Continuity of Pharmaceutical Care for Psychiatric Patients

Heshu Abdullah-Koolmees

Cover (illustration): Anne Koolmees & Heshu Abdullah-Koolmees
Cover design: Loes van den Berg (www.printpaint.nl)
Layout inside work: CO2 PREMEDIA BV
Printed by: Gildeprint – The Netherlands

The research presented in this thesis was performed at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University.

CIP-gegevens Koninklijke Bibliotheek, Den Haag
Abdullah-Koolmees, H.
Continuity of Pharmaceutical Care for Psychiatric Patients
Thesis Utrecht University – with ref. – with summary in Dutch
ISBN/EAN: 978-94-6108-956-4

Continuity of Pharmaceutical Care for Psychiatric Patients

Continuïteit van Farmaceutische Zorg voor Psychiatrische Patiënten

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar te
verdedigen op woensdag 29 april 2015 des middags te 2.30 uur

door

Heshu Abdullah-Koolmees

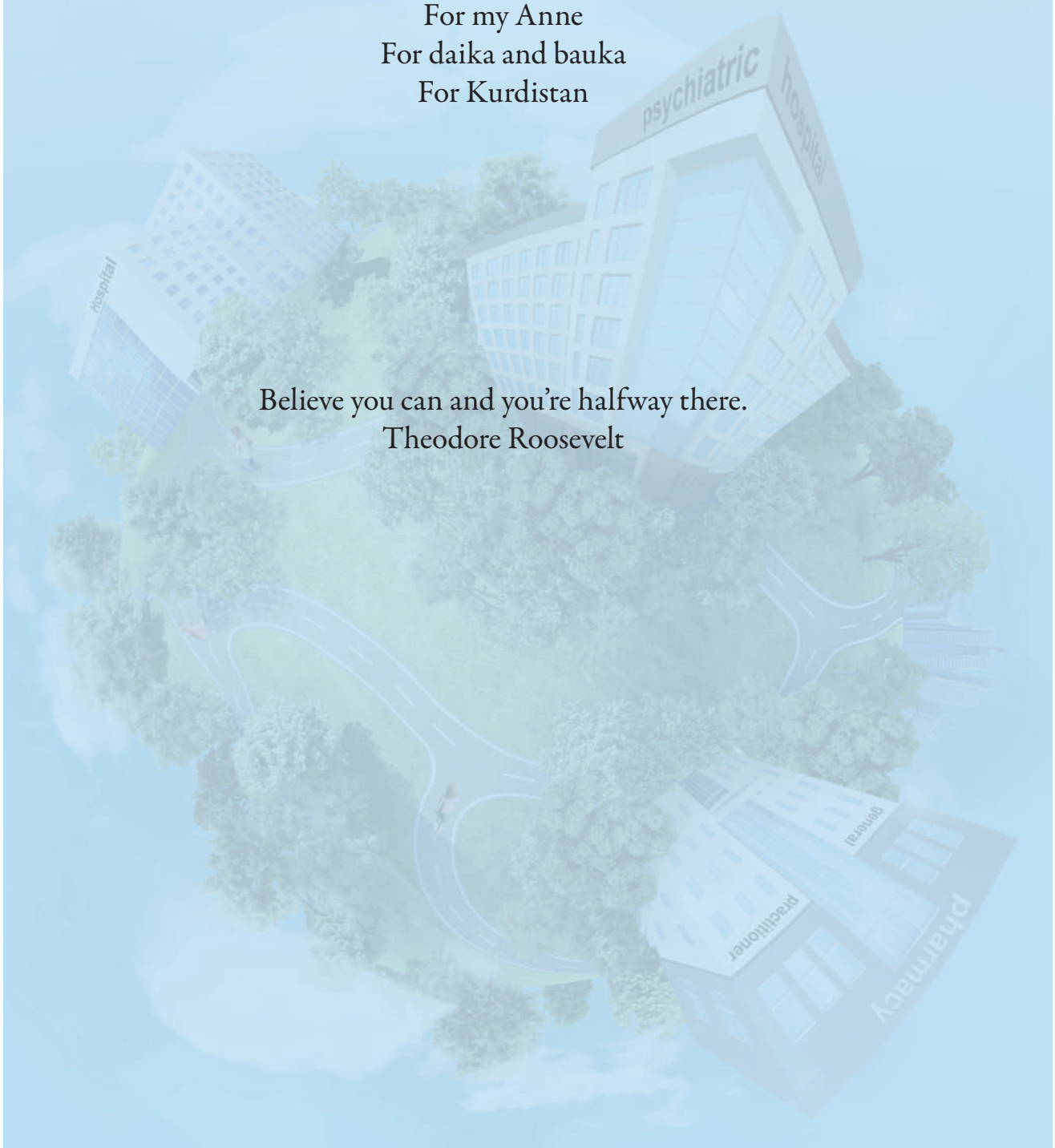
geboren op 12 april 1985 te Sulaimanja, Irak

Promotor: Prof. dr. A.C.G. Egberts

Copromotoren: Dr. E.R. Heerdink

Dr. H. Gardarsdottir

For my Anne
For daika and bauka
For Kurdistan



Believe you can and you're halfway there.
Theodore Roosevelt

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1
Introduction

Background

Psychiatric diseases are common. Already in 2001, the World Health Organization reported that a quarter of the world population is affected by psychiatric diseases at least once in their life. (1,2) In addition, the year-prevalences of the most common psychiatric diseases currently range from ~1% for schizophrenia and 1-9% for mood disorders to 2-18% for anxiety disorders. (2-4) As the mean age of the world population increases, the burden of psychiatric diseases is expected to increase even further. (5,6) Psychiatric diseases are known to have a great impact on a patient's health and his/her quality of life. (5,7-9) For example, psychiatric diseases such as schizophrenia and depression are associated with high individual mental strain, impaired psychosocial function, difficulties to cope with daily life activities and impaired school and occupational performances. Almost 15% of the total Disability Adjusted Life Years (DALYs) in European countries are accountable to psychiatric conditions. (5) Psychiatric diseases are also known to have an impact on national healthcare services, since psychiatric diseases require for example the arrangement of specialized healthcare services, accessible and adapted educational programs, incentives to help patients finding a job, and housing enabling patients to live and be active in the community. (10,11)

The medical treatment of psychiatric patients is often a combination of pharmacological and non-pharmacological interventions such as psycho-education, social support, and counseling. However, pharmacotherapy is frequently the first option used to stabilize a psychiatric disease. (10,11) As a result, a high proportion of psychiatric patients are using at least one psychiatric medication. Psychiatric medications are known to frequently cause (somatic) side effects because of their effect on a wide range of receptors of the central nervous system. For example, some antipsychotics and antidepressants are known to cause weight gain, and lithium may cause kidney and thyroid related problems. (3,12-18) Apart from the somatic side effects caused by psychiatric medication, psychiatric patients are also at an increased risk for somatic comorbidity. As a consequence, the use of somatic medication is more common in psychiatric patients than in the general population. For example, the prevalence of diabetes in psychiatric patients is 1.5-2 times higher than in the general population. (3,12,13,19) Because psychiatric patients are at an increased risk for somatic disease on top of the psychiatric disease they are already suffering from, their life expectancy is generally shorter. The mean age of patients with severe mental illness is estimated to be 10-25 years shorter than that of the general population. (9)

Although there are many studies on the prevalence of somatic diseases in psychiatric patients, little is known about the type, extent, quality and continuity of prescribing and use of somatic medication in psychiatric patients.

Continuity of Psychiatric and Somatic Pharmaceutical Patient Care

The effective treatment of a psychiatric disease, its (somatic) side effects and any concurrent somatic diseases is important for the patient's overall health and wellbeing. The chronic nature of many psychiatric and concurrent somatic diseases implies that the continuity of both psychiatric and somatic pharmaceutical care requires particular attention. (20-32) Pharmaceutical patient care includes several aspects of medication use such as careful monitoring of prescribing, the use and the effects of medication used to treat psychiatric and somatic disease, the occurrence of drug related problems, attitudes, concerns and knowledge about medication. (33) In this thesis, we focus on one aspect of pharmaceutical care being the continuation of prescribing across settings. Discontinuity of prescribing may be intended (e.g. stopping a drug due to a severe side effect) or non-intended. Any non-intended discontinuity of psychiatric and somatic pharmaceutical care needs to be observed and factors associated with the discontinuity of pharmaceutical care should be closely monitored and acted upon. Such factors may relate to patient characteristics, disease characteristics and characteristics of health care settings.

Patient Characteristics

Adherence to psychiatric and somatic medication is decisive for the continuity of pharmaceutical patient care in psychiatric patients. As adequate adherence to any medication is determined by both the willingness as well as the ability of the patient to take a medicine, both aspects should be carefully considered when prescribing medications to psychiatric patients and when monitoring the overall patient's health.

Currently, it is generally acknowledged that when assessing adherence to medication three phases of treatment need to be considered, namely the initiation (does the patient decide to start the prescribed treatment), implementation/execution (does the patient use the medications as prescribed; dose, frequency, times), and discontinuation (does the patient decide to (temporarily) stop treatment) of medication use. Factors that are known to be influencing adherence, i.e. patient behavior, are amongst others the patient's acceptance of his/her need to be treated with the medications prescribed, the amount of knowledge on the disease characteristics, knowledge about benefits and risks of the medication, distrust in the medication's effectiveness, fear of side-effects, the complexity of the medication dosing regimen and patient-health care provider relations. Practical reasons such as ease of use, the frequency and number of dosages and the formulation characteristics (e.g. size, taste, dosage form) may further influence the patient's overall adherence to both psychiatric and somatic medication. (34-44) The latter aspect may be especially important in children and the elderly, as they may have greater difficulties

swallowing tablets and capsules, and as they may need to be treated with lower doses requiring fractions of the commercially available formulations. (45,46)

Disease Characteristics

The characteristics of the psychiatric disease may have an impact on the continuity of pharmaceutical patient care through its effect on patient behavior. For example, some patients with schizophrenia may not accept that they are actually ill or they may think that the psychiatric medication is threatening their life. As a result, they may not acknowledge the need to take any medication, or they may be overly concerned about the medications prescribed resulting in suboptimal adherence to their medications. As another example, depression episodes can be accompanied with apathy resulting in suboptimal or even the complete lack of patient adherence. Patients may also suffer from manic episodes where they are feeling better/cured and consider that there is no longer any need to take their psychiatric medications. (30,36-44,47,48)

Because of low adherence with antipsychotics, patients with psychotic disorders are frequently treated with long-acting medication (e.g. intramuscular depot injections). This is because long-acting antipsychotics may only need to be given once per 2 to 4 weeks, often by a health care professional and not the patient himself/herself as is common for patients suffering from schizophrenia. (7,48)

The characteristics of the psychiatric disease may also have an impact on the continuity of pharmaceutical patient care through the fact that the psychiatric condition may grow worse and patients can suffer from relapses. When the disease worsens, patients feel ill and may need to be hospitalized. In such cases, patients may be unable to provide adequate information to the health care providers about the medication they are using (or should be using) at the time of hospitalization. Subsequently, the transition from the outpatient to the inpatient setting may result in (temporary) unintended discontinuation of pharmaceutical patient care. (47)

Health Care Settings

Any discontinuity of pharmaceutical patient care may also be related to characteristics of (national) healthcare systems. When patients are relocated from an outpatient to an inpatient setting (hospital, nursing home, mental institution) and vice versa or when patients are relocated between different inpatient settings, unintended discontinuation of pharmaceutical care may occur because a lack of information on a patient's medication history. For example, Karapinar-Çarkit et al. and Stuffken et al. reported that somatic medications are more often discontinued when patients are admitted to general hospitals.

(49-59) Also, Stuffken et al. reported that the continuity of psychiatric medication is at risk when patients are hospitalized for a somatic disease. (59) The currently available studies on the continuity of pharmaceutical patient care mainly report on the changes of general care when patients are admitted to or discharged from a general hospital. The studies conducted in psychiatric patients generally focus on the continuation of psychiatric medication, but not on the continuation of somatic medication. (21,42,48,60-65) These show that psychiatric patients commonly discontinue psychiatric medication. However, studies on the overall continuity of pharmaceutical care in patients admitted to and discharged from a psychiatric hospital are scarce and fragmented. (21,42,48,60-65)

In psychiatric hospitals, patients may be at an increased risk for the discontinuation of somatic pharmaceutical patient care because health care providers are focusing on the patients' psychiatric disease and symptoms. Moreover, the health care professionals working in a psychiatric hospital may neither be trained to treat the wide variety of somatic diseases the patient may suffer from nor may they be able to manage the concurrent use of psychiatric as well as one or several somatic medications. Furthermore, psychiatric patients are subject to more transitions, which are known to increase the risk for the discontinuity of pharmaceutical patient care as has been explained before. For example, 13-60% of patients with schizophrenia or mood disorders are rehospitalized within twelve months after discharge. (66-68)

To assure the adequate continuity of both somatic and psychiatric patient care, it is essential that health care professionals working in both the primary and secondary care, as well as those involved in somatic and psychiatric diseases know who is responsible for which aspect of the patients' health. Therefore, documentation and exchange of information between the primary and secondary care and vice versa is essential.

Objectives

The overall objective of this thesis is to assess the continuation of pharmaceutical patient care, namely the prescribing aspects, in psychiatric patients. In order to realize this goal, the following three sub-objectives were defined:

- to determine the prevalence of somatic medication use in psychiatric patients;
- to assess the association between the change in health care setting and continuity of pharmaceutical patient care; and
- to assess the association between continuation of antipsychotic care and rehospitalization.

Outline of This Thesis

In Chapter 2 the focus is on investigating the prevalence and continuity of somatic care in psychiatric patients. Chapter 2.1 describes the prevalence of somatic medication use in hospitalized psychiatric patients on ten time points between 2006 and 2010 and changes in medication use. Chapter 2.2 explores discontinuation and switch of somatic medication during the first seven days of psychiatric hospitalization compared to the year before hospitalization and what the related factors are. Chapter 2.3 focuses on the quality of anticoagulant care in terms of anticoagulant treatment and factors related to discontinuation of patients' anticoagulant care during psychiatric hospitalization.

Chapter 3 focuses on continuity of psychiatric and somatic care for psychiatric patients. Chapter 3.1 explores discontinuation and other medication changes in use of psychiatric and/or somatic medication in patients discharged from a psychiatric hospital. In Chapter 3.2, we investigate the association between adherence to antipsychotics during three phases of medication use (initiation, implementation, and discontinuation) and rehospitalization during the first year after discharge. In Chapter 3.3 the risk of rehospitalization is predicted in patients treated with antipsychotics and discharged from a psychiatric hospital, using patient, disease and treatment characteristics, patients' beliefs and attitudes towards antipsychotic medication, and health care providers' expectations towards patients' adherence and probability of rehospitalization.

Finally, the findings of this thesis are discussed in Chapter 4 from a broader perspective.

References

(1) Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004;(420)(420):21-27.

(2) Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, et al. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004 Jun 2;291(21):2581-2590.

(3) American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. 2004;27(2):596-601.

(4) Nationaal Kompas Volksgezondheid. Schizophrenia and Anxiety disorders [Dutch]. 2014; Available at: www.nationaalkompas.nl. Accessed December, 30, 2014.

(5) Kaplan W, Virtz WJ, Mantel-Teeuwise A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World 2013 Update. 2013; Available at: www.who.int. Accessed November, 11, 2014.

(6) Rijksinstituut voor volksgezondheid en milieu. Volksgezondheid Toekomst Verkenning 1997. VII Health and care in the future. 1997 1997;ISBN 90 352 1873 6(VII Health and care in the future).

(7) European Medicines Agency, Science Medicines Health. Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia 2012; Available at: http://www.ema.europa.eu. Accessed December, 1, 2014.

(8) European Medicines Agency, Science Medicines Health. Guideline on clinical investigation of medicinal products in the treatment of depression 2013; Available at: www.ema.europe.eu. Accessed December, 1, 2014.

(9) World Health Organisation. Mental Health. 2014; Available at: www.who.int/mental_health/en/. Accessed December, 1, 2014.

(10) Trimbos-instituut. Trend report Metal Health Care 2012. Part 2A: acces and use of care. Mental Health Care in Primary Care. The rol of the general practitioner and psychologist. [Dutch]. 2012 2012;www.trimbos.nl/webwinkel, AF1223.

(11) van Dijk S, Knispel A, Nuijen J. Trimbos-instituut, Mental Health Care in tables. [Dutch]. 2010 2011;www.trimbos.nl/webwinkel, AF1109.

(12) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010 Jun;25 Suppl 2:S22-8.

(13) Iacovides A, Siamouli M. Comorbid mental and somatic disorders: an epidemiological perspective. Curr Opin Psychiatry 2008 Jul;21(4):417-421.

(14) Stoklosa J, Ongur D. Rational antipsychotic choice: weighing the risk of tardive dyskinesia and metabolic syndrome. Harv Rev Psychiatry 2011 Sep-Oct;19(5):271-276.

(15) Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr 2011 Nov 8:1-10.

(16) Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 1999 Dec;21(6):449-456.

(17) Shim JC, Shin JG, Kelly DL, Jung DU, Seo YS, Liu KH, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry 2007 Sep;164(9):1404-1410.

(18) Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol 2012 Jun;32(3):309-316.

(19) Miller BJ, Paschall CB,3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. Psychiatr Serv 2006 Oct;57(10):1482-1487.

(20) Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ 1998 Oct 31;317(7167):1181-1184.

(21) Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008 Apr 30;8:32.

(22) Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004 Aug;55(8):886-891.

(23) Law MR, Soumerai SB, Ross-Degnan D, Adams AS. A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. J Clin Psychiatry 2008 Jan;69(1):47-53.

(24) dosReis S, Johnson E, Steinwachs D, Rohde C, Skinner EA, Fahey M, et al. Antipsychotic treatment patterns and hospitalizations among adults with schizophrenia. Schizophr Res 2008 Apr;101(1-3):304-311.

(25) Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 1997;23(4):637-651.

(26) Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007 Oct;23(10):2305-2312.

(27) Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008 Jan;34(1):173-180.

(28) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011 Jun;168(6):603-609.

(29) Jung SH, Kim WH, Choi HJ, Kang MH, Lee JS, Bae JN, et al. Factors affecting treatment discontinuation and treatment outcome in patients with schizophrenia in Korea: 10-year follow-up study. Psychiatry Investig 2011 Mar;8(1):22-29.

(30) Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res 2002 Oct 1;57(2-3):209-219.

(31) Herings RM, Erkens JA. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. Pharmacoepidemiol Drug Saf 2003 Jul-Aug;12(5):423-424.

(32) De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol 2014 Oct;78(4):684-698.

(33) World Health Organization. The Role of the Pharmacist in the Health Care System. Available at: http://apps.who.int/medicinedocs/en/d/Jh2995e/2.2.html. Accessed February, 16, 2015.

(34) Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One 2013 Dec 2;8(12):e80633.

(35) Robinson DG. Medication adherence and relapse in recent-onset psychosis. Am J Psychiatry 2011 Mar;168(3):240-242.

(36) Geers HC, Bouvy ML, Heerdink ER. Influence of therapeutic complexity on medication adherence in the Netherlands. Arch Intern Med 2011 May 9;171(9):864-5; author reply 865.

(37) Karow A, Czekalla J, Dittmann RW, Schacht A, Wagner T, Lambert M, et al. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. J Clin Psychiatry 2007 Jan;68(1):75-80.

(38) Karow A, Pajonk FG. Insight and quality of life in schizophrenia: recent findings and treatment implications. Curr Opin Psychiatry 2006 Nov;19(6):637-641.

(39) Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006 Mar;83(1):53-63.

(40) Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008 Jan;69(1):106-113.

(41) Hugenholtz GW, Heerdink ER, Meijer WE, Stolker JJ, Egberts AC, Nolen WA. Reasons for switching between antipsychotics in daily clinical practice. Pharmacopsychiatry 2005 May;38(3):122-124.

(42) van Geffen EC, van Hulten R, Bouvy ML, Egberts AC, Heerdink ER. Characteristics and reasons associated with nonacceptance of selective serotonin-reuptake inhibitor treatment. Ann Pharmacother 2008 Feb;42(2):218-225.

(43) van Geffen EC, Heerdink ER, Hugtenburg JG, Siero FW, Egberts AC, van Hulten R. Patients' perceptions and illness severity at start of antidepressant treatment in general practice. Int J Pharm Pract 2010 Aug;18(4):217-225.

(44) van Geffen EC, Hermsen JH, Heerdink ER, Egberts AC, Verbeek-Heida PM, van Hulten R. The decision to continue or discontinue treatment: experiences and beliefs of users of selective serotonin-reuptake inhibitors in the initial months--a qualitative study. Res Social Adm Pharm 2011 Jun;7(2):134-150.

(45) van Riet-Nales DA, de Neef BJ, Schobben AF, Ferreira JA, Egberts TC, Rademaker CM. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013 Sep;98(9):725-731.

(46) Notenboom K, Beers E, van Riet-Nales DA, Egberts TC, Leufkens HG, Jansen PA, et al. Practical Problems with Medication Use that Older People Experience: A Qualitative Study. J Am Geriatr Soc 2014 Dec;62(12):2339-2344.

(47) Procyshyn RM, Barr AM, Brickell T, Honer WG. Medication errors in psychiatry: a comprehensive review. CNS Drugs 2010 Jul;24(7):595-609.

(48) Boden R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res 2011 Dec;133(1-3):36-41.

(49) Stuffken R, Egberts TC. Discontinuities in drug use upon hospital discharge. Pharm World Sci 2004 Oct;26(5):268-270.

(50) Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in the Netherlands. Ann Pharmacother 2008 Jul;42(7):933-939.

(51) Karapinar-Carkit F, Borgsteede SD, Zoer J, Smit HJ, Egberts AC, van den Bemt PM. Effect of medication reconciliation with and without patient counseling on the number of pharmaceutical interventions among patients discharged from the hospital. Ann Pharmacother 2009 Jun;43(6):1001-1010.

(52) Karapinar F, van den Bemt PM, Zoer J, Nijpels G, Borgsteede SD. Informational needs of general practitioners regarding discharge medication: content, timing and pharmacotherapeutic advice. Pharm World Sci 2010 Apr;32(2):172-178.

(53) Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005 Aug 30;173(5):510-515.

(54) Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care--a large-scale follow-up study. Eur J Clin Pharmacol 2007 Aug;63(8):783-790.

(55) Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012 May;73(5):691-705.

(56) Stuffken R, van Hulten RP, Heerdink ER, Movig KL, Egberts AC. The impact of hospitalisation on the initiation and long-term use of benzodiazepines. Eur J Clin Pharmacol 2005 Jun;61(4):291-295.

(57) Uitvlugt EB, Siegert CEH, Oosterhof P, Janssen MJA, Nijpels G, Karapinar-Çarkıt F. Medication information transfer on hospital discharge: insufficient implementation in daily practice. PW wetenschappelijk platform 2014 December 12;8(12):222-8.

(58) Karapinar-Carkit F, van Breukelen BR, Borgsteede SD, Janssen MJ, Egberts AC, van den Bemt PM. Completeness of patient records in community pharmacies post-discharge after in-patient medication reconciliation: a before-after study. Int J Clin Pharm 2014 Aug;36(4):807-814.

(59) Stuffken R, Heerdink ER, Souverein PC, Egberts AC. The association between hospitalization and continuity of psychotropic drug use. 2013;7(7/8):88-93.

(60) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.

(61) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia. Am J Psychiatry 2011 Mar 1.

(62) Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000 Feb;51(2):216-222.

(63) Berger A, Edelsberg J, Sanders KN, Alvir JM, Mychaskiw MA, Oster G. Medication adherence and utilization in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: a retrospective cohort study. BMC Psychiatry 2012 Aug 2;12:99-244X-12-99.

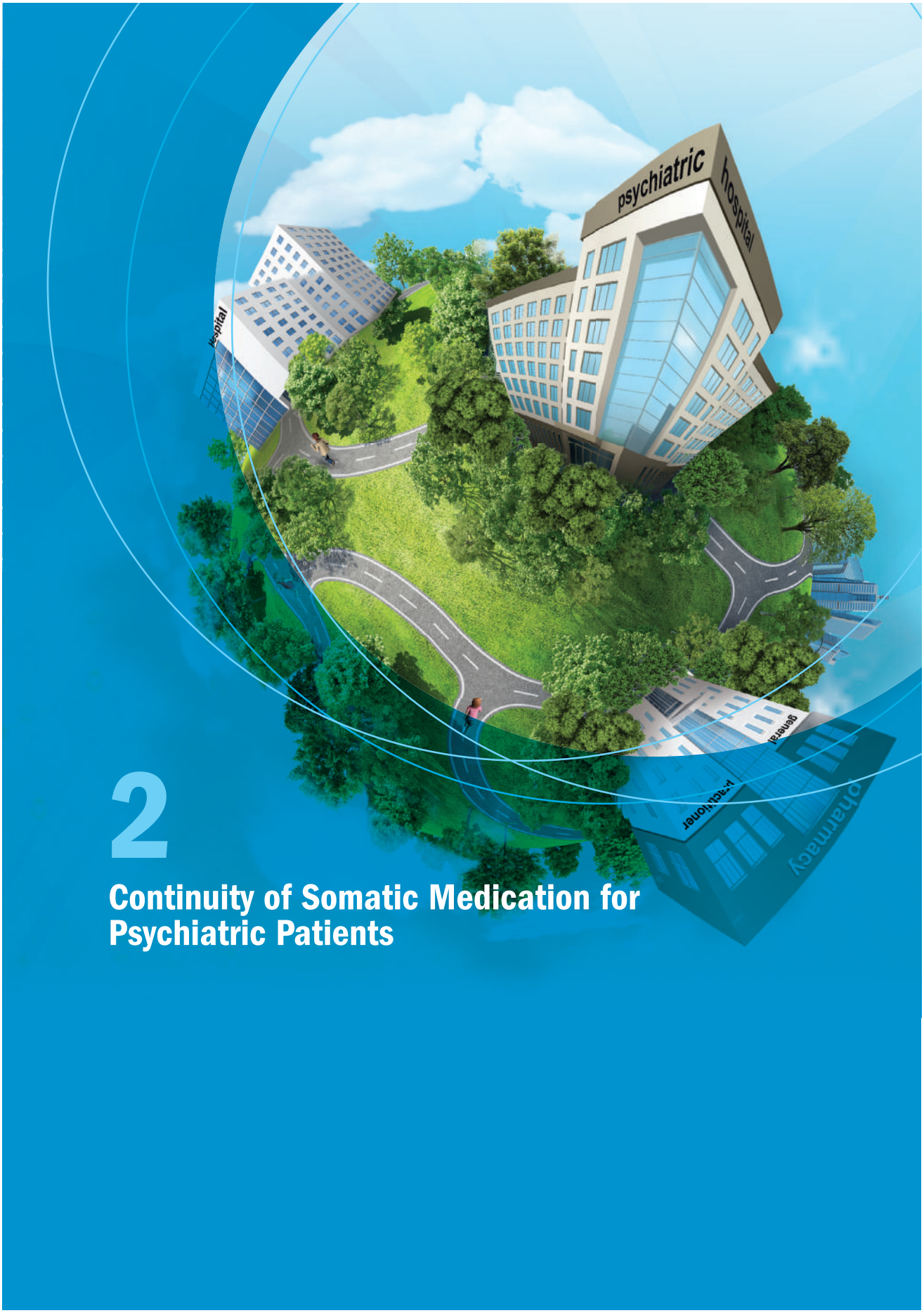
(64) Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand 2009 Jan;119(1):78-84.

(65) van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med 2006 Aug 14-28;166(15):1666-1667.

(66) Borckardt JJ, Madan A, Barth K, Galloway S, Balliet W, Cawley PJ, et al. Excess health care service utilization and costs associated with underrecognition of psychiatric comorbidity in a medical/surgical inpatient setting. Qual Manag Health Care 2011 Apr-Jun;20(2):98-102.

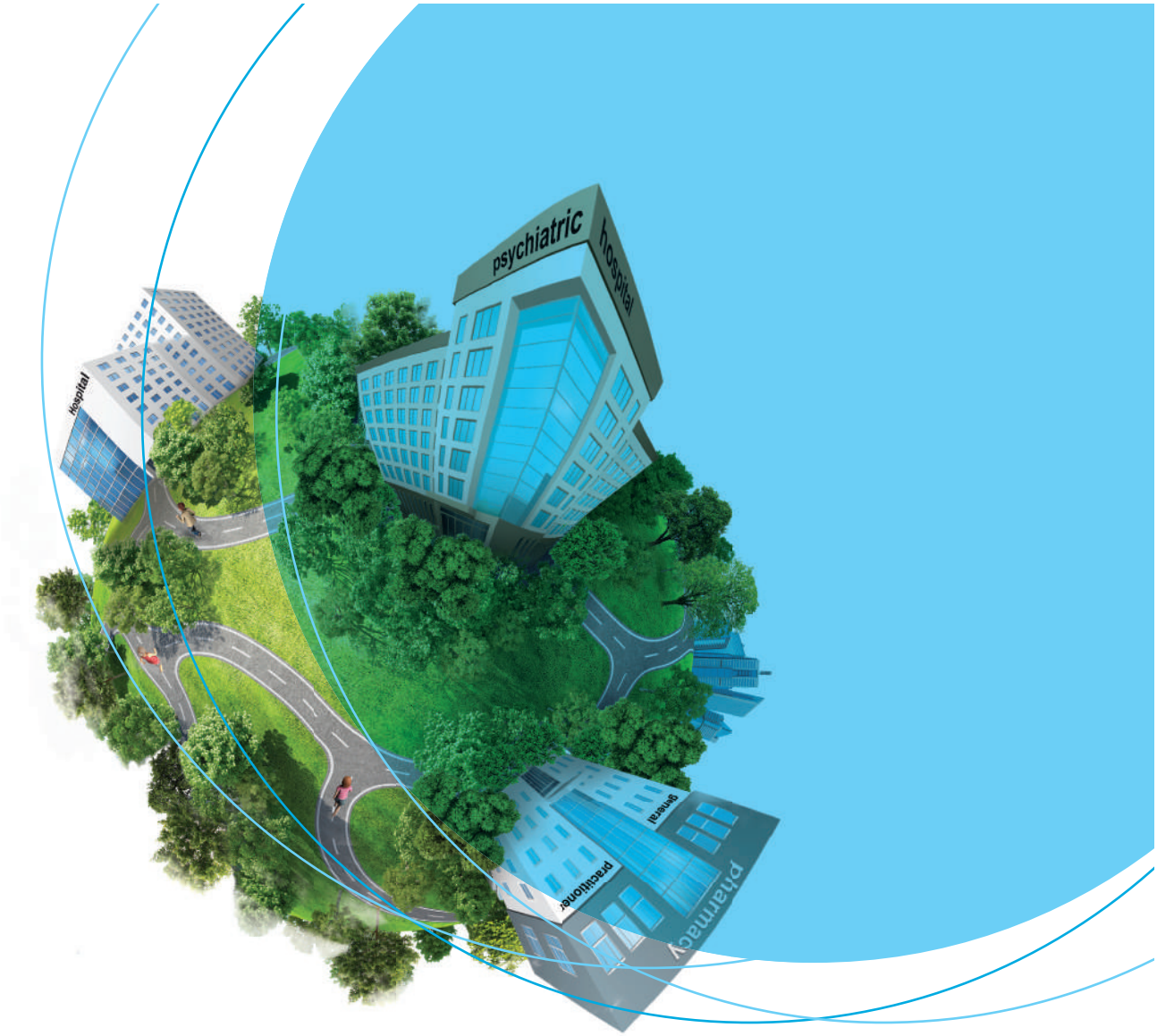
(67) Zhou Y, Rosenheck RA, Mohamed S, Fan N, Ning Y, He H. Retrospective assessment of factors associated with readmission in a large psychiatric hospital in Guangzhou, China. Shanghai Arch Psychiatry 2014 Jun;26(3):138-148.

(68) Vigod SN, Kurdyak PA, Dennis CL, Leszcz T, Taylor VH, Blumberger DM, et al. Transitional interventions to reduce early psychiatric readmissions in adults: systematic review. Br J Psychiatry 2013 Mar;202(3):187-194.



2

Continuity of Somatic Medication for Psychiatric Patients



2.1

Prevalence of Medication Use for Somatic Disease in Institutionalized Psychiatric Patients

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Pharmacopsychiatry 2013; 46:274-280

Abstract

Background

Psychiatric patients may use medications for their psychiatric condition as well as for treating concurrent somatic diseases or somatic side effects of psychiatric medicines. The objective of this study was to estimate the prevalence of use of medication for somatic disease in institutionalized psychiatric patients and changes therein during 2006-2010.

Methods

A cross-sectional study in institutionalized psychiatric patients was performed. Medication use for somatic disease on ten time points between 2006 and 2010 was investigated and stratified by gender, age, psychiatric medication class, and the number of different psychiatric medication classes used.

Results

The prevalence of use of medication for somatic disease increased from 67.5% in 2006 to 76.9% in 2010. The median number of medications used for somatic disease per patient was 3 between 2006 and 2010. Approximately one-third (34.1%) of the patients received ≥3 medications intended for treating somatic disease in 2006 which increased to 46.3% in 2010. In 2010, the prevalence of medication use for somatic disease was highest for analgesics and antirheumatics (34.0%), acid and bowel related medication (25.6%) and anticholinergic medication (24.2%). Medication use for somatic disease was highest in patients ≥60 years (95.3%), patients treated with more than one psychiatric medication class (87.5%) and patients treated with mood stabilizers (90.6%).

Conclusions

Somatic medication use is high in institutionalized psychiatric patients. More attention is needed for co-use of psychiatric and somatic medications to prevent side effects, drug-disease or drug-drug interactions. More research is needed to investigate if somatic care is optimal in institutionalized psychiatric patients.

Introduction

Psychiatric patients may use medication for their psychiatric condition as well as for treating concurrent somatic diseases. De Hert and colleagues reported that 30% of patients in a psychiatric hospital had prescriptions for somatic medication in 1999-2003 and about 60% in 2007. (1) A study about drug interactions reported that psychiatric patients used also somatic medication such as cardiovascular medications (12.0%), dietary supplements (8.2%) and gastrointestinal medications (5.9%). (2) The common use of somatic medication can be related to a higher prevalence of somatic disease and symptoms in psychiatric patients. (1,3-5) For example, diabetes mellitus, obesity, gastrointestinal, cardiovascular, respiratory and skin diseases have been shown to be common in psychiatric patients which might result in higher prevalence of use of somatic medication in these patients when compared with the general population. (1,3-8) Use of somatic medication might also be due to association between psychiatric diseases with medically unexplained physical symptoms (MUPS). (9-15) In addition, psychiatric treatment and other medicines acting on the central nervous system often cause side effects which may be treated with somatic medication. (1-5,16-24)

During the past years the physical status of psychiatric patients has received more attention and guidelines have been made which aim to reduce side effects of psychiatric treatments, to improve physical health and to treat concurrent somatic diseases. (1,3,4,18-20,25-29) In addition to co-use of psychiatric and somatic medications in psychiatric patients due to co-existence of psychiatric and somatic symptoms and/or diseases, the psychiatric patient population is aging which is also accompanied by an increased prevalence of somatic disease. (2) The common co-use of psychiatric and somatic medication in psychiatric patients may lead to side effects, drug-disease or drug-drug interactions.

To assess whether treatment of somatic diseases is optimal in psychiatric patients, knowledge on the prevalence of medication for somatic disease is needed. The extent of use of medication for somatic disease by institutionalized psychiatric patients is unknown. The aim of the present study was to estimate the prevalence of use of medication for somatic disease in institutionalized psychiatric patients and changes therein during 2006-2010.

Materials and Methods

Setting and Study Population

The setting of this study was Altrecht Mental Health Care (Altrecht), a conglomeration of four psychiatric institutions in The Netherlands serving a population of 800,000 inhabitants. During the study period Altrecht had 945-1000 beds and provided both inpatient and outpatient care to patients with a wide range of mental diseases. (30)

Medication is provided to inpatients by the institute's hospital pharmacy. The hospital files contain information on unique patient number, gender, birth date, type of care (inpatient and outpatient), psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, edition IV (DSM-IV), Global Assessment of Functioning score (GAF score), start and end of admission and medication use. Data on medication use included for each patient the start and end date of use, type of medication used and dosage. Medication was coded according to the WHO ATC/DDD coding system. (31)

All patients institutionalized on one or more of ten defined time points between January 1, 2006 and December 31, 2010 were included in this retrospective cross-sectional study, including patients discharged on the defined time points. The study was approved by the institution's scientific board and performed in accordance with the Code of Conduct for the use of data in Health Research of The Federation of Dutch Medical Scientific Societies.

Outcome

The outcome of this study was the prevalence of use of medication for somatic disease in institutionalized psychiatric patients. Prevalence of use of medication for somatic disease was assessed for the third Wednesday of April and October from 2006 till 2010 (i.e. April 19, 2006; October 18, 2006; April 18, 2007; October 17, 2007; April 16, 2008; October 15, 2008; April 15, 2009; October 21, 2009; April 21, 2010 and October 20, 2010). The third Wednesday of April and October were chosen because they did not fall in the summer holiday time. Wednesday is also in the middle of the working week with all the prescriptions of the weekend processed. Additionally, number of potential drug-drug interactions and number of patients with potential drug-drug interactions were assessed for the last time point, October 20, 2010.

Information on all prescribed medication of patients institutionalized at Altrecht between January 1, 2006 and December 31, 2010 were extracted from the hospital data files. Patients were defined as user of medication when they had at least a single medicine prescription on the defined time point. Somatic medication was defined as all non-psychiatric medication. Drug-drug interactions were reconstructed by combining the software G-standard of October 2010 and medications used on time point October 20, 2010. G-standard is an evidence-based professional guideline for the management of drug-drug interactions, developed and also maintained by the Scientific Institute of Dutch Pharmacists. Drug-drug interactions are classified for potential clinical relevance scale in A to F categories, from not very serious to potentially lethal and for evidence in 0 to 4 from not proven to very well proven. (32)

Data Analysis

The overall prevalence of use within each specific medication class was assessed on each time point between 2006 and 2010. The median number of medications for somatic

disease received per patient was also estimated (ATC fifth level). All medications with a frequency of ≥1.9 per 100 prescriptions were investigated between January 1, 2006 and December 31, 2010. The medications were classified per indication. For an overview of the medication classes investigated, see Appendix. In addition, the group "any somatic medication" was investigated including all medications for somatic diseases. Prescriptions for contraceptives, dermatologicals without an active substance and other preparations without an active substance were excluded. The prevalence was stratified by gender, age group (<20 years; ≥20 to < 40 years; ≥40 to <60 years, and ≥60 years), use of psychiatric medication and number of different psychiatric medication used (no use of psychiatric medication, use of medication from one psychiatric medication class or use of medication from more than one psychiatric medication class). The psychiatric medication classes were divided into antipsychotics, mood stabilizers (lithium, carbamazepine, valproic acid and lamotrigine), anxiolytics and sedatives (incl. promethazine), antidepressants, and other psychotropics (psychostimulants, drugs used in addictive disorders and other). Psychiatric diagnoses were grouped by schizophrenia and psychotic disorders; bipolar disorders; depressive and anxiety disorders; delirium, dementia, amnestic and other cognitive disorders (cognitive disorders); substance-related disorders; other diagnosis and unknown diagnosis. The patient's psychological, social and occupational functioning was presented as mean GAF score (score 100-81, normal variants; 80-61, slight disability; 60-51, moderate disability and 50-1, serious disability). (33) Pearson's Chi square analysis was performed to compare the prevalence of use of medication for somatic disease on the different time points using the most recent point October 20, 2010 as a reference. The frequency of drug-drug interactions was assessed as number of patients that had at least one potential drug-drug interaction and the number of prescribed medications that generated a potential drug-drug interaction. The interactions were classified in following categories: psychiatric medication interacting with other psychiatric medication (PP), psychiatric medication interacting with somatic medication (PS), and somatic medication interacting with somatic medication (SS). The nature of the most frequent potential drug-drug interactions with evidence (at least category 1) was investigated. All analyses were performed by using IBM SPSS Statistics, version 19.0.

Results

The total number of institutionalized patients on the time points ranged from 886 to 940 (Table 1). The mean age of the study population was between 43.0 years (SD: 18.9) in April 2010 and 44.9 years (SD: 19.1) in October 2009 and the mean patient's GAF score was between 44.8 (SD: 11.3) and 47.3 (SD: 11.3). The most common diagnoses among the patients were schizophrenia and psychotic disorders (47.2% in October 2009) and depressive and anxiety disorders (23.8% in October 2010).

Table 1: Patient characteristics at the different time points.

	Time points									
Characteristics	**April 2006**	**October 2006**	**April 2007**	**October 2007**	**April 2008**	**October 2008**	**April 2009**	**October 2009**	**April 2010**	**October 2010**
N	901	917	913	911	928	938	940	926	922	886
Age in years (SD)	43.9 (18.8)	44.4 (19.0)	44.4 (18.8)	44.5 (19.0)	44.5 (18.8)	44.1 (19.1)	43.9 (19.1)	44.9 (19.1)	43.0 (18.9)	43.8 (19.0)
Female (%)	51.6	48.3	47.4	46.9	46.7	46.6	48.9	47.6	47.4	44.8
Antipsychotics (%)	59.8	60.3	62.0	62.2	63.1	63.3	62.8	64.9	65.8	67.8
Antidepressants (%)	33.6	35.3	36.0	34.5	36.9	36.0	35.4	36.6	34.5	38.1
Mood stabilizers (%)	18.0	20.5	20.0	19.8	18.6	16.8	18.3	16.6	16.7	16.6
Anxiolytics and sedatives (%)	66.6	67.1	70.5	69.9	69.5	68.0	64.8	66.7	63.4	69.4
Other psychotropics (%)	3.7	3.7	4.7	4.9	5.9	6.2	6.7	7.3	6.8	8.2
GAF score* (SD)	45.8 (11.3)	47.3 (11.3)	47.2 (11.0)	46.4 (11.0)	46.7 (12.0)	45.6 (11.3)	46.1 (11.9)	45.7 (11.5)	44.8 (11.3)	45.4 (11.9)
Psychiatric diagnoses (DSM-IV):**										
Schizophrenia and psychotic disorders (%)	45.5	44.9	43.2	44.5	44.1	46.1	46.0	47.2	46.1	45.6
Bipolar disorders (%)	7.3	7.2	7.0	6.1	7.3	5.5	6.1	5.3	4.6	6.7
Depressive and anxiety disorders (%)	20.4	20.1	20.3	20.3	23.8	22.2	21.5	23.2	22.5	23.8
Cognitive disorders (%)	6.8	7.7	7.7	7.2	7.8	8.1	8.2	7.3	7.3	7.2
Substance-related disorders (%)	15.4	16.6	17.2	17.9	19.4	21.3	19.1	20.5	21.5	22.2
Other diagnosis (%)	26.7	26.0	26.3	23.9	28.7	27.8	29.4	27.8	29.6	27.0
Unknown diagnosis (%)	5.3	7.4	9.2	10.0	6.4	6.3	5.6	6.7	8.0	6.2

* GAF score: Global Assessment of Functioning score, which was measured in about 82 – 89% of the patients.

** Total exceeds 100% because of multiple diagnoses.

In October 2010 the majority of the patients (91.0%) used at least one medication of any type with 76.9% using at least one medication for somatic disease (Table 2). Almost half (44.8%) of the patients were female. The patients had a mean age of 43.8 years (SD: 19.0) and 37.1% of the patients were between ≥20 and <40 years of age. The most commonly used psychiatric medications in the study population were antipsychotics (67.8%) followed by anxiolytics and sedatives (69.4%) and antidepressants (38.1%). 12.5% of the patients used no psychiatric medication, 18.2% of the patients used medication from one psychiatric medication class and the rest (69.3%) used medication from more than one psychiatric medication class.

Prevalence of use of medication for somatic disease varied from 67.5% to 76.9%, with the highest prevalence in October 2010 and lowest in April 2006. The median number of medications used for a somatic disease per patient stayed stable at 3 between April 2006 and October 2010 (Figure 1). However, the proportion of patients using ≥3 somatic medications increased from 34.3% in April, 2006 to 46.2% in October, 2010.

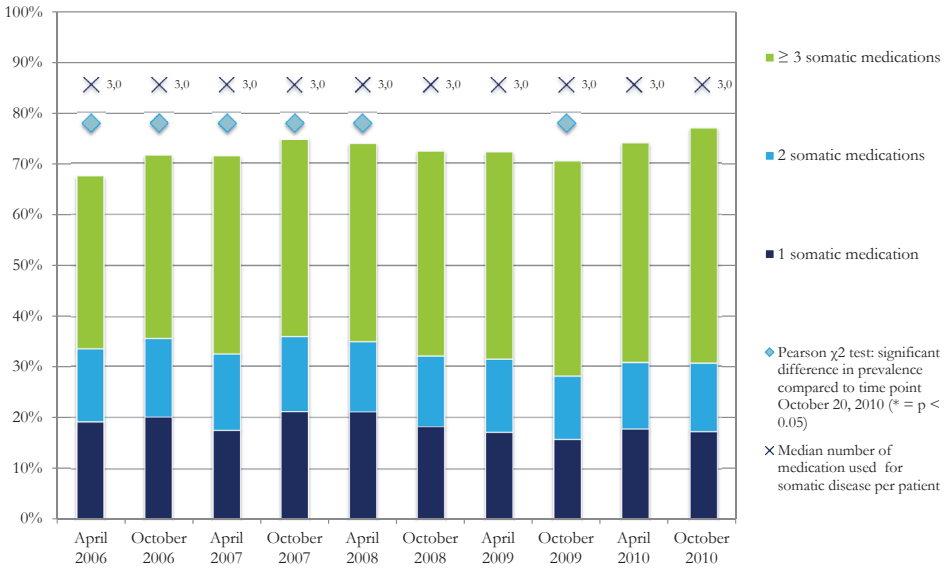


Figure 1: Proportions of patients using 1, 2 and ≥3 medications for somatic disease on each time point.

In October 2010, the prevalence of medication used for somatic disease was highest for analgesics and antirheumatics (33.9%), acid and bowel related medications (25.6%) and anticholinergic medications (24.0%). Overall, males had approximately equal prevalence of use of medication for somatic disease as females (76.9% vs. 76.8%). However, males more frequently got dispensed antidiabetics, systemic antifungals and antibiotics, vitamins, lipid lowering medications, anticholinergic medications and dermatologicals while females more often used acid and bowel related medications, laxatives, cardiovascular

Table 2: Prevalence of drugs used on October 20, 2010 (overall and stratified). Colors of the stratified classes: Number of psychiatric medication classes used, gender and age groups: the darkest indicates the highest prevalence; Psychiatric medication classes: dark to light = highest to lowest prevalence.

Prevalence	Total patients (N)	Any somatic medication (%)	Acid & bowel related medications (%)	Laxatives (%)	Anti-diabetics (%)	Cardiovascular medications (%)	Lipid lowering medications (%)	Asthma and COPD medications (%)	Antihistamines (%)	Thyroid medications (%)	Systemic antifungals and antibiotics (%)	Analgesics and antirheumatics (%)	Vitamins (%)	Dermatologicals (%)	Anti-cholinergic medications (%)
Overall	**886**	76.9	25.6	23.3	11.1	22.2	11.1	12.9	3.4	5.6	3.0	34.0	11.3	21	24.2
Female	**397**	76.8	29.7	30.2	10.8	24.9	10.1	13.9	4.8	10.1	2.3	39.5	10.8	20.7	21.2
Male	**489**	76.9	22.3	17.6	11.2	20.1	11.9	12.1	2.2	2.0	3.7	29.4	11.7	21.3	26.6
Age < 20 years	**66**	48.5	3.0	13.6	1.5	0.0	1.5	9.1	4.5	0.0	0.0	10.6	0.0	12.1	3.0
Age ≥20 and < 40 years	**329**	64.7	16.4	13.7	3.3	7.2	4.0	8.5	4.6	1.2	2.1	21.0	4.6	17.6	23.4
Age ≥40 and <60 years	**300**	84.7	29.3	24.0	15.0	24.3	16.7	16.7	2.3	5.3	2.0	42.7	10.7	24.7	31.7
Age ≥60 years	**191**	95.3	43.5	41.9	21.5	52.9	17.8	15.7	2.6	15.7	7.3	50.8	27.7	24.1	20.9
No use of psychiatric medication	**111**	27.9	5.4	5.4	4.5	7.2	1.8	5.4	3.6	1.8	1.8	8.1	1.8	8.1	0.0
Use of medication from 1 psychiatric class	**161**	70.2	21.7	19.3	7.5	18.0	6.8	6.2	3.1	3.7	2.5	26.1	10.6	18.0	9.9
Use of medication from >1 psychiatric class	**614**	87.5	30.3	27.5	13.2	26.1	13.8	16.0	3.4	6.8	3.4	40.7	13.2	24.1	32.2
Antipsychotics	**601**	86.2	28.3	26.8	12.8	23.1	12.8	14.6	3.0	5.8	3.3	36.9	12.5	23.5	35.1
Antidepressants	**338**	85.5	38.2	30.2	14.2	29.3	16.0	14.5	3.6	8.0	2.7	42.6	13.3	22.5	20.1
Mood stabilizers	**147**	90.5	36.7	38.1	17.0	30.6	19.0	15.0	4.1	13.6	3.4	48.3	12.9	27.9	34.7
Anxiolytics and sedatives	**615**	86.8	29.6	27.6	13.5	26.5	13.5	15.4	3.7	6.8	3.1	41.1	13.8	24.4	31.9
Other psychotropic medications	**73**	79.5	28.8	16.4	9.6	23.3	11.0	17.8	4.1	1.4	6.8	43.8	9.6	27.4	16.4
Schizophrenia and psychotic disorders	**404**	83.9	21.8	23.5	12.1	18.6	10.9	12.9	2.0	5.0	2.5	33.7	11.9	26.2	41.3
Bipolar disorders	**59**	83.1	32.2	32.2	25.4	42.4	16.9	22.0	3.4	10.2	5.1	44.1	13.6	15.3	35.6
Depression and anxiety disorders	**211**	73.0	30.8	25.1	9.5	25.6	9.5	10.0	5.2	9.5	1.4	37.0	9.0	15.6	10.4
Cognitive disorders	**64**	96.9	46.9	42.2	20.3	59.4	21.9	9.4	3.1	9.4	3.1	59.4	31.3	26.6	6.3
Other or unknown diagnosis	**453**	71.1	24.7	19.2	7.1	16.6	8.4	13.7	4.2	2.6	2.6	32.0	10.2	18.5	17.9

medications, asthma and COPD medications, analgesics and antirheumatics, thyroid medications and antihistamines.

Patients of 60 years and older had the highest prevalence of use of medication for somatic disease (95.3%) and had also the highest prevalence of use of 9 out the 13 somatic medication classes (see Table 2). Patients treated with more than one psychiatric medication had the highest prevalence of use of medication for somatic disease compared to patients not using psychiatric medication and patients using medication from only one psychiatric medication class, except for the prevalence of antihistamines which was between 3.1 – 3.6% for all users. Patients not using any psychiatric medication had the lowest prevalence of any medication use for somatic disease (27.9%). Within the psychiatric medication classes, patients using mood stabilizers most frequently used a medication for somatic disease (90.5%) followed by patients using anxiolytics and sedatives (86.8%). Patients with cognitive disorders received a medication for somatic disease (96.9%) followed by patients with schizophrenia and psychotic disorders (83,9%) and patients with bipolar disorders (83.1%).

There were 659 potential drug-drug interactions detected. 285 of the 886 (32.2%) of the patients had at least one potential drug-drug interaction, with an average of 2.3 potential drug-drug interactions per patient. The most prevalent potential drug-drug interactions for these patients were the interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) excl. COXIBs and serotonergic working medications (34 times of 659 drug-drug interactions) and between rennin-angiotensin system (RAS) inhibitors and diuretics (22 times of 659 drug-drug interactions). The most counted drug-drug interaction was between anti-parkinson medications (e.g. anticholinergic medications) and antipsychotics (449 of 659 drug-drug interactions) however this is an intended combination. Generally anti-parkinson medications (e.g. anticholinergic medications) are prescribed to treat extrapyramidal side effects of antipsychotics. The frequency of potential drug-drug interactions for PP class was 13, for PS class 573, and for SS class 73. Table 3 shows most frequent potential drug-drug interactions with at least evidence of category 1.

Discussion

The prevalence of use of medication for somatic disease in institutionalized psychiatric patients is high compared to the general population. (34) The proportion of patients using ≥3 somatic medications increased between 2006 and 2010. The prevalence of medication use for somatic disease was highest for analgesics and antirheumatics, acid and bowel related medication and anticholinergic medication. Furthermore, patients ≥60 years, patients treated with more than one psychiatric medication class and patients treated with mood stabilizers had highest prevalence of medication use for somatic disease.

Table 3: Most frequent potential drug–drug interactions. Clinical relevance scale: A to F categories, from not very serious to potentially lethal. Evidence: 0 to 4 categories, from not proven to very well proven.

Drug-drug interactions	Potential clinical outcome	Evidence-relevance category	Frequency
SS class			
RAS inhibitors + diuretics	Hypotension	3B/D*	22
Beta blockers + NSAIDs	Decreased effectiveness of antihypertensive effect	3C	6
Digoxin + diuretics (causing low potassium levels)	Increased toxicity of digoxin	3A	5
Diuretics + NSAIDs	Decreased antihypertensive effect	3C	4
NSAIDs (excl. COXIBs) + corticosteroids	Gastrointestinal ulcer risk	3C	4
Acetylsalicylic acid + NSAIDs (excl. ibuprofen and COXIBs)	Gastrointestinal ulcer risk	3C	4
PS class			
NSAIDs (excl. COXIBs) + serotonergic medication	Gastrointestinal ulcer risk	2C	34
Lithium + diuretics	Side effects/toxicity due to increased lithium blood concentration	3D	5
PP class			
Pimozide + SSRIs (citalopram, escitalopram, fluoxetine, paroxetine and sertraline)	Pimozide blood concentration increases with increased risk of side-effects/toxicity	3A	6
Tricyclic antidepressants + SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)/trazodon/duloxetine	Risk of serotonine syndrome	3A/D/F*	4

* Evidence relevance category depends on which SSRI was used.
S: somatic.
P: psychiatric.

Our results are in line with the findings of De Hert and colleagues reporting that 60% of psychiatric patients had prescriptions for somatic medication in 2007. (1) In addition, Haueis and colleagues reported that cardiovascular medications, dietary supplements and gastrointestinal medications as most common medications for somatic use which is in agreement with our findings. (2) Although the high prevalence of medication for somatic use is likely caused by a high prevalence of somatic disease (1,3-8), the fact that somatic medication is used to treat side effects caused by psychiatric treatment and MUPS is likely to play a role. (1,3-5,9-14,16-24) Psychiatric medications acting on the central nervous system can cause side effects which could be treated by somatic medication such as the use of anticholinergic agents (e.g. biperiden) to treat extrapyramidal side effects of antipsychotic use. Another example is laxatives which are frequently prescribed to treat constipation caused by several psychiatric treatments like antidepressants and antipsychotics. The increase in prevalence of medication used for treating somatic

disease between 2006 and 2010 might also in parts be explained by the physical status of psychiatric patients which got more attention in the last years. (1,3,4,18-20,25-29) De Hert and colleagues showed that use of somatic medication doubled after physical health screening and monitoring protocol was implemented in a psychiatric hospital. (1)

Patients of 60 years and older had the highest prevalence of use of any medication for somatic disease, in addition to the highest prevalence of use in 9 out of 13 somatic medication classes. Higher age is accompanied with more somatic illness and psychiatric population is also aging which could be the reasons for these outcomes. (2) Patients using medication from more than one psychiatric medication class had the highest prevalence of medication use for somatic disease which might suggest that patients suffering from more psychiatric illness have more somatic disease.

Approximately half of the patients used three or more medications for somatic disease. Especially patients treated with more than one psychiatric medication are treated with multiple medications for their psychiatric and somatic diseases and are exposed to polypharmacy. Co-use of psychiatric medications and medication for somatic diseases can have clinical consequences for the patient and can lead to side effects, drug-disease or drug-drug interactions. (2,21-23,35,36) For example, about 42% of patients using antidepressants (e.g. SSRIs among antidepressants) used also analgesics and antirheumatics such as NSAIDs. Research has shown that this type of co-use can result in an increased risk of gastrointestinal adverse outcomes such as bleeding, especially when other bleeding risk factors are apparent such as high age or a history of earlier gastrointestinal bleeding. (37,38) Acid and bowel related medications which was also one of the most prevalent medications used by the institutionalized psychiatric patients, could be prescribed to prevent these side effects. Another example is the co-use of lithium with other medications. Patients using mood stabilizers (including users of lithium) had highest prevalence for cardiovascular medications (e.g. diuretics) and analgesics and antirheumatics such as NSAIDs. Lithium blood concentration is influenced by diuretics and NSAIDs and therefore has to be monitored as high concentrations could result in side effects and intoxications due to the narrow therapeutic range of lithium.

Polypharmacy management is important for effectiveness of therapy and for safety in these patients. (2,35,36) The psychiatrist is usually the primary treating physician of the psychiatric patients and is mainly responsible for treating the somatic diseases. Therefore health care professionals; like psychiatrists, pharmacists and general practitioners; need to share information and expertise for institutionalized psychiatric patients. Also after institutionalization information exchange is necessary when patients receive ambulatory care across primary and secondary care. As polypharmacy is known as the most important medication-related potential risk factor for medication-related hospitalizations, medication review is recommended for psychiatric patients on regular basis to prevent

potential medication-related problems, e.g. over- and underconsumption, side effects and drug-drug or drug-disease interactions. (39)

Although it has been shown that prevalence of somatic illness is higher in psychiatric patients than in the general population (1,3-8), this is the first study we are aware of assessing actual prevalence of medication use for somatic disease in institutionalized psychiatric patients. The institutions register all use of medications, including use of over the counter medication (e.g. paracetamol and NSAID's). The prevalence measured in this study induces the real situation of medication use. For some as-needed medication such as pain medications it is not possible to determine with certainty these were used because patients had prescriptions on the time points. On the other hand, earlier research showed that as-need medications are frequently administered and therefore are expected to be used by the patients. (40) Patients may have used over the counter medication which is not registered in the patient files and may cause an underestimation of the prevalence, although the number of these patients is expected to be low. Another limitation of our study is not knowing whether a medicine was used as a psychiatric medication or for a somatic indication. Some of the anti-epileptics are used as mood stabilizers. Therefore, we opted for defining a mood stabilizing medication class instead of an anti-epileptic class. It is not recorded in the database whether the prescriber knew if there was a potential interaction between the medication, thus if an interaction was intended or unintended. Drug-drug interaction between anti-parkinson medications (e.g. anticholinergic medications) and antipsychotics was most detected interaction. However, anti-parkinson medications are prescribed to treat side effects of antipsychotics and thus consciously combined. Our findings only apply to institutionalized psychiatric patients as data of outpatient settings and General Practice were not included in our study. Furthermore, this study was performed in one area in The Netherlands. However, the setting was a conglomeration of four institutions with each institution having its own prescribing policy and serving a population of 800,000 inhabitants.

Conclusions

In conclusion, somatic medication use is high in institutionalized psychiatric patients. More attention is needed for co-use of psychiatric and somatic medications to prevent side effects, drug-disease or drug-drug interactions. Health care providers should be aware of the consequences when use of several medications are combined which needs to be monitored and managed to improve their effectiveness and safety. More research is needed to investigate if somatic care is optimal in institutionalized psychiatric patients.

References

(1) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010 Jun;25 Suppl 2:S22-8.

(2) Haueis P, Greil W, Huber M, Grohmann R, Kullak-Ublick GA, Russmann S. Evaluation of drug interactions in a large sample of psychiatric inpatients: a data interface for mass analysis with clinical decision support software. Clin Pharmacol Ther 2011 Oct;90(4):588-596.

(3) American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. 2004;27(2):596-601.

(4) De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry 2011 Aug;199(2):99-105.

(5) Iacovides A, Siamouli M. Comorbid mental and somatic disorders: an epidemiological perspective. Curr Opin Psychiatry 2008 Jul;21(4):417-421.

(6) Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999 Aug;187(8):496-502.

(7) Miller BJ, Paschall CB,3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. Psychiatr Serv 2006 Oct;57(10):1482-1487.

(8) Mookhoek EJ, Van De Kerkhof PC, Hovens JE, Brouwers JR, Loonen AJ. Skin disorders in chronic psychiatric illness. J Eur Acad Dermatol Venereol 2010 Oct;24(10):1151-1156.

(9) Katsamanis M, Lehrer PM, Escobar JI, Gara MA, Kotay A, Liu R. Psychophysiologic treatment for patients with medically unexplained symptoms: a randomized controlled trial. Psychosomatics 2011 May-Jun;52(3):218-229.

(10) Simon GE, VonKorff M. Somatization and psychiatric disorder in the NIMH Epidemiologic Catchment Area study. Am J Psychiatry 1991 Nov;148(11):1494-1500.

(11) Walker EA, Roy-Byrne PP, Katon WJ. Irritable bowel syndrome and psychiatric illness. Am J Psychiatry 1990 May;147(5):565-572.

(12) Walker EA, Roy-Byrne PP, Katon WJ, Li L, Amos D, Jiranek G. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. Am J Psychiatry 1990 Dec;147(12):1656-1661.

(13) Andreski P, Chilcoat H, Breslau N. Post-traumatic stress disorder and somatization symptoms: a prospective study. Psychiatry Res 1998 Jun 15;79(2):131-138.

(14) Engel CC,Jr, Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for gulf war-related health concerns. Psychosom Med 2000 Nov-Dec;62(6):739-745.

(15) Deary IJ. A taxonomy of medically unexplained symptoms. J Psychosom Res 1999 Jul;47(1):51-59.

(16) Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 2011 Dec;21(6):517-535.

(17) Stoklosa J, Ongur D. Rational antipsychotic choice: weighing the risk of tardive dyskinesia and metabolic syndrome. Harv Rev Psychiatry 2011 Sep-Oct;19(5):271-276.

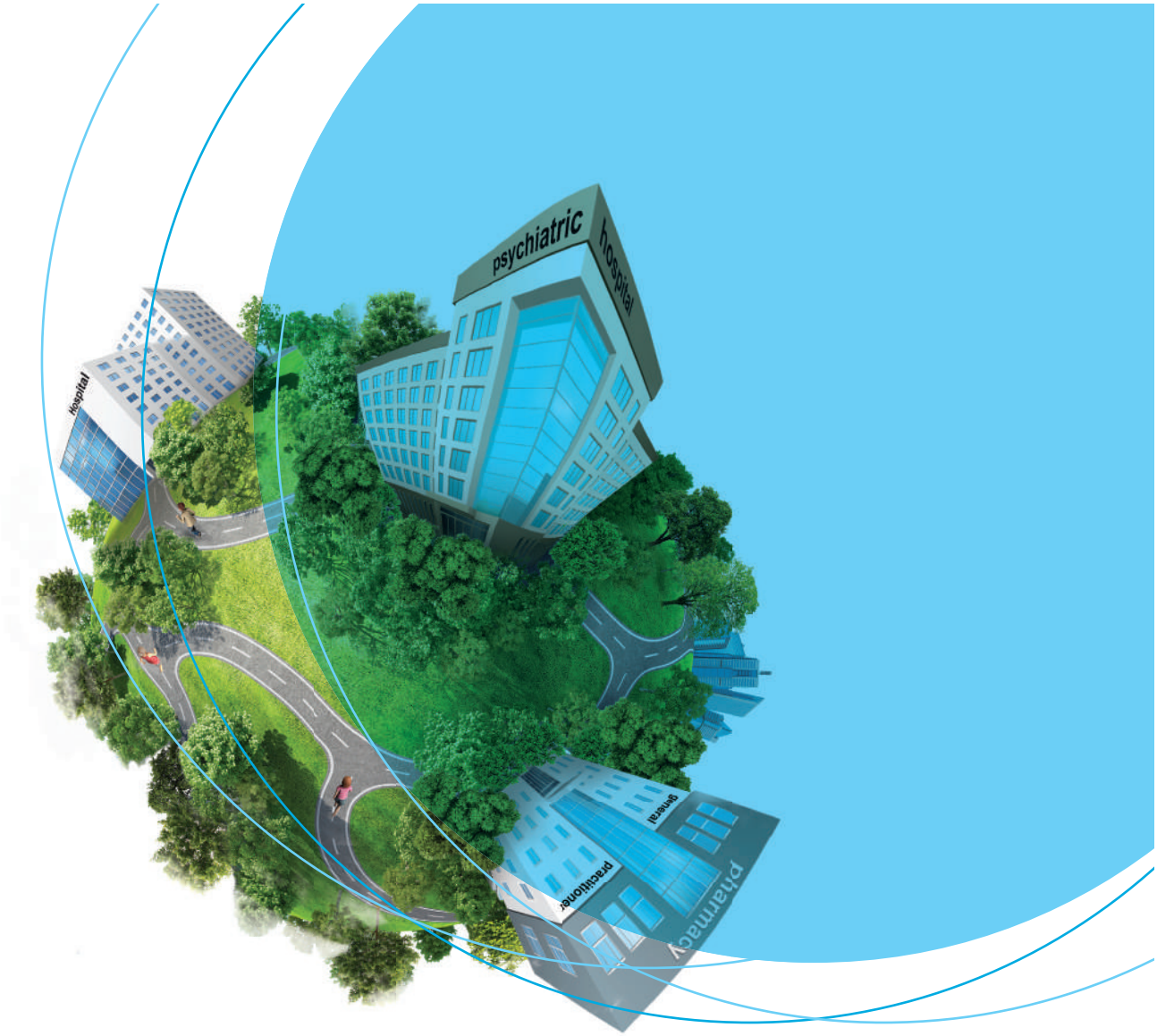
(18) Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. Drugs Aging 2012 Jan 1;29(1):15-30.
(19) Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr 2011 Nov 8:1-10.
(20) Crews MP, Howes OD. Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. Hum Psychopharmacol 2012 Jan;27(1):15-23.
(21) Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 1999 Dec;21(6):449-456.
(22) Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 2009 Jun;29(3):259-266.
(23) Shim JC, Shin JG, Kelly DL, Jung DU, Seo YS, Liu KH, et al. Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry 2007 Sep;164(9):1404-1410.
(24) Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol 2012 Jun;32(3):309-316.
(25) Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010 Jan;36(1):71-93.
(26) Citrome L, Yeomans D. Do guidelines for severe mental illness promote physical health and well-being? J Psychopharmacol 2005 Nov;19(6 Suppl):102-109.
(27) Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Schizophrenia Patient Outcomes Research Team (PORT). The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010 Jan;36(1):94-103.
(28) Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, “just the facts” 5. Treatment and prevention. Past, present, and future. Schizophr Res 2010 Sep;122(1-3):1-23.
(29) National Institute for Health and Clinical Excellence. Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. Nice, 2009; Available at: http://www.nice.org.uk/CG82quickrefguide.
(30) Altrecht MHC. Annual Report 2010 of Altrecht/Jaardocument 2010. 2010:19-94.
(31) WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. 2010.
(32) Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009 Aug;68(2):187-193.
(33) Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry. A review of three unidimensional scales (CGAS, GAF, GAPD). Eur Child Adolesc Psychiatry 2004 Oct;13(5):273-286.
(34) The Health Care Insurance Board. GIP databank. Accessed July 2, 2012.
(35) Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. Clin Interv Aging 2008;3(2):383-389.

(36) Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE. Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther 2004 Jul;76(1):85-96.
(37) Mort JR, Aparasu RR, Baer RK. Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammatory drugs: review of the literature. Pharmacotherapy 2006 Sep;26(9):1307-1313.
(38) Vandraas KF, Spigset O, Mahic M, Slordal L. Non-steroidal anti-inflammatory drugs: use and co-treatment with potentially interacting medications in the elderly. Eur J Clin Pharmacol 2010 Aug;66(8):823-829.
(39) Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in The Netherlands. Arch Intern Med 2008 Sep 22;168(17):1890-1896.
(40) Goedhard LE, Stolker JJ, Nijman HL, Egberts AC, Heerdink ER. Aggression of psychiatric patients associated with the use of as-needed medication. Pharmacopsychiatry 2007 Jan;40(1):25-29.

Appendix

Table: Medication classes and ATC code(s). (31)

Medication classes	ATC code(s)
Somatic	
Acid & bowel related medications	A02A, A02B and A03A
Laxatives	A06A
Antidiabetics	A10A and A10B
Cardiovascular medications	B01A, B02B, C01, C02A, C02C, C02K, C02N, C03, C04A, C07A, C08C, C08D and C09
Lipid lowering medications	C10A and C10B
Asthma and COPD medications	R03A and R03B
Antihistamines	R06A excl. R06AD02
Thyroid medications	H03A and H03B
Systemic antifungals and antibiotics	J01A, J01C, J01E, J01F, J01M, J01X and J02A
Analgesics and antirheumatics	N02A, N02B and M01A
Vitamins	A11C, A11D, A11G, A11H and B03B
Dermatologicals	D except D02A A – E/X
Anti-cholinergic medications	N04A
Any somatic medication	All ATC codes excl. D02A A – E/X, G02B, G03A, N05, N06, N07B, N03AF01, N03AG01, N03AX09 and R06AD02.
Psychiatric	
Antipsychotics (excl. lithium)	N05A excl. N05AN
Mood stabilizers (lithium. carbamazepine. valproic acid and lamotrigine)	N05AN, N03AF01, N03AG01 and N03AX09
Anxiolytics and sedatives (incl. promethazine)	N05B, N05C and R06AD02
Antidepressants	N06A
Other psychotropics	N06B, N07B, N03AX11 and N03AE01



2.2

Discontinuation of Somatic Medication During Psychiatric Hospitalization

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Annals Pharmacother 2014; 48:1415-1424

Abstract

Background

Psychiatric hospitalization can increase the risk of discontinuation of pharmacotherapy, which may negatively influence patients' health. To investigate the association between psychiatric hospitalization and discontinuation of somatic medication.

Methods

A retrospective crossover study was performed in patients admitted to a psychiatric hospital (index date), which got somatic medication dispensed during the three months prior to hospitalization. Discontinuation of somatic medication was investigated at the following time points: index date and, 3, 6, and 9 months before the index date. Relative risks (RR) with 95% confidence intervals (95% CI) of discontinuing somatic medication at the index date versus the time points before the index date were estimated using Cox regression.

Results

In all, 471 hospitalized patients were included in the study. 38.9% of the patients were discontinuers on the index date. RR for discontinuation of ≥1 somatic medication was 1.88 (95% CI = 1.55-2.27) at the index date compared with the other time points, and highest for patients <45 years (RR = 2.83; 95% CI = 1.92-4.18).

Conclusions

Psychiatric hospitalization was associated with an almost doubled risk of discontinuation of somatic medication. Future studies should address the influence of discontinuation of care on patients' health.

Introduction

Psychiatric patients usually use medication for their psychiatric diseases, but may also use medication for somatic diseases and symptoms. (1-8) In an earlier study, we found a prevalence of 67% to 77% for medication use for somatic diseases in institutionalized psychiatric patients. (1) The high prevalence of somatic medication use can partly be explained by a higher prevalence of several somatic diseases such as diabetes, obesity, and cardiovascular diseases in psychiatric patients compared with the general population. (2-8) Psychiatric patients may also use somatic medication to treat side effects of psychiatric medication. (2-5, 9-16)

Patient transitions between health care settings (eg. hospitalization) may intentionally or unintentionally result in increased risk of discontinuation of their pharmacotherapy. (17-19) For example, we showed that approximately a quarter of patients discontinued anticoagulant care (medication and/or international normalized ration [INR] monitoring) during psychiatric hospitalization. (19) Intentional changes could be related to the reason for hospitalization, changes in a patient's clinical condition, loss of indication after medication reconciliation, ineffectiveness of medication, or of side effects. (17) Unintentional discontinuation of pharmacotherapy can occur if there is insufficient communication between health care providers and/or with the patient on hospital admission. (17) The risk for unintentional discontinuation of patients' somatic medication may be greater than that of psychiatric medication when admitted to a psychiatric hospital, because psychiatric health care providers focus on the psychiatric disease(s) of the patient. Psychiatric health care providers are usually also more familiar with psychiatric medication than somatic medication. Discontinuation of care may negatively influence patients' health. The primary aim of this study was to investigate whether psychiatric hospitalization is associated with discontinuation of somatic medication and what the related factors are. The secondary aim was to assess whether psychiatric hospitalization is associated with switch of somatic medication within the same therapeutic group.

Methods

Setting

The Psychiatric Case Register Middle Netherlands registers inpatient and outpatient care of psychiatric services in the province of Utrecht in The Netherlands, including Altrecht. (20) The setting of our study was the Altrecht Institute for Mental Health Care, a conglomeration of psychiatric hospitals that serves about 800 000 inhabitants in the central region of The Netherlands. The hospitals had a total of 782 beds in 2012, treating patients with a wide range of mental diseases and providing both inpatient and outpatient care. (21) Medication is provided to inpatients by the institute's hospital pharmacy.

The hospital files contain information on unique patient number, gender, birth date, psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, edition IV, date of diagnosis, Global Assessment of Functioning (GAF) score, type of care (inpatient and outpatient), department of admission, and start and end of admission from 2006. These data were linked to medication use in the hospitals. Data on medication use included the start and end date of use, type of used medication and dosage. Medication was coded according to the World Health Organization (WHO) anatomical therapeutic chemical and the Defined Daily Dose (ATC/DDD) coding system. (22) Only patients insured by Achmea health insurance during the year prior to psychiatric hospitalization were included, allowing for assessment of medication use prior to hospitalization. Outpatient medication history contained all outpatient prescriptions, from general practitioners and other physicians. The outpatient medication history contained information about gender, birth date, date of dispensing, and medication dispensed, coded according to the WHO ATC/DDD coding system. The study was approved by the institution's scientific board, and performed in accordance with The Federation of Dutch Medical Scientific Societies' Code of Conduct for the use of data in Health Research.

Design and Study Population

This retrospective crossover study was conducted in patients who were admitted to a psychiatric hospital between January 1, 2007, and December 31, 2009, and received at least 1 prescription of somatic medication of interest in the 3 months before hospitalization. This was an observational, follow-up study where each patient served as his or her own control. Somatic medications of interest were oral antidiabetics, insulins, lipid-lowering medication, anticoagulants, antithrombotics, cardiovascular medication, and acid- and bowel-related medication (Appendix 1). The somatic medications included in this study were selected for their widespread and chronic use. Some are used to treat life-threatening diseases (oral antidiabetics, insulins, anticoagulants, antithrombotics, and cardiovascular medication), and others are indicated for treatment of less severe diseases or to prevent diseases (lipid-lowering medication and acid-and bowel-related medication). The first day of the first admission was considered as the index date. The study period included psychiatric hospitalization and the 1 year prior to this hospitalization. Only patients without an admission to a psychiatric hospital during the year before the index date were included in the study population.

Outcomes

The primary study outcome was the incidence of "discontinuation" of a somatic medication of interest. This was assessed at different time points. The time points investigated were the index date and 3, 6, and 9 months before the index date. At each time point, the medication dispensed in the 3 months before the time point was compared with the somatic medication dispensed during the 3 months after the time point (Figure 1) except for the index date medication dispensed in the first 7 days of admission,

which was compared with the dispensed medication in the 0 to 3 months before the index date. Patients were classified as discontinuers when a somatic medication was not dispensed after a time point compared with the previous period (Appendix 2). Somatic medication was assumed to be dispensed during hospitalization from the start date of the prescription until end date of the prescription, as registered in the patient hospital files. The secondary outcome was "switch". Patients were classified as switchers when a medication was changed to another medication within the same therapeutic group (with the first 4 characters of the ATC classifications being the same) for example, patients who switched from rosuvastatin (C10A007) to simvastatin (C10AA01); see Appendix 1 and 2. Patients were classified as continuers when they had no discontinuation or switch of their somatic medication.

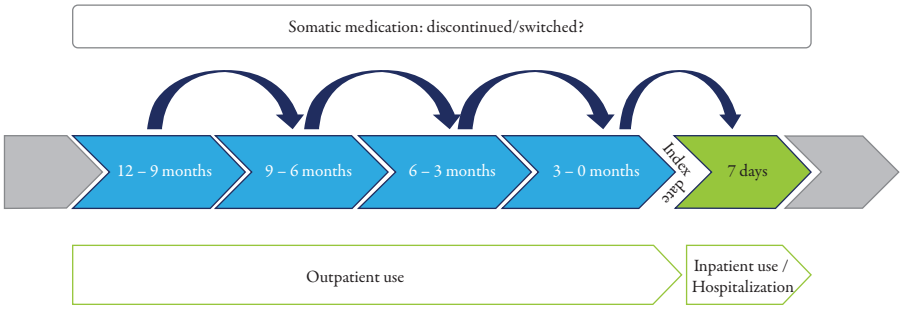


Figure 1: Time of follow-up: at the time points 9, 6, and 3 months, the dispensed medication from 9 to 6 months, 6 to 3 months, and 3 to index date before admission were compared with the medication dispensed from 12 to 9 months, 9 to 6 months, and 6 to 3 months before the index date, respectively. At the index date, medication dispensed in the first 7 days of hospitalization was compared with the dispensed medication in the last 3 months before the index date.

Data Analysis

The number of patients in whom somatic medication was discontinued or switched was assessed on each time point. Incidences of discontinuation and switch of somatic medication on the index date were compared with the incidences of discontinuation and switch of somatic medication on the time points prior to hospitalization. The time points 3, 6, and 9 months before hospitalization was included to gain information about the discontinuation and switch of somatic medication in a period without psychiatric hospitalization. Only patients' time points, where a somatic medication was used during a control period, were included in the analysis. Therefore, the total number of patients varied per time point. The time points before hospitalization were used as a control period to measure if discontinuation and switch of the somatic medication occurred as often during psychiatric hospitalization as in the year prior to psychiatric hospitalization. Cox regression was conducted. Relative risks are reported using the Cox model with time as constant for each patient in the Cox model. RRs with 95% CIs for discontinuation and switch of the somatic medication were estimated overall and stratified by patient characteristics. Statistical significance was determined at $P<0.05$, yielding 95% CI. Patient

characteristics investigated were gender, age (<45, 45-59, and ≥60 years), duration of psychiatric hospitalization (<8 days, 8-20 days, 21-59 days, and ≥60 days), and department of admission (psychogeriatric or nonpsychogeriatric). In addition, whether the somatic medication was ever dispensed during hospitalization was assessed. All analyses were performed using IBM Software package SPSS 20.0 for Windows.

Results

In all, 1564 patients were identified who were admitted to one of the psychiatric hospitals between January 1, 2007 and December 31, 2009, with no admission during the year before the index date who were insured. A total of 471 (30.1%) patients had at least 1 somatic medication of interest dispensed during the 3 months prior to the index date. The mean age of the 471 patients was 57.6 years (SD=16.7); 193 of them were male (41.0%) and the mean patient GAF score was 48.7 (SD=11.7, Table 1). The most common diagnoses were depressive and anxiety disorders (39.9%), and schizophrenia and other psychotic disorders (21.7%). During the 3 months prior to the index date, 16.8% of the patients had at least 1 prescription for oral antidiabetics, 5.9% for insulins, 29.5% for lipid lowering medication, 7.2% for anticoagulants, 19.1% for antithrombotics, 59.0% for cardiovascular medication, and 54.1% for acid and bowel related medication (Table 1).

Overall, 38.9% of the patients had at least 1 somatic medication discontinued at the index date, whereas 21.7% (range: 20.4% to 22.6%) of the patients had any somatic medication discontinued on any of the other time points in the year prior to hospitalization (Figure 2). When patients were stratified by the specific somatic medication they used, it was found that 17.7% of oral antidiabetics (7.3% [mean] in the year before the index date), 14.3% of insulins (8.0% in the year before the index date), 15.1% of lipid lowering medication (7.9% in the year before the index date), 2.9% of anticoagulants (20.7% in the year before the index date) and 7.8% of antithrombotics (9.5% in the year before the index date) were discontinued on the index date (Table 2). Discontinuation most often occurred in users of cardiovascular (34.9% at index date, 19.9% in the year before index date) and acid- and bowel-related medication (34.9% at the index date and 13.5% in the year before the index date).

RR for discontinuation of specific somatic medication (Table 2) was highest for acid- and bowel-related medication (2.92; 95% CI = 1.92-4.44), and lipid-lowering medication (2.66; 95% CI = 1.30-5.45). Overall, the patients had an RR of 1.88 (95% CI = 1.55-2.27) for discontinuation of at least 1 somatic medication at the index date compared with the other time points in the year before the index date. Male patients had an RR of 1.99 (95% CI = 1.48-2.69) and females an RR of 1.80 (95% CI = 1.44 – 2.31) for discontinuation of any somatic medication. When stratified by age, patients younger than 45 years had the highest RR for discontinuation of any somatic medication (RR = 2.83; 95% CI = 1.92-4.18). RR for discontinuation of any somatic medication (Table 3) was highest for users

Table 1: Characteristics of the study population (N = 471) on the index date.

Characteristics	N = 471	%
Gender		
Male	193	41.0
Age, years		
< 45 years	113	24.0
45 – 59 years	139	29.5
≥60 years	219	46.5
Hospitalisation related characteristics		
Diagnosis at admission (%)		
Depressive and anxiety disorders	188	39.9
Schizophrenia and other psychotropic disorders	102	21.7
Delirium, dementia, amnestic and other cognitive disorders	84	17.8
Substance-related disorders	73	15.5
Bipolar disorders	38	8.1
Other diagnosis	103	21.9
Unknown	50	10.6
Duration of admission (days)		
<8 days	103	21.9
8 – 20 days	99	21.0
21 – 59 days	122	25.9
> 60 days	147	31.2
GAF score (*registered in 86.4% of patients)		
0-25	14	3.0
26-50	247	52.4
51-75	143	30.4
76-100	3	0.6
Unknown	64	13.6
Ward of admission:		
Nonpsychogeriatric wards	270	57.3
Psychogeriatric wards	201	42.7
Medication use prior to hospitalisation		
Psychiatric medication (%)		
Antipsychotics	177	37.6
Antidepressants	273	58.0
Mood stabilizers	66	14.0
Anxiolytics and sedatives	311	66.0
Other psychiatric medication	35	7.4

Characteristics	N = 471	%
Somatic medication (%)		
Oral antidiabetics	79	16.8
Insulins	28	5.9
Lipid lowering medication	139	29.5
Anticoagulants	34	7.2
Antithrombotics	90	19.1
Cardiovascular medication	278	59.0
Acid and bowel related medication	255	54.1

* GAF, Global Assessment of Functioning.

Table 2: Relative risks (RR) of discontinuation of specific somatic medications at the index date compared with the time points during the year prior to psychiatric hospitalization in patients with psychiatric hospitalization.[a]

Patients using somatic medication:	Index date	Time points before index date	RR (95% CI) discontinuation
	N (%) discontinuation	N (%) discontinuation	
Oral antidiabetics	79 (17.7)	219 (7.3)	2.65 (1.19 – 5.88)
Insulins	28 (14.3)	75 (8.0)	1.64 (0.39 – 6.88)
Lipid lowering medication	139 (15.1)	369 (7.9)	2.66 (1.30 – 5.45)
Anticoagulants	34 (2.9)	92 (20.7)	0.21 (0.03 – 1.74)
Antithrombotics	90 (7.8)	242 (9.5)	1.06 (0.35 – 3.19)
Cardiovascular medication	278 (34.9)	709 (19.9)	1.61 (1.20 – 2.14)
Acid and bowel related medication	255 (34.9)	548 (13.5)	2.92 (1.92 – 4.44)

[a] Time point index date: first 7 days of psychiatric hospitalization. Time points before index date include the time points 3, 6, and 9 months before the index date.

of antidiabetics (1.98; 95% CI = 1.28-3.06) and users of acid and bowel related medication (1.73; 95% CI = 1.29-2.34). Patients hospitalized for a week or shorter had the highest RR (2.81; 95% CI = 1.87-4.21) for discontinuation of any somatic medication when stratified by hospitalization duration (Table 2). Patients admitted to nonpsychogeriatric wards had an RR of 2.45 (95% CI = 1.91-3.14) for discontinuation of any of their somatic medications.

Switch of at least 1 somatic medication occurred in 27.0% of the patients at the index date with an RR of 2.61 (95% CI = 2.05-3.32) and in 11.7% (range = 11.3%-11.9%) of the patients on the time points in the year prior to hospitalization (Figure 2). When stratified by age, patients between 45 and 59 years were found to have the highest RR of switching any somatic medication (Table 3; RR = 3.61; 95% CI = 2.21-5.89). RR of switch was highest for users of acid- and bowel-related medication (3.31; 95% CI = 2.32-4.72), and users of antithrombotics (3.10; 95% CI = 1.96-4.91). Patients hospitalized for 21 to 59 days

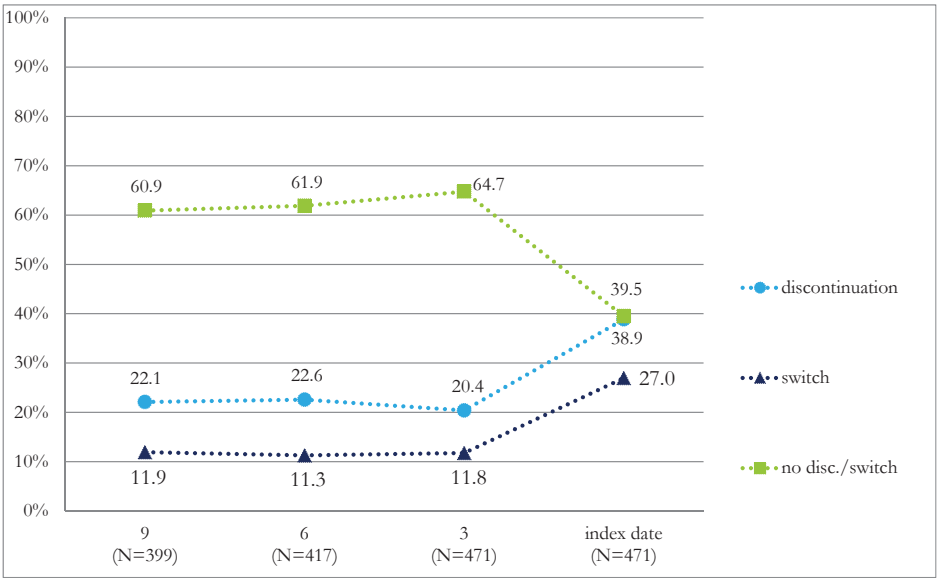


Figure 2: Percentage of patients who discontinued, switched, and continued (no disc./switch = no discontinuation/switch) their somatic medication at the index date and during the year prior (9, 6, and 3 months) to psychiatric hospitalization in 2007-2009. Only patients' time points, where a somatic medication was used during a control point, were included in the analysis.

had the highest risk of switch during the index date (RR = 2.99; 95% CI = 1.81-4.95). Patients admitted to nonpsychogeriatric wards had a lower RR for switch of any somatic medication than patients admitted to psychogeriatric wards; RRs were 2.33 (95% CI = 1.64-3.31) and 2.90 (95% CI = 2.08-4.03) respectively.

It was found that 39.5% of the patients continued all their somatic medications at the index date, whereas 62.5% (range = 60.9-64.7%) of the patients continued all their somatic medications without any discontinuation or switch of their somatic medication, at the time points during the year before hospitalization. The risk of discontinuation or a switch of any somatic medication of interest was 2.10 (95% CI = 1.80-2.45) at the index date compared with the time points before the index date.

When the short hospitalizations (1-2 days) were excluded, discontinuation of at least 1 somatic medication on the index date was 35.8% and thus still higher when compared with the time points before the index date. Discontinuation of somatic medications at the 3 time points in the year before hospitalization were comparable to each other (P >0.05). We also looked at the somatic medications during the entire hospitalization period to see if the somatic medication was ever dispensed during hospitalization. Dispensing occurred for 97.1% of users of anticoagulants, 92.2% of users of antithrombotics, 87.1% of users of lipid lowering medication, 85.7% of users of insulins, 83.5% of users of oral antidiabetics, and 69.0% for users of acid- and bowel-related medication. Patients used more than

Table 3: Discontinuation and Switch of Any Somatic Medication of Interest in Patients With a Psychiatric Hospitalization.[a]

Patients	Index date		
	N	% discontinuation	% switch
Overall	471	38.9	27.0
Gender:			
Male	193	39.9	29.0
Female	278	38.1	25.5
Age category:			
< 45 years	113	49.6	15.9
45 – 59 years	139	38.1	26.6
≥60 years	219	33.8	32.9
Somatic medication:			
Oral antidiabetics	79	46.8	35.4
Insulins	28	46.4	46.4
Lipid lowering medication	139	38.1	36.7
Anticoagulants	34	17.6	32.4
Antithrombotics	90	30.0	48.9
Cardiovascular medication	278	41.7	27.3
Acid and bowel related medication	255	45.1	34.1
Duration of hospitalisation (days):			
< 8 days	103	53.4	28.2
8 – 20 days	99	31.3	31.3
21 – 59 days	122	34.4	25.4
≥60 days	147	37.4	24.5
Type of ward at index date:			
Nonpsychogeriatric wards	270	45.2	21.1
Psychogeriatric wards	201	30.3	34.8

Abbreviation: RR, relative risk.

a Time point index date: first 7 days of psychiatric hospitalization.

Time points before index date include the time points 3, 6, and 9 months prior to the index date.

1 medication from the cardiovascular medication group; at least one cardiovascular medication was dispensed in 81.7% of the patients during hospitalization.

Time points before index date			RR (95% CI) discontinuation	RR (95% CI) switch
N	% discontinuation	% switch		
1287	20.4	11.0	1.88 (1.55 – 2.27)	2.61 (2.05 – 3.32)
515	19.8	11.5	1.99 (1.48 – 2.69)	2.70 (1.87 – 3.89)
772	20.7	10.6	1.80 (1.41 – 2.31)	2.55 (1.86 – 3.51)
291	16.8	8.6	2.83 (1.92 – 4.18)	2.07 (1.12 – 3.80)
382	20.2	7.6	1.87 (1.32 – 2.67)	3.61 (2.21 – 5.89)
614	22.1	14.2	1.51 (1.14 – 2.01)	2.44 (1.78 – 3.33)
219	23.7	32.2	1.98 (1.28 – 3.06)	1.07 (0.69 – 1.66)
75	42.7	28.0	1.53 (0.72 – 3.22)	1.11 (0.56 – 2.19)
369	27.1	24.4	1.46 (1.02 – 2.09)	1.52 (1.05 – 2.19)
92	45.7	18.5	0.22 (0.07 – 0.73)	1.57 (0.67 – 3.66)
242	27.7	15.3	1.19 (0.73 – 1.93)	3.10 (1.96 – 4.91)
709	28.2	14.0	1.37 (1.07 – 1.76)	2.17 (1.59 – 2.95)
548	25.2	12.0	1.73 (1.29 – 2.34)	3.31 (2.32 – 4.72)
233	19.7	14.6	2.81 (1.87 – 4.21)	2.14 (1.27 – 3.58)
316	23.7	11.7	1.38 (0.89 – 2.12)	2.54 (1.57 – 4.12)
337	19.3	8.9	1.76 (1.19 – 2.61)	2.99 (1.81 – 4.95)
401	19.0	10.0	1.90 (1.34 – 2.71)	2.61 (1.66 – 4.12)
729	18.1	9.6	2.45 (1.91 – 3.14)	2.33 (1.64 – 3.31)
558	23.3	12.7	1.28 (0.94 – 1.74)	2.90 (2.08 – 4.03)

Discussion

Psychiatric hospitalization was associated with an almost doubled risk of discontinuation of somatic medication when compared with the year before. Patients <45 years old, those hospitalized for 7 days or fewer, admitted to nonpsychogeriatric wards, and users of acid- and bowel-related medication had the highest relative risk for somatic medication discontinuation during hospitalization.

Our results are in line with the findings of Stuffken et al., who found that the RR of discontinuing medication was 2 times higher in patients admitted to a general hospital than in nonhospitalised patients. (17) They found that discontinuation of medication occurred more often (55.2%) than switching (6.9%) of medication. Our overall results are also in line with our earlier study on discontinuation of anticoagulant care, which showed that anticoagulant therapy was discontinued in almost a quarter of patients during psychiatric hospitalization. (19) Discontinuation of anticoagulants occurred less often compared with our prior study. The reasons could be that in this study we only investigated discontinuation of anticoagulant medication whereas in our prior study discontinuation was defined as discontinuation of the anticoagulant medication in combination with missing INR measurement during hospitalization. In addition, in this study, anticoagulant refill data prior to hospitalization was used whereas in our prior study, data from the Thrombosis and Laboratory Services were used, containing information about whether patients were treated with anticoagulants and involving a longer study period. The time between dispensing of anticoagulants was 3 months for 82% of the prescriptions. Dose fluctuation of the anticoagulants could have resulted in an extended duration of use, which would, because of the definition of discontinuation of somatic medication in our study, resulted in some patients being classified as discontinuers.

Risk of discontinuation of somatic medication was higher in younger patients and those admitted to nonpsychogeriatric wards. However, age and type of ward are correlated because, most patients admitted to psychogeriatric wards are ≥60 years old. Patients admitted to psychogeriatric wards did not show a statistically significant increase in risk of discontinuation of somatic medication. This is also in line with the results from our prior study on discontinuation of anticoagulant therapy. (19) The main difference between these wards is that somatic and psychiatric care are highly integrated in psychogeriatric wards with psychiatrists/geriatricians being familiar with somatic illnesses. In contrast, in nonpsychogeriatric wards the psychiatrist is responsible for both psychiatric and somatic care and can consult general practitioners on somatic treatment. Psychiatrists may also focus more on the psychiatric condition of the patient. (19) Furthermore, a complete physical exam is not routine and therefore somatic diseases may stay unnoticed by the treating physician.

An explanation for higher discontinuation during the first 7 days of psychiatric hospitalization rates might be because of the short duration of hospitalization. However, discontinuation was also higher on the index date in patients with a longer hospitalization compared with the time points prior to the index date and medication should be continued at admission despite duration of hospitalization. It is also possible that patients with a short hospitalization (of 7 days or shorter) used home medication during hospitalization without a clinical order. However, in clinical practice home medication should not be used during hospitalization. Switch of somatic medication of interest was also highest during psychiatric hospitalization. The hospital drug formulary is possibly the most important reason for the switching of somatic medication. (17)

Medication reconciliation could have resulted in discontinuation of somatic medication at psychiatric hospitalization. This could be because: patients were not using the somatic medication anymore, somatic medication was inappropriate, or polypharmacy was inappropriate. (23) Inappropriate polypharmacy can contribute to either an exacerbation of a medical condition or a drug interaction which might have influenced the control of the psychiatric condition, translating to poor quality of health. However, we find it highly unlikely that medication reconciliation was the reason for discontinuation of somatic medication. First, there was an increase in the number of somatic medication dispensed during psychiatric hospitalization and therefore apparently somatic medication had to be continued. Second, guidelines for medication reconciliation or for transfer of information on medication at hospitalization and discharge were only made available from January 2011 and thus not available during the study period. (19, 24) Third, psychiatric status or symptoms get the highest priority of health care providers at psychiatric hospitalization. Furthermore, patients might also have discontinued their somatic medication prior to the psychiatric hospitalization leading to intentional discontinuation at admission.

Somatic medication could also have been discontinued unintentionally. This can be caused by the psychiatric condition of the patient at psychiatric hospitalization getting the highest priority or lack of information on somatic disease and medication. The psychiatric condition can also lead to a patients' noncompliance with the somatic medication and the patient not informing the psychiatrist about somatic medication use. Furthermore, lack of information about somatic disease and medication history can also contribute to discontinuation of somatic medication during psychiatric hospitalization. (19)

Discontinuation of somatic medication can have different consequences. The direct consequence is that patients do not receive their somatic medication during hospitalization. Discontinuation of the somatic medication can also have direct clinical consequences for example, in insulin and oral antidiabetic users, glycemic control can worsen. Discontinuation of some cardiovascular medication can lead to hypertension. (25) The clinical consequences of discontinuation of the somatic medication can also affect recovery from the underlying psychiatric disease(s) negatively. Treatment of

somatic diseases is important together with treatment of psychiatric diseases for the patient's overall health. (8) Sometimes, patients use medication that is not appropriate (anymore) for example when the indication is no longer present. Discontinuation of somatic medication can then be positive for patients' health.

Does somatic medication remain discontinued after discharge? When somatic medication is discontinued during hospitalization, do psychiatrists pay attention to a patient's somatic diseases and discontinued somatic medication? Continuation of medication, independent of chronic use, is important to prevent health deterioration on the long term and save health costs.

To our knowledge, this is the first study to investigate the association between psychiatric hospitalization and discontinuation of somatic medication. Although reasons for hospitalization were not investigated, it is highly improbable that somatic medication use contributed in any way to psychiatric hospitalization, and so (intentional) discontinuation could not have been based on the highly unlikely scenario of somatic medication interfering with the patient's psychological state to the point where the intervention of psychiatric hospitalization is needed. (19, 21) For this study we compared discontinuation of somatic medication of a great number of patients (during psychiatric hospitalization) to several time points in the year prior to psychiatric hospitalization to determine the influence of psychiatric hospitalization. Only fully linked patients were included (which is in line with earlier studies). (26, 27) Continuous use of chronically used pharmacotherapy is very important which is the reason for choosing 7 days for the index date. Outside the period of 7 days, we also determined whether somatic medication was ever dispensed during psychiatric hospitalization.

A limitation of our study can be the difference between the length of the time points prior to hospitalization and the index date, and comparing refill data with hospital files. However, nonhospitalized patients are responsible for their own medication and can go to the community pharmacy when they need their medication, which is usually prescribed for 90 days at maximum. Health care providers are responsible for the medication of the patients during hospitalization and medication use is recorded daily. Another limitation was that we did not have information on the amount of medication the patient still had at home, leading to a delayed refill of the medication. However, chronically used medication needs to be used as prescribed and refilled regularly. Another limitation of our study is that neither the patients nor the psychiatrists were asked about reason for discontinuation of the somatic medication.

For medication use in the year before hospitalization, only declared medication data were used, meaning that only medication delivered and declared to insurance was considered for research. This may have caused an underestimation of somatic medication users in the year prior to psychiatric hospitalization. Accidental use, and use of over the counter

acid and bowel related medication was not declared to insurance. On the other hand, the study represents the patients, all of whom had a prescription for their medication and picked up their medication at their community pharmacy.

Conclusions

In conclusion, discontinuation of somatic medication occurs almost twice as often at psychiatric hospitalization when compared with the year prior to hospitalization. Changes in patients' medication need to be recorded in patient files. More research is needed about whether discontinuation of somatic medication during psychiatric hospitalization is intended or unintended and how this influences patient health. Transitional care programs should pay extra attention to continuation of somatic medication in psychiatric patients.

Acknowledgements

We thank Dr. P.C. Souverein for his support with the data.

References

(1) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Prevalence of medication use for somatic disease in institutionalized psychiatric patients. Pharmacopsychiatry 2013 Nov;46(7):274-280.

(2) American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. 2004;27(2):596-601.

(3) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010 Jun;25 Suppl 2:S22-8.

(4) De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry 2011 Aug;199(2):99-105.

(5) Iacovides A, Siamouli M. Comorbid mental and somatic disorders: an epidemiological perspective. Curr Opin Psychiatry 2008 Jul;21(4):417-421.

(6) Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999 Aug;187(8):496-502.

(7) Miller BJ, Paschall CB,3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. Psychiatr Serv 2006 Oct;57(10):1482-1487.

(8) Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. Br J Psychiatry 2012 Dec;201(6):435-443.

(9) Stoklosa J, Ongur D. Rational antipsychotic choice: weighing the risk of tardive dyskinesia and metabolic syndrome. Harv Rev Psychiatry 2011 Sep-Oct;19(5):271-276.

(10) Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr 2011 Nov 8:1-10.

(11) Crews MP, Howes OD. Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. Hum Psychopharmacol 2012 Jan;27(1):15-23.

(12) Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 1999 Dec;21(6):449-456.

(13) Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 2009 Jun;29(3):259-266.

(14) Haueis P, Greil W, Huber M, Grohmann R, Kullak-Ublick GA, Russmann S. Evaluation of drug interactions in a large sample of psychiatric inpatients: a data interface for mass analysis with clinical decision support software. Clin Pharmacol Ther 2011 Oct;90(4):588-596.

(15) Katsamanis M, Lehrer PM, Escobar JI, Gara MA, Kotay A, Liu R. Psychophysiologic treatment for patients with medically unexplained symptoms: a randomized controlled trial. Psychosomatics 2011 May-Jun;52(3):218-229.

(16) Simon GE, VonKorff M. Somatization and psychiatric disorder in the NIMH Epidemiologic Catchment Area study. Am J Psychiatry 1991 Nov;148(11):1494-1500.

(17) Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in the Netherlands. Ann Pharmacother 2008 Jul;42(7):933-939.
(18) Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005 Aug 30;173(5):510-515.
(19) Abdullah-Koolmees H, Gerbranda T, Deneer VH, Tjoeng MM, De Ridder AJ, Gardarsdottir H, et al. Discontinuation of anticoagulant care during admission to a psychiatric hospital. Eur J Clin Pharmacol 2012 Oct 23;69(4):1025-1029.
(20) Laan W, Termorshuizen F, Smeets HM, Boks MP, de Wit NJ, Geerlings MI. A comorbid anxiety disorder does not result in an excess risk of death among patients with a depressive disorder. J Affect Disord 2011 Dec;135(1-3):284-291.
(21) Altrecht MHC, 2013. Annual Report 2013 of Altrecht/Jaarverslag 2013. 2013; Available at: http://www.jaarverslagaltrecht.nl/. Accessed October, 7th, 2013.
(22) WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. 2010.
(23) Prins MC, Drenth-van Maanen AC, Kok RM, Jansen PA. Use of a structured medication history to establish medication use at admission to an old age psychiatric clinic: a prospective observational study. CNS Drugs 2013 Nov;27(11):963-969.
(24) Policy document: transfer of information on medication [in Dutch]. 2008; Available at: http://www.medicatieoverdracht.nl/. Accessed August 1, 2012.
(25) Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006 Sep 25;166(17):1836-1841.
(26) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.
(27) Smeets HM, Laan W, Engelhard IM, Boks MP, Geerlings MI, de Wit NJ. The psychiatric case register middle Netherlands. BMC Psychiatry 2011 Jun 29;11:106-244X-11-106.

Appendix 1

Table: Patients were included if they had a dispensing for these medications during the 3 months prior to hospitalization. (22)

Medication groups	Drug names and ATC-code*	Therapeutic switch groups
Oral antidiabetics	▪ Blood glucose lowering drugs, excl. insulins, A10B	▪ A10B
Insulins	▪ Insulins and analogues, A10A	▪ A10A
Lipid lowering medication	▪ Lipid modifying agents, plain, C10A ▪ Lipid Modifying agents, combinations, C10B	▪ C10A, C10B
Anticoagulants	▪ Acenocoumarol, B01AA07 ▪ Phenprocoumon, B01AA04	▪ B01AA07, B01AA04
Antithrombotics	▪ Acetylsalicylic acid, B01AC06 ▪ Carbasalate calcium, B01AC08	▪ B01AC06, B01AC08
Cardiovascular medication	▪ Cardiac glycosides, C01A ▪ Antiarrhythmic, class I and III, C01B ▪ Vasodilators used in cardiac diseases, C01D ▪ Low-ceiling diuretics, thiazides, C03A ▪ High-ceiling diuretics, C03C ▪ Potassium-sparing agents, C03D ▪ Diuretics and potassium-sparing agents in combination, C03E ▪ Beta blocking agents, C07A ▪ Selective calcium channel blockers with mainly vascular effects, C08C ▪ Selective calcium channel blockers with diuretic cardiac effects, C08D ▪ ACE inhibitors, plain, C09A ▪ ACE inhibitors, combinations, C09B ▪ Angiotensin II antagonists, plain, C09C ▪ Angiotensin II antagonists, combinations, C09D	▪ C01A ▪ C01B ▪ C01D ▪ C03A, C03C, C03D, C03E, C07A ▪ C08C, C08D ▪ C09A, C09B, C09C, C09D
Acid and bowel related medication	▪ Antacids, A02A ▪ Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), A02B	▪ A02A, A02B

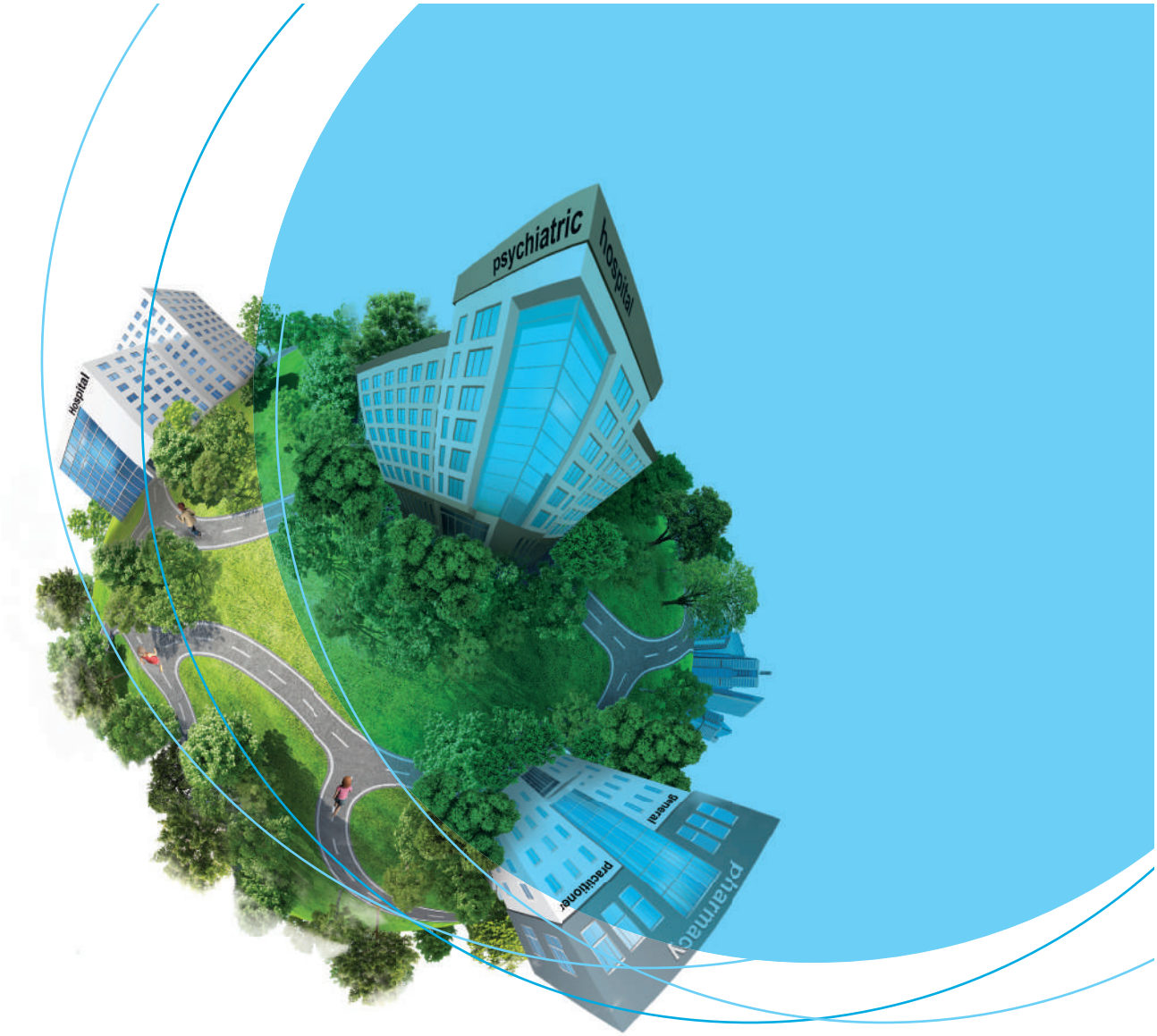
* ATC stands for anatomical therapeutic chemical and is used for classification of drugs.

Appendix 2

Table: Definition of medication use.

Medication use patterns	Definition
Continuous	Medication is continued, active substance remains unchanged compared to previous period.
Switch	Medication is changed to another substance within the same therapeutic group and the first 4 characters of the ATC* classifications are the same (e.g. simvastatin (*C10AA01*) instead of rosuvastatin (*C10A007*)).
Discontinuation	Patients were classified as discontinuers when a somatic medication was discontinued at the time point compared to the previous period.

* ATC stands for anatomical therapeutic chemical and is used for classification of drugs.



2.3

Discontinuation of Anticoagulant Care During Admission in a Psychiatric Hospital

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Eur J Clin Pharmacol 2013; 69:1025-1029

Abstract

Background

Continuation of coumarin therapy is important to prevent thromboembolic events. Continuation of medication, unrelated to the reason for hospital admission, may be at risk due to the patient's psychiatric status and the involvement of several physicians in patient care.

Methods

We performed a retrospective follow-up study of users of orally administered anticoagulants who were admitted to a psychiatric hospital. Information on patient characteristics, anticoagulant use, and International Normalized Ratio (INR) measurements was collected. Discontinuation of anticoagulant care was defined as no anticoagulant dispensing during the first 7 days of hospitalization and/or no INR measurement during hospitalization. Relative risks (RR) of discontinuation, overall and stratified by patient characteristics, was estimated using Cox regression analysis.

Results

Of 111 patients, 24.3% had their anticoagulant care discontinued. For 17.1%, no anticoagulant was dispensed during the first week, and 13.5% had no INR measurement during hospitalization.

Conclusions

Admission to a psychiatric hospital leads to discontinuation of anticoagulant care in 24.3% of patients, with highest risk of discontinuation in patients admitted to nonpsychogeriatric wards. More research is needed to evaluate the clinical impact of this finding.

Introduction

Change of health care setting often leads to changes in pharmacotherapy. (1-3) Stuffken et al. found that in 63.1% of hospitalized, patients one or more medications are changed, of which stopping the medication was the most frequently (55.2%). Medication changes can be intentional, but lack of information or communication between physicians at the time of hospitalization can induce unintentional changes. (3-7) A type of unintentional change in this setting is unintentional medication discontinuation, which may jeopardize patient safety. (3-9)

Health care providers of patients admitted to psychiatric hospitals focus on psychiatric disease(s) and symptoms. Little is known about discontinuation of somatic medication during admission to a psychiatric hospital. Anticoagulant therapy (coumarins) is prescribed to treat and prevent thromboembolic complications and is monitored by measuring the International Normalized Ratio (INR). Both continuation and monitoring of coumarin therapy are important to prevent thromboembolic events and bleeding complications. (10-12) If either medication or monitoring is discontinued, the preventive effect of medication is lost, and risk of bleeding may increase. (13) In the Preventable Hospital Admissions Related to Medications (HARM) study, anticoagulants were identified as one of the major causes of medication-related hospital admissions (5.6% of the unplanned hospital-related admissions). (9) In addition, anticoagulation control is poorly controlled during the prehospitalization period which is associated with unplanned hospitalizations. (14,15) Correct continuation of anticoagulant therapy during hospital admission and optimizing therapy quality during hospitalization is essential for patient safety.

The aim of this study was to assess the quality of anticoagulant care in terms of continuation of anticoagulant treatment and monitoring during psychiatric hospitalization and factors related to discontinuation of anticoagulant care.

Methods

The setting of this study was Altrecht Mental Health Care, a conglomeration of four psychiatric hospitals in The Netherlands. Altrecht serves a population of 800 000 individuals. Both psychiatric and somatic care is provided to patients during hospitalization. Information was available on unique patient number, gender, date of birth, zip code, type of care (inpatient/outpatient), start and end date of admission, psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, edition IV (DSM-IV), date of diagnosis, and information on medication dispensed during hospitalization (e.g. unique patient number, dispensed medications, dosage, start and end date of dispensing). In The Netherlands, orally administered anticoagulant therapy

(acenocoumarol/phenprocoumon; ATC group B01AA04 and B01AA07) for outpatients is entirely monitored and adjusted by the regional Thrombosis and Laboratory Services (TLS). (11) Management of anticoagulant therapy of hospitalized patients can either be transferred to the hospital or continued by the TLS as decided by the physician.

We conducted a retrospective follow-up study of patients admitted to Altrecht between 1 January 2000, and 31 December 2006 who were treated by the TLS and were using acenocoumarol/phenprocoumon during the 60 days prior to index date and who were admitted for at least 7 days. Date of admission was considered the index date. The study was approved by the hospital's scientific board and performed in accordance with the Code of Conduct for the Use of Data in Health Research of The Federation of Dutch Medical Scientific Societies.

The primary study outcome was discontinuation of anticoagulant care. Data on anticoagulant therapy and INR measurements were collected from the TLS, in addition to date of birth, gender and zip code. Patients were considered to have discontinuation of anticoagulant care if the anticoagulant was not continued during the first seven days of hospitalization and/or there were no INR measurements performed during their hospitalization. An arbitrary grace period of 7 days was chosen to allow for overlap of home medication and hospital medication, although in principle, no home medication is supposed to be used during hospitalization. At least one INR measurement was required during hospitalization because INR is normally measured once every 2-3 weeks. The number of patients with a coumarin prescription but no INR measurement (Yes coumarin; No INR), and patients without a coumarin prescription with/without an INR measurement (No coumarin; Yes/No INR) were measured. The number of patients without any prescription during the first 7 days of admission or without INR measurement during hospitalization was measured separately. For discontinuation patients, TLS files were analyzed for date and reason (intentional vs. unintentional) for discontinuation. Patient characteristics considered possibly associated with discontinuation were age, gender, type of coumarin used before the index date (acenocoumarol/phenprocoumon), duration of hospitalization (7-20; 21-59, ≥60 days), psychiatric diagnosis, and ward of admission. Psychiatric diagnoses were grouped by depressive, psychotic, cognitive disorders, and other/unknown psychiatric disorders. Ward of admission was classified as psychogeriatric (specialized wards for patients ≥60 years) or non-psychogeriatric wards. Crude and adjusted relative risks (RRs) with 95% confidence intervals (CI) were estimated for each patient characteristic using a Cox regression analysis. Statistical significance was determined at p value <0.05, yielding 95% CI. All statistical analysis was performed using SPSS, version 19.0.

Results

One hundred and eleven patients were monitored and treated by the TLS with acenocoumarol or phenprocoumon within the 60 days before the index date (Table 1). Mean patient age was 68.7 [standard deviation (SD): 14.2] years, 45.9% were female, and 80.2% used acenocoumarol; 41.4% patients used anticoagulant therapy for atrium fibrillation, 12.6% for thrombosis prevention, 15.3% for having an artificial heart valve, 6.3% for preventing myocardial infarction, 23.4% for other indications and in on patient, the indication was unknown. Median hospital admission duration was 60.0 (range: 7-580) days and 65.8% of patients were admitted to psychogeriatric wards.

Twenty-seven patients (24.3%) had their anticoagulant care discontinued; eight (7.2%) patients had a coumarin prescription but no INR measurement; 19 (17.1%) patients had no coumarin prescription with/without an INR measurement during hospitalization. For 17.1%, no anticoagulant was dispensed during the first week, and 13.5% had no INR measurement. Risk of anticoagulant care discontinuation was 5.30 times higher in patients admitted to nonpsychogeriatric wards than in patients admitted to psychogeriatric wards (52.6% vs. 9.6%; RR = 5.30, 95% CI = 2.00-14.00). Patients <60 years were four times more likely to have discontinuation of anticoagulant care than patients ≥60 years (61.5% vs. 12.9%; RR = 3.99, 95% CI = 1.56-10.21). Patients using phenprocoumon (RR = 1.47, 95% CI = 0.58-3.74) and with psychotic disorders (RR = 1.33, 95% CI = 0.40-4.34) had higher risk of anticoagulant care discontinuation, although this was not statistically significant (Table 1). For patients of whose anticoagulant therapy was discontinuation, TLS files at the were analyzed for date and reason. For three of the 27 patients (11.1%), there was information about discontinuation but for the remaining 24 (88.9%), no information was provided to the TLS by the psychiatric hospitals or patient health care providers.

Table 1: Discontinuation of anticoagulant care.

Patients	N	%[1]
Overall	111	
Age (years)		
<60	26	23.4
≥60	85	76.6
Sex		
Male	60	54.1
Female	51	45.9
Coumarin anticoagulant (before index date)		
Acenocoumarol	89	80.2
Phenprocoumon	22	19.8
Duration of hospitalisation (days)		
7 – 20	16	14.4
21 – 59	39	35.1
≥60	56	50.5
Psychiatric diagnosis (DSM-IV) at index date		
Depressive disorder	37	33.3
Cognitive disorders	23	20.7
Psychotic disorder	16	14.4
Other or unknown disorders	35	31.5
Type of ward at index date		
Psychogeriatric wards	73	65.8
Non-psychogeriatric wards	38	34.2

INR: Intrnational Normalized Ratio, RR: relative risk, CI: confidence interval, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, edition IV.

* Adjusted for age, gender, type of coumarin used before index date, duration of hospitalisation and psychiatric diagnosis at index date.

** Adjusted for type of ward, gender, type of coumarin used before index date, duration of hospitalisation and psychiatric diagnosis at index date.

%[1]: percentage of total sample size. Any discontinuation of anticoagulant care is the sum of the two different discontinuation categories (Yes Coumarin No INR + No Coumarin Yes/No INR).

%[2]: percentage of that subcategory.

Discontinuation of anticoagulant care categories			Relative risks (RR)	
Yes coumarin-No INR (%[2])	No coumarin-Yes/No INR (%[2])	Any discontinuation of anticoagulant care (%[2])	Crude RR (95% CI)	Adjusted RR (95% CI)
8 (7.2)	19 (17.1)	**27 (24.3)**		
6 (23.1)	10 (38.5)	**16 (61.5)**	4.76 (2.21 – 10.25)	3.99 (1.56 – 10.21)*
2 (2.4)	9 (10.6)	**11 (12.9)**	Reference	Reference
4 (6.7)	11 (18.3)	**15 (25.0)**	1.06 (0.50 – 2.27)	0.91 (0.41 – 1.99)*
4 (7.8)	8 (15.7)	**12 (23.5)**	Reference	Reference
6 (6.7)	10 (11.2)	**16 (18.0)**	Reference	Reference
2 (9.1)	9 (40.9)	**11 (50.0)**	2.78 (1.29 – 5.99)	1.47 (0.58 – 3.74)*
2 (12.5)	4 (25.0)	**6 (37.5)**	2.33 (0.83 –6.56)	1.47 (0.50 – 4.32)*
3 (7.7)	9 (23.1)	**12 (30.8)**	1.92 (0.81 – 4.54)	1.61 (0.67 –4.32)*
3 (5.4)	6 (10.7)	**9 (16.1)**	Reference	Reference
3 (8.1)	6 (16.2)	**9 (24.3)**	Reference	Reference
1 (4.3)	2 (8.7)	**3 (13.0)**	0.54 (0.15 – 1.98)	0.82 (0.21 –3.22)*
2 (12.5)	3 (18.8)	**5 (31.3)**	1.29 (0.43 – 3.83)	1.33 (0.40 – 4.34)*
2 (5.7)	8 (22.9)	**10 (28.6)**	1.18 (0.48 – 2.89)	0.78 (0.31 – 1.97)*
2 (2.7)	5 (6.8)	**7 (9.6)**	Reference	Reference
6 (15.8)	14 (36.8)	**20 (52.6)**	5.49(2.32 – 12.98)	5.30 (2.00 – 14.00)**

Discussion

Admission to a psychiatric hospital leads to discontinuation of anticoagulant care in 24.3% of patients and is most frequently seen in patients admitted to non-psychogeriatric wards.

Discontinuation of anticoagulant care could be related to psychiatric condition, lack of admission information on somatic disease, or the ward of admission. Poor psychiatric condition likely means the highest priority is given to treating symptoms, possibly with less attention to somatic condition. (16) Psychiatric condition could also result in patient noncompliance before and at the time of hospitalization. Unintended discontinuation occurs during admission in general hospitals. (3, 5, 7) Lack of information about somatic disease and medication history may also result in unwanted discontinuation of somatic care at psychiatric hospitalization. Health care providers get information about somatic diseases and medication from the patient, their family, by contacting the patient's general practitioner, or the community pharmacy. In The Netherlands, each patient has a single general practitioner and the majority has a single community pharmacy responsible for their medication. TLS is responsible for INR measurements and dosage adjustment of anticoagulant therapy. Care is generally well organized due to short communication lines. Despite direct communications, discontinuation of anticoagulant care occurred in our study. During the study period, no guidelines for patient reconciliation at hospitalization were available. Since 1 January 2011 guidelines are in place in The Netherlands for transfer of information on medication at hospitalization and discharge. (6)

For patients whose anticoagulant therapy was discontinuation, TLS files were analyzed for date and reason of discontinuation. In our study, there was TLS information about discontinuation for only three of the 27 patients (11.1%). These patients were considered to have discontinued therapy intentionally. For the remaining 24 patients, no information was provided by the psychiatric hospitals or patient health care providers. Therefore, for these 24 patients (88.9%), discontinuation of anticoagulant care was considered as most likely unintentionally. Discontinuation of anticoagulant therapy is one example of the critical link between outpatient and hospital care. We do not know if other somatic therapies are discontinued during hospitalization. Continuation of somatic therapies in a psychiatric hospital is important for effectiveness and safety of therapy for the patient.

In our study, it is evident that ward of admission plays an important role; patients admitted to nonpsychogeriatric wards were clearly at a higher risk of anticoagulant care discontinuation than those admitted to psychogeriatric wards. The difference between psychogeriatric wards and non-psychogeriatric wards is the highly integrated nature of psychiatric and somatic care at psychogeriatric wards without regards to the type of physician responsible for patient care. In nonpsychogeriatric wards a psychiatrist is ultimately responsible for both somatic and psychiatric care and a general practitioner

can be consulted for somatic care. Psychiatrists in non-psychogeriatric wards focus on the patient's psychiatric status and are probably less often confronted with patients suffering from complicated somatic illnesses than psychiatrists and/or geriatricians in psychogeriatric wards. Also, their knowledge regarding complicated somatic diseases is likely to be less than that of psychiatrist and/or geriatricians in psychogeriatric wards due to less experience.

This is the first study we are aware of to investigate discontinuation of anticoagulant care during psychiatric hospitalization. Reasons for hospitalization were not investigated; however, it is highly unlikely that discontinuation of anticoagulant care was intended due to the psychiatric condition of the patient in most cases (88.9%) and was unlikely the cause of psychiatric hospital admission. (17) Although the consequences of discontinuation were not studied, discontinuation of chronic anticoagulant therapy leads to loss of its preventive effect. (13) Our study population included two patients hospitalized for ≤20 days who were treated with phenprocoumon. The main treating physician could have decided to skip an additional INR measurement because of the long half-life of phenprocoumon. On the other hand, hospitalization has been associated with poor anticoagulation control. (14) Therefore, phenprocoumon users with hospitalization of ≤20 days were included.

Conclusions

Admission to a psychiatric hospital leads to discontinuation of anticoagulant care in 24.3% of patients. Patients admitted to non-psychogeriatric wards are five times more at risk of anticoagulant care discontinuation than patients admitted to psychogeriatric wards. More research is needed regarding reasons and clinical consequences of discontinuation of anticoagulant care. Discontinuation of other somatic therapies during psychiatric hospitalization should be investigated.

References

(1) Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care--a large-scale follow-up study. Eur J Clin Pharmacol 2007 Aug;63(8):783-790.

(2) Stuffken R, van Hulten RP, Heerdink ER, Movig KL, Egberts AC. The impact of hospitalisation on the initiation and long-term use of benzodiazepines. Eur J Clin Pharmacol 2005 Jun;61(4):291-295.

(3) Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005 Aug 30;173(5):510-515.

(4) Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in the Netherlands. Ann Pharmacother 2008 Jul;42(7):933-939.

(5) Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care 2006 Apr;15(2):122-126.

(6) Policy document: transfer of information on medication [in Dutch]. 2008; Available at: http://www.medicatieoverdracht.nl/. Accessed August 1, 2012.

(7) Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med 2005 Feb 28;165(4):424-429.

(8) Bell CM, Brener SS, Comrie R, Anderson GM, Bronskill SE. Quality measures for medication continuity in long-term care facilities, using a structured panel process. Drugs Aging 2012 Apr 1;29(4):319-327.

(9) Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 Sep 22;168(17):1890-1896.

(10) Schalekamp T, de Boer A. Pharmacogenetics of oral anticoagulant therapy. Curr Pharm Des 2010;16(2):187-203.

(11) Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med 2005 Jul 11;165(13):1527-1532.

(12) van Geest-Daalderop JH, Sturk A, Levi M, Adriaansen HJ. Extent and quality of anti-coagulation treatment with coumarin derivatives by the Dutch Thrombosis Services. Ned Tijdschr Geneeskd 2004 Apr 10;148(15):730-735.

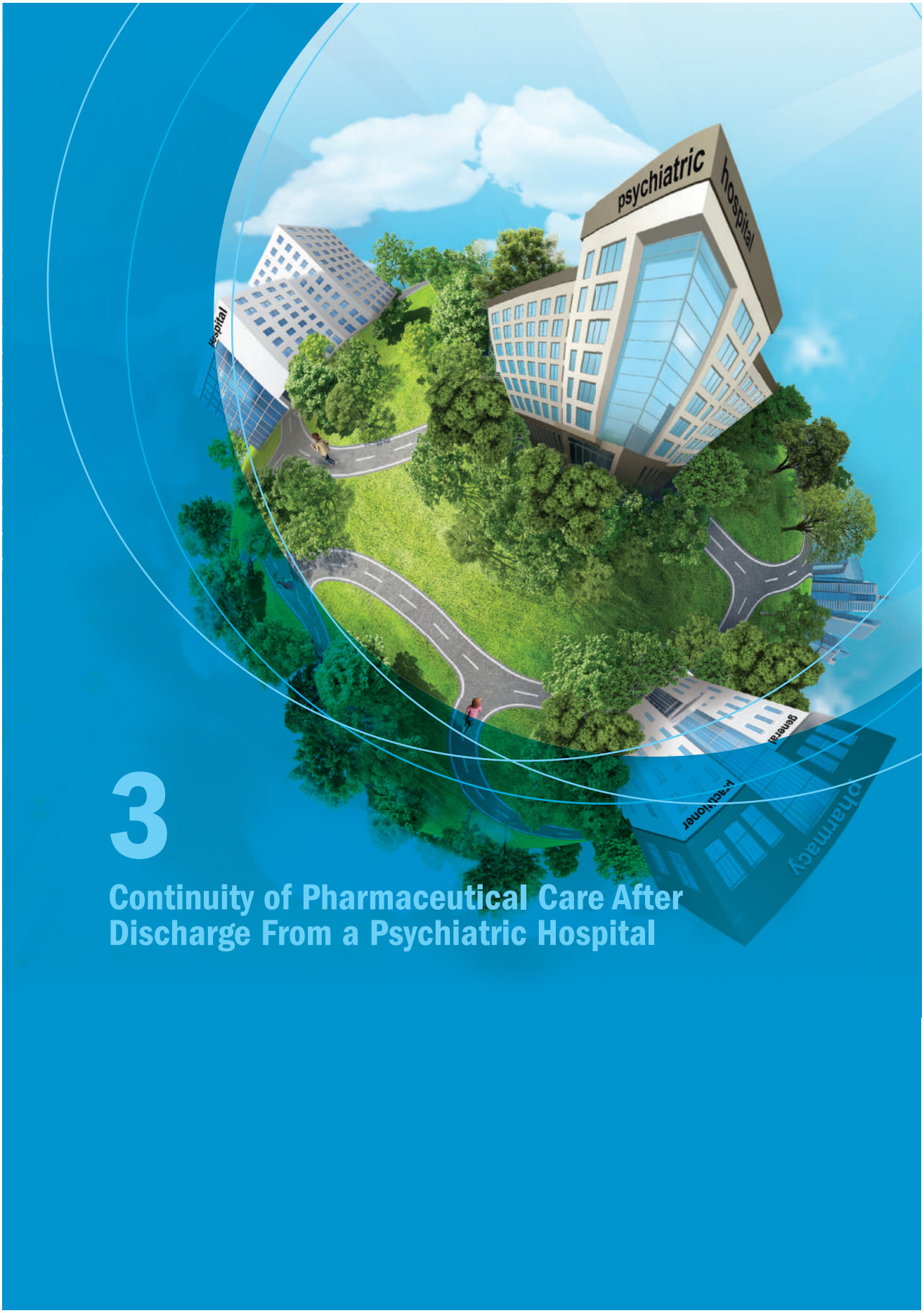
(13) Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. Arterioscler Thromb Vasc Biol 2009 Mar;29(3):298-310.

(14) van Walraven C, Forster AJ. Anticoagulation control in the peri-hospitalization period. J Gen Intern Med 2007 Jun;22(6):727-735.

(15) van Walraven C, Austin PC, Oake N, Wells P, Mamdani M, Forster AJ. The effect of hospitalization on oral anticoagulation control: a population-based study. Thromb Res 2007;119(6):705-714.

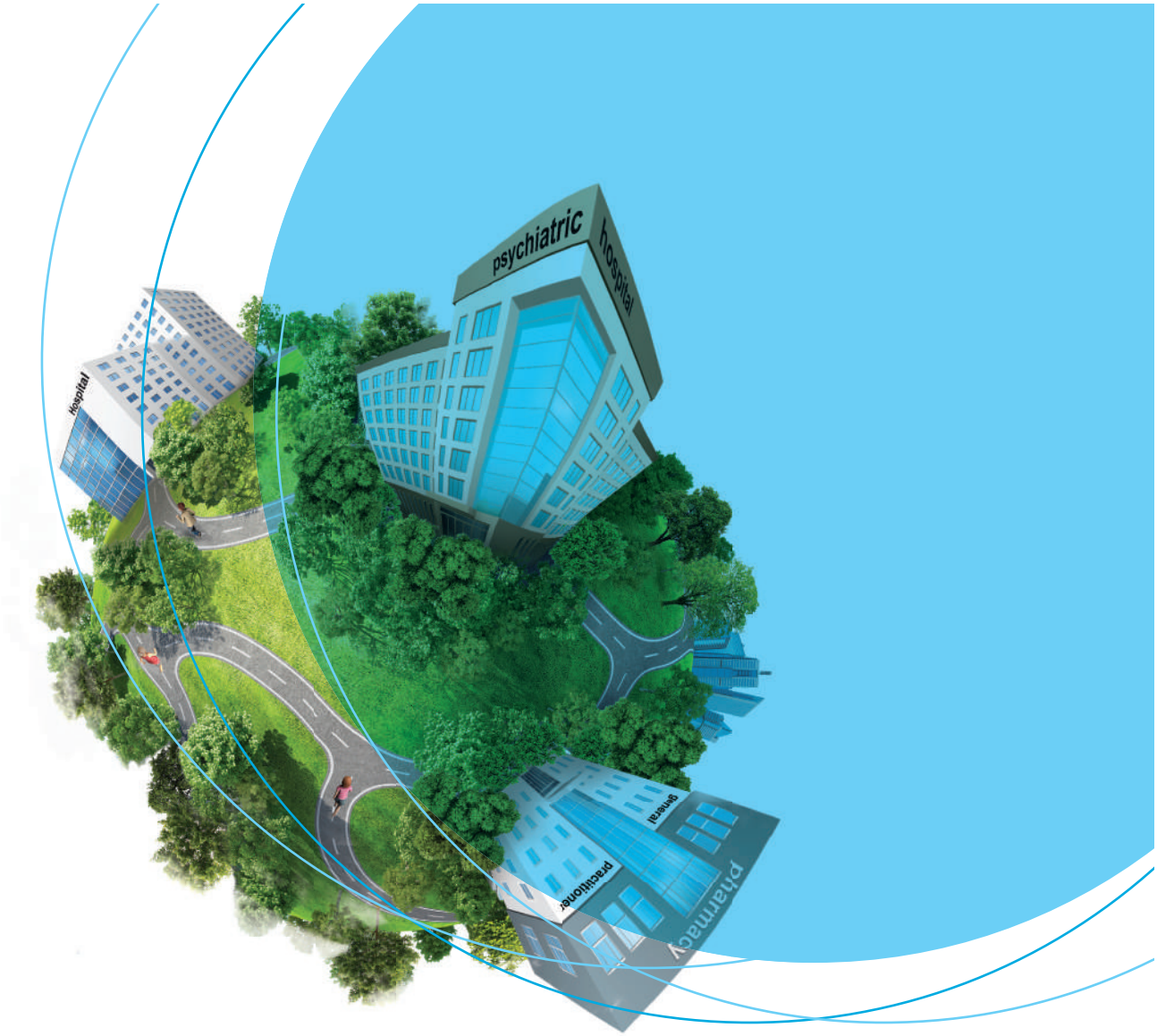
(16) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010 Jun;25 Suppl 2:S22-8.

(17) Altrecht MHC. Annual Report 2010 of Altrecht/Jaardocument 2010. 2010:19-94.



3

Continuity of Pharmaceutical Care After Discharge From a Psychiatric Hospital



3.1

Medication Discontinuation in Patients After Discharge From a Psychiatric Hospital

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Submitted for Publication

Abstract

Background

Patients discharged from a psychiatric hospital may be at risk for intentional or unintentional discontinuation of their medication. To assess discontinuation and other medication changes in use of psychiatric and/or somatic medication after discharge from a psychiatric hospital.

Methods

A retrospective, follow-up study was conducted in patients discharged from four psychiatric hospitals in The Netherlands between 2006-2009. Patients' medication used during the last two days of hospitalization was compared to medication dispensed during the three months after discharge. Changes in psychiatric and somatic medication use were investigated; medication changes were defined as discontinuation, start, or switch. When medication dispensed after discharge was unchanged then patients were classified as continuers. Relative risks (RR) with 95% confidence intervals (95% CI) of discontinuation were estimated using Cox regression analysis.

Results

1324 patients were included of which 69.8% discontinued and 9.7% switched one or more medications. 47.4% started a medication, which was not dispensed during the last two days of hospitalization, and 13.7% continued all medication after discharge without a discontinuation or change at all. In the 644 patients using antipsychotics, 25.2% discontinued. Of 292 patients using cardiovascular medications, 28.4% discontinued. RR for discontinuation of a medication was highest in patients using as-needed medication prior to discharge (RR = 1.85, 95% CI = 1.55-2.20).

Conclusions

Discharge from a psychiatric hospital was accompanied with medication discontinuation in almost 70% of the patients. Discontinuation of somatic medication was more frequent than psychiatric medication. Medication discontinuation can be intentional but it seems unlikely that about quarter of antipsychotics and cardiovascular medications is discontinued which is used chronically. More research is needed to assess if these medication discontinuations are intentional or unintentional and its consequences for patients' overall health.

Introduction

Change of health care setting, e.g. admission to and discharge from a hospital, is often accompanied with changes in patients' medication. (1-6) Studies show that 40-98% of patients discharged from a general hospital have one or more medication changes after discharge, e.g., discontinued or started a medication. (2, 6) Medication discontinuation can be intentional and unintentional. Intentional medication discontinuation may be due to medication review in the hospital given the patients' condition. Unintentional medication discontinuation can occur due to insufficient communication (including associated administrative errors) between health care providers from primary and secondary care and unclear prescribing responsibilities. (7, 8) In addition, when patients are discharged, the responsibility for medication management shifts from the health care provider to the patient. Patients may decide not to refill medication or not to take medication as prescribed (non-adherence). (8-12)

For patients discharged from a psychiatric hospital where discontinuation in medication may relate to the psychiatric medication as well as the somatic medication. Somatic medication is used for treatment of somatic comorbidities and side effects of psychiatric medication. (3, 13-33) In two earlier studies we showed that psychiatric hospitalization is associated with discontinuation of somatic medication such as anticoagulant care and cardiovascular medication. (1, 34) Discontinuation of psychiatric as well as somatic medication may influence patients' health. (12) Up to now, most studies on medication discontinuation at transition of care have been performed in general hospital settings but little is known about the medication discontinuation in patients discharged from a psychiatric hospital. Therefore, the aim of this study was to assess discontinuation and other changes in psychiatric and somatic medication in patients discharged from a psychiatric hospital.

Methods

Setting

The Psychiatric Case Register Middle Netherlands (PCR-MN) contains the inpatient and outpatient care of psychiatric services in the province Utrecht, The Netherlands. (35) The setting of our study was Altrecht institute for mental health care within PCR-MN, a conglomeration of four psychiatric hospitals serving about 800,000 inhabitants in the central region of The Netherlands. The hospitals had a total of 746 beds in 2013, treating patients with a wide range of mental diseases and providing both inpatient and outpatient care. (36) Inpatients' medication was provided by the hospital pharmacy in Altrecht. These files included information on unique patient number, gender, birth date, type of care (inpatient and outpatient), and start and end of admission from 2006. Medication was coded according to the World Health Organization (WHO) anatomical therapeutic

chemical and the Defined Daily Dose (ATC/DDD) coding system. (37) Information about medication use included the start and end of use, type and dosage of medication used. Information on outpatient medication use for patients insured with Achmea (the largest insurance company in the region) was available from the Achmea Health Database. The study was approved by the institution's scientific board, and performed in accordance with The Federation of Dutch Medical Scientific Societies' Code of Conduct for the use of data in Health Research.

Design & Study Population

A retrospective follow-up study was conducted in psychiatric patients of all ages who had been hospitalized for at least 7 days and were discharged from one of the four psychiatric hospitals between 1 January 2006 and 31 December 2009. Day of discharge was defined as the index date. Hospitalizations with less than 7 days elapsing between discharge and the following admission were considered as one hospitalization. Patients were selected if information on their outpatient medication use was available for at least three months after psychiatric hospitalization. The choice of three months follow-up is based on the most common prescription duration for medication in The Netherlands. The study period included psychiatric hospitalization and three months after discharge or until rehospitalization whichever came first (Figure 1).

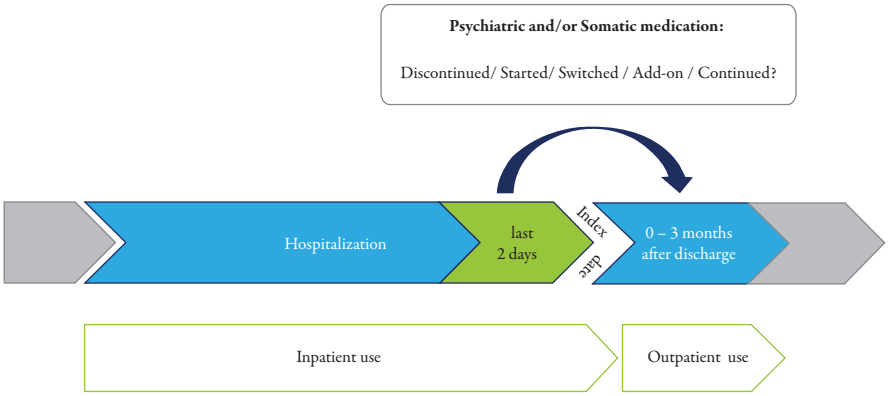


Figure 1: Time of follow-up. The medication dispensed during the three months after discharge was compared to the medication used during the last two days of hospitalization.

Medication was divided in two classes, namely "any somatic medication" and "any psychiatric medication" (Appendix 1). Furthermore, frequently used somatic and psychiatric medications were classified by indication (Appendix 1). (14) Somatic medication was classified as follows: cardiovascular medications, laxatives, acid and bowel related medications, anti-cholinergic medications, asthma and COPD medications, lipid lowering medications, vitamins, analgetics, antidiabetics, dermatologicals, thyroid medications, and antibiotics and antifungals. Psychiatric medication was classified as antipsychotics, antidepressants, mood stabilizers, anxiolytics and sedatives and other

psychotropics. Additionally, we defined an "any medication" class including all somatic and psychiatric medication. Prescriptions of over the counter medication, contraceptives, dermatologicals and other preparations without an active substance were excluded.

Outcomes

The main outcome of this study was discontinuation of psychiatric and somatic medication after discharge from a psychiatric hospital. Medication was considered discontinued when medication used during the last two days of hospitalization was not dispensed during the three months after discharge. Discontinuation after discharge is considered likely to be unintentional if the discontinued medication was used before admission and during the last two days of hospitalization. Therefore, it was also investigated whether the discontinued medication was dispensed during the three months prior to hospitalization using the ATC code level 4. This was performed for patients where medication history was available for the three months prior to the psychiatric hospitalization. The other medication changes after discharge were defined as start, switch, add-on, and continuation. Patients were classified as starters if they got a medication dispensed post discharge, which was not used during the last two days of hospitalization. To investigate if these were restarters, any dispensing of the medicine (ATC code level 4) was investigated during the three months prior to hospitalization. This was performed for patients where medication history was available for the three months prior to the psychiatric hospitalization. Restarters are assumed to be unintentional for psychiatric medication because otherwise it would be used during the last two days of hospitalization. If patients got dispensed a medication within the same therapeutic group (same ATC level 4 code, for example switching from haloperidol to quetiapine) then they were classified as switchers. When patients got two medications after discharge matching the ATC code level 4 of a medication used during the last two days of hospitalization, the medication closest to the index date was used to define the category of use. Patients were classified in the add-on category when after discharge the same medication was simultaneously dispensed with another medication from the same therapeutic group (same ATC level 4 code, for example olanzapine with halopeidol). When medication used during the last two days of hospitalization was dispensed within three months after discharge the patients were classified as continuers.

Data Analysis

Incidences of discontinuation, start, switch, add-on, and continuation of medication after discharge from a psychiatric hospital were investigated. Patient characteristics possibly associated with discontinuation of medication were investigated including gender, age (<45years; 45-59 years; >60 years), duration of hospitalization (categorized in tertiles to obtain three equally divided groups: 7-36 days; 37-96 days; ≥97 days), diagnosis at discharge according to DSM-IV TR, type of ward at discharge, and use of as-needed medication before discharge. DSM diagnoses were classified as: schizophrenia and psychotic disorders; bipolar disorders; depressive and anxiety disorders; delirium, dementia, amnestic and other cognitive disorders (cognitive disorders); substance-related

disorders; and other diagnosis and unknown diagnosis. (1, 34) Cox proportional hazards regression was conducted to estimate the relative risks of discontinuation for each patient characteristic with 95% confidence intervals. Statistical significance was determined at $P<0.05$. Time was considered as constant. The data analysis was performed using IBM Software package SPSS 20.0 for Windows.

Results

1324 patients were included in this study. Their mean age was 44.8 years (Standard Deviation (SD) 18.8 years), 664 (50.2%) were male and the mean patients' GAF score was 48.6 (SD: 11.9) (Table 1). The most common diagnoses were schizophrenia and other psychotic disorders (35.9%), depressive and anxiety disorders (28.9%), and substance-related disorders (20.4%). Median duration of hospitalization was 63 days (range 7-1424 days) with 1047 (79.1%) of the patients being discharged from nonpsychogeriatric wards. The majority of the patients (81.3%) used at least one medication during the last two days of hospitalization of which 83.6% used a psychiatric medication. The most commonly used psychiatric medication were anxiolytics and sedatives (64.2%), followed by antipsychotics (48.6%), antidepressants (34.8%), and mood stabilizers (15.6%). More than half (58.5%) of the patients used at least one somatic medication of which 22.1% used cardiovascular medications, 15.9% laxatives, and 15.4% acid and bowel medications (Table 2).

69.8% (752) of the 1077 patients discontinued at least one medication after discharge (Table 2), thus medication was not dispensed after discharge. Of 1029 patients using psychiatric medication 47.2% discontinued at least one psychiatric medication. 850 patients used anxiolytic and sedative, which 52.1% of them discontinued. 35.2% of the 71 other psychotropics users were also discontinuers, followed by 25.2% of 644 antipsychotic users, 14.6% of 206 mood stabilizer users, and 13.9% of 461 antidepressant users. Somatic medication was discontinued in 48.8% of the 774 patients with the chronic used discontinued somatic medications being cardiovascular medication (28.4% of 292 patients), acid and bowel related medication (24.5% of 204 patients), antidiabetics (22.6% of 84 patients), and lipid lowering medication (15.8% of 114 patients). Discontinuation of any medication was 69.8% as mentioned. When only chronic used medication was included (excluding vitamins, antifungals and antibiotics, and dermatologicals and as-needed medication), 39.7% of 1067 patients still had any medication discontinued, 24.3% (of 1029) discontinued any psychaitric medication, and 47.5% (of 600) discontinued any somatic medication. 92.2% (693 of 752) of the patients where medication was discontinued at discharge had 3 month medication history prior to hospitalization available. 44.4% of these patients got the discontinued medication dispensed prior to hospitalization.

Table 1: Characteristics of the study population.

Characteristics	N=1324	%/SD/Range
Gender (%)		
Male	664	50.2
Mean age in years (SD)	44.8	18.8
<45 years	707	53.4
45 – 59 years	319	24.1
≥60 years	298	22.5
Median duration of hospitalization (range)	63.0	7-1424
7-36 days	445	33.6
37-96 days	437	33.0
≥97 days	442	33.4
Mean GAF score (SD)	48.6	11.9
0-25	42	3.2
26-50	658	49.7
51-100	439	33.2
Unknown	185	14.0
Time to rehospitalization (%)		
7 days – <1 month after discharge	98	7.4
1 – <2 months after discharge	58	4.4
2 – <3 months after discharge	60	4.5
≥3 months or no rehospitalization	1108	83.7
Diagnosis at discharge (%)*		
Schizophrenia and other psychotropic disorders	475	35.9
Depressive and anxiety disorders	382	28.9
Substance-related disorders	270	20.4
Cognitive disorders	122	9.2
Bipolar disorders	118	8.9
Other diagnosis	365	27.6
Unknown	96	7.3
Type of ward at discharge (%)		
Nonpsychogeriatric	1047	79.1
Psychogeriatric	277	20.9
Year of discharge (%)		
2006	249	18.8
2007	354	26.7
2008	405	30.6
2009	316	23.9

* Total exceeds 100% because of multiple diagnoses.

Table 2: Medication use in 1324 patients on the last two days of hospitalization and the proportion of medication: discontinued, started, switched, and continued (without any medication switched or discontinued). The proportions are shown for any medication and stratified for different medication classes after discharge from a psychiatric hospital.

Medication use in the last two days of hospitalization	N	% of 1324	Discontinued (%)	%[1] of discontinuers used before hospitalization	Switched (%)	Continued (%)	Starters (% of 1324)	Restarters (% of starters)
Any medication	1077	81.3	69.8	40.8	9.7	27.5	47.4	42.6
Any psychiatric medication	1029	77.7	49.4	29.6	4.8	50.1	21.7	51.9
Anxiolitics and sedatives	850	64.2	52.1	41.4	3.1	46.4	14.2	52.1
Antipsychotics	644	48.6	25.2	54.7	2.8	72.4	8.2	44.2
Antidepressants	461	34.8	13.9	46.7	1.7	84.4	8.5	50.0
Mood stabilizers	206	15.6	14.6	14.0	0.5	85.4	2.5	45.5
Other psychiatric medication	71	5.4	35.2	12.0	0.0	64.8	1.7	40.9
Any somatic medication	774	58.5	68.0	31.0	7.8	31.4	37.8	32.4
Cardiovascular medications	292	22.1	28.4	60.2	5.1	69.5	5.5	28.8
Laxatives	210	15.9	57.6	24.0	2.9	40.0	3.0	15.0
Acid & bowel related medications	204	15.4	24.5	52.0	9.3	66.2	3.9	39.2
Anti-cholinergic medications	179	13.5	50.8	11.0	0.6	48.6	2.7	16.7
Asthma and COPD medications	119	9.0	62.2	35.1	1.7	37.8	3.3	29.5
Lipid lowering medications	114	8.6	15.8	88.9	2.6	81.6	1.9	56.0
Vitamins	110	8.3	93.6	1.0	0.0	6.4	0.2	50.0
Analgesics	89	6.7	51.7	32.6	5.6	42.7	7.6	32.0
Antidiabetics	84	6.3	22.6	78.9	0.0	77.4	1.5	50.0
Dermatologicals	77	5.8	79.2	11.5	2.6	19.5	7.9	18.1
Thyroid medications	49	3.7	93.9	8.7	0.0	6.1	0.7	55.6
Antibiotics and antifungals	33	2.5	69.7	34.8	0.0	30.3	9.5	17.5

[1] Proportions of medication discontinued that were dispensed during three months prior to hospitalization.

47.4% of the patients started a medication during follow up that was not used during the 2 days prior to discharge. 21.7% of the patients started a psychiatric medication and 37.8% a somatic medication, respectively. 91.1% (571 of 627) of patients who started a medication after discharge had 3 month medication history prior to hospitalization was available. For almost half (46.6%) of the patients, the medication started after discharged was also dispensed in the three months prior to hospitalization.

About 4.5% switched a psychiatric medication, which most often occurred for anxiolitics and sedatives (3.1%) and antipsychotics (2.8%). 5.6% of the patients switched somatic medication after discharge with the most frequent switches for acid & bowel related medications (9.3%) and analgesics (5.6%). 1.8% of the patients got an add-on medication dispensed after discharge. When stratified, 0.9% of the patients were classified as add-on for a psychiatric medication and 0.9% were classified as add-on for a somatic medication. 9.7% of the patients switched medication after discharge (Table 3).

13.7% of the 1077 patients continued all medication after discharge. 27.5% of the 1077 patients continued all medication after discharge without switching or discontinuing but started a medication that was not used during hospitalization (Figure 2, Table 2). Half (50.1%) of the 1029 users of any psychiatric medication continued all their psychiatric medication, and 31.4% of the 774 patients using somatic medications continued after discharge. The medication most commonly continued were mood stabilizers (85.4%), followed by antidepressants (84.4%) and antipsychotics (72.4%).

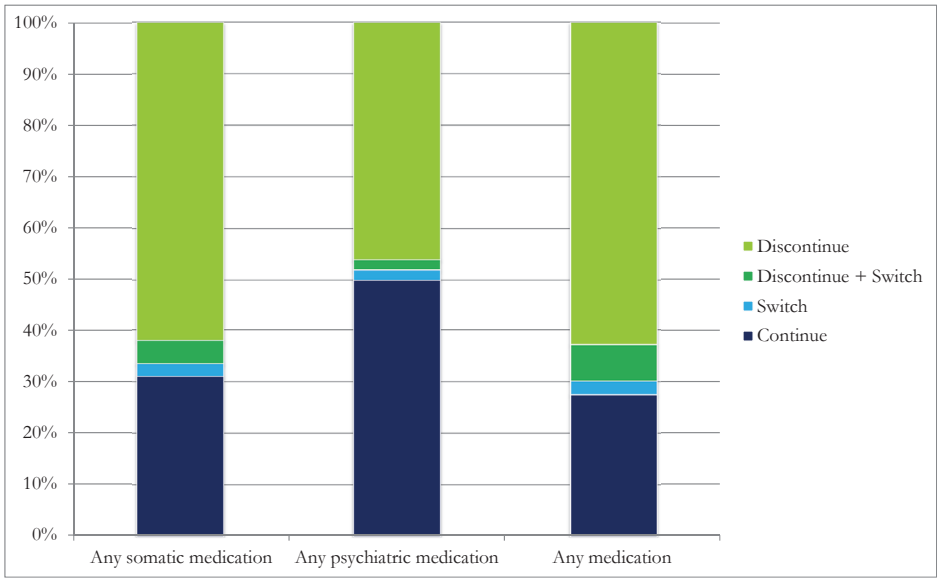


Figure 2: Proportion of patients discontinued, discontinued and switched, switched, and continued (without any medication switched or discontinued) any, psychiatric and somatic medication after discharge from a psychiatric hospital.

Males (RR = 1.15, 95% CI = 0.99-1.33) and patients with schizophrenia and other psychotropic disorders (RR = 1.10, 95% CI = 0.95-1.28) had a slightly higher risk of medication discontinuation after discharge, although this was not statistically significant. Patients <45 years and 45-59 years had lower risk (of medication discontinuation when compared to patients ≥60 years or RR = 0.86, 95% CI = 0.72-1.02) and RR = 0.91 (95% CI = 0.75-1.11), respectively. Patients with shorter hospital admissions (7-36 days) had a lower risk of discontinuation (RR = 0.88, 95% CI = 0.74-1.05) than patients with longer hospitalizations (≥97 days). Patients discharged from nonpsychogeriatric wards had an RR of 0.88 (95% CI = 0.75-1.04) compared to patients discharged from psychogeriateric wards. No significant difference in risk of discontinuation was found for the year of discharge. Patients using as-needed medication before discharge had a higher risk of discontinuing any medication in general (RR = 1.85, 95% CI = 1.55-2.20). Risk of discontinuation was 0.85 times lower for patients with depressive and anxiety disorders (95% CI = 0.72-0.99), Table 3.

Discussion

Almost 70% of the patients discontinued a medication after discharge from a psychiatric hospital. Discontinuation of somatic medication was more frequent than psychiatric medication. Almost half of the patients started a new medication after discharge, which was not used on the last two days of hospitalization.

Our study is in line with results from earlier studies on medication discontinuation for patients discharged from a general hospital or when change of setting occurred. (1-6, 34) These showed that 40 to 57% of the patients had a medication discontinued after discharge and 40 to 98% had a medication change. (1-6) The most frequent discontinued classes of psychiatric medication were anxiolytics and sedatives. Anxiolytics and sedatives are often used as-needed and only during hospitalization or unstable periods thus it is likely that these were not needed anymore after discharge and therefore discontinued.

Discontinuation was higher for somatic medication than psychiatric medication. This might be partially explained by temporary indications or specific hospital guideline/practices such as for use of vitamins, dermatologicals, antibiotics and antifungals, laxatives, and analgetics. Observing high discontinuation after discharge is more likely for some types of medication as during hospitalization all medication use is registered. This would explain the high discontinuation rates of analgetics (NSAIDs) as this can be purchased over the counter without a prescription after discharge. Also, in case of as-needed medication, e.g. asthma and COPD medication, these might not be refilled regularly every three months. Furthermore, medication reconciliation around discharge can also have resulted in intentional discontinuation of some medication. Health care providers might decide to discontinue a medication due to various reasons such as the medication

Table 3: Relative risks for patients' medication to be discontinued after discharge from a psychiatric hospital.

Characteristics	N	N Discontinuation	%	Relative risks (RR) Crude RR (95% CI)
Overall	1077	752	69.8	
Gender (%)				
Male	529	396	74.9	1.15 (0.99-1.33)
Female	548	356	65.0	Reference
Age groups				
<45 years	539	356	66.0	0.86 (0.72-1.02)
45 – 59 years	269	189	70.3	0.91 (0.75-1.11)
≥60 years	269	207	77.0	Reference
Duration of hospitalization				
7-36 days	346	227	65.6	0.88 (0.74-1.05)
37-96 days	369	256	71.9	0.93 (0.79-1.11)
≥97 days	362	269	74.3	Reference
Diagnosis at discharge				
Schizophrenia and other psychotropic disorders	409	303	74.1	1.10 (0.95-1.28)
Depressive and anxiety disorders	307	190	61.9	0.85 (0.72-1.00)*
Substance-related disorders	232	172	74.1	1.08 (0.91-1.28)
Type of ward at discharge				
Nonpsychogeriatric	822	556	67.6	0.88 (0.75-1.04)
Psychogeriatric	255	196	76.9	Reference
Year of discharge (%)				
2006	179	114	63.7	0.84 (0.67-1.06)
2007	290	190	65.5	0.87 (0.71-1.06)
2008	344	248	72.1	0.95 (0.79-1.15)
2009	264	200	75.8	Reference
Having an as-needed medication				
Yes	732	599	81.8	1.85 (1.55-2.20)*
No	345	153	44.3	Reference

* $p<0.05$

not being needed anymore; inappropriateness of some medication or inappropriate polypharmacy. (38) However, in our study discontinuation and other changes due to medication reconciliation are unlikely as guidelines for medication reconciliation or for transfer of information on medication at hospitalization and discharge were only made available after the study period (from January 2011). (34, 39) Another reason for observing medication discontinuation might be due to the patients not refilling medication that they might have at home. However, medication used chronically is refilled regularly.

Patients' noncompliance, which has been reported to be ca. 50% among psychiatric patients, can also result in not refilling prescriptions regularly, resulting in observed discontinuation in our study. (10-12, 33) Medication changes can also have occurred unintentionally. Patients' medication can be discontinued or changed unintentionally after discharge from hospital due to insufficient communication between health care providers of primary and secondary care or insufficient communication between patients and health care providers. Discontinuation of somatic medication can occur due to late or non-arrival of information during the transition from secondary care to primary due to administrative errors or if information from secondary care is not registered in the patient files in the primary care. (5) Discontinuation of the somatic medication can also occur if general practitioners (GPs) are not informed about changes in the pharmacotherapy upon discharge. GPs are often responsible for prescribing the somatic medication after discharge and patients are responsible for continuation of their health care. If the GP does not prescribe medication then patients needs to take actions by themselves to get a prescription or continue the medication as it was during the hospitalization. The GP does not have an overview nor does not monitor the continuity of health care. Patients have to take care of their medication with their health care providers from primary care, e.g. the GPs and the ambulatory psychiatrist, when they are discharged. Patients need to communicate with different health care providers for their health care. Some patients might find this difficult and may not succeed in organizing their health care and thus in getting a prescription for their medication. The ambulatory psychiatrist treating outpatients is responsible for the psychiatric pharmacotherapy. The psychiatrist from secondary care prescribes only the first prescriptions of the psychiatric medication, which are dispensed after discharge. Discontinuation of psychiatric as well as somatic medications, whether intentional or unintentional, may influence patients' health positively or negatively. (12) It is unknown whether patients and health care providers know that medication was discontinued or changed after discharge whether it was intentionally or unintentionally. Earlier studies in patients discharged from general hospitals have shown that medication changes are documented in less than 50% of the patients. (5, 40)

Medication discontinuation might have clinical consequences. We found that 28.4% of the patients discontinued cardiovascular medications, 15.8% lipid lowering medications, and 22.6% antidiabetics which is reason of concern. Cardiovascular medications, lipid lowering medications and antidiabetics are examples of medication that should be used chronically. Discontinuing these medications can lead to destabilization of hypertension, cholesterol, and blood glucoses control. On the other hand, discontinuation of some medication might be warranted such as discontinuing medication that is not appropriate (anymore) like anxiolytics and sedatives. It is therefore important that discontinuation in patients' medication should be well documented and transferred between health care providers when patients are discharged to prevent medication errors and possible related harms. (40)

In our study, start of a medication after discharge was investigated and specifically if patients got medications dispensed that were prescribed prior to hospitalization. Almost four out of five patients started a medication that was also used before the psychiatric hospitalization. We did not have information on the reason for starting these medications. Different scenarios for starting are possible such as having to be used again after discharge, or because they were temporary or unintentionally discontinued during the psychiatric hospitalization, or they were unintentionally started again after discharge. (38) For example, among the psychiatric medication antipsychotics (44.2%) and antidepressants (50.0%) around half of the starters were restarters. This means that the medication was used before admission but was not used anymore during the last two days of hospitalization. During psychiatric hospitalization treatment of psychiatric diseases are evaluated and changed if needed till patients' disease and symptoms are stabilized. If antipsychotics and antidepressants are not part of the treatment then they are discontinued before discharge and patients are switched to another medication if necessary. It is therefore highly unlikely that restart of psychiatric medication such as antipsychotics and antidepressants are intentional which were not used right before discharge. Of the somatic medications cardiovascular medication (28.8%) was most often restarted after discharge. We find it highly unlikely that cardiovascular medication and somatic medication in general was the reason of psychiatric hospitalization. Cardiovascular medication is usually used chronically. The reason for not using these medications during hospitalization might be intentional, e.g., not needed or could not be used due to patients' situation, or unintentional.

After discharge from a psychiatric hospital 9.7% of the patients switched a medication. The proportion of patients switched a medication after discharge was smaller than at hospitalization as reported in our earlier study (27%). (1) At hospitalization hospital formularies play an important role for switch of medication. Switch at discharge can occur because patients are switching back to a medication, which were dispensed before psychiatric hospitalization. At the other hand, for the patients switch of medication is yet another change of medication and might be worrisome. Patients need to be informed about the switch and need to be convinced to use the new medication.

To our knowledge, this is the first study investigating discontinuation of psychiatric and somatic medication after a discharge from a psychiatric hospital. We were able to study a large number of discharged patients, including a study period spanning several years for which primary and secondary data were combined. A limitation of our study is that we did not know medication discontinuations were intentional or unintentional. In addition, when patients got their medication dispensed after discharge, we assumed they were using it. However, noncompliance to medication is very common and getting medication dispensed does not mean that patients are using the medication. (33) In our study, only dispensed medication was included. We had no information on the medication patients might still have at home, which could lead to a delayed refill of the

medication. However, medication used chronically needs to be used as prescribed and refilled regularly. Another limitation is that a part of the study population had a follow-up time of 7 days to one month after discharge due to rehospitalization. These patients had a shorter follow-up compared with other patients having a longer follow-up period and thus had more time to refill their medication. However, a small proportion of the patients had a short follow-up (7.4%). The majority of the patients (83.7%) had a follow-up of at least three months after discharge. Another limitation of our study could be the lack of information on hospitalization at other hospitals, although we consider this unlikely for the majority of the patients.

Health care providers need to be aware of the risk of medication discontinuation and other medication changes after discharge. Change of setting puts patients at a higher risk for discontinuation of medication. Therefore medication reconciliation and transition of information are important between health care providers of primary and secondary care. (5, 38) When health care providers decide to discontinue medication, date and reason for medication discontinuation needs to be recorded in patient files. Treatment of both somatic and psychiatric diseases is important for the patient's overall health. (41) Future research is needed to assess to what extent medication discontinuation and changes at discharge are intentional or unintentional and how they influence patients' overall health.

Conclusions

In conclusion, almost 70% of the patients discontinued one or more medications after discharge from a psychiatric hospital. Somatic medication was more often discontinued and started after discharge than psychiatric medication. Medication discontinuation can be intentional but it seems unlikely that medication intended for chronic use such as cardiovascular medication had to be discontinued. Also, substantial discontinuation of psychiatric medication, 25.2% of antipsychotics and 13.9% of antidepressants, is worrisome. More research is needed to assess if these medication discontinuations and other changes are intentional or unintentional and its consequences for patients' overall health.

References

(1) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Discontinuation of Somatic Medication During Psychiatric Hospitalization. Ann Pharmacother 2014; 48: 1415-24.

(2) Stuffken R, Egberts TC. Discontinuities in drug use upon hospital discharge. Pharm World Sci 2004; 26: 268-70.

(3) Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in The Netherlands. Ann Pharmacother 2008; 42: 933-9.

(4) Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005; 173: 510-5.

(5) Karapinar F, van den Bemt PM, Zoer J, Nijpels G, Borgsteede SD. Informational needs of general practitioners regarding discharge medication: content, timing and pharmacotherapeutic advice. Pharm World Sci 2010; 32: 172-8.

(6) Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care--a large-scale follow-up study. Eur J Clin Pharmacol 2007; 63: 783-90.

(7) Corry M, Bonner G, McEntee S, Dugan J, MacAuley D. Hospitals do not inform GPs about medication that should be monitored. Fam Pract 2000; 17: 268-71.

(8) Himmel W, Kochen MM, Sorns U, Hummers-Pradier E. Drug changes at the interface between primary and secondary care. Int J Clin Pharmacol Ther 2004; 42: 103-9.

(9) Bolas H, Brookes K, Scott M, McElnay J. Evaluation of a hospital-based community liaison pharmacy service in Northern Ireland. Pharm World Sci 2004; 26: 114-20.

(10) Zhou Y, Rosenheck RA, Mohamed S, Fan N, Ning Y, He H. Retrospective assessment of factors associated with readmission in a large psychiatric hospital in Guangzhou, China. Shanghai Arch Psychiatry 2014; 26: 138-48.

(11) Tomko JR, Ahmed N, Mukherjee K, Roma RS, Dilucente D, Orchowski K. Evaluation of a discharge medication service on an acute psychiatric unit. Hosp Pharm 2013; 48: 314-20.

(12) Vigod SN, Kurdyak PA, Dennis CL, Leszcz T, Taylor VH, Blumberger DM, Seitz DP. Transitional interventions to reduce early psychiatric readmissions in adults: systematic review. Br J Psychiatry 2013; 202: 187-94.

(13) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010; 25 Suppl 2: S22-8.

(14) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Prevalence of medication use for somatic disease in institutionalized psychiatric patients. Pharmacopsychiatry 2013; 46: 274-80.

(15) American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. 2004; 27: 596-601.

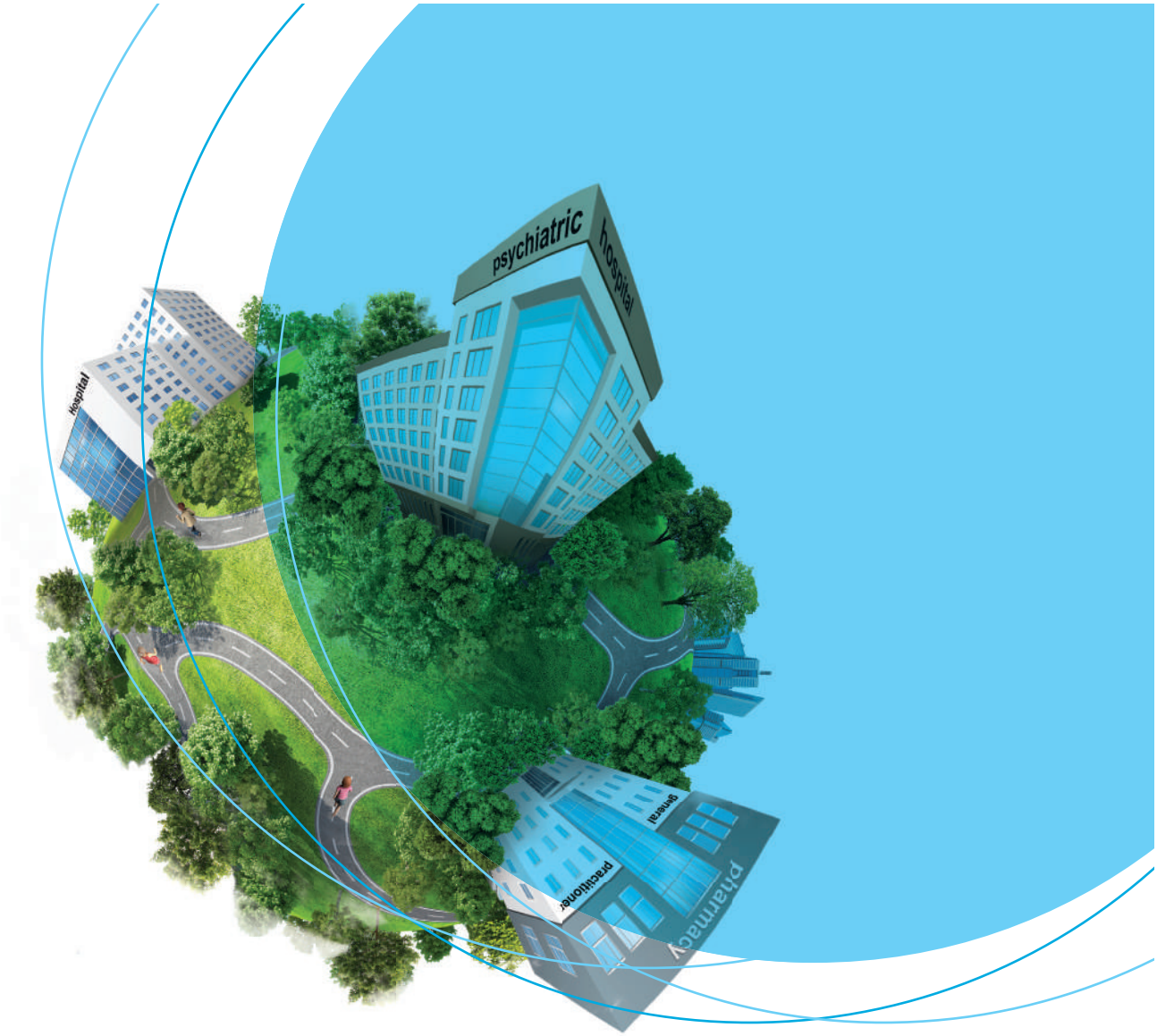
(16) De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, van Winkel R, Mitchell AJ. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry 2011; 199: 99-105.

(17) Iacovides A, Siamouli M. Comorbid mental and somatic disorders: an epidemiological perspective. Curr Opin Psychiatry 2008; 21: 417-21.
(18) Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999; 187: 496-502.
(19) Miller BJ, Paschall CB,3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. Psychiatr Serv 2006; 57: 1482-7.
(20) Mookhoek EJ, Van De Kerkhof PC, Hovens JE, Brouwers JR, Loonen AJ. Skin disorders in chronic psychiatric illness. J Eur Acad Dermatol Venereol 2010; 24: 1151-6.
(21) Katsamanis M, Lehrer PM, Escobar JI, Gara MA, Kotay A, Liu R. Psychophysiologic treatment for patients with medically unexplained symptoms: a randomized controlled trial. Psychosomatics 2011; 52: 218-29.
(22) Simon GE, VonKorff M. Somatization and psychiatric disorder in the NIMH Epidemiologic Catchment Area study. Am J Psychiatry 1991; 148: 1494-500.
(23) Walker EA, Roy-Byrne PP, Katon WJ. Irritable bowel syndrome and psychiatric illness. Am J Psychiatry 1990; 147: 565-72.
(24) Walker EA, Roy-Byrne PP, Katon WJ, Li L, Amos D, Jiranek G. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. Am J Psychiatry 1990; 147: 1656-61.
(25) Andreski P, Chilcoat H, Breslau N. Post-traumatic stress disorder and somatization symptoms: a prospective study. Psychiatry Res 1998; 79: 131-8.
(26) Engel CC,Jr, Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for gulf war-related health concerns. Psychosom Med 2000; 62: 739-45.
(27) Deary IJ. A taxonomy of medically unexplained symptoms. J Psychosom Res 1999; 47: 51-9.
(28) Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 2011; 21: 517-35.
(29) Stoklosa J, Ongur D. Rational antipsychotic choice: weighing the risk of tardive dyskinesia and metabolic syndrome. Harv Rev Psychiatry 2011; 19: 271-6.
(30) Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. Drugs Aging 2012; 29: 15-30.
(31) Sylvestre MP, Abrahamowicz M, Capek R, Tamblyn R. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. Int Psychogeriatr 2011;: 1-10.
(32) Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. J Clin Psychopharmacol 2012; 32: 309-16.
(33) Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand 2009; 119: 78-84.
(34) Abdullah-Koolmees H, Gerbranda T, Deneer VH, Tjoeng MM, De Ridder AJ, Gardarsdottir H, Heerdink ER. Discontinuation of anticoagulant care during admission to a psychiatric hospital. Eur J Clin Pharmacol 2012; 69: 1025-9.

(35) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, Heerdink ER. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010; 43: 221-4.
(36) Altrecht MHC, 2013. Annual Report 2013 of Altrecht/Jaarverslag 2013; 2013: 19-94; http://www.jaarverslagaltrecht.nl/; 2014-07-17.
(37) WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011.
(38) Prins MC, Drenth-van Maanen AC, Kok RM, Jansen PA. Use of a structured medication history to establish medication use at admission to an old age psychiatric clinic: a prospective observational study. CNS Drugs 2013; 27: 963-9.
(39) Policy document: transfer of information on medication [in Dutch]; 2012; http://www.medicatieoverdracht.nl/; 2014-07-17.
(40) Karapinar-Carkit F, van Breukelen BR, Borgsteede SD, Janssen MJ, Egberts AC, van den Bemt PM. Completeness of patient records in community pharmacies post-discharge after in-patient medication reconciliation: a before-after study. Int J Clin Pharm 2014; 36: 807-14.
(41) Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. Br J Psychiatry 2012; 201: 435-43.

Appendix 1: Medication classes and ATC code(s).

Medication classes	ATC CODE(S)
Somatic	
Acid & bowel related medications	A02B and A03A
Laxatives	A06A
Antidiabetics	A10A and A10B
Cardiovascular medications	B01A, B02B, C01, C02A, C02C, C02K, C02N, C03, C04A, C07A, C08C, C08D and C09
Lipid lowering medications	C10A and C10B
Asthma and COPD medications	R03A and R03B
Antihistamines	R06A excl. R06AE03, R06AD02 and R06AX26
Thyroid medications	H03A and H03B
Antifungals and antibiotics	J01A, J01C, J01E, J01F, J01M, J01X and J02A
Analgesics and antirheumatics	N02A, N02B and M01A, excl. N02BE01 and N02BE51
Vitamins	A11C, A11D, A11G, A11H and B03B excl. A11GA01, A11HA03, A11HA02 and B03BB01
Dermatologicals	D except D01AC09, D01AC01, D01AC02, D10AE01, D01AE15, D1AF, D11AX01, D02A A – E/X, D04AB07, D06BB03 and D06BB06.
Anti-cholinergic medications	N04A
Any somatic medication	All ATC codes excl. A11GA01, A11HA03, A11HA02, B03BB01, D01AC09, D01AC01, D01AC02, D10AE01, D01AE15, D1AF, D11AX01, D02A A – E/X, D04AB07, D06BB03 and D06BB06, G02B, G03A, N05, N06, N07B, N02BE01, N02BE51, N03AF01, N03AG01, N03AX09 R06AE03, R06AD02 and R06AD02.
Psychiatric	
Antipsychotics (excl. lithium)	N05A excl. N05AN
Mood stabilizers (lithium. carbamazepine. valproic acid and lamotrigine)	N05AN, N03AF01, N03AG01 and N03AX09
Anxiolytics and sedatives (incl. promethazine)	N05B, N05C and R06AD02
Antidepressants	N06A
Other psychotropics	N06B, N07B, N03AX11 and N03AE01
Any psychiatric medication	N05A, N03AF01, N03AG01 and N03AX09, N05B, N05C, R06AD02, N06A, N06B, N07B, N03AX11 and N03AE01



3.2

The Effect of Non-adherence to Antipsychotics on Rehospitalization in Patients with Psychotic Disorders

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Submitted for Publication

Abstract

Background

Many patients diagnosed with psychotic disorders are non-adherent to their antipsychotic medication leading to increased risk for rehospitalization. The aim of this study was to assess the association between adherence to antipsychotic drugs (APs) during three phases of medication use (initiation, implementation, and discontinuation) and rehospitalization during the first year after discharge.

Methods

In this retrospective follow-up study the study population included adult patients that were discharged from 4 psychiatric hospitals, with a diagnosis of psychotic disorder, that were hospitalized for ≥7 days, and who used oral APs at discharge. The main clinical outcome was psychiatric hospitalization within one year after discharge. Adherence to APs (exposure) was measured during the three phases of medication use (initiation, implementation and discontinuation). Adherence to APs during the initiation phase was assessed by comparing the risk of rehospitalization in those initiating and in those never initiating APs. Risk of rehospitalization was further assessed for those initiating during the 2nd week and initiating >2 weeks after discharge compared with patients initiating in the first week after discharge. For those initiating use during the first month, the implementation and discontinuation of antipsychotic drug use was assessed during the 2-12 months following discharge both overall and also separately during, 2nd to 3rd month, 4th to 6th month, and 7th to 12th month. Implementation and discontinuation was defined as continuers (reference), irregular users and discontinuers. Relative risks were measured using Cox regression analysis as hazard risks for rehospitalization with 95% confidence intervals.

Results

Of 320 included patients, 64.4% were male and had a mean age of 42.5 years (Standard Deviation (SD): 15.2), 77.8% initiated APs during the first month, and 44.4% was rehospitalized within 1 year after discharge. Patients never initiating antipsychotic use during follow up had a higher risk of rehospitalization (RR = 3.65; 95%CI: 2.42-5.51) when compared with those initiating use. Patients initiating use in the 2nd week had a 4.14 times (95% CI: 1.43-12.03) higher risk of rehospitalization during the first month after discharge, when compared with those initiating within one week from discharge. None of the patients intiating use after >2 weeks from discharge was rehospitalized thus the RR could not be assessed. Discontinuation of antipsychotic medication was associated with an RR of 2.29 (95% CI: 1.18-4.46) to be rehospitalized during the 2-12 months following discharge.

Conclusions

Not initiating antipsychotic medication is associated with higher risk of rehospitalization in patients with psychotic disorders. In addition, discontinuation of antipsychotic medication during 2nd to 12th month after discharge was associated with a higher relative risk of rehospitalization.

Introduction

There is ample evidence for the effectiveness of antipsychotics in the treatment of schizophrenia in reducing the number of recurrent psychotic episodes. (1) Likewise, patients with treatment failure have a high risk of relapse resulting in acute psychosis, leading to (re)hospitalizations and considerable economic costs. (2-12) About half of the patients with schizophrenia have a relapse within a period of two years after their first psychotic episode. (13) Laan and colleagues reported that 34% of patients discharged from a psychiatric hospital with treated schizophrenia were readmitted within six months. Research has shown that patients who are less adherent to antipsychotic therapy have at least a two times higher risk to be rehospitalized than those that adhere to antipsychotic therapy. (3,14,15) Studies show that adherence is a problem in patients suffering from schizophrenia reporting that about half of the patients are non-adherent to their antipsychotic medication. (12,15,16) Reasons for non-adherence include amongst others the lack of knowledge of the disease severity, the (fear of) side-effects, difficulty recognizing their own symptoms, non-effectiveness, not acknowledging the need for antispychotic therapy or distrust in the effectiveness. (17-20)

Medication use is a dynamic process that can be divided into three phases: initiation, implementation, and discontinuation. (21) During each phase the patient has the possibility to adhere completely, incompletely or to not use the therapy at all. The first phase, initiation consists of starting to use the medication prescribed by the physician. The second phase, implementation, describes the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen. In those that initiate therapy implementation can be seen/measured as continuous use or with gaps between antipsychotic prescriptions. The last phase, discontinuation, concerns stopping using the medication. Different aspects of non-adherence can be measured and different factors may play a role in influencing adherence to pharmacotherapy in each phase.

Most research investigating adherence to antipsychotic medication has focussed on a more general approach for assessing adherence, e.g. identifying patients being adherent or non-adherent during a predefined study period. (2-11,22) By investigating adherence in a more sophisticated way, i.e., by looking specifically into adherence during each phase of medication use and investigate the association with rehospitalization, better tailored interventions could be developed to target non-adherence and subsequently prevent rehospitalizations.

The aim of this study was to assess the association between non-adherence to antipsychotics and rehospitalization during the first year after discharge. Non-adherence to antipsychotic medication was assessed for the three phases of medication use including initiation, implementation, and discontinuation of antipsychotic therapy.

Methods

Setting

The Psychiatric Case Register Middle Netherlands (PCR-MN) registers all in- and outpatient psychiatric care provided in the province of Utrecht, The Netherlands, including Altrecht Mental Health Care. (23) The setting of this study was Altrecht Mental Health Care, a conglomeration of four psychiatric hospitals in The Netherlands serving a population of 800,000 inhabitants, with a total of 746 beds in 2013, treating patients with a wide range of mental diseases and providing both inpatient and outpatient care. (23) Medication was provided to inpatients by the institute's hospital pharmacy. The hospital files contained information on unique patient number, gender, birth date, psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-IV, date of diagnosis, Global Assessment of Functioning (GAF) score, type of care (inpatient and outpatient), department of admission, start and end of admission and medication use from 2006. For each patient, data on medication included the start and end date of use, and type of medication used and dosage. Only patients insured by Achmea health insurance during the year after psychiatric hospitalization were included. (15) This allowed for assessment of outpatient medication use in the year after hospitalization. Inpatient data were anonymously linked to outpatient data. Outpatient medication history contained all outpatient dispensing information covering prescriptions from general practitioners and all other physicians. The outpatient medication history contained information about gender, birth date, date of dispensing and medication dispensed. Medication types dispensed in The Netherlands are coded according to the World Health Organization (WHO) anatomical therapeutic chemical and the Defined Daily Dose (ATC/DDD) coding system. (24) The study was approved by the institution's scientific review board, and performed in accordance with The Federation of Dutch Medical Scientific Societies' Code of Conduct for the use of data in Health Research.

Design and Study Population

This retrospective follow-up study included adult patients (≥18 years) with a diagnosis of psychotic disorder (DSM-IV diagnosis codes 293, 295, 297.1, 297.3, 298.8 of 298.9) who were discharged from the psychiatric hospitals between 2006 and 2009 and were treated with an oral antipsychotic at discharge (ATC: N05A excl. lithium). For each patient, only the first hospitalization of seven days or longer during the study period was included. (15) The study period included psychiatric hospitalization and a follow-up of up to one year after discharge or until rehospitalization whichever came first (=end of follow-up).

Outcomes

The main clinical outcome in this study was psychiatric rehospitalization within one year after discharge. A subsequent hospitalization of a patient was considered a rehospitalization if the time between two subsequent hospitalizations exceeded seven

days. (15,25,26) Hospitalizations with less than seven days elapsing between discharge and the following admission were considered as one hospitalization.

Adherence

Adherence to antipsychotic medication (ATC code N05A, excluding lithium) during the year after discharge was assessed for each of the three phases of medication use – initiation, implementation, and discontinuation. The theoretical duration of each dispensed antipsychotic prescriptions was estimated in days based on the number of units dispensed and the prescribed daily dosage. Patients could get their antipsychotic dispensed too early or too late resulting in gaps between or overlaps of two subsequent prescriptions. If a subsequent antipsychotic dispensing was dispensed prior to the theoretical end date of a previous antipsychotic dispensing, the number of overlapping days was added to the theoretical end date of the subsequent antipsychotic dispensing. (27)

Initiation, Implementation, and Discontinuation

In The Netherlands, patients are not dispensed antipsychotic medication to take home from the hospital at discharge. Only when they are discharged just before or in the weekend they might get antipsychotic medication covering max 2-3 days. Patients are therefore expected to refill prescription(s) from their community pharmacy during the first week after discharge. The initiation of antipsychotic medication was first measured during the year after discharge (0-365 days) and defined as initiating antipsychotic use or not initiating antipsychotic use. Initiation was further investigated during the 1st month (0-31 days) and during the 12 months after discharge and divided into the following categories: antipsychotic dispensed during the 1st week following discharge, during the 2nd week following discharge, and >2 weeks following discharge.

For patients initiating use, their implementation and discontinuation of antipsychotics was assessed during the 2nd to 12th month (32-365 days) following discharge. Implementation and discontinuation of antipsychotic drug use was defined into different antipsychotic treatment patterns; continuers, irregular users and discontinuers. Patients without gaps between subsequent antipsychotic prescriptions were defined as continuous users, patients with gaps between two subsequent prescriptions of <3 weeks were defined as irregular users and patients with a gap of ≥3 weeks between prescriptions were defined as discontinuers.

Confounders

Variables considered as potential confounders were age at discharge, gender, duration of index hospitalization, history of substance use, number of antipsychotics used at discharge (1 or 2), and use of depot antipsychotics at discharge. (14,28-30) A confounder was included in the multivariate analysis when the coefficient for RR changed by >10%.

Data Analysis

A Kaplan-Meier analysis was performed to measure the time to initiation of the antipsychotic medication and the time to rehospitalization (One Minus Survival Function). Risk of rehospitalization during follow up was compared for those not initiating antipsychotics compared with those initiating antipsychotics. In addition, the risk was further assessed in those initiating antipsychotic use in the 2nd week and after >2 weeks following discharge when compared with patients initiating during the first week following discharge (reference). The association between adherence to antipsychotics and rehospitalization during the different phases of medication was further estimated for specific time intervals using a risk set design. This involves comparing patients hospitalized with those not (yet) hospitalized at each moment during the follow up time that rehospitalization occurs. Initiation was assessed during the first month following discharge comparing risk of rehospitalization in those initiating antipsychotic use in the 2nd week and in those initiating >2 weeks following discharge with the risk of rehospitalization in patients initiating use during the first week following discharge (reference). For the implementation and discontinuation, the risk of rehospitalization for irregular users and discontinuers was compared with the risk of rehospitalization in continuous users (reference) for the whole follow up period (2nd to 12th months) as well as for the time intervals including the 2nd and the 3rd month (32-93 days), 4th to 6th month (94-183 days) and 7th to 12th month (184-365) following discharge. Relative risks (RR) of rehospitalization were measured by means of cox proportional hazards regression as hazard risks with 95% confidential intervals (95% CI). Statistical significance was determined at p value <0.05. Results are indicated in this paper with "*" when p<0.05, "**" when p<0.01, and "***" when p<0.001. First, crude relative risks for the association between antipsychotic adherence and rehospitalization were assessed. Second, relative risks for the association between antipsychotic adherence and rehospitalization were adjusted for potential confounders. All data analysis were performed using IBM Software package SPSS (version 20.0), and statistical software R (version 2.15.1) for Windows.

Results

A total of 320 patients was included. The mean age was 42.5 years (Standard Deviation (SD): 15.2), 206 (64.4%) were male and most patients (72.5%) were diagnosed with schizophrenia (Table 1). The mean patient GAF score was 44.9 (SD: 12.6) and median duration of hospitalization was 64.0 days (range: 7-1409). 296 (92.5%) patients used only oral antipsychotics and 24 patients (7.5%) used both oral and depot oral antipsychotics at discharge. 87.2% of the 320 patients picked up their antipsychotic medication during one year after discharge with most patients (77.8%) picking up their antipsychotic within one month (Figure 1). Most patients got an olanzapine dispensed after discharge (30.6%) followed by risperidon (16.3%). 142 (44.4%) patients were rehospitalized within one year after discharge (Figure 2), 34 (10.6%) during the 1st month, 33 (10.3%) during the 2nd and

3rd month, 32 (10.0%) during the 4th to 6th month. The median time to rehospitalization was 126 days (range: 7-364).

Table 1: Patient characteristics at discharge.

Characteristics	N patients
Total	320
Mean age (years, SD)	42.5 (15.2)
<45 years	192 (60.0%)
45 – 59 years	81 (25.3%)
≥60 years	47 (14.7%)
Gender	
Male	206 (64.4%)
Diagnosis of psychotic disorders	
DSM-IV 298.x – brief psychotic disorder	79 (24.7%)
DSM-IV 295.x – schizophrenia	232 (72.5%)
Other diagnosis: DSM-IV 293.x – psychotic disorder due to medical condition or DSM-IV 297.x – delusional disorder	9 (2.8%)
Psychiatric co-morbidities (DSM IV-codes)	
History of substance use	55 (17.2%)
No history of substance use	265 (82.8%)
Median duration of baseline hospitalization (range)	64.0 (7-1409)
7 – 20 days	57 (18.2%)
21 – 59 days	97 (30.8%)
≥60 days	166 (50.9%)
Number of antipsychotics (AP) used within 7 days before discharge	
Used single oral AP	290 (90.6%)
Used two oral APs	30 (9.4%)
Oral/depot antipsychotic used within 7 days before discharge	
Used only oral AP	296 (92.5%)
Used oral AP and depot AP	24 (7.5%)

Patients that did not initiate antipsychotic medication had a greater risk (RR = 3.65, 95% CI: 2.42-5.51***, adjusted for age, diagnosis and history of substance use) to be rehospitalized compared with patients that initiated antipsychotic medication. Patients that initiated antipsychotic medication use during the 2nd week after discharge had an RR of 0.96 (95% CI: 0.52-1.77*) and those that initiated after 2 weeks had an RR of 0.42 (95% CI: 0.23-0.75**) of being rehospitalized within a year after discharge compared with those who initiated during the 1st week after discharge. However, when assessing the risk of being rehospitalized in the first month following discharge we found a fourfold higher risk of rehospitalization in those initiating use during the 2nd week after discharge (RR = 4.14, 95% CI: 1.43-12.03**) when compared with those that started during the first week

(Table 2). None of the patients that initiated AP use after >2 weeks from discharge was rehospitalized in the first month thus the RR could not be assessed.

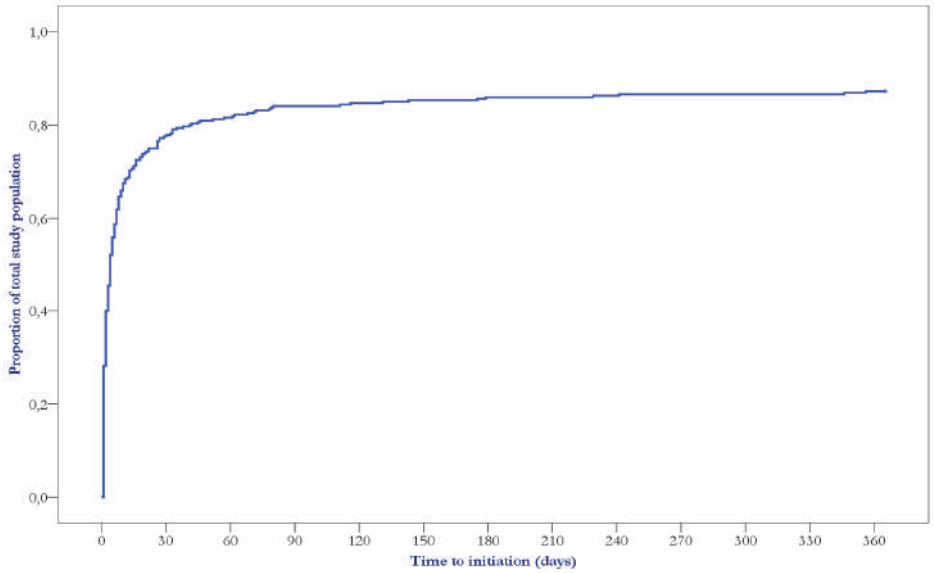


Figure 1: Time from discharge until an antipsychotic medication is dispensed from the community pharmacy.

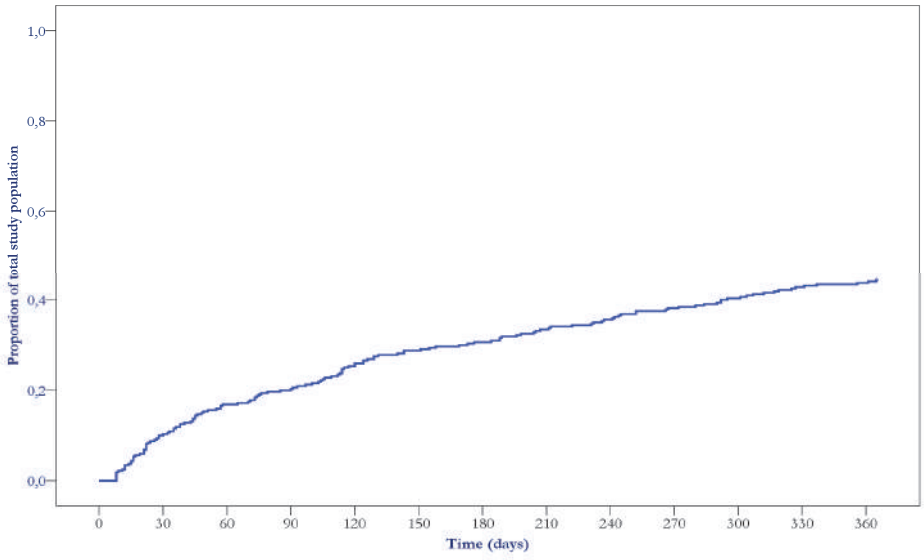


Figure 2: Proportion of patients with psychotic disorders rehospitalized during a year following discharge from a psychiatric hospital.

Table 2: The risk of rehospitalization during the initiation phase of antipsychotic drug use (N=279).

Patients	1st month[1]		12 months[2]	
Initiated	RR Crude	RR Adjusted	RR Crude	RR Adjusted
In 1st week	Ref	Ref	Ref	Ref
In 2nd week	4.43 (1.52-12.89)**	4.14 (1.43-12.03)**	1.02 (0.56-1.86)	0.96 (0.52-1.77)
After >2 weeks	NA	NA	0.48 (0.27-0.85)*	0.42 (0.23-0.75)**

* p<0.05. **p<0.01.
Ref = Reference. NA=Not applicable.
1 Adjusted for use of depot antipsychotics.
2 Adjusted for diagnosis, age, and history of substance abuse.

Table 3: The risk of rehospitalization during implementation and discontinuation phase for those initiated antipsychotic medication during 1st month after discharge (N=249).

Adherence	2nd to 12th month[1]		2nd to 3rd month[2]		4th to 6th month[3]		7th to 12th month[4]	
	RR Crude	RR Adjusted	RR Crude	RR Adjusted	RR Crude	RR Adjusted	RR Crude	RR Adjusted
Continuers	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Irregular users	1.10 (0.66-1.84)	1.12 (0.67-1.87)	0.73 (0.26-1.99)	0.73 (0.26-1.99)	1.08 (0.41-2.85)	1.26 (0.47-3.39)	1.54 (0.73-3.23)	1.69 (0.80-3.57)
Dis-continuers	1.84 (0.95-3.53)	2.29 (1.18-4.46)*	2.63 (0.76-9.13)	2.63 (0.76-9.13)	4.47 (1.71-11.65)**	5.68 (2.09-15.48)***	0.56 (0.13-2.39)	0.63 (0.15-2.69)

* p<0.05. **p<0.01. ***p<0.001
RR = relative risk. 95% CI = 95% Confidence Interval
1 Adjusted for diagnosis, age, and history of substance abuse.
2 There were no confounders.
3 Adjusted for diagnosis and number of antipsychotics.
4 Adjusted for diagnosis.

Implementation and discontinuation were assessed for those patients that initiated antipsychotic during the 1st month after discharge, Table 3. Risk of rehospitalization for irregular users was 1.12 times higher than for continuous users during the 2nd to 12th month after discharge (RR = 1.12, 95% CI = 0.67-1.87). Although not significant, the risk was lower during the 2nd and 3rd month (RR = 0.73, 95% CI: 0.26-1.99) in irregular users, but increased during the 4th to 6th month (RR = 1.26, 95%CI: 0.47-3.39) and the 7th to 12th month (RR = 1.69, 95% CI: 0.80-3.57). On the other hand, discontinuers had a twofold risk of being rehospitalized during the 2nd to 12th month (RR = 2.29, 95% CI: 1.18-4.46*) when compared with those continuing antipsychotic use. This risk was also present during the 2nd and 3rd month (RR = 2.63, 95% CI: 0.76-9.13) and increased to 5.68 (2.09-15.48***) during the 4th to 6th month. Only during the 7th to 12th month discontinuers were less frequently rehospitalized (RR = 0.63, 95% CI: 0.15-2.69) but this did not reach statistical significance.

Discussion

The aim of this study was to assess the association between non-adherence to antipsychotic medication and rehospitalization during the first year after discharge. Non-adherence to antipsychotic medication was assessed for the three phases of medication use being initiation, implementation, and discontinuation. We found that not initiating antipsychotic medication after discharge was associated with a higher risk of rehospitalization. Further, those that did not initiate antipsychotic medication within the first week after discharge had a higher risk of rehospitalization during the 1st month following discharge. In addition, patients that did start, but subsequently discontinued antipsychotic medication had a twofold risk of rehospitalized during 2nd to 12th month after discharge when compared with those that continued antipsychotic therapy.

Almost half of patients (44.4%) included in our study were rehospitalized within one year after discharge, which is comparable with what has been reported in earlier studies. (2-12) The rate of rehospitalization was highest during the first two months after discharge (Figure 1). Although few earlier studies have distinguished between moments of rehospitalization, this is in line of the results of Zilber and colleagues. They showed that rehospitalization of psychiatric patients was highest during the 1st month after discharge. (25) Most patients, or 77%, initiated antipsychotic use within one month from discharge which is comparable with results from Reutfors and colleagues reporting that 53.1% (95% CI: 49.9-56.4%) initiate antipsychotics within one week and 80.2% within 6 months (95% CI: 77.4-82.8%) after discharge. (26)

In our study we found that initiation of antipsychotic medication is associated with risk of rehospitalization. Patients not initiating antipsychotic medication had a higher risk of being rehospitalized within a year following discharge. In addition, patients initiating in the 2nd week or later and those who did not initiate antipsychotics were more frequently rehospitalized during the 1st month after discharge. This is in line with earlier findings although other studies use different adherence measures. Not using antipsychotics continuously and having gaps in antipsychotic medication are frequently associated with (re)hospitalization. (2-5,7,9,10,13-15,26,31,32) For instance, Boden et al. reported that no initiation of antipsychotic medication after discharge was accompanied with higher risk for patients to be rehospitalized. (14)

In our study, non-adherence was associated with higher risk of rehospitalization. Irregular users seemed to have a 1.12 to 1.69 higher RR to be rehospitalized than continuous users during the whole year after discharge, although not statistically significant. Also, discontinuers had a significantly twofold increased risk of rehospitalization when compared with those continuing use. This is comparable with earlier findings that show that gaps between antipsychotic prescriptions and antipsychotic non-adherence in general is associated with risk of rehospitalization. (2-5,7,9,10,13-15,31-33) Relative risk for

discontinuers was only lower during the 7th to 12th month after discharge compared with continuous users. However, these were patients that had been treated with antipsychotics for at least 7 months without a relapse thus these might represent patients with a milder disease severity.

Non-adherence to antipsychotic therapy is often not actively monitored and can therefore be overlooked by the patients' care providers. (33) Community pharmacists have a unique insight into patients' use of medication and could play an important role in intervening and signaling when patients engage in non-initiation, insufficient implementation or discontinuation. Early identification of patients with a high risk for rehospitalization is important as it allows for intensifying the monitoring of these patients which could prevent rehospitalization. (2-11) Patients at risk for non-adherence should therefore be identified and strategies developed to improve their adherence during the various phases of medication use. These could be in form of patient participation, educating patient about their medicines, or a more intensive cooperation between psychiatrists and pharmacists.

To the best of our knowledge, this is the first study that investigated the association between adherence to antipsychotic drugs by looking specifically at the different phases of medication use (i.e. initiation, implementation, and discontinuation) and rehospitalization in patients with psychotic disorders. Previous studies often apply a more general classification of patients as adherent or non-adherent and do not distinguish between different phases of antipsychotic use. Our method allows for the identification of specific intervention points that can be tackled in future research on minimization of relapse in patients with psychotic disorders.

We assumed that patients with a psychotic disorder should be prescribed antipsychotic medication after discharge based on the applicable guidelines, which state that patients need to continue their medication for at least 1 year after reaching remission. (34,35) No information was available on disease status, support of relatives to refill medication, and therapeutic alliance between patients, reason of rehospitalization and their health care providers to distinguish between intentional or unintentional antipsychotic discontinuation. The different phases of adherence were based on refills. We did not know how patients used their medication at home. (36) A limitation of our study could be that we did not have information about hospitalization in other hospitals, which would have led to an underestimation of rehospitalizations. Patients could have been admitted to another psychiatric hospital if they migrated to another province or when the included psychiatric hospitals were full. However, this seems unlikely for the majority of the patients. This study was performed in one region in The Netherlands. However, with regards to patients characteristics the patients included in our study were comparable with other studies. Olanzapine and risperidon were the most prescribed antipsychotics, which was also the case in previous studies from Sweden and Finland. (26,37)

Conclusions

In conclusion, rehospitalization was most frequent during the first two months following discharge. Not initiating antipsychotic medication is associated with a higher risk of rehospitalization in patients with psychotic disorders. In addition, discontinuation of antipsychotic medication during 2nd to 12th month after discharge was associated with a higher relative risk of rehospitalization. Patients at risk for non-adherence should be identified and strategies developed to improve their adherence during the various phases of medication use. Future, prospective studies are needed to assess to what extent patient care can then be improved by implementing these strategies.

References

(1) Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ 1998 Oct 31;317(7167):1181-1184.

(2) Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008 Apr 30;8:32.

(3) Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004 Aug;55(8):886-891.

(4) Law MR, Soumerai SB, Ross-Degnan D, Adams AS. A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. J Clin Psychiatry 2008 Jan;69(1):47-53.

(5) dosReis S, Johnson E, Steinwachs D, Rohde C, Skinner EA, Fahey M, et al. Antipsychotic treatment patterns and hospitalizations among adults with schizophrenia. Schizophr Res 2008 Apr;101(1-3):304-311.

(6) Fenton WS, Kane JM. Clinical challenges in the psychopharmacology of schizophrenia. Schizophr Bull 1997;23(4):563-565.

(7) Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007 Oct;23(10):2305-2312.

(8) Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008 Jan;34(1):173-180.

(9) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011 Jun;168(6):603-609.

(10) Jung SH, Kim WH, Choi HJ, Kang MH, Lee JS, Bae JN, et al. Factors affecting treatment discontinuation and treatment outcome in patients with schizophrenia in Korea: 10-year follow-up study. Psychiatry Investig 2011 Mar;8(1):22-29.

(11) Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res 2002 Oct 1;57(2-3):209-219.

(12) Herings RM, Erkens JA. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. Pharmacoepidemiol Drug Saf 2003 Jul-Aug;12(5):423-424.

(13) Ohmori T, Ito K, Abekawa T, Koyama T. Psychotic relapse and maintenance therapy in paranoid schizophrenia: a 15 year follow up. Eur Arch Psychiatry Clin Neurosci 1999;249(2):73-78.

(14) Boden R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res 2011 Dec;133(1-3):36-41.

(15) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.

(16) Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002 Oct;63(10):892-909.

(17) Prins MC, Drenth-van Maanen AC, Kok RM, Jansen PA. Use of a structured medication history to establish medication use at admission to an old age psychiatric clinic: a prospective observational study. CNS Drugs 2013 Nov;27(11):963-969.
(18) Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008 Jan;69(1):106-113.
(19) Karow A, Pajonk FG. Insight and quality of life in schizophrenia: recent findings and treatment implications. Curr Opin Psychiatry 2006 Nov;19(6):637-641.
(20) Karow A, Czekalla J, Dittmann RW, Schacht A, Wagner T, Lambert M, et al. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. J Clin Psychiatry 2007 Jan;68(1):75-80.
(21) Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012 May;73(5):691-705.
(22) McIntosh AM, Conlon L, Lawrie SM, Stanfield AC. Compliance therapy for schizophrenia. Cochrane Database Syst Rev 2006 Jul 19;(3)(3):CD003442.
(23) Altrecht MHC, 2013. Annual Report 2013 of Altrecht/Jaarverslag 2013. 2013; Available at: http://www.jaarverslagaltrecht.nl/. Accessed October, 7th, 2013.
(24) WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. 2010.
(25) Zilber N, Hornik-Lurie T, Lerner Y. Predictors of early psychiatric rehospitalization: a national case register study. Isr J Psychiatry Relat Sci 2011;48(1):49-53.
(26) Reutfors J, Brandt L, Stephansson O, Kieler H, Andersen M, Boden R. Antipsychotic prescription filling in patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 2013 Dec;33(6):759-765.
(27) Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010 Apr;63(4):422-427.
(28) Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000 Feb;51(2):216-222.
(29) Gorwood P. Factors associated with hospitalisation of patients with schizophrenia in four European countries. Eur Psychiatry 2011 May;26(4):224-230.
(30) Hugenholtz GW, Stolker JJ, Heerdink ER, Nolen WA, Leufkens HG. Short-acting parenteral antipsychotics drive choice for classical versus atypical agents. Eur J Clin Pharmacol 2003 Mar;58(11):757-760.
(31) Remington G, Kwon J, Collins A, Laporte D, Mann S, Christensen B. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. Schizophr Res 2007 Feb;90(1-3):229-237.
(32) Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care 2002 Aug;40(8):630-639.

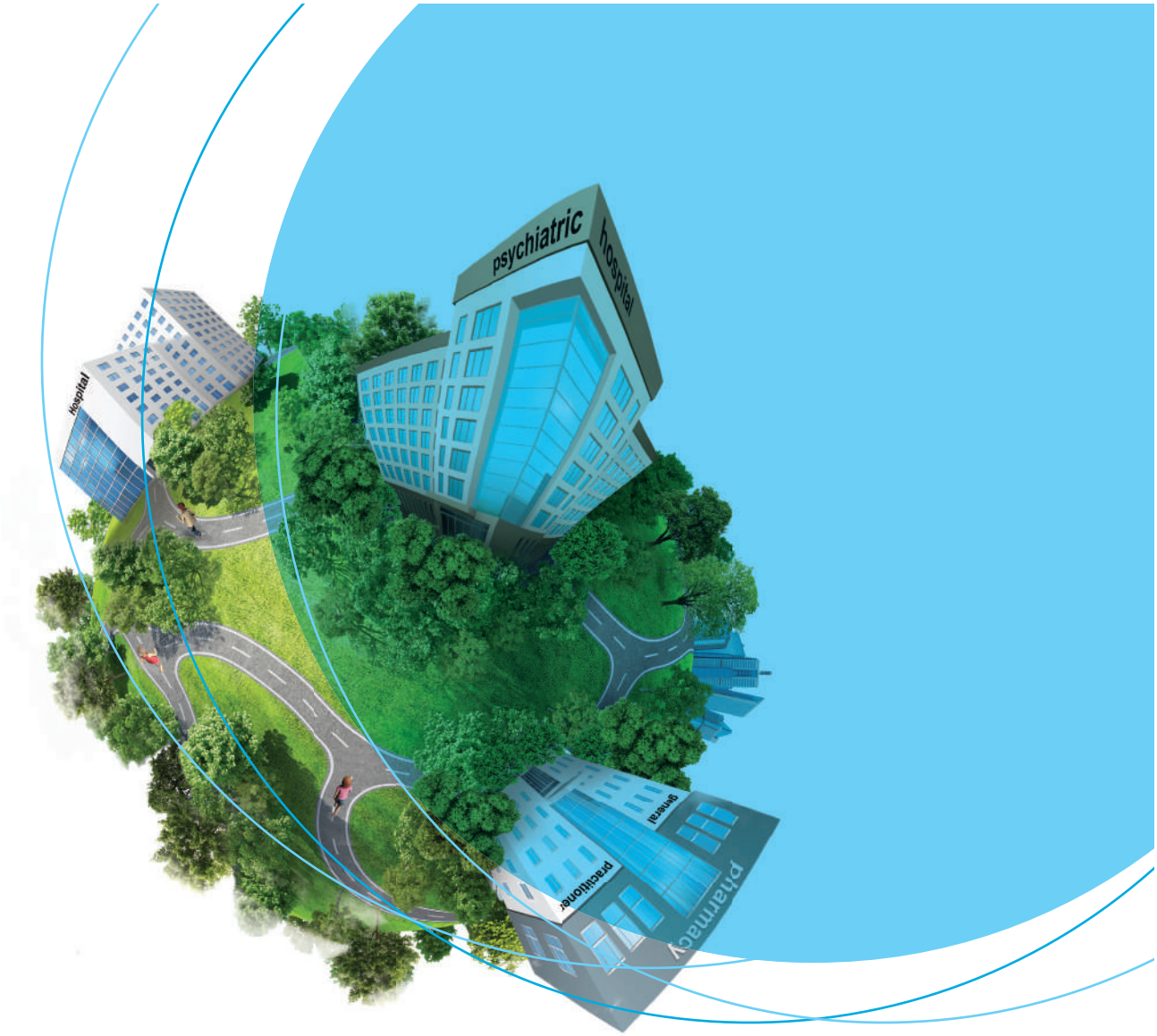
(33) Hui CL, Chen EY, Kan C, Yip K, Law C, Chiu CP. Anti-psychotics adherence among out-patients with schizophrenia in Hong Kong. Keio J Med 2006 Mar;55(1):9-14.

(34) American Psychiatric Association. PRACTICE GUIDELINE FOR THE Treatment of Patients With Schizophrenia Second Edition. 2004; Available at: http://psychiatryonline.org/. Accessed December 21, 2014.

(35) NICE guidelines. Psychosis and schizophrenia in adults: treatment and management. 2014; Available at: http://www.nice.org.uk/guidance/cg178. Accessed December 21, 2014.

(36) Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand 2009 Jan;119(1):78-84.

(37) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia. Am J Psychiatry 2011 Jun;168(6):603-609.



3.3

Predicting Rehospitalization in Patients Treated with Antipsychotics: a Prospective Observational Study

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Submitted for Publication

Abstract

Background

Prediction of rehospitalization in patients on antipsychotics is important to identify patients who need additional support. The aim of this study was to identify factors that predict rehospitalization in patients treated with antipsychotics.

Methods

In this prospective observational study, adult patients suffering from psychotic or bipolar I disorders who had been hospitalized in a psychiatric hospital for ≥7 days and treated with oral antipsychotics at discharge were included. The outcome of interest was rehospitalization within six months after discharge. Four prediction models using Cox proportional hazards for rehospitalization were constructed including the following characteristics: 1. patient/disease characteristics, 1+2. patient/disease and medication characteristics, 1+2+3. patient/disease and medication characteristics, and patients' attitude towards medicine use 1+2+3+4. patient/disease and medication characteristics, patients' attitude towards medicine use, and health care provider assessments. Risk scores were calculated for the prediction model with highest area under the receiver operating characteristic curve (AUC_{ROC}) by multiplying all regression coefficients by 10, summing them and then adding 14.

Results

87 Patients were included of which 33.3% was rehospitalized within six months after discharge. The model that included patient/disease (duration of index hospitalization, diagnosis, and age) and medication characteristics (number of antipsychotic agents in use and patient was reminded of taking medication by others), attitude towards medicine use (beliefs groups), and health care provider assessments (prediction of rehospitalization by the nurse, and whether the physician and the nurse discussed antipsychotic adherence during hospitalization) had the highest predicting ability (AUC_{ROC}=0.74). Patients in the upper tertile had a risk score between 34.1 and 52.0 and were most often rehospitalized (62.1%), patients in the middle tertile had a risk score between 24.7 and 34.0 and 31.0% were rehospitalized, and the lower tertile had a risk score of 0.0 to 24.6 and 6.9% were rehospitalized.

Conclusions

Rehospitalization was best predicted by a combination of variables from the patient/disease and medication characteristics, patients' attitude towards medicine use, and health care providers assessment. The risk scores can relatively easily be assessed at discharge to predict rehospitalization within six months after discharge.

Introduction

There is ample evidence for the effectiveness of antipsychotics in the treatment of psychotic and bipolar I disorders. However, relapse-rates are high in patients with psychotic and bipolar I disorders discharged from hospital with antipsychotic medication, leading to episodes of acute psychosis/mania and (re)hospitalizations. Up to 34% of the patients have a relapse within six months after hospitalization for a psychotic episode. (12) This has a high impact on quality of life of patients and may lead to considerable economic costs. (1-15) About half of the patients with psychotic or bipolar I disorders are (partially) non-adherent with their antipsychotic treatment either by not initiating the medication, skipping dosages, or discontinuing treatment. (2,11-14,16) In an earlier study we found that late or no initiation of antipsychotic medication after discharge as well as discontinuation were associated with a higher risk of rehospitalization. (Chapter 3.2) A 2.4 greater probability of hospitalization has been reported in those who are less than 80% adherent to antipsychotic therapy. (17)

It would be useful to be able to early identify patients at higher risk for rehospitalization in order to provide these patients with additional support. Previous studies have shown that patient, disease and treatment characteristics including age, duration of hospitalization, and severity of disease can be predictors for rehospitalization, as well as type of treatment and early non-adherence with antipsychotic medication. (18,19) Health care providers, both psychiatrists and nursing staff, may have insights in patients' adherence, which may be used to predict future success of therapy. (21) It is unknown whether patients' attitude towards medication therapy is a predictor for relapse in patients being treated with antipsychotics. Patients' attitude towards medication use has two important dimensions: necessity and concern. Necessity reflects the perceived need for use of the medication by the patient, while concern measures the fear of negative outcomes from use of the medication, such as side effects, and addiction. (13,20)

The aim of this study was to predict the risk of rehospitalization in patients treated with antipsychotic medication discharged from a psychiatric hospital, using patient, disease and treatment characteristics, patients' beliefs and attitudes towards antipsychotic medication, and health care providers' expectations towards patients' adherence and probability of rehospitalization.

Methods

Setting

This study was performed in nine departments of Altrecht Mental Health Care (Altrecht), a conglomeration of five psychiatric hospitals in The Netherlands serving a total population of 800,000 inhabitants. Patients with a wide range of mental diseases are treated here and

both inpatient and outpatient care is provided. (22) Medication for inpatients is provided by the external hospital pharmacy Brocacef. The hospital files contain information about patient characteristics and data on medication use during hospitalization. Information about patients' medication dispensed during the six months before and after discharge was collected from patients' community pharmacy. Date of discharge was considered as index date. The study period included the six months following the index date or until patients were rehospitalized (=end of follow-up) whichever came first. The study was approved by the institution's scientific board, and performed in accordance with The Federation of Dutch Medical Scientific Societies' Code of Conduct for the use of data in Health Research.

Design and Study Population

A prospective, observational study was performed in which patients were followed from discharge up to six months or until rehospitalization, whichever came first. The study population included adult patients (≥18 years) with a psychotic or bipolar I disorder that were treated with oral antipsychotics at discharge (ATC: N05A excl. lithium) and who were hospitalized for 7 days or longer. (12) Psychotic disorder was defined as having one of the following diagnoses: DSM-IV diagnosis codes 293, 295, 297.1, 297.3, 298.8 or 298.9 and bipolar disorder I as DSM-IV diagnosis codes 296 (excl. 296.89 and 296.9) during hospitalization. If patients were rehospitalized within 7 days after discharge, we considered this hospitalization as a part of the index hospitalization. (12,18,23) Patients discharged between May 2013 and April 2014 were eligible for participation in the study and received information about the study from a nurse or a researcher (KE) prior to being discharged from Altrecht. Those patients who gave informed consent filled in general questions before discharge regarding gender, age, their community pharmacy, and the Beliefs about Medicines Questionnaire (Appendix 1). Besides the questions for the patients, the nurse and the physician involved in patients' treatment both filled in a health care provider's questionnaire on patients' expected adherence, probability of rehospitalization and therapeutic relationship which will be explained later on (Appendix 2).

Outcome

The main clinical outcome was (time to) psychiatric rehospitalization within six months after discharge. Patients were considered to be rehospitalized when the time between discharge and rehospitalization was at least 7 days. (12,18,23)

Patient and Diseases Characteristics

Patient characteristics collected from the hospital files were gender, age (continuous), diagnosis, duration of index hospitalization (continuous in days and categorized in tertiles to obtain three equally divided groups: 7-29, 30-60, ≥61 days), history of substance use (yes/no, according to DSM-IV TR), department at discharge (closed/open unit), first admission in a psychiatric hospital (yes/no), residential situation after discharge (alone,

living with others or homeless/unknown), and Global Assessment of Functioning (GAF) score at discharge (continuous). (14,24-26)

Medication Characteristics

Data on medication characteristics were obtained from the hospital files and included number of antipsychotics prescribed at discharge (1 agent or ≥2 agents), type of antipsychotic medication (first generation, second generation (largest group=reference group), or both), and number of different medicines used besides antipsychotic medication at discharge (number of co-medications). (27) Medication related information from the patients' questionnaire investigated were:

- Whether patients picked up their medication at their community pharmacy themselves (yes/no),
- If someone was always available to remind patients to take medication (yes/no/now and then), and
- If somebody else was giving patients their medication when they were not taking it (yes/no).

Finally, initiation of antipsychotic medication after discharge (initiated within 7 days or >7 days) was assessed based on information from patients' community pharmacy medication history. Patients were expected to get their first antipsychotic prescription dispensed within 7 days after discharge. In The Netherlands, patients do not receive antipsychotic medication at discharge to use at home but are expected to pick up their medication at a community pharmacy. However, when the discharge was just before or during the weekend, the patient could get medication for a maximum duration of three days. Furthermore, if the patient refilled their antipsychotic medication before admission, and had still enough antipsychotic medication at home, this was taken into account.

Attitude Towards Medicines Use

The attitude towards antipsychotic medication was assessed with the Belief about Medicines Questionnaire (BMQ-specific), consisting of the necessity and the concerns subscales. The necessity subscale, consisting of five statements, measures patients' beliefs about the necessity to take antipsychotic medication while the concerns subscale, consisting of six statements, measures patients' concerns about their antipsychotic medication (Appendix 1). (20) Each statement was scored by the patient on a 5-point Likert scale, 1 (strongly disagree), 2 (disagree), 3 (uncertain), 4 (agree) or 5 (strongly agree). The total scores of the two subscales were each summed, divided by the total number of statements in the scale and then multiplied by 5. Patients were divided into four different belief groups accepting (necessity score 15-25, concerns score 5-15), indifferent (necessity score 5-15, concerns score 5-15), skeptical (necessity score 5-15, concerns score 15-25), and ambivalent (necessity score 15-25, concerns score 15-25). (20,28) General beliefs about medication were measured using the BMQ-general scale consisting of the subscales harm

and overuse. Both subscales consist of four statements. The scores of the 4 statements for harm and overuse were summed and used as a continuous variable.

Health Care Providers Assessement

Both physicians and nurses (health care providers), which were involved in patients' treatment before discharge filled in a questionnaire including questions on:

- Whether they had asked the patient whether he/she was adherent with antipsychotics during admission (yes, no, do not know anymore)
- Whether they had discussed antipsychotic adherence to medication with the patient during admission (yes, no, do not know anymore)
- How they considered their patient-health care provider/therapeutic relationship (good or moderate/bad)
- The prediction whether the patient would use antipsychotic medication after discharge (yes, no, I do not know)
- The prediction of the patient's antipsychotic adherence after discharge (scale 0-100%, continuous and categorized as: ≤80% and >80%)
- The prediction on risk on rehospitalization (scale 0-100%, continuous and categorized as: ≤50% and >50%)

Data Analysis

First, all the variables of the patient/disease and medication characteristics, patients' attitude towards medicine use, and health care providers assessment were investigated in a univariate analysis using Cox proportional hazards. Second, the variables of the four groups -patient/disease characteristics, medication characteristics, patients' attitude towards medicine use, and health care providers assessment- were analyzed using backward selection. Starting with all variables in the model for each group, variables were subsequently excluded from the model if their p-value≥0.20. Four prediction models were analyzed to assess whether rehospitalization could be predicted at discharge. The first prediction model consisted of the patient/disease characteristics that had a p-value<0.20 after backward selection (model 1). The variables of the medication characteristics that had a p-value<0.20 after backward selection were used in the second prediction model together with the variables that remained from the patient/disease characteristics (model 1+2). In the third prediction model the remaining values from the patient/disease and medication characteristics and the patients' attitude towards medicine use were included as a predictor (model 1+2+3). The three previous models were combined with the health care providers assessments in the fourth prediction model (model 1+2+3+4). The four prediction models were also separately analyzed for patients with and without schizophrenia. Relative risks were measured as hazard ratios with 95% confidence intervals (95% CI) using Cox proportional hazards. The data analysis was performed using SPSS for Windows, version 20.0. The area under the receiver operating characteristic (ROC) curve (AUC_{ROC}) was assessed for the four prediction models by using the library 'risksetROC' in statistical software R version 3.1.2. (29) A risk score was calculated for

the prediction model with the highest predicting ability AUC_{ROC} by multiplying all regression coefficients by 10, summing them and then adding 14. Subsequently, the risk score was categorized in tertiles to obtain three equally divided groups with proportion of patients rehospitalized. (30) Finally, for the internal consistency of the different scales of the BMQ Cronbach's alpha test was performed.

Results

87 patients gave informed consent and were included in this study, 16 patients refused to participate. Patients' mean age was 38.4 years (Standard Deviation (SD): 12.1), the majority of the patients was male (59.8%) and most of them had a previous hospitalization (89.7%) (Table 1). 20.7% used two or more antipsychotic agents at discharge, most patients (74.7%) used second generation antipsychotics. 34 (39.1%) patients were diagnosed with schizophrenia, 13 (14.9%) with schizoaffective disorder, 18 (20.7%) patients had brief psychotic disorder and 22 (25.3%) were diagnosed with bipolar disorder I. 1 of the 87 (1.15%) patients was rehospitalized within 7 days after discharge, therefore this hospitalization was considered as a part of the index hospitalization.

The mean score on the necessity subscale of the BMQ-specific was 16.6 (SD 4.2), 15.2 (SD 3.3) on the concern subscale, 12.9 (SD: 3.0) on the overuse subscale and 10.2 (SD 2.8) on the harm subscale. Internal consistency of the subscales was variable; α=0.81 for necessity, α=0.57 for concerns, α=0.62 for overuse, α=0.57 for harm. Figure 1 shows the distribution of the patients in the four categories for the BMQ specific scale. Most patients were either in the ambivalent (37.9%) or in the accepting (32.2%) group. Furthermore 20.7% of the patients were in the skeptical group and 9.2% in the indifferent group. 18.2% of the ambivalent patients were rehospitalized, 42.9% of the accepting, 50.0% of the skeptical, and 25.0% of the indifferent.

Questionnaires assessing adherence and risk for rehospitalization were filled in both by nurses and by physicians (42.5% psychiatrists, 19.5% psychiatrists in training, 33.3% physicians, and 4.6% nurse practitioners). Median estimation of adherence by physicians as well as by the nurses was 75 (0-100). In 31.0% of the patients the physician predicted that the patient would be rehospitalized (prediction of rehospitalization >50%), comparable with the nurses who predicted rehospitalization in 33.3% of the patients. Most patients had a good therapeutic relationship with their health care provider according to the physician (69.0%), and the nurses (72.4%).

29 (33.3%) patients were rehospitalized within six months with a median time to rehospitalization of 32 days (range: 12-181 days). 12.6% of the patients were rehospitalized within 1 month after discharge, and 21.8% within 3 months.

Table 1: Demographic and clinical characteristics of the patients at discharge.

Characteristics	N
Total	87
Mean age (years, (SD))	38.4 (12.1)
Gender	
Male	52 (59.8%)
Diagnosis of psychotic disorder	
Brief psychotic disorder	18 (20.7%)
Schizophrenia	34 (39.1%)
Schizoaffective disorder	13 (14.9%)
Bipolar disorder I	22 (25.3%)
Duration of baseline hospitalization (days, (median, range))	48 (7-371)
7-29 days	28 (32.2%)
30-60 days	31 (35.6%)
≥61 days	28 (32.2%)
Number of antipsychotic agents (AP) used at discharge	
1 antipsychotic agent	69 (79.3%)
≥2 antipsychotic agents	18 (20.7%)
Type of antipsychotic medication	
Second generation	65 (74.7%)
First generation	13 (15.0%)
Combination	9 (10.3%)
Department at discharge	
Open unit	73 (83.9%)
Closed unit	14 (16.1%)
First admission	
Yes	9 (10.3%)
No	78 (89.7%)
Residential situation	
Alone	40 (46.0%)
Living with others	45 (51.7%)
Other/homeless	2 (2.3)
Mean GAF score (SD)	46.0 (11.7)
History of substance use	
No	64 (73.6%)
Yes	23 (26.4%)

Table 2 shows the results of the univariate analysis of the variables. Of the patient/disease characteristics, e.g. RR for duration of hospitalization (RR = 0.99, 95% CI: 0.98-1.00) and age (RR = 1.02, 95% CI: 0.99-1.05) had a $p<0.20$. For the medication characteristics,

patients that picked up their own medication at their community pharmacy were more at risk to be rehospitalized compared with patients that got their medication delivered or picked up by others (RR = 1.45, 95% CI = 0.87-2.39). Patients who were not reminded to take their antipsychotic medication (RR = 3.32, 95% CI = 1.13-9.78), and patients that were now and then reminded (RR = 2.41, 95% CI = 0.68-8.54) by someone else were also more often rehospitalized compared to patients that were always reminded. Among the beliefs groups, skeptical patients had a threefold higher risk of rehospitalization than ambivalent patients (RR = 3.38, 95% CI = 1.20-9.50). Increase of 1 unit for the harm score gave an RR of 0.92 (0.81-1.04) and for the overuse score an RR of 1.02 (0.90-1.15). Of the health care providers assessment variables, patients for whom a nurse predicted a risk of >50% for rehospitalization had a twofold higher risk of rehospitalization compared with patients with a nurse prediction of ≤50% for rehospitalization (RR = 2.13, 95% CI = 1.03-4.42).

Table 3 shows the results of the multivariate analysis of the four prediction models including patient/disease and medication characteristics, patients' beliefs about medicines, and health care providers.

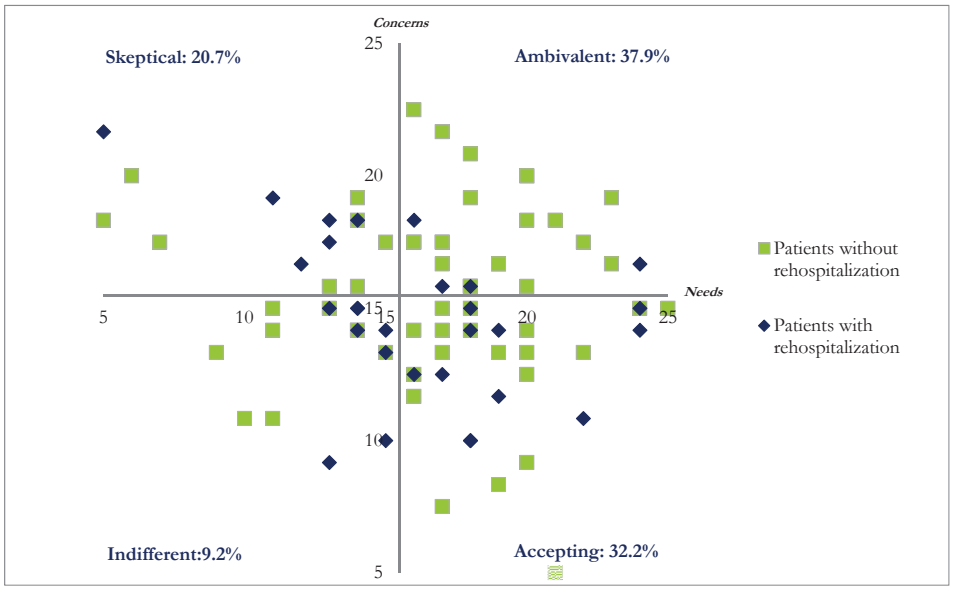


Figure 1: This scatter plot shows the distribution of patient's scores of the BMQ (Beliefs about Medicine Questionnaire) specific statements in the four belief groups: accepting, ambivalent, skeptical, and indifferent. The X-axis represents the scores of the necessity subscale and the Y-axis the scores of the concerns subscale.

Model 1: Patient/Disease Characteristics

Three variables remained in model 1 from the patient/disease characteristics. Duration of index hospitalization predicted rehospitalization giving a relative risk of 0.99 (95% CI: 0.98-1.00) per day. All diagnosis were significantly different from schizophrenia,

whereas diagnosis of bipolar disorder I resulted in the lowest RR of 0.36 (95% CI: 0.31-1.00). AUC_{ROC} for model 1 was 0.69.

Table 2: Univariate analysis for the variables of patient/disease and medication characteristics, patients' attitude towards the medicine use and health care providers' assessment.

Variables	N (%) rehospitalized	HR (95% CI)
Patient and disease characteristics		
Duration of index hospitalization		0.99 (0.98-1.00)*
Diagnosis of psychotic disorder		
Schizophrenia	34 (44.1)	Reference
Schizoaffective disorder	13 (23.1)	0.49 (0.14-1.71)
Brief psychotic disorder	18 (33.3)	0.66 (0.26-1.70)
Bipolar disorder I	22 (22.7)	0.44 (0.16-1.20)*
Gender		
Male	52 (34.6)	Reference
Female	35 (31.4)	0.99 (0.47-2.01)
Age (years)		1.02 (0.99-1.05)*
Residential situation		
Alone	40 (40.0)	Reference
Living with others	45 (26.7)	0.62 (0.29-1.31)
Other/unknown	2 (50.0)	1.13 (0.15-8.57)
History of substance use		
No	64 (34.4)	Reference
Yes	23 (30.4)	0.82 (0.35-1.92)
First admission		
Yes	9 (33.3)	Reference
No	78 (33.3)	1.03 (0.31-3.40)
GAF score		1.01 (0.98-1.05)
Department at discharge		
Open unit	73 (32.9)	Reference
Closed unit	14 (35.7)	1.01 (0.38-2.64)
Medication characteristics		
Number of AP used at discharge		
1 antipsychotic agent	69 (36.2)	Reference
≥2 antipsychotic agents	18 (22.2)	0.56 (0.20-1.61)
Type of AP		
First generation	13 (30.8)	0.72 (0.25-2.06)
Second generation	65 (38.5)	Reference
Combination of both	9 (0.0)	NA

Variables	N (%) rehospitalized	HR (95% CI)
Number of co-medication at discharge	87 (33.3)	1.03 (0.99-1.15)
Patients themselves picked up medication at community pharmacy		
No	21 (19.0)	Reference
Yes	66 (37.9)	1.45 (0.87-2.39)*
Someone was always available to remind patients to take medication		
Yes	26 (15.4)	Reference
No	43 (44.2)	3.32 (1.13-9.78)**
Now and then	18 (33.3)	2.41 (0.68-8.54)*
Somebody else was giving patients their medication when they were not taking it		
Yes	18 (22.2)	Reference
No	68 (36.8)	1.68 (0.59-4.84)
Unknown	1 (0.0)	NA
Initiated AP within 7 days after discharge		
Yes	62 (33.9)	Reference
No	19 (42.1)	1.25 (0.55-2.82)
Unknown	6 (0.0)	NA
Patients' attitude towards medication use		
Belief groups		
Ambivalent	33 (18.2)	Reference
Skeptical	18 (50.0)	3.38 (1.20-9.50)**
Indifferent	8 (25.0)	1.50 (0.30-7.44)
Accepting	28 (42.9)	2.62 (0.98-7.00)*
BMQ-general		
Harm score	87 (33.3)	0.92 (0.81-1.04)*
Overuse score	87 (33.3)	1.02 (0.90-1.15)
Health care providers assessment		
Physician discussed AP adherence during admission		
Yes	71 (32.4)	Reference
No	15 (33.3)	1.06 (0.40-2.79)
Do not know anymore	1 (100.0)	NA
Nurse discussed AP adherence during admission		
Yes	65 (38.5)	Reference
No	21 (19.0)	0.45 (0.16-1.30)*
Do not know anymore	1 (0.0)	NA

Variables	N (%) rehospitalized	HR (95% CI)
Physician asked whether patient was adherent to AP		
Yes	62 (37.1)	Reference
No	24 (25.0)	0.66 (0.27-1.61)
Do not know anymore	1 (0.0)	
Nurse asked whether patient was adherent to AP		
Yes	64 (37.5)	Reference
No	22 (22.7)	0.58 (0.22-1.52)
Do not know anymore	1 (0.0)	NA
Therapeutic relationship according to physician		
Good	60 (36.7)	Reference
Moderate/bad	27 (25.9)	0.71 (0.30-1.66)
Therapeutic relationship according to nurse		
Good	63 (31.7)	Reference
Moderate/bad	24 (37.5)	1.18 (0.54-2.59)
Physician predicted patient would use AP after discharge		
Yes	72 (37.5)	Reference
No	7 (0.0)	NA
I do not know	8 (25.0)	0.63 (0.15-2.65)
Nurse predicted patient would use AP after discharge		
Yes	73 (35.6)	Reference
No	7 (42.9)	1.28 (0.39-4.22)
I do not know	7 (0.0)	NA
AP adherence prediction by physician (%)	87 (34.4)	1.04 (0.99-1.02)
AP adherence prediction by nurse (%)	87 (34.4)	1.00(0.99-1.02)
Rehospitalization prediction by physician (%)		
Prediction ≤50%	60 (35.0)	Reference
Prediction >50%	27 (29.6)	0.77 (0.34-1.75)
Rehospitalization prediction by nurse (%)		
Prediction ≤50%	58 (25.9)	Reference
Prediction >50%	29 (48.3)	2.13 (1.03-4.42)**

*p<0.2, **p<0.05
AP=antipsychotics. NA=not applicable

Model 1+2: Patient/Disease and Medication Characteristics

Number of antipsychotics and whether someone always reminded patients to take medication remained significant in the backward selection of the medication characteristics. These two variables were used in model 1+2 together with the selected patient/disease variables. Results of the second model are shown in Table 3. Model 1+2 gave an AUC_{ROC} of 0.71.

Model 1+2+3: Patient/Disease and Medication Characteristics and Patients Beliefs about Medicines

The four belief groups remained in the backward selection among the variables of patients' beliefs about medicines. In the analysis of model 1+2+3, the four belief groups together with the patient/disease and medication characteristics were used to predict rehospitalization. Highest RR was predicted for patients who were now and then reminded to take medication (RR = 3.08, 95% CI = 0.81-11.80) compared with patients that always were reminded by someone else, and patients being skeptical (RR = 2.91, 95% CI = 0.93-9.11) compared with ambivalent patients (Table 3, model 3). AUC_{ROC} for model 3 was 0.72.

Model 1+2+3+4: Patient/Disease and Medication Characteristics, Patients Beliefs about Medicines and Health Care Providers

Three variables of the health care providers assessment remained in the model when combined with the patient/disease and medical characteristics and the four beliefs groups. The three variables were physician and nurse discussed AP adherence during admission and prediction of rehospitalization by the nurse. The results of model 1+2+3+4 are shown in Table 3. Highest RR was predicted for skeptical patients (RR = 4.70, 95% CI = 1.37-16.13) compared with ambivalent patients, followed by patients that were not reminded to take their medication (RR = 2.31, 95% CI = 0.71-7.47). Model 1+2+3+4 had an AUC_{ROC} of 0.74.

Risk Score of Rehospitalization

The risk score was calculated for model 1+2+3+4 as it had the highest AUC_{ROC} (Table 4 and 5). This model was transformed in a scoring rule based on the regression coefficient for the selected variables (Table 3). The total score was assessed for all the patients and can be considered as a measure for prediction of rehospitalization at discharge. The patients had a score ranged from 0 to 52. Patients were categorized in tertiles based on their score. Proportion of rehospitalized patients was assessed for the three categories being 6.9% in the patients with a risk score of 0.0 to 24.6, 31.0% in the patients with a risk score of 24.7 to 34.0, and 62.1% in the patients with a risk score of 34.1-52.0. Time to rehospitalization was 26 days (range: 22-30) for the lower tertile, 32 days (range: 15-181) for the middle tertile, and 38 days (range: 12-165) for the upper tertile. Patients in the upper tertile had an RR of 12.44 (95% CI: 2.88-53.77) to be rehospitalized and in the middle tertile an RR of 5.21 (95% CI: 1.13-24.13) compared with patients in the lower tertile.

Rehospitalization in Patients With and Without Schizophrenia

The prediction models were analyzed for both patients with and without schizophrenia. Rehospitalization was best predicted for patients with schizophrenia by a combination of variables from the patient/disease (duration of index hospitalization, GAF score and age) and medical characteristics (patients themselves picked up medication at community

Table 3: Results of the multivariate prediction models.

Variables	Model 1	Model 1+2	Model 1+2+3	Model 1+2+3+4
Patient and disease characteristics				
Duration of index hospitalization	0.99 (0.98-1.00)**	0.99 (0.99-1.00)*	0.99 (0.99-1.00)	0.99 (0.99-1.00)
Diagnosis				
Schizophrenia	Reference	Reference	Reference	Reference
Brief psychotic disorder	0.40 (0.15-1.08)*	0.37 (0.14-0.98)**	0.42 (0.15-1.17)*	0.66 (0.20-2.21)
Schizoaffective disorder	0.39 (0.11-1.39)*	0.41 (0.11-1.43)*	0.45 (0.12-1.71)	0.46 (0.11-1.89)
Bipolar disorder I	0.36 (0.31-1.00)**	0.26 (0.09-0.75)**	0.28 (0.10-0.84)**	0.50 (0.14-1.78)
Age	1.03 (0.99-1.06)*	1.02 (0.98-1.05)	1.03 (0.99-1.07)*	1.03 (0.98-1.07)
Medication characteristics				
Number of antipsychotics at discharge				
1 AP agent		Reference	Reference	Reference
≥2 AP agents		0.51 (0.17-1.57)	0.49 (0.16-1.55)	0.72 (0.21-2.53)
Someone was always available to remind patients to take medication				
Yes		Reference	Reference	Reference
No		3.20 (1.05-9.71)**	2.85(0.89-9.12)*	2.31 (0.71-7.47)*
Now and then		3.11 (0.86-11.23)*	3.08 (0.81-11.80)*	2.09 (0.50-8.79)
Patients' attitude towards medication use				
Beliefs groups				
Ambivalent			Reference	Reference
Skeptical			2.91 (0.93-9.11)*	4.70 (1.37-16.13)**
Indifferent			1.16 (0.22-6.09)	1.78 (0.32-9.93)
Accepting			1.26 (0.42-3.80)	1.95 (0.58-6.52)
Health care providers assessment				
Physician discussed AP adherence during admission				
Yes				Reference
No				2.00 (0.57-6.98)
Do not know anymore				NA
Nurse discussed AP adherence during admission				
Yes				Reference
No				0.29 (0.08-1.07)*
Do not know anymore				NA
Rehospitalization prediction by nurse				
Prediction ≤50%				Reference
Prediction >50%				1.93 (0.70-5.36)
AUC_{ROC} (6 months)	**0.69**	**0.71**	**0.72**	**0.74**

*p<0.2, **p<0.05
AP=antipsychotics. NA=not applicable

Table 4: Regression coefficient of the predictors obtained from model 1 + 2 + 3 + 4 with assigned score.

Predictor	Regression coefficient	Score*
Duration of index hospitalization	-0.003	-0.03
Diagnosis		
Schizophrenia	Reference	0
Brief psychotic disorder	-0.420	-4.2
Schizoaffective disorder	-0.781	-7.8
Bipolar disorder I	-0.691	-6.9
Age	0.025	0.25
Number of antipsychotics at discharge		
1 antipsychotic agent	Reference	0
≥2 antipsychotic agents	-0.325	-3.3
Someone was always available to remind patients to take medication		
Yes	Reference	0
No	0.837	8.4
Now and then	0.737	7.4
Patients' attitude towards medicine		
Beliefs groups		
Ambivalent	Reference	0
Skeptical	1.549	15.5
Indifferent	0.575	5.8
Accepting	0.665	6.7
Physician discussed AP adherence during admission		
Yes	Reference	0
No	0.692	6.9
Do not know anymore	NA	0
Nurse discussed AP adherence during admission		
Yes	Reference	
No	-1.227	-12.3
Do not know anymore	NA	0
Rehospitalization prediction by nurse ≤50%	Reference	0
Rehospitalization prediction by nurse >50%	0.659	6.6

* The score is obtained by multiplying each regression coefficient by 10, and then rounded to nearest integer, summing them and adding 14 to the summed risk score.

pharmacy and someone was always available to remind patiets to take medication), patients' attitude towards medication use (beliefs groups and harm score), and health care providers assessment (rehospitalization prediction by the nurse), Appendix 3. The highest RR was for skeptical patients (RR = 24.72, 95% CI: 0.76-799.56) compared with ambivalent patients, patients that were now and the remineded by someone to take medication (RR = 6.91, 95% CI = 0.41-117.23) compared with patients that were always

reminded, and patients picked up medication themselves at community pharmacy (RR = 2.62, 95% CI = 0.30-22.84). The prediction model had an AUC_{ROC} of 0.86.

Rehospitalization was best predicted for patients without schizophrenia by a combination of variables from the patient/disease (GAF score and residential situation) and medication characteristics (patients initiated antipsychotics within 7 days after discharge), and health care providers assessment (antipsychotic adherence prediction, rehospitalization prediction by both the physician and the nurse), Appendix 4. The highest RR was for patients for whom the nurse predicted a rehospitalization >50% (RR = 3.38, 95% CI = 0.71-14.84) and patients that did not initiate antipsychotic medication within 7 days after discharge (RR = 2.70, 95% CI = 0.79 - 9.28). The prediction model had an AUC_{ROC} of 0.80.

Table 5: Distribution of patients rehospitalized within risk score category.

Risk score category[1]	Total N of patients	Patients rehospitalized (%)[2]	Median time to rehospitalization (range)	HR (95% CI)
0.0 to 24.6	29	6.9	26 (22-30)	Reference
24.7 to 34.0	29	31.0	32 (15-181)	5.21 (1.13-24.13)*
34.1 to 52.0	29	62.1	38 (12-165)	12.44 (2.88-53.77)*
Overall	87	33.3	32 (12-181)	

* $p<0.05$

[1] The calculated of the total risk score was rounded to nearest integer.

[2] Incidence of rehospitalization within each risk score category.

Discussion

The aim of this study was to identify patients with psychotic or bipolar I disorders treated with antipsychotics at risk for rehospitalization within six months from discharge. Rehospitalization was best predicted by a combination of variables from patient/disease and medical characteristics, patients beliefs about medicines, and health care providers assessment, all variables that are relatively easily obtainable at discharge or shortly after discharge.

In our study we found the strongest predictors to be duration of index hospitalization, diagnosis, age, number of antipsychotic agents in use, if somebody else was giving patients their medication when they were not taking it, beliefs groups, prediction of rehospitalization by the nurse, and whether the physician and the nurse discussed antipsychotic adherence during hospitalization. As reportedd by Lang et al. who found that hospitalization in patients with schizophrenia could be predicted with history of substance abuse, new starters of antipsychotic medication, adherence, and number of co-medication, including anticholinergic use. (19) Our results are also in line with

Perkinson and colleagues that reported that health care providers' rated assessement of medication adherence was correlated with how patients refilled their medication. They also measured necessity of treatment and the ones that believed need for treatment was low were more likely to be rehospitalized also when other questionnaires were used (the Rating of Medication Influences Scale and the Insight and Treatment Attitudes Questionnaire). This is in agreement with our results that patients skeptical towards their medication were at a greater risk of rehospitalization. (21,31)

History of substance use and number of co-medication at discharge, did not remain in our prediction models while it remained in the prediction model of Lang et al. Our predictors may differ from the study of Lang et al. due to several differences in study design. We included variables related to patient/disease and medication characteristics, patients beliefs about medicines, and health care providers assessment while Lang et al. only included patient/disease and medication characteristics. Furthermore, Lang et al. included only patents with at least two refills for antispychotic drugs, included both in- and outpatients and had any hospitalization, general as well as psychiatric, as main outcome while we included patients that were discharged and had psychiatric rehospitalization as an outcome. Psychiatric patients have a higher prevalence of somatic disease, thus both higher somatic as well as psychiatric hospitalization rates are expected. (27) Due to their inclusion criteria patients without any refill after discharge were missed and their results can not be applied for these patients. Besides this, their study population consisted of two different groups, namely inpatients and outpatients. The risk of (re)hospitalization for these patients could be different, because risk of hospitalization is highest during a month after discharge as seen in this study and also reported by Zilber et al. and in the study of Chapter 3.2. (18)

In other studies physicians overestimated their patients' adherence to pharmacotherapy. However, in our study as well in the study of Perkins et al., health care providers were able to predict adherence as well as risk of rehospitalization. (21,31-36) Of the health care providers, nurses, were better able to predict rehospitalization than physicians in our study. This could be because nurses have a more frequent contact with patients during the hospitalization than physicians and patients are more likely to share their thoughts about their disease and treatment with the nurses.

In our study we found that the model including a combination of the patient/disease and medication characteristics, patients beliefs about medicines, and health care providers assessment had the highest ability in predicting rehospitalization. Despite that the AUC_{ROC} only marginally increased from 0.69 to 0.74, we still recommend combining the different groups of variables. First, it will give an overall reflection of patients' disease and characteristics, and treatment including antipsychotic medication, number of co-medication, and patient-health care provider assessment. Secondly, the patients' attitude towards medicine use and the health care provider questionnaires are short thus

it takes little effort to fill these in. The beliefs groups that remained in the prediction models were based on the BMQ specific. Future research must show if only the BMQ-specific can be used because the outcomes of the BMQ-general did not remain in the prediction models. Filling in the questionnaires can be implemented in the patients' discharge procedure to identify patients at a higher risk of rehospitalization at discharge. Future research is needed to assess whether stratification is needed for patients with and without schizophrenia.

To the best of our knowledge this is the first study where predictors of rehospitalization are identified combining patient/disease and medication characteristics, patients beliefs about medicines, and health care provider assessment of adherence. The questionnaires were completely filled in by everyone involved in this study. Patients filled in the questionnaire by themselves. If patients did not understand a question/statement, one of the researchers (KE) explained and assisted patients. For the first refill after discharge stockpiling (antipsychotic refill before hospitalization) was taken into account. Another strength of this study is that psychiatric rehospitalizations in the whole region were included and not only rehospitalization in the four included hospitals. Both the physician and the nurse which were involved in patients' treatment before discharge were involved in this study. Medication characteristics included information on number of co-medication, antipsychotic initiation after discharge, whether patients refilled their medication themselves, if somebody else was giving patients their medication when they were not taking it. Thus, medication characteristics medication use during and after hospitalization was taken into account. Even though other studies made prediction models, they did not calculate a risk score based on all the variables.

Although this was a prospective study without any intervention in patients' treatment, health care providers might have spent more attention to antipsychotic adherence after discharge. This could have resulted in a better monitoring of adherence resulting in less rehospitalizations. Nonetheless, 33.3% of the patients were rehospitalized in the six months following discharge which is comparable with what previous studies have reported. (37-39) Patients were told at inclusion that there were no right or wrong answers, the results would not be discussed with their psychiatrist or anyone else, and the results would be processed anonymously in this study. Despite these facts patients may have filled in socially desirable answers. Although the power for the prediction model in all the patients had a power of 0.80, power decreased when patients were stratified by having diagnosis of schizophrenia or other diagnosis.

Conclusions

Rehospitalization was best predicted by a combination of variables from the patient/disease and medication characteristics, patients' attitude towards medicine use, and health care providers assessment. These variables are relatively easily available at discharge to predict rehospitalization within six months after discharge. Risk scores can be assessed at discharge to identify patients with a higher risk to be rehospitalized.

Acknowledgements

The authors are thankful to the patients, Altrecht Mental Health Care and the community pharmacies for their contribution in this study. Also, we thank D. Yazir for helping with the collection of the medication history and Dr. Md Jamal Uddin for helping with the statistical analyses.

References

(1) Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008 Apr 30;8:32.

(2) Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004 Aug;55(8):886-891.

(3) Law MR, Soumerai SB, Ross-Degnan D, Adams AS. A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. J Clin Psychiatry 2008 Jan;69(1):47-53.

(4) dosReis S, Johnson E, Steinwachs D, Rohde C, Skinner EA, Fahey M, et al. Antipsychotic treatment patterns and hospitalizations among adults with schizophrenia. Schizophr Res 2008 Apr;101(1-3):304-311.

(5) Fenton WS, Kane JM. Clinical challenges in the psychopharmacology of schizophrenia. Schizophr Bull 1997;23(4):563-565.

(6) Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007 Oct;23(10):2305-2312.

(7) Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008 Jan;34(1):173-180.

(8) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011 Jun;168(6):603-609.

(9) Jung SH, Kim WH, Choi HJ, Kang MH, Lee JS, Bae JN, et al. Factors affecting treatment discontinuation and treatment outcome in patients with schizophrenia in Korea: 10-year follow-up study. Psychiatry Investig 2011 Mar;8(1):22-29.

(10) Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res 2002 Oct 1;57(2-3):209-219.

(11) Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002 Oct;63(10):892-909.

(12) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.

(13) Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand 2009 Jan;119(1):78-84.

(14) Boden R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res 2011 Dec;133(1-3):36-41.

(15) Ohmori T, Ito K, Abekawa T, Koyama T. Psychotic relapse and maintenance therapy in paranoid schizophrenia: a 15 year follow up. Eur Arch Psychiatry Clin Neurosci 1999;249(2):73-78.

(16) Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012 May;73(5):691-705.
(17) Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care 2002 Aug;40(8):630-639.
(18) Zilber N, Hornik-Lurie T, Lerner Y. Predictors of early psychiatric rehospitalization: a national case register study. Isr J Psychiatry Relat Sci 2011;48(1):49-53.
(19) Lang K, Meyers JL, Korn JR, Lee S, Sikirica M, Crivera C, et al. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. Psychiatr Serv 2010 Dec;61(12):1239-1247.
(20) Verhoef TI, Redekop WK, Bouvy ML, Dorenbos B, Karwar Z, van Schie RM, et al. Beliefs about medicines in Dutch acenocoumarol and phenprocoumon users. Br J Clin Pharmacol 2014 Aug;78(2):422-429.
(21) Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008 Jan;69(1):106-113.
(22) Altrecht MHC. Annual Report 2010 of Altrecht/Jaardocument 2010. 2010:19-94.
(23) Reutfors J, Brandt L, Stephansson O, Kieler H, Andersen M, Boden R. Antipsychotic prescription filling in patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 2013 Dec;33(6):759-765.
(24) Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000 Feb;51(2):216-222.
(25) Gorwood P. Factors associated with hospitalisation of patients with schizophrenia in four European countries. Eur Psychiatry 2011 May;26(4):224-230.
(26) Hugenholtz GW, Stolker JJ, Heerdink ER, Nolen WA, Leufkens HG. Short-acting parenteral antipsychotics drive choice for classical versus atypical agents. Eur J Clin Pharmacol 2003 Mar;58(11):757-760.
(27) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Prevalence of medication use for somatic disease in institutionalized psychiatric patients. Pharmacopsychiatry 2013 Nov;46(7):274-280.
(28) Aikens JE, Nease DE,Jr, Nau DP, Klinkman MS, Schwenk TL. Adherence to maintenance-phase antidepressant medication as a function of patient beliefs about medication. Ann Fam Med 2005 Jan-Feb;3(1):23-30.
(29) Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics 2005 Mar;61(1):92-105.
(30) Bouvy ML, Heerdink ER, Leufkens HG, Hoes AW. Predicting mortality in patients with heart failure: a pragmatic approach. Heart 2003 Jun;89(6):605-609.
(31) Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006 Mar;83(1):53-63.

(32) Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, et al. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res 2005 Feb 28;133(2-3):129-133.

(33) Byerly MJ, Thompson A, Carmody T, Bugno R, Erwin T, Kashner M, et al. Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia. Psychiatr Serv 2007 Jun;58(6):844-847.

(34) Remington G, Kwon J, Collins A, Laporte D, Mann S, Christensen B. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. Schizophr Res 2007 Feb;90(1-3):229-237.

(35) Zeller A, Taegtmeyer A, Martina B, Battegay E, Tschudi P. Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. Hypertens Res 2008 Sep;31(9):1765-1771.

(36) Miller LG, Liu H, Hays RD, Golin CE, Beck CK, Asch SM, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? J Gen Intern Med 2002 Jan;17(1):1-11.

(37) McGorry PD, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry 2008 Oct;7(3):148-156.

(38) Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. Am J Geriatr Pharmacother 2011 Feb;9(1):11-23.

(39) Stuffken R, Heerdink ER, Souverein PC, Egberts AC. The association between hospitalization and continuity of psychotropic drug use. 2013;7(7/8):88-93.

Appendix 1 - Basic questionnaire for the patients and patients' attitude towards medicine use (BMQ)

Basic questionnaire for the patients

1. How do you receive your medication?
   - ○ I pick it up at the pharmacy (patients themselves)
   - ○ The pharmacy delivers my medication to my home
   - ○ My friends/family pick it up at the pharmacy for me
   - ○ Professionals/people from my assisted living facility pick it up from the pharmacy for me
   - ○ I get depot/semap/acemap from the nurses at Altrecht
   - ○ I get my oral medication from the nurses at Altrecht

2. What is your living situation?
   - ○ I live alone and am independent
   - ○ I live alone with housing counseling
   - ○ I live with my family/partner
   - ○ I live with other people and get assistance

3. Do people remind you to take your medication?
   - ○ Yes
   - ○ No
   - ○ Now and then

4. When you do not take your medication, do you receive your medication from someone else?
   - ○ Yes
   - ○ No

BMQ specific (scored on a 5-point Likert scale; 1 (strongly disagree), 2 (disagree), 3 (uncertain), 4 (agree) or 5 (strongly agree))

5. My health, at present, depends on my medicines
6. Having to take medicines worries me
7. My life would be impossible without medication
8. I sometimes worry about the long-term effects of my medicines
9. Without my medicines I would be very ill
10. My medicines are a mystery to me
11. My health in the future will depend on my medicines
12. My medicines disrupt my life
13. I sometimes worry about becoming too dependent on my medicines
14. My medicines protect me from becoming worse
15. These medicines have unpleasant side effects

BMQ general (scored on a 5-point Likert scale 1 (strongly disagree), 2 (disagree), 3 (uncertain), 4 (agree) or 5 (strongly agree))

16. Physicians prescribe too many medicines
17. People who take medicines should stop their treatment for a while now and again
18. Most medicines are addictive
19. Natural remedies are safer than medicines
20. Medicines do more harm than good
21. All medicines are poisons
22. Physicians place too much trust in medicines
23. If physicians had more time with patients they would prescribe fewer medicines

Appendix 2 - Questionnaire for the health care providers

1. How are you involved in the treatment of the patient (physician)?
   - ○ Clinical psychiatrist (during the last admission)
   - ○ Ambulatory psychiatrist
   - ○ Physician (not in training to become a specialist)
   - ○ Psychiatrist trainee
   - ○ Other:

2. How do you estimate patient's antipsychotic adherence after discharge? (0% bad, 100% very good)
   .....%

3. Have you discussed adherence to antipsychotics with this patient during the admission?
   - ○ Yes
   - ○ No
   - ○ I do not know

4. Have you asked the patient during the admission whether he/she is adherent?
   - ○ Yes
   - ○ No
   - ○ I do not know

5. How do you assess your professional relationship with this patient?
   - ○ Good
   - ○ Moderate
   - ○ Bad

6. Predict: is this patient going to use his/her antipsychotic medication following discharge?
   - ○ Yes
   - ○ No
   - ○ I do not know

7. Predict: do you think that this patient will continue his/her antipsychotic medication during the six months after discharge?
   - ○ Yes
   - ○ No
   - ○ I do not know

8. How long do you expect this patient to continue his/her antipsychotic medication after discharge?
   ..... Months

9. Do you think that this patient will be rehospitalized in the next six months? (0% no rehospitalization, 100% rehospitalization)
   .....%

Appendix 3

Results of the multivariate prediction models for patients with schizophrenia.

Variables	Model 1	Model 1+2	Model 1+2+3	Model 1+2+3+4
Patient and disease characteristics				
Duration of index hospitalization	0.99 (0.98-1.00)*	1.00 (0.98-1.01)	0.99 (0.99-1.01)	0.99 (0.99-1.01)
GAF score	1.04 (0.98-1.10)*	1.05 (0.99-1.11)*	1.06 (1.00-1.14)*	1.06 (0.99-1.14)*
Age	1.06 (1.00-1.11)**	1.04 (0.99-1.10)*	1.09 (1.02-1.17)**	1.09 (1.02-1.17)**
Medication characteristics				
Number of co-medication		1.17 (0.96-1.43)*	1.38 (1.00-1.91)**	1.39 (1.01-1.91)**
Patients themselves picked up medication at community pharmacy				
No		Reference	Reference	Reference
Yes		3.61 (0.81-16.01)*	2.27 (0.30-21.83)	2.62 (0.30-22.84)
Someone was always available to remind patients to take medication				
Yes		Reference	Reference	Reference
No		3.20 (0.75-13.61)*	2.20 (0.24-20.08)	2.33 (0.20-26.85)
Now and then		4.84 (0.59-39.43)*	6.78 (0.41-113.48)*	6.91 (0.41-117.23)*
Patients' attitude towards medication use				
Beliefs groups				
Ambivalent			Reference	Reference
Skeptical			26.84 (1.18-613.17)**	24.72 (0.76-799.56)*
Indifferent			0.63 (0.01-28.69)	0.62 (0.01-27.99)
Accepting			1.90 (0.10-34.60)	1.74 (0.06-50.62)
Harm score			0.71 (0.51-0.99)**	0.71 (0.51-0.99)**
Health care providers assessment				
Rehospitalization prediction by nurse				
Prediction ≤50%				Reference
Prediction >50%				0.93 (0.21-4.14)
AUC_{ROC} (6 months)	**0.72**	**0.81**	**0.86**	**0.86**

*p<0.2, **p<0.05
AP=antipsychotics.

Appendix 4

Results of the multivariate prediction models for patients without schizophrenia.

Variables	Model 1	Model 1+2	Model 1+2+3	Model 1+2+4
Patient and disease characteristics				
GAF score	0.96 (0.92-1.01)*	0.97 (0.92-1.01)*	0.97 (0.92-1.01)*	0.97 (0.92-1.01)*
Residential situation				
Alone	Reference	Reference	Reference	Reference
Living with others	0.36 (0.11-1.19)*	0.33 (0.10-1.09)*	0.33 (0.10-1.09)*	0.26 (0.07-0.99)**
Other/unknown	1.77 (0.21-14.76)	2.17 (0.25-19.14)	2.17 (0.25-19.14)	1.47 (0.15-14.64)
Medication characteristics				
Initiated AP within 7 days after discharge				
Yes		Reference	Reference	Reference
No		2.67 (0.89-7.97)*	2.67 (0.89-7.97)*	2.70 (0.79-9.28)*
Unknown		NA	NA	NA
Health care providers assessment				
AP adherence prediction by physician (%)				1.03 (1.00-1.07)*
Rehospitalization prediction by physician				
Prediction ≤50%				Reference
Prediction >50%				0.45 (0.07-2.75)
Rehospitalization prediction by nurse				
Prediction ≤50%				Reference
Prediction >50%				3.38 (0.77-14.84)*
AUC_{ROC} (6 months)	**0.65**	**0.71**	**0.71**	**0.80**

*p<0.2, **p<0.05
AP=antipsychotics.

4

General Discussion

Most hospitalized psychiatric patients use several types of medications concurrently. Besides medications indicated for treatment of their psychiatric condition(s) i.e. psychiatric medication, they often take other medications to treat the side effects of their psychiatric mediations or to treat the somatic diseases they suffer from, i.e. somatic medications. In fact, more than three quarters of the psychiatric patients use at least one somatic medication. (1) Ideally, psychiatric patients receive pharmaceutical care according to the treatment plan prepared by their health care providers such as their psychiatrist, general practitioner or pharmacist. Continuous pharmaceutical patient care in psychiatric patients aims at continuing the appropriate use of medications and amending or stopping their inappropriate use, while providing relevant information on the use of the medications to patients themselves as well as their health care providers across the different settings. As a consequence, the continuity of pharmaceutical patient care relates to the behavior and performance of the health care providers as well as the patients themselves.

The continuity of pharmaceutical patient care includes several aspects of medication use. (2) These aspects may for example relate to preventing use of medications for periods longer than clinically needed, which frequently happens for some types of psychiatric medications such as benzodiazepines; preventing duplications in the type of medications prescribed; treating any somatic diseases that occur concomitantly with psychiatric diseases; reaching psychiatric as well as somatic treatment effectiveness and; the prevention of medication withdrawal symptoms. The latter event occurs frequently after the use of some types of psychiatric medications such as antidepressants and antipsychotics. Thus, it is obvious that it is important to identify and closely monitor aspects relevant to the continuity of pharmaceutical patient care. Further, the continuity of pharmaceutical patient care includes patients' support in the use as well as the patients' ability and willingness to accept medication during the three phases of medication use, namely 1) the initiation of the pharmacotherapeutic intervention i.e. does the patient decide to start the prescribed medications; 2) the implementation and execution of the intervention i.e. does the patient use the medications as prescribed with respect to e.g. the recommended dose, the dosing frequency or the recommended dosing times; and 3) the discontinuation of the intervention i.e. does the patient decide to follow the recommendation to stop a medication, to reduce the dosing frequency or to reduce the dose.

Continuity of pharmaceutical care is a challenging task as the current health care system is decentralized and fragmented, implying that health care providers do not always have (immediate) access to the complete medication overview. Because psychiatric patients are often admitted to general as well as psychiatric hospitals, they frequently have to take their psychiatric and somatic medications in different and repeatedly changing settings, implying that different health care providers from primary and secondary care with various area of expertise will take care of them. For example, a patient may start taking medications at home (domiciliary setting); then following admission to a psychiatric hospital the

patient should continue the use of the medication throughout the hospitalization under supervision of several psychiatric health care providers; and finally the patient will be discharged and is expected to continue the use of the medications at home prescribed by health care providers from both primary and secondary care. In some cases rather than discharged, the patient may be rehospitalized to another general or psychiatric hospital. Figure 1 shows an example of the path a psychiatric patient may undergo through the different health care settings and thus the transitions in pharmaceutical care.

		Admission	*Discharge*	*Admission*	
	Domiciliary setting (inpatient care)	**Hospitalization (outpatient care)**	**Domiciliary setting (inpatient care)**	**Rehospitalization (outpatient care)**
Type of pharmacist involved	Community Pharmacist	Hospital Pharmacist	Community Pharmacist	Hospital Pharmacist
Type of health care provider who provided normal daily care	Nurse			Nurse
Type of health care provider who is (mainly) prescribing somatic medications	General Practitioner, other physicians	Other physicians	General Practitioner, other physicians	Other physicians
Type of health care provider who is (mainly) prescribing psychiatric medications	Ambulatory psychiatrist	Hospital psychiatrist	Ambulatory psychiatrist	Hospital psychiatrist
The only constant person who is involved in each step of the complete path	**Patient**	**Patient**	**Patient**	**Patient**

Figure 1: An example of the steps in the path a psychiatric patient may undergo.

Medications can be changed intentionally or unintentionally. Both intentional and unintentional changes may have a negative effect on the continuity of pharmaceutical care in psychiatric patients and may consequently, contribute to adverse drug events and/or compromise efficacy. (3) Earlier research has focused on the continuation of psychiatric care in patients admitted to or discharged from a psychiatric hospital or on the continuation of somatic care in patients admitted to or discharged from a general hospital. As a consequence, it is often not known whether all medications i.e. those somatic as well as psychiatric medications, are continued during admissions or after discharge from psychiatric hospitals. However, such information is relevant to evaluate the current system and to propose any necessary interventions to assure the appropriate continuity of care.

The overall objective of this thesis was to assess the continuation of pharmaceutical patient care, namely, the prescribing aspects in psychiatric patients. In order to realize this goal, the following three sub-objectives were defined.

- To assess the prevalence of somatic medication use in psychiatric patients.
- To assess the association between the change in health care setting and the continuity of pharmaceutical patient care.

- To assess the association between the continuation of antipsychotic care and rehospitalization.

Facts and frequencies

The use of somatic medications is high in psychiatric patients admitted to psychiatric hospitals. We found that 67.5-76.9% of the patients admitted to a psychiatric hospital in the Netherlands were using at least one somatic medication. (1) De Hert and colleagues found that 30% of patients in a psychiatric hospital had prescriptions for somatic medications in 1999-2003 and about 60% in 2007. (4)

It is commonly acknowledged that the risk of discontinuation of medication is high when patients are admitted to or discharged from general hospitals. (5-8) For example, Stuffken et al. and Grimmsmann et al. reported that in patients admitted to a general hospital at least one medication was discontinued in 25%-63% of the patients at admission and in 40-98% of patients following discharge. (5-10) Prins et al. and van der Linden et al. found that risk of discontinuing medication at transitions of health care settings increases with the number of medications used by the patient. The same applies to continuing medication that should have been stopped (11,12) Also, Stuffken et al. reported that the continuity of psychiatric medication is at risk when patients are hospitalized for a somatic disease. (13) As indicated by the studies in this thesis, the risk of discontinuity of somatic medication was highest when patients were admitted to a psychiatric hospital. We found that 38.9% of the patients using somatic medication discontinued the use of at least one somatic medication during the first week of psychiatric hospitalization. For instance, 34.9% of the cardiovascular and acid-and bowel-related medications were discontinued during this first week, and 17.7% of the oral antidiabetics. (9) In addition, we found that the monitoring of pharmacotherapy may fail during admission to psychiatric hospitals as in almost 25% of the hospitalized patients either anticoagulant medication and/or International Normalized Ratio (INR) monitoring was discontinued. (14) Moreover, we found that discontinuation of pharmaceutical care also frequently occurred following discharge, with at least a single medication being discontinued in almost 70% of psychiatric patients. Only 13.7% of the patients continued all the medications used prior to the admission following discharge. Of all patients using antipsychotics, 25.2% discontinued the use of their antipsychotic medications, and of all patients using cardiovascular medications, 28.4% discontinued a cardiovascular drug. (Chapter 3.1)

Obviously, the continuity of pharmaceutical care is important for the treatment and stabilization of psychiatric diseases after discharge. Therefore, we assessed the association between antipsychotic adherence and psychiatric rehospitalization in patients with psychotic disorders during the first year after discharge. Patients who did not initiate antipsychotic medication use during the follow up had a higher risk of rehospitalization

(RR = 3.65; 95% CI: 2.42-5.51) when compared to patients who did initiate use. We found that initiation of antipsychotic medication in the 2nd week after discharge was associated with a 4 times higher risk of psychiatric rehospitalization within one month after discharge (RR = 4.14, 95% CI: 1.43-12.03). For patients who initiated the use of psychiatric medication during the first month after the discharge from the psychiatric hospital, those who discontinued use had a twofold (RR = 2.29; 95% CI: 1.18-4.46) risk for rehospitalization during 2nd to 12th month after discharge when compared to those continuing. Irregular users had a relative risk of 1.12 (95% CI: 0.67-1.87) to be rehospitalized during 2nd to 12th month after discharge compared to continuous users, whereas the discontinuers were at a 2.29 (95% CI: 1.18-4.46) times more risk for rehospitalization. (Chapter 3.2) In this context, irregular users were defined as psychiatric patients who had a maximum gap of 20 days between two subsequent antipsychotic prescriptions; continuous users were defined as patients that had no gap between two subsequent antipsychotic prescriptions and discontinuous users as patients who had a gap of 21 days or longer between two subsequent antipsychotic prescriptions

It is important to identify which patients are at a greater risk for rehospitalization. In a prospective study in patients with psychotic or bipolar I disorder we found that rehospitalization can be predicted by various factors. These factors were e.g. if the patient was reminded of taking medications by others; if the patient's belief in their medication could be considered as skeptical, any prediction of rehospitalization by the nurse; and whether the physician and the nurse discussed adherence to antipsychotics with the patient during hospitalization. We found that rehospitalization could best be predicted when combining information on clinical and medication characteristics, patients' beliefs about medicines (BMQ), and health care provider assessments. (Chapter 3.3)

Table 1: An overview of the studies in this thesis, the type of medications investigated and the relevant transitions in patient care.

Study	Type of medication	Transition of care
2.1 Prevalence of medication use for somatic disease in institutionalized psychiatric patients.	Somatic	Outpatient → Inpatient care
2.2 Discontinuation of somatic medication during psychiatric hospitalization	Somatic	Outpatient → Inpatient care
2.3 Discontinuation of anticoagulant care during admission to a psychiatric hospital	Somatic	Outpatient → Inpatient care
3.1 Medication discontinuation in patients after discharge from a psychiatric hospital	Somatic and Psychiatric	Inpatient → Outpatient care
3.2 The effect of non-adherence to antipsychotics on rehospitalization in patients with psychotic disorders	Psychiatric	Inpatient → Outpatient care
3.3 Predicting rehospitalization in patients treated with antipsychotics: a prospective observational study	Psychiatric	Inpatient → Outpatient care

In this general discussion we will put the presented studies into a broader perspective (Table 1). First, possible determinants for (dis)continuity of pharmaceutical patient care in psychiatric patients will be described (theme I). Second, improvement of the continuity of pharmaceutical patient care in psychiatric patients will be presented (theme II); and third, aspects of study methodology i.e. the aspects of how research is performed and which data are available are discussed together with implications of study methodology for future research (theme III) in psychiatric patients will be presented.

Theme I: Determinants of Continuity

Several determinants may influence the continuity of pharmaceutical patient care. These determinants are patient characteristics, the characteristics of the psychiatric disease(s), the existence of any concurrent somatic diseases, the characteristics of the health care setting including any transitions in settings and the characteristics of the health care providers (Figure 2). In the next paragraphs it will be discussed how these determinants contribute to continuity of (pharmaceutical) patient care.

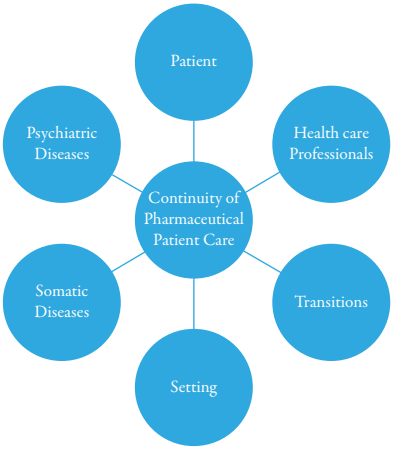


Figure 2: Determinants that may contribute to the continuity of pharmaceutical patient care when patients move across different settings.

Patient

The behavior of the patient in relation to taking medications can be influenced by the underlying psychiatric disease and consequently, it may have an impact on patient adherence to medication and therewith the continuity of pharmaceutical patient care. As a first example, patients with psychiatric diseases such as psychotic disorders might lack disease insight and have low beliefs in or a negative attitude towards the medications recommended in the treatment plan. All this may have a negative effect on patient adherence. As a second example, depression can be accompanied with apathy leading to suboptimal adherence or even non-adherence. (3,15-22) As a third example, psychiatric

diseases such as schizophrenia may negatively affect patients' cognition. Again this may have a negative impact on patient adherence. (3)

Patients' beliefs in medication can be measured with the Beliefs about the Medicine Questionnaire (BMQ). This is s a validated questionnaire where the patients' beliefs are measured on two axes: necessity and concerns, and that takes 5-10 minutes to be filled in. Necessity reflects the perceived need for the use of the medication by the patient, while concerns measure the fear of negative outcomes from the use of the medications such as side effects and addiction. (23,24) We showed (Chapter 3.3) that the BMQ together with patient/disease, and medication characteristics and health care providers assessments, can generally be used to identify patients who are at higher risk for rehospitalization within six month after discharge. Based on the necessity and concern scores, patients can be classified as ambivalent, skeptical, indifferent, or accepting. We found that patients who are skeptical (RR = 4.70, 95% CI = 1.37-16.13), accepting (RR = 1.95, 95% CI: 0.58-6.52) or indifferent (RR = 1.78, 95% CI: 0.32-9.93) about their medication were more likely to be rehospitalized in comparison to patients who are ambivalent. (Chapter 3.3) Skeptical patients had the highest relative risk to be rehospitalized and therefore they need additional support to prevent rehospitalization. This finding is in line with evidence from other authors who showed that psychiatric patients who think medications are less necessary and who have more concerns about the use of these medications are also more often non-adherent. (23,25-29) Thus, indeed patients' disease and beliefs are predictive as to whether patients will continu their medication. As mentioned earlier in the paragraph Facts and Frequencies, we showed that patients′ beliefs about their antipsychotic medication at discharge was predictive for rehospitalization. Besides the necessity of adherence to the recommended pharmaceutical treatment plan, patients have their own responsibility for the continuity of their pharmaceutical patient care. This responsibility relates to providing information to their health care providers about their medication use, effectiveness, and side effects.

Psychiatric medications may cause side effects. For example, weight gain in case of antipsychotics or antidepressant use. If patients experience inconvenienced side effects they may decide to discontinue their medications without consulting their psychiatrist. Intentional discontinuation of medications can also occur when patients feel no effect or when they consider that the medication is ineffective. The latter is frequently observed with some antidepressants. (30,31) When the psychiatric disease is treated and stabilized, patients may also believe that there is no need to continue medication use, and, as a consequence, they may discontinue their use. Thus, patients and health care providers should discuss the importance of medication continuation, including the effectiveness and acceptability of side effects.

Psychiatric Diseases

Psychiatric diseases are often chronic. As these diseases can usually not be cured, the goal of treatment is mainly to stabilize the patients' psychiatric status. (32,33) Symptoms like psychosis or depression can recur when patients' psychiatric disease destabilizes. As mentioned earlier, we showed that patients' non-adherence to antipsychotics resulted in increased risk of psychiatric rehospitalization, which is an indicator for destabilization of the patients' psychiatric disease. (Chapters 3.2 and 3.3) Moreover, patients' destabilization, which often involves a change of setting, can result in discontinuity of pharmaceutical patient care. (9,14, Chapter 3.1) We also show that a change of setting results in discontinuation of at least one psychiatric medication in half of the psychiatric patients discharged from a psychiatric hospital. From all patients got medications dispensed during hospitalization, two thirds of the patients discontinued a medication after discharge. (Chapter 3.1)

As psychiatric diseases are chronic and often feature relapses, medications need to be tailored to the disease status of the patient. This tailoring includes e.g. dose finding, switching between medications, and discontinuation of medication temporally. Changes in medication use can cause confusion about which medication should be continued or it may cause discrepancies between several medication overviews of the different health care providers involved in the pharmaceutical care of the patient. Such differences may also result in the discontinuation of pharmaceutical patient care when such overviews are compared and the incorrect conclusion is drawn. Somatic diseases and medications can also interact with the patient's psychiatric diseases and the psychiatric medications used to treat the psychiatric disease may cause side effects. Both factors may contribute to the destabilization of a patients' psychiatric status and consequently, to exacerbation of psychiatric symptoms, which in turn can lead to the discontinuity of pharmaceutical patient care. The co-occurrence of psychiatric and somatic diseases often implies that psychiatric patients will be treated with psychiatric as well somatic medications concurrently. Such concurrent use, i.e. polypharmacy, may result in drug-drug interactions and adverse drug events and thus medication related problems. (3,34,35) Medication related problems could have an influence on patients' health leading to medication-related hospital admissions. (34) As such admissions involve a change in setting and as this might influence the continuity of pharmaceutical patient care, polypharmacy could contribute to the discontinuation of pharmaceutical patient care. (3)

Somatic Diseases

Until some decades ago, health care for psychiatric and somatic diseases was separated, with the main focus on treatment of the patients' psychiatric disease(s) in psychiatric settings. (4,36-38) However, during recent years, several guidelines for screening and monitoring of somatic health in psychiatric patients were set up by (inter)national groups, for example on the screening of metabolic syndrome in patients with schizophrenia. Unfortunately, these guidelines did not find their way into daily practice immediately.

Nevertheless, health care providers have become more aware of the importance of somatic health in psychiatric patients and this topic has received more attention among psychiatric health care providers. (4,39) Although we were not able to measure if discontinuation of somatic medication was intentional or unintentional, we consider that the risk of unintentional change in a patients' somatic medication is greater when a patient is admitted to a psychiatric hospital than when the patient is admitted to a general hospital (14) This is due to the fact that the main focus and familiarity of the psychiatric health care providers is on the psychiatric diseases or medication rather than the somatic diseases or medication. As psychiatric patients are ageing, the use of somatic medications in psychiatric patients is expected to increase in the future and therewith the occurrence of polypharmacy. The increase of somatic medication use and polypharmacy may further contribute to the discontinuation of pharmaceutical patient care.

Setting & Transitions

Admission and Hospitalization

A change of setting may be accompanied with intended and unintended changes in medication use. As mentioned earlier, we found that admission to psychiatric hospitalization was associated with changes in medication, including discontinuation and switching of somatic medication. (9,14) Therefore, the applicable guidelines state that medication reconciliation should be conducted in order to prevent errors/unintentional discontinuation or changes in patients' pharmaceutical care. (40) The guidelines also clearly state that the patients should be informed about any intended changes in their medications and that this information needs to be transferred after discharge to the patients' health care providers in the primary care. This approach is based on the assumption that the occurrence of medication errors will be reduced if patients know when, how and why their medication is changed.

The proportion of patients that discontinue a somatic medication decreases with the increased duration of the psychiatric hospitalization. (9) This is probably due to the fact that psychiatrists will have more time to receive the patient medication overview of the outpatient care or to initiate somatic treatment on the basis of their own observations. However, some patients who were using chronic somatic medication did not receive these medications even after two weeks of hospitalization. As some somatic diseases clearly need continuous treatment, we consider that the reason for discontinuation of somatic medications needs to be documented in the patient medication overview. We also consider that this underlines the importance of the adequate transfer of information between settings. Although, we did not have information about whether discontinuation of medication was intentional or unintentional, it is highly unlikely that for example about a quarter of the antipsychotic and cardiovascular medications were intentionally discontinued after discharge because these medications are intended for continuous use. (Chapter 3.1)

Discharge

The responsibility of medication management shifts partly from the health care provider to the patient and his/her primary and secondary care health care providers after discharge. Patients generally find it difficult to be responsible for their own pharmaceutical care when they are not sufficiently prepared for this task during their stay in the hospital. In this thesis we show that more than two thirds of the patients admitted to psychiatric hospitals have at least one medication discontinued after discharge. (Chapter 3.1) Furthermore, when investigating adherence to antipsychotics we found that not initiating antipsychotic medication use was associated with rehospitalization. (Chapters 3.2 and 3.3) These results underline the need of adequate patient support during hospital stay and after discharge. Although, guidelines for medication transfer/medication reconciliation are in place in the Netherlands, these guidelines have not yet been implemented completely as recently reported by Uitvlugt et al. (41) Patients need to be informed about how to continue their medication upon discharge from hospital. This can be organized in different ways. For example, patients can get a specific pharmaceutical consult. In such consults, the way that pharmaceutical care should be continued, including any change or discontinuation, can be discussed using teach back methods to make sure the patient has understood the medication changes. This approach has already been implemented in several general hospitals. (42) The consultation can be done by a pharmaceutical consultant, who can contact the (hospital) pharmacist or psychiatrist where needed. The patient may also be trained to take responsibility for his/her medication during their stay in the hospital. This approach is currently used in some psychiatric hospitals. The approach allows the health care providers to make a good guess of how adherent the patient will be upon discharge.

Documentation of Information and Transfer of Information

In outpatient care, only the start date of medication is registered with the current system focusing on the first and second refill of the medication. However, the intended stop date, the duration of use or the date at which the continued use of the medication will be re-evaluated, is often not registered. More attention should be paid to the intended duration of medication use, with a special focus on when and why a medication is to be discontinued. Furthermore, patients are often not informed about the consequences of intentional or unintentional discontinuation. There is no "discontinuation" conversation between the physician and the patient, or between the pharmacist and the patient. Information leaflets also often do not contain information on the duration of medication use or how patients could discontinue the medication. Besides this, the reason of discontinuation is not communicated between settings and if communicated, it is often not recorded in the patient's medication history. (43) Even if it is recorded, it is not always recorded uniformly and therefore the information is normally not shared with other health care providers. As a result, hardly anybody knows why or when medication is discontinued including the patients themselves, physicians, and community pharmacies. This knowledge gap can contribute to the unintentional restart of medications. (12)

Health Care Providers

It is evident that health care providers play an important role in the continuity of pharmaceutical care in psychiatric patients. We showed that patients admitted to nonpsychogeriatric wards had a five times greater risk of discontinuing anticoagulant care than patients admitted to psychogeriatric wards. We also found that patients admitted to nonpsychogeriatric wards had an almost 2.5 fold risk for their somatic medications to be discontinued compared to the year prior to hospitalization, while this risk was not significantly different for patients admitted to psychogeriatric wards. (Chapters 2.2 and 2.3) In the Netherlands, psychiatric and somatic care is highly integrated in psychogeriatric wards with both a geriatrician and a psychiatrist involved in the patients' care. Both health care providers take the overall patients' pharmaceutical care into consideration including somatic care. In contrast, in nonpsychogeriatric wards, a psychiatrist is ultimately responsible for both psychiatric as well as the somatic patient care. Psychiatrists working on nonpsychogeriatric wards can consult general practitioners regarding somatic care when needed. Nevertheless, it is known that they tend to keep their main focus on patients' psychiatric status. Also, they may be less often confronted with complicated somatic diseases in comparison to their colleagues working at psychogeriatric wards.

In the prospective study of Chapter 3.3 we found that nurses were better able to predict rehospitalization of patients with psychotic or bipolar I disorder in contrast to physicians/psychiatrists (trainee). This finding may be explained by the fact that the contact between nurses and patients is more intense and/or involving many more hours, than that of psychiatrist. Also, patients are more likely to share their thoughts about their disease and treatment with nurses. These aspects could explain the better prediction by the nurse. Being able to predict which patients are at a higher risk of being rehospitalized can possibly help health care providers to pay more attention to these patients. Rehospitalization prevention is in favor of patient deterioration and considerable economic costs. (44)

Theme II: Improving Continuity of Pharmaceutical Care

Different aspects of the current health care system offer room for improvement. In this section, recommendations on the five aspects will be discussed, namely the cooperation between health care providers themselves and with patients; importance of communication, patient support and medication review; adherence; psychogeriatric versus nonpsychogeriatric wards; ICT in health care systems; medication reconciliation; and identifying patients at risk for rehospitalization.

Cooperation Between Health Care Providers Themselves and With Patients

Psychiatrists play a key role in the assessment of patients' medication use when they are admitted to and discharged from psychiatric hospitals. Together with pharmacists, they

play a key role in informing other health care providers which medications the patient was using at the time of discharge and which medications should be continued after discharge when the patient will be treated in the outpatient care or when the patient is transferred to another institutional setting. Assessment of medication use at admission and informing other health care providers need to be fulfilled for every patient as a part of transitions. The community pharmacist has an overview of medications dispensed in the outpatient care and the hospital pharmacist for medication dispensed during the psychiatric hospitalization. The community and hospital pharmacist could exchange information on patients' medication history in order to assure continuation of pharmaceutical care, thereby preventing unintentional discontinuation and or re-initiation of medication caused by lack of information exchange during transitions between health care settings. Exchange of patients' medication history can be done in form of sharing patients' medication overview or as pharmacotherapeutic consult between outpatient and inpatient health care providers. Both community and hospital pharmacists need to cooperate at any transition in settings and exchange information about patients' medication for every patient. Such cooperation should result in an appropriate evaluation of the patients' medications. Therefore, it is of importance that the responsibilities of each health care professional is clear, that they know which actions they should undertake and how the patient should be monitored. All this should be investigated to measure if the continuity of pharmaceutical care can be improved in psychiatric patients. (45-47) In order to develop appropriate measures to improve cooperation between health care providers, this aspect needs further investigation. As patients are the only constant factor in the health care continuum they also have a responsibility of their own to inform their health care providers regarding unintentional changes. As patients may not understand the necessity of such feedback, it is important that the necessity of the provision of information on patient adherence to health care providers is adequately explained to the patients. Also, patients need to be informed about the importance of their role at the moment of transition between health care settings, in medication reconciliation, and medication reviews. Therefore, health care providers and patients need to reach concordance about treatment plan and patient's role.

Importance of Communication, Patient Support and Medication Review

In order to improve the continuity of pharmaceutical care, patients need to be informed about their responsibility and they should be supported/instructed before and after discharge about the importance of continuing their medication, including the intended duration of medication use, and the consequences discontinuation. Similar to what is already done in general hospitals, a pharmaceutical consultant can perform this conversation with the patient before its discharge from the psychiatric hospital. Pharmaceutical consultants are pharmacy technicians who have completed an additional 3-year bachelor program that is focused on pharmaceutical patient care. (42) After discharge, the counseling could be taken over by the community pharmacist. The community pharmacist can bring solutions to practical problems such as side effects or factors that negatively affect patient

adherence. In addition, the community pharmacist can cooperate with the ambulatory psychiatrist for monitoring and performing medication reviews thereby assuring that the correct medications are being used upon discharge. Further, psychiatric patients may use several medications concurrently thus their medications needs to be structurally reviewed by pharmacists, psychiatrists, and general practitioner at regular intervals. In these reviews, besides effectiveness, improvement, and the concurrent use of psychiatric as well as somatic medication, prevention of harmful effects and the general adherence of antipsychotics should be addressed. (3,11,48) Also, patients need to be involved in this medication reviews when information is gathered about the treatment plan and any adjustments after the medication review.

Adherence

Non-adherence to antipsychotic therapy is often not actively monitored and can therefore be overlooked by the patients' health care providers. (49) Community pharmacists have a unique insight into the use of medications by the patients and they could play an important role in intervening and signaling when patients engage in non-initiation, insufficient implementation or discontinuation of the recommended medications. Community pharmacists do not only support patients with taking their medications, but they also co-operate with other health care providers. A more intense co-operation between pharmacists and health care providers could result in reduction of the risk for rehospitalization. Pharmacists need to receive information from the psychiatric hospital when patients are discharged to monitor whether patients initiate/implement/discontinue antipsychotic medication after discharge. Pharmacists could contact their patients when they do not initiate medications in time, use their medications irregularly (low implementation) or discontinue their antipsychotics. The pharmacist can also inform the patients' ambulatory psychiatrist about medication non-initiation, low implementation or discontinuation. Actions that may be undertaken by the pharmacists are for example first towards the patient e.g. sending a reminder to refill medication or discussing medication use (e.g. minimize patients' fear of side effects or patient's distrust towards medication). If the patient does not improve medication use, both health care providers can review patients' treatment plan together. Furthermore, pharmacists are able to support patients in using their antipsychotic medication and come up with solutions when patients experience side effects or have difficulties to be adherent. To what extent patient care can be improved by this more intense co-operation needs further investigation. Early identification of patients with a high risk for rehospitalization is important for caregivers and policy makers as it allows for intensifying the monitoring of these patients and could prevent rehospitalization. (21,44,50-57)

Psychogeriatric vs. Nonpsychogeriatric Wards

As mentioned earlier, patients admitted to psychogeriatric wards had less discontinuation of their medications. Nonpsychogeriatric wards can also improve the continuity of pharmaceutical care of their patients by cooperating and learning from psychogeriatric

wards. Nonpsychogeriatric wards need to be aware of somatic diseases and somatic medication use among psychiatric patients. This can be achieved by screening patients at admission or by the application of transfer of medication and treatment in close corporation with a general practitioner and hospital pharmacist. The overall patients' disease and medication should be taken into account during the screening in a multidisciplinary setting of health care providers.

ICT in Health Care Systems

Our current health care system would benefit from being expanded, giving more attention to medication discontinuation. The stop date of a medication should be recorded in the community pharmacy systems just as currently occurs in the hospital pharmacy systems. In addition, the discontinuation of the medication should be discussed at the time when the medication is initiated as well as during transitions between health care settings. It is important to realize that besides the patients themselves, also health care providers and family members can be kept responsible for the continuation of the recommended therapy. Patients may fail in informing their health care providers, but they may not do so on purpose. Therefore, patients need to be well informed about their own responsibility in the continuation of pharmaceutical patient care. In addition, a national electronic patient dossier is considered helpful to patients in order to have a complete overview of their medications and to share it with their health care providers where needed.

Medication Reconciliation

Guidelines for medication reconciliation and the transfer of medications between health care settings have been in place since 2011. Unless otherwise justified, health care providers are expected to follow the recommendations outlined. The studies in this thesis assess the discontinuation of medication during hospitalization and after discharge during a time period, 2000-2009, when these guidelines were not obligatory. (9,14) We found that medication is discontinued and that other medication changes occur during admission and after discharge. Future research should investigate the impact of implementing the medication reconciliation on medication discontinuation during transition between health care settings. Future research is also needed regarding the nature of the changes that occur in patients' medication upon hospital admission or at discharge. Are these changes intentional or unintentional? Knowledge about unintentional changes will help to reevaluate the current guidelines for medication reconciliation and transfer of medication to prevent unintentional discontinuations. Future research also needs to investigate how these changes influence patients' overall health and health outcomes. Documentation of intentional changes is also important to prevent any unintended continuation.

Identifying Patients at Risk for Rehospitalization

As mentioned earlier the proportion of patients with psychotic and bipolar I disorder that is rehospitalized is high. We have shown in Chapter 3.3 that we are able to predict

for patients with psychotic or bipolar I disorder which of them are at a greater risk of rehospitalization at discharge. A risk score was created based on information on patient/disease and medical characteristics, patients' attitude towards medicine use, and health care providers assessment that can be used to assess the risk of rehospitalization. Future studies should focus on the identification of interventions that should be undertaken in order to minimize rehospitalization in patients who are at a higher risk. These interventions can involve, e.g. increased monitoring, identification of reasons for non-adherence, or the application of patient support based on individual needs. Further evaluation is needed to assess the additive effect of using the risk score to identify patients that receive rehospitalization risk-minimizing interventions compared to usual care.

Theme III: Aspects of Study Methodology

Different aspects need to be taken into account with regards to study methodology when performing clinical or pharmacoepidemiological research in psychiatric patients. These aspects are related to study design, type of data source, patient adherence, i.e. as determinant or outcome, and outcome, which will be discussed, in the next paragraph. Finally, implications for future studies will be addressed.

Study Design

As mentioned, psychiatric patients are more often (re)hospitalized than the general population. (58,59) Rehospitalization in patients with psychotic disorders discharged from a psychiatric hospital occurs more often during the first months after discharge when compared to the rest of the year. (Chapter 3.2) Therefore, it is of important that studies take account of the factor time when associations are measured such as adherence and rehospitalization. Time is important when the relative risk on the outcome is not constant over time. Furthermore, defining time periods are needed to clarify that for example the relative risk for the association between adherence and rehospitalization is variable over time. We took time into account in our study on rehospitalizations in psychiatric patients (Chapter 3.2) by applying a risk set design. Risk sets were made each time a patient was rehospitalized and rehospitalized patients were compared to non-rehospitalized patients. By applying this method we were able to measure the association between different phases of adherence and rehospitalization. Also, the relative risk was changing during the year after discharge, being highest in the first two months after discharge.

Data Sources

Continuation of pharmaceutical care can be measured when longitudinal data are available where the patients can be followed over time and through various transitions in pharmaceutical care. Ideally, longitudinal data should contain information from all health care providers of a patient. It is difficult to follow patients over long periods of

time including information on all health care provides as the data is most often spread over different settings and thus different databases. Although such detailed longitudinal data is available in the Netherlands, such as Psychiatric Case Registry used in some of our studies, single setting studies are the norm as it is difficult to link databases of different settings.

One of the options to create longitudinal data is the electronic patient file. Another option could be the linking of databases from different settings. Linking is often only possible for a certain proportion of the patients and we have no knowledge if discontinuation of pharmaceutical care differs in those patients in whom linking is not possible. If information cannot be linked for a part of the patients between databases, then these patients could be difficult to find. This needs further investigation. In such cases the linking could be achieved through birthdate or zip code or, as already done in the Nordic countries, by patient security number, i.e. a unique number for each individual used in all the systems. (60) Although, difficulties in the linking of databases can be overcome, there is still a problem regarding the uniformity of data storage. Coding standards for data storage are important when several data sources are to be used at the same time.

As often, databases on prescribing and or dispensing are used in studies about continuity of pharmaceutical care, which do not allow for the distinction between intentional and unintentional changes/discontinuations in medication. (6,9, Chapter 3.1) If reason for change and discontinuation of medication would be registered in these databases, the researchers could differentiate between intentional and unintentional discontinuation and changes in pharmaceutical care. This would provide researchers with the opportunity to focus on unintentional changes and to identify the causes of unintentional medication changes.

Setting

The pharmaceutical care of psychiatric patients is distributed over several parts of the health care system. In view of the frequent number of transitions between the systems, and considering that the data from the different systems are difficult to link, it is also difficult to conduct research in psychiatric patients. (48,61)

The available data from the outpatient care such as data from insurance companies on the reimbursement of medications dispensed by the community pharmacy and the data from the inpatient care such as the medication histories from the hospital pharmacy are not necessarily representative of the medication the patients actually use as patients may not always adhere to therapy.

As indicated earlier, it is important to combine data from the outpatient and the inpatient care to measure the continuation of pharmaceutical care in psychiatric patients. In the most ideal situation health care systems register data continuously over time, such as the

start and end date of the prescription, the indication for prescribing, and the reason of discontinuation. Continuity of pharmaceutical care can be assessed more precisely if this information is available in health care systems. In daily practice health care setting systems are different and researchers need to take this into consideration when defining their exposures and or outcomes.

In this thesis we used data of the Psychiatric Case Registry (PCR-MN). The PCR-MN is a registry containing longitudinal data for patients using psychiatric services in the Utrecht Region in the Netherlands from both outpatient and inpatient care. The PCR-MN can be linked to Achmea Health Database for Achmea insured patients. Achmea is the biggest health care insurance company in the Utrecht region. (61) Achmea Health Database contains various health care related data including all declared prescriptions from the outpatient care (e.g. prescriptions form the General Practitioner and medication dispensed from community pharmacy prescribed by all the health care providers) data with inpatient care data. Research can be done in patients found in PCR-MN for research questions related to outpatient and inpatient care. Assumptions need to be made based on available variables as for example for indication for medication prescribing/dispensing. Often, the indication for the medication is derived from the clinically indications registered for that specific medication.

Adherence Measurement

We studied adherence to antipsychotic as a determinant for rehospitalization. However, adherence can also be studied as an outcome after longer duration of hospitalizations and as continuity of care as has been done in other studies. (15,62) Adherence plays an important role in the treatment of psychotic disorders and can be measured using various methods and definitions such as assessing prescription refill patterns, using questionnaires, asking the patient and/or the psychiatrist, electronic monitoring and measuring blood levels. For example, adherence is measured by assessing the medication possession ratio (MPR), which represents the proportion of antipsychotic days in the follow-up period based on prescription refill data. However, MPR does not give any information about when medication is used in the follow-up period. (63,64) Adherence can also be measured more precisely by using the Medication Event Monitoring System (MEMS). (65) The MEMS involves a medication bottle cap that records each time the bottle is opened. This allows health care providers to check when patients open their MEMS medication bottle. However, the use of MEMS can be limited by its costs. Moreover, patients may be not willing to use them. In addition, medication adherence can be measured by measuring the concentration of the medication in the blood. Measuring blood concentrations has some limitations. First, effective blood levels are not known for each medication. Second, patients may be not willing to collaborate if medications' blood concentrations should be measured frequently.

In our studies refill data was used to measure patients' adherence. Adherence should optimally be measured in a way that it would provide information about when patients initiate, implement, and discontinue their medication as described by Vrijens et al. We applied this approach in Chapter 3.2 where we investigated the association between adherence and rehospitalization of psychiatric patients. (66) Earlier studies found an association between antipsychotic adherence and rehospitalization. However, these studies only measured if patients were adherent or non-adherent and did not distinguish between the initiation, implementation, and discontinuation of medication. Thus, our method enabled an evaluation on which aspects of adherence patients may fail, whereas the earlier studies did not provide such clarity. (44,50,64,67,68) In Chapter 3.2, we found that aspects of adherence differed over time. For example, initiation of antipsychotic medications was of importance during the first month after discharge, and discontinuation during the 4th to 6th month after discharge.

Outcomes

Earlier research measured the continuation of pharmaceutical care as study outcome by comparing the medication use before and after discharge. (6,67) These studies did not take into account medication use during hospitalization. However, in our studies we measured continuation of pharmaceutical care taking into account of the medication use in both the inpatient and outpatient care. In Chapters 2.2 and 2.3 we compared the medication dispensing before hospitalization to the medication used during hospitalization and vice versa. Furthermore, in Chapter 3.1 to 3.3 medication use during hospitalization was compared to medication use after discharge. The biggest advantage of our methodology is that we were able to take account of the changes during the first days of admission and the actual medication use just before discharge. With the application of this methodology, we were also able to measure the medications which were discontinued during hospitalization but started again after discharge in contrary to earlier research.

Rehospitalization is often used as an outcome in studies on continuity of care. In this thesis (Chapters 3.2 and 3.3), rehospitalization was measured in patients with psychotic or bipolar disorders during 1 year and 6 months after discharge. Current research on rehospitalization of patients discharged from general hospitals focuses more on rehospitalization within one month after discharge. Our results show that patients with psychotic or bipolar I disorder still have a high risk of rehospitalization during the 6-12 months after discharge and discontinuation of antipsychotic medication is associated with rehospitalization during the whole year after discharge (Chapter 3.2). These result support a recommendation for applying longer follow up periods lied when investigating rehospitalization. Besides rehospitalization and discontinuations, other outcomes should be studied, including outcomes for somatic diseases. For example, Routine Outcome Monitoring (ROM) is implemented in several psychiatric hospitals and can be used in follow-up studies to assess status and/or progress of patient's psychiatric status. Outcomes related to discontinuation of somatic medications or somatic (and psychiatric) diseases

are for example somatic (re)hospitalization, survival, quality of life, and side effects of medications.

Implications of Study Methodology for Future Research

Longitudinal data is needed to perform future research through outpatient and inpatient care. Data storage should be standardized and more information should be coded in the current systems such as indication for medication prescribing or clinical outcomes. In addition, outcomes such as the reason of (re)hospitalization can also be measured more precisely. If data would be coded, this would also make it possible to take other variables such as taking the disease status into account when performing research. Moreover, more insight into clinical outcomes is needed such as blood glucoses in patients using diabetes medication and stroke in patients on anticoagulants. Clinical outcomes should be studied especially during hospitalizations and after discontinuation of medication. This will help to evaluate whether psychiatric as well as somatic pharmacotherapies are used as intended and if patients are adequately treated for their somatic diseases. It may also give insight into whether any hospitalization contributes to the stabilization of clinical outcomes of somatic diseases.

We encourage measuring the different aspects of adherence in future studies in patients with any somatic and psychiatric diseases, and the importance of accounting for time by means of e.g. risk set design. This will give insight about which patients are at most risk to be rehospitalized at various time points following discharge. Future studies must show if the variables predicting rehospitalization in patients with psychotic or bipolar I disorder (Chapter 3.3) can be used to prevent rehospitalization and how to support patients who are at higher risk. As most hospitalizations occur during the first month after discharge it is important to monitor whether patients initiate their antipsychotic medication in this period. Measuring the three aspects of adherence will better inform health care providers and researchers when patients initiate (after discharge), how long patients use their medication (implementation), and when patients discontinue their antipsychotic medication in contrast to earlier used methods. Therefore, we recommend distinguishing between different aspects of adherence in future studies to understand when patients fail and when patient support should be available.

Conclusions of This Thesis

The research presented in this thesis has enriched the understanding of the continuation of pharmaceutical care, namely prescribing aspects, in psychiatric patients. The findings from this thesis show that:

- that the prevalence of somatic medication use is high in hospitalized psychiatric patients;
- transition from one healthcare setting to another, both admission and discharge, is accompanied with the discontinuation of both psychiatric and somatic medication;
- discontinuation of antipsychotic medication after discharge is associated with an elevated risk of rehospitalization of patients with psychotic disorders; and
- rehospitalization for patients with psychotic or bipolar I disorder can be best predicted by combining clinical and medication characteristics, patients' beliefs about medicines, and health care provider assessment.

The pharmaceutical care in psychiatric patients is complex due to transitions between health care settings and involvement of several health care providers from both primary and secondary care. There is obviously room for improvement when it comes to ascertaining continuation of pharmaceutical patient care. Pharmaceutical patient care should to be organized in a multidisciplinary setting, patients need to be aware of their responsibility and get involved in their own pharmaceutical care. We trust that our results find their way to health care providers and policy makers involved in providing pharmaceutical care to psychiatric patients. Moreover, we hope that our findings will help motivating researchers to perform future studies to investigate how pharmaceutical patient care can be improved in psychiatric patients.

References

(1) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Prevalence of medication use for somatic disease in institutionalized psychiatric patients. Pharmacopsychiatry 2013 Nov;46(7):274-280.

(2) World Health Organization. The Role of the Pharmacist in the Health Care System. Available at: http://apps.who.int/medicinedocs/en/d/Jh2995e/2.2.html. Accessed February, 16, 2015.

(3) Procyshyn RM, Barr AM, Brickell T, Honer WG. Medication errors in psychiatry: a comprehensive review. CNS Drugs 2010 Jul;24(7):595-609.

(4) De Hert M, van Winkel R, Silic A, Van Eyck D, Peuskens J. Physical health management in psychiatric settings. Eur Psychiatry 2010 Jun;25 Suppl 2:S22-8.

(5) Stuffken R, Egberts TC. Discontinuities in drug use upon hospital discharge. Pharm World Sci 2004 Oct;26(5):268-270.

(6) Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in the Netherlands. Ann Pharmacother 2008 Jul;42(7):933-939.

(7) Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. CMAJ 2005 Aug 30;173(5):510-515.

(8) Grimmsmann T, Schwabe U, Himmel W. The influence of hospitalisation on drug prescription in primary care--a large-scale follow-up study. Eur J Clin Pharmacol 2007 Aug;63(8):783-790.

(9) Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER. Discontinuation of Somatic Medication During Psychiatric Hospitalization. Ann Pharmacother 2014 Jul 30.

(10) Karapinar F, van den Bemt PM, Zoer J, Nijpels G, Borgsteede SD. Informational needs of general practitioners regarding discharge medication: content, timing and pharmacotherapeutic advice. Pharm World Sci 2010 Apr;32(2):172-178.

(11) Prins MC, Drenth-van Maanen AC, Kok RM, Jansen PA. Use of a structured medication history to establish medication use at admission to an old age psychiatric clinic: a prospective observational study. CNS Drugs 2013 Nov;27(11):963-969.

(12) van der Linden CM, Kerskes MC, Bijl AM, Maas HA, Egberts AC, Jansen PA. Represcription after adverse drug reaction in the elderly: a descriptive study. Arch Intern Med 2006 Aug 14-28;166(15):1666-1667.

(13) Stuffken R, Heerdink ER, Souverein PC, Egberts AC. The association between hospitalization and continuity of psychotropic drug use. 2013;7(7/8):88-93.

(14) Abdullah-Koolmees H, Gerbranda T, Deneer VH, Tjoeng MM, De Ridder AJ, Gardarsdottir H, et al. Discontinuation of anticoagulant care during admission to a psychiatric hospital. Eur J Clin Pharmacol 2012 Oct 23;69(4):1025-1029.

(15) Geers HC, Bouvy ML, Heerdink ER. Influence of therapeutic complexity on medication adherence in the Netherlands. Arch Intern Med 2011 May 9;171(9):864-5; author reply 865.

(16) Karow A, Czekalla J, Dittmann RW, Schacht A, Wagner T, Lambert M, et al. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. J Clin Psychiatry 2007 Jan;68(1):75-80.

(17) Karow A, Pajonk FG. Insight and quality of life in schizophrenia: recent findings and treatment implications. Curr Opin Psychiatry 2006 Nov;19(6):637-641.

(18) Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrhino F, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res 2006 Mar;83(1):53-63.

(19) Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008 Jan;69(1):106-113.

(20) Hugenholtz GW, Heerdink ER, Meijer WE, Stolker JJ, Egberts AC, Nolen WA. Reasons for switching between antipsychotics in daily clinical practice. Pharmacopsychiatry 2005 May;38(3):122-124.

(21) Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res 2002 Oct 1;57(2-3):209-219.

(22) Boden R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res 2011 Dec;133(1-3):36-41.

(23) Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand 2009 Jan;119(1):78-84.

(24) Verhoef TI, Redekop WK, Bouvy ML, Dorenbos B, Karwar Z, van Schie RM, et al. Beliefs about medicines in Dutch acenocoumarol and phenprocoumon users. Br J Clin Pharmacol 2014 Aug;78(2):422-429.

(25) Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne R. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. J Affect Disord 2009 Jul;116(1-2):51-55.

(26) Beck EM, Cavelti M, Kvrgic S, Kleim B, Vauth R. Are we addressing the 'right stuff' to enhance adherence in schizophrenia? Understanding the role of insight and attitudes towards medication. Schizophr Res 2011 Oct;132(1):42-49.

(27) Beck EM, Vogelin R, Wirtz M, Cavelti M, Kvrgic S, Vauth R. Do patients with schizophrenia distinguish between attitudes toward antipsychotic medication and pharmacotherapy in general? Validation of the Beliefs About Medication Questionnaire. J Nerv Ment Dis 2012 Jan;200(1):33-43.

(28) Aakre JM, Medoff DR, Dixon LB, Kreyenbuhl JA. Beliefs about antipsychotic versus hypoglycemic medications among individuals with serious mental illness and type 2 diabetes. Patient Prefer Adherence 2012;6:389-394.

(29) Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One 2013 Dec 2;8(12):e80633.

(30) van Geffen EC, van Hulten R, Bouvy ML, Egberts AC, Heerdink ER. Characteristics and reasons associated with nonacceptance of selective serotonin-reuptake inhibitor treatment. Ann Pharmacother 2008 Feb;42(2):218-225.

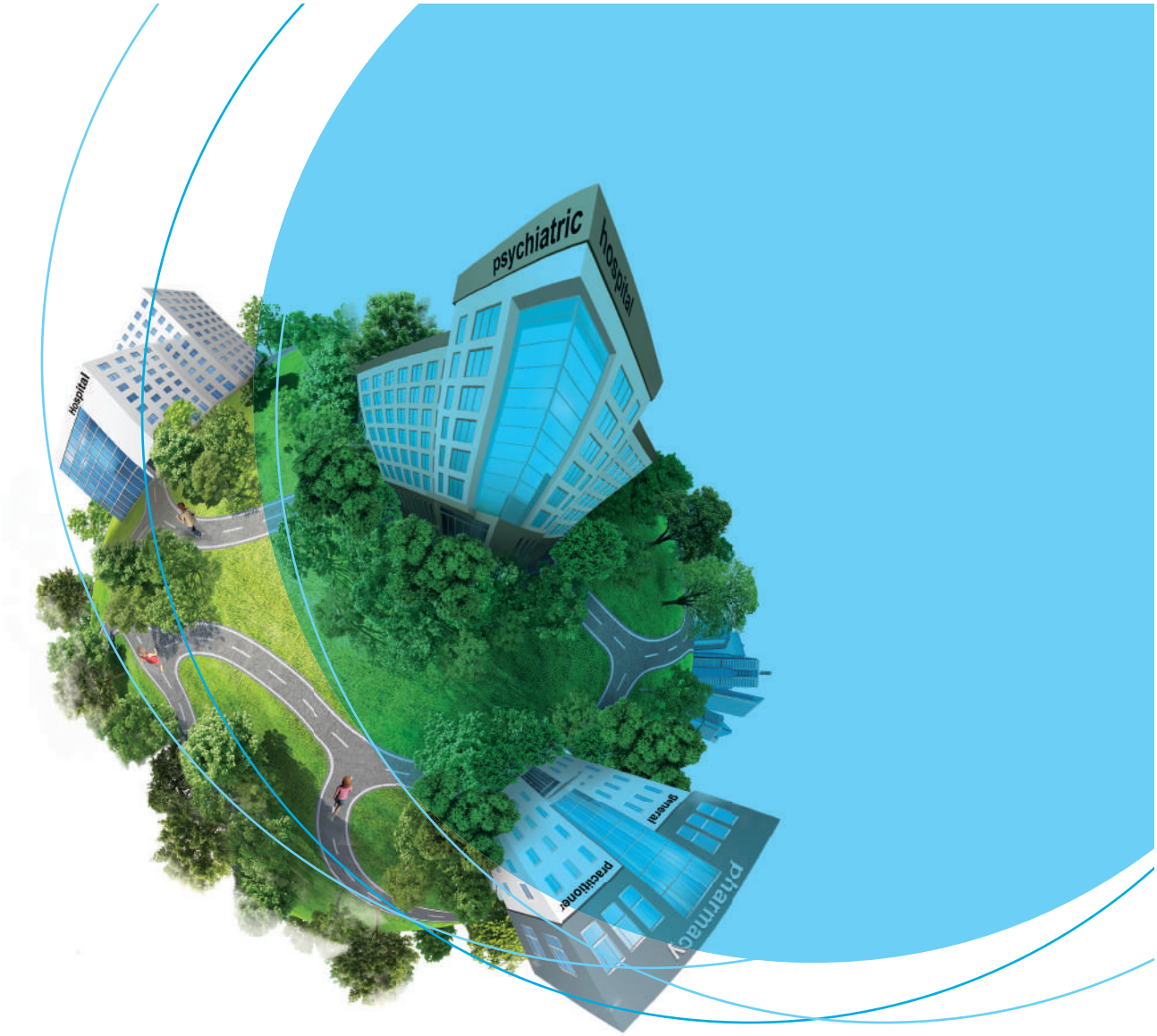
(31) van Geffen EC, Heerdink ER, Hugtenburg JG, Siero FW, Egberts AC, van Hulten R. Patients' perceptions and illness severity at start of antidepressant treatment in general practice. Int J Pharm Pract 2010 Aug;18(4):217-225.
(32) Trimbos-instituut. Trend report Metal Health Care 2012. Part 2A: acces and use of care. Mental Health Care in Primary Care. The rol of the general practitioner and psychologist. [Dutch]. 2012 2012;www.trimbos.nl/webwinkel, AF1223.
(33) van Dijk S, Knispel A, Nuijen J. Trimbos-instituut, Mental Health Care in tables. [Dutch]. 2010 2011;www.trimbos.nl/webwinkel, AF1109.
(34) Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 Sep 22;168(17):1890-1896.
(35) Stafford AC, Alswayan MS, Tenni PC. Inappropriate prescribing in older residents of Australian care homes. J Clin Pharm Ther 2011 Feb;36(1):33-44.
(36) Druss BG. Improving medical care for persons with serious mental illness: challenges and solutions. J Clin Psychiatry 2007;68 Suppl 4:40-44.
(37) National Institute for Health and Clinical Excellence. Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. Nice, 2009; Available at: http://www.nice.org.uk/CG82quickrefguide.
(38) Stoklosa J, Ongur D. Rational antipsychotic choice: weighing the risk of tardive dyskinesia and metabolic syndrome. Harv Rev Psychiatry 2011 Sep-Oct;19(5):271-276.
(39) De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry 2011 Aug;199(2):99-105.
(40) Policy document: transfer of information on medication [in Dutch]. 2008; Available at: http://www.medicatieoverdracht.nl/. Accessed August 1, 2012.
(41) Uitvlugt EB, Siegert CEH, Oosterhof P, Janssen MJA, Nijpels G, Karapinar-Çarkıt F. Medication information transfer on hospital discharge: insufficient implementation in daily practice. PW wetenschappelijk platform 2014 December 12;8(12):222-8.
(42) Karapinar-Carkit F, Borgsteede SD, Zoer J, Smit HJ, Egberts AC, van den Bemt PM. Effect of medication reconciliation with and without patient counseling on the number of pharmaceutical interventions among patients discharged from the hospital. Ann Pharmacother 2009 Jun;43(6):1001-1010.
(43) Karapinar-Carkit F, van Breukelen BR, Borgsteede SD, Janssen MJ, Egberts AC, van den Bemt PM. Completeness of patient records in community pharmacies post-discharge after in-patient medication reconciliation: a before-after study. Int J Clin Pharm 2014 Aug;36(4):807-814.
(44) dosReis S, Johnson E, Steinwachs D, Rohde C, Skinner EA, Fahey M, et al. Antipsychotic treatment patterns and hospitalizations among adults with schizophrenia. Schizophr Res 2008 Apr;101(1-3):304-311.
(45) Gray S, Urwin M, Woolfrey S, Harrington B, Cox J. Copying hospital discharge summaries to practice pharmacists: does this help implement treatment plans? Qual Prim Care 2008;16(5):327-334.
(46) Calvert SB, Kramer JM, Anstrom KJ, Kaltenbach LA, Stafford JA, Allen LaPointe NM. Patient-focused intervention to improve long-term adherence to evidence-based medications: a randomized trial. Am Heart J 2012 Apr;163(4):657-65.e1.

(47) Paquette-Lamontagne N, McLean WM, Besse L, Cusson J. Evaluation of a new integrated discharge prescription form. Ann Pharmacother 2001 Jul-Aug;35(7-8):953-958.
(48) Leendertse AJ, de Koning GH, Goudswaard AN, Belitser SV, Verhoef M, de Gier HJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. J Clin Pharm Ther 2013 Oct;38(5):379-387.
(49) Hui CL, Chen EY, Kan C, Yip K, Law C, Chiu CP. Anti-psychotics adherence among out-patients with schizophrenia in Hong Kong. Keio J Med 2006 Mar;55(1):9-14.
(50) Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008 Apr 30;8:32.
(51) Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr Serv 2004 Aug;55(8):886-891.
(52) Law MR, Soumerai SB, Ross-Degnan D, Adams AS. A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. J Clin Psychiatry 2008 Jan;69(1):47-53.
(53) Fenton WS, Kane JM. Clinical challenges in the psychopharmacology of schizophrenia. Schizophr Bull 1997;23(4):563-565.
(54) Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007 Oct;23(10):2305-2312.
(55) Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008 Jan;34(1):173-180.
(56) Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011 Jun;168(6):603-609.
(57) Jung SH, Kim WH, Choi HJ, Kang MH, Lee JS, Bae JN, et al. Factors affecting treatment discontinuation and treatment outcome in patients with schizophrenia in Korea: 10-year follow-up study. Psychiatry Investig 2011 Mar;8(1):22-29.
(58) Borckardt JJ, Madan A, Barth K, Galloway S, Balliet W, Cawley PJ, et al. Excess health care service utilization and costs associated with underrecognition of psychiatric comorbidity in a medical/surgical inpatient setting. Qual Manag Health Care 2011 Apr-Jun;20(2):98-102.
(59) Zilber N, Hornik-Lurie T, Lerner Y. Predictors of early psychiatric rehospitalization: a national case register study. Isr J Psychiatry Relat Sci 2011;48(1):49-53.
(60) Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, Norgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. Pharmacoepidemiol Drug Saf 2013 Jul;22(7):691-699.
(61) Smeets HM, Laan W, Engelhard IM, Boks MP, Geerlings MI, de Wit NJ. The psychiatric case register middle Netherlands. BMC Psychiatry 2011 Jun 29;11:106-244X-11-106.
(62) Reutfors J, Brandt L, Stephansson O, Kieler H, Andersen M, Boden R. Antipsychotic prescription filling in patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 2013 Dec;33(6):759-765.
(63) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.

(64) Valenstein M, Kavanagh J, Lee T, Reilly P, Dalack GW, Grabowski J, et al. Using a pharmacy-based intervention to improve antipsychotic adherence among patients with serious mental illness. Schizophr Bull 2011 Jul;37(4):727-736.
(65) Brain C, Allerby K, Sameby B, Quinlan P, Joas E, Karilampi U, et al. Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS((R))) in the Swedish COAST-study. Eur Neuropsychopharmacol 2013 Dec;23(12):1754-1762.
(66) Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012 May;73(5):691-705.
(67) Laan W, Does Y, Sezgi B, Smeets HM, Stolker JJ, Wit NJ, et al. Low treatment adherence with antipsychotics is associated with relapse in psychotic disorders within six months after discharge. Pharmacopsychiatry 2010 Aug;43(6):221-224.
(68) Ohmori T, Ito K, Abekawa T, Koyama T. Psychotic relapse and maintenance therapy in paranoid schizophrenia: a 15 year follow up. Eur Arch Psychiatry Clin Neurosci 1999;249(2):73-78.

5

Summary & Samenvatting


psychiatric hospital
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General

5.1

Summary

Background

Psychiatric diseases are common. The World Health Organization reported in 2001 that a quarter of the world population is affected by psychiatric diseases at least once in their life. Psychiatric diseases are known to have a great impact on patients' health and their quality of life. The medical treatment of psychiatric patients often involves a combination of pharmacological and non-pharmacological interventions such as psycho-education, social support, and counseling. Psychiatric medications are known to frequently cause (somatic) side effects and prevalence of somatic disease in psychiatric patients is high. As a consequence, the use of somatic medication is more common in psychiatric patients than in the general population.

The effective treatment of a psychiatric disease, its (somatic) side effects and any concurrent somatic diseases is important for the patient's overall health and wellbeing. The chronic nature of many psychiatric and concurrent somatic diseases implies that the continuity of both psychiatric and somatic pharmaceutical care requires particular attention. Discontinuity of pharmaceutical care may be intended (e.g. stopping a drug due to a severe side effect) or non-intended. Any non-intended discontinuity in psychiatric and somatic pharmaceutical care needs to be observed and factors associated with the discontinuity of pharmaceutical care should be closely monitored and acted upon.

Chapter 1

In the introduction (Chapter 1) the determinants of continuity of pharmaceutical care, i.e. continuation of pharmacotherapeutic prescribing, in psychiatric patients admitted to and discharged from a psychiatric hospital are described. The currently available studies on the continuity of pharmaceutical patient care mainly report on the changes of general care when patients are admitted to or discharged from a general hospital. The studies conducted in psychiatric patients generally focus on the continuation of psychiatric medication, but not on the continuation of somatic medications. These studies show that psychiatric patients commonly discontinue their psychiatric medication. However, studies on the overall continuity of pharmaceutical care in patients admitted to and discharged from a psychiatric hospital are scarce and fragmented.

Based on the current knowledge, the overall objective of this thesis was to assess the continuation of pharmaceutical care in psychiatric patients. In order to realize this goal, three sub-objectives were defined. The first was to determine the prevalence of somatic medication use in psychiatric patients. Secondly, to assess the association between transitions between healthcare settings and the continuity of pharmaceutical patient care and lastly, to assess the association between continuation of antipsychotic care and rehospitalization.

Chapter 2

The results of studies that investigated the prevalence and continuity of somatic care in psychiatric patients were presented in Chapter 2. In Chapter 2.1 the prevalence of somatic medication use in hospitalized psychiatric patients and changes in medication use were assessed on ten time points between 2006 and 2010. We found that the prevalence of use of medication for somatic disease increased from 67.5% in 2006 to 76.9% in 2010 among hospitalized psychiatric patients. The median number of medications used for somatic diseases per patient was 3 between 2006 and 2010. Approximately one-third (34.1%) of the patients received ≥3 medications intended for treating somatic disease in 2006 which increased to 46.3% in 2010. In 2010, the prevalence of medication use for somatic diseases was highest for analgesics and antirheumatics (34.0%), acid and bowel related medication (25.6%), and anticholinergic medication (24.2%). The majority of patients aged ≥60 years (95.3%), patients treated with more than one psychiatric medication class (87.5%), and patients treated with mood stabilizers (90.6%) used somatic medications.

In Chapter 2.2 discontinuation and switch of somatic medication was explored in 471 patients during the first week of psychiatric hospitalization compared to the year before hospitalization, and the related factors were evaluated. 38.9% of the patients discontinued and 27.0% switched somatic medication during the first week of hospitalization. Discontinuation was more frequent during the first week of hospitalization when compared to discontinuation during the year before hospitalization (38.9% vs 20.4%, relative risk [RR]=1.9; 95% Confidence Interval [CI]=1.6-2.3). Patients <45 years had the highest risk of discontinuing somatic medication (RR=2.8; 95% CI=1.9-4.2) during the first week of hospitalization. In addition, patients switched their somatic medication more frequently during the first week of hospitalization than during the year before (27.0% vs 11.0%, RR=2.6; 95% CI = 2.1-3.3). This study showed that psychiatric hospitalization was associated with an almost doubled risk of discontinuation of somatic medication. Patients <45 years old, those hospitalized for 7 days or less, patients admitted to nonpsychogeriatric wards, and users of acid- and bowel-related medication had the highest risk of discontinuing somatic medication during the first week of hospitalization.

Chapter 2.3 focused on the quality of anticoagulant care in terms of anticoagulant treatment and factors related to discontinuation of patients' anticoagulant care during psychiatric hospitalization. We studied users of orally administered anticoagulants who were admitted to a psychiatric hospital. Discontinuation of anticoagulant care was defined as no oral anticoagulant dispensing during the first week of hospitalization and/or no International Normalized Ration (INR) measurement during hospitalization. Of the 111 patients included, discontinuation of anticoagulant care occurred in 24.3% of the patients. For 17.1% of the patients no oral anticoagulant was dispensed during the first week and 13.5% had no INR measurement during hospitalization. The risk of

discontinuation was higher in patients admitted to nonpsychogeriatric wards compared with those admitted to psychogeriatric wards (52.6% vs 9.6%, RR=5.5, 95% CI =2.3-12.9).

Chapter 3

In Chapter 3 we focused on the continuity of psychiatric and somatic care for psychiatric patients. Discontinuation and other changes in use of psychiatric and/or somatic medication in patients discharged from a psychiatric hospital were explored in Chapter 3.1. Patients discharged from four psychiatric hospitals in the Netherlands between 2006 and 2009 were included in this study. Patients' medication use during the last two days of hospitalization was compared with medication dispensed during the three months after discharge. Medication changes assessed included discontinuation, start, or switch of medication. Patients without any change in medication dispensed after the discharge were considered as continuers. Of 1324 patients, 69.8% discontinued and 9.7% switched one or more medications. 47.4% started a medication, which was not dispensed during the last two days of hospitalization, and 13.7% continued all medication dispensed during the last two days of hospitalization. Of the 644 patients using antipsychotic medication and the 292 patients using cardiovascular medication during the 2 days prior to discharge, 25.2% and 28.4% discontinued their antipsychotic and cardiovascular medication after discharge, respectively. The risk of discontinuation was highest in patients using as-needed medication prior to discharge (RR=1.9, 95% CI=1.6-2.2).

In Chapter 3.2, the association between adherence to antipsychotics during three phases of medication use (initiation, implementation, and discontinuation) and rehospitalization during the first year after discharge was investigated. In this retrospective follow-up study, the study population included adult patients who were discharged from four psychiatric hospitals, with a diagnosis of psychotic disorder, that were hospitalized for ≥7 days, and who used oral antipsychotics at discharge. Of the 320 included patients, 77.8% initiated antipsychotics during the first month after discharge, and 44.4% were rehospitalized within 1 year after discharge. Patients never initiating antipsychotics during follow up had a higher risk of rehospitalization (RR=3.7; 95% CI: 2.4-5.5) when compared with patients who initiated antipsychotics during follow up. Patients initiating antipsychotic use during the 2nd week after discharge and those initiating more than 2 weeks after discharge had a 4.4 times (95% CI: 1.5-12.9) and 2.5 (95% CI: 1.2-5.1) higher risk of rehospitalization during the first month after discharge, respectively, when compared with those initiating antipsychotics within one week from discharge. Patients who discontinued their antipsychotic medication had a twofold higher risk (RR=2.3; 95% CI: 1.2-4.5) to be rehospitalized during the 2nd to 12th months following discharge when compared with patients that continued antipsychotic use.

In Chapter 3.3 the risk of rehospitalization within six months after discharge was predicted in adult patients suffering from psychotic or bipolar I disorders who were hospitalized in a psychiatric hospital for ≥7days and were treated with oral antipsychotics at discharge. Four models predicting rehospitalization were constructed including the following characteristics:

- 1. patient/disease characteristics,
- 1+2. patient/disease and medication characteristics,
- 1+2+3. patient/disease and medication characteristics, and patients' attitude towards medicine use, and
- 1+2+3+4. patient/disease and medication characteristics, patients' attitude towards medicine use, and health care provider assessments.

Risk scores were calculated for the prediction model with the highest area under the receiver operating characteristic curve (AUC_{ROC}). 87 Patients were included of whom 33.3% were rehospitalized within six months after discharge. The model including patient/disease (duration of index hospitalization, diagnosis, and age) and medication characteristics (number of antipsychotics in use and if patient was reminded of taking medication by others), attitude towards medicine use, and health care provider assessments (prediction of rehospitalization by the nurse, and whether the physician and the nurse discussed adherence to antipsychotics during hospitalization) had the highest predicting ability (AUC_{ROC}=0.74). Patients in the upper tertile (risk score 34.1-52.0) were most often rehospitalized (62.1%). 31.0% of the patients in the middle tertile (risk score 24.7-34.0) and 6.9% of the patients in the lower tertile (risk score 0.0-24.6) were rehospitalized.

Chapter 4

In Chapter 4, we summarized the main findings of our studies, discussed possible determinants for (dis)continuity of pharmaceutical patient care, aspects of study methodology, and placed them into a broader perspective of implications for daily practice and future research in psychiatric patients.

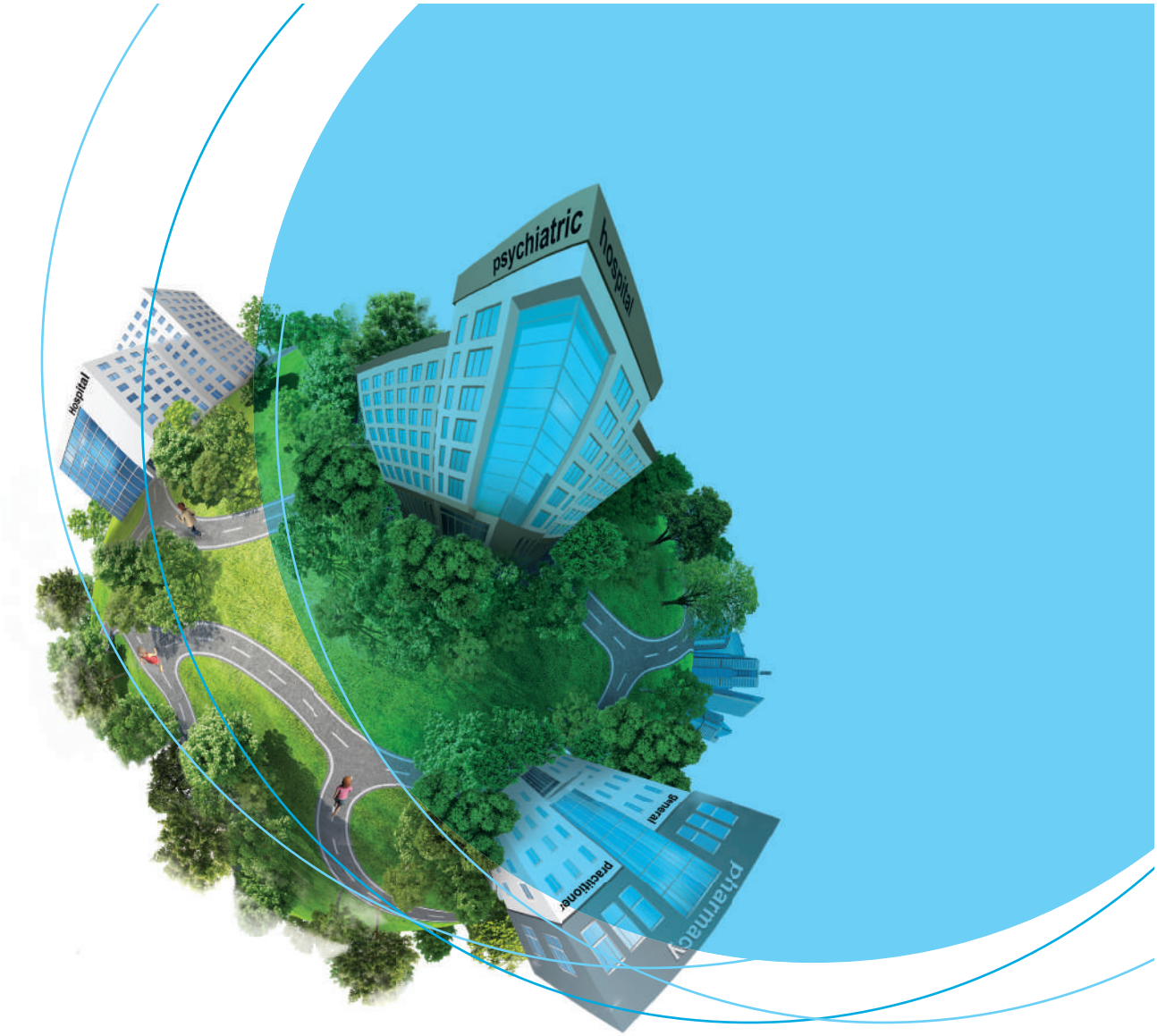
Conclusions of This Thesis

The research presented in this thesis has enriched the understanding of the continuation of pharmaceutical care, i.e. in terms of prescribing, in psychiatric patients. The findings from this thesis show that:

- the prevalence of somatic medication use is high in hospitalized psychiatric patients;
- transition from one healthcare setting to another, both admission and discharge, is accompanied with the discontinuation of both psychiatric and somatic medication;

- discontinuation of antipsychotic medication after discharge is associated with an elevated risk of rehospitalization in patients with psychotic disorders; and
- rehospitalization of patients with psychotic or bipolar I disorder can be best predicted by combining clinical and medication characteristics, patients' beliefs about medicines, and health care provider assessment.

The pharmaceutical care in psychiatric patients is complex due to transitions between health care settings and involvement of several health care providers from both primary and secondary care. There is obviously room for improvement in continuation of pharmaceutical patient care. Pharmaceutical patient care should to be organized in a multidisciplinary setting, patients need to be aware of their responsibility and get involved in their own pharmaceutical care.



5.2

Samenvatting

Achtergrond

Psychiatrische aandoeningen komen vaak voor. De Wereldgezondheidsorganisatie (WHO) rapporteerde in 2001 dat een kwart van de wereldbevolking minimaal één keer in hun leven een psychiatrische aandoening zal hebben. Psychiatrische aandoeningen hebben een grote invloed op de gezondheid en kwaliteit van leven. De behandeling van een psychiatrische aandoening bestaat vaak uit een combinatie van farmacologische en niet-farmacologische interventies zoals psycho-educatie, sociale ondersteuning en begeleiding. Psychiatrische geneesmiddelen veroorzaken vaak bijwerkingen, zowel somatische (lichamelijke) als psychische. Daarnaast hebben psychiatrische patiënten een hogere kans op bijkomende somatische aandoeningen. Dit heeft als gevolg dat psychiatrische patiënten vaker somatische geneesmiddelen gebruiken dan de algemene populatie.

Voor de algehele gezondheid en het welzijn van de patiënt is het belangrijk dat er een goede afstemming is tussen de behandeling van de psychiatrische aandoening, somatische aandoening en mogelijke (somatische) bijwerkingen van de gegeven medicatie. De continuïteit van zowel psychiatrische als somatische farmaceutische zorg vraagt/verdient bijzondere aandacht, omdat veel psychiatrische en somatische aandoeningen chronisch zijn. Discontinuïteit van farmaceutische zorg kan bedoeld of onbedoeld (onbewust) plaatsvinden. Een voorbeeld van bedoelde discontinuering van medicatie is het stoppen van een geneesmiddel vanwege bijwerkingen. Het is van belang om factoren die geassocieerd zijn met onbewuste discontinuïteit van farmaceutische zorg te kennen, nauwlettend te monitoren en zo nodig beleid daarop te sturen.

Hoofdstuk 1

De introductie (hoofdstuk 1) beschrijft de determinanten van continuïteit van zorg voor psychiatrische patiënten die opgenomen zijn in of ontslagen zijn uit een psychiatrisch ziekenhuis. De in de literatuur beschreven onderzoeken over de continuïteit van farmaceutische patiëntenzorg rapporteren met name over veranderingen van de algemene zorg wanneer patiënten worden opgenomen in of ontslagen uit een algemeen ziekenhuis. De onderzoeken die zijn uitgevoerd bij psychiatrische patiënten richten zich in het algemeen op de continuïteit van psychiatrische geneesmiddelen, maar niet op de continuïteit van somatische geneesmiddelen. Deze onderzoeken laten zien dat psychiatrische patiënten vaak het gebruik van psychiatrische geneesmiddelen discontinueren. De onderzoeken over de algehele continuïteit van farmaceutische zorg bij patiënten die zijn opgenomen in of ontslagen uit een psychiatrisch ziekenhuis zijn echter schaars en gefragmenteerd.

Het doel van dit proefschrift is om de continuïteit van de farmaceutische zorg van met name aspecten van voorschrijven aan psychiatrische patiënten beter in kaart te brengen. Om dit doel te realiseren, zijn de volgende drie subdoelen gedefinieerd:

1. het bepalen van de prevalentie van somatisch geneesmiddelengebruik bij psychiatrische patiënten;
2. het bepalen van de associatie tussen transities in de zorg (zoals ziekenhuisopname en ontslag) en de continuïteit van farmaceutische patiëntenzorg;
3. het bepalen van de associatie tussen continuïteit van gebruik van antipsychotica en het risico op heropname.

Hoofdstuk 2

In hoofdstuk 2 worden de resultaten van onderzoek naar de prevalentie en de continuïteit van somatische zorg in psychiatrische patiënten gepresenteerd. In hoofdstuk 2.1 zijn de prevalentie van het gebruik van somatisch geneesmiddelen van opgenomen psychiatrische patiënten en de veranderingen in geneesmiddelengebruik op tien tijdspunten tussen 2006 tot 2010 bepaald. De prevalentie van het geneesmiddelengebruik voor somatische aandoeningen nam toe van 67,5% in 2006 tot 76,9% in 2010. Patiënten gebruikten 3 (mediaan) somatische geneesmiddelen. Ongeveer een derde (34,1%) van de patiënten kreeg ≥3 geneesmiddelen bedoeld voor de behandeling van somatische aandoeningen in 2006, wat toenam tot 46,3% in 2010. De meest gebruikte somatische geneesmiddelen waren analgetica en antireumatica (34,0%), maag- en darmmiddelen (25,6%) en anticholinergica (24,2%). De meerderheid van de patiënten die somatische geneesmiddelen gebruikten waren ≥60 jaar (95,3%), werden behandeld met geneesmiddelen uit meer dan één psychiatrische geneesmiddelenklasse (87,5%) en behandeld met stemmingsstabilisatoren (90,6%).

In hoofdstuk 2.2 is de discontinuïteit en het switchen van somatische geneesmiddelen onderzocht bij 471 patiënten tijdens een opname in een psychiatrisch ziekenhuis en de daaraan gerelateerde factoren vergeleken met het jaar voor opname. 38,9% van de patiënten discontinueerden en 27,0% switchten somatische geneesmiddelen gedurende de eerste week van ziekenhuisopname. Discontinuïteit kwam vaker voor tijdens opname dan gedurende het jaar voor opname (38,9% vs 20,4%, relatieve risico [RR] = 1.9; 95% betrouwbaarheidsinterval [BI] = 1.6-2.3). Patiënten jonger dan 45 jaar hadden het hoogste risico om een somatisch geneesmiddel te discontinueren (RR=2,8; 95% BI=1,9-4,2). Tevens switchen patienten vaker hun somatische geneesmiddelen gedurende opname, vergeleken met het jaar ervoor (27,0% vs 11,0%, RR=2,6; 95% BI = 2,1-3,3). Deze studie laat zien dat een opname in een psychiatrisch ziekenhuis geassocieerd was met ongeveer een verdubbeling van het risico op discontinuïteit van somatische geneesmiddelen. Patiënten jonger dan 45 jaar, die 7 dagen of korter waren opgenomen, of opgenomen op een niet-psychogeriatrische afdeling en gebruikers van maag- en darmmiddelen, hadden het hoogste risico op discontinuïteit van somatische geneesmiddelen tijdens ziekenhuisopname .

Hoofdstuk 2.3 beschrijft de kwaliteit van therapie met anticoagulantia (antistollingsmiddelen) en factoren gerelateerd aan discontinuïteit van anticoagulantiatherapie van patiënten tijdens opname in een psychiatrisch ziekenhuis. We hebben gebruikers van orale cumarinederivaten, die werden opgenomen in een psychiatrisch ziekenhuis, bestudeerd. Discontinuïteit van anticoagulantiatherapie was gedefinieerd als het niet krijgen van een orale anticoagulantia gedurende de eerste week van de ziekenhuisopname en/of geen bepaling van de INR tijdens de ziekenhuisopname. Van de 111 patiënten, was er bij 24,3% sprake van discontinuïteit van anticoagulantiatherapie. Voor 17,1% van de patiënten waren er geen orale anticoagulantia verstrekt tijdens de eerste week en bij 13,5% was er geen INR bepaald tijdens de ziekenhuisopname. Het risico op discontinuïteit was het hoogst in patiënten opgenomen op niet-psychogeriatrische afdelingen t.o.v. psychogeriatrische afdelingen (52,6% vs. 9,6%, RR = 5,5, 95% BI = 2,3-13.0).

Hoofdstuk 3

In hoofdstuk 3 is de continuïteit van psychiatrische en somatische farmaceutische zorg voor psychiatrische patiënten bestudeerd. In hoofdstuk 3.1 hebben we de discontinuïteit en andere veranderingen in het gebruik van psychiatrische en/of somatische geneesmiddelen bestudeerd van patiënten die ontslagen waren uit een psychiatrisch ziekenhuis tussen 2006 en 2009. Om veranderingen in het geneesmiddelengebruik in kaart te brengen is het geneesmiddelengebruik gedurende de laatste twee dagen van ziekenhuisopname vergeleken met geneesmiddelen verstrekt gedurende de eerste drie maanden na ontslag. Op basis van de geneesmiddelveranderingen zijn patiënten geclassificeerd in de categorieën “discontinue”, “start”, of “switch”. Wanneer de geneesmiddelen die verstrekt werden na ontslag hetzelfde waren als voor ontslag, zijn deze patiënten geclassificeerd in de categorie “continue”. Van de 1324 patiënten is 69,8% geclassificeerd in de categorie discontinue en 9,7% in de categorie switch. Van de patiënten staartte 47,4% een geneesmiddel dat niet was gebruikt gedurende de laatste twee dagen van ziekenhuisopname. 13,7% continueerde alle geneesmiddelen na ontslag zonder discontinuïteit of enige andere verandering. Van de 644 patiënten die antipsychotica gebruikten, discontinueerde 25,2% één of meerdere van deze antipsychotica. Van de 292 patiënten die cardiovasculaire geneesmiddelen gebruikten, discontinueerde 28,4% een of meerdere van deze cardiovasculaire geneesmiddelen. Het relatieve risico voor discontinuïteit van een geneesmiddel was het hoogst bij patiënten die ‘zo nodig’ geneesmiddelen gebruikten voor ontslag (RR = 1,9, 95% BI = 1,6-2,2).

De associatie tussen therapietrouw van antipsychotica gedurende de drie fasen van geneesmiddelengebruik en heropname gedurende één jaar na ontslag is onderzocht in hoofdstuk 3.2. De drie fases van het geneesmiddelengebruik zijn initiëren, implementeren en discontinueren. De studiepopulatie, geïncludeerd in deze retrospectieve follow-up studie, bestond uit patiënten die waren ontslagen uit een van vier deelnemende psychiatrische ziekenhuizen. De patiënten hadden een diagnose van psychotische stoornissen,

waren ≥7 dagen opgenomen en gebruikten antipsychotica bij ontslag. Van de 320 geïncludeerde patiënten initieerde 77,8% het antipsychoticum gedurende de eerste maand na ontslag. 44,4% van alle patiënten werd heropgenomen binnen één jaar na ontslag. Patiënten die nooit een antipsychoticum initieerden tijdens follow-up, hadden een hoger risico op heropname vergeleken met patiënten die wel het antipsychoticum initieerden (RR = 3,7; 95% BI: 2,4-5,5). Patiënten die in de 2e week na ontslag of later dan 2 weken antipsychotica initieerden hadden respectievelijk een 4,4 (95% BI: 1,5-13,0) en 2,5 maal (95% BI: 1,2-5,1) hoger risico op heropname gedurende de eerste maand na ontslag, vergeleken met patiënten die binnen een week na ontslag antipsychotica initieerden. Discontinuïteit van antipsychotica was geassocieerd met een relatief risico van 2,3 (95% BI: 1,2-4,5) om heropgenomen te worden tijdens de 2e tot 12e maand na ontslag.

In hoofdstuk 3.3 is het risico van heropname binnen zes maanden na ontslag voorspeld voor volwassen patiënten met psychotische of bipolaire I stoornissen, opgenomen in een psychiatrisch ziekenhuis voor een periode van ≥7 dagen en die werden behandeld met orale antipsychotica. Met behulp van Cox regressie zijn vier predictiemodellen samengesteld met de volgende kenmerken:

- 1. Patiënt- en ziekte karakteristieken,
- 1+2. Patiënt-, ziekte- en geneesmiddelkarakteristieken,
- 1+2+3. Patiënt-, ziekte- en geneesmiddelkarakteristieken en attitude van patiënten ten aanzien van geneesmiddelengebruik, en
- 1+2+3+4. Patiënt-, ziekte- en geneesmiddelkarakteristieken, attitude van patiënten met betrekking tot geneesmiddelengebruik en inschatting van de zorgverleners.

Voor de 4 predictiemodellen zijn 'area under the receiver operating characteristic curves' (AUC_{ROC}) berekend. Voor het predictiemodel met het hoogste AUC_{ROC}, zijn er risicoscores berekend. 87 patiënten zijn geïncludeerd waarvan 33,3% werd heropgenomen binnen zes maanden na ontslag. Heropname kon het beste worden voorspeld met het predictiemodel 1+2+3+4 (AUC_{ROC}=0.74). De berekende risicoscores uit het predictiemodel 1+2+3+4 varieerden van 0,0 tot 52,0 en zijn vervolgens opgedeeld in tertielen, te weten 0,0 tot 24,6; 24,7 tot 34,0 en 34,1 en 52,0. Van patiënten in het hoogste tertiel werd 62,1% heropgenomen, 31,0% van de patiënten in het middelste tertiel werd heropgenomen en 6,9% van de patiënten in het laagste tertiel.

Hoofdstuk 4

In hoofdstuk 4 zijn de belangrijkste bevindingen van dit proefschrift samengevat. Ook zijn de mogelijke determinanten van (dis)continuïteit van farmaceutische patiëntenzorg en aspecten van onderzoeksmethodologie bediscussieerd. Deze aspecten worden tevens in een breder perspectief gezet voor toepassing in klinische, dagelijkse praktijk en toekomstig onderzoek bij psychiatrische patiënten.

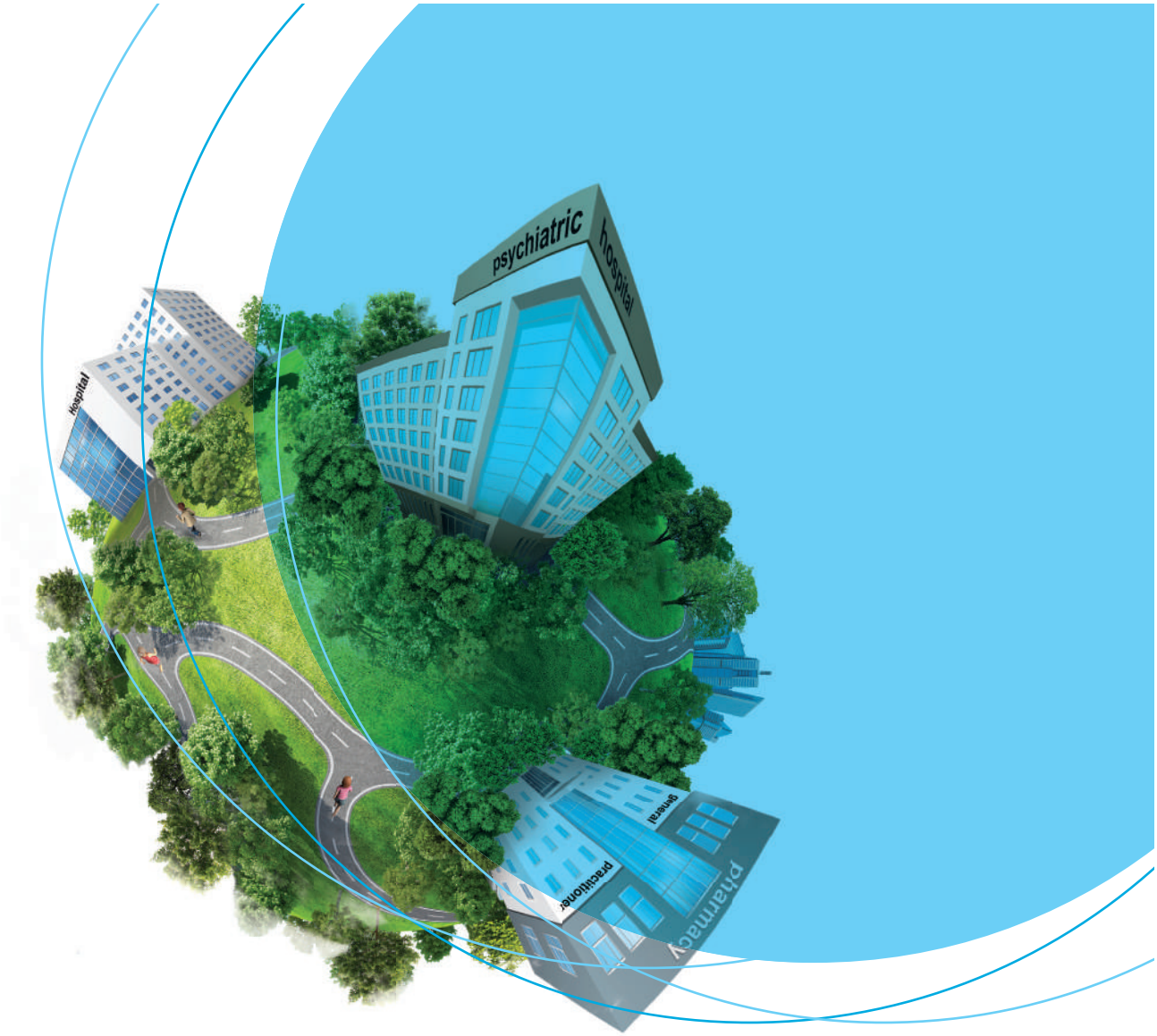
Conclusies van dit Proefschrift

De studies gepresenteerd in dit proefschrift hebben de kennis over de continuïteit van farmaceutische zorg over psychiatrische patiënten vergroot en aangescherpt. De bevindingen van dit proefschrift laten zien dat:

- de prevalentie van het gebruik van somatische geneesmiddelen hoog is bij opgenomen psychiatrische patiënten;
- transities in de zorg, bij zowel opname als ontslag, gepaard gaan met discontinuïteit van psychiatrische en somatische geneesmiddelen; en
- heropname van patiënten met psychotische of bipolaire I stoornissen het beste kan worden voorspeld door de combinatie van patiënt-, ziekte- en geneesmiddelkarakteristieken, attitude van patiënten ten aanzien van geneesmiddelengebruik en inschatting van de zorgverleners.

De farmaceutische zorg van psychiatrische patiënten is complex door transities in de zorg en betrokkenheid van meerdere zorgverleners uit zowel eerste als tweede lijn. Er is ruimte voor verbetering van de continuïteit van de farmaceutische patiëntenzorg. De farmaceutische patiëntenzorg dient te worden georganiseerd in een integrale multidisciplinaire setting, patiënten dienen bewust te zijn van hun eigen verantwoordelijkheid en te worden betrokken in hun eigen farmaceutische zorg.

6
Appendices



6.1

Acknowledgements

Ik ben God enorm dankbaar om altijd de dingen te doen, die ik wilde en waarvan ik droomde. Als kind van een jaar of 10 wist ik dat ik wilde gaan promoveren als ik groot was en me zou gaan verdiepen in een onderwerp voor een bepaalde groep patiënten...

Vrijwel direct na mijn studie werd één van mijn dromen werkelijkheid, namelijk een promotieplek. Met heel veel enthousiasme ben ik aan mijn promotie begonnen. De afgelopen vier jaar waren heel afwisselend, boeiend en uitdagend. Een periode waarin ik heel veel heb mogen leren en met diverse mensen plezierig heb kunnen samenwerken. Ik wil iedereen bedanken die een bijdrage heeft geleverd aan mijn promotieonderzoek. Sommigen van hen wil ik in het bijzonder bedanken.

De afgelopen jaren ben ik begeleid door een super promotieteam bestaande uit Prof. Dr. A.C.G. Egberts, Dr. E.R. Heerdink en Dr. H. Gardarsdottir. Bijzonder deskundige mensen waar ik altijd op kon en kan rekenen en die voor mij klaar stonden. Onze overleggen waren efficiënt en nuttig maar er was ook tijd voor een luchtige opmerking met een koekje erbij.

Beste Toine, mijn promotor, toen ik net begonnen was aan het 1e jaar van de opleiding farmacie, woonde ik een hoorcollege van jou bij over bijwerkingen van geneesmiddelen. Dit hoorcollege was heel boeiend en maakte veel indruk op mij en de anderen in de zaal door de indrukwekkende bijwerkingen van geneesmiddelen. Ik was heel blij toen ik hoorde dat ik door jou begeleid zou worden tijdens mijn promotie. Onze besprekingen waren altijd heel effectief en leerzaam. Maar vooral jouw visie op de dagelijkse praktijk en onderzoek en hoe je het groter geheel ziet is mij erg bijgebleven. Daarnaast vind ik dat je toch ook zoveel details onthoudt. Ondanks dat je het drukst had van ons allemaal, reageerde je bijna altijd als één van de eersten op mijn e-mails en stukken. Dankjewel voor alle inspiratie, motivatie, steun en de bloemen bij het inleveren van mijn manuscript.

Beste Rob, mijn co-promotor, met jou had ik het eerste gesprek over mijn promotie. Ik bewonder hoe je de samenhang van onderzoeken door verschillende promovendi aan elkaar weet te koppelen zonder daarbij details uit het oog te verliezen. Ik stond in het begin verbaasd te kijken van het feit dat je zo gemakkelijk dubbele spaties in een uitgeprinte stuk haalde. Inmiddels heb ik dat van jou overgenomen. Soms als ik een vraag mailde, kreeg ik niet direct een reactie terug, maar tijdens ons wekelijkse overleg bleek dat je erover had nagedacht en zelfs de volgende stappen had uitgedacht. Bedankt voor je begeleiding van afgelopen jaren.

Beste Helga, mijn co-promotor, jou zag ik voor het eerst tijdens het eerste promotie overleg. Vanaf het begin was er direct een klik. Je stond altijd klaar voor me en nam altijd de tijd voor de databewerking, analyses en de papers maar ook het alledaagse. Daarnaast heb je me leren programmeren in FoxPro, wat mij zelfs enthousiast heeft gemaakt en

deze kennis soms doorgeef aan andere studenten. Door jou ben ik methodologie leuk gaan vinden. Zo bijzonder hoe je naar een artikel kijkt en de consistentie van opbouw en woordgebruik bewaakt en denkt in mogelijkheden. Tijdens mijn promotietraject bleken onze interesses zoals hardlopen en reizen dichtbij elkaar te liggen. Ook privé hebben we een aantal keer gezellig afgesproken en samen gegeten met Mattijs, Gunar, Andri en Anne. Ook jou ben ik enorm dankbaar dat je een van de begeleiders was.

Dit promotietraject is begonnen door het samenwerkingsverband met de vroegere ziekenhuisapotheek van Altrecht en de Universiteit Utrecht. In het eerste jaar heb ik mijn promotie gecombineerd met mijn werkzaamheden in de ziekenhuisapotheek van Altrecht. Hiervoor heeft Drs. L.J. Stoker zich altijd sterk gemaakt.
Beste Lennart, je hebt altijd geknokt voor het behouden van het promotietraject en de samenwerking tussen Universiteit Utrecht en ziekenhuisapotheek van Altrecht, later van Brocacef. Je hebt me in contact gebracht met mensen betrokken bij de behandeling van psychiatrische patiënten en meegedacht over hoe ik de praktijk beter kon leren kennen. Ook tijdens mijn werkzaamheden in de ziekenhuisapotheek heb ik veel kunnen leren over de medicatiebehandeling van psychiatrische patiënten. Ook van de dagdienstactiviteiten die ik bij Altrecht heb mogen doen, zijn van groot profijt tijdens mijn studie, maar ook in mijn huidige werkzaamheden. Bedankt voor je betrokkenheid en je input bij het opstellen van de studies.

Vanuit Altrecht is de psychiater-directeur Drs. J. Vuyk betrokken geweest. Beste Judith, onze meetings en telefoongesprekken waren altijd zo leuk. Ik heb veel van je mogen leren over de echte dagelijkse praktijk in een GGZ instelling en over behandeling van ambulante patiënten. Ook heb je me met veel mensen van de werkvloer in contact gebracht, waarmee ik heb meegelopen om praktijkervaring op te doen. Tevens heb je actief meegedacht over hoe we de onderzoeken konden uitvoeren en de juiste mensen betrokken om de DANA studie op te starten om genoeg patiënten te includeren. Dank voor jouw bijdragen aan mijn studie en de inzichten in de GGZ. Ondanks je drukke agenda, stond je altijd voor me klaar.

De onderzoeken in dit proefschrift zijn mede mogelijk gemaakt door Altrecht. Ik wil daarom Altrecht, m.n. de afdelingen van de Willem Arntsz betrokken bij de DANA studie, opname coördinatie, de Commissie Wetenschappelijk Onderzoek en de mensen van Psygis Quarant in het Deltahuis bedanken voor hun bijdragen. Ook wil ik alle patiënten bedanken die mee hebben gedaan met de DANA studie.

Drs. A.J.M. de Ridder. Beste Alex, dank voor je betrokkenheid bij de studie over anticoagulantiatherapie en het indienen van het eerste onderzoeksvoorstel. De wijze waarop je ideeën operationaliseert en deze zichtbaar maakt binnen Altrecht om ons onderzoek te delen met andere collega's, is uniek.

Ook is bij de DANA studie Dr. L.E. Goedhard betrokken geweest. Beste Laurette, ik was blij dat je mee wilde denken hoe we het onderzoek konden uitrollen op de afdelingen en de patiënten konden benaderen met vragenlijsten. Verrassend vond ik het om bij jou thuis te mogen komen eten en daarna te kijken hoe we de data het beste konden extraheren.

Ook wil ik de oud-collega's van de oude ziekenhuisapotheek Altrecht bedanken voor jullie interesse naar mijn onderzoek maar ook daarbuiten. In het bijzonder wil ik Hester bedanken voor het verzorgen van de extracties. Het correct gepresenteerd krijgen van data uit Crystal Reports bleek een uitdaging die jij steeds wist te overwinnen.

Voor de studie over discontinuïteit van anticoagulantiatherapie heb ik samengewerkt met Drs. M.M. Tjoeng, Dr. V. Deneer en Drs. T. Gerbranda. Beste Mathieu, Vera en Tjestke, dank voor de samenwerking en de mooie studie die we gezamenlijk hebben gepubliceerd.

Ik wil Fabian Temorshuizen, Hugo Smeets en Janneke Giele-Eshuis van het Julius centrum bedanken die mij geholpen hebben bij het aanvragen van data bij het Psychiatrisch Casus Register Midden Nederland en Achmea Health Database.

Voor de retrospectieve studie over heropnames (hoofdstuk 3.2) heb ik de hulp gehad van Drs. S.V. Belitser. Beste Svetlana, statistiek en data-analyse is jou op het lijf geschreven. Hoe ingewikkeld de analyse en het programmeren ook, niks was je te veel. Voor de ingewikkelde statistische vragen kon ik altijd bij je langskomen. Ik heb genoten van het delen van onze ideeën over onderzoek en het dagelijkse leven en ik heb veel van je geleerd, waarvoor dank

Dr. P.C. Souverein, beste Patrick, DE FoxPro goeroe! Bewonderenswaardig hoe jij kan programmeren en grote databestanden kan bewerken met ingewikkelde en ellenlange syntaxen om daarmee ingewikkelde vragen om te zetten in hele eenvoudige coderingen. Heel veel dank voor je hulp.

De leden van de beoordelingscommissie: Prof. Dr. M.L. Bouvy, Prof. Dr. N.J. de Wit, Prof. Dr. I.M. Engelhard, Prof. Dr. K. Taxis en Dr. A. Maras wil ik bedanken voor de inhoudelijke beoordeling van mijn manuscript.

Ook de dames van het secretariaat oftewel de drie musketiers, Ineke, Anja en Suzanne, verdienen bijzondere aandacht voor het regelen van de praktische zaken en gezellige conversaties. Dit geldt ook voor Willem, voor wat betreft de IT gerelateerde zaken.

Het is fijn om te promoveren in een omgeving waar iedereen bezig is met onderzoek. Al waren de onderwerpen soms heel uiteenlopend, we kregen allemaal te maken met zaken zoals analyse, het indienen van een onderzoeksvoorstel, etc.

I want to thank all my colleagues of Pharmacoepidemiology and Clinical Pharmacology for the "gezelligheid", nice cake moments and their interest: my running mates Yared and Lucie, Arjo, Alfi, Rianne (van Schie), Rianne (van Rossum-van den Ham), Arjen Geerts, Talitha, Sander, Sanni, Hamid, Neda, Fariba, Daphne, Renate, Susanne, Sander, Niloufar, Francisco, Fereshta and Ali. We had so much fun during ISPE. Dear Soulmaz, it feels like we have known each other for years. We had fun sharing our PhD things, girly stuff and shopping off course. Yasser, I enjoyed our conservations about research, our countries, language and food. Thanks for your help with calling the beadle. Professor (to be :)) Jamal, thanks for sharing your statistical knowledge. Your explanations were always useful. Good luck in Bangladesh, I will miss our talks. Corinne, het was leuk om samen naar promoties te gaan, met elkaar mee te denken over de statistiek en andere promotiezaken en natuurlijk gezellig te squashen. Marcel Kooij, leuk om onze ideeën over onderzoek te delen en dank voor het meelezen.

Ook wil ik mijn collega's van de ziekenhuisapotheek van het Diakonessenhuis bedanken voor hun interesse. Het is uitdagend om wetenschappelijk onderzoek en dagelijkse praktijk te combineren.

Beste Dr. Gerard Hugenholtz, eind 2011 zocht ik een nieuwe uitdaging die goed te combineren was met mijn promotieonderzoek. Bedankt voor het mede mogelijk maken van deze combinatie. Fantastisch dat ik bij jullie in opleiding mag. Drs. Emile Kuck, ik heb bewondering voor je grote kennis. Ik mag me gelukkig prijzen met jou en Gerard als opleiders.

Beste Dr. Elke Brouwers, afgelopen jaren heb ik zoveel geleerd van de projecten die ik samen met jou in het ziekenhuis heb gedaan. Fijn dat we deze samenwerking kunnen continueren en er voor te zorgen nog meer verbeteringen vanuit de apotheek door te voeren op andere afdelingen van het Diakonessenhuis. Bedankt voor de leerzame momenten waarop we sparde over promoties of onze ervaringen deelden.

Tijdens mijn promotieonderzoek heb ik drie geweldige master farmaciestudenten, Kamjar Elmi, Dilek Yazir en Lotte Minnema mogen begeleiden die ik ook langs deze weg wil bedanken voor hun tomeloze inzet. Kamjar als drijvende kracht achter de inclusie van DANA uit te rollen en het contact met de patiënten met als resultaat dat we samen aantal geïncludeerde patiënten hebben gehaald. Dilek, met wie ik samen als "datanerds" data extraheerden uit verschillende systemen en haar werk deed met grote zelfstandigheid. Ten aanzien van de predictiemodellen heeft Lotte veel ondersteuning geboden bij het uitdenken ervan en vaak proactief de volgende stap al had opgepakt. Alle drie bijzonder veel dank voor jullie bijdrage!

Lieve vrienden, waaronder Eelke & Jeffrey, Darya, Farmacievriendinnen, Ayşe en SCO-vrienden, het was druk maar altijd leuk om met jullie te ontspannen. Gollan gyan, onze vriendschap is heel bijzonder. Het was altijd leuk om bij te kletsen en te ontspannen, picknicken of joggen. Hellan friends for life!

Beste Dr. Fatma Karapinar-Çarkit, het is zover. Bij jouw promotie leek mijn promotie nog zover weg...dankjewel voor alle leuke, motiverende dagen/avonden en meelezen. Altijd een goede combinatie van gezelligheid en hard werken. We hebben aan een half woord voldoende om elkaar te begrijpen. Lieve Fatma en Ömer, bedankt voor alles!

Beste Dr. Diana van Riet-Nales, ik heb zo'n enorme bewondering voor je doorzettingsvermogen. Het was fijn om samen te werken bij een van ons, dat we elkaar konden motiveren en dat je hebt meegelezen, met name in de laatste fase van onze promotie. Ik hoop dat we samen nog vele mooie onderzoeken kunnen opzetten.

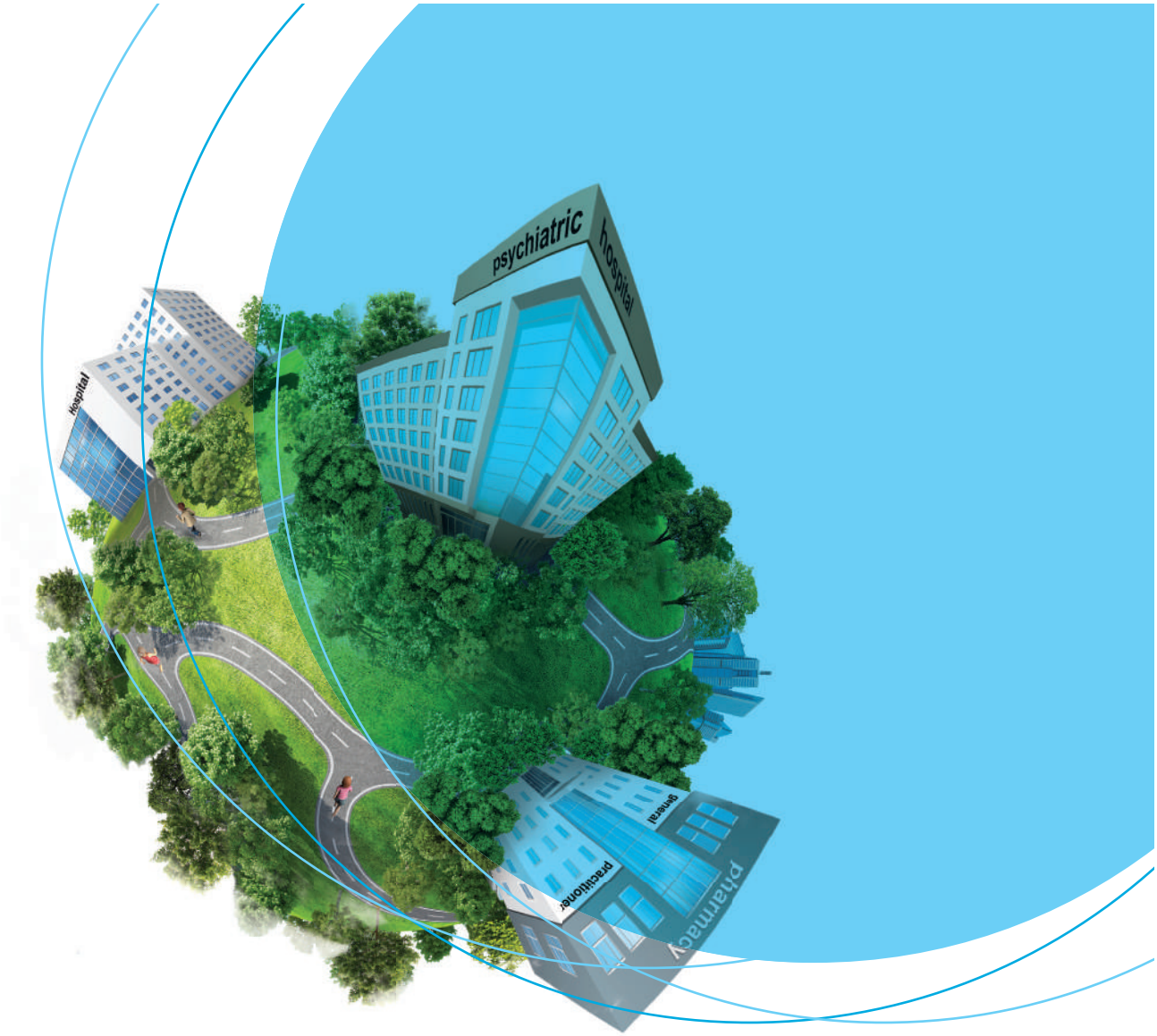
Lieve Drs. Arlette Scheifes, het klikte al vanaf de eerste keer. Ondanks dat onze promoties van elkaar verschillen, kunnen we zoveel met elkaar delen en van elkaar leren. Je voelt exact aan wanneer we elkaar moeten bellen om bij te praten. We begrijpen elkaar zo snel ook al spreken we elkaar niet dagelijks. Veel succes bij de afronding van je promotie.

Lieve schoonouders, papa Arie en ma Ankie, jullie zijn altijd benieuwd naar hoe het gaat met de onderzoeken en leven altijd mee. Bedankt voor jullie steun en interesse!

Shene, lieve sis, ik kijk uit naar je diploma-uitreiking. Ondanks dat de gezondheidszorg niet jouw ding is, ben je altijd benieuwd naar hoe het ging met mijn promotieonderzoek. Follow your heart. I'm proud of you!
Mijn lieve broer Shwan, fijn om je aan mijn zijde te hebben als paranimf. We are so much alike. Ook op jou kan ik altijd rekenen. Ik kijk uit naar jouw diploma-uitreiking. Shw, proud of you!

Daya gyan u Baba gyan, dllakanm. Eua rohu dllmn. Agar eua nabunaya qad na agashtm bam rozha. Am dktoraya bo euaya. Xua euaman le nasenet. Zor, zorm xosh aun chauakanm.

Mijn lieve man Anne, my soulmate. Zo fijn om alles samen te doen en altijd op je te kunnen rekenen. Al vanaf VWO was je erbij en bent er altijd voor me! Dankzij jou is mijn promotieonderzoek af! Je motiveert me en steunt me onvoorwaardelijk. Het is de afgelopen jaren heel druk geweest...we gaan meer tijd krijgen voor leuke dingen en de wereld verder verkennen. Ik hou zielsveel van je!



6.2

List of Co-authors

List of Co-authors Presented in This Thesis

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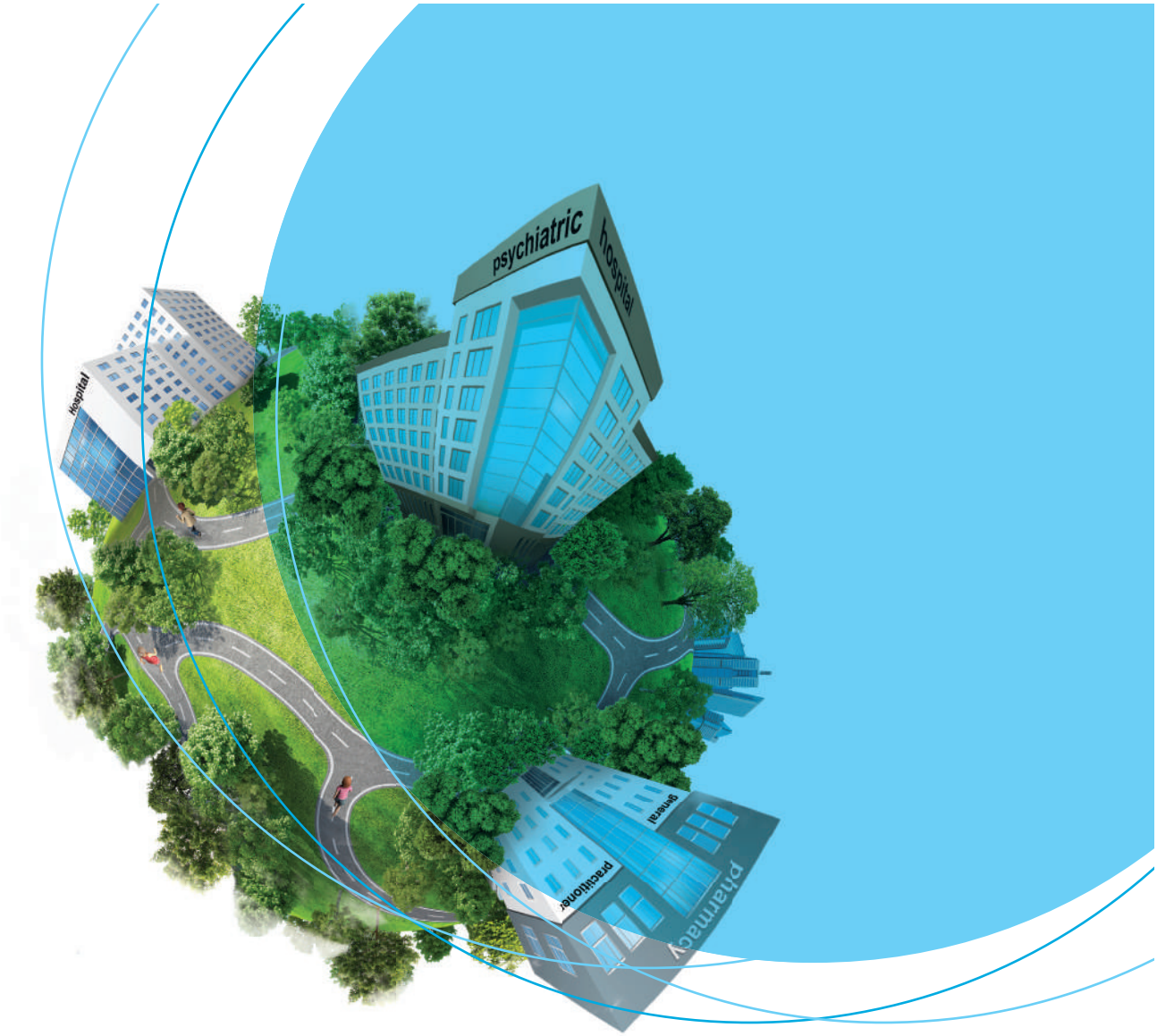


6.3

List of Publications

Publications related to this thesis

Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER Discontinuation of Somatic Medication During Psychiatric Hospitalization. Ann Pharmacother 2014 Nov;48(11):1415-24.

Abdullah-Koolmees H, Gardarsdottir H, Stoker LJ, Vuyk J, Egberts TC, Heerdink ER Prevalence of medication use for somatic disease in institutionalized psychiatric patients. Pharmacopsychiatry 2013 Nov;46(7):274-280.

Abdullah-Koolmees H, Gerbranda T, Deneer VH, Tjoeng MM, De Ridder AJ, Gardarsdottir H, Heerdink ER.
Discontinuation of anticoagulant care during admission to a psychiatric hospital. Eur J Clin Pharmacol 2012 Oct 23;69(4):1025-1029.

Publications unrelated to this thesis

Sitsen JMA, Vasbinder E, Abdullah-Koolmees H
Geeneeskundig Jaarboek 2015, 1st edition ed. The Netherlands: Bohn Stafleu van Loghum; 2015.

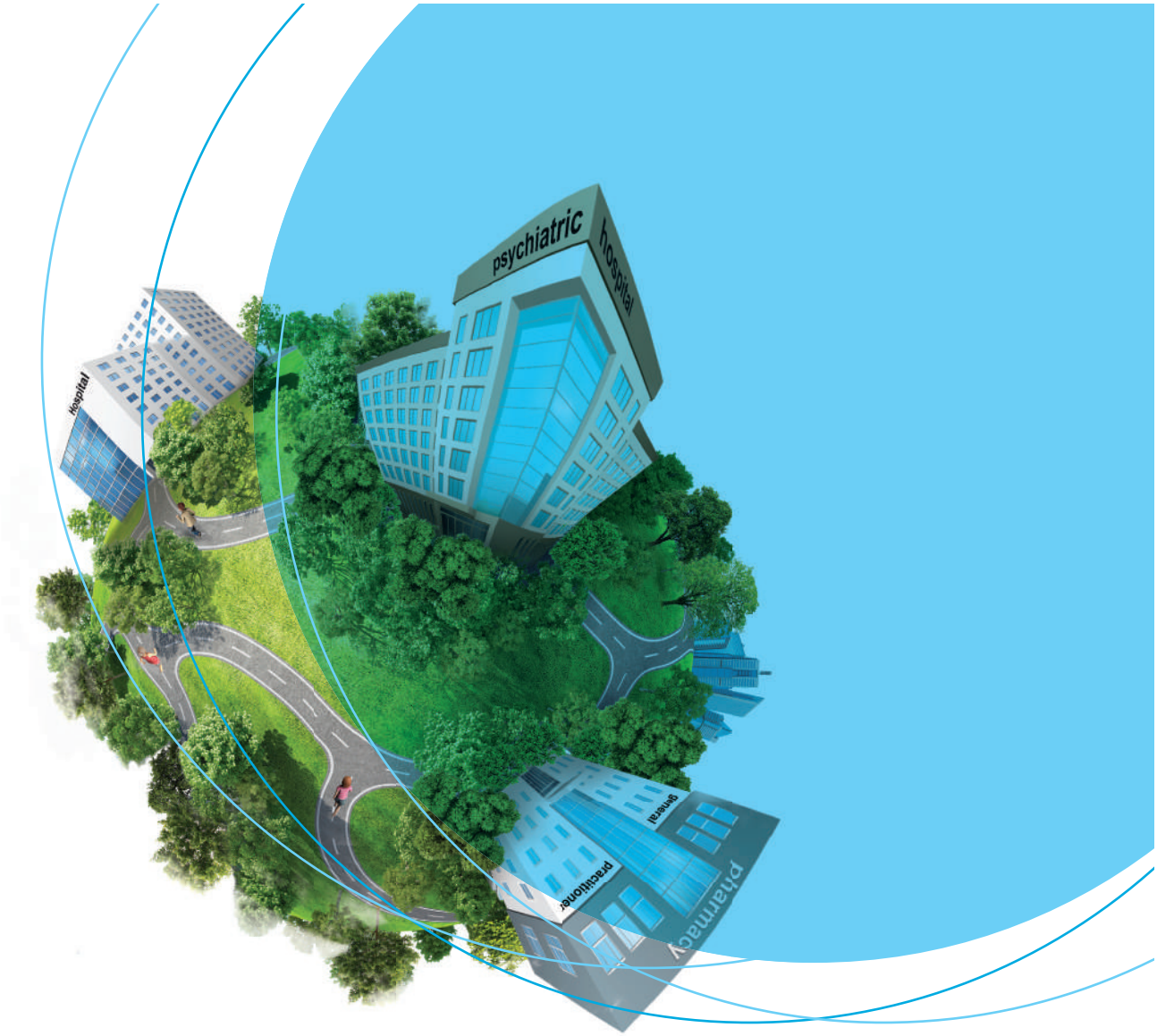
Sitsen JMA, Vasbinder E, Abdullah H, van Genugten M
Geeneeskundig Jaarboek 2014, 1st edition ed. The Netherlands: Bohn Stafleu van Loghum; 2014.

Sitsen JMA, Vasbinder E, Abdullah H, van Genugten M
Geeneeskundig Jaarboek 2013, 1st edition ed. The Netherlands: Bohn Stafleu van Loghum; 2013.

Sitsen JMA, Vasbinder E, Abdullah H, van Grinsven M
Geeneeskundig Jaarboek 2012, 1st edition ed. The Netherlands: Bohn Stafleu van Loghum; 2012.

Sitsen JMA, Vasbinder E, Abdullah H, Debisarun V, van Grinsven M, Groen E
Geeneeskundig Jaarboek 2011, 1st edition ed. The Netherlands: Bohn Stafleu van Loghum; 2011.

H. Abdullah-Koolmees, R. Muller, M. Nettekoven
Per ongeluk risperidon toegediend. Pharm Weekblad 2011 Jul.



6.4

The CNS Clinical Pharmacoepidemiology Research Group

Background

Central Nervous System Clinical Pharmacoepidemiology is one of the research themes of the division of Pharmacoepidemiology & Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS). The division of Pharmacoepidemiology & Clinical Pharmacology consists of a multidisciplinary team of young and internationally oriented researchers. The research program is directed at the epidemiological, therapeutic and policy aspects of drug use and their effects. The mission of the research program is to contribute to the knowledge of and decision-making in the effectiveness, safety and economics of drug usage. In bridging the gap between the science of pharmacoepidemiology and the 'real world' of patients' drug usage and public health, the program covers a variety of methods and approaches from (molecular) epidemiology, pharmacovigilance, practice research and policy analysis. The myriad of research strategies provides an excellent environment for thoughtful learning and innovation in system therapeutics.
The Central Nervous System Clinical Pharmacoepidemiology research group focuses on the use and effects of psychotropic drugs in psychiatry and neurology, both in ambulatory care and in clinical settings. Principle investigators of this research group are Dr. Eibert R. Heerdink and Prof. Dr. Toine C.G. Egberts. There is close collaboration with psychiatric hospitals including Altrecht and GGZ Centraal and with the University Medical Centre Utrecht.
Contact: www.uu.nl/science/pharmacoepidemiology

Theses from the CNS clinical pharmacoepidemiology research group:

Dr. Adrienne Einarson (2015)
Antidepressant use in pregnancy: knowledge transfer and translation of research findings. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. E.R. Heerdink.

Dr. Els van den Ban (2014)
ADHD medication use and long-term consequences. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. H. Swaab, Dr. E.R. Heerdink.

Dr. Jochem Gregoor (2013)
Genetic Determinants of Antipsychotic Drug Response. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. J. van de Weide, Dr. E.R. Heerdink.

Dr. Arne Risselada (2012)
Genetic determinants for metabolic abnormalities. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. H. Mulder, Dr. E.R. Heerdink.

Dr. Bart Kleijer (2011)
Balancing the benefits and risks of antipsychotics. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. M.W. Ribbe, Dr. E.R. Heerdink, Dr. R. van Marum.

Dr. Wilma Knol (2011)
Antipsychotic induced parkinsonism in the elderly: assessment, causes and consequences. (Co)promotores: Prof. Dr. A.F.A.M. Schobben, Prof. Dr. A.C.G. Egberts, Dr. P.A.F. Jansen, Dr. R. van Marum.

Dr. Inge van Geijlswijk (2011)
Melatonin in sleepless children. Everything has a rhythm? (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. H. Vaarkamp, Dr. M. Smits.

Dr. Maurits Arbouw (2010)
Assessment of pharmacotherapy in Parkinson's disease. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. H.J. Guchelaar, Prof. Dr. C. Neef, Dr. K.L.L. Movig.

Dr. Laurette Goedhard (2010)
Pharmacotherapy and aggressive behaviour in psychiatric patients. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. H. Nijman, Dr. E.R. Heerdink, Dr. J.J. Stolker.

Dr. Jeroen Derijks (2009)
Effects of antidepressants on glucose homeostasis. Effects and mechanisms. (Co) promotores: Prof. Dr. A.C.G. Egberts, Dr. E.R. Heerdink, Dr. G.H.P. de Koning, Dr. R. Janknegt.

Dr. Helga Gardarsdottir (2009)
Drug treatment episodes in pharmacoepidemiology: antidepressant use as a model. (Co) promotores: Prof. Dr. A.C.G. Egberts, Dr. E.R. Heerdink.

Dr. Kim Gombert - Handoko (2009)
Treatment failure in epilepsy: exploring causes of ineffectiveness and adverse effects. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. Y.A. Hekster, Dr. J. Zwart-van Rijkom, Dr. W. Hermens.

Dr. Tessa Ververs (2009)
Antidepressants during pregnancy, risks for mother and child. (Co)promotores: Prof. Dr. G.H. Visser, Prof. Dr. A.F.A.M. Schobben, Dr. E. Mulder.

Dr. Emmeke Wammes – van der Heijden (2009)
Migraine and ischemia. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. C. Tijssen.

Dr. Katja van Geffen (2008)
Initiation, execution and discontinuation of antidepressant therapy: considerations and decisions of patients. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. E.R. Heerdink, Dr. R. van Hulten.

Dr. Mirjam Knol (2008, summa cum laude)
Depression and diabetes. Methodological issues in etiologic research. (Co)promotores: Prof. Dr. D.E. Grobbee, Prof. Dr. A.C.G. Egberts, Dr. M. Geerlings, Dr. E.R. Heerdink.

Dr. Ingeborg Wilting (2008)
Patterns and clinical outcomes of lithium treatment. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. W.A. Nolen, Dr. E.R. Heerdink.

Dr. Hans Mulder (2007)
CYP2D6 and 5HT2c polymorphisms in psychiatric pharmacotherapy. (Co)promotores: Prof. Dr. A.C.G. Egberts, Dr. F.F.W. Wilmink.

Dr. Gerard Hugenholtz (2005)
Antipsychotics in daily clinical practice: patterns, choices and consequences. (Co) promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. W.A. Nolen, Dr. E.R. Heerdink.

Dr. Hamid Rahimtoola (2003)
Transitions in migraine treatment. (Co)promotores: Prof. Dr. A.C.G. Egberts, Prof. Dr. H.G.M. Leufkens, Dr. C.C. Tijssen.

Dr. Igor Schillevoort (2002)
Drug-induced extrapyramidal syndromes. (Co)promotores: Prof Dr. H.G.M. Leufkens, Prof Dr. R.A.C. Roos, Dr. R.M.C. Herings.

Dr. David van de Vijver (2002)
Quality of the pharmacological treatment of patients with Parkinson's disease. (Co) promotores: Prof Dr. A.J. Porsius, Prof Dr. R.A.C. Roos, Prof Dr. A. de Boer.

Dr. Joostjan Stolker (2002)
Struggles in prescribing: determinants of psychotropic drug use in multiple clinical settings. (Co)promotores: Prof Dr. W.A. Nolen, Prof Dr. H.G.M. Leufkens, Dr. E.R. Heerdink.

Dr. Welmoed Meijer (2002)
The value of observational research on antidepressant use: a broadened perspective. (Co)promotores: Prof Dr. H.G.M. Leufkens, Prof Dr. W.A. Nolen, Dr. E.R. Heerdink.

Dr. Kris Movig (2002)
Detection and elucidation of adverse neuropsychiatric adverse effects. (Co)promotores: Prof Dr. A.C.G. Egberts, Prof Dr. H.G.M. Leufkens.

Dr. Rolf van Hulten (1998)
Blue boy – why not? (Co)promotores: Prof Dr. A. Bakker, Prof Dr. H.G.M. Leufkens, Dr. K.B. Teeuw.

Dr. Toine Egberts (1997)
Pharmacoepidemiologic approaches to the evaluation of antidepressant drugs. (Co) promotores: Prof Dr. A. Bakker, Prof Dr. H.G.M. Leufkens, Dr. G.H.P. de Koning.