling [9]. Furthermore, this negative relationship between external rewards and intrinsic motivation seems to be present both during, and after incentives are being offered [10]. Therefore, it is conceivable that offering financial incentives reduces patients' motivation, as they may stop their medication intake when incentives are no longer offered. This could negatively affect the long-term treatment, particularly of patients with schizophrenia.

Motivation for treatment, however, is a multidimensional concept. According to the Self-Determination Theory (SDT [11]), motivation to engage in activities ranges from "activities that are completely initiated and controlled by external social forces (such as financial incentives), to activities that are fully self-determined." Within this continuum, SDT defines three types of motivation [12]. *External* motivation refers to individuals who seek treatment or help due to social pressure or in order to avoid punishment or achieve external rewards (e.g., monetary rewards). *Introjected* motivation states that internal or personal conflicts (e.g., feelings of guilt, shame or anxiety) are the primary reason for remaining in treatment. Finally, *identified* motivation refers to individuals who personally identify with the goals of therapy – who, rather than being motivated by qualifying for rewards or avoiding internal conflicts, seek treatment for themselves. Here, we consider identified motivation as the most self-determined form of motivation, and view this subtype as intrinsic motivation [13].

The aim of this study was to explore, in the context of Money for Medication (M4M), a randomised controlled trial [6], whether offering patients financial incentives to take antipsychotic depot medication reduced their motivation for treatment. Motivation was assessed during a 12-month intervention and a 6-month follow-up period. We also explored the role of clinical variables that have an impact on treatment motivation, such as illness insight [14], medication adherence and the side-effects of antipsychotic medication.

## 5.2 Methods

### 5.2.1. Study design and patients

Between May 2010 and October 2014, a total of 169 patients participated in our M4M randomised controlled trial; a detailed account of the study design has been published in the main trial paper [6]. Patients were recruited from three mental healthcare institutions in the Netherlands: Dual Diagnosis Center Palier, Parnassia, and BavoEuropoort. These organisations primarily treat patients with psychotic disorders and other severe mental illnesses (often with comorbid substance use). Eligible patients were aged 18-65 years, had a psychotic disorder classified by the DSM-IV, had been prescribed or had an indication to start antipsychotic depot medication, were participating in outpatient treatment, and had given written informed consent. Patients were excluded if they were unable to participate due to cognitive impairments or had insufficient understanding of the Dutch language. Before participating in this study, all patients provided written informed consent. The study was approved by the Dutch Medical Ethical Trial Committee of Erasmus University Medical Center (registration number NL31406.097.10), and was registered in the Netherlands Trial Register (NTR2350).

### 5.2.2. Procedure

Patients were selected from the caseloads of the participating treatment teams on the basis of the selection criteria, and were informed about the study by their clinicians. Patients who participated were interviewed at baseline, and after 12 and 18 months. They received €20 remuneration for each completed interview. After the baseline interview, they were randomly assigned to 12 months, either of treatment as usual, or of treatment as usual plus financial incentives to take the antipsychotic depot medication. Randomisation was stratified by treatment site and three potential prognostic factors: sex, comorbid substance-use disorder (absent vs. present), and compliance with antipsychotic medication in the 4 months before baseline (<50% vs. ≥50%). The principal investigator had no influence on the enrolment process. Patients, clinicians, interviewers, and research assistants were masked to group allocation before, but not after, assignment.

### 5.2.3. Treatment as usual and intervention

Patients were randomly assigned to the intervention (n=84) or the control group (n=85). The control group received treatment as usual (TAU), both during the 12-month intervention period and during the 6-month follow-up phase. This treatment was provided by community mental health teams. During TAU, clinicians encouraged patients to take their antipsychotic

depot medication as prescribed. If necessary, crisis services were used, or patients were admitted to hospital. All patients received their depot medication at the outpatient clinic, where it was administered by psychiatric nurses.

Patients in the intervention group received TAU, plus a financial reward for every depot of antipsychotic medication they took during the 12-month intervention period. The maximum reward was €30 per month. The amount per taken depot varied according to the frequency of the prescription, which ranged between one and four times per month (i.e., between €7.50 and €30 per depot). After the intervention period, all patients entered the 6-month follow-up period and received TAU without financial incentives.

### 5.2.4. Outcomes

To assess patients' overall motivation for treatment, we used a supplement to the Dutch translation of the Health of the Nation Outcome Scales (HoNOS).[15,16] During this structured interview, one item specifically measured motivation (supplement B; "How motivated are you for your current treatment?"), which was rated on a 5-point scale ranging from 0 (no problems) to 4 (very severe problems). On the basis of the skewed response distributions, treatment motivation scores were dichotomised into "no or mild problems" (scores 0, 1 and 2) and "severe problems" (scores 3 and 4). During the course of the study many patients were lost-to-follow up, as they did not show up for appointments with the interviewers. After 12 months, HoNOS motivation scores were available for 131 patients (78%: 66 intervention vs. 65 control); after 18 months, they were available for 109 patients (64%: 60 intervention vs. 49 control).

We also assessed treatment motivation using the Dutch version of the Treatment Entry Questionnaire (TEQ).[12,17,18] This questionnaire consists of 27 items and distinguishes three subtypes of motivation: (1) external, (2) introjected, and (3) identified. External motivation included 12 items (e.g., "*The reason I am in treatment is because other people have pressured me to be here*"); introjected motivation included 6 items (e.g., "*I plan to go through with treatment, because I will feel ashamed of myself if I don't*); and identified motivation included 9 items (e.g., "*I decided to follow treatment because it feels important to me to personally deal with my problems*). Each item was rated on a scale from 1 (strongly disagree) to 7 (strongly agree). Subscale scores were computed by summing the item scores, with higher scores reflecting a higher level of external, introjected or intrinsic motivation. The TEQ was added after about half of the patients were already interviewed at baseline. Therefore, the TEQ was administered to 85 patients at baseline (42 intervention and 43 controls). After 12 months, TEQ scores were available for 61 patients (72%: 27 intervention vs. 34 control); after 18 months, they were available for 49 patients (58%: 21 intervention vs. 28 control).

### 5.2.5. Motivation covariates

To explore factors influencing treatment motivation, we analysed the effects of illness insight, side-effects, and medication adherence. To measure patients' level of illness insight at baseline, we used the Dutch version of the Positive and Negative Syndrome Scale (PANSS).[19] For item A12 of the PANSS ("Do you have a psychiatric disorder or mental health problem?") patients were asked to elaborate their answers. Responses were scored on a scale from 1 (illness insight present) to 7 (active denial of having a psychiatric disorder). To monitor common side-effects associated with the use of antipsychotic medication, we also used the 17-item Antipsychotic Side-effect Checklist (ASC).[20] Each item was rated as "symptom present" or "symptom absent", and the total number of reported side-effects was calculated (range: 0-17). Finally, we measured medication adherence, which was defined as the Medication Possession Ratio (MPR; [21]), i.e., the number of depots of antipsychotic medication received, divided by the total number of depots of antipsychotic medication prescribed during the 12-month intervention and 6-month follow-up period.

### 5.2.6. Statistical analyses

HoNOS motivation scores were dichotomised into "no or mild problems" or "severe problems" at baseline, and after 12 and 18 months. Baseline differences, response rates and motivation trajectories were analysed using (multivariate) logistic and multinomial regression. Sensitivity analyses were conducted using different cut-off scores and trajectory classifications to explore the effect of the dichotomization and combination of HoNOS scores. For TEQ motivation scores, we used generalised linear models with a gamma distribution and logit link to analyse differences between treatment groups. Regression models were compared on the basis of the log-likelihood ratio. In our adjusted models we entered stratification variables as covariates. As the participating mental healthcare teams were reorganised during the study, treatment site was not included. In TEQ motivation models we added baseline values, illness insight, medication side-effects and medication adherence as cofactors. Extended reports on sensitivity analyses and modelling results are available on request from the corresponding author. All statistical analyses were performed using SPSS (version 21.0).

## 5.3 Results

Table 1 presents the sociodemographic and clinical characteristics of all patients at baseline (n=169).

### 5.3.1. Trajectories of motivation (baseline – 12 months)

Four categories were distinguished: (1) patients with mild or no problems at baseline and after 12 months (n=106; 81%); (2) patients with severe motivational problems at baseline, who showed an improved treatment motivation after 12 months (n=13; 10%); (3) patients with severe motivational problems at baseline, who did not improve (n=8; 6%); and (4) patients with mild or no problems at baseline who showed severe motivational problems after 12 months (n=4; 3%). Patients with HoNOS scores at baseline and after 12 months (n=131) were compared with patients who had only HoNOS baseline scores (n=35). Logistic regression analyses were performed with patient status (i.e., being in the subgroup or not) as dependent variable and with patient characteristics as predictor variables (i.e., age, gender, substance-use disorder, medication adherence, ethnicity, income, and illness insight). There were no significant differences between the HoNOS subgroups (not reported here to save space).

Between trajectories there were no differences for the intervention and control patients (β=-0.412, 95% CI -1.15-0.33, p=0.274; reference category 1). Sensitivity analysis yielded similar results.

### 5.3.2 Main effects on motivation subtypes

We compared patients with TEQ scores at baseline and after 12 months (n=61) with those who had only a TEQ baseline measure (n=24). This showed a significant difference for baseline medication adherence (β=0.35, 95% CI 0.01-0.06, p=0.008). The TEQ subgroup (n=61) also showed a difference with the rest of the sample (n=108) for baseline medication adherence (β=0.03 95% CI: 0.02-0.05, p=0.000) and substance use (β=1.24 95% CI: 0.48-1.99, p=0.001).

Adjusted regression models consisted of the stratification variables (i.e., condition, gender, substance use, and baseline medication adherence), and baseline motivation. After 12 months of offering financial incentives, we found no effects of treatment condition on any type of motivation assessed on the TEQ. There were no mean score differences in external motivation between the intervention group (19.4 [SD:7.0]) and control group (20.4 [SD:6.4] (adjusted difference of 0.37 points (95% CI -2.5–3.2, p=0.799)). Similarly, the mean score difference in introjected motivation was non-significant between the intervention group (18.4 [SD:9.4]) and control group (21.0 [SD:10.1] (adjusted difference of -2.4 points (95% CI -6.2–1.4, p=0.222)). Finally, we found that the mean score for identified motivation was not lower in the intervention group (27.5 [SD:9.8]) than in the control group (27.9 [SD:9.4]) (adjusted difference of -0,91 points (95% CI -4.4–2.61; p=0.613)).

**Table 1. Patient characteristics and clinical status at baseline**

| Variable | Total (n=169) | Intervention group (n=84) | Control group (n=85) |
|---|---|---|---|
| Age mean (SD), years | 40.7 (9.8) | 40.6 (9.4) | 40.7 (10.2) |
| Gender, *N* (%) | | | |
| - Male | 127 (75.1) | 61 (72.6) | 66 (77.6) |
| Patients > 50% medication adherence, *N* (%) | 135 (79.9) | 68 (80.0) | 67 (79.8) |
| Place of treatment, *N* (%) | | | |
| - The Hague | 46 (27.2) | 18 (21.4) | 18 (21.2) |
| - Rotterdam | 123 (72.8) | 66 (78.6) | 67 (78.8) |
| Substance use disorder, *N* (%) | 94 (55.6) | 48 (57.1) | 46 (54.1) |
| Antipsychotic Medication side effects, mean (SD) | 4,8 (4,0) | 5,3 (4,0) | 4,3 (3,9) |
| Illness insight; median (interquartile range) (range 1-7) | 3 (1-4) | 3 (1-4) | 2 (1-4) |
| Health of the Nation Outcome Scales (HoNOS), *N* (%) | | | |
| - No motivational problems | 136 (80.4) | 66 (78.6) | 70 (82.3) |
| - Severe motivational problems | 28 (16.6) | 17 (20.2) | 11 (12.9) |
| - Item missing | 5 (3.0) | 1 (1.2) | 4 (4.8) |
| Treatment Entry Questionnaire, (TEQ) *N* (%) | 85 (50.3) | 42 (50.0) | 43 (50.6) |
| - External motivation; mean (SD), (range 12-84) | 18.4 (7.8) | 17.6 (8.1) | 19.0 (7.6) |
| - Introjected motivation; mean (SD), (range 6-42) | 18.7 (10.6) | 19.3 (9.4) | 18.2 (9.4) |
| - Identified motivation; mean (SD), (range 9-63) | 28.5 (10.0) | 28.6 (10.9) | 28.5 (9.2) |

### 5.3.3. Motivation covariates

To explore the association with motivation, we added the following to the model: medication side-effects, illness insight (assessed at baseline), and medication adherence (Table 2). Only illness insight had significant main effects on introjected motivation (β=-1,33 95% CI: 2,47 – -0,19, p=0,023) and identified motivation (β=-1,65 95% CI: -2,72 – -0,59, p=0,002). This suggests that less illness insight (reflected by higher scores) is associated with less introjected motivation for treatment, and less identified motivation for treatment. There was no interaction effect of illness insight and condition on either introjected motivation (β=0,49 95% CI: -1,80 – 2,78, p=0,675) or identified motivation (β=0,63 95% CI: -1,43 – 2,69, p=0,548).

### 5.3.4. Follow-up period (baseline – 18 months)

After the 6-month follow-up period, HoNOS motivation supplement scores were available for 109 patients (64%). These were divided into four categories: (1) patients who continued (during 12-18 month follow-up) to have mild or no motivational problems for treatment (n=81; 75%); (2) patients who had previously had severe motivational problems (at baseline), but had

**Table 2. Coefficients for regression model, adjusted for medication side-effects, illness insight, or medication adherence**

| | External motivation | | | Introjected motivation | | | Identified motivation | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p value | β | 95% CI | p value | β | 95% CI | p value |
| **Intercept** | 12.45 | 2.96; 21.94 | 0.011 | 5.71 | -6.01; 17.41 | 0.341 | 7.41 | -3.85; 18.67 | 0.197 |
| **Condition** | 0.37 | -2.49; 3.23 | 0.799 | -2.39 | -6.22; 1.44 | 0.222 | -0.91 | -4.42; 2.61 | 0.613 |
| **Gender** | 1.61 | -1.82; 5.04 | 0.358 | 0.57 | -4.09; 5.24 | 0.811 | -3.76 | -8.04; 0.52 | 0.085 |
| **Substance use** | 1.09 | -1.88; 4.06 | 0.472 | 0.77 | -3.26; 4.79 | 0.708 | -0.28 | -3.97; 3.42 | 0.884 |
| **Medication adherence baseline*** | -0.03 | -0.11; 0.06 | 0.548 | 0.04 | -0.07; 0.16 | 0.506 | 0.09 | -0.02; 0.19 | 0.103 |
| **Motivation baseline~** | 0.43 | 0.25; 0.61 | < 0.001 | 0.61 | 0.41; 0.81 | < 0.001 | 0.56 | 0.39; 0.72 | < 0.001 |
| **Medication side-effects** | -0.12 | -0.54; 0.29 | 0.571 | -0.11 | -0.67; 0.46 | 0.714 | 0.34 | -0.16; 0.84 | 0.181 |
| **Illness insight** | -0.29 | -1.13; 0.54 | 0.486 | -1.33 | -2.47; -0.19 | 0.023 | -1.65 | -2.72; -0.59 | 0.002 |
| **Medication adherence 12 months** | -0.03 | -0.14; 0.07 | 0.542 | -0.02 | -0.16; 0.12 | 0.796 | 0.02 | -0.11; 0.15 | 0.711 |

* Medication adherence in the 4 months prior to baseline ~Motivation measured at baseline for each type of motivation

now improved (n=9; 8%); (3) patients who continued to have severe motivational problems throughout the study (from 0-18 months, n=8; 7%); and (4) patients who had had mild or no motivational problems before but had severe problems at follow-up (n=11; 10%). Per category, there were no differences between the number of intervention and control patients.

The adjusted model for 18-month TEQ scores showed no significant differences between the intervention and control groups for external motivation (β=0.89 95% CI: -4.68 – -2.89, p=0.644), introjected motivation (β=-1.47 95% CI: -5.77 – -2.83, p=0.449), and identified motivation (β=-2.15 95% CI: -6.14 – -1.84, p=0.291). There was a significant main effect for illness insight on identified motivation (β=-1.24 95% CI: -2.44 – -0.03, p=0.044), but no interaction effect of illness insight and treatment condition.

## 5.4 Discussion

This study was intended to establish whether offering patients financial incentives to take antipsychotic depot medication would reduce their motivation for treatment. Our findings suggest that it did not. Over time, patients who received financial incentives did not differ with respect to various types of motivation from those who received treatment as usual. In addition, after the discontinuation of financial incentives, their medication adherence remained significantly higher.

After 12 months, 91% of the patients showed no or only mild motivational problems. During the 6-month follow-up period, when financial incentives were no longer offered, a majority of the patients (83%) were still motivated for treatment, whereas relatively few (17%) reported having little motivation for or resistance to their current treatment. In sum, this study indicates that offering and then discontinuing financial incentives to patients with psychotic disorders does not reduce their motivation for clinical treatment. It is particularly noteworthy that intrinsic motivation for treatment (which refers to individuals who identify personally with the goals of therapy) was not lower in patients who received financial incentives than in control patients. Similarly, patients' external motivation for treatment was not higher after they had received financial incentives.

### 5.4.1. Strengths and limitations

This is the first study to assess the impact of financial incentives on patients' motivation for treatment. Using two questionnaires, HoNOS addendum and TEQ, to assess treatment motivation, we found that offering financial incentives had produced no negative consequences.

The TEQ enabled us to measure motivationand also to distinguish three subtypes of motivation.

However, the first limitation is that loss to follow-up was considerable for the motivational outcome measures in this study as patients often did not show up for scheduled appointments with the interviewers. Organisational factors prevented us from administering the TEQ to more than only a subgroup of patients and selection bias is likely to be an issue. The higher levels of medication adherence and fewer diagnoses of substance-use disorder in this subgroup showed that they performed somewhat better at the start of treatment than the rest of the sample did. These patients may therefore have been more motivated throughout the study: for example, they may have had a high intrinsic motivation for treatment. As there was a danger that financial incentives would make them susceptible to adhering to treatment more for the external rewards than for themselves, it is important to note that there was no change in their intrinsic motivation when the financial incentives ended. For other patient characteristics, this subgroup did not differ significantly from the rest of the sample.

The second limitation is that overall treatment motivation was assessed on the basis of one item from the HoNOS-addendum scale, which thus reduced psychometric validity.

Another limitation is that, when the incentives ended, external motivation for treatment did not differ between the intervention group and the control group. It might be argued that the financial incentives may not have been great enough to cause major changes in patients' external motivation for treatment. However, they were sufficient to improve patients' medication adherence during the intervention period [6], and medication adherence remained significantly higher for the intervention group when financial incentives were no longer offered.

### 5.4.2. Further implications

Even though types of motivation did not differ between the intervention and control groups, there was a significant main effect for illness insight. Poor illness insight at study entrance appears to have been associated with less introjected and intrinsic motivation for treatment. These effect sizes were rather small, however. Also, when the intervention had finished, there seemed to be no so-called "crowding out" effect [22]. In other words, not only had patients not become externally motivated when the incentives were removed, they had not lost their intrinsic motivation.

### 5.4.3. Conclusions

Financial incentives improve adherence to antipsychotic depot medication in patients with psychotic disorders. The current study suggests that offering such incentives does not reduce patients' motivation for clinical treatment. It is particularly relevant that patients who received

financial incentives had neither lower intrinsic motivation for treatment nor higher external motivation. These results remained similar during the follow-up period, when incentives were no longer offered. Financial incentives can therefore be seen as an effective and relatively safe intervention for improving depot-medication adherence among patients with psychotic disorders.

## Acknowledgements

We thank the patients, research assistants, clinicians, and healthcare facilities who participated in this study.

## References


1. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res [Internet]. Elsevier Ireland Ltd; 2010 Apr 30 [cited 2013 Aug 7];176(2–3):109–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20185182
2. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee T a, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry [Internet]. 2006 Oct;67(10):1542–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17107245
3. Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide : systematic review of risk factors. Br J Psychiatry. 2005;187:9–20.
4. Llorca P-M. Partial compliance in schizophrenia and the impact on patient outcomes. Psychiatry Res [Internet]. Elsevier Ireland Ltd; 2008 Nov 30 [cited 2013 Aug 23];161(2):235–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18849080
5. Fazel S, Zetterqvist J, Larsson H, Langstrom N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. Lancet. 2014;384:1206–14.
6. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Staring ABP, Mulder CL. Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial. The Lancet Psychiatry [Internet]. 2017;4(3):199–207. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2215036617300457
7. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, et al. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics : cluster randomised controlled trial. BMJ [Internet]. 2013;345:f5847(347). Available from: http://dx.doi.org/doi:10.1136/bmj.f5847
8. Deci EL, Ryan RM, Koestner R. A Meta-Analytic Review of Experiments Examining the Effects of Extrinsic Rewards on Intrinsic Motivation. Psychol Bull. 1999;125(6):627–68.
9. Deci EL, Ryan RM. The ‘ What ’ and ‘ Why ’ of Goal Pursuits : Human Needs and the Self-Determination of Behavior The ‘ What ’ and ‘ Why ’ of Goal Pursuits : Human Needs and the Self-Determination of Behavior. Psychol Inq. 2000;11(4):227–68.
10. Moller AC, Buscemi J, McFadden HG, Hedeker D, Spring B. Financial motivation undermines potential enjoyment in an intensive diet and activity intervention. J Behav Med. 2013;37(5):819–27.
11. Deci EL, Ryan RM. Intrinsic motivation and self-determination in human behavior. New York: Plenum; 1985.
12. Wild TC, Cunningham J a, Ryan RM. Social pressure, coercion, and client engagement at treatment entry: A self-determination theory perspective. Addict Behav [Internet]. 2006 Oct [cited 2013 Aug 23];31(10):1858–72. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-33846056148&partnerID=40&md5=7ed6d31dd32cad79f760118cb0d76b44
13. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev [Internet]. Taylor & Francis; 2015;9(3):323–44. Available from: http://dx.doi.org/10.1080/17437199.2014.941722
14. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL. Depot-medication compliance for patients with psychotic disorders : the importance of illness insight and treatment motivation. Neuropsychiatr Dis Treat. 2016;12:269–74.
15. Bebbington P, Brugha T, Hill T, Marsden L, Window S. Health of the Nation Outcome Scales (HoNOS). Br J Psychiatry [Internet]. 1999;174(MAY):389–94. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-0032921734&partnerID=40
16. Mulder CL, Staring ABP, Loos J, Buwalda VJA, Kuijpers S, Systema S, et al. De Health of the Nation Outcome Scales ( honos ) als instrument voor ‘ routine outcome assessment. Tijdschr Psychiatr. 2004;6(5):273–84.

17. Ryan RM, Plant RW, O'Malley SS. Initial Motivations for Alcohol Treatment Relations with Patient Characteristics, Treatment Involvement and Dropout. Addict Behav. 1995;20(3):279–97.
18. Jochems EC, Mulder CL, Duivenvoorden HJ, van der Feltz-Cornelis CM, van Dam A. Measures of Motivation for Psychiatric Treatment Based on Self-Determination Theory: Psychometric Properties in Dutch Psychiatric Outpatients. Assessment [Internet]. 2014 Jan 2 [cited 2014 Jan 17];1–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24391079
19. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale ( PANSS ) for Schizophrenia. Schizophr Bull. 1987;13(2):261–72.
20. Weiden PJ, Miller AL. Which side effects really matter? Screening for common and distressing side effects of antipsychotic medications. J Psychiatr Pract. 2001;7(January):41–7.
21. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The Expert Consensus Guideline Series: Adherence Problems in Patients with Serious and Persistent Mental Illness. J Clin Psychiatry. 2009;70(4):1–46.
22. Frey BS, Jegen R. Motivation Crowding Theory : A Survey of Empirical Evidence , REVISED VERSION Juni 2000. J Econ Surv. 2001;15(49):589–611.

# Chapter 6

## Ethical acceptability of offering financial incentives for taking antipsychotic depot medication: patients' and clinicians' perspectives after a 12-month randomized controlled trial

Ernst L Noordraven
Maartje H M Schermer
Peter Blanken
Cornelis L Mulder
André I Wierdsma

*BMC Psychiatry 2017, 17:313.*

## Abstract

### Background

A randomized controlled trial 'Money for Medication'(M4M) was conducted in which patients were offered financial incentives for taking antipsychotic depot medication. This study assessed the attitudes and ethical considerations of patients and clinicians who participated in this trial.

### Methods

Three mental healthcare institutions in secondary psychiatric care in the Netherlands participated in this study. Patients (n = 169), 18–65 years, diagnosed with schizophrenia, schizoaffective disorder or another psychotic disorder who had been prescribed antipsychotic depot medication, were randomly assigned to receive 12 months of either treatment as usual plus a financial reward for each depot of medication received (intervention group) or treatment as usual alone (control group). Structured questionnaires were administered after the 12-month intervention period. Data were available for 133 patients (69 control and 64 intervention) and for 97 clinicians.

### Results

Patients (88%) and clinicians (81%) indicated that financial incentives were a good approach to improve medication adherence. Ethical concerns were categorized according to the four-principles approach (autonomy, beneficence, non-maleficence, and justice). Patients and clinicians alike mentioned various advantages of M4M in clinical practice, such as increased medication adherence and improved illness insight; but also disadvantages such as reduced intrinsic motivation, loss of autonomy and feelings of dependence.

### Conclusions

Overall, patients evaluated financial incentives as an effective method of improving medication adherence and were willing to accept this reward during clinical treatment. Clinicians were also positive about the use of this intervention in daily practice. Ethical concerns are discussed in terms of patient autonomy, beneficence, non-maleficence and justice. We conclude that this intervention is ethically acceptable under certain conditions, and that further research is necessary to clarify issues of benefit, motivation and the preferred size and duration of the incentive.

## 6.1 Introduction

Patients with psychotic disorders often have problems adhering to their prescribed antipsychotic medication [1], making it difficult to control their psychiatric symptoms. Non-adherence has also been associated with an increased risk of hospital admissions, suicide attempts, violence, self-harm, substance use and treatment costs [2–4]. Unfortunately, interventions to improve adherence such as psychoeducation or adherence therapy have not been consistently successful for patients with schizophrenia [5].

Although providing financial incentives for taking anti-psychotic depot medication is an effective intervention for improving adherence [6–9], clinicians and healthcare workers have several ethical reasons for criticising the use of financial incentives among patients with severe mental illnesses. For example, 76% managers of assertive outreach teams surveyed in England stated one or more ethical reason for refusing to provide this intervention [10]. First, patients may feel bribed or coerced into taking their medication – because they need income, for example [11]. Second, the therapeutic relationship might be damaged if patients receive financial incentives, possibly undermining voluntary medication adherence [6]. Finally, if illness or medication impairs patients' decision-making capacities, it is unreasonable to expect them to make informed decisions about their treatment process, including the incentive [12]. This raises ethical concerns about respecting patient autonomy.

Offering financial incentives may also have negative consequences on patients' intrinsic motivation for treatment [13–15]. If financial incentives are offered only to non-adherent patients and are eventually removed, patients could refuse all medication ('crowding out effect') [16] or may deliberately become non-adherent in order to receive financial incentives again [17]. Similarly, many patients with severe mental illnesses are vulnerable or have impaired decision-making capacity, which sometimes gives clinicians the feeling they are 'buying' their patients.

A focus group study by Priebe and colleagues [18] explored the attitudes of different stakeholders (i.e. patients, psychiatrists, nurses, social workers, psychologists and multidisciplinary teams) towards the ethical acceptability of financial incentives. They identified several themes – including coercion, effectiveness and perverse incentive – that dominated the discussion. Each stakeholder group tended to indicate the same discussion threads. However, few patients (n = 27) participated in this study, and neither patients nor clinicians had any actual experience of using financial incentives.

As prior research has thus focused on clinicians' beliefs about applying this intervention [19], greater attention should be paid to evaluating the ethical concerns and considerations of patients who have had practical experience of financial incentives. We therefore report on patients and clinicians who participated in *Money for Medication*, a randomized controlled

trial [9] in which patients were offered financial incentives for taking anti-psychotic depot medication for a 12-month intervention period. The opinions of patients and clinicians on this intervention were organized on the basis of the four-principles approach of Beauchamp and Childress [20]. This pragmatic approach [21] was used to categorize ethical arguments into one of the following ethical principles: autonomy (the right of competent patients to make their own decisions, and the obligation to respect the decision-making capacities of autonomous persons); beneficence (the obligation to provide benefits and to balance benefits against risks); non-maleficence (the obligation to avoid causing harm); and justice (the obligation of fairness in the distribution of benefits and risks).

## 6.2 Methods

### 6.2.1. Design

Data were collected in the context of *Money for Medication* (M4M), a multicentre, open-label, parallel-group, randomized controlled trial [9]. The study was approved by the accredited Dutch Medical Ethical Trial Committee at Erasmus University Medical Center (NL31406.097.10; file number P13.258) and registered with the Netherlands Trial Register (NTR2350).

### 6.2.2. Participants

Participants were included at three mental health-care institutions in secondary psychiatric care services in the Netherlands: the Dual Diagnosis Center (CDP) Palier, Parnassia, and BavoEuropoort. Primarily these organisations treat patients with psychotic and other severe mental disorders (often with comorbid substance use). In general, at the start of the study, these patients received voluntary treatment and are motivated by the clinicians to accept their medication. Involuntary outpatient treatment was not an in- or exclusion criterion for participation in the study. Eligible patients were aged between 18 and 65 years, had a psychotic disorder (such as schizophrenia, schizoaffective disorder or another psychotic disorder) classified by psychiatrists using the DSM-IV; had been prescribed antipsychotic depot medication or had an indication to start using depot medication; and were participating in outpatient treatment. All patients had given written informed consent before the baseline interview was conducted. Exclusion criteria were: inability to participate due to cognitive impairments (as determined by the clinicians on the basis of their clinical judgement or stated in the patients' record) and/or insufficient understanding of Dutch (observation of research assistants during interviews). Patients who initially met the inclusion criteria were informed

about the study by their clinicians and were asked to participate. If a patient declined to participate, this decision was registered anonymously to allow assessment of selection bias.

### 6.2.3. Procedure and data collection

In total, 879 patients from the mental healthcare teams were assessed for eligibility; 710 patients were excluded because:(1) they had no prescription or indication for antipsychotic depot medication (n = 460), (2) did not react to requests for participation in the trial (n = 101), (3) refused participation (n = 28), (4) or various other reasons (n = 121), including being admitted to a hospital, moving house to a different city, transfer to another treatment team, imprisonment, or insufficient information to be contacted. Between May 21, 2010 and October 15, 2014, 169 patients were randomly allocated to 12 months of experimental treatment (M4M) or to 12 months of treatment as usual (TAU; control condition). Randomisation was stratified by treatment site and suspected prognostic factors: sex, comorbid substance-use disorder (absent vs present), and compliance with antipsychotic medication in the 4 months before baseline (<50% vs ≥50%). During the intervention period, no patients refused participation due to the content of the study. TAU consisted of outpatient treatment provided by community mental-health teams and flexible assertive-community-treatment teams.

Patients in the intervention group (M4M) received treatment as usual, plus a financial reward each time they received their prescribed depot of antipsychotic medication during the 12-month experimental study phase. The maximum amount they received was €30 per month. The rewards were paid out by the patients' treating nurses as soon as the patient had received the injection or had swallowed the penfluridol. The methods and results of the study have been described in Noordraven et al. [9].

### 6.2.4. Assessment and questionnaire

After the 12-month intervention period, patients' and clinicians' attitudes and opinions were assessed using a short questionnaire constructed for the study. The first question asked whether this intervention was a 'good idea' or a 'bad idea'. Next, two open-ended questions asked about the advantages and disadvantages of using financial incentives. Nineteen statements then addressed ethical considerations on the consequences of M4M on topics such as the therapeutic relationship, intrinsic motivation, inequality between patients, and patient vulnerability (Additional file 1 shows our complete questionnaire). Items were scored on a 5-point scale (1 = strongly disagree, 5 = strongly agree) and dichotomized into 'disagree' (scores 1, 2, 3) and 'agree' (scores 4 and 5). To assess the effect of alternative breakpoints, sensitivity analyses were performed; no relevant differences were found. All interviews were conducted by extensively trained research assistants (Master's-level psychologists).

To explore the different components of ethical concerns, each statement was categorized post-hoc into one of the four ethical principles (Table 1): 'autonomy' (items 4, 7, 18; expressed in statements such as 'if they receive money for their depot medication, patients will feel forced to accept their depots' and 'it is not permissible to buy patients by giving them money to take their medication'); 'beneficence' (items 1, 2, 3, 5, 6, 11, 15, 19; expressed in statements such as 'patients will accept their depots more often if they receive money' and 'money for depots improves patients' motivation to use depot medication'); 'non-maleficence' (items 9, 12, 13, 14; expressed in statements such as 'Money for depots is harmful to the therapeutic relationship' and 'if someone receives money for his depot, he won't gain insight into his problems'); and 'justice' (item 8, expressed in a single statement: 'jealousy will arise if some patients receive money for their depots and others do not'). Statements that did not fit the description of these principles were labelled as 'other considerations' (items 16, 17).

We also described the commonest advantages and disadvantages named spontaneously by patients and clinicians in response to the open-ended questions. Using descriptive statistics, we identified differences between patients and clinicians, and explored the differences between patients who had actually received the intervention (M4M group) and those who had not (TAU group). All analyses were performed using SPSS version 21.0.

## 6.3 Results

After the 12-month intervention period, interview data were available for 133 patients and 97 clinicians (Table 2). Patients lost to follow-up showed no significant differences relative to patients who had outcome data after 12 months, and were distributed equally across conditions (17 intervention and 19 control). Because of (repeated) non-attendance, we were unable to conduct follow-up interviews for these patients. However, they did not actively withdrew their consent to participate in our study, nor did they report any (ethical) concerns as reason for non-attendance. Overall, 88% of the patients and 81% of the clinicians reported that the M4M project was a good idea. These percentages were similar between patients from the intervention group (92%) and the control group (84%).

### 6.3.1. Patients versus clinicians

*Autonomy*

Around 33% of the patients and clinicians reported that if patients were offered money, they would feel dependent, pressured or coerced to accept their anti-psychotic depots.

*Beneficence*

Patients (79%) and clinicians (72%) believed that patients would be more adherent to their antipsychotic depot medication if financial incentives were used. Similarly, a majority of patients (72%) and clinicians (82%) agreed that 'money for depots would improve the motivation to use depot medication'. However, only 58% of patients and 42% of clinicians agreed with the statement that 'money for depots is beneficial for patients wellbeing'.

*Non-maleficence*

Although few patients (23%) agreed with the idea that 'if someone receives money for his depot, he won't gain insight into his problems,' more clinicians (35%) were worried about this negative consequence. While clinicians (71%) also agreed with the statement that financial incentives would provoke patients into follow treatment less for themselves but more for the money, this opinion was shared by fewer patients (38%). A majority of the patients (84%) and clinicians (84%) stated that they did not expect the therapeutic relationship to suffer from the use of monetary rewards.

*Justice*

This statement referred to the obligation to treat like cases alike. A majority of the patients (62%) and clinicians (71%) believed that jealousy would occur if some patients received money for their depots but others did not.

*Other considerations*

While most patients (76%) agreed with the statement that it would be good to reward good behaviour with money, fewer clinicians (38%) did so. Nearly half the patients (49%) agreed that giving money for depots was ethically acceptable, an opinion shared by a third of clinicians (34%).

### 6.3.2. Between patients: Experimental group versus control group

Overall, the ratings on the questionnaire items did not differ significantly between intervention and control patients. Intervention patients rated M4M somewhat more positively than control patients on only two items: 'money for depots will work in daily practice' (77% vs. 59%) and it is 'ethically acceptable to give money for depots' (57% vs. 41%).

### 6.3.3. Spontaneously reported advantages and disadvantages

Eighty-two patients and 87 clinicians spontaneously reported five advantages of using financial incentives: increased compliance (15 patients (18%) vs. 40 clinicians (46%)); increased

motivation for treatment (15 patients (18%) vs. 32 clinicians (37%)); more money to spend (34 patients (41%) vs. 5 clinicians (6%)); more time to talk with patients (11 patients (13%) vs. 1 clinician (1%)); and improved illness insight (7 patients (9%) vs. 9 clinicians (10%)). Similarly, 27 patients and 74 clinicians named five potential disadvantages: becoming dependent and refusing all depots when financial incentives were no longer offered (7 patients (26%) vs. 24 clinicians (32%)); becoming externally motivated for treatment (7 patients (26%) vs. 23 clinicians (31%)); the unfairness of some patients not receiving financial incentives (10 patients (37%) vs. 6 clinicians (8%)); the possibility that patients would not gain illness insight (1 patient (4%) vs. 12 clinicians (16%)); and the risk that patients would use the money to buy drugs (2 patient (7%) vs. 8 clinicians (11%)).

**Table 1. Characteristics of patients and clinicians**

| Variable | Patients (n=133) | Clinicians (n=97) |
|---|---|---|
| **Age, mean (SD) years** | 40.3 (9.4) | 41.5 (12.5) |
| **Gender, *N* (%)** | | |
| - Male | 99 (74) | 35 (37) |
| **Duration of illness mean (SD), years** | 12.1 (8.3) | - |
| **Diagnosis, *N* (%)** | | |
| - Schizophrenia paranoid type | 75 (56.4) | - |
| - Schizoaffective disorder | 15 (11.3) | - |
| - Psychotic disorder NOS | 14 (10.5) | - |
| - Schizophrenia disorganized type | 9 (6.8) | - |
| - Other schizophrenic disorder | 20 (15.0) | - |
| **Working experience, mean (SD), years** | - | 14.4 (11.4) |
| **Job description, *N* (%)** | | |
| - Psychiatrist | - | 9 (9) |
| - Psychologist | - | 11 (11) |
| - Social worker | - | 15 (15) |
| - Social psychiatric nurse | - | 20 (21) |
| - Nurse | - | 25 (26) |
| - Intern | - | 9 (9) |
| - Other | - | 8 (8) |

**Table 2. Patients' and clinicians' agreement with ethical aspects of the Money for Medication intervention to improve medication adherence**

| Ethical concern | Statement | Patients (N=133) | Clinicians (N=97) |
|---|---|---|---|
| **Autonomy** | *'Patients will feel dependent if they receive money for their depots'* | 33% (44) | 31% (30) |
| | *'If they receive money for their depot medication, patients will feel forced to accept their depots'* | 36% (47) | 27% (26) |
| | *'It is not permissible to buy patients by giving them money to take their medication'* | 21% (27) | 16% (15) |
| **Beneficence** | *'To give money for depots is good'* | 68% (91) | 47% (46) |
| | *'Giving money for depots emphasizes the things that are going well'* | 51% (66) | 33% (32) |
| | *'Money could just be the right push to accept your depot'* | 72% (96) | 88% (85) |
| | *'Money for depots improves patients' motivation to use depot medication'* | 72% (95) | 82% (80) |
| | *'Money for depots will work in daily practice'* | 67% (89) | 53% (51) |
| | *'Money for depots helps to get into a positive flow'* | 62% (81) | 61% (59) |
| | *'Patients will accept their depots more often when they receive money'* | 79% (103) | 72% (70) |
| | *'Money for depots is beneficial for patients wellbeing'* | 58% (76) | 42% (41) |
| | *'If patients receive money for their depot they will accept it more often'* | 75% (98) | 79% (77) |
| **Non-maleficence** | *'If someone receives money for his depot, he won't gain insight into his problems'* | 23% (30) | 35% (34) |
| | *'Money for depots is harmful to the therapeutic relationship'* | 16% (21) | 16% (16) |
| | *'If patients no longer receive money for their depots they will stop to accept their depots'* | 36% (47) | 37% (45) |
| | *'Money for depots will provoke patients to follow their treatment less for themselves but more for the money'* | 38% (49) | 71% (69) |
| **Justice** | *'Jealousy will arise if some patients receive money for their depots and others do not'* | 62% (82) | 71% (69) |
| **Other** | *'Giving money for depots is ethically acceptable'* | 49% (64) | 34% (33) |
| | *'It is good to reward good behavior with money'* | 76% (99) | 38% (37) |

## 6.4 Discussion

This 12-month randomized controlled trial explored patients' and clinicians' ethical concerns regarding the use of financial incentives to improve adherence to anti-psychotic depot medication. In general, patients viewed such incentives as an effective method of improving their adherence, and were willing to accept them during clinical treatment. Clinicians were also positive about using this intervention in clinical practice, and had ethical concerns that were similar to those identified by their patients.

However, even though they reported that offering financial incentives was a good idea, only a minority of the clinicians and about half of the patients believed this intervention to be ethically acceptable. These answers show the complex and possible ambivalent attitudes about using financial incentives. Patients might be pragmatic and state that they think of this intervention as a 'good idea'; believing it will be efficient in daily practice, for example. At the same time, independent from this practical oriented vision, they might believe this intervention is not an ethical practice. Although these results may seem contradictory, they may be two sides of the same coin. An example to illustrate this point is the classic trolley thought-experiment [22]: a dilemma between killing 1 person in order to save 5. Most people would reason from a rational point of view this would be a valid choice to make ('good idea'), while at the same time, still believing that it is overall unethical to end an-other persons' life ('ethical acceptability'). In this study, patients and clinicians believed that monetary payments would improve medication adherence, even though both groups were worried that jealousy would occur if some patients received monetary payments and others did not. Ethical concerns were grouped on the basis of the four-principles approach in terms of patient autonomy, beneficence, non-maleficence and justice.

### 6.4.1. Autonomy

From a consequentialist standpoint, a given intervention would be legitimate if the outcomes were beneficial. In this case, financial incentives increased medication adherence, which was the primary aim of the study [9]. However, we would argue that it is not sufficient to focus only on the outcomes of an intervention: the act of giving financial incentives itself should also be evaluated independently of its consequences. Regardless of the outcomes, 'bribing' or coercing patients into using medication would be ethically problematic. To respect patients' autonomy, one should therefore evaluate the amount of money being offered [23]. If, for example, patients were offered €1000 per depot taken (whether weekly or monthly), they would likely cross their personal boundaries more easily, and might feel coerced into accepting their medication.

Particularly among patients with a psychosis, who are often in need of financial support, the payment should not be that high to make them feel forced to accept medication [24].

While some 30% of the patients in this study believed that patients would feel forced or dependent if offered monetary payments, we would argue that it is legitimate to offer incentives that make patients feel slightly pressured –but not coerced or manipulated- to take their depots [25]. We also believe that outright coercion was not involved in our study, since no consequences were attached to rejection of the medication and financial reward: patients who rejected depots were not forced to take their medication, nor were they admitted involuntarily. In practice, the size of the payment should be chosen in a way that always leaves patients with a fair opportunity to say no, if they really do not want to do something. To respect patient autonomy and prevent coercion, the use of incentives should not be considered before carefully weighing the size of the payment in relation to the specific patient population, and before considering whether the incentive being offered is unconditional.

### 6.4.2. Beneficence

A majority of the patients and clinicians were convinced that offering financial incentives would increase adherence to antipsychotic depot medication. However, only around 50% of them believed this intervention would also benefit patients' wellbeing. The fact that the increased medication adherence in this study did not lead to improved clinical outcomes, such as better quality of life or fewer hospital admissions [9], shows a complex association between adherence and patients' wellbeing. This makes it difficult to conclude whether this intervention is truly beneficial. Offering financial incentives did benefit the number of accepted depots – which was our primary aim – and patients and clinicians alike acknowledged that patients' motivation to accept their medication had improved.

Although medication non-adherence has been shown to be associated with various negative clinical outcomes, such as increased risk of hospital admissions, suicide attempts, violence or substance abuse, our study did not improve clinical outcomes. We would nonetheless argue in favour of using monetary payments: they are effective for improving medication adherence and there are various reasons why we did not find improvements in clinical outcomes. While these reasons have been discussed in depth elsewhere [9], they should be summarized briefly here. First, our overall study was designed primarily to improve adherence and to study the effectiveness of using financial rewards. At 12 months, the study may have been too short to detect any improvements in clinical symptoms, especially among chronically ill patients with a mean illness duration of about 12 years. But we should also note that clinical outcome measures did not get worse during the intervention period, and there were no indications that M4M negatively affected patient autonomy or therapeutic relationships.

Therefore, we believe that it is ethically acceptable to use M4M in clinical practice, even though we found no improvements on clinical outcomes.

### 6.4.3. Non-maleficence

An important concern in previous studies is that financial incentives would undermine the therapeutic relationship between patients and clinicians. Clinicians might feel reluctant to offer payments if these could damage or disrupt the relationships with their patients, which are often built with great difficulty and over long periods of time. After the 12-month intervention period, however, patients and clinicians did not report any indications that the therapeutic relationship had suffered from the use of monetary rewards. In addition, patients in the M4M condition did not report more side effects of medication, nor did they use more alcohol or illicit drugs than patients in the control group.

Another ethical concern was the concept of 'motivation'. Clinicians believed that patients would follow treatment less for themselves and more for the money. They are worried that externally motivated patients will stop to take their medication when incentives are no longer given, since it has been shown that initial positive behaviour changes cannot be sustained after withdrawal of external rewards [26]. Patients, however, disagreed with these concerns. Furthermore, we found that during the 6 month follow-up period, the intervention group still accepted more depots than patients from the control group. This shows that financial incentives can be discontinued without the danger of patients becoming completely non-adherent or less adherent than before receiving financial payments.

### 6.4.4. Justice

While some patients received money and other patients did not, a majority of patients and clinicians reported that jealousy could occur. If this intervention were used only with non-adherent patients, this could lead adherent patients to become non-adherent on purpose, or to complain about unequal treatment. Clinicians also suspected that patients might reject their medication if payments were no longer offered, while patients themselves did not expect this to happen. For reasons of justice and to overcome this problem of inequality, we therefore recommend that all patients are offered payments for accepting their depot medication [23] – as in our study – without making distinctions based on previous levels of adherence.

### 6.4.5. Strenghts and limitations

Our study is one of the first to collect empirical data on patients' and clinicians' opinions after patients have received financial incentives for accepting antipsychotic depot medication. This is important: the opinions of patients with psychotic disorders are often overlooked, but are

crucial if we wish to improve treatment. Another advantage of our study is that patients and clinicians all experienced the intervention in daily practice. Their opinions were thus based in practice much more than if the intervention had merely been discussed hypothetically.

A limitation of the study is that our questionnaire was not constructed on the basis of a previously defined theoretical model: instead, we retrospectively categorized each statement into one of the four main ethical principles and explored patients' and clinicians' different views on the intervention. Another limitation is that selection bias may have occurred with respect to the total population of patients on depot medication. Patients who participated might have been biased towards a more positive attitude on using financial incentives, simply because all patients wanted to participate in this study, and showed up for appointments to conduct our interviews. However, we found no differences between patients who actually received financial incentives (M4M group) and those who did not (TAU group).

### 6.4.6. Conclusions

In clinical practice, patients and clinicians were positive about the use of financial payments to improve adherence to antipsychotic depot medication. Importantly, the fear that financial incentives would harm the therapeutic relationship was not confirmed. At the same time, however, more than half of the patients and clinicians reported to have ethical concerns (e.g. jealousy or reduced illness insight). Therefore, we consider the use of monetary incentives to take anti-psychotic depot medication to be ethically acceptable on four conditions: the amount offered should be moderate, the offer should be unconditional (i.e. there are no consequences if the patient refuses); the incentives should be made available to all patients; and a monitoring system should be in place to track changes in patients' health and/or well-being.

However, it still remains unclear to what extent this type of intervention affects internal and external motivation for treatment, and for how long monetary payments should be offered. Our results showed that when financial payments were no longer offered, most patients from the intervention group continued to have improved adherence rates, whereas others relapsed. This indicates that for most patients, temporary incentives might be sufficient to improve their motivation for medication intake over a longer period of time, while for others, continuous payments might be more suitable to maintain higher adherence rates. Longer follow-up periods are needed to examine whether sustained improved adherence might be associated with better clinical outcomes. For practical purposes, however, and to prevent difficulties (e.g. jealousy, inequality between patients, risks of becoming non-adherent on purpose in order to receive incentives), we recommend offering financial incentives to all patients without making distinctions.

Future research should also examine the optimal level of incentives; if incentives are too substantial, this could increase the likelihood of bribing patients into doing something they might not want, instead of offering them an independent choice. Also, higher incentives might harm the therapeutic relationship. The incentive in the present study was pragmatically chosen based on promising results from an earlier pilot study and another RCT [8, 27]. In addition, and from a more practical perspective, almost all patients received social welfare, which they might lose when receiving a substantial source of extra income (e.g. ≥€30). For these reasons, we believe the amount of 30 euro is relatively adequate, but this needs to be addressed in future studies.

To conclude, our study suggests that, under certain conditions, money for medication is an ethically acceptable intervention for improving medication adherence. Issues of benefit, motivation and the size and duration of the incentive should be clarified in further research.

## Acknowledgements

We thank the patients, research assistants, clinicians, and healthcare facilities who participated in this study.

## References


1. Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry. 2006;67:1542–50.
2. Ascher-svanum H, Ph D, Zhu B, Faries D, Lacro JP, Pharm D, et al. A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia. J Clin Psychiatry. 2006;67:1114–23.
3. Ward A, Ishak K, Proskorovsky I, Caro J. Compliance with refilling prescriptions for atypical antipsychotic agents and its association with the risks for hospitalization, suicide, and death in patients with schizophrenia in Quebec and Saskatchewan: a retrospective database study. Clin Ther. 2006; 28:1912–21. doi:10.1016/j.clinthera.2006.11.002.
4. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010;176:109–13. doi:10.1016/j.psychres.2009.05.004.
5. Gray R, Bressington D, Ivanecka A, Hardy S, Jones M, Schulz M, et al. Is adherence therapy an effective adjunct treatment for patients with schizophrenia spectrum disorders? A systematic review and meta-analysis. BMC Psychiatry. 2016;16:90. doi:10.1186/s12888-016-0801-1.
6. Claassen D, Fakhoury W, Ford R, Priebe S. Money for medication: financial incentives to improve medication adherence in assertive outreach. Psychiatr Bull. 2007;31:4–7.
7. Staring ABP, Van der Gaag M, Mulder CL. Schizophrenia and antipsychotic medication - better adherence, better outcomes? Schizophr Res. 2013;151: 296–7. doi:10.1016/j.schres.2013.10.035.
8. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, et al. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics : cluster randomised controlled trial. BMJ. 2013;345:f5847. doi:10.1136/bmj.f5847.
9. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Staring ABP, Mulder CL. Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (money for medication): a multicentre, open-label, randomised controlled trial. Lancet Psychiatry. 2017;4:199–207. doi:10.1016/S2215-0366(17)30045-7.
10. Claassen D. Financial incentives for antipsychotic depot medication: ethical issues. J Med Ethics. 2007;33:189–93. doi:10.1136/jme.2006.016188.
11. Shaw J. Is it acceptable for people to be paid to adhere to medication? BMJ. 2007;335:232. doi:10.1136/bmj.39286.399514.BE.
12. Cairns R, Maddock C, Buchanan A, David AS, Hayward P, Richardson G, et al. Prevalence and predictors of mental capacity in psychiatric inpatients. Br J Psychiatry. 2005;187:379–85. doi:10.1176/appi.psy.48.4.309.
13. Promberger M, Marteau TM. When do financial incentives reduce intrinsic motivation? Comparing behaviors studied in psychological and economic literatures. Health Psychol. 2013;32:950–7. doi:10.1037/a0032727.
14. Kendall T. Paying patients with psychosis to improve adherence. Br Med J. 2013;347:1–2. doi:10.1136/bmj.f5782.
15. Brown RCH. Social values and the corruption argument against financial incentives for healthy behaviour. J Med Ethics. 2017:140–4. doi:10.1136/ medethics-2016-103372.
16. Burton A, Marougka S, Priebe S. Do nancial incentives increase treatment adherence in people with severe mental illness? A systematic review. Epidemiol Psychiatr Sci. 2010;19:233–42. doi:10.1017/S1121189X00001160.
17. Szmukler G. Financial incentives for patients in the treatment of psychosis. J Med Ethics. 2009;35:224–8. doi:10.1136/jme.2008.027151.
18. Priebe S, Sinclair J, Burton A, Marougka S, Larsen J, Firn M, et al. Acceptability of offering financial incentives to achieve medication adherence in patients with severe mental illness: a focus group study. J Med Ethics. 2010;36:463–8. doi:10.1136/jme.2009.035071.

19. Highton-Williamson E, Barnicot K, Kareem T, Priebe S. Offering financial incentives to increase adherence to antipsychotic medication: the clinician experience. J Clin Psychopharmacol. 2015;35:120–7. doi:10.1097/JCP.0000000000000276.
20. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York, Oxford: Oxford University Press; 2012.
21. Bloch S, Green SA. "an ethical framework for psychiatry": comment. Br J Psychiatry. 2006;189:7–13. doi:10.1192/bjp.188.1.7.
22. Foot P. The problem of abortion and the doctrine of the double effect. Oxford Rev. 1967:5–15. doi:10.1093/0199252866.001.0001.
23. Burns T. Is it acceptable for people to be paid to adhere to medication? BMJ. 2007;335:233. doi:10.1136/bmj.39286.422639.BE.
24. Szmukler G, Appelbaum PS. Treatment pressures, coercion and compulsion in mental health care. J Ment Health. 2008;17:229–31. doi:10.1080/09638230802156731.
25. Nelson RM, Beauchamp T, Miller V a, Reynolds W, Ittenbach RF, Luce MF. The concept of voluntary consent. Am J Bioeth 2011;11:6–16. doi:10.1080/15265161.2011.583318.
26. Dickerson FB, Tenhula WN, Green-Paden LD. The token economy for schizophrenia: review of the literature and recommendations for future research. Schizophr Res. 2005;75:405–16. doi:10.1016/j.schres.2004.08.026.
27. Staring ABP, Mulder CL, Priebe S. Financial incentives to improve adherence to medication in five patients with schizophrenia in the Netherlands. Psychopharmacol Bull. 2010;43:5–10.

# Chapter 7

## Medical and Social Costs after Using Financial Incentives to Improve Medication Adherence: Results of a One Year Randomised Controlled Trial

Ernst L Noordraven
Andre I Wierdsma
Peter Blanken
Anthony Bloemendaal
Cornelis L Mulder

*Submitted*

## Abstract

Offering a financial incentive ('Money for Medication') is effective in improving adherence to treatment with depot antipsychotic medications. However, data on financial costs of medication adherence-enhancing interventions are rare. We investigated the cost-effectiveness in terms of medical costs and judicial expenses of using financial incentives to improve adherence.

The effects of financial incentives on depot medication adherence were evaluated in a randomised controlled trial. Patients in the intervention group received €30 a month over 12 months if antipsychotic depot medication was accepted. The control group received mental health care as usual. For 134 patients outcomes were calculated based on self-reported service use and delinquent behaviour and expressed as standard unit costs to value resource use.

The financial incentive resulted in higher average costs related to mental health care and lower medical costs related to other healthcare services. Relevant differences in social costs related to delinquent behaviour were not found. Although wide confidence intervals indicate uncertainty, incremental cost-effectiveness ratio's (ICER) indicate that it costs €2080 for achieving a 20% increase in adherence or €3332 for achieving over 80% adherence.

Conclusion: offering money as financial incentive for increasing compliance may be cost-effective, but did not lead to an overall cost reduction as compared to care as usual.


**Keywords**: financial incentives, health care costs, psychosis, antipsychotics, adherence

## 7.1 Introduction

Adherence to treatment with antipsychotic depot medication is associated with remission from symptoms and improved social outcomes [1]. Yet 25% to 50% of people with schizophrenia are non-adherent to their medication regimen due to a lack of illness insight or side effects [2]. Results of randomized controlled trials suggest that offering a financial incentive ('Money for Medication') is effective in improving adherence [3, 4]. However, this type of behavioural intervention is controversial not only for ethical reasons, but also because immediate healthcare expenditures increase and the effect of adherence on social and economic outcomes may be long-term. Direct costs increase both because a modest financial incentive is offered over an extended period and because logistical arrangements to distribute money in a community mental health context need to be addressed. On the other hand, adherence to antipsychotic medication may be associated with lower risk of psychiatric hospital admissions and may decrease other health and social care costs. In addition, a decrease of psychotic symptoms may contribute to patients' quality of life and better social adjustment, which could lower societal costs. However, data on cost-effectiveness of medication adherence-enhancing interventions are rare [5]. And although first economic outcomes for offering financial incentives point in the right direction, effect estimates show wide confidence intervals [6].

Therefore, we investigated the medical costs and judicial costs after offering financial incentives to achieve better adherence. In a trial studying the effects of financial incentives on depot-adherence and psychosocial outcomes [4], we found a significant improvement in adherence rates, although no effects were found on psychosocial outcomes, including quality of life. Here our focus is on patients' health care consumption (admissions, contacts with clinicians, and other healthcare professionals) and costs that incurred because of illegal activities. We did not study cost-effectiveness in terms of QALY's, since the intervention did not affect quality of life, which was a secondary outcome. We investigated the differences in direct medical costs (related to psychiatric treatment), medical costs related to other healthcare services, and judicial costs, between the intervention and control group, and how these costs are related to better antipsychotic medication adherence. To estimate expenditures from a societal perspective, costs were calculated by multiplying resource use with official charge standards.

## 7.2 Methods

### 7.2.1. Medical and Judicial Costs

The effect of financial incentives on depot medication adherence was evaluated in a randomised controlled trial: 169 patients with a psychotic disorder were randomised to intervention or control groups, stratified by treatment site, sex, comorbid substance-use disorder, and medication compliance [7]. Patients in the control group received mental and primary health care as usual. Patients in the intervention group received the same treatment plus €30 a month over 12-months if antipsychotic depot medication was fully taken. For 35 patients no data were available regarding costs, yet baseline and follow-up proportions of patients using services correspond. Therefore we calculated for 134 (79%) patients direct medical costs and costs related to other healthcare services based on standard unit costs to value resource use at baseline and after 12-months follow-up. Data were collected from the patients' file, from the depot acceptance registration forms, and from questionnaires that assessed use of healthcare services and delinquent behaviour.

### 7.2.2. Costs related to service use

The Treatment Inventory Cost in psychiatric patients (TiC-P) [8] is a frequently used generic self-report outcome measure in adult patients with a psychiatric diagnosis. Validity of self-report service use is acceptable [9]. The full version of the questionnaire includes health care use, medication, and absence of work or other activities. The items concern the volume of medical consumption and productivity loss over the past four weeks. We used the part of the TiC-P that comprises 14 structured questions on contacts within the mental health care sector and contacts with other health services, ranging from general practitioner to homecare. Following the guidelines of the Dutch manual of costing studies in health care [10], total costs were calculated as the sum of the product of reported frequencies and the reference price regarding the type of healthcare use. Mental health care costs were considered as part of treatment related direct costs, whereas other medical consumption was labelled as general medical costs related to other healthcare services. Table 1 summarizes the medical cost items, reference prices, and the number of contacts or hospital days at baseline.

### 7.2.3. Costs related to delinquency

The Self-Reported Delinquency questionnaire (SRD) provides an account of a wide range of illegal acts, including facts not reported to the Justice Department. Self-reported delinquency scales have been widely used, although the validity is not well-established and item difficulty varies across subgroups [11]. We copied the questionnaire from the Dutch version of the

**Table 1. Service unit costs and average costs per patient at baseline (previous four weeks)**

| | Unit costs € | n (%) patients using service | Average costs per patient (SD) |
|---|---|---|---|
| **Medical costs related to psychiatric treatment** | | | |
| Contact with a caregiver from a regional institute for outpatient mental healthcare | 113 | 150 (89%) | 408.3 (509.4) |
| Contact with a psychiatrist, psychologist or psychotherapist at a private (group) practice | 95 | 16 (10%) | 14.1 (66.1) |
| Contact with a psychiatrist, psychologist or psychotherapist (i.e. outpatient visit in hospital) | 95 | 11 (7%) | 12.4 (69.2) |
| Contact with a clinic for alcohol and drugs | 31 | 2 (1%) | 5.5 (66.9) |
| Participation in a self-help group | 58 | 4 (2%) | 3.1 (22.2) |
| Day- or part-time psychiatric hospital treatment | 278 | 5 (3%) | 28.5 (267.9) |
| Psychiatric hospitalisation | 446 | 6 (4%) | 393.2 (2832.8) |
| **Subtotal average sum**<br>excluding hospitalisation | | 169 (100%) | 901.4 (2982.5)<br>508.2 (682.8) |
| **Medical costs related to other healthcare services** | | | |
| Contact with a general practitioner | 33 | 44 (26%) | 13.1 (25.8) |
| Contact with a company doctor | 33 | 2 (1%) | 0.4 (3.6) |
| Contact with a medical specialist (i.e. outpatient visit in hospital) | 92 | 17 (10%) | 21.8 (102.0) |
| Contact with a physiotherapist | 33 | 3 (2%) | 1.2 (10.7) |
| Contact with a social worker | 65 | 33 (20%) | 37.7 (125.2) |
| Home care | 20 | 17 (10%) | 13.4 (47.5) |
| Contact with an alternative healer | 51 | 2 (1%) | 1.8 (17.5) |
| Day- or part-time treatment | 278 | - | - |
| Other hospital* | 170 | - | - |
| Hospitalisation | 446 | 3 (2%) | 39.6 (310.9) |
| **Subtotal average sum**<br>excluding hospitalisation | | 169 (100%) | 91.2 (337.5)<br>54.7 (127.6) |
| **Total medical costs** | | | 992.6 (3008.8) |
| Total costs, excluding hospitalisation | | | 559.8 (702.1) |

* Other than a general hospital, an academic hospital, or a rehabilitation center

**Table 2. Unit costs to value delinquent behaviour and average costs per patient at baseline (previous four weeks)**

| | Unit costs [a] € | n (%) patients | Average Costs per patient (SD) |
|---|---|---|---|
| Damaged a vehicle | 1910 | 3 (2%) | 34.5 (255.2) |
| Damaged public objects [b] | 733 | 3 (2%) | 8.9 (80.5) |
| Besmirched something [b] | 733 | 3 (2%) | 8.9 (80.5) |
| Arson | 1449 | - | - |
| Changed price labels in a shop [b] | 549 | 1 (1%) | 3.3 (42.6) |
| Shoplifting | 1960 | 10 (6%) | 167.3 (1027.6) |
| Stole something at work | 1960 | - | - |
| Stole a bicycle or scooter | 1960 | 1 (1%) | 11.8 (152.1) |
| Stole something of a car | 1910 | - | - |
| Buying stolen goods | 1694 | 4 (2%) | 81.6 (584.1) |
| Soled something stolen | 1694 | 5 (3%) | 51.0 (290.4) |
| Stole something out of a car | 1960 | - | - |
| Car theft [c] | 5000 | - | - |
| Burglary [d] | 4667 | 1 (1%) | 28.1 (362.2) |
| Pickpocketing | 1960 | 1 (1%) | 11.8 (152.1) |
| Robbery | 20.939 | 2 (1%) | 252.3 (2291.4) |
| Aggressive behavior | 1819 | 2 (1%) | 11.0 (141.6) |
| Violent behavior | 4234 | 2 (1%) | 76.5 (733.0) |
| Armed violence | 4234 | - | - |
| Total | | 169 (100%) | 744.9 (3615.4) |

[a] Unit costs based on Goorden et al (2016) unless otherwise specified; [b] Groot et al. (2007); [c] van Ours & Vollaard (2013); [d] Vollaard (2010)

INternational CAnnabis Need of Treatment study (INCANT) [12, 13, 14]. The SRD questionnaire examines the frequency of minor delinquent acts, such as vandalism or shop lifting, as well as criminal acts, such as handling stolen goods or armed robbery. Patients were asked to report on the number of times the specified delinquent behaviour was performed in the last 4 weeks. Contrary to health care contacts, types of delinquency have no generally accepted reference costs. However, Goorden et al. [15] estimated costs based on annual judicial expenses and the number of registered crimes and violations broken down into categories

comparable to categories used in the SRD. We followed this approach to differentiate costs linked to the SRD items; the unit prices were multiplied by the reported frequency of the specific delinquent behaviour and summed to obtain an estimate of the total delinquency costs. Table 2 shows the list of types of delinquent behaviour, unit prices, and the reported frequencies at baseline.

### 7.2.4. Statistical analysis

Medical costs are typically characterized by an asymmetry of the distribution because some patients have minimal costs or specific standard cost amounts and other patients may have disproportionately high costs. Generalized linear models using a log-gamma distribution, have been suggested to account for this kind of highly skewed data [16]. We used the GenLin procedure in SPSS version 21 to model differences in direct mental healthcare costs, medical costs related to other healthcare services, and judicial costs between the intervention and control groups. Means and standard deviations are reported to describe the costs per category of service use and type of delinquency and to illustrate the asymmetry of cost data. Both medical and judicial total costs are dominated by items that are infrequent but have relatively high unit prices. Table 1 shows that an important part of the average medical costs per patient comes from only a few patients who were hospitalised. In table 2 the social costs of robbery stand out. Therefore, we looked at differences in the sum of costs both with and without including hospitalisation costs. Multivariable analysis focussed on the main effect of the intervention on medical and judicial costs, adjusting for stratification variables (i.e. gender, baseline compliance and substance use). Statistical significance of the regression coefficient was tested using the Wald-test and a conventional .05 significance level. In addition, an incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental total costs per year by the incremental effects and creating a bootstrapped 95% confidence interval based on 1000 replications. First, we considered the incremental costs of achieving a 20% increase in adherence following Henderson et al. (2015) [6]. Secondly, we calculated the incremental costs of achieving 'good' adherence i.e., taking at least 80% of the prescribed depot medications over the 12-month intervention period, since this cut-off has been recommended by expert consensus guidelines [17].

## 7.3 Results

The trial demonstrated that financial incentives are effective in improving treatment adherence in patients with psychotic disorder. An adherence difference of 14.9% (95%-CI: 8.9%, 20.9%) was found for the medication possession ratio, and the difference in the proportion of patients achieving good (≥ 80%) adherence levels was 33.1% (95%-CI: 20.2% to 45.4%) in favour of in the intervention group [4]. This result is reflected in higher costs related to psychiatric treatment at 12-months follow-up in the intervention condition compared to care as usual. However, regression analysis controlling for stratification variables indicated a statistically insignificant difference in total medical costs between the intervention and control group (B=.517, SE=.282, p=.067). Table 3 shows that this difference is due to costs of psychiatric hospitalisation, not as much to more frequent regular contacts with outpatient mental health care excluding hospitalisations (B=.251, SE=.206, p=.222).

In the intervention group average medical costs related to other healthcare services were somewhat higher compared to the control group (€529.7 versus €484.1), but lower after excluding hospitalisation (€52.1 versus €78.5). Fewer patients in the Money-for-Medication program visited their GP, a medical specialist, or social worker. This effect was in the expected direction but small (statistical models did not adequately converge).

Table 2 illustrates that delinquent behaviour is not very common among patients with psychotic disorder. Minor offences are most frequently reported but less than 6% of patients are involved in shoplifting incidents or buying and selling stolen goods. At 12-months follow-up very few patients reported delinquent behaviour (Table 4) and only small differences in related social costs were found comparing the intervention group and the control group (€248.4 versus €229.3; B=.607, SE=.420, p=.149).

On average, the maximum of 30 euro extra cost item as financial incentive per patient per month constitutes about 3% of average total mental healthcare costs (€1062) and less than 7% of outpatient medical costs (€449). Extrapolating costs, excluding hospitalisation, in the previous four weeks at 12 months follow-up to total costs per patient per year, averaged to €9273 (SD 13512) in the Money-for-Medication group and to €7900 (SD 19089) in the care-as-usual group. Incremental cost-effectiveness ratio's (ICER) showed wide confidence intervals indicating a high level of uncertainty. Incremental total costs were €2080 (95%-CI: -37972 to 34811) for achieving a 20% increase in adherence and €3332 (95% CI -22675 to 28128) for taking at least 80% of the prescribed depot medications over the 12-month intervention period.

**Table 3. Service costs at 12 months follow-up (previous four weeks)**

| | Intervention Group n (%) patients | Average costs (SD) | Control Group n (%) patients | Average costs (SD) |
|---|---|---|---|---|
| **Medical costs related to psychiatric treatment** | | | | |
| Contact with a caregiver from a regional institute for outpatient mental healthcare | 58 (91%) | 410.1 (532.5) | 60 (87%) | 269.9 (361.1) |
| Contact with a psychiatrist, psychologist or psychotherapist at a private (group) practice | 5 (8%) | 12.1 (55.3) | 17 (25%) | 33.5 (78.3) |
| Contact with a psychiatrist, psychologist or psychotherapist (i.e. outpatient visit in hospital) | 2 (3%) | 2.9 (16.7) | 3 (4%) | 4.1 (19.5) |
| Contact with a clinic for alcohol and drugs | - | - | 1 (1%) | 0.9 (7.5) |
| Participation in a self-help group | 3 (5%) | 17.2 (93.4) | 1 (1%) | 1.7 (13.9) |
| Day- or part-time psychiatric hospital treatment | - | - | 1 (1%) | 4.0 (33.5) |
| Psychiatric hospitalisation | 3 (5%) | 613.3 (2788.7) | 3 (4%) | 433.1 (2284.4) |
| Intervention costs financial incentives | 64 (100%) | 28.6 (3.2) | 0 (0%) | 0 (0.0) |
| **Subtotal average sum**<br>excluding hospitalisation | | **1062.9 (3031.5)**<br>449.6 (530.4) | | **788.8 (2379.3)**<br>355.7 (463.9 |
| **Medical costs related to other healthcare services** | | | | |
| Contact with a general practitioner | 16 (25%) | 8.8 (15.8) | 22 (32%) | 15.5 (28.2) |
| Contact with a company doctor | 1 (1%) | 0.5 (4.1) | 1 (1%) | 0.5 (4.0) |
| Contact with a medical specialist (i.e. outpatient visit in hospital) | 3 (5%) | 4.3 (19.6) | 9 (13%) | 14.7 (40.6) |
| Contact with a physiotherapist | 2 (3%) | 4.6 (33.2) | 2 (3%) | 3.3 (21.3) |
| Contact with a social worker | 9 (14%) | 20.6 (64.8) | 12 (17%) | 50.6 (241.9) |
| Home care | 5 (8%) | 16.6 (60.9) | 5 (7%) | 10.7 (43.2) |
| Contact with an alternative healer | - | - | - | - |
| Day- or part-time treatment | - | - | 1 (1%) | 32.2 (267.7) |
| Hospitalisation | 4 (6%) | 494.8 (2246.4) | 3 (4%) | 407.2 (2263.5) |
| **Subtotal average sum**<br>excluding hospitalisation | | **529.6 (2241.7)**<br>52.0 (117.8) | | **484.0 (2266.6)**<br>78.4 (278.4) |
| **Total costs**<br>excluding hospitalization | 64 (100%) | **1592.5 (3700.7)**<br>484.4 (538.9) | 69 (100%) | **1272.8 (3223.7)**<br>432.5 (536.1) |

**Table 4. Delinquent behaviour costs at 12 months follow-up (previous four weeks)**

| | Intervention Group n (%) patients | Average costs (SD) | Control Group n (%) patients | Average costs (SD) |
|---|---|---|---|---|
| Damaged a vehicle | - | - | - | - |
| Damaged public objects | - | - | - | - |
| Besmirched something | - | - | - | - |
| Arson | - | - | - | - |
| Changed price labels in a shop | - | - | - | - |
| Shoplifting | 1 (1%) | 28.8 (237.7) | - | - |
| Stole something at work | - | - | - | - |
| Stole a bicycle or scooter | - | - | 1 (1%) | 148.5 (1206.3) |
| Stole something of a car | - | - | - | - |
| Buying stolen goods | 3 (4%) | 75.9 (460.0) | - | - |
| Soled something stolen | 1 (1%) | 24.9 (205.4) | 1 (1%) | 25.7 (208.5) |
| Stole something out of a car | 1 (1%) | 28.8 (237.7) | - | - |
| Cartheft | - | - | - | |
| Burglary | - | - | - | - |
| Pickpocketing | 1 (1%) | 28.8 (237.7) | - | - |
| Robbery | - | - | - | - |
| Agressive behavior | - | - | - | - |
| Violent behavior | - | - | 1 (1%) | 55.1 (447.8) |
| Armed violence | 1 (1%) | 62.3 (513.4) | - | - |
| **Total** | **64 (100%)** | **248.4 (856.2)** | **69 (100%)** | **229.3 (1477.4)** |

## 7.4 Discussion

Providing a financial incentive to improve adherence to depot medication in psychotic patients resulted in higher average costs directly related to mental health care and lower costs related to other health care services. Relevant differences in social costs related to delinquent behaviour were not found.

An increase in medication compliance was reflected in mental healthcare costs, which were higher in the Money-for-Medication group compared to the control group. In contrast, medical costs related to other health care services were somewhat lower in the intervention

group. Effects in terms of medical costs were in the expected direction but differences between the intervention and control group were not statistically significant. Social costs related to delinquency concerned few patients and only minor and non-significant differences were found comparing the intervention and control group.

Intervention costs are low considering a modest maximum financial incentive of 360 euro per patient per year. Ultimately, policy-makers should decide whether they agree to extra expenses and what improvements in medication adherence they aim to achieve. Currently no threshold values are available for the ICER-values in the range of €2000 for achieving a 20% increase in adherence, and just over €3000 for 'good' (80% or higher) medication adherence. Interestingly, these figures are in line with the results of Henderson et al. [6]. This suggests that in the western world we may be able to increase compliance with depot medication to an appropriate level when we are willing to invest extra. Future studies using longer intervention and follow-up periods are needed to investigate cost-effectiveness also with respect to quality of life.

**Limitations**

- Medical and judicial cost items were patient reported over a four weeks' time span, which may reduce memory bias, but may not adequately reflect variability in the level of health service use or delinquent behaviour in our 12-month study period.
- National reference costs per health care contact or type of delinquency are crude estimates of the true mental healthcare cost, medical costs related to other health care services, and social costs.
- The Self-Reported Delinquency questionnaire originally was aimed at adolescents and may be less suited for mapping delinquent behaviour in psychiatric patients
- Frequency of other social parameters (e.g. participation in volunteer work) were not assessed.
- Invested time per patient to arrange appointments for proving depot medication was not monitored, so it remains unclear whether implementing M4M did actually save or cost extra time.
- The study was underpowered for the analysis of highly skewed cost data, resulting in wide bootstrapped confidence intervals for incremental cost-effectiveness ratios.
- Financial benefits of M4M in terms of reductions in medical costs (both direct and related to other healthcare services) might become manifest only after a longer period of time than could be covered in this study.

## Acknowledgements

We would like to thank all the patients, research assistants, clinicians and health care facilities that participated in this study.

## References


1. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S (2011) Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 127:83–92
2. Barnes TRE, Shingleton-Smith A, Paton C (2009) Antipsychotic long-acting injections: prescribing practice in the UK. Br J Psychiatry Suppl 52:S37-42
3. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, David AS, O'Connell N, Forrest A, Burns T (2013) Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics : cluster randomised controlled trial. BMJ. doi: 10.1136/bmj.f5847
4. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Staring ABP, Mulder CL (2017) Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial. The Lancet Psychiatry 4:199–207
5. Oberjé EJM, De Kinderen RJA, Evers SMAA, Van Woerkum CMJ, De Bruin M (2013) Cost effectiveness of medication adherence-enhancing interventions: A systematic review of trial-based economic evaluations. Pharmacoeconomics 31:1155–1168
6. Henderson C, Knapp M, Yeeles K, Bremner S, Eldridge S, David AS, O'Connell N, Burns T, Priebe S (2015) Cost-effectiveness of financial incentives to promote adherence to depot antipsychotic medication: Economic evaluation of a cluster-randomised controlled trial. PLoS One 10:1–18
7. Noordraven EL, Audier CH, Staring A, Wierdsma AI, Blanken P, van der Hoorn B, Roijen L, Mulder CL (2014) Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. BMC Psychiatry 14:343
8. Hakkaart van Roijen L (2002) Trimbos / iMTA questionnaire for Costs associated with Psychiatric Illness ( TiC-P ). iMTA 7:5–45
9. Somers JM, Moniruzzaman A, Currie L, Rezansoff SN, Russolillo A, Parpouchi M (2016) Accuracy of reported service use in a cohort of people who are chronically homeless and seriously mentally ill. BMC Psychiatry 16:41
10. Timman R, Bouwmans C, Busschbach JJ V, Hakkaart-Van Roijen L (2015) Development of the Treatment Inventory of Costs in Psychiatric Patients: TIC-P Mini and Midi. Value Heal 18:994–999
11. Piquero AR, Macintosh R, Hickman M (2002) The Validity of a Self-reported Delinquency Scale. Sociol Methods Res 30:492–529
12. Hendriks V, van der Schee E, Blanken P (2011) Treatment of adolescents with a cannabis use disorder: Main findings of a randomized controlled trial comparing multidimensional family therapy and cognitive behavioral therapy in The Netherlands. Drug Alcohol Depend 119:64–71
13. Elliot DS, Huizinga D, Ageton SS (1985) Explaining Delinquency and Drug Use. Sage Publications, Beverly Hills, CA.
14. WODC (1991) Wetenschappelijk Onderzoek en Documentatie Centrum Documentatie Vragenlijst Internationaal Onderzoek Selfreport Delictgedrag (Questionnaire International Study Self-Report Deliquency). Ministry of Justice, Den Haag
15. Goorden M, van der Schee E, Hendriks VM, Hakkaart-van Roijen L (2016) Cost-effectiveness of multidimensional family therapy compared to cognitive behavioral therapy for adolescents with a cannabis use disorder: Data from a randomized controlled trial. Drug Alcohol Depend 162:154–161
16. Gregori D, Petrinco M, Bo S, Desideri A, Merletti F, Pagano E (2011) Regression models for analyzing costs and their determinants in health care: an introductory review. Int J Qual Heal care J Int Soc Qual Heal Care 23:331–41
17. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP (2009) The Expert Consensus Guideline Series: Adherence Problems in Patients with Serious and Persistent Mental Illness. J Clin Psychiatry 70:1–46

# Chapter 8

General discussion, conclusions, and recommendations

## 8.1 Introduction

Non-adherence to antipsychotic medication severely limits the effectiveness of the medical treatment of schizophrenia and captures the central theme of this thesis. A comprehensive overview is provided in Chapter 1, in which we present the results from randomized controlled trials aiming to improve adherence to antipsychotic medications. Different interventions, inclusion criteria, study periods, and various assessments of medication adherence make it difficult, if not impossible, to compare studies directly. In order to improve comparability between studies, we discuss the need for more generic measures and definitions of adherence.

The main objective of the research project described in this thesis was to assess whether financial incentives are effective for improving adherence to antipsychotic depot medication among patients with psychotic disorders. We conducted a randomized controlled trial, called Money for Medication, in which patients were offered financial incentives for taking their antipsychotic depot medication. Our study protocol (Chapter 2) describes the details of this trial, including the primary and secondary outcome measures, procedures and assessments. Our results showed that, after 12 months of offering financial incentives, medication adherence was about 14% higher for the intervention group than for the control group. After a 6 month follow-up period, in which financial incentives were no longer offered, differences in adherence decreased to 7%, but remained significant (Chapter 3).

Furthermore, we explored the association of two risk factors for (non-)compliance, treatment motivation and illness insight, with acceptance of depot medication at baseline. Results showed that motivation for treatment was more important than illness insight for accepting medication at baseline (Chapter 4). Also, we repeatedly measured various subtypes of motivation for treatment during the course of this study. There were no differences in treatment motivation between the intervention and control group after the intervention and follow-up period (Chapter 5). This indicated that our intervention did not directly affect treatment motivation, even after financial incentives were discontinued.

In Chapter 6, we described ethical aspects of the intervention. We investigated ethical concerns and opinions of both patients and clinicians after using financial incentives in clinical practice. Overall, both groups were positive about this intervention and ethical concerns were discussed in terms of patients' autonomy, beneficence, non-maleficence and justice. Finally, we assessed the costs of this intervention, which showed no numerous financial benefits of Money for Medication over care as usual, not offering financial incentives (Chapter 7).

Apart from these findings, important dilemmas deserve attention when using financial incentives in clinical practice. For instance, do all patients prescribed antipsychotic depot medication need to receive this intervention, and for how long? Do financial incentives support

better clinical outcomes? And does motivation for treatment decreases after receiving payments over a long period? We will discuss (1) the effectiveness of financial incentives on adherence, (2) the relationship between adherence and outcomes, and (3) the influence of financial incentives on patients' motivation for treatment.

## 8.2 Financial incentives for improving medication adherence

### 8.2.1 Efficacy

We demonstrated in our study (Chapter 3), that adherence to antipsychotic depot medication successfully improved by offering financial incentives among patients with psychotic disorders. After 12 months, the adjusted mean adherence rate, defined by the Mean Possession Ration (MPR), was 14% higher in the intervention group (94%) than in the control group (80%). Importantly, 95% of the patients in the intervention group achieved adherence levels of 80% or higher, compared with 59% of patients in the control group. During the 6-month follow-up period, when the offer of financial incentives was discontinued, the positive effects on medication adherence decreased, but adherence levels remained 7% higher in the intervention group (83%) than in the control group (76%).

These results supported previous findings in which financial incentives successfully improved adherence among non-adherent patients [1, 2]. Furthermore, we provided new information about the applicability of this intervention, since we included both adherent and non-adherent patients. The overall effect was mainly caused by patients who showed low adherence rates at baseline; those patients who had the most room for improvement (from 52% to 91%). Patients in the intervention group with high medication adherence at baseline showed little improvement in MPR, mainly because they had less room for improvement (i.e. 100% being the maximum acceptance rate; ceiling effect). Importantly, adherence rates remained high for these patients in the intervention group at baseline (97%) and after 12 months (97%). By contrast, patients in the control group with high adherence rates at baseline (98%) had lower adherence after 12 months (81%). This indicates that some patients are likely to become less adherent over time, justifying the provision of financial incentives also to currently adherent patients [3].

### 8.2.2. Effectiveness over time

Contingency Management (CM) has shown direct positive effects for adhering to medication, but also on other health related behaviors such as illicit psychoactive drug use and smoking cessation [4]. However, these effects seem to diminish after the incentives are removed [5].

In a randomized controlled trial where patients received vouchers for delivering drug-free urine samples [6], stimulant use reduced after the 16 week treatment period. However, after stopping CM, differences between the intervention and control group did not remain significant at follow-up assessments at 26 and 52 weeks. Similarly, 3 months of prize-based CM significantly improved the submission of negative stimulant- and alcohol urine samples between the intervention and control group [7]. Again, these differences disappeared during 6-months follow-up, after stopping CM. It seems that prizes and vouchers are only effective during the time period in which they are offered. It remains unclear whether this is the same for using financial incentives, and what happens when they are no longer offered.

Our results showed a significant increase in medication adherence after 12 months of offering financial incentives. However, after a 6 month follow-up period in which financial incentives were no longer offered, the initial MPR difference of about 14%, decreased to around 7%. This indicates that using financial incentives is mostly effective for as long as it is offered, as the positive effects on medication adherence diminish over time, after incentives are withdrawn. Thus, a small 'crowding-out' effect [8] did occur in our study: after incentives were withdrawn patients did become less adherent, but did not stop accepting their depot medication completely [9]. This indicates that financial incentives can be safely applied, without strong negative effects on adherence when stopping the incentives. Other research has indicated that a substantial effect of financial incentives on medication adherence, occurs within the first 3 months of the intervention and is sustained over 1 year [10]. These authors suggest that if incentives show no improvements within the first 3 months, one should be careful to expect any improvements later. Furthermore, a meta-analysis was conducted among fifteen randomized and 6 non-randomized studies which used financial incentives for adherence to medications for tuberculosis, substance abuse, HIV, hepatitis, schizophrenia, and stroke prevention [11]. These findings indicated that studies with longer intervention periods (e.g. >24 weeks) showed larger effect sizes than studies with shorter durations (e.g. 12 weeks). This suggests that it is more effective to offer financial incentives over longer periods of time.

In conclusion, financial incentives are most effective as long as they are offered, and there does not seem to be a learning effect: when incentives are no longer in place, adherence returns to pre-intervention levels. Therefore, we recommend continuing with this intervention over time for all patients. Later, we will discuss ethical dilemmas that accompany this recommendation.

## 8.3 Medication adherence and psychosocial outcomes

Some studies found better psychosocial outcomes after improvement of medication adherence [12, 13]. In our study, however, psychiatric symptoms, quality of life and other measures of psychosocial functioning did not improve in the group of patients who were offered financial incentives, as compared to the control group. There are various reasons why intervention studies aiming to improve medication adherence sometimes fail to improve clinical or psychosocial outcomes.

First, this may be due to a floor effect (PANNS scores were already low at the start of the intervention), or due to the fact that the levels of adherence in the control group were high enough not to cause a deterioration in symptom levels during the study- and follow-up period. In addition, post-hoc analyses of the data of our RCT (reported in Chapter 3) showed no significant association between baseline depot-acceptance (MPR ratio at baseline) and PANNS scores at baseline (results not shown), meaning that the level of adherence is not strongly related to the level of symptoms, at least not cross-sectional. Thus, the association between level of depot-adherence and level of psychiatric symptoms is complicated, despite overwhelming observational evidence showing that non-adherence is associated with an increase or relapse of symptoms [14–17].

Second, the follow-up period of 12 months may have been too short to detect significant improvements in psychosocial outcomes, including quality of life. Especially among patients with a chronic mental illness and an average illness duration of 12 years, it may be not realistic to expect detectable improvements within a relatively short time period, in spite of improved medication adherence. Also, the questionnaires might not have been sensitive enough to detect small differences in psychosocial outcomes [18]. Importantly, patients' clinical functioning did not worsen during the intervention period.

Third, improved medication adherence in itself might not be sufficient to improve complex outcomes such as psychosocial functioning or quality of life. Improving these outcomes might require additional interventions focusing on other factors, such as psychotherapy [19], active involvement of the social-support system [20], (volunteer) work [21] and physical exercise [22], and the establishment of a structured daily schedule [23].

Other studies which also used financial incentives to change health-related behavior, succeeded in improving primary outcomes such as abstinence from smoking, drug- or alcohol use [24–26], but also did not succeed in improving secondary outcomes including psychiatric symptoms [27].

Finally, non-adherence to medication may be a *consequence* rather than a cause of persistent and medication-resistant psychotic symptoms [28]. This may be the reason why patients who,

-after experiencing no positive effects of antipsychotic medication-, become non-adherent. In these patients, an adherence-promoting intervention may increase adherence, but this will not have an effect on (medication-resistant) psychiatric symptoms. The indirect association between adherence to antipsychotic medication and psychotic symptoms, however, seems to be complex and depending on medication- and patient-related variables [29, 30].

In sum, there are various reasons why studies may find no improvements in clinical or psychosocial outcomes. Our overview (Chapter 1) indicated that around 50% of the intervention studies successfully improved medication adherence among patients with psychotic disorders. Only 33% of these studies seemed to obtain improved psychiatric symptoms as well. However, large heterogeneity remains an important problem and makes it difficult to compare all studies (due to large variations in assessment methods, duration of intervention- and follow-up periods, sample sizes, baseline symptom severity, or individual variations in responsiveness to antipsychotic drug treatment). Comparability between studies could improve if future studies strive for more homogenous measures of adherence, for example the MPR in patients receiving depot medication. Furthermore, longer intervention- and follow-up periods are recommended in combination with more frequent assessments over time in order to capture a more accurate course of illness for psychotic disorder patients. Expectations about improving psychiatric and psychosocial outcomes should also become more realistic and will not happen overnight, since most patients in our studies suffer from severe and chronic mental illness. Finally, interventions primarily aimed to improve medication adherence seem insufficient to improve complex outcomes such as social functioning or quality of life.

## 8.4 Medication adherence and motivation for treatment

For patients with schizophrenia, impaired motivation for treatment is associated with poor adherence and functional outcomes [31]. Therefore, it is important to study whether Money for Medication (i.e. the use financial incentives upon taking medication) may undermine patients' motivation for treatment when providing the incentives, or after withdrawing them [32].

First, our cross-sectional study (Chapter 4) explored the relationship between motivation for treatment, illness insight and adherence to depot medication. Patients with poor insight and high motivation for treatment were more adherent (MPR of 94%) with their depot medication than patients with poor insight and low motivation (61%). Counterintuitively, patients with high insight and high motivation for treatment were less adherent (73%) than those with poor insight and high motivation. This shows that motivation for treatment at study entrance was more strongly associated with depot-medication adherence than illness insight. Apparently,

insight does not necessarily leads to adherence. For instance, patients having insight that antipsychotic drugs lead to symptom improvement may not necessarily take their medication as prescribed in a phase of symptomatic remission. They might believe they can start again taking medication when symptoms are getting worse. In contrast, other patients may continue taking antipsychotic medication because they have the insight to do so based on earlier experiences (e.g. experiences of relapse after stopping of medication), and this may not necessarily be based on direct illness insight. These findings indicate, that being motivated to take medication, whether to stay or to get better or for other reasons, may be a more important factor in terms of improving depot-medication compliance than having illness insight.

Second, we assessed whether offering financial incentives to take antipsychotic depot medication would reduce patients' motivation for treatment (Chapter 5). Our findings suggest that it did not. After the 12 month intervention-period, 91% of the patients showed no or only mild motivational problems. During the 6 month follow-up period, a majority of the patients (83%) were still motivated for treatment, whereas relatively few (17%) reported having little motivation for or resistance to their current treatment. In addition, these results remained similar with respect to various types of motivation (i.e. intrinsic, extrinsic and introjected), during the intervention- and follow-up period, and did not differ between patients from the intervention- and control group.

In sum, offering and then discontinuing financial incentives to patients with psychotic disorders did not reduce their overall motivation for clinical treatment. In particular, both intrinsic and extrinsic motivation for treatment showed no measurable differences between patients from the intervention and control group. This suggests that offering financial incentives is a safe intervention and does not undermine patients' motivation for treatment.

## 8.5 Limitations

Several limitations deserve our attention when interpreting the results of this study, such as selection bias, lack of blinding, invested time because of the intervention, and the ability of this intervention to improve psychosocial outcomes.

Selection bias remains a challenge for many adherence-intervention studies, in particular the problem of inclusion of completely non-adherent patients into RCT's. It can be very difficult for clinicians to motivate patients to participate in an RCT who are completely non-adherent, who are not motivated for treatment and sometimes require assertive outreach. Often, these completely non-adherent patients experience difficulties in primary self-care such as getting out of bed, lack of personal hygiene, lack of proper housing, or they might not trust

the mental health care facility (often as part of their paranoid psychosis). Psychotic symptoms such as paranoia or acoustic hallucinations can be a complicating factor, making it difficult for them to understand that these studies could potentially benefit them. In our study, we were less successful in recruiting non-adherent patients, since adherence rates at study entrance were relatively high (i.e. around 76%). Consequently, the included patients are more stable than completely non-adherent patients. As stated above, this ceiling effect also seems an important reason for not finding psychosocial benefits; patients' subjective quality of life and psychosocial functioning were already relatively high at study entrance, leaving little room for improvement.

Lack of blinding is another problem for this type of open-label randomized controlled trials. In the current study, masking of patients to receipt of a financial reward was not possible. However, we collected quantitative primary outcome data (Medication Possession Ratio's) from patients' records. This type of outcome data is not sensitive to blinding.

In practice, Money for Medication might have led to more enthusiasm among the mental healthcare teams who tried harder or invested more time to give patients their depot medication. Therefore, it may not have been the financial incentive itself that caused the behavioral change (taking more depots), but merely the enthusiasm and extra invested time of the nurses providing money after depot acceptance. Unfortunately, we were not able to register the invested amount of time per patient for organizing and administering the depot medication and providing financial incentives. In contrast, one might argue that the extra amount of invested time by clinical staff is an inherent part of the intervention. We think, however, that the extra amount of time was very limited, since providing money is a simple procedure, and nurses told us that patients in the intervention group showed up precisely on time (or even earlier), leading perhaps to less time needed for providing depot medication.

Finally, our intervention might have been too simplistic and not sufficient enough to improve complex clinical outcomes, such as psychiatric symptomology, psychosocial functioning and quality of life. This might require additional interventions focusing on social factors [33] such as active involvement of the social-support system [20], (volunteer) work [21], physical exercise [22], and the establishment of a structured daily schedule [23]. Additionally, improvements on these outcomes may not occur within 12 months, but require longer intervention and follow-up periods.

In sum, it may be that offering financial incentives to patients who have large difficulties in adherence, may be even more efficient than has been found in our study. In addition, it seems important for future studies to also include patients with high symptom levels. Perhaps offering financial incentives to a very non-adherent group may have beneficial effects on psychosocial outcomes as well, including less relapses and less hospitalizations, and may be more cost-effective. This warrants further research.

## 8.6 Implications and pitfalls

A comment on our manuscript was published in Lancet Psychiatry entitled: 'Money for Medication' as "*A simple, effective intervention that nobody wants to provide*" [34]. Offering financial incentives may have proven to be effective for improving medication adherence [2, 9] but it seems unlikely to become common practice in mental health care clinics. Barriers for clinicians, patients and the community could prevent this intervention from becoming implemented in routine clinical treatment, despite the intervention being very effective.

### 8.6.1 Clinician barriers

For patients with psychotic disorders, offering financial incentives has proven effective for improving antipsychotic medication adherence. However, clinicians might be worried that financial incentives could harm their patients and interfere with clinical treatment, since providing financial incentives can be seen as bribing patients to take depot-medication.

In the current study however, increased medication intake did not lead to more antipsychotic medication side-effects, such as social withdrawal or reduction of emotional responsiveness. In other words, doing harm does not seem to be a valid reason not to give financial incentives for improving depot-acceptance. Furthermore, clinicians were worried that patients would spend their money on (illegal) substances. Importantly, we did not find that intervention patients had higher severity ratings of alcohol or drug abuse than those who did not received financial incentives.

Another concern among clinicians is that the therapeutic relationship may suffer from using monetary rewards. Patients may no longer discuss their thoughts and feelings, talk with, or listen to their clinician, unless they get rewarded. Also, staff might be hesitant to risk their therapeutic relationships, which are often established over longer periods of time, and with great difficulties. From this perspective, it is understandable that clinicians are reluctant to implement this intervention. In our study, neither patients nor clinicians actively reported any concerns about the therapeutic relationship, although we did not systematically study this. Therefore, we believe that financial incentives do not interfere with the therapeutic relationship. Furthermore, caregivers worry about 'buying' their patients to take their medications while these patients often have no or very low income. Our ethical study (Chapter 6) showed that the majority of the patients did not feel forced or dependent by receiving financial incentives and that patient autonomy remained unaffected. This indicates that the size of the incentive was chosen appropriately: Patients did not feel coerced, although they took more depots. Clinicians (71%) also agreed with the statement that financial incentives would provoke patients to follow treatment less for themselves but more for the money, although this opinion was shared by

fewer patients (38%). Fortunately, we also found that patients kept their motivation for treatment both during and after the intervention period (Chapter 5).

Finally, in the other clinical trial in which financial incentives were offered for accepting antipsychotic depot medication [2], clinicians could chose to either continue or stop with the intervention after the 12-month intervention period had ended. Interestingly, no clinicians continued the use of incentives during this 12 month follow-up period, and they also did not offer financial incentives to any control group patients after the trial had ended [35]. They reported that financial constraints or lack of funding were the most important reasons for not continuing with the incentives. Together, these findings indicate that clinicians can offer their patients financial incentives for accepting depot medication safely, without harming their patients and without negative effects on their therapeutic relationship with the patients or patients' motivation for treatment.

### 8.6.2 Patient barriers

Social stigma remains an important dilemma. A recent study investigated determinants for accepting antipsychotics and found that symptoms of schizophrenia are considered as more distressful, less treatable and associated with higher social stigma than chronic somatic illnesses [36]. Such negative representations of schizophrenia may stimulate non-adherence and may not be easily changed by offering external rewards.

Furthermore, offering money may send an ambiguous message as it implies that patients need to do something they might otherwise not do. However, patients take depot medication for gaining better symptom control (possibly preventing relapse), making it easy to provide a rationale for giving a reward for accepting depot medication.

Another barrier is that some patients indicated that they were worried that jealousy would arise if only some patients would receive money and others not. This could stimulate patients to become non-adherent on purpose in order to receive financial rewards. To overcome this problem, we would recommend offering this intervention to all patients, independent of the level of adherence, and discuss with the patient whether he or she wants to use this option and explain how it could benefit them. However, this does not automatically imply that all patients like to be offered incentives.

Finally, as stated above, some patients with psychotic illnesses are difficult to engage in treatment, sometimes due to high symptom severity. Usually, a higher level of psychotic symptoms is associated with less illness insight [37], which might explain why patients sometimes show lower treatment motivation. This association between a high level of psychotic symptoms, and low motivation for treatment is called the motivation paradox [38]. These patients however seem to be most in need of treatment, while at the same time they have

low motivation. Financial incentives may overcome this problem in this specific group (not included in our study) by stimulating patients to engage in treatment by providing them a financial incentive to accept depot medication.

### 8.6.3 Community barriers

Regarding the possible costs for society, this intervention itself seems to be rather inexpensive, although no clear cost-reductions were found (H8). And if it cannot be proven to be highly cost-effective, why would any insurance company pay for this intervention? This is a legitimate concern that could prevent this intervention from becoming applied in clinical practice. Perhaps that longer study periods are needed to detect clinical and financial benefits, for example because in the long-term less hospital admissions are needed in patients who remain adherent to depot medication.

Another concern is the public debate or social stigma about patients with schizophrenia. In other words, it seems very difficult to explain why people should be paid to do something that is in their own interest. Especially for health care insurance companies, this makes it difficult to provide such interventions. The most pragmatic solution would be to show the financial gains for society when providing financial incentives, making a profitable 'business case' which might convince insurance companies.

Finally, the practical and logistic implementation of providing financial incentives within mental health care clinics might be difficult. Clinics have no experience in distributing financial incentives and storing money. This may seem as a minor problem, but the practical execution of this study was quite labor-intensive. It required detailed administration, accurate handling of sometimes large sums of cash, and the presence of other healthcare workers to ensure open and transparent delivery and outtake of money, each time depot medications were administered. These obstacles can be overcome by providing clear protocols for the administration.

## 8.5 Recommendations

This study was successful in improving medication adherence, which was the primary goal. However, in order to also detect improvements in psychiatric symptoms and psychosocial outcomes, future research should include longer study periods and also patients with lower adherence at baseline. For example, offering financial incentives for three years or more, may lead to maintained high adherence rates, possibly leading to better psychiatric and psychosocial outcomes and, ultimately, reduced costs. However, ongoing drugs or alcohol use is associated with intrinsic motivation deficits [39] and might interfere with patients' psychiatric and

psychosocial improvements [40]. Therefore, also rewarding abstinence, together with rewarding medication adherence might be a useful combination. It may even be more effective rewarding abstinence for improving psychosocial outcomes, than offering financial incentives for rewarding adherence.

In addition, improved medication adherence might not be sufficient to improve psychosocial functioning or quality of life. In order to improve such outcomes, the social support system of patients plays an important role and should be more involved (e.g. psychotherapy or system therapy). This might require additional interventions focusing on social factors such as active involvement of the social-support system, (volunteer) work or physical exercise.

In sum, offering financial incentives is a very effective way of improving adherence with antipsychotic depot medication, and we encourage the implementation of this intervention in daily clinical practice.

## References


1. Staring ABP, Mulder CL, Priebe S (2010) Financial incentives to improve adherence to medication in five patients with schizophrenia in the Netherlands. Psychopharmacol Bull 43:5–10
2. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, David AS, O'Connell N, Forrest A, Burns T (2013) Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics : cluster randomised controlled trial. BMJ. doi: 10.1136/bmj.f5847
3. Valenstein M, Blow FC, Copeland LA, Mccarthy JF, Zeber JE, Qmon L, Bingham CR, Stavenger T (1998) Poor Antipsychotic Adherence Among Patients With Schizophrenia : Medication and Patient Factors. 255–264
4. Petry NM, Alessi SM, Rash CJ (2013) A randomized study of contingency management in cocaine-dependent patients with severe and persistent mental health disorders. Drug Alcohol Depend 130:234–237
5. Benishek LA, Dugosh KL, Kirby KC, Matejkowski J, Clements NT, Seymour BL, Festinger DS (2014) Prize-based contingency management for the treatment of substance abusers: A meta-analysis. Addiction 109:1426–1436
6. Rawson RA, McCann MJ, Flammino F, Shoptaw S, Miotto K, Reiber C, Ling W (2006) A comparison of contingency management and cognitive-behavioral approaches for stimulant-dependent individuals. Addiction 101:267–274
7. Roll JM, Petry NM, Stitzer ML, et al (2006) Contingency management for the treatment of methamphetamine use disorders. Am J Psychiatry 163:1993–1999
8. Promberger M, Marteau TM (2013) When do financial incentives reduce intrinsic motivation? comparing behaviors studied in psychological and economic literatures. Health Psychol 32:950–7
9. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Staring ABP, Mulder CL (2017) Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial. The Lancet Psychiatry 4:199–207
10. Pavlickova H, Bremner SA, Priebe S (2015) The effect of financial incentives on adherence to antipsychotic depot medication: Does it change over time? J Clin Psychiatry 76:e1029–e1034
11. Petry NM, Rash CJ, Byrne S, Ashraf S, White WB (2012) Financial reinforcers for improving medication adherence: Findings from a meta-analysis. Am J Med 125:888–896
12. Farooq S, Nazar Z, Irfan M, Akhter J, Gul E, Irfan U, Naeem F (2011) Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS). Br J Psychiatry 199:467–72
13. Gray R, Wykes T, Edmonds M, Leese M, Gournay K (2004) Effect of a medication management training package for nurses on clinical outcomes for patients with schizophrenia: cluster randomised controlled trial. Br J Psychiatry 185:157–62
14. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S (2011) Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 127:83–92
15. Suzuki T, Remington G, Arenovich T, Uchida H, Agid O, Graff-Guerrero A, Mamo DC (2011) Time course of improvement with antipsychotic medication in treatment-resistant schizophrenia. Br J Psychiatry 199:275–280
16. Knapp M (2004) Non-adherence to antipsychotic medication regimens: associations with resource use and costs. Br J Psychiatry 184:509–516
17. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM (2010) Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res 176:109–13

18. Leucht S, Tardy M, Komossa K, et al (2012) Maintenance treatment with antipsychotic drugs for schizophrenia ( Review ) Maintenance treatment with antipsychotic drugs for schizophrenia. Cohcrane Database Syst Rev. doi: 10.1002/14651858.CD008016.pub2.Copyright
19. Rosenbaum B, Harder S, Knudsen P, Køster A, Lindhardt A, Lajer M, Valbak K, Winther G (2012) Supportive Psychodynamic Psychotherapy versus Treatment as Usual for First-Episode Psychosis: Two-Year Outcome. Psychiatry Interpers Biol Process 75:331–341
20. Norman RMG, Malla AK, Manchanda R, Harricharan R, Takhar J, Northcott S (2005) Social support and three-year symptom and admission outcomes for first episode psychosis. Schizophr Res 80:227–234
21. McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A (2007) Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. Am J Psychiatry 164:437–441
22. Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, Elliott R, Nuechterlein KH, Yung AR (2017) Aerobic exercise improves cognitive functioning in people with schizophrenia: A systematic review and meta-analysis. Schizophr Bull 43:546–556
23. Minato M, Zemke R (2004) Time use of people with schizophrenia living in the community. Occup Ther Int 11:177–191
24. McDonell MG, Srebnik D, Angelo F, McPherson S, Lowe JM, Sugar A, Short R a, Roll JM, Ries RK (2013) Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness. Am J Psychiatry 170:94–101
25. Sigmon SC, Patrick ME (2012) The use of financial incentives in promoting smoking cessation. Prev Med (Baltim) 55 Suppl:S24-32
26. Blanken P, Hendriks VM, Huijsman IA, van Ree JM, van den Brink W (2016) Efficacy of cocaine contingency management in heroin-assisted treatment: Results of a randomized controlled trial. Drug Alcohol Depend 164:55–63
27. McDonell MG, Leickly E, McPherson S, Skalisky J, Srebnik D, Angelo F, Vilardaga R, Nepom JR, Roll JM, Ries RK (2017) A Randomized Controlled Trial of Ethyl Glucuronide-Based Contingency Management for Outpatients With Co-Occurring Alcohol Use Disorders and Serious Mental Illness. Am J Psychiatry appi.ajp.2016.1
28. Brenner HD, Merlo MCG (1995) Definition of therapy-resistant schizophrenia and its assessment. Eur Psychiatry 10:11–17
29. Velligan DI, Sajatovic M, Hatch A, Kramata P, Docherty JP (2017) Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence 11:449–468
30. Haddad PM, Brain C, Scott J (2014) Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Dove Med Press 5:43–62
31. Gard DE, Fisher M, Garrett C, Genevsky A, Vinogradov S (2009) Motivation and its Relationship to Neurocognition, Social Cognition, and Functional Outcome in Schizophrenia. Schizophr Res 115:74–81
32. Deci et al. (1999) II.pdf.
33. Yesufu-Udechuku A, Harrison B, Mayo-Wilson E, Young N, Woodhams P, Shiers D, Kuipers E, Kendall T (2015) Interventions to improve the experience of caring for people with severe mental illness: systematic review and meta-analysis. Br J Psychiatry 206:268–74
34. Burns T (2017) A simple, effective intervention that nobody wants to provide. The Lancet Psychiatry 4:172–173
35. Priebe S, Bremner SA, Lauber C, Henderson C, Burns T (2016) Financial incentives to improve adherence to antipsychotic maintenance medication in non-adherent patients: A cluster randomised controlled trial. Health Technol Assess (Rockv) 20:v-121
36. Berna F, Göritz AS, Llorca PM, Vidailhet P, Fond G, Moritz S (2017) Would I take antipsychotics, if I had psychotic symptoms? Examining determinants of the decision to take antipsychotics. Prog Neuro-Psychopharmacology Biol Psychiatry 77:155–163

37. Mintz AR, Dobson KS, Romney DM (2003) Insight in schizophrenia: A meta-analysis. Schizophr Res 61:75–88
38. Mulder CL, Jochems E, Kortrijk HE (2014) The motivation paradox: higher psychosocial problem levels in severely mentally ill patients are associated with less motivation for treatment. Soc Psychiatry Psychiatr Epidemiol 49:541–8
39. Bahorik AL, Greeno CG, Cochran G, Cornelius JR, Eack SM (2017) Motivation deficits and use of alcohol and illicit drugs among individuals with schizophrenia. Psychiatry Res 253:391–397
40. Weibell MA, Hegelstad WTV, Auestad B, et al (2017) The Effect of Substance Use on 10-Year Outcome in First-Episode Psychosis. Schizophr Bull 43:843–851

# Appendices

Summary

Nederlandse samenvatting

Curriculum Vitae

PhD Portfolio

List of publications

Dankwoord

## Summary


### Background

Non-adherence to antipsychotic medication severely limits the effectiveness of the pharmaceutical treatment of schizophrenia and captures the central theme of this thesis. The main objective of our research project, called Money for Medication, was to assess whether financial incentives are effective for improving adherence to antipsychotic depot medication among patients with psychotic disorders.

### Literature overview

We first conducted a systematic overview of the available literature (**Chapter 1**), to gain better understanding of the relationship between antipsychotic medication adherence and clinical outcomes. In total, 29 randomized controlled trials between 1996 and 2017 were included which primarily aimed to improve adherence. Out of the 24 studies that assessed medication adherence, 13 studies (54%) found that adherence to antipsychotic medication improved for patients receiving different types of (psychological-, social-, behavorial or a combination of these) interventions. Psychiatric symptoms improved in 33% of these studies. Furthermore, few studies also assessed social functioning and quality of life. In these studies, improvement in symptoms was accompanied by better functional outcomes and higher ratings on quality of life. Together, these results indicate that improved adherence not automatically leads to better clinical outcomes.

However, when comparing all studies, excessive variation occurred on many levels regarding: the assessment of outcomes, adherence problems and symptom severity at baseline, patient settings, intervention types and duration, and length of follow-up periods. This large heterogeneity makes it difficult to draw definite conclusions about when and how improvements in adherence lead to better clinical outcomes.

### Money for Medication (protocol and results)

We conducted a randomized controlled trial, called Money for Medication, in which patients were offered financial incentives for taking their antipsychotic depot medication. Our study protocol describes the details of this trial (**Chapter 2**). In sum, we conducted a multicentre, open-label, randomised controlled trial at three mental health-care institutions in secondary psychiatric care services in the Netherlands. Eligible patients were aged 18–65 years, had been diagnosed with schizophrenia or another psychotic disorder, had been prescribed antipsychotic depot medication or had an indication to start using depot medication, and were participating in outpatient treatment. Patients (n=169) were randomly assigned (1:1), via computer-generated

randomisation with a block size of four, to receive 12 months of either treatment as usual plus a financial reward for each depot of medication received (€30 per month if fully compliant; intervention group; n=84) or treatment as usual alone (control group; n=85).

Randomisation was stratified by treatment site and suspected prognostic factors: sex, comorbid substance-use disorder (absent vs present), and compliance with antipsychotic medication in the 4 months before baseline (<50% vs. ≥50%). Patients, clinicians, interviewers, and research assistants were masked to group allocation before, but not after, group assignment. The primary outcome was the Medication Possession Ratio (MPR), defined as the number of depots of antipsychotic medication received divided by the total number of depots of antipsychotic medication prescribed during the 12 month intervention period. Patients were followed-up for 6 months, during which time no monetary rewards were offered for taking antipsychotic medication. Additionally, the effectiveness of the experimental intervention was assessed in terms of psychosocial functioning, substance use, medication side-effects, quality of life, motivation, cost-utility and patients' and clinicians' attitudes towards M4M (secondary outcomes).

We demonstrated in our study **(Chapter 3)**, that adherence to antipsychotic depot medication successfully improved by offering financial incentives among patients with psychotic disorders. After 12 months, the adjusted mean adherence rate, defined by the Mean Possession Ration (MPR), was 14% higher in the intervention group (94%) than in the control group (80%). Importantly, 95% of the patients in the intervention group achieved adherence levels of 80% or higher, compared with 59% of patients in the control group. During the 6-month follow-up period, when the offer of financial incentives was discontinued, the positive effects on medication adherence decreased, but adherence levels remained 7% higher in the intervention group (83%) than in the control group (76%). Although medication adherence improved, we found no differences in patients' psychiatric symptoms, psychosocial functioning, hospital admissions, or subjective quality of life. In sum, financial incentives are an effective way of improving adherence to antipsychotic depot medication among patients with psychotic disorders. Further research is needed to study the long-term effects of this intervention.

**Motivation, illness insight and medication adherence**

In our cross-sectional study using baseline data of the RCT described in Chapter 3, we explored the relationship between motivation for treatment, illness insight and adherence to depot medication (**Chapter 4**). Patients with poor insight and high motivation for treatment were more adherent (MPR of 94%) with their depot medication than patients with poor insight and low motivation (61%). Counter intuitively; patients with high insight and high motivation for

treatment were less adherent (73%) than those with poor insight and high motivation. This shows that motivation for treatment at study entrance was more strongly associated with depot-medication adherence than illness insight. Apparently, being motivated to take medication, whether to get better or for other reasons, may be a more important factor than having illness insight in terms of improving depot-medication compliance.

Additionally, we assessed whether offering financial incentives to take antipsychotic depot medication would reduce patients' (intrinsic) motivation for treatment (**Chapter 5**). Our findings suggest that it did not. After the 12 month intervention-period, 91% of the patients showed no or only mild motivational problems. During the 6 month follow-up period, a majority of the patients (83%) were still motivated for treatment, whereas relatively few (17%) reported having little motivation for or resistance to their current treatment. In addition, these results remained similar with respect to various types of motivation (i.e. intrinsic, extrinsic and introjected), during the intervention- and follow-up period, and did not differ between patients from the intervention- and control group. In sum, we could not find evidence that offering and then discontinuing financial incentives to patients with psychotic disorders reduced their overall motivation for clinical treatment. This suggests that offering financial incentives is a safe intervention and does not undermine patients' motivation for treatment.

**Ethical considerations**

In **Chapter 6**, we investigated ethical concerns and opinions of both patients (n=133) and clinicians (n=97) after using financial incentives in clinical practice. Structured questionnaires were administered after the 12-month intervention period. All ethical concerns were grouped on the basis of the four-principles approach in terms of patient autonomy, beneficence, non-maleficence and justice.

In clinical practice, patients (88%) and clinicians (81%) were positive about the use of financial payments to improve adherence to antipsychotic depot medication. Importantly, the fear that financial incentives would harm the therapeutic relationship was not confirmed. At the same time, however, more than half of the patients and clinicians reported to have ethical concerns (e.g. jealousy or reduced illness insight). Therefore, we consider the use of monetary incentives to take anti-psychotic depot medication to be ethically acceptable on four conditions: the amount offered should be moderate, the offer should be unconditional (i.e. there are no consequences if the patient refuses); the incentives should be made available to all patients; and a monitoring system should be in place to track changes in patients' health and/or well-being. Further research is necessary to clarify issues of benefit, motivation and the preferred size and duration of the incentive.

### Costs of financial incentives

Finally, we investigated the cost-effectiveness in terms of medical costs and judicial expenses of using financial incentives to improve adherence (**Chapter 7**). For 134 patients outcomes could be calculated based on self-reported service use and delinquent behaviour expressed as standard unit costs to value resource use. The financial incentive resulted in higher average costs related to mental health care and lower medical costs related to other healthcare services. Relevant differences in social costs related to delinquent behaviour were not found. Although wide confidence intervals indicated uncertainty, incremental cost-effectiveness ratio's (ICER) showed that it costs €2080 for achieving a 20% increase in adherence or €3332 for achieving over 80% adherence. In sum, offering money as financial incentive for increasing compliance did not lead to an overall cost reduction as compared to care as usual.

### Discussion

This study was successful in improving medication adherence, which was the primary goal. However, in order to also detect improvements in psychiatric symptoms and psychosocial outcomes, future research should include longer study periods and also more patients with lower adherence at baseline (**Chapter 8**). For example, offering financial incentives for three years or more, may lead to maintained high adherence rates, possibly leading to better psychiatric and psychosocial outcomes and, ultimately, reduced costs. However, ongoing drugs or alcohol use is associated with intrinsic motivation deficits and might interfere with patients' psychiatric and psychosocial improvements. Therefore, rewarding abstinence, together with rewarding medication adherence might be a useful combination. In dual diagnosis patients (severe mental illness in combination with an addiction disorder), it may even be more effective rewarding abstinence for improving psychosocial outcomes, than offering financial incentives for rewarding adherence.

In addition, improved medication adherence alone might not be sufficient to improve psychosocial functioning or quality of life. In order to improve such outcomes, the social support system of patients plays an important role and should be more involved (e.g. system therapy). This might require additional interventions focusing on social factors such as active involvement of the social-support system, (volunteer) work or physical exercise.

In sum, we found that both patients and clinicians were positive to use this intervention in clinical practice, patients did not become more non-adherent after the incentives were no longer offered as compared to the period before the intervention, and patients' motivation for treatment remained unaffected. Therefore, offering financial incentives is a very effective and safe method of improving adherence with antipsychotic depot medication, and we encourage the implementation of this intervention in daily clinical practice.

# Nederlandse samenvatting

## Achtergrond

Het niet volgens voorschrift nemen van antipsychotische medicatie (medicatie ontrouw) beperkt in ernstige mate de effectiviteit van farmacologische behandelingen voor schizofrenie. Het primaire doel van het project *"Money for Medication"* was om de effectiviteit te onderzoeken van het aanbieden van financiële beloningen ter bevordering van de medicatietrouw voor antipsychotische depotmedicatie bij patiënten met een psychotische stoornis.

## Literatuuroverzicht

Een systematische literatuurstudie is uitgevoerd om de relatie tussen therapietrouw aan antipsychotische depotmedicatie en klinische uitkomsten beter te duiden (**Hoofdstuk 1**). Er werden in de periode tussen 1996 en 2017 in totaal 29 gerandomiseerde studies met controlegroep gevonden die als primaire doelstelling hadden de medicatietrouw te verbeteren. Er waren 5 onderzoeken die uitsluitend klinische symptomen hebben gemeten als indicator voor medicatietrouw. Van de 24 studies die medicatietrouw hebben gemeten, waren er 13 studies (54%) die een verbeterde inname van antipsychotische medicatie lieten zien, nadat patiënten verschillende interventies hadden gevolgd (psychologisch, sociaal, gedragsmatig, of een combinatie van beide). De psychiatrische symptomen verbeterden significant in 33% van de studies met een betere medicatietrouw. Daarnaast hebben 9 studies ook het sociaal functioneren en de kwaliteit van leven gemeten. In deze studies werd zowel een verbetering van symptomen gevonden, alsmede enige verbetering van functionele uitkomsten en hogere waardering van kwaliteit van leven. Deze resultaten laten zien dat een verbetering van medicatietrouw niet automatisch leidt tot een verbetering van klinische uitkomsten.

Bij het vergelijken van alle studies is echter opgemerkt dat er een zeer grote variatie aanwezig is wat betreft: de operationalisatie en meting van medicatietrouw, ernst van de symptomen en medicatie-ontrouw bij aanvang van de studies, patiënt-kenmerken, type en lengte van de interventies en de verschillende lengtes van de *follow-up* perioden. Deze grote heterogeniteit maakt het moeilijk om conclusies te trekken over wanneer en op welke manier verbeteringen in medicatietrouw tot betere klinische uitkomsten leiden.

## Money for Medication (protocol en resultaten)

We hebben een gerandomiseerde gecontroleerde studie uitgevoerd, *Money for Medication*, waarbij patiënten een financiële beloning kregen wanneer zij hun antipsychotische depot medicatie zouden innemen. In het studieprotocol worden de details van dit onderzoek nader beschreven (**Hoodstuk 2**). Samenvattend werd deze studie uitgevoerd op meerdere

locaties (*multicentre*) van 2e en 3e lijns GGZ instellingen in Nederland, waarbij deelnemers en onderzoekers niet geblindeerd waren voor de conditie waaraan de patiënten werden toegewezen (*open label*). Geschikte patiënten waren tussen de 18 en 65 jaar, gediagnostiseerd met schizofrenie of een andere psychotische stoornis, kregen antipsychotische depotmedicatie voorgeschreven (of hadden een indicatie om hier mee te starten) en waren ambulant in zorg. Patiënten (n=169) werden gerandomiseerd toegewezen aan hun conditie (1:1) met behulp van een door de computer aangemaakt randomisatieboek. Gedurende 12 maanden ontvingen patiënten uit de interventiegroep (n=84) bij de standaardbehandeling gemiddeld 30 euro per maand voor het innemen van hun depot medicatie. Patiënten uit de controlegroep (n=85) ontvingen alleen de standaardbehandeling.

De randomisatieprocedure werd gestratificeerd op basis van de locaties van de afdelingen en mogelijk modererende factoren waaronder: geslacht, aanwezigheid van een comorbide stoornis in het gebruik van middelen en de hoogte van antipsychotische medicatietrouw in de 4 maanden voorafgaand aan het onderzoek (<50% of ≥50%). Patiënten, behandelaars, interviewers en onderzoeksassistenten waren niet blind voor de toegewezen conditie nadat de randomisatie was uitgevoerd. De primaire uitkomst was de zogeheten *Medication Possession Ratio* (MPR): het aantal geaccepteerde antipsychotische medicatie depots, gedeeld door het totaal aantal voorgeschreven depots, gedurende de interventieperiode van 12 maanden. Na deze interventieperiode volgde een follow-up periode van 6 maanden waarin geen financiële beloningen werden aangeboden. Daarnaast werd de effectiviteit van de experimentele interventie ook gemeten aan de hand van secundaire uitkomstmaten zoals het psychosociaal functioneren, middelengebruik, bijwerkingen van de antipsychotische medicatie, kwaliteit van leven, motivatie voor behandeling, zorgkosten en de attitudes van patiënten en behandelaars over het aanbieden van financiële beloningen (M4M).

Dit onderzoek laat zien dat het aanbieden van financiële beloningen een effectieve methode is om de medicatietrouw te verbeteren bij patiënten met psychotische stoornissen op depotmedicatie (**Hoofdstuk 3**). Na 12 maanden was de gemiddelde MPR 14% hoger in de interventiegroep (94%) dan in de controlegroep (80%). Ook het aantal patiënten met voldoende medicatietrouw (MPR≥80%) was na de interventieperiode significant hoger in de interventiegroep (95%) dan in de controlegroep (59%). Na de follow-up periode van 6 maanden (waarin geen financiële beloningen meer werden aangeboden) was er een afname van medicatietrouw, maar bleef de MPR significant hoger in de interventiegroep (83%) dan in de controlegroep (76%). Ondanks de toename in medicatietrouw, was er geen verschil tussen beide groepen gedurende de interventieperiode in klinische uitkomstmaten zoals symptomen, psychosociaal functioneren, aantal ziekenhuis opnames of de kwaliteit van leven. Samenvattend blijkt het aanbieden van financiële beloningen in de klinische praktijk

een effectieve methode om de medicatietrouw te verbeteren bij patiënten met psychotische stoornissen op depotmedicatie.

**Motivatie, ziekte-inzicht en medicatietrouw**

In dit cross-sectionele deelonderzoek van M4M zijn baseline data gebruikt (voorafgaand aan de interventieperiode) om de relatie tussen motivatie voor behandeling, ziekte-inzicht en medicatietrouw voor antipsychotische depots te exploreren (**Hoofdstuk 4**). Patiënten met weinig ziekte-inzicht en een hoge motivatie voor behandeling waren meer medicatietrouw (MPR van 94%) dan patiënten met weinig ziekte-inzicht en weinig behandelmotivatie (MPR van 61%). Het bleek echter dat patiënten met veel ziekte-inzicht én een hoge behandelmotivatie minder medicatietrouw waren (73%) dan patiënten met weinig ziekte-inzicht en een hoge behandelmotivatie. Dit laat zien dat motivatie voor behandeling in de maanden voorafgaand aan de start van de studie sterker geassocieerd was met medicatietrouw dan met ziekte-inzicht. Het lijkt er op dat gemotiveerd zijn voor behandeling – ongeacht de achterliggende reden – een belangrijkere factor is dan ziekte-inzicht voor de medicatietrouw bij antipsychotische depots.

Daarnaast hebben we onderzocht of het aanbieden van financiële beloningen voor het nemen van antipsychotische depot medicatie de intrinsieke motivatie voor behandeling zou verminderen (**Hoofdstuk 5**). Onze resultaten suggereren dat dit niet het geval is. Na de interventieperiode van 12 maanden rapporteerden 91% van de patiënten geen of slechts milde motivatieproblemen. Na de follow-upperiode van 6 maanden was de meerderheid van de patiënten (83%) nog steeds gemotiveerd voor behandeling en rapporteerden een klein deel van de patiënten (17%) weinig motivatie voor of actieve weerstand tegen hun huidige behandeling. Deze resultaten bleven gelijk met betrekking tot verschillende vormen van behandelmotivatie (i.e. intrinsiek en extrinsiek) tijdens zowel de interventie- als de follow-up periode en verschilden daarnaast niet tussen patiënten van de interventie- en controlegroep. Samenvattend hebben we niet gezien dat het aanbieden van financiële beloningen aan patiënten met psychotische stoornissen (en hier vervolgens weer mee stoppen) heeft geleid tot een afname van motivatie voor het volgen van een behandeling. Deze resultaten suggereren dat het aanbieden van financiële beloningen een relatief veilige interventie is, welke geen schade zal toebrengen aan de behandelmotivatie van patiënten.

**Ethische overwegingen**

In **hoofdstuk 6** hebben we de ethische overwegingen en meningen van zowel patiënten (n=133) en behandelaars (n=97) onderzocht na het gebruik van financiële beloningen in de klinische praktijk. Gestructureerde vragenlijsten werden afgenomen na afloop van de interventieperiode van 12 maanden. Alle ethische overwegingen werden ingedeeld op basis van

4 ethische principes: de autonomie van patiënten, voordelen van de interventie, niet-schaden, en rechtvaardigheid.

In de klinische praktijk bleken patiënten (88%) en behandelaars (81%) over het algemeen enthousiast over het gebruik van financiële beloningen ter verbetering van de medicatietrouw voor antipsychotische depots. Belangrijk is dat de angst voor het beschadigen van de therapeutische relatie door het aanbieden van beloningen niet of nauwelijks werd gerapporteerd. Echter, meer dan de helft van de patiënten en behandelaars hadden ethische bezwaren (bijvoorbeeld het ontstaan van jaloezie tussen patiënten of vermindering van ziekte-inzicht). Toch beschouwen wij het gebruik van financiële beloningen ter verbetering van de medicatietrouw ethisch toelaatbaar, mits er voldaan wordt aan de volgende vier criteria: het aangeboden bedrag moet niet te groot zijn, het aanbod dient onvoorwaardelijk te zijn (er zijn geen consequenties als een patiënt weigert om gebruik te maken van het aanbod), het aanbod van een beloning dient aan alle patiënten te worden gedaan en toezicht of een controlesysteem dient aanwezig te zijn om veranderingen in de gezondheid en het welzijn van patiënten vast te stellen. Vervolgonderzoek is nodig om meer duidelijkheid te verkrijgen over de voordelen van de interventie, de motivatie om deze interventie toe te passen, de grootte van de beloning en de duur van de interventieperiode.

**Kosten van financiële beloningen**

Tot slot hebben we de kosteneffectiviteit onderzocht met betrekking tot de medische en de maatschappelijke kosten na het gebruik van financiële beloningen om medicatietrouw te verbeteren (**Hoofdstuk 7**). De uitkomsten voor 134 patiënten konden worden berekend op basis van zelf-rapportage vragenlijsten omtrent zorggebruik en delinquent (of crimineel) gedrag. De financiële beloningen zorgden voor hogere gemiddelde kosten gerelateerd aan de geestelijke gezondheidszorg en lagere medische kosten gerelateerd aan overige gezondheidszorg voorzieningen. Er werden geen noemenswaardige verschillen gevonden wat betreft maatschappelijke kosten gerelateerd aan delinquent gedrag. De *incremental cost-effectiveness ratio's* (ICER) laten zien dat het €2080 kost om een verbetering van 20% medicatietrouw te bereiken of €3332 om een niveau van medicatietrouw van boven de 80% te behalen. Grote betrouwbaarheidsintervallen geven echter de onzekerheid van deze schattingen aan. Samenvattend leidt het aanbieden van financiële beloningen ter verbetering van de medicatietrouw niet tot een vermindering van de algehele kosten in vergelijking met de standaardbehandeling.

**Discussie**

Het aanbieden van financiële beloningen blijkt een effectieve methode om de medicatietrouw te verbeteren. Eerder onderzoek heeft de effectiviteit van deze interventie aangetoond bij patiënten met een uitsluitend lage medicatietrouw. Het huidige onderzoek, *Money for medication,* heeft tevens patiënten geïncludeerd met een hoge medicatietrouw en vergroot daardoor de generaliseerbaarheid van de resultaten. Echter, in ons onderzoek observeerden we geen verbeteringen in psychiatrische symptomen en andere psychosociale uitkomstmaten. Om wel effecten te vinden op psychiatrische symptomen en andere psychosociale uitkomstmaten, zijn mogelijk langere interventieperioden nodig, evenals het includeren van patiënten die hun medicatie volledig weigeren bij aanvang van de studie (**Hoofdstuk 8**). Het zou bijvoorbeeld mogelijk zijn om financiële beloningen gedurende 3 jaar of langer aan te bieden, wat tot langdurige en verhoogde medicatietrouw zou kunnen leiden. Dit zou vervolgens ook tot beter psychisch en psychosociaal functioneren kunnen leiden en uiteindelijk tot minder kosten.

Daarnaast is uitsluitend het verbeteren van de medicatietrouw wellicht ontoereikend om vooruitgang in het psychosociaal functioneren of de kwaliteit van leven te bewerkstelligen. Om dit te bereiken is een breder behandelaanbod noodzakelijk, zowel op het gebied van de psychiatrische problematiek (psychotherapie o.a.) als op het gebied van het sociaal functioneren op andere leefgebieden (sociaal netwerk, wonen, werken en financiën).

**Conclusies**

Zowel patiënten als behandelaars rapporteerden positieve ervaringen over het gebruik van deze interventie in de klinische praktijk. Nadat de financiële beloningen niet meer werden aangeboden accepteerden patiënten alsnog in hogere mate depotmedicatie als vóór de interventieperiode, al zagen we wel dat de effecten afnamen. Daarnaast bleef de behandelmotivatie van patiënten hetzelfde tijdens het onderzoek. Om deze redenen is het aanbieden van financiële beloningen een effectieve en veilige methode om de medicatietrouw te verbeteren bij antipsychotische depots. Het implementeren van deze interventie in de klinische praktijk wordt daarom aanbevolen.

# Curriculum Vitae

Ernst Leonard Noordraven was born on October 5th 1989 in Nijmegen, the Netherlands. In 2007, he obtained his atheneum degree at the NSG high school in Nijmegen. Afterwards, he moved to Amsterdam and studied psychology at the University of Amsterdam, where he received his master's degree in clinical psychology in 2012. His masterthesis, about the detection of concealed information, was nominated for the FMG-Student research Prize and published in the Journal of Applied Cognitive Psychology (2013). Following this line of research he moved to Gothenburg, Sweden (2012-2013), conducting research in criminal and legal psychology within the CLIP group (Criminal, Legal and Investigative Psychology) at the University of Gothenborg. In july 2013, he returned to the Netherlands and started working on his PhD project, Money for Medication, at the Erasmus Medical Center and BavoEuropoort, Rotterdam. During this period (2014-2016), he obtained his research master in Clinical Epidemiology at the National Institute for Health and Epidemiological Sciences (NIHES) at the University of Rotterdam. From september 2016, he started working part time, as a treating psychologist at the Center for Dual Diagnosis (CDP), Palier, the Hague. After finishing his PhD, he continued working at the CDP on a full time basis from January, 2018.

# PhD Portfolio

**Name PhD student**: E.L. Noordraven
**Erasmus MC Department**: Psychiatry
**PhD Period**: Jun 2013 - Feb 2018

**Promotor**: prof. dr. C.L. Mulder
**Copromotoren**: dr. A.I. Wierdsma
dr. P. Blanken

| PhD training | Year | Hours | ECT |
|---|---|---|---|
| ***General courses*** | | | |
| - BROK ('Basiscursus Regelgeving en Organisatie') | 2013 | 32 | |
| - Cursus PANSS afname | 2013 | 8 | |
| - Cursus afname SCID-I & SCID-II | 2013 | 9 | |
| - Research Integrity | 2014 | | 0.3 |
| ***NIHES Research Master Clinical Epidemiology*** | 2014 - 2016 | | 70 |
| - Study Design | | | 4.3 |
| - Biostatistical Methods I: Basic Principles | | | 5.7 |
| - Development Research Proposal | | | 2.5 |
| - Biostatistical Methods II: Classical Regression Models | | | 4.3 |
| - Research Period Health Sciences | | | 29.6 |
| - Oral Research Presentation | | | 1.4 |
| - English Language | | | 1.4 |
| - Introduction to Medical Writing | | | 1.1 |
| - Required courses (total) | | | 11.4 |
| - Elective courses (total) | | | 9.2 |
| ***Presentations and (inter)national conferences*** | | | |
| - Various presentations at Erasmus MC, Parnassia Groep and mental health institutions | 2013 - 2017 | | |
| - Voorjaarscongres Nederlandse Vereniging voor Psychiatrie (oral presentation) | 2014, 2016 | | |
| - 3th European Congress on Assertive Outreach, Oslo, Norway (oral presentation) | 2015 | | |
| - International Congress on Schizophrenia Research, Berlin, Germany (oral presentation) | 2015 | | |
| - World Psychiatric Association, Cape Town, South Africa (oral presentation) | 2016 | | |

| | |
|---|---|
| - 5th International Congress on Dual Disorder, Madrid, Spain (oral presentation) | 2017 |
| - 4th European Congress on Assertive Outreach, Hamburg, Germany (oral presentation) | 2017 |
| - Voorjaarscongres Nederlandse Vereniging voor Psychiatrie (poster presentation) | 2018 |

***Teaching***

| | |
|---|---|
| Supervising 1 masterthesis (clinical psychology) and 2 studies for psychiatrists in training ('aios') | 2015 - 2016 |

# List of publications

**International**

- Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL (2018) Medical and social costs after using financial incentives to improve medication adherence: result of a one year randomised controlled trial (*submitted*)
- Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL (2018) The effect of financial incentives on patients' motivation for treatment: result of Money for Medication," a randomised controlled trial (*accepted may 2018, BMC Psychiatry*)
- Noordraven EL, Schermer MHN, Blanken P, Mulder CL, Wierdsma AI (2017) Ethical acceptability of offering financial incentives for taking antipsychotic depot medication: patients' and clinicians' perspectives after a 12-month randomized controlled trial. BMC Psychiatry 17:313
- Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Staring ABP, Mulder CL (2017) Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial. The Lancet Psychiatry 4:199–207
- Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL (2016) Depot-medication compliance for patients with psychotic disorders: the importance of illness insight and treatment motivation. Neuropsychiatr Dis Treat 12:269–274
- Noordraven EL, Audier CH, Staring A, Wierdsma AI, Blanken P, van der Hoorn B, Roijen L, Mulder CL (2014) Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. BMC Psychiatry 14:343
- Noordraven EL, Verschuere BJ (2013) Predicting the Sensitivity of the Reaction Time-based Concealed Information Test. Appl Cogn Psychol 27:328–335

**National**

- Neven A., Noordraven EL (2017). Contingentie management bij een stoornis in het gebruik van alcohol. Tijdschr Psychiatr 59:751.
- Noordraven EL, Lek J, Mulder CM (2017) Money for medication. Financiële beloningen ter verbetering van medicatietrouw. Psyfar VS 55–60
- Noordraven E (2017) Financiële beloning en medicatietrouw bij patiënten met psychotische stoornissen. Tijdschr Psychiatr 59:306–307
- Mulder CL, Noordraven EL, Staring AB. (2014) commentaar. Ned Tijdschr Geneeskd 23–24

## Dankwoord

Tijdens de uitvoering van mijn promotieonderzoek heb ik veel nieuwe mensen ontmoet. Iedereen heeft op zijn eigen manier bijgedragen en mij geholpen dit project succesvol af te ronden. Onderzoek doen is vaak een eenzame bezigheid en toch heb ik mij de afgelopen jaren altijd gesteund gevoeld door de mensen om mij heen. Door de aanmoedigingen van ieder van jullie en de vele gesprekken en discussies is het me gelukt om met enthousiasme aan het onderzoek te blijven werken. Ik ben erg dankbaar voor iedereen die hieraan heeft bijgedragen.

Ten eerste wil ik alle patiënten bedanken die hebben meegewerkt aan het onderzoek. Jullie inzet heeft veel nieuwe informatie opgeleverd en er voor gezorgd dat we de kennis over het gebruik van beloningen bij psychiatrische patiënten hebben kunnen uitbreiden. Daarmee hebben jullie een belangrijke bijdrage geleverd aan het verbeteren van de patiëntenzorg binnen de GGZ.

Prof. dr. Mulder, beste Niels, als promotor van het onderzoek heb je me vanaf het begin gestimuleerd om presentaties te geven, contacten te leggen en om naar congressen te gaan en hier vooral plezier uit te halen. Je bezit een unieke mix van enthousiasme, humor, motivatie en energie die ik altijd heb bewonderd. Je hebt me veel vertrouwen gegeven en er voor gezorgd dat ik mezelf in de afgelopen jaren op meerdere vlakken heb kunnen ontwikkelen. Daar ben ik erg dankbaar voor. Soms was het moeilijk om definitieve beslissingen te nemen, maar je was (ondanks een drukke agenda) altijd bereikbaar en wellicht nog belangrijker, benaderbaar. Tot slot heb ik het erg gewaardeerd dat je ook oog had voor het leven buiten de wetenschap en was je persoonlijk geïnteresseerd en heel betrokken in de afgelopen jaren. Ik had me geen betere en leukere promotor kunnen wensen. Dankjewel voor alles!

Dr. Wierdsma, beste André, je bent de afgelopen 5 jaar mijn copromotor geweest en hebt me daarbij zeer goed gesteund. Je hebt me de ruimte en het vertrouwen gegeven om fouten te maken en me op de juiste momenten bijgestuurd om een meer zelfstandige en onafhankelijke onderzoeker te worden. Je hebt me geleerd om verantwoordelijke beslissingen te nemen en dagelijks geholpen met statistische analyses en schrijfwerk, waarbij je met veel geduld alles hebt uitgelegd. Ik kon altijd bij je terecht voor advies, waardoor je een betrouwbare en veilige basis vormde tijdens mijn promotietraject. Ook op persoonlijk vlak konden we het goed met elkaar vinden: als kamergenoten beperkten onze gesprekken zich zelden tot statistiek en werd dagelijks de gehele wereldproblematiek doorgenomen. Ik kijk met erg veel plezier terug op onze tijd samen op het Erasmus MC. Zonder jou zou ik het proefschrift niet hebben kunnen voltooien. Ik heb je vertrouwen, kennis, rust en humor altijd zeer gewaardeerd en ik ben je heel dankbaar voor alle hulp die je me hebt gegeven.

Dr. Blanken, beste Peter, als copromotor ben ik je dankbaar voor al je kritische en

opbouwende commentaren tijdens het schrijven van onze manuscripten. Altijd wist je de vinger op de zere plek te leggen waardoor de artikelen tot een hoger niveau kwamen en ik zelf ook kritischer ben geworden in het schrijven en analyseren. Naast je oog voor detail heb je altijd veel steun en vertrouwen uitgesproken in het project en was je een heel fijne en actieve begeleider om naast me te hebben. Bedankt voor al je hulp en enthousiasme in de afgelopen jaren, ik heb het zeer gewaardeerd.

Drs. Bloemendaal, beste Tony, als lid van de begeleidingscommissie en als manager zorg heb je zowel inhoudelijk als praktisch een belangrijke bijdrage geleverd aan het onderzoek. Je hebt het project in moeilijke tijden overeind weten te houden en actief meegedacht met onderwerpen en nuttige feedback geleverd op alle artikelen. Daarnaast was je altijd geïnteresseerd en betrokken bij de voortgang van het project en heb je me gestimuleerd om in de klinische praktijk te gaan werken op het CDP. Daarvoor ben ik je erg dankbaar.

Dr. Staring, beste Tonnie, je hebt veel pionierswerk verricht voor dit onderzoek waardoor ik met een vliegende start kon beginnen. Je was altijd enthousiast en je hebt me goed geholpen met het meedenken en herschrijven van veel artikelen. Daarnaast bewaakte je goed de klinische relevantie van de onderwerpen en kwam je regelmatig met nieuwe ideeën. Ik ben blij dat je wilde deelnemen in mijn begeleidingscommissie. Bedankt voor al je hulp.

Beste Pia, hartelijk dank voor je onvoorwaardelijke steun van het project en de mogelijkheid om het onderzoeksproject te combineren met de klinische praktijk. Je hebt veel geduld gehad, praktische ondersteuning geboden en de middelen beschikbaar gesteld om het onderzoek succesvol te kunnen afronden. Ik heb je belangstelling, vertrouwen en inhoudelijke betrokkenheid zeer gewaardeerd.

Voor hun deelname in de kleine leescommissie van het proefschrift wil ik graag bedanken prof. dr. Kushner, prof. dr. Van der Gaag en prof. dr. Franken. Beste Steven, Mark en Ingmar, hartelijk dank voor jullie belangstelling, tijd en aandacht voor mijn onderzoeksproject. Ik ben er trots op dat jullie in mijn commissie konden deelnemen en heb jullie opmerkingen en suggesties zeer gewaardeerd.

Prof. dr. Schermer, beste Maartje, bedankt voor je enthousiasme en het meeschrijven en denken omtrent de ethiek van deze interventie. Daarnaast heb je altijd veel belangstelling getoond gedurende het project en ik ben erg blij dat je wilde deelnemen in de grote leescommissie.

Voor hun deelname in de grote leescommissie wil ik graag bedanken prof. dr. Veling en prof. dr. Delespaul. Ik ben erg blij dat jullie de tijd konden vrij maken en aandacht hebben willen besteden aan het lezen van dit proefschrift.

Beste Anneke, dankjewel voor al je praktische en organisatorische steun in de afgelopen jaren. Zonder jou zouden veel dingen nooit op tijd zijn geregeld en waren de agenda's van de

leden van de begeleidingscommissie nooit synchroon gaan lopen.

Ik wil graag al mijn collega's van de afdeling psychiatrie van het Erasmus MC bedanken voor hun belangstelling, gesprekken en betrokkenheid in de afgelopen jaren.

Beste Astrid, je deur stond altijd open en ik ben je erg dankbaar voor alle momenten dat ik even bij je kon binnen wandelen. Je hebt een heel goed gevoel voor humor en ik kijk met veel plezier terug op alle momenten die we hebben kunnen delen tijdens de dagelijkse werkzaamheden en vele congressen. Daarnaast heb je me altijd verstandig advies kunnen geven en wist je een hoop te relativeren. Ik ben blij dat je deur zo dichtbij was en dankjewel voor alle goede steun tijdens de afgelopen jaren.

Beste Richard, of moet ik zeggen dr. Wesseloo? We hebben een vergelijkbare route afgelegd: gelijktijdig het promotietraject doorlopen en samen de NIHES colleges en examens gevolgd. Ik het altijd zeer gewaardeerd bij je binnen te kunnen lopen voor inhoudelijke discussies en vond het erg leuk om samen te studeren tijdens onze research master. Tot slot hebben we ook veel kunnen lachen en relativeren: "allemaal gekkigheid!".

Beste Babette, Bert-Jan, Bernice, Eline J., Eline P., Femke, Ibrahim, Janneke, Nina, Roos, Stefanie en Vandhana, wat een geluk om jullie als collega's te hebben. Dagelijks samen lunchen en onze promotieperikelen met elkaar delen heb ik altijd erg gewaardeerd. Daarnaast kon ik altijd met jullie overleggen en dat bracht me veel ontspanning, maar ook energie om verder te gaan met het onderzoek. En natuurlijk alle mooie momenten en fijne herinneringen tijdens onze vele congressen (Maastricht, Oslo, Berlijn, Kaapstad, Hamburg).

Beste Bart, Cézanne, Charlotte, Daniël, Inga en Leonie, wat hebben jullie me goed geholpen bij het afnemen van alle interviews en het voorbereidende werk van het project. Jullie hebben nauwkeurig en met veel geduld alle data weten te verzamelen binnen een lastige doelgroep, verdeeld over wisselende locaties. Zonder jullie zou het nooit gelukt zijn, veel dank!

Ik wil graag al mijn collega's op het CDP bedanken die hebben geholpen om mijn onderzoek succesvol te kunnen afronden. Jullie zijn een fantastisch team en werken elke dag met veel inzet en toewijding met zeer complexe patiënten. Zonder jullie was het me niet gelukt om alle data te verzamelen en ik ben erg dankbaar deel uit te maken van jullie team. In het bijzonder wil ik daarbij bedanken voor hun belangstelling, steun en vertrouwen tijdens de afgelopen jaren: Annette, Arjen, Hella, Iris, Jipke, Michel en Sara.

Beste Mart, dankjewel voor het ontwerpen van de mooie en originele cover. Ik vind het heel leuk dat jij het ontwerp hebt gemaakt en waardeer alle tijd en moeite die je erin hebt gestopt!

Beste Bas, Bob, Bruno, Hanne, Joren, Marissa, Marieke en Sam, ik heb jullie steun, advies en belangstelling de afgelopen jaren erg gewaardeerd. Het heeft me altijd gemotiveerd om het onderzoek af te maken en ik ben erg dankbaar voor onze vriendschappen!

Beste Jantje, je hebt me de afgelopen jaren altijd gesteund en gemotiveerd om nieuwe dingen te proberen. Daarnaast heb je altijd veel vertrouwen in me gehad en alle ruimte gegeven om mezelf te ontwikkelen. Je enthousiasme en energie zijn bewonderenswaardig en heel aanstekelijk. We hebben sinds het begin van mijn studie op onze befaamde Palace een unieke vriendschap opgebouwd die gelukkig nooit meer voorbijgaat. Dankjewel voor alles maatje!

M'n boys: Bouke, Chris, Luuk, Ruud en Saro. Jullie zijn niet alleen de afgelopen jaren, maar al sinds de brugklas mijn grote steun en toeverlaat. Altijd kan ik bij jullie terecht en hebben jullie veel belangstelling getoond. Jullie houden me scherp, zetten me aan tot denken en zijn voortdurend een solide, veilige en betrouwbare basis. Dit zorgt voor veel rust en vormt een belangrijk onderdeel waardoor ik zoveel heb kunnen groeien. Ik koester warme herinneringen aan onze vele gesprekken, het samen lachen en huilen, onze vakanties en ik denk met een grote glimlach aan alle nieuwe en dierbare herinneringen die voor ons in het verschiet liggen. Wat ben ik blij met jullie.

Beste Daan, vanaf ons eerste studiejaar zijn we twee handen op een buik. We hebben veel promotieperikelen samen kunnen delen en altijd kon ik bij je terecht voor steun of geruststelling. We hebben een hoop mooie momenten meegemaakt sinds onze studie en veel plezier gehad als huisgenoten op de unieke Taksteeg. Ik ben ontzettend blij met onze waardevolle vriendschap en trots dat je mijn paranimf bent. Dankjewel voor alles.

Beste Niels, lieve bro, we hebben werkelijk alles samen meegemaakt en van kleins af aan heb ik altijd bij jou kunnen afkijken om dingen te leren. In zowel fijne als moeilijke momenten die we hebben meegemaakt ben je altijd een zeer stabiele en veilige steun. Je weet me altijd te verrassen en verstandig advies te geven. Uiteraard vind ik het heel bijzonder dat je mijn paranimf bent en kijk ik uit naar alle jaren die nog voor ons liggen. Love you bro.

Lieve papa en mama, bedankt voor al jullie steun de afgelopen jaren. Jullie hebben me gestimuleerd om mijn interesses te volgen en laten opgroeien in een omgeving van zowel kunst en wetenschap. Allebei op unieke wijze hebben jullie me veel vertrouwen gegeven en er voor gezorgd om vooruit te komen. Ik heb me daardoor kunnen ontwikkelen tot wie ik nu ben. Dankjewel voor alle warmte in huis ondanks soms moeilijke omstandigheden. Ik kijk met plezier uit naar de jaren die voor ons liggen in goede gezondheid.

Lieve Annemiek, lieve Dushi, dankjewel voor al je steun en het vertrouwen dat je me altijd weet te geven. Zowel tijdens het schrijven van het onderzoek, als ver daarbuiten. Je houdt me met beide benen op de grond en laat me vaak genoeg zien waar het in het leven om draait. Samen reizen, dansen in de woonkamer, klimmen, uitgebreid koken en ons gekeuvel dat nooit zal ophouden. Je bent de vrouw met wie ik oud wil worden. En zoals je weet, we worden samen 90. Ik hou van je.