Adherence to treatment with antipsychotics in patients with first-episode psychosis

A Multi-Method Approach

by

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Scientific Environment

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Author

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Summary

Background and aim

Adherence to treatment recommendations is a crucial aspect of health care in general, and especially in mental health care. However, it has been given less concern in everyday clinical practice than needed. In inpatients the medicines are usually given by healthcare professionals, who observe that they are taken, creating a sense of certainty that adherence will continue in the post-acute setting when patients have been discharged. Rates of adherence in patients with mental illness differ in different studies, but overall findings have indicated that less than 50% of patients fully adhere to treatment. Non-adherence or poor adherence to medication might have a negative impact on the course of illness resulting in relapse, re-hospitalization, poor outcome and increased consumption of health services and costs.

The overall aim of this thesis was to explore the complexity of the adherence to medication treatment by patients with psychosis. This was done, first by assessing the degree that (i) physicians followed treatment

algorithms, (ii) patients followed the physicians' recommendations, and (iii) adherence influenced outcome. The next step was an in depth investigation of the reasons for deviation from standards by interviewing physicians and patients mainly on current knowledge and attitudes regarding antipsychotic medication.

Methods

Adopting a mixed-methods approach helped us to perceive the adherence issue from more than one perspective and gaining deeper insights into reasons for patients' non-adherence. In the first study, we adopted a quantitative approach to assess patients' adherence to psychiatrists' recommendations and psychiatrists' adherence to treatment guidelines. A qualitative approach was adopted in the second and third studies, to investigate in depth the reasons for deviation from standards by interviewing patients and psychiatrists.

Results

The first study revealed that 62% of the physicians adhered to the local medical algorithm. However, while the initial medical intervention followed the international standards, the physicians failed to adhere to algorithms in

the one-year follow-up of medication regimes. Fifty-six percent of patients used their medicines more than 75% of the time. Patient adherence to medication was significantly associated with good outcomes. Study 2 showed that patients do not choose to jeopardize their medication regime independently. Healthcare staff plays an important role in maintaining good adherence by being empathetic and supportive in the admission phase, giving tailored information according to the patients' condition and involving patients when making treatment decisions. Study 3 highlighted how the role of the government in complicating the adherence issues by demanding the regional health authorities to establish a medication-free treatment option for patients with severe mental illnesses. However, despite all the internal and external pressure faced by psychiatrists, this did not affect their professional integrity in medical decisions based on guidelines, expertise and research studies.

Conclusion

A range of factors influence medication adherence, and an individualised approach is important in order to intervene successfully.

List of publications (in order of appearance)

Paper I

Yeisen RAH, Joa I, Johannessen JO, Opjordsmoen S. Use of medication algorithms in first episode psychosis: a naturalistic observational study. *Early Interv Psychiatry,* 2016; 10: 503-510.

Paper II

Yeisen RAH, Bjornestad J, Joa I, Johannessen JO, Opjordsmoen S. Experiences of antipsychotic use in patients with early psychosis: a two-year follow-up study. *BMC Psychiatry*, 2017; 17: 299.

Paper III

Yeisen RAH, Bjornestad J, Joa I, Johannessen JO, Opjordsmoen S. Psychiatrists' reflections on a medication-free program for patients with psychosis. Submitted to *Journal of Psychopharmacology*

Abbreviations

FEP	First episode psychosis
TIPS	Early intervention and treatment of psychosis
SDM	Shared decision-making
ICC	The Intraclass Correlation Coefficient
IPA	Interpretative phenomenological analysis
CPG	Clinical Practice Guidelines

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1. Introduction

Psychosis is a difficult term to define and is frequently misused, in not only the media such as newspapers, social media, movies, and television, but unfortunately among mental health professionals. Psychosis is a group of complicated mental disorders, with a multifactorial etiology, and has a significant impact on patients, their families and the society. The most common diagnoses in the psychosis spectrum are schizophrenia, schizoaffective disorder, delusional disorder and acute psychotic disorder (WHO, 1992, 2015). Although schizophrenia is the most common and best known psychotic illness, it is not synonymous with psychosis, but is just one of many psychotic disorders (Stahl, 2008). Schizophrenia usually presents as a constellation of symptoms that include perceptual misinterpretation with hallucinations, delusions, movement and behavior disturbances, cognitive impairment and emotional dysfunction. The disorder may cause severe disability, particularly work disability (in regard to obtaining or maintaining employment) (Jobe & Harrow, 2010). In addition, depression is common in schizophrenia, with many individuals experiencing depressive

symptoms especially once the psychotic episode resolves (Birchwood, Iqbal, Chadwick, & Trower, 2000).

Most people with a schizophrenia diagnosis must not only cope with their own thoughts and feelings regarding schizophrenia, but also the conceptions of the general population who often have a stigmatising attitude toward schizophrenia (Crisp, Gelder, Rix, Meltzer, & Rowlands, 2000).

Over a lifetime, about 1% of the population will develop schizophrenia (J. McGrath, Saha, Chant, & Welham, 2008). The lifetime risk of suicide in schizophrenia is approximately 5%. Risk factors with a strong association with later suicide included being young, male, and with a high level of education. Illness-related risk factors are important predictors, with number of prior suicide attempts, depressive symptoms, active hallucinations and delusions, and the presence of insight all having a strong evidential basis. A family history of suicide and comorbid substance misuse is also positively associated with later suicide. The only consistent protective factor for suicide is delivery and adherence to effective treatment (Hor & Taylor, 2010). The life expectancy of a patient with schizophrenia may be 20 to 30 years shorter than that of the general population, not only due to suicide but

in particular due to premature cardiovascular disease (Parks, Svendsen, Singer, Foti, & Mauer, 2006; Tiihonen et al., 2009; Torniainen et al., 2015). Accelerated mortality from premature cardiovascular disease in schizophrenia patients is caused not only by genetic factors and lifestyle choices such as smoking, unhealthy diet, and lack of exercise leading to obesity and diabetes but also, unfortunately, by treatment with some antipsychotic drugs, which can cause an increased incidence of obesity and diabetes and thus increase risk of cardiovascular disease.

Schizophrenia continues to be a high cost illness because of the complex health needs associated with the disorder. In the United States, over 20 percent of all social security benefit days are used for the care of schizophrenia patients (Joukamaa et al., 2001). Despite the shifting balance of care away from hospital-based care, the health care costs of treating and supporting people with schizophrenia remains high (Mangalore & Knapp, 2007). The direct and indirect costs of schizophrenia in health care represent 1.1% of total national health care expenditures. Productivity losses associated with morbidity constitute the major cost burden of schizophrenia in societies (Charrier, Chevreul, & Durand-Zaleski, 2013).

The first onset of psychosis often occurs during late adolescence or early adulthood (Maurer & Riecher-R, 1993). In the Scandinavian Early Intervention in Psychosis study (TIPS study of first-episode psychosis patients) approximately 28 % of patients had the diagnosis of schizophrenia at first presentation, but the rate had increased to 52 % after two years (Haahr et al., 2008). Patients in that study treated with antipsychotics along with supporting psychotherapy and family involvement.

Medicalisation of psychosis has made antipsychotic pharmacotherapy the sine qua non of psychosis treatment (McGlashan, 2012), alongside with family involvement and supportive psychotherapy (Salokangas & McGlashan, 2008). Even though treatment of patients with first episode psychosis (FEP) has made progress over the past few decades, and could prevent psychotic progression, the long-term management of psychotic illness remains a challenge (Salokangas & McGlashan, 2008). In early psychosis treatment, timing makes a lasting difference, whereas treatment type and/or intensity does not (McGlashan, 2012).

Long duration of untreated psychosis is associated with poorer clinical prognosis and psychosocial functioning (Salokangas & McGlashan, 2008).

Previous studies reveal that the risk of relapse following the discontinuation of antipsychotics is extremely high, up to 70% (Di Capite, Upthegrove, & Mallikarjun, 2016; Thomas, 2013). Studies have found varying rates of adherence in schizophrenia patients, but overall findings indicate that less than 50% of patients fully adhere to medication treatment (Higashi et al., 2013; Zygmunt, Olfson, Boyer, & Mechanic, 2002).

The first aim of this thesis was to determine the medication adherence rate in "real world" clinical settings in a Norwegian specialised mental health service and then to gain a better understanding of the reasons that some FEP patients do not follow the recommendation of the physician.

Medical algorithms are evidence-based guidelines, which help physicians to make decisions based on recent reviews and meta-analyses for improving quality of care (Gaebel, Riesbeck, & Wobrock, 2011). In spite of the increased number of such clinical guidelines and the intention to improve the services by practicing these guidelines, we have very little knowledge of to what extent clinical guidelines are implemented in everyday routine clinical practice in the mental health services (Forsner, Wistedt, et al., 2010). Attitudes in the society and other recommendations from the health

authorities might also influence the implementation of guidelines in everyday practice. Non-adherence to medical algorithms is a matter of concern because of the impact on quality of care (Bettinger, Crismon, Trivedi, Grannemann, & Shon, 2004; Melfi et al., 1998). The second aim of this thesis was to investigate physicians' adherence to a medical algorithm and to determine factors associated with non-adherence.

Adopting a multi-method design with both a qualitative and quantitative approach helped us developing rich insights into these phenomena of interest that cannot been fully understood using only a quantitative or a qualitative method. Diversity in research methods considers a major strength in this study.

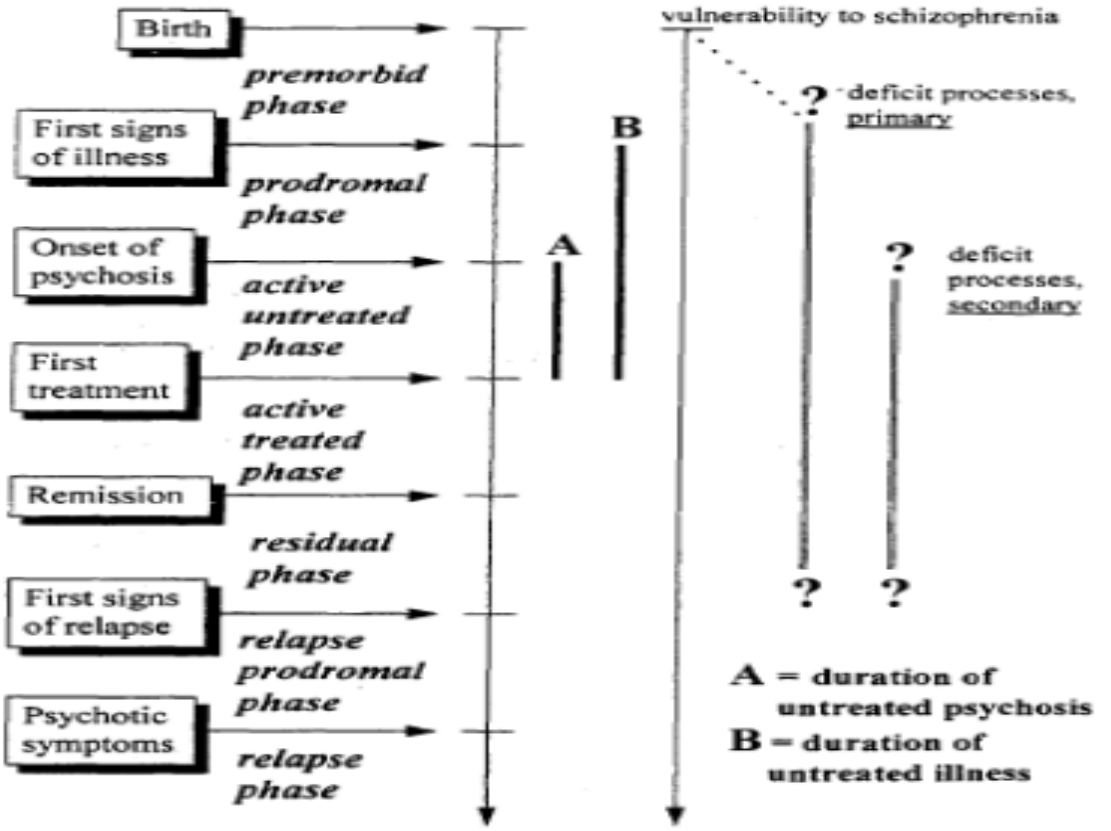
2. Background

2.1 General information about psychotic disorders

Treatment of schizophrenia and other non-affective psychotic disorders has within the past decades made substantial progress with promising new developments in psychosocial treatment (Fusar-Poli, McGorry, & Kane, 2017; Salokangas & McGlashan, 2008). Despite this, it remains a significant burden on the individual, family and society (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2016), because of the usual first onset in early adulthood. It is also estimate that approximately one third to half of diagnosed patients will experience a chronic course even after comprehensive treatment (Bromet, Naz, Fochtmann, Carlson, & Tanenberg-Karant, 2005; Hegelstad et al., 2012; McGlashan, 1988; Norman et al., 2012). Schizophrenia is still a disorder with a relatively poor outcome despite the advent of the modern era of psychopharmacological treatment and psychosocial rehabilitation. Thus, when we look at the recent literature, we find both promising and disappointing features associated with outcome and recovery in schizophrenia (Jobe & Harrow, 2010).

A typical course of psychotic disorder can follow a path like this. First there is a premorbid phase, where there are per definition no signs of the illness, followed by a prodromal period (also often termed as an Ultra High Risk-period, can be several years long) often characterised by some deterioration in personal functioning and development of unspecific symptoms. The prodromal period is usually followed by an acute episode marked by hallucinations, delusions, and behavioral disturbances. These 'positive symptoms' might be accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological and psychosocial interventions, symptoms diminish and often disappear for any people and remission may achieve. Although sometimes a number of negative symptoms may remain. This phase, which can last for many years, may be interrupte by relapse and recurrent acute psychotic episodes, which may need additional intervention (Larsen et al., 2001).

Figure 1. Early course of schizophrenia: Phases and definitions



The incidence of schizophrenia was long held to be homogeneous worldwide but this has been challenged by reports of significant variation in incidence between and within countries according to gender distribution, urbanicity and, in particular, migration and ethnicity (Bourque, van der Ven,

& Malla, 2011; Cantor-Graae & Selten, 2005; Jablensky et al., 2000; Jongsma et al., 2018; Kirkbride et al., 2017; John McGrath et al., 2004; Zolkowska, Cantor-Graae, & McNeil, 2001). The increased risk for schizophrenia and related disorders affects not only first generation immigrants, with a personal history of migration, but also second generation immigrants born to one or two migrant parents in the host country (Bourque et al., 2011). McGrath et al. found the incidence of schizophrenia to be 15/100,000 persons, with little difference between males and females. The median lifetime morbid risk for schizophrenia was 7.2/1,000 persons. Based on the standardised mortality ratio, people with schizophrenia have a two- to threefold increased risk of dying (median standardized mortality ratio = 2.6 for all-cause mortality), and this differential gap in mortality has increased over recent decades (J. McGrath et al., 2008). While Baldwin et al. revealed that the annual incidence of "all psychoses" was 31.6/100,000 in a population aged >15 and it was higher in males than in females (Baldwin et al., 2005). Additionally it has been found that the incidence varied between different places around the world. Compared with native-born individuals, migrants have an increased incidence and prevalence of schizophrenia. Exposures related to urbanicity, economic status, and latitude is associated

with various frequency measures (J. McGrath et al., 2008). FEP studies that only focus exclusively on first-episode schizophrenia at the expense of other diagnoses, may according to Baldwin et al. miss the essential diversity of FEP (Baldwin et al., 2005).

2.1.1 Insight

Insight is the patient's awareness of (i) having a mental disorder, (ii) the social consequences of the disorder, (iii) the need for treatment, (iv) symptoms and (v) attribution of symptoms to this disorder. Evidence suggests that poor insight is a manifestation of the illness itself rather than a coping strategy. Previous studies estimate that between 50% and 80% of patients with schizophrenia do not believe they have a disorder (Buckley, Hasan, Friedman, & Cerny, 2001). Studies have been conducted to determine the magnitude and direction of the relationship between insight and symptom domains and to determine moderator variables. Results indicated that there was a small negative relationship between insight and global, positive and negative symptoms. There was also a small positive

relationship between insight and depressive symptoms (Buckley et al., 2001; T. E. Smith, Hull, Israel, & Willson, 2000).

Patients must not only cope with their own thoughts and feelings regarding schizophrenia, but also the conceptions of the general population, who often regard schizophrenia with a stigmatising attitude (Crisp et al., 2000). Poor insight has been linked to poorer treatment adherence, poorer clinical outcome, poorer social function, vocational dysfunction, and difficulties developing working relationships with mental health professionals. Conversely, greater insight has been associated with higher levels of dysphoria, lowered self-esteem, and decreased well-being and quality of life (Lysaker, Roe, & Yanos, 2007). As for the impact of age on lack of awareness of the need for medication. A study found that the course of insight impairment follows a U-Shaped curve, where insight impairment is severe during first episodes, modestly improves over midlife and declines again in later life (Pousa et al., 2017).

2.1.2 Stigma about mental illness

Stigma had always been inextricably attached to psychiatric illness, psychiatric patients and even psychiatric health personnel. Stigma may stem from the fact that it is difficult to accept behavior that is unlike the standard norm. Lack of knowledge in society about the biological aspects of psychiatric illnesses has led to the belief that the specialty of psychiatry is unscientific and unlike other medical specialties (Bhugra et al., 2015). Schizophrenia seems to be the most stigmatising condition in that respect. Experiencing schizophrenia is not limited to illness symptoms, but it is accompanied by the reactions of the society (Schulze & Angermeyer, 2003). In public and media mentally ill patients, and schizophrenia patients particularly, have been perceived to be unpredictable, aggressive, dangerous, frightening, unreasonable, mentally retarded, and with lack of self-control (Angermeyer & Matschinger, 1995; Schulze & Angermeyer, 2003). The media perpetuate stigmatisation. People with schizophrenia and their relatives are aware and bothered by the stereotypes about mental illness held by the public and disseminated by the media (Schulze & Angermeyer, 2003).

Although psychiatric treatment has changed significant with the introduction of psychotropic medication and community care, coercive treatment and custodial care are still linked to the treatment of people with schizophrenia in the eyes of the public (Schulze & Angermeyer, 2003). Antipsychotics may also produce side effects (for instance, extrapyramidal symptoms), which might mark the person as having a mental illness more than the original symptoms of illness do, which in turn leads to labelling and iatrogenic stigmatisation (Sartorius, 2002). Many persons feel that taking medication is not accepted because it suggest some type of inherent weakness or inability to function without chemicals (Fink, 1992). Others think psychiatric treatments are ineffective, and accordingly this reduces their likelihood of seeking help (Corrigan, 2005).

The public image of psychiatrists is largely negative and based on insufficient knowledge about their training, expertise and purpose of their work. For example, it is not widely known that psychiatrists are medical doctors, and the duration of their training is underestimated. They are ascribed a low status among physicians (Laux, 1977; Sartorius et al., 2010).

Among medical students, results of studies on this issue were mixed and sometimes contradictory. Some studies revealed that the views of the psychiatric specialty among medical students were that psychiatry is unscientific, imprecise, ineffective and a low status discipline. Sources for this low status included old opinions from their childhood, at school or even at the university (A. Buchanan & Bhugra, 1992). Other studies report positive changes in attitudes of medical students during their education in medical school, either over the course of time or after completion of psychiatric training (Sartorius et al., 2010). Furthermore, in a study psychiatrists themselves reported to be satisfied with their profession and felt that their specialty was intellectually challenging (Blumberg & Flaherty, 1982).

Media and portrayals in the cinema may have more sinister consequences for mental health staff and students by deeming them to be somewhat eccentric (Byrne, 2004). The general depiction of psychiatry in the news and entertainment media is predominantly negative. In a media commentary, psychiatry was portrayed as “a discipline without true scholarship, scientific methods, or effective treatment techniques” (Sartorius et al., 2010; Sharf, 1986).

2.2 Treatments of Psychosis

Psychosis is usually a prolonged and severe disorder with a swinging illness course that places a great demand on proper personal treatment facilitation. The treatment be flexible and tailored to each individual patient. A treatment plan should contain more than just medication and it is important to engage the patient actively in decision-making. Only 24% of the recommendations of clinical guidelines are reserved for medication and most of these are coupled with offering cognitive-behavioral therapy (CBT) and/or family intervention to all patients (NICE, 2014).

The course and outcome of FEP is dependent on the treatment of the patient in the initial stage of illness. The duration of psychosis before treatment is an important predictor of outcome in first-episode psychosis (Larsen et al., 2011). A prolonged period of psychosis experienced before the initiation of antipsychotic treatment is associated with lower levels of symptomatic and functional recovery from the first psychotic episode. This association appears to be independent of the effect of other variables also associated with prognosis and to persist into the chronic stage of illness (D. O. Perkins, Gu, Boteva, & Lieberman, 2005). Outcomes for schizophrenia

patients are poorer than those for other psychotic and nonpsychotic patients. A consistent feature during early phases is more recurrent psychopathology for many patients. Even after the first 10 years, outcome and the potential for periods of complete recovery are poorer for schizophrenia than for other psychotic and nonpsychotic disorders (Jobe & Harrow, 2010). Acute psychotic symptoms could reflect an active morbid process which, if not ameliorated by antipsychotic drug treatment, may result in lasting morbidity. Delay between onset of psychotic symptoms and first treatment may be an important factor influencing the long-term functioning (Black et al., 2001; Larsen et al., 2001; Murru & Carpiniello, 2016).

Central elements in the treatment of psychosis are medication in addition to family focused treatment/ family involvement, and supportive psychosocial interventions (Leucht et al., 2013; Leucht et al., 2009). Studies have revealed that the use of antipsychotics was associated with lower mortality. Mortality rate were found to be 10-fold among those patients not using any antipsychotic when compared with their matched controls (Tiihonen et al., 2011; Tiihonen et al., 2009; Torniainen et al., 2015). Lack of antipsychotic treatment may be the most important treatment-related factor contributing to excess mortality in schizophrenia and this demands

attention to improve adherence to antipsychotic treatment among these patients (Torniainen et al., 2015).

Pharmacological treatment of psychotic symptoms is often regarded as a prerequisite for a successful psychosocial treatment. In patients with schizophrenia, most controlled clinical trials with antipsychotic medications have shown that antipsychotics are significantly more effective than placebo in the acute phase, and they also prevent relapse when used continuously over years (Karson, Duffy, Eramo, Nylander, & Offord, 2016; Opjordsmoen et al., 2009). In the acute setting, early induction of an atypical antipsychotic at the a minimum effective dose is the standard recommendation in most guidelines (Buchanan et al., 2009; NICE, 2014). With antipsychotic treatment, symptomatic remission is achieved by as many as 80% of individuals affected by a FEP (Bowtell, Ratheesh, McGorry, Killackey, & O'Donoghue, 2017; Malhi, Adams, Moss, & Walter, 2010). Following remission, most guidelines recommend maintenance treatment with an atypical antipsychotic medication at minimum effective dose, for a duration of one to two years (Bowtell et al., 2017; Taylor, Paton, & Kapur, 2012). However, more recently, the benefits of long-term maintenance treatment have been questioned, with a call for more research to guide treatment

duration (Bowtell et al., 2017; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013). Whilst there are risks associated with the long-term use of antipsychotic medication, there are also risks associated with discontinuation, as high relapse rates have been observed (De Hert et al., 2015; Suzuki et al., 2014b; Zipursky, Menezes, & Streiner, 2014). With each psychotic relapse, a longer time until symptom remission is expected, or the symptoms may not respond to treatment, and subsequently the patient has increased risk for developing a chronic psychotic disorder (Lindenmayer et al., 2009; Thomas, 2013). The course and outcome of FEP is dependent on the treatment of the patient in the initial stage of illness. Several studies have shown that the earlier a person with schizophrenia gets treatment then the milder the course of illness (Larsen et al., 2007). In the TIPS 1 study (with inclusion of patients between 1997-2001), the course of the illness of early detection patients was characterised by less negative, depressive and cognitive symptoms compared to patients from the control sectors at 5 years follow-up (Larsen et al., 2011). At 10 year follow-up it was reported that early detection and intervention improves outcome, reduces levels of distress and more than doubles the chances for recovery (Hegelstad et al., 2012).

2.2.1 Treatment adherence

Definitions

The complexity of medication-taking behavior has led to the emergence and use of at least three considerably controversial terms compliance, adherence and concordance. The term compliance is defined in English dictionary as: The act or process of complying to a desire demand or proposal or, with coercion. In medical context the term is defined as: “The extent to which the patient’s behavior matches the prescriber’s recommendations”(Haynes, Taylor, & Sackett, 1979). However, its use is declining as it implies a lack of patient involvement (Playle & Keeley, 1998).

Adherence is defined in English dictionary as: the fact of someone behaving exactly according to rules, beliefs, etc. The term adherence in medical context is defined as: “the extent to which the patient’s behavior matches agreed recommendations from the prescriber.’ It has been adopted by many as an alternative to compliance, in an attempt to emphasise that the patient is free to decide whether to adhere to the doctor’s recommendations and that failure to do so should not be a reason to blame the patient

(Barofsky, 1978). Adherence extends the definition of compliance by emphasising the need for agreement. Thus, the term of good and bad adherence clearly has no place, but referring to high/ favorable or low/ unfavorable adherence is perfectly acceptable (Horne et al., 2005).

We can also find the term concordance. In the medical field, it is a relatively recent term, used mainly in the UK. It attempts to re-conceptualize the problem of compliance. Its definition has changed over time from a focused on the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, to a wider concept encompassing prescribing communication to patient support in taking medication. Concordance is sometimes used, incorrectly, as a synonym for adherence (Horne et al., 2005).

The term adherence has been chosen by the WHO and some experts in the field to describe patients' medication-taking behavior (Horne et al., 2005; WHO, 2003b). The main reason is that adherence requires the patient's agreement to the recommendations. The main focus of this thesis is on patients' medication-taking behavior and implementation of guidelines, and the term adherence will cover these elements.

Assessment

Adherence, partial adherence and non-adherence is poorly defined and standardised in the literature. Hence, estimating adherence behavior is a challenging process. While some studies consider patients taking 80% of their medication as adherent (Caro, Ishak, Huybrechts, Raggio, & Naujoks, 2004; Mabotuwana, Warren, Harrison, & Kenealy, 2009); others consider patients adherent if they almost always take their medicines (Novick et al., 2010). Even in studies utilising the same methodology to assess adherence, definitions of an adherent participant may variate broadly. Increasing consensus regarding these issues is necessary to improve our understanding of adherence and the development of more effective treatments (Velligan et al., 2006).

There are many methods for evaluating and assessing patients' adherence, with varying levels of validity and reliability. Patients' self-report, pharmacy refill, pill counts, use of electronic monitoring devices or biological assays are the common used methods (Leppee, Boskovic, Culig, & Eric, 2012; Osterberg & Blaschke, 2005; Schoenthaler & Ogedegbe,

2008; Schroeder, Fahey, Hay, Montgomery, & Peters, 2006a). The choice of a method for measuring adherence to a medication regimen should be based on the usefulness and reliability of the method in light of the researcher's or clinician's goals. Specific methods may be more applicable to certain situations, depending on the type of adherence being assessed, the precision required, and the intended application of the results (Farmer, 1999).

Each method used to assess adherence to oral medications has its own drawbacks. The most common method used to assess adherence in both general and adherence studies was the report of the patient. Self-report was utilised alone or in combination with other methods. Patients' self-report appears to offer advantages for assessing adherence in 'naturalistic' studies and may have the potential for more widespread application in both clinical and research settings (Garfield, Clifford, Eliasson, Barber, & Willson, 2011; Velligan et al., 2006).

Valid measurement of medication adherence plays a crucial role in healthcare and health research. Self-reporting assessment is a more valid method for measuring adherence compared to those obtained through electronic monitoring and can significantly predict clinical outcomes. Self-

report medication adherence measures can provide actionable information despite their limitations. These are preferred when speed, efficiency, and low-cost measures are required, as is often the case in clinical care (Nguyen, Caze, & Cottrell, 2014; Schroeder, Fahey, Hay, Montgomery, & Peters, 2006b; Stirratt et al., 2015).

This model suggests that rather than trying to determine the single best assessment strategy, efforts should continue to develop a portfolio of valid and reliable self-report measures that can be optimally applied depending on the situation. Retrospective prescription claims database analyses lack the details of daily dosing that are available with prospective electronic monitoring; however, as these tools are often the only sources available for assessing adherence, it is suggested that this caveat is noted when describing adherence in these instances. We adopted both electronic medication records for inpatients and self-reporting assessment for outpatients in Study 1.

Consequences of non-adherence

Effective management of schizophrenia requires continuous long-term treatment in order to keep symptoms under control and to prevent relapse (American.Psychiatric.Association, 2006). Despite the critical importance of medication, non-adherence to prescribed drug treatments has been recognised as a problem worldwide and may be the most challenging aspect of treating patients with schizophrenia (WHO, 2003a). Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that 74% of patients had discontinued medication within the first 18 months (Higashi et al., 2013; Lieberman et al., 2005) . Despite the fact that adherence behavior is difficult to study from a methodological point of view, the scientific information available to date does provide many important leads for the engaged clinician to manage the adherence issue. The large number of studies indicates that adherence is an issue that is pertinent far beyond the treatment of patients with schizophrenia or other psychiatric disorders. Non-adherence or poor adherence to medication has a negative impact on the course of illness resulting in relapse, re-hospitalisation, poor outcome and increased consumption of health services and costs (Fitzgerald et al., 2009; Hong, Reed, Novick, Haro, & Aguado,

2011; Kim E, 2011; Mangalore & Knapp, 2007). However, this issue is underestimated by clinicians (Byerly et al., 2005). Meta-analyses of data from a number of countries concluded that a 50% improvement in adherence would decrease 1-year re-hospitalisation rates by 12% (Knapp, King, Pugner, & Lapuerta, 2004; Weiden & Olfson, 1995).The prevalence of non-adherence in schizophrenia is high and has been reported to range from 20% to 56% depending on the clinical setting, definition and assessment of adherence, duration of study, and characteristics of the study population (Lacro, Dunn, Dolder, Leckband, & Jeste, 2002). Rates of adherence in patients with mental illness across studies, but overall findings have indicated that less than 50% of patients fully adhere to medication treatment (Kane, Kishimoto, & Correll, 2013; Lingam & Scott, 2002; Scott & Pope, 2002; von Bormann, Robson, & Gray, 2015).

Non-adherence to antipsychotics represents one of the main causes of relapse (Robinson et al., 1999; Suzuki et al., 2014a). Non-adherence to antipsychotic medication among people with FEP is associated with relapse rates of almost 80% after one year without medication and 96% after two years, which has serious consequences (M. Hill et al., 2010; Tiihonen et al., 2011).

The economic burden due to loss of efficacy is higher during the first post discharge year, whereas the burden from non-adherence is higher in the second year. Because loss of medication efficacy and medication non-adherence act synergistically on relapse, substantial inpatient cost savings can be realised by linking better pharmacologic treatments of psychosis with more effective strategies to manage medication non-adherence (Fitzgerald et al., 2009). One of the challenges is the possibility to use the same drug over time. Discontinuation rates in FEP are high even though better adherence is suggested for second-generation antipsychotics (Opjordsmoen et al., 2009).

2.2.2 Evidence based guidelines and medication algorithms

During the last two decades, an increasing number of clinical guidelines, based on the recent reviews and meta-analyses, have been developed to assist clinicians in making decisions. But only a few implementation studies of psychiatric guidelines have been carried out, and there is a lack of studies on their long-term effects (Forsner, Wistedt, et al., 2010). The aim has been to contribute to closing the gap between research evidence (what is known) and routine clinical practice (what is done).Several treatments are now

considered as evidence-based. This includes pharmacological treatments (such as antipsychotic drugs) and psychosocial therapies (such as cognitive behavioral therapy, work with families, psycho-education, supported employment, illness management and recovery, and integrated treatment of psychosis and substance abuse). In spite of the increased number of new clinical guidelines and the intention to improve the services by practicing these guidelines, there is a lack of knowledge of the implementation of clinical guidelines in everyday routine clinical practice in the mental health services. The few implementation studies reported in a recent Cochrane review (Barbui et al., 2014), indicate that it remains unclear whether treatment guidelines have any positive impact on the performance of mental health services, or whether they improve outcomes for patients (such as quality of life, mental state, employment and admissions to hospital). Other studies, however, have demonstrated that adherence to treatment guidelines reduce the probability of relapse and enhances treatment outcome (Melfi et al., 1998; Schneider et al., 2005; Trafton, Humphreys, Harris, & Oliva, 2007).

Antipsychotic medication is highly agreed upon as evidence based effective treatment for psychosis. However, it is important to limit

polypharmacy, avoid high doses and fast increase in doses, differentiate dosage in different phases and situations, and try clozapine if two other antipsychotics have not had an effect, according to recent algorithms (Johannessen, Fjell, & Kalhovde, 2013; NICE, 2014). The degree of clinicians` adherence to algorithms is unknown (Rush, March 1999.).

2.2.3 Shared decision-making

In the last decade, the clinician-patient relationship has become more of a partnership. There is a growing interest in shared decision-making (SDM) in which the clinician and patient go through all phases of the decision-making process together, share treatment preferences, and reach an agreement on treatment choice (Joosten et al., 2008). There is an international consensus about the importance of SDM. However, there is no universally accepted definition (de Silva, 2012). SDM is an interactive process in which patients and physicians collaborate to make health care decisions. At a practical level, health care decision-making usually involves a shared responsibility. Because most of medical care involves chronic illness, the patient necessarily has responsibility for his or her own care on a

daily basis (Adams & Drake, 2006). Promoting the use of accurate scientific information and active patient involvement in decisions are two of the fundamental tenets of evidence-based medicine. Shared decision-making is therefore a fundamental component of evidence-based medicine. In the mental health field, however, shared decision-making is a relatively novel and somewhat controversial concept. The basic aspects of shared decision-making have rarely been made explicit in mental health settings (Adams & Drake, 2006; Forrest, 2004). Joosten et al. argued that SDM is particularly suitable for long-term decisions, especially in the context of a chronic illness, and when the intervention contains more than one session (Joosten et al., 2008). Patients clearly want medical information. Nearly all patients (>90%) express a strong desire for information on illnesses, treatments and medication side effects (Adams & Drake, 2006; Degner et al., 1997). The evidence on the impact of shared decision-making on clinical outcomes is mixed. Many studies have examined the importance of the patient-physician relationship, the quality of communication, and the amount of patient participation or control for the patient satisfaction, adherence, and clinical outcomes (Adams & Drake, 2006; Stewart & Brown, 2001).

Some studies argue that SDM in psychiatry leads to better outcomes, including increased compliance (Hamann, Leucht, & Kissling, 2003), associated with an increase of patient autonomy (Joosten et al., 2011), and in many cases might help in destigmatising this group of patients (Hamann et al., 2006).

The main ways that researchers have measured whether decisions are being shared: asking patients whether they have been involved in decisions; asking clinicians whether they have involved patients in decisions; examining patient records for evidence of shared decision making; asking clinicians for feedback about what they would do in hypothetical situations; observing encounters between clinicians or trainees and simulated patients or observing encounters between patients and clinicians or audio or video taping consultations and watching them later (de Silva, 2012). In this study we adopted the first two methods for assessing SDM.

3. Aims and research questions

The adherence issue has not been adequately addressed among patients with psychotic disorders in routine clinical practice. Moreover, it is possible that different factors may predict future adherence versus current adherence. A large number of studies indicate that adherence is an issue that is pertinent beyond the treatment of patients with schizophrenia or other psychiatric disorders. This work encompasses different methodologies and has provided many pieces that supplement the adherence puzzle. However, a better understanding of the factors associated with medication non-adherence is needed so that any modifiable risk factors can be identified and managed using appropriate interventions.

Our research questions in this context are:

- To which extent do psychiatrists follow the antipsychotics treatment guidelines set up by the health service authorities?
- To which extent do the patients follow the instructions made by the psychiatrists?

The next step was to describe more in depth the reasons for deviation from standards by interviewing physicians and patients mainly on current experiences, knowledge and attitudes.

4. Material and Methods

4.1 Design

In research it is crucial to choose a research approach that is appropriate to the purpose of the study (Ringsted, Hodges, & Scherpbier, 2011). A multi-method research involves quantitative and qualitative research techniques, methods, approaches or concepts are combined into a single study. Its central premise is that the use of both approaches, in combination, provides a better understanding and solution of research problems than either approach alone. In general, healthcare issues have dimensions that cannot be investigated using a single research approach (John W. Creswell, 2010). Adherence in psychosis is no exception and the decision to use a multi-method approach for this project was hence due to the complexity of this issue. The decision to use a multi-design was determined at the outset of the research process.

Quantitative and qualitative methods each have inherent biases and weaknesses, and using both approaches may offer a stronger design in which these weaknesses are offset by strengths of the other approach. One of the main strengths in a multi-methods research is that it enhances chances

for a holistic perspective, displays a broader understanding and increased flexibility (Giddings & Grant, 2006), which can be advantageous when conducting research on complex public health problems (Giddings & Grant, 2006; Sale, Lohfeld, & Brazil, 2002). However, a mixed design has its challenges. Creswell (Creswell, Fetters, & Ivankova, 2004) argue that the lack of explicit practice guidelines to researchers may lead many novice researchers to adopt incompatible research strategies. Method-experience gap influences the credibility; using a mixed method approach requires knowledge and skill in both research approaches, but most researchers tend to have expertise in one particular area (Giddings & Grant, 2006; Hesse-Biber, 2010). Another limitation is that it takes more time both at the beginning and at the end (Giddings & Grant, 2006).

For our research we adopted the explanatory sequential design method (Venkatesh, Brown, & Bala, 2013), in which we first collected and analyzed quantitative data (study 1), which has the priority for addressing the research questions for the two qualitative studies, studies 2 and 3. In each of these studies, we recruited unique participants; data were collected and analyzed from each study separately.

Study 1 methodology

The purpose of this study was to determine whether attending physicians or psychiatrists followed up the drug algorithm by investigating completed drug treatment in the ward and outpatient departments, and additionally to investigate if they followed-up their patients according to both the local and national guidelines. The second aim was to determine whether patients adhered to the physicians' medical recommendation. We conducted an extensive survey on the use of antipsychotics in patients with first episode psychosis aged 15–65 years. An anonymous file audit survey (use of the electronic patient administrative system) of consecutively admitted patients at the hospital ward for the treatment of first-episode psychosis (F19.5, F20.0-F29), and of patients who started treatment in adult psychiatric outpatient departments in the period between 01/09/09 to 31/12/11 was conducted. A quantitative method was used for this study (Study 1) helping us to determine the degree of adherence in the area we live in compared to other places in the world. Using a non-experimental research design gave us the opportunity to explore the situation in our hospital (Burns R.B., 1981). Retrospective cohorts are observational in design and sometimes referred to as historic cohorts. Adopting a retrospective cohort design helped us to

examine a larger data set over a longer observation period because databases of healthcare records had already been collected. This method reduces the risk of bias during measurements as the research question and expected outcome were not known at the time when data were collected. However, we used only available data from the past without having any control over the nature or quality of the measurements; thus, important data may not have been recorded (Altman, 1999).

Study 2 & 3 methodology:

The main feature of a quantitative method is that people, generally looked upon as identical and react similarly. However, it has limitations in masking phenomena such as lived experiences, social interactions, patients' perspective of doctor-patient interactions and other contextual issues (Sale et al., 2002). Qualitative research is a broad umbrella term for research methodologies that describe and explain persons' experiences, behaviors, interactions and social contexts without the use of statistical procedures or quantification. A common aim in qualitative research is to systematically

investigate people's perspectives as presented by themselves, in their own words (Fossey, Harvey, McDermott, & Davidson, 2002).

The aim of Study 2 was to gain a deeper understanding of the contextual factors that influenced patients' decision to adhere to the recommendation of taking antipsychotics. Survey data obtained in study 1 were one-dimensional, and contextual factors related to the research question that are critical for patients in making adherence decisions were missing. A qualitative research method allows for greater in-depth understanding of these types of contextual issues. In this project, we carried out a thematic analytic qualitative approach within an interpretative-phenomenological framework in studies 2 and 3. The interpretative element implies that data generated from a reflexive dialogue between participants and researcher throughout the interview. The phenomenological element entails that significant knowledge collected from the lived experiences of the study participants, and that the central aim was to discover and interpret the meaning of such experiences within their broader contexts (Fossey et al., 2002). In Study 2 we performed 20 individuals interviews with participants two years after they had been diagnosed with first episode psychosis and met inclusion criteria for this study.

A qualitative method with its specific theoretical assumptions is a flexible method that helps investigate specific areas where there is not a well defined scale. For example, adverse effects of antipsychotics are often present, but vary in severity. Patients experience different side effects and therefore there are multiple realities that are each valid and truthful (Laverty, 2003). It is difficult to be objective when we try to understand the reasons for patients discontinuing their antipsychotics. We need to interact with patients, listen to their experiences and how they interpret their world to understand them and empower to optimise the given care.

Interviews

Interviews are used in most types of qualitative research. Semi-structured interviews allow the researcher and participant to engage in a dialogue whereby initial questions are modified in the light of the participants' responses, and the investigator is able to probe interesting and important areas which arise (J. Smith, 2015). The experiences of the participants can be approached more closely through a fusion of the researchers' and the participants' horizons, meaning that new understanding comes from a

continuously developing, dynamic and reflexive dialogue between participants and researchers (Gadamer, 1989).

The semi-structured interviews used to facilitate more focused exploration of a specific topic, using an interview guide. Interview guides usually have a list of questions and prompts designed to guide the interview in a focused, yet flexible and conversational, manner (Fossey et al., 2002). A semi-structured interview guide was developed in Study 2 based on collaboration between one recovered service-user counselor and the researchers, as well as based on literature regarding antipsychotic medication and adherence. Additionally, three pilot interviews were conducted with three FEP patients. The interview guide was modified somewhat after these interviews, but the core-parts remained the same. The author performed all interviews.

A similar qualitative method was used in Study 3 aiming to facilitate that psychiatrists express their experience and opinions freely. One pilot interview was conducted with an external psychiatrist. The interview guide was modified somewhat after this interview but retained the core

components . We conducted interviews with 23 psychiatrists working in different psychiatric departments.

To capture topics not adequately covered by the interview, in both studies, an open ended category was added to the end of each interview, in which participants could provide additional information that had not been elicited. Interviews were audiotaped and transcribed verbatim for the purpose of analysis.

4.2 Participants

Unique participants recruited for each study with data collected and analyzed in each study separately, but the final interpretations made using both data sources.

In Study 1 the researcher started including patients that were 15-65 (mean=25) years old with a FEP diagnosis (F19.5, F20.0-F29.0 according to ICD-10) (WHO, 2011) from 01.09.2009 to 31.12.2011 and who had been observed by a treating clinician for at least 6 months. The researchers started

the study at one inpatient ward, but because of delayed inclusion, the researcher team had to expand our study to two other unites. At the end 55 patients met the inclusion criteria of our study (32 inpatients and 23 outpatients), while 51 (25 inpatients and 26 outpatients) had been excluded. Although the sample in this study was somewhat small, it was fairly representative and sufficient to give us the results we wished to find. Descriptive statistics was adopted for data analyzing.

In Study 2 we started including patients from the ongoing TIPS-2 study (2002- present) (Joa et al., 2008). Participants were recruited consecutively when attending the 2-year follow-up sessions (calculated from inclusion date in the TIPS-2 study). Obtaining a sample of participants who are intimately familiar with the topic is critical (Hill, Thompson, & Williams, 1997). Our goal was to set the criteria for the population prior to collecting data (which has been called criterion-based sampling), so that we can know to whom the results are applicable and can provide a meaningful context for the reader to interpret and understand the results (Hill et al., 1997).

Based on these assessments, only participants who had used antipsychotic medication were included. Twenty-six eligible candidates

were contacted. Out of these, five participants refused study participation and we were unable to obtain to consent from a sixth person. Recruiting stopped after including 20 participants, as the research team considered the last two interviews did not contribute substantially new information (Hill et al., 1997). In this study, patients were assessed, by patient self-report, as to adhere to their medication if they followed their physician's recommendations for at least six months prior to the 2-year follow-up, although adherence prior to this might have been irregular. Interviews were conducted between June 2015 and January 2016.

In Study 3 psychiatrists were recruited consecutively from inpatient wards and outpatient clinics to ensure diverse working experiences. Twenty-seven eligible candidates were contacted. One psychiatrist did not want to participate; one psychiatrist was only partially at work due to illness, and two could not prioritise our study at that time. The sample size was decided on the basis of stability of findings (Hill et al., 1997). We stopped recruiting after including 23 participants, as we considered the last two interviews not contribute substantially new information. Interviews were conducted between February 2017 and March 2017.

4.3 Analysis

Paper 1

Statistical analysis

In paper I the statistical package SPSS (version 22.0; SPSS Inc., Chicago, IL, USA) was used. Student's t-test was used for normal distributed data. A chi-square test was used for categorical data. ICC (The Intraclass Correlation Coefficient) was used for reliability analysis (Shrout & Fleiss, 1979). Data are presented in frequencies, percentages or descriptive according to what was most appropriate. A stratified, random sample of 14 cases was selected for reliability analysis. Study forms and clinical vignettes were used for testing agreement on scoring of outcome.

Patients' adherence assessment

Data were extracted by an extensive file audit survey (using the electronic patient administrative record system) and from individual patient medical records. Doctors', nurses' and psychologists' notes for each patient

were reviewed for six to 13 months after inclusion depending on the available data. Data were collected at intake, 3, 6 and 12 months follow-up. Data pertaining to antipsychotic medication were registered, such as generic drug name, starting date, dosage, date of any termination, maximum dose used, most commonly used dosage, results from serum tests, possible change of medication and reasons for discontinuation. Also recorded were reasons for drug changes, any use of coercive medication or treatments, patients' adherence with medication.

At 3, 6 and 12 months, the degree of adherence was calculated and divided into categories based on medication administration records for inpatients and for outpatients using self-reporting and prescription refills as follows:

- Patient non adherent 0%: when the patient refused medication or had an adherence percentage less than 15% of the time.
- Patient adherent 25%: when the patient rarely used prescribed drugs, about 15–35% of the time.

- Patient adherent 50%: when the patient used the drugs occasionally/sometimes, about 35–65% of the time.
- Patient adherent 75%: when the patient used the drugs frequently/often, about 65–85% of the time.
- Patient adherent 100%: when the drug was taken at least 85% of the time.

Psychiatrists' adherence assessment

We had two local algorithms; the first one was created in 2002 for all psychosis patients in outpatient clinics. The second algorithm was created in 2009, when a new hospital inpatient ward was opened, with responsibility for treatment of FEP patients (in the catchment area).

The new (inpatients) algorithm was made based on the old one updated with recent research recommendations. These algorithms provide the psychiatrist with three stages of action pertaining to the prescription of antipsychotic medication. For outpatient departments, first choice drugs are alphabetically listed: (olanzapine (10–20 mg), quetiapine (up to 750 mg), risperidone (2–4 mg) or other second generation antipsychotics).

Perphenazine is the only drug at level two, with the third level of choice being clozapine. Each drug to be used for at least eight weeks (with the exception of cases where severe side effects arise) before considering switching of drugs.

The inpatient ward algorithm is more restrictive, with risperidone (0.5 mg up to 2 mg within the first 2 weeks) being the only first level drug of choice. The second level offers a choice of olanzapine (5–20 mg) or quetiapine (50–600 mg), whereas clozapine remains at the third level. Unless there are side effects, each drug must be tried for at least eight weeks before switching is considered.

Psychiatrists' adherence to algorithm has been assessed in three stages; start, switch 1 and switch 2.

At baseline ('Start' – first antipsychotic drug of choice), the following five descriptive categories were used:

1. The doctor has followed the algorithm.

2. The doctor did not follow the algorithm, but his/her decision was empirically based and acceptable.

3. The doctor did not follow the algorithm (another drug chosen).

4. The doctor did not follow the algorithm (no antipsychotics were given).

5. The doctor did not follow the algorithm (antipsychotics were given, but dosage or duration of medical treatment were insufficient).

At the second data recording point ('switch 1'), one of the following three descriptions was used:

1. No switching (no need for changing drugs).

2. Switching to another antipsychotic drug according to algorithm.

3. Protocol not followed (deviations from algorithm, e.g. failure to prescribe or change drugs despite patient's clinical status).

At the third data recording point ('switch 2' –clozapine phase), one of the following three descriptions was used:

1. No need for switching.

2. The patient started treatment with clozapine after 6 months, or after trying two other different antipsychotics.

3. The patient was not prescribed clozapine despite it being indicated according to the protocol.

The first author read each patient's electronic record, made an abstract of the clinical condition and the psychosocial functioning and then completed the adherence form. All cases subsequently reviewed and discussed by the research team, who then made the final consensual decision on adherence.

Outcome assessment

The outcome form described three possible outcomes, measured at the last follow-up. The first author read each patient's electronic record, made an abstract of the clinical condition and the psychosocial functioning and then filled in the form. All cases were subsequently reviewed and discussed

by the research team, which made the final consensual decision on outcome based on GAF.

A. Good outcome

Patient in remission, as assessed either by his/her treating physician, according to the discharge summary when applicable, or from descriptions of the patient's functional status (such as being back at school or work, living independently, etc.).

B. Intermediate/fair outcome

Clinical condition is variable, with symptom levels fluctuating. The patient has been experiencing occasional periods of functional impairment.

C. Poor outcome

Clinical descriptions indicate persistent psychotic symptoms or poor levels of functioning.

Paper 2 & 3

Analysis

Phenomenological analytic techniques emphasize meaning comprehension to understand the subjective meaning of experiences and situations for the participants themselves, as opposed to how these meanings might fit with researchers' conceptions. Thus the aim in Interpretative Phenomenological Analysis (IPA) is to try to understand the content and complexity of those meanings rather than measure their frequency. This involves the researcher engaging in an interpretative relationship with the transcript. These meanings are not transparently available, but must be obtained through a sustained engagement with text and a process of interpretation (Braun & Clarke, 2013).

The analytical procedure involved six stages of analysis:

Stage 1: familiarizing with the data. The first step is reading and re-reading the whole data description to get a sense of the entire description. The phenomenological approach is holistic since it realizes that the meanings

within a description can have forward and backward references and so analyses of the first part of the description without awareness of the last part is too incomplete.

Stage 2: generating initial codes. The interviews need to be broken into parts in order to be dealt with holistically and to establish some ‘‘units of meaning’’.

Stage 3: searching for themes. This is the most important step in which codes with similar words or relationships are clustered into groups. These clustered groups were used to produce themes.

Stage 4: reviewing themes. In this stage we undertook refinement of the themes that we created in the previous stage. Data within themes should cohere together meaningfully.

Stage 5: defining and naming themes. Here we identified the essence of each theme, and determined the aspect of the data captured by each theme. At the end of this stage, the scope and content of each theme must be described in a few sentences.

Stage 6: producing the report. It is important to provide a concise, coherent, logical, non-repetitive, and interesting account of the story from the data, within and across themes.

While we used literature, our knowledge about the adherence issue, and the results from Study 1 for development of interview guidelines, but we tried to approach the data from a fresh or unbiased perspective when analyzing the data. “Forgetting” the literature is important because one of the primary features of qualitative research is that researchers do not specify in advance the factors of importance but allow the data to speak for itself (Hill et al., 1997).

The team discussed each case thoroughly and tried to understand the coding within the context of the overall dynamics. To strengthen the credibility of the study, four authors in Study 2 and three authors in Study 3 conducted the five step procedure independently. In collaboration with remaining authors, all researchers compared their interpretations, agreed on themes with accompanying quotes, and validated the findings (Hill et al., 1997).

Reflexivity, scientific team and analytic cooperation

Pre understandings include researchers' pre-existing experiences, hypotheses, perspectives, prejudices and frames of reference, which may influence any part of the research process (Malterud, 1993). In line with reflexive methodology (Binder, Holgersen, & Moltu, 2012), the researchers outlined any personal and corporative issues which may have affected our interaction with the subjects or our interpretation of the data. Further, the researchers illustrated the method they used to deal with these challenges. The analysis team consisted of four members from various clinical and academic backgrounds, all with a particular interest in severe mental illness. These differences can be seen as facilitating a rich description of the data, which often is required when examining an under researched area. On the other hand, differences implied that the process of reaching coherent results, particularly in the interpretative analytic work, could be a challenge. As it was clear to us that such differences may have existed, we mapped differences in viewpoints in the preparatory phases of the study. This allowed us to overcome possible disagreement by developing tailored decision rules to resolve disagreement ahead of analysis. The researchers

agreed on the following decision rules for the analytic process: 1) Have an open attitude and seek consolidation rather than conflict whenever differences were discovered; 2) resolve minor disagreement utilizing the principle of parsimoniousness (i.e. Occam's razor: when two competing theories make the same predictions, the simpler one is better); 3) to resolve major disagreement we applied A) an inductive principle using the raw data as a compass guiding us to the description of the phenomena at issue which seemed most true to the participants' lived experience, and B) Then apply the principle of the best argument as described above.

4.4 Ethical Considerations

The Regional Ethics Committee in Norway (2015/72/REK vest) approved this study. Study one was approved by the Norwegian Data Inspectorate. Written consent was not required because the Regional Committee on Ethics in Medical Research agreed that the study used only observational hospital clinical data, and no experimental or other interventions were carried out. TIPS-2 is approved by Regional Ethical Committee (REK vest 015.03) and collaborates with TOP REK Øst (#493-03-01179, 630-04, 689-05250). Written informed consent was obtained from all participants in the study.

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Participants were pleased to share their experiences, and were delighted that someone was interested in their ``stories``. People in a difficult situation often want to talk about it, and a conversation can be a good tool to work through these experiences (Arman & Rehnsfeldt, 2006). For the qualitative investigations, research indicates that interview studies may empower participants (Kitzinger, 1995) and enhance their feeling of self worth (Reason & Riley, 2008). The author experience of the interviews was that

the participants showed a great trust by revealing some details of their living experience. They were explicit that they did not consider the author as a representative of the hospital, but as a neutral external person who was interested in their history. This established a good relationship with participants while at the same time ensured the authors independence as a researcher (Kvale & Olesen, 2006).

Several participants said they had decided to participate because this was a research study done by, as they called the author a ``medication expert``, and because they felt it is useful to share their experiences with health personnel helping them to gain new knowledge and improve the health-care services. Participation was voluntary. Participants were informed that refusing to participate would have no consequences for them and they could withdraw from the study at any time. All the interview data treated confidentially. The name lists were stored separately from the interview data. Only the first author had access to the codes connecting the interviews to the name lists and audio files. The data in all publications is anonymous and non-identifiable.

5. Synopsis of the papers

5.1 Paper 1

In the first paper `` Use of medication algorithms in first episode psychosis: a naturalistic observational study`` only 62% of the physicians adhered to the local medical algorithm. However, all first choices of drugs (100%) were made according to international standards. Olanzapine was the most common antipsychotic drug of choice at the initiation of medical treatment, followed by risperidone, quetiapine and aripiprazole. Hospital physicians at inpatient wards initiated antipsychotics significantly earlier than did physicians in the outpatient departments. Of the 15 patients who were prescribed antipsychotics on their day of admission, 13 were inpatients. Although the majority of physicians adhered to national and international standards, when choosing the first antipsychotic, the follow-up of initial courses of medication in this sample failed to adhere to the local algorithm.

Fifty-six percent of patients used their medicine more than 75% of the time, 22% had between 26% and 74% adherence and 22% adhered less than 25%.

Adherence in the inpatient group tended to be better than for participants recruited as outpatients, with adherence percentages of at least 75 recorded in 65.6% vs. 43.5% of, respectively. Patient adherence was significantly associated with good outcome. Older patients and inpatients had more favorable outcomes than younger patients and outpatients.

5.2 Paper 2

In this paper `` Experiences of antipsychotic use in patients with early psychosis: a two-year follow-up study``, 70% of the included patients had no earlier psychiatric treatment history prior to the present episode. Patients reported several factors to have a prominent impact on adherence to their antipsychotics. The textual analysis resulted in four related themes, reflecting FEP patients' experiences over the last 2 years; 1) Admission as a crucial stage, 2) Sufficient information at the right time, 3) A plea for shared decision-making, and 4) Attitude to antipsychotics echoes beneficial effects and illness insight. Health-care staff have an important role in maintaining good adherence. It seems that, according to these patients, positive experiences of the hospital admission, sufficient and timely information,

involvement in decision-making, as well as insight and the experience of beneficial effect of antipsychotics have a considerable impact on adherence to medication in our patient group.

5.3 Paper 3

In this paper ``Psychiatrists' reflections on a medication-free program for patients with psychosis`` the textual analysis resulted in four interrelated themes; 1) Medication-free treatment: An unscientific option for a stigmatized patient group, 2) When the minority is in charge: The loudest voices get their opinions heard, 3) Patients with psychotic symptoms: The paradox of "lack of insight'' and choice of treatment, and 4) Professionalism vs. ideology disregarding science. Psychiatrists assessed medication-free treatment for patients with severe mental disorders as not empirically based and resulting from an unscientific process where some dissatisfied users had been allowed to control public discourse and influence decision makers through aggressive use of social media. The paradox of "lack of insight'' and choice of treatment for patients with active symptoms of psychosis, was

put forward as a particularly severe example of medication-free treatment as a potential harmful treatment choice and an area where they opposed authority demand. The participants believed that the new recommendation can aggravate the adherence issue for this patient group. They were afraid it would expand the gap between science and society, adding another reason for non-adherence in addition to existing ones. However, the pressure they are expose to from different sources like the government, unsatisfied service users and their relatives, psychiatrists stated that they had based their medical decision on science and evidence-based guidelines.

6. General discussion

6.1 Discussion of the results

The main aim of this thesis was to investigate factors affecting adherence to treatment with antipsychotics in patients with psychosis. To achieve this, we sub-divided the study into three separate investigations, using a multi-method research design. First; we assessed patients' adherence to psychiatrists' recommendations and psychiatrists' adherence to evidence based guidelines, and to which degree adherence was associated with outcome. Secondly; we investigated factors affecting adherence from the perspective of service-users, including specific, personally relevant experiences. Thirdly; we investigated the impact of the new recommendation by the government of a medication-free treatment alternative on adherence from the perspective of psychiatrists.

Medication adherence in patients with first episode psychosis

The adherence rate was 56% (paper I), defined as those who used their medicines more than 75% of the time, in a sample of 55 first admitted

inpatients and outpatients with psychosis from three hospital units. Although the sample was relatively small after excluding 51 patients, it was considered fairly representative, not biased and comprehensive. We collected the sample from one hospital; collecting a larger sample would have required more time from the researcher.

As noted in the introduction of this thesis, the methodology of adherence measurement is challenging. We have in this thesis adopted patients' self-report (paper I and II), electronic medication records for inpatients (paper I) and blood level concentration when available in some cases. The choice of these methods for measuring adherence was based on the availability of information and patients' situations/ admission place. Patients' self-report offer advantages for assessing adherence in 'naturalistic' studies and may have the potential for more widespread application in both clinical and research settings (Garfield et al., 2011; Jonsdottir et al., 2010; Velligan et al., 2006). Valid measurement of medication adherence plays a crucial role in healthcare and health research (Jonsdottir et al., 2010; Nguyen et al., 2014).

Non-adherence is a major public health problem, which is frequent across all domains of antipsychotics (Higashi et al., 2013; Yalcin-Siedentopf et al., 2014). We should consider the international difference in health-care services when comparing studies of adherence, and the definitions of an adherent subject in each study. While some studies consider patients taking up to 80% of their medication as adherent (Caro et al., 2004; Kane et al., 2013; Mabotuwana et al., 2009); others consider patients adherent if they almost always take their medicines (Novick et al., 2010). In this thesis, we considered patients adherent when they used their medicine more than 75% of the follow-up time.

The adherence rate in this study, as mentioned, was 56%, which is consistent with previous studies. Perkins et al. reviewed a number of naturalistic first-episode psychosis studies, which showed that by six months of treatment 33% - 44% of patients are non-adherent and, by one year, as many as 59% are non-adherent (Perkins et al., 2008b). Another review reported that the mean rate of medication non-adherence in patients with schizophrenia ranged from 41.2% to 49.5% (Lacro et al., 2002). Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that 74% of patients had discontinued medication

within 18 months, and also other studies confirm the high rate of discontinuation (Higashi et al., 2013; H. Jonsdottir et al., 2009; Lieberman et al., 2005; S. Opjordsmoen et al., 2009).

We found that good adherence was associated with good outcome (paper I). A European study confirms our finding by showing that non-adherence was associated with poorer long-term clinical outcomes and had economic implications for health-care providers (Hong et al., 2011). Bowtell et al. showed that 45.8% of patients who discontinued their antipsychotic medication after a first episode of psychosis, experienced relapse (Bowtell et al., 2017). Another study revealed that interruption of antipsychotic treatment was associated with a five-fold increased risk of relapse (Winton-Brown et al., 2017).

Another important aim for this thesis was to identify reasons for non-adherence in this patients group. We found (Paper II) an association between adherence and positive experiences of the hospital admission, sufficient and timely information, involvement in decision-making, and insight and the experience of beneficial effect of antipsychotics.

Patients with psychotic disorders pose additional challenges that increase risk for and frequency of non-adherence (Higashi et al., 2013). Lack of insight or lack of awareness of the illness (Chan et al., 2014; Perkins et al., 2008a) is a major challenge and one of the common reasons for non-adherence (Higashi et al., 2013; Sevy, Nathanson, Visweswaraiah, & Amador, 2004). Most of the patients in Study 2 retrospectively, reported that poor insight into their illness during the acute phase was perceived as making it harder for them to commit to any treatment, including treatment with antipsychotics. Furthermore, poor insight into illness alongside a perceived poor patient-staff alliance leads to inadequate communication about medication (Velligan et al., 2009). This may underpin our finding such that patients in Study 2 stated they had insufficient information about their medication at the acute stage, while psychiatrists in Study 3 stated that they gave patients appropriate and adequate information according to their illness condition.

Both patients and physicians (paper II and III) reported adverse effects and lack of medication efficiency to be a barrier to adherence. This is in line with other studies (Hudson et al., 2004; Kauppi, Hätönen, Adams, & Välimäki, 2015; Velligan et al., 2009).

Professional support, information and involvement have been shown to be important predictors of treatment adherence in people using antipsychotics (Gray, Wykes, & Gournay, 2002; Kikkert et al., 2006; Olfson et al., 2000), which supports our findings (paper II).

Although, researchers have attempted to identify variables that predict adherence, many studies have focussed solely on clinical and patient characteristics (Haddad, Brain, & Scott, 2014; Lambert et al., 2004). For example, a direct association between patients' admission experience and adherence has hardly been highlighted in previous studies. A study showed that the reception of patients by the medical staff may have a crucial impact on adherence, regardless of legal status of admission (Opjordsmoen et al., 2010). Despite not having a key theme in the interview guide addressing admission experiences, all patients seemed to feel a need to talk about it, whether it was pleasant or not. It seems that the first contact with staff has a considerable impact on alliance and trust during the treatment process to follow, which in turn affects adherence to medication, especially after discharge (paper II). Patients and health personnel may have different ideas about what is important for achieving good adherence. These discrepancies may cause healthcare personnel to fail to notice or understand why patients

stop taking their medication (Kauppi et al., 2015; Scott & Pope, 2002). Therefore, it is important to consider subjective attitudes and concerns of patients about their illness and medication (Rettenbacher et al., 2004). Understanding patients' needs helps personnel to design and use effective interventions to support adherence, which should be based on a mutual understanding between patients and personnel (Kikkert et al., 2006).

Psychiatrists adherence to algorithm and guidelines

Although guidelines and algorithms in mental healthcare can improve the quality of medication use (Barnes & Paton, 2012), clinical practice guidelines are not always used in practice (Barbui et al., 2014; Forsner, Hansson, Brommels, Wistedt, & Forsell, 2010), and implementation strategies do not always result in improved adherence to guideline recommendations (Keating et al., 2017). The study revealed that 61.8% of the physicians adhered to the medication algorithm (paper I) in the start-up phase. However, during follow-up of initial medication they failed to adhere to the algorithm. An implementation study of clinical guidelines in

psychiatry showed that initially only 42.6% adhered to the treatment guidelines and it showed a considerable improvement in adherence after implementation (Forsner, Wistedt, et al., 2010). A study by McGlynn et al. (McGlynn et al., 2003) of adults living in 12 metropolitan areas of the United States found that participants received recommended care 54.9% of the time. In an observational study of 10 Dutch guidelines, it was concluded that general practitioners followed guideline recommendations in only 61% of relevant situations (Grol, Dalhuijsen, Thomas, Rutten, & Mokkink, 1998). Furthermore, in an analysis of 41 studies of the implementation of mental health guidelines including for depression, schizophrenia, and addiction, Bauer found that physicians adhered to guidelines only 27% of the time in both cross-sectional and pre-post studies and 67% of the time in controlled trials (Bauer, 2002; Francke, Smit, de Veer, & Mistiaen, 2008; Steinberg, Greenfield, Wolman, Mancher, & Graham, 2011).

Clinical guidelines should be updated when new evidence suggests the need for modification of clinically important recommendations. They should be updated if new evidence shows that a (i) recommended intervention causes previously unknown substantial harm; (ii) a new intervention is significantly superior to a previously recommended intervention from an

efficacy or harms perspective; or (iii) a recommendation can be applied to new populations (Steinberg et al., 2011). This was not the case when the Norwegian government approved the new medication-free treatment for patients with severe mental illnesses (Paper III). No new evidence has been published in support of no-use of antipsychotics in the acute phase for patients with psychotic disorders. All participants in paper III criticized the medication-free treatment program for being unclear, unprofessional and for not being based on science. Only in psychiatry the benefits of one of the great pharmacological breakthroughs in the history of medicine would be questioned over a half century after its introduction to clinical practice (J. A. Lieberman, 2018) . Numerous studies by eminent researchers in many countries have documented the therapeutic efficacy of antipsychotics in relieving the acute psychotic symptoms of schizophrenia and preventing their recurrence (Davis & Andriukaitis, 1986; De Hert et al., 2015; Di Capite et al., 2016). Given the obvious acute and prophylactic benefits of antipsychotics, and the possibility that they may be disease modifying, it is hard to understand why there would still be questions as to their effectiveness (J. A. Lieberman, 2018).

Guidelines should aim to influence the treatment behavior of practitioners. However, they are not intended to dictate all aspects of care for patients. Individual factors such as personal preferences, comorbidity, concurrent medications and previous experience with medication will have an impact on the choices made in clinical practice (Steinberg et al., 2011). However, studies are needed to show that physicians exposed to guidelines provide better treatment. Participants (paper III) perceived the medication-free program as unprofessional because of the lack of accordance with the national guidelines accompanied by absence of research to underpin the benefits of this treatment proposal. Guidelines should be empirically tested before being called "evidence based" (Linden, Westram, Schmidt, & Haag, 2008). It is important for the target users to assess the quality of guidelines so that they can have confidence in the recommendations made (Keating et al., 2017). Development of high-quality clinical guidelines occur by using an unbiased, independent, expert panel including research investigators, health professionals, methodologists, and representatives of the public without conflicts of interest (Steinberg et al., 2011).

6.2 Methodological considerations

6.2.1 Mixed method research approach

Mixed method research provides strength that offset the weakness of both quantitative and qualitative research. It provides more evidence for studying a research problem than either approach alone. In this thesis quantitative research is weak in understanding the context in which people talk about why they adhere or not to their medication. Further, quantitative researchers are in the background, and their personal biases and interpretations are seldom discussed. Qualitative research makes up for these weaknesses. Further, as the qualitative approach has challenges with generalizability the necessity of a quantitative extension seems required to test the generalizability of the qualitative findings. This bridging between research paradigms seems fruitful, both regarding the evaluation of the adherence issue but also if the aim is to answer research questions broadly.

6.2.2 Sample representability

Paper I& II

Psychiatric services in Norway are publicly funded. Outpatient clinics are equally distributed and offer a similar quality of care such as the inpatient wards and across all city districts regardless of socioeconomic differences. Thus, the sample would be representative for people with FEP who live in the area, where treatment and health care is available for anyone suffering from a severe mental disorder. The inclusion area for this study covered the southern part of Rogaland country and the study sample represents an unselected cohort. In study one FEP patients, which admitted to an inpatient ward, were included, but because of a low participant rate, the research team decided to expand inclusion to two outpatient clinics. Patients were recruited consecutively.

However, some degree of selection bias can be assumed in Study 2. Some patients refused to participate. The researcher interviewed those who came to their two years follow-up. Very impaired patients that declined health care follow-up were not included in the study.

Paper III

In a phenomenological study, the participants may be located at a single site. Most importantly, they must be individuals who have all experienced the phenomenon being explored and can articulate their lived experiences. The more diverse the characteristics of the individuals, the more difficult it will be for the researcher to find common experiences, themes and the overall essence of experience for all participants (J. W. Creswell & Inquiry, 2007). All the psychiatrists are working at the same hospital, which can be seen as a limitation. However, some of them had work experience from other cities in Norway and others had experiences from other countries, which contributed to the enrichment of our data sources.

6.2.3 Validity and reliability of assessments

Paper I

The aim of this retrospective study was to investigate the adherence rate in a population with FEP. After reviewing the available information it became clear that more than one method should be used to assess adherence. Measurement of serum concentration of antipsychotics is available in both inpatients and outpatients clinics but is not used regularly. Adherence assessments in the inpatient ward were more reliable since patients were under observation and control of healthcare providers. On the other hand, self-report was the only available method for the patients in both outpatient departments and for the time period before re-hospitalization.

At the end of the baseline data collection period, a stratified, random sample of 14 cases was selected, comprising both hospitalized and outpatient individuals. Study forms and clinical vignettes were used for testing agreement on scoring of outcome. The reliability of this measurement was 0.6 (ICC).

Paper II & III

Data collected in Study 1 using rigorous methods had the potential to maximise external validity and increase the likelihood that responses to key research questions in Studies 2 and 3 are not influenced by others.

The increased interest in qualitative research has led to concerns by readers and reviewers about their quality. Hill et al. believe that it is preferable to use a primary team of three to five people to conduct the analyses and one to two auditors to review and provide feedback on the analyses (Hill et al., 1997). The research team consisted of four members in Study 2 and three members in Study 3 for these tasks. The team members did first examine the data independently. Thereafter they came together to present and discuss their ideas with the whole team, five members in both studies, until they reached a single unified version that all team members endorsed as the best representation of the data. Using several researchers provides a variety of opinions and perspectives, helps to circumvent the biases of any one person, and is helpful for capturing the complexity of the data. Individual researchers could easily miss crucial nuances of the data because their biases or expectations might influence their understanding of

the data. Groupthink is minimized because team members independently examine the data prior to discussions with the team and an outside auditor serves as an additional check of the team's judgments. The consensus process relies on mutual respect equal involvement, and shared power (Hill et al., 1997).

The aim of qualitative research is not to generalize about the distribution of experiences or processes. Therefore, qualitative research makes no claim of the generalizability of findings to a specified larger population in a probabilistic sense. Rather, qualitative researchers are interested in the applicability of their findings, based on how the nature and processes involved in experiences generalize. Hence, the aim is to make logical generalizations to a theoretical understanding of a similar class of phenomena, for which atypical settings, or cases, may be as relevant as typical ones. The applicability of findings from one setting to another depends on the likeness between the bodies of knowledge, or contexts, as judged by those wishing to apply the findings. Hence, the presented description of the research setting, findings and interpretations needs to provide sufficient detail for others to determine the applicability of the research findings to their own settings. The onus is on qualitative

researchers to provide an adequate detailed description, while the onus is on the reader to evaluate its applicability in another setting (Fossey et al., 2002).

6.2.4 Strength and weaknesses

The studies included in this thesis have several strengths. The work was financially supported by Stavanger University Hospital and was independent of sponsorship from the pharmaceutical industry. Additionally, it illuminates a set of complex research questions from multiple perspectives. This is mainly due to the mixed method research approach. Coherent and convergent findings across methodologies strengthen study findings (Alvesson & Skoldberg, 2009). The sample is judged to be fairly representative of patients and psychiatrists in the Norwegian healthcare system. The sample was well characterized and reliability testing was performed for central themes. The first author was not a part of the ongoing clinical treatment setting. Interviews conducted by a neutral person resulted in participants feeling able to talk more freely about their experiences.

Finally, five authors, from different professions (pharmacist, psychiatrist, psychiatric nurse, psychologist), performed analysis independently. This increase the reliability and validity of our results.

However, the studies have some weaknesses. The sample in Study 2 consisted of patients who gave informed consent to participate in a comprehensive research project, TIPS. This means that patients that deny all treatment did not consent to participate in the study.

Recency of experience is an important factor to think about when selecting participants. The more distant the experience, the more likely participants may not remember the actual experience, but to fill in the blanks in memory to fit with how they choose to remember the event. Memory failure and common distortions are well documented (Hill et al., 1997). When retrospective descriptions are obtained from interview as raw data there is a possibility of error or deceit on the part of the participant. However they are not crucial as the interest is in how the participant experienced situations even if they come through memory modes, because the manner in which situations stand out in memory and are remembered by participants when interviewed is important in phenomenological research (J. Smith, 2015).

7. Implications for research and practice

This study provides valuable information on patient adherence and how it could be improved. The study highlighted that patients want to be treated as a unique person with an illness and with individual needs; patients have a need to collaborate with professionals and shared in decision making regarding their medication; timely information and importantly health care givers should be more aware about admission routines by using more time and resources. Although most of these messages are not new, they are relevant and still need to be emphasized. More patient-centered interventions should be developed in clinical practice to respond to the wide variety of individual needs and life situations. Future research should also aim to incorporate perspectives and views from the patients close relations as parents, spouses and children because managing psychotic symptoms including adherence to medication affects more than the individual patients but the whole family.

It is very important to follow the treatment algorithm in clinical practice, on the assumption that these algorithms are based on evidence based research. In this study, one focus has been on a local system adherence to an

antipsychotic medication protocol; the results from this study can be used to future research aimed at developing and measure system or organizational fidelity to national medication guidelines. Further on the power of social media and its role in feeding stigma is underestimated. Psychiatrists must participate more actively in the societal debate to reduce the gap between science and the societal image of mental disorders.

8. Conclusion

Non-adherence to medication treatment is frequent across all types of medicine and despite treatment advances non-adherence issue remain. However, patients with psychotic disorders pose additional challenges that increase the risk for and frequency of non-adherence. Although of great importance for treatment outcome, clinicians generally spend too little time discussing and addressing attitudes and behaviours towards adherence. Importantly, the experience of admission to a psychiatric unit might in itself have a significant impact on adherence, and healthcare givers should be more aware about it.

More clinical and research emphasis should be placed on finding better solutions for the identification and management of treatment non-adherence, particularly in patients with psychotic disorders.

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Appendix A

Paper I

Appendix B

Paper II

Appendix C

Paper III

Appendix D

Approval from REK for TIPS II

Appendix E

The Norwegian Data Inspectorate

Appendix F

Approval from REK for Study II