Antipsychotics, brain morphology and duration of untreated illness in schizophrenia

Antipsychotica, hersenmorfologie en de onbehandelde ziekteduur bij schizofrenie

Geartsje Boonstra

ISBN 978-90-8891-257-3

Printed by: Proefschriftmaken.nl || Printyourthesis.com
Published by: Uitgeverij BOXPress, Oisterwijk

Antipsychotics, brain morphology and duration of untreated illness in schizophrenia

Antipsychotica, hersenmorfologie en de onbehandelde ziekteduur bij schizofrenie

(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 dinsdag 12 april 2011 des ochtends te 10.30 uur

door

Geartsje Boonstra
geboren op 28 december 1973 te Amersfoort

Promotoren:	Prof. dr. R.S. Kahn
	Prof. dr. D.E. Grobbee
Co-promotoren:	Dr. H. Burger
	Dr. N.E.M. van Haren

Opgedragen aan

Mijn moeder Leni en mijn vader Jan

Tante Annie

‘Ik weet niet hoe ik beginnen moet,’ zei hij. De eekhoorn leunde achterover in zijn stoel en keek de kraai ernstig aan. De kraai zag er somber uit. Zijn veren waren dof en verfomfaaid en er was weinig glans in zijn ogen.
‘Dat geeft niet,’ zei de eekhoorn vriendelijk. ‘Begin anders maar middenin.’
‘Nou ja, ‘zei de kraai, ‘als er een blaadje van de boom valt denk ik dat het op mij wil vallen, en ik denk dat ze me willen storen als ik slaap, want ik word telkens wakker en dan hoor ik een gebonk en gesuis. Vlak bij mijn oor! Ik heb zoveel argwaan, eekhoorn!’
De eekhoorn legde zijn vingertoppen tegen elkaar en deed alsof hij de kraai goed begreep. Argwaan, dacht hij, wat is argwaan? Zou het een soort soep zijn? Het klinkt als een zwart soort soep met hompen van het een of ander erin....

(Toon Tellegen; Misschien wisten zij alles)

Table of contents

Chapter 1

Introduction

In psychiatric practice there is still an untold number of important clinical questions to be solved. Carrying out the research presented in this thesis has given me insight in the enormous efforts that are made over the entire world to contribute to evidence based medicine.
This thesis concentrates on the subjects first-episode schizophrenia, (prophylactic) antipsychotic medication, duration of untreated illness and its relation to brain morphology.

The cluster of symptoms that we call schizophrenia constitutes a chronic and lifelong disorder. The incidence in the Netherlands of non-affective psychosis is about 0.02‰[10], which is comparable to the worldwide incidence of 0.01‰[48]. This amounts to about a 1% lifetime chance to develop schizophrenia, although on an individual level risk factors, or protecting factors, may be present[58]. Symptoms of schizophrenia are often clustered into 'positive' and 'negative' symptoms. Positive symptoms, often described as psychosis or the active stage of the disease, include hallucinations (e.g. hearing voices while there are no people speaking, having visions that are not seen by other people), delusions (having convictions that are not possible according to the laws of nature, or that are deviant from commonly accepted knowledge or thoughts, even in the culture the patient belongs to) and formal thought disorders (such as incoherence of speech). Negative symptoms reflect absence of normal behaviour, such as inactivity because of lack of motivation and poverty of speech or emotional unresponsiveness[2]. Currently, we use the Diagnostic and Statistical Manual of Mental Disorders – IV-Text Revised[2] to classify specific clusters of symptoms as schizophrenia. This classification, and its earlier editions, has made it possible to perform research in the group of patients suffering from schizophrenia. Since there are many possible combinations of the above mentioned symptoms, schizophrenia is a heterogeneous disease. This is also reflected by the fact that after the first episode of psychosis the course of illness is variable and difficult to predict in individual cases. Some patients may never recover from their first episode, some patients do recover and subsequently experience one or more episodes of psychosis (relapses) and some may never experience another episode of psychosis[48,96].
Typically, the first symptoms of schizophrenia occur during early adolescence. Schizophrenia often has an insidious onset and is in many cases preceded by a decline in functioning before the onset of psychosis. Antipsychotic treatment is in clinical practice usually not started at the exact the start of the symptoms be-

cause of patient-, doctor- or other delay. Duration of untreated psychosis (DUP), duration of prodrome (DPD) and duration of untreated illness (DUI) have all been used to characterise the duration of the period before the start of treatment or the onset of psychosis. Clinical and functional outcome variables found to be associated with DUI[23,63,76] and DPD[29,40,65]. In these cases longer DUI or DPD was associated with poorer outcome. This is the reason that programs for early detection of first-episode psychosis have been developed and installed, also in the Netherlands[62]. By finding cases earlier, and starting treatment earlier, it is hoped to ameliorate the prognosis of the patients. However, many studies could not replicate a relationship between outcome and DUI or DPD[8,18,33,40,43,44,65,74,87]. More convincing is the effect of DUP as two reviews established a small to moderate effect of DUP on outcome in schizophrenia, including symptom remission and functional rehabilitation[66,80].

Interestingly, poorer outcome in schizophrenia has also been associated with smaller brain volumes[11,69] and excessive brain volume loss over time[12,13,37,38] found by using Magnetic Resonance Imaging (MRI), for review see[47,51].
Magnetic resonance imaging (MRI) has been useful in revealing subtle structural brain abnormalities in patients suffering from schizophrenia relative to, for example, healthy controls. One of the main advantages of MRI is that brain scans are acquired in vivo without exposure of the brain to radiation. Furthermore it enables the quantification of gray and white matter of the brain. Many studies include a region of interest (ROI) measurement of brain structures by manually delineating an a priori defined region or structure. Although the anatomical validity is high in these measurements, this type of analysis is very time consuming since the brain is divided in many 'slices' by MRI, and each slice has to be manually processed (i.e. a structure delineated). Using this and other MRI techniques a range of structural brain abnormalities has been reported in schizophrenia. In both chronic and first-episode schizophrenia studies similar brain volume reductions have been found[89,95,97], such as a smaller cerebral volume and larger ventricular volumes. Additionally, accumulating evidence indicates a progressive loss of tissue in schizophrenia patients, before and after the onset of the disease, relative to healthy controls[38,47,77,78]. It remains unclear whether these changes are caused by the illness, the influence of antipsychotic medication or by outcome.
As mentioned before, DUP, DPD and DUI as well as brain volume (change) are associated with poorer outcome. Therefore, one could hypothesise that DUP, DUI

or DPD through their effect on outcome, are associated with (change in) brain abnormalities in schizophrenia patients. Indeed, cross-sectional studies provide evidence for an association between brain abnormalities and a longer DUP, DUI or DPD[4,6,19,20,42,53,57,64,79,90,92]. So far, no studies looked at the relationship between DUP, DUI or DPD, outcome and global brain volume change over time. In **Chapter 5** we describe a study that aimed to investigate the relationship between DUI, global brain volume after a first episode and brain volume change during a 5-year interval, and outcome (both at baseline as well as after about 5 years of treatment) in first-episode schizophrenia patients.

The treatment of psychosis and schizophrenia typically involves long-term antipsychotic use. Its goal is to ameliorate symptoms and to reduce the risk of relapse, i.e. reappearance of psychosis. While the efficacy of antipsychotics in preventing relapse in schizophrenia patients who have experienced multiple episodes is beyond doubt[24,30], it is still unclear whether schizophrenia patients, after full recovery from their first psychotic episode, need prophylactic treatment. Importantly, approximately 15% of first-episode schizophrenia patients will never experience another psychotic episode after withdrawal of medication[83,96]. Additionally, (longterm) antipsychotic use may induce side-effects. Among the most troublesome effects are the neurological: extrapyramidal symptoms including Parkinsonism, akathisia, dystonia and tardive dyskinesia[5]. Atypical antipsychotic drugs also induce weight gain[34,85,98]. Weight gain leads to increases in triglycerides and cholesterol, and may induce insulin resistance and diabetes[3,61]. The combination of weight gain, hypercholesterolaemia and diabetes, as well as a risk on undertreatment, increases the cardiovascular risk in schizophrenia patients[82,88]. Other side-effects are drowsiness, dizziness, sedation, constipation, tachycardia and sexual side-effects[55,81]. Also, changes in brain morphology have been associated with the use of antipsychotics[73,94]. Most side-effects appear to be reversible upon discontinuation, although tardive dyskinesia can (partially) persist after discontinuation[31]. These considerations raise the question whether certain patients, once clinically stable, may be taken off their medication without an unacceptable increase in relapse risk, thereby preventing a needless risk of adverse effects. After all the first principle in medicine throughout the centuries remains "primum non nocere" or "firstly, do no harm". Five randomised studies examined the effect of antipsychotic discontinuation in patients who had experienced a single psychotic episode[15,22,45,50,68]. However, either the duration of remission was short, with

consequent uncertainty about the stability of patients[15,22,45,50], the patients in the continuation group were put on a new antipsychotic regimen[15], the study sample was very small[68], or no tapering period was installed[45,50,68]. Together, these studies could not resolve the issue whether patients, after remission from their first psychotic episode, should be continued on antipsychotic medication. Indeed, the most recent guideline of the American Psychiatric Association for the treatment of patients with schizophrenia[58] skirts the issue stating that medication discontinuation after either "at least 1 year of symptom remission" or "optimal response while taking medication" is the only prudent alternative for "indefinite antipsychotic maintenance therapy" in patients who experienced a single psychotic episode. **Chapter 2** describes a randomised trial comparing, in clinical practice, the effect of gradual withdrawal of antipsychotic treatment with continuation in schizophrenia patients who had remitted from a single psychotic episode, and who had been clinically stable for at least one year. In **Chapter 2** we also report a pooled analysis of the odds for hospitalisation after withdrawal of antipsychotics compared to continuation by combining the results of the present trial and the, to our knowledge, only published withdrawal trial in 1-year stable and remitted first-episode schizophrenia patients[68]. We aimed to contribute to resolving the question whether first-episode schizophrenia patients should continue their antipsychotic medication indefinitely or alternatively find justification for withdrawal of their treatment after 1 year of stable remission.
If this study confirms that the proportion of first episode patients in which antipsychotic drugs may be successfully withdrawn is large, implementation is no issue as this strategy is already part of many international and national treatment standards. Instead, the study then provides a scientific basis. If the proportion in which discontinuation is successful appears relatively small, however, this finding would challenge the correctness of the standards and call for more research in this area.

As was mentioned before, antipsychotic use has been found to be associated with structural brain changes, as was the disease schizophrenia itself[47,89,94,95,97]. Increasing evidence suggests that the often replicated brain volume decrease in schizophrenia[97] is progressive over time[12,25,35,47,49,78]. Although some of the progressive brain changes appear related to the course of illness[11-13,38,49,59] it has been an issue of debate what, if any, is the influence of medication. Some argue, based on research in monkeys, that the loss of grey matter in schizophrenia can be at-

tributed to the use of typical or atypical antipsychotic medication[26]. In contrast, in studies in schizophrenia patients, loss of grey matter volume appears to be attenuated by atypical antipsychotics, but not by haloperidol[39,60,70].
One of the best replicated findings in schizophrenia is the increase in caudate nucleus volume being related to intake of typical antipsychotics[52,53]. It has been suggested that changing treatment to atypical antipsychotics appears to 'normalise' this effect[17,56,86]. However, investigated longitudinally, the use of atypical antipsychotic medication has been related to stable[32,41,91], increasing[32,67] and decreasing[14,21,27,28,56,86] volumes of basal ganglia.
Differentiating between antipsychotic-induced changes and those inherent to the disease would be most valid through randomisation of antipsychotic-naïve first-episode patients to treatment or placebo in comparison to healthy controls. However, this design is clearly coupled with ethical issues. One alternative design is to longitudinally study brain volumes in patients who discontinue their medication, or not. Guidelines offer the psychiatrist the possibility to discontinue antipsychotic medication in remitted and stable first-episode schizophrenia patients[58]. The NICE guideline[54] states that "it is uncertain whether maintenance drug treatment is required for all people with schizophrenia. Around 20% of individuals will only experience a single episode". To assess medication-related changes in brain volume over time we compared, in **Chapter 3**, remitted and stable schizophrenia patients in whom atypical antipsychotic medication was either discontinued or continued in a one-year follow-up magnetic resonance imaging (MRI) study.
In this introduction we described many side-effects of antipsychotics. As a part of the studies described in **Chapter 2** and **Chapter 3** we monitored movement disorders and weight gain, as well as other side-effects. In **Chapter 4** we compare the difference in change in these side-effects over time between patients that continue and discontinue their antipsychotic regimen.

In the introduction we also mentioned the fact that these side effects are not always completely reversible after discontinuation of antipsychotic therapy[31]. This obliges us to consider antipsychotic treatment as unwished for in patients that do not have a disease forming a scientifically underlayed indication for it. We chose to research the prescription of antipsychotic treatment in general practice. Surprisingly, up to 80% of all antipsychotics are reported to be prescribed in primary care[9,36,46,71,84]. Furthermore, 1-3.2% of general practice patients receives an-

tipsychotic drugs when investigated cross-sectionally and approximately 10% of the general practitioner-patient encounters in which a psycho-active drug is prescribed involves an antipsychotic[1,9,46,72,75]. Thus, prescription of antipsychotics seems relatively common in general practice. It therefore seems suitable to investigate the indications for these drugs in general practice. There has been concern about off-label use (Off-label use defined as the use of a drug outside the licensed indication) of antipsychotics[7,16,72,84,93,99]. Although off-label use can partly be attributed to following guidelines based on proof from large randomised controlled trials, minimal evidence may support other off-label use. It is estimated that 30-50% of all prescriptions of antipsychotics is for off-label use[7,72,84,99]. However, it is largely unknown which conditions give rise to off-label antipsychotic prescribing by general practitioners (GPs). **Chapter 6** describes a study that investigates possible motives for off-label prescription, where we associated six predefined diagnostic categories, four of them being off-label indications for antipsychotic treatment in the Netherlands, with new antipsychotic use in a case-control study using anonymous electronic medical records and pharmacy prescription data from a large population of GP patients in The Netherlands. In **Chapter 7** all the findings are drawn together for a general discussion, while **Chapter 8** contains a Dutch summary of this PhD-thesis.

References

1. Alonso J., Angermeyer M.C., Bernert S. et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004;(420):55-64.
2. American Psychiatic Association. Diagnostic and Statistical Manual - IV - Text Revised (DSM-IV-TR). Fourth ed. Washington DC: American Psychiatric Press, 2000:1-496.
3. Ananth J., Parameswaran S. and Gunatilake S. Side effects of atypical antipsychotic drugs. *Curr Pharm Des* 2004;10(18):2219-2229.
4. Angelopoulos E.K., Markianos M., Daskalopoulou E.G. et al. Changes in central serotonergic function as a correlate of duration of illness in paranoid schizophrenia. *Psychiatry Res* 2002;110(1):9-17.
5. Arana G.W. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry* 2000;61 Suppl 8:5-11.
6. Bangalore S.S., Goradia D.D., Nutche J. et al. Untreated illness duration correlates with gray matter loss in first-episode psychoses. *Neuroreport* 2009;20(7):729-734.
7. Barbui C., Danese A., Guaiana G. et al. Prescribing second-generation antipsychotics and the evolving standard of care in Italy. *Pharmacopsychiatry* 2002;35(6):239-243.
8. Barnes T.R., Hutton S.B., Chapman M.J. et al. West London first-episode study of schizophrenia. Clinical correlates of duration of untreated psychosis. *Br J Psychiatry* 2000;177:207-211.
9. Beardsley R.S., Gardocki G.J., Larson D.B. et al. Prescribing of psychotropic medication by primary care physicians and psychiatrists. *Arch Gen Psychiatry* 1988;45(12):1117-1119.
10. Boonstra N., Wunderink L., de Wit P.H. et al. [The administrative incidence of non-affective psychoses in Friesland and Twente]. *Tijdschr Psychiatr* 2008;50(10):637-643.
11. Buchsbaum M.S., Shihabuddin L., Brickman A.M. et al. Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophr Res* 2003;64(1):53-62.
12. Cahn W., Hulshoff Pol H.E., Lems E.B. et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry* 2002;59(11):1002-1010.
13. Cahn W., van Haren N.E., Hulshoff Pol H.E. et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006;189:381-382.
14. Chakos M.H., Lieberman J.A., Alvir J. et al. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995;345(8947):456-457.
15. Chen E.Y., Hui C.L., Lam M.M. et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010;341:c4024.
16. Chen H., Reeves J.H., Fincham J.E. et al. Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia medicaid enrollees in 2001. *J Clin Psychiatry* 2006;67(6):972-982.
17. Corson P.W., Nopoulos P., Miller D.D. et al. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *Am J Psychiatry* 1999;156(8):1200-1204.

18. Craig T.J., Bromet E.J., Fennig S. et al. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *Am J Psychiatry* 2000;157(1):60-66.
19. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. *Schizophr Res* 2007;91(1-3):87-96.
20. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. *Neuroimage* 2007;35(4):1613-1623.
21. Crespo-Facorro B., Roiz-Santianez R., Perez-Iglesias R. et al. Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(8):1936-1943.
22. Crow T.J., Macmillan J.F., Johnson A.L. et al. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 1986;148:120-127.
23. Crumlish N., Whitty P., Clarke M. et al. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *Br J Psychiatry* 2009;194(1):18-24.
24. Davis J.M., Janicak P.G., Singla A. et al. Maintenance antipsychotic medication. In: Barnes T., editor. Antipsychotic Drugs and Their Side-Effects. 1st ed. London: Academic Press Limited, 1993:183-203.
25. DeLisi L.E., Sakuma M., Tew W. et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 1997;74(3):129-140.
26. Dorph-Petersen K.A., Pierri J.N., Perel J.M. et al. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology* 2005;30(9):1649-1661.
27. Ebdrup B.H., Glenthoj B., Rasmussen H. et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci* 2010;35(2):95-104.
28. Frazier J.A., Giedd J.N., Kaysen D. et al. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 1996;153(4):564-566.
29. Fusar-Poli P., Meneghelli A., Valmaggia L. et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry* 2009;194(2):181-182.
30. Gilbert P.L., Harris M.J., McAdams L.A. et al. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry* 1995;52(3):173-188.
31. Glazer W.M., Morgenstern H., Schooler N. et al. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. *Br J Psychiatry* 1990;157:585-592.

32. Glenthoj A., Glenthoj B.Y., Mackeprang T. et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. *Psychiatry Res* 2007;154(3):199-208.
33. Gonzalez-Blanch C., Crespo-Facorro B., varez-Jimenez M. et al. Pretreatment predictors of cognitive deficits in early psychosis. *Psychol Med* 2008;38(5):737-746.
34. Green A.I., Lieberman J.A., Hamer R.M. et al. Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res* 2006;86(1-3):234-243.
35. Gur R.E., Cowell P., Turetsky B.I. et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 1998;55(2):145-152.
36. Hamann J., Ruppert A., Auby P. et al. Antipsychotic prescribing patterns in Germany: a retrospective analysis using a large outpatient prescription database. *Int Clin Psychopharmacol* 2003;18(4):237-242.
37. Haren v.N.E., Cahn W., Hulshoff Pol H.E. et al. Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. *Schizophr Res* 2003;64(1):41-52.
38. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 2008;63(1):106-113.
39. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Focal Gray Matter Changes in Schizophrenia across the Course of the Illness: A 5-Year Follow-Up Study. *Neuropsychopharmacology* 2007;2057-2066.
40. Harrigan S.M., McGorry P.D. and Krstev H. Does treatment delay in first-episode psychosis really matter? *Psychol Med* 2003;33(1):97-110.
41. Heitmiller D.R., Nopoulos P.C. and Andreasen N.C. Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. *Schizophr Res* 2004;66(2-3):137-142.
42. Ho B.C., Alicata D., Ward J. et al. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *Am J Psychiatry* 2003;160(1):142-148.
43. Ho B.C., Andreasen N.C., Flaum M. et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 2000;157(5):808-815.
44. Hoff A.L., Sakuma M., Razi K. et al. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *Am J Psychiatry* 2000;157(11):1824-1828.
45. Hogarty G.E., Goldberg S.C., Schooler N.R. et al. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. *Arch Gen Psychiatry* 1974;31(5):603-608.
46. Hohmann A.A., Larson D.B., Thompson J.W. et al. Psychotropic medication prescription in U.S. ambulatory medical care. *DICP* 1991;25(1):85-89.

47. Hulshoff Pol H.E. and Kahn R.S. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34(2):354-366.
48. Jablensky A., Sartorius N., Ernberg G. et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl* 1992;20:1-97.
49. Job D.E., Whalley H.C., Johnstone E.C. et al. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 2005;25(4):1023-1030.
50. Kane J.M., Rifkin A., Quitkin F. et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 1982;39(1):70-73.
51. Kempton M.J., Stahl D., Williams S.C. et al. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophr Res* 2010;120(1-3):54-62.
52. Keshavan M.S., Bagwell W.W., Haas G.L. et al. Changes in caudate volume with neuroleptic treatment. *Lancet* 1994;344(8934):1434.
53. Keshavan M.S., Rosenberg D., Sweeney J.A. et al. Decreased caudate volume in neuroleptic-naive psychotic patients. *Am J Psychiatry* 1998;155(6):774-778.
54. Kuipers E. and Kendall T. Schizophrenia (update). Antoniou J., Barnes T., Bhui K. et al., eds. Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). 1-399. 2009. London, National Institute for Health and Clinical Excellence . Clinical guidelines CG82.
55. Lader M. Some adverse effects of antipsychotics: prevention and treatment. *J Clin Psychiatry* 1999;60 Suppl 12:18-21.
56. Lang D.J., Kopala L.C., Vandorpe R.A. et al. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *Am J Psychiatry* 2004;161(10):1829-1836.
57. Lappin J.M., Morgan K., Morgan C. et al. Gray matter abnormalities associated with duration of untreated psychosis. *Schizophr Res* 2006;83(2-3):145-153.
58. Lehman A.F., Lieberman J.A., Dixon L.B. et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161(2 Suppl):23.
59. Lieberman J., Chakos M., Wu H. et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry* 2001;49(6):487-499.
60. Lieberman J.A., Tollefson G.D., Charles C. et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 2005;62(4):361-370.
61. Lindenmayer J.P., Czobor P., Volavka J. et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry* 2003;160(2):290-296.
62. Linszen D., Dingemans P. and Lenior M. Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: ethical implications. *Schizophr Res* 2001;51(1):55-61.
63. Loebel A.D., Lieberman J.A., Alvir J.M. et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* 1992;149(9):1183-1188.

64. Madsen A.L., Karle A., Rubin P. et al. Progressive atrophy of the frontal lobes in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. *Acta Psychiatr Scand* 1999;100(5):367-374.
65. Malla A.K., Norman R.M., Manchanda R. et al. One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophr Res* 2002;54(3):231-242.
66. Marshall M., Lewis S., Lockwood A. et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005;62(9):975-983.
67. Massana G., Salgado-Pineda P., Junque C. et al. Volume changes in gray matter in first-episode neuroleptic-naive schizophrenic patients treated with risperidone. *J Clin Psychopharmacol* 2005;25(2):111-117.
68. McCreadie R.G., Wiles D., Grant S. et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. *Acta Psychiatr Scand* 1989;80(6):597-602.
69. Molina V., Hernandez J.A., Sanz J. et al. Subcortical and cortical gray matter differences between Kraepelinian and non-Kraepelinian schizophrenia patients identified using voxel-based morphometry. *Psychiatry Res* 2010;184(1):16-22.
70. Molina V., Reig S., Sanz J. et al. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr Res* 2005;80(1):61-71.
71. Mond J., Morice R., Owen C. et al. Use of antipsychotic medications in Australia between July 1995 and December 2001. *Aust N Z J Psychiatry* 2003;37(1):55-61.
72. Mortimer A.M., Shepherd C.J., Rymer M. et al. Primary care use of antipsychotic drugs: an audit and intervention study. *Ann Gen Psychiatry* 2005;4:18.
73. Navari S. and Dazzan P. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med* 2009;39(11):1763-1777.
74. Norman R.M., Townsend L. and Malla A.K. Duration of untreated psychosis and cognitive functioning in first-episode patients. *Br J Psychiatry* 2001;179:340-345.
75. Osborn D.P., Levy G., Nazareth I. et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. *Arch Gen Psychiatry* 2007;64(2):242-249.
76. Owens D.C., Johnstone E.C., Miller P. et al. Duration of untreated illness and outcome in schizophrenia: test of predictions in relation to relapse risk. *Br J Psychiatry* 2010;196:296-301.
77. Pantelis C., Velakoulis D., McGorry P.D. et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003;361(9354):281-288.
78. Pantelis C., Yucel M., Wood S.J. et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005;31(3):672-696.
79. Penttila M., Jaaskelainen E., Haapea M. et al. Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophr Res* 2010;123(2-3):145-152.

80. Perkins D.O., Gu H., Boteva K. et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005;162(10):1785-1804.
81. Potkin S.G., Gharabawi G.M., Greenspan A.J. et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophr Res* 2006;85(1-3):254-265.
82. Raedler T.J. Cardiovascular aspects of antipsychotics. *Curr Opin Psychiatry* 2010;23(6): 574-581.
83. Ram R., Bromet E.J., Eaton W.W. et al. The natural course of schizophrenia: a review of first-admission studies. *Schizophr Bull* 1992;18(2):185-207.
84. Rijcken C.A., Boelema G.J., Slooff C.J. et al. Off-label use of antipsychotics in the community pharmacy: the sex differences. *Pharmacopsychiatry* 2003;36(5):187-191.
85. Saddichha S., Manjunatha N., Ameen S. et al. Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in India: a randomized, double-blind, controlled, prospective study. *J Clin Psychiatry* 2007;68(11):1793-1798.
86. Scheepers F.E., de Wied C.C., Hulshoff Pol H.E. et al. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology* 2001;24(1):47-54.
87. Selten J.P., Veen N.D., Hoek H.W. et al. Early course of schizophrenia in a representative Dutch incidence cohort. *Schizophr Res* 2007;97(1-3):79-87.
88. Stahl S.M., Mignon L. and Meyer J.M. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand* 2009;119(3):171-179.
89. Steen R.G., Mull C., McClure R. et al. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry* 2006;188:510-518.
90. Takahashi T., Suzuki M., Tanino R. et al. Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. *Psychiatry Res* 2007;154(3):209-219.
91. Tauscher-Wisniewski S., Tauscher J., Christensen B.K. et al. Volumetric MRI measurement of caudate nuclei in antipsychotic-naive patients suffering from a first episode of psychosis. *J Psychiatr Res* 2005;39(4):365-370.
92. Théberge J., Al-Semaan Y., Drost D.J. et al. Duration of untreated psychosis vs. N-acetylaspartate and choline in first episode schizophrenia: a 1H magnetic resonance spectroscopy study at 4.0 Tesla. *Psychiatry Res* 2004;131(2):107-114.
93. Trifiro G., Spina E., Brignoli O. et al. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999-2002. *Eur J Clin Pharmacol* 2005;61(1):47-53.
94. Vita A. and De P.L. The effects of antipsychotic treatment on cerebral structure and function in schizophrenia. *Int Rev Psychiatry* 2007;19(4):429-436.
95. Vita A., De P.L., Silenzi C. et al. Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophr Res* 2006;82(1):75-88.

96. Wiersma D., Nienhuis F.J., Slooff C.J. et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 1998;24(1):75-85.
97. Wright I.C., Rabe-Hesketh S., Woodruff P.W. et al. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 2000;157(1):16-25.
98. Zipursky R.B., Gu H., Green A.I. et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. *Br J Psychiatry* 2005;187:537-543.
99. Zitman F.G. [Neuroleptics as anxiolytics and antidepressive agents]. *Ned Tijdschr Geneeskd* 1988;132(9):378-379.

Chapter 2

Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: results from an aborted randomised trial and mini meta-analysis

Geartsje Boonstra, Huibert Burger, Diederick E. Grobbee, René S. Kahn

International Journal of Psychiatry in Clinical Practice, published online 2010

Abstract

Objective: To assess the effect of withdrawal of antipsychotic treatment on relapse risk in remitted first-episode schizophrenia patients.
Methods: First-episode 1-year stable and remitted outpatients with a schizophrenic disorder were randomly allocated to continuation of their antipsychotic regimen for at least 6 months (N=9), or gradual withdrawal (N=11). Primary outcome was the difference in cumulative relapse-free survival at 9 months. Additionally, we pooled the odds ratios of 2 studies that randomised 1-year stable and remitted first-episode schizophrenia patients.
Results: Recruitment was terminated prematurely October 26, 2005. The cumulative relapse-free survival was 88% (SE=0.12) in the continuation and 18% (SE=0.12) in the discontinuation group (p=0.001) at 9 months follow-up. The pooled analyses yielded an odds on relapse of 8.5 after discontinuation compared to continuation (OR=8.5, p=0.025).
Conclusions: Discontinuation of antipsychotic medication markedly increases the risk of relapse in stable remitted first-episode schizophrenia patients. In future studies the topics safety monitoring and sampling of patients should receive extra attention.

Introduction

Schizophrenia is a chronic and lifelong disorder, characterised by recurrent psychotic episodes and a decline in functioning. Treatment typically involves long-term antipsychotic use. While the efficacy of antipsychotics in preventing relapse in schizophrenia patients who have experienced multiple episodes is beyond doubt[6,11], it is still unclear whether schizophrenia patients, after full recovery from their *first* psychotic episode, need prophylactic treatment. Careful discontinuation of antipsychotic medication in such patients can be considered since approximately 15% of first-episode schizophrenia patients will never experience another psychotic episode after withdrawal of medication[12,25,28] while its long-term continuation may induce serious, yet often reversible, side-effects.
Five randomised studies examined the effect of antipsychotic discontinuation in patients who had experienced a single psychotic episode[3,5,14,18,23]. However, either the duration of remission was short, with consequent uncertain stability of

patients [3,5,14,18], the patients in the continuation group were put on a new antipsychotic regimen[3], the study sample was very small[23], or no tapering period was installed[3,14,18,23]. Together, these studies have not resolved the issue whether patients, after remission from their first psychotic episode, should be continued on their antipsychotic medication. Indeed, the most recent guideline of the American Psychiatric Association for the treatment of patients with schizophrenia[22] skirts the issue stating that medication discontinuation after either "at least 1 year of symptom remission" or "optimal response while taking medication" is the only prudent alternative for "indefinite antipsychotic maintenance therapy" in patients who experienced a single psychotic episode.

We conducted a randomised trial comparing, in clinical practice, the effect of gradual withdrawal of antipsychotic treatment with continuation in schizophrenia patients who had remitted from a single psychotic episode, and who had been clinically stable for at least one year. We performed a pooled analysis of the odds for hospitalisation after withdrawal of antipsychotics compared to continuation by combining the results of the present trial and the, to our knowledge, only published withdrawal trial in 1-year stable and remitted first-episode schizophrenia patients[23]. We aimed to contribute to resolving the question whether first-episode schizophrenia patients should continue their antipsychotic medication indefinitely or alternatively find justification for withdrawal of their treatment after 1 year of stable remission.

Methods

Trial

Eligible patients were aged 16 to 55 years, treated in a tertiary or secondary psychiatric centre in The Netherlands, and diagnosed with schizophrenia, schizophreniform or schizoaffective disorder (Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) as assessed with the Structured Clinical Interview for DSM-IV Axis I disorders[9]. Included were patients in clinical remission and stable after their first treated psychotic episode, with scores of three or less over the previous year on each core psychosis item of the Positive and Negative Syndrome Scale[19] (PANSS), i.e. delusions, conceptual disorganisation, hallucinatory behavior and suspiciousness or persecution. Exclusion criteria were medication non-compliance during the past year, use of mood-stabilisers at inclusion and

in the patient history, severe neurological illness, current suicidal ideation or a history of a serious suicide attempt. Duration of remission, suicidal ideation and compliance were assessed by interviewing the patient and his doctor. Patients were enrolled (G.B.) between July 24, 2002 and June 15, 2005. The Medical Ethics Review Board of the University Medical Centre Utrecht approved the study. Written informed consent was obtained from each participant.

Patients were randomised to gradual discontinuation of the antipsychotic regimen they used at inclusion over a period of six to twelve weeks, or to continuation of this medication for at least six months. In the latter group, any subsequent tapering had to take place within six to twelve weeks. To adhere to current practice the actual pattern of tapering was left at the discretion of the treating psychiatrist as were concomitant treatments, such as psychosocial treatments, psychoeducation or casemanagement. These latter treatments were not systematically installed or offered, nor monitored. An independent expert created randomisation lists, stratified for centre and gender, with randomly permuted blocks of four allocation codes. For the primary outcome, relapse was defined as a score of at least four on any PANSS core psychosis item *and* a 20% increase in the total PANSS score, *or* hospitalisation for any psychiatric indication. The PANSS is a well-established and reliable scale for the assessment of severity of symptoms of schizophrenia[20]. The criteria of a 20% increase in total PANSS score[4] and hospitalisation[2,7,8,13] have been used previously in efficacy studies. Hospitalisation was added as another objective criterion for relapse, as this was decided upon by the treating physician instead of the researcher. Thus bias arising from unblinded PANSS scoring was excluded and comparison to similar studies (using relapse criteria equaling more severe relapse) was facilitated[5,14,23]. Lastly, in this way the date of hospitalisation could be used in the case of untimely (long after hospitalisation) notification of deterioration, instead of a later assessment using the PANSS criterion. During two years of follow-up, patients were evaluated every two months by one of two trained researchers from the University Medical Centre Utrecht (Intraclass Correlation Coefficient for PANSS measurements 0.92, Cronbach's alpha 96.5) with extra visits in case of suspecting relapse. Each visit the PANSS was administered and medication status was assessed. In case of relapse, an antipsychotic was reinitiated. Medication compliance was monitored using the Medication Adherence Rating Scale (MARS), and each visit medication dosage and intake was discussed[26]. Haloperidol dose-equivalence (H-EQ) was

calculated as follows (ratio haloperidol:other antipsychotic): Risperidone 1:1, olanzapine 1:2.5, quetiapine 1:100[17] and zuclopentixol 1:5[27].

To demonstrate equivalence of the two arms, defined as an absolute two-year relapse risk difference less than 25%, with 95% certainty and 80% power, a sample size of 63 per group was estimated[24]. Only intention-to-treat analyses were performed. Kaplan-Meier curves enabled graphical comparison of cumulative relapse-free survival between the randomised groups. Differences were tested for statistical significance using the logrank-test with a two sided p-value less than 0.05 indicating statistical significance. Cox-regression was performed to estimate a hazard ratio (HR) with a 95% confidence interval (CI) as a measure of relative risk (RR), and to make adjustments if, despite randomisation, the groups appeared dissimilar at baseline. The primary analyses were based on censoring after maximally nine months follow-up, preventing dilution of the effect because of cross-over to withdrawal in the continuation group. This period was chosen because of the obligatory six months continuation, and possible subsequent tapering period of maximally three months. Secondary analyses were performed over the total follow-up of two years. Finally, the data were analysed with psychiatric hospitalisation (for psychotic relapse) as outcome using the logrank-test and Cox-regression as described above. Baseline variables were tested for equality using the t-test for continuous data and the Pearson Chi Square test for nominal data.

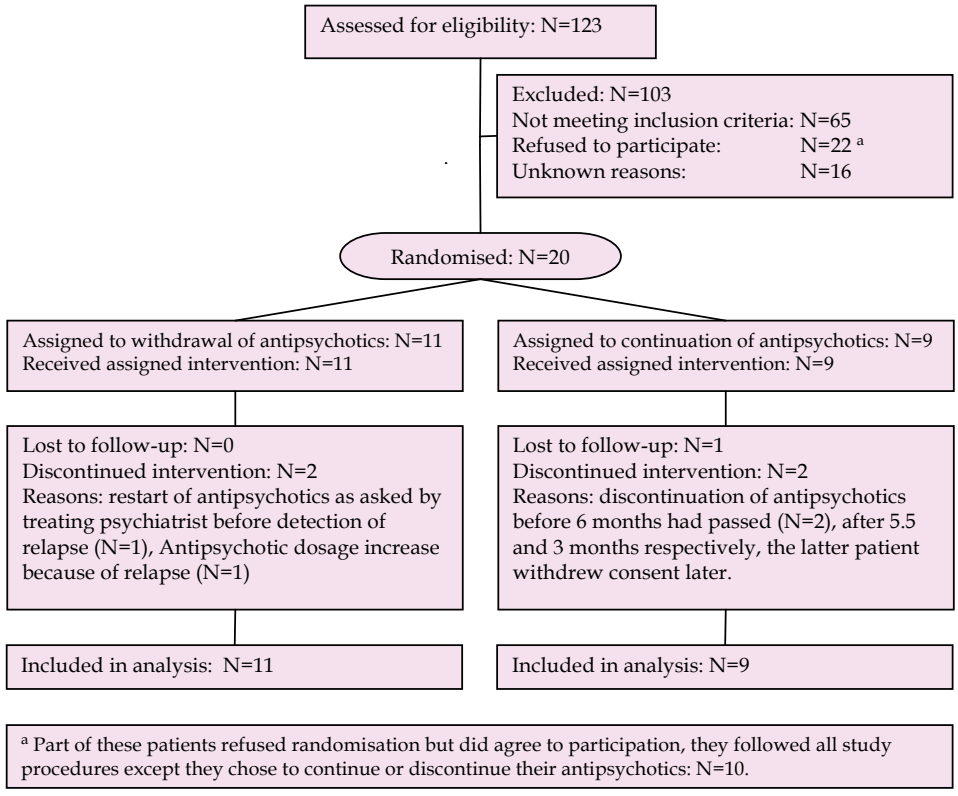
To uncover an unacceptably high risk difference in a timely manner, a priori a safety analysis was planned which sequentially tested at each relapse whether the difference in absolute relapse-risk had exceeded 25% with a one-sided certainty of 95%. For this analysis the more severe relapses were included (as defined a priori), i.e. with PANSS scores of five or more on core psychosis items *and* a 20% increase in the total PANSS score, or hospitalisation for any psychiatric indication[4].

Meta-analysis

To detect published trials that randomised 1-year stable and remitted first-episode schizophrenia patients to either continuation or discontinuation of their antipsychotic regimen, Pubmed and Embase databases were searched with the following query: Schizophrenia AND first episode AND (discontinuation OR

discontinued OR discontinue OR withdrawal OR withdrawn OR withdraw OR stopping OR stopped OR stop OR placebo). Four studies[5,10,18,23] were retrieved examining first-episode schizophrenia patients. References were checked for more relevant research, yielding one more study[14]. Only two of these studies randomised 1-year stable and remitted first-episode schizophrenia patients[10,23]. One of these was excluded because it reported incomplete data making it impossible to calculate a valid odds ratio. A fixed effects Mantel-Haenszel pooled odds ratio of 1-year hospitalisation (for reason of psychotic relapse) contrasting the withdrawal and the continuation group, was calculated together with a 95% confidence interval, combining the results of our study with the single other retrieved study. A test for heterogeneity was performed.

Figure 1. Flowchart of recruitment, randomisation, follow-up and analysis.



Results

Trial

Twenty outpatients were recruited from July 24, 2002 to June 15, 2005 in 11 centers with a maximum of 5 patients per centre: University Medical Centre Utrecht (N=5), Symfora Group (N=1), The Meerkanten (N=3), Regional Institution for Mental Health Care (RIAGG) Amersfoort and surroundings (n=1), RIAGG Zaanstreek-Waterland (N=3), Mental Health Care Institution (GGZ) North-Holland-North Schagen/Den Helder (N=1), GGZ 's-Hertogenbosch (N=2), GGZ Delft (N=1), GGZ Midden-Kennemerland (N=1), GGZ Altrecht (N=1) and GGZ Middle-Brabant (N=1). The flow of participants is shown in **Figure 1**.

Nine patients were randomised to continuation and 11 to gradual discontinuation of antipsychotics. Baseline characteristics (**Table 1**) were evenly distributed. At the time of analyses, nine patients had completed follow-up, and one had dropped out after 4 months. The dropped out patient was a male of 34 years old, randomised to continuation. Median follow-up was 650 days (range, 103-773 days). In the withdrawal group, all but one patient discontinued the medication, two patients relapsed during tapering. Furthermore, one patient did *not* experience relapse after discontinuation. In the continuation group four patients discontinued their antipsychotics after at least six months of medication use. The mean of all average MARS scores (maximum score 10, minimum score 0) obtained per (antipsychotic using) patient during the study was 6.9 (SE=0.71) in the discontinuation group and 7.0 (SE=0.66) in the continuation group. No patient ever had a score of 10 or a score below 4.

Kaplan-Meier analyses (**Figure 2**) showed a cumulative relapse-risk at the time of maximum intervention contrast, i.e. nine months, of 12% (SE=0.12) in the continuation and 82% (SE=0.12) in the discontinuation group (p-value for difference=0.001). Cumulative relapse-risk at two years was 45% (SE=0.20) in the continuation, and 91% (SE=0.09) in the withdrawal group (p=0.001). Cox-regression analysis with censoring after nine months of follow-up yielded a HR (≈RR) of 15.2 (95%CI: 1.9-122.9). The HR was 7.1 (95%CI: 1.9-26.9) over two years of follow-up. Using hospitalisation (for psychotic relapse) as relapse criterion yielded a nine month relapse-risk of 0% in the continuation group and 36% (SE=0.15) in the discontinuation group (p=0.054) while two year relapse-risk was 12% (SE=0.12) and 36% (SE=0.15) respectively (p=0.19). Cox-regression analysis with censoring

Table 1. Baseline characteristics.

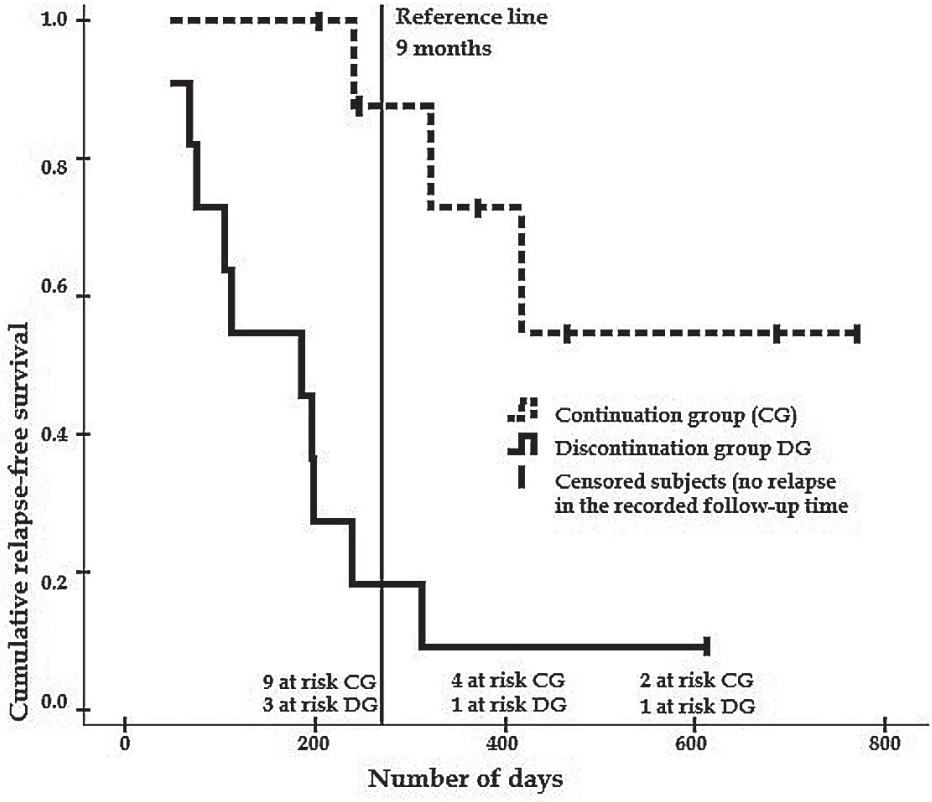
Characteristic[a]	Continuation group (N=9)	Withdrawal group (N=11)
Age, y	28.0 (22-45)	30.4 (21-45)
Male / Female, N	7/2	10/1
Schizophrenia[b], N	4	6
Schizoaffective disorder[b], N	3	5
Schizophreniform disorder[b], N	2	0
Olanzapine[c], N	5	7
Risperidone[c], N	1	2
Quetiapine[c], N	3	1
Zuclopenthixol[c], N	0	1
Antipsychotic dose per day, H-EQ	2.0 (2-8)	4.0 (2-7.5)
Remission, y	1.3 (1.0-4.4)	1.7 (1.0-13.7)
Hospitalisation, days	75 (0-589)	29 (0-247)
Duration of illness, y	2.0 (1.3-7.2)	3.1 (1.3-14.3)
Total PANSS score[d]	53 (37-64)	45 (38-66)

H-EQ: Haloperidol equivalents, PANSS: Positive And Negative Syndrome Scale. [a] Data are given as median (range) except where indicated otherwise. [b] Diagnosis. [c] Antipsychotic medication. [d] The PANSS has 30 items on a 7-points scale, thus the maximum score is 210 and the minimum score 30.

after nine months and two years of follow-up yielded a HR of 60.9 (95%CI: 0.02-191492.2) and a HR of 3.9 (95%CI: 0.4-34.8) respectively.

During the trial it appeared that, in contrast with continuation, gradual withdrawal from antipsychotic medication was almost invariably followed by relapse leading to reinstatement of antipsychotic therapy. Further randomisation to discontinuation was therefore considered unethical and recruitment was terminated prematurely on 26 October, 2005. At that time, the sequential safety analysis demonstrated a statistically significant risk difference (p=0.04).
Ten patients agreed to participate in the study without randomisation (See **Figure 1**). They were included for purposes of research with follow-up magnetic resonance imaging. Their baseline characteristics did not differ from the patients participating in the trial (data not shown).

Figure 2. Kaplan-Meier curve comparing cumulative relapse-free survival between remitted stable first-episode schizophrenia patients that were randomised to continuation or withdrawal of antipsychotic treatment.



Meta-analysis

Pooled analysis of one-year hospitalisation risks (**Table 2**) of the 35 patients in the current study and the study by McCreadie[23] resulted in a Mantel Haenszel fixed effects odds ratio of 8.5 (95%CI: 1.3-55.1) for discontinuation of antipsychotic treatment compared to continuation (p=0.024). The test for heterogeneity was not significant (p=0.44).

Table 2. Size of pooled studies, randomisation groups, numbers of hospitalised patients and odds ratio for one-year hospitalisation.

Study	Total N	DG, N	HDG, N	HCG, N	OR (95%CI)
McCreadie, 1989	15	7	4	0	4.6 (0.4-51.1)
Boonstra, this article	20	11	4	1[a]	21.9 (0.9-523.4)
Total	35	18	8	1	8.5 (1.3-55.1)

N: number of patients, DG: Discontinuation group, HDG: Hospitalisation discontinuation group, HCG: Hospitalisation continuation group, OR: Odds ratio, 95%CI: 95% confidence interval. [a] One patient discontinued treatment after 6 months while being in the continuation group, and experienced relapse after that.

Discussion

A markedly increased risk of a psychotic relapse was observed after gradual discontinuation of antipsychotic medication in a group of clinically stable, remitted first-episode schizophrenia patients, as compared with continuation of such treatment. The pooled analysis confirms the increased risk of hospitalisation within a year after discontinuation of antipsychotic therapy in this category of schizophrenia patients.

Strengths

To our knowledge, this is the first study in which remitted first-episode schizophrenia patients who had been clinically stable *for at least one year*, were randomised to discontinuation, *preceded* by gradual reduction, or continuation of their antipsychotic treatment. The open nature of the trial, i.e. no blinding to medication status, no use of placebo, and the treating psychiatrist managing the actual pattern of tapering and concomitant treatments, enables generalisation of the results to clinical practice.

At the time this study started, a one year period was considered to be an appropriate period before contemplating antipsychotic discontinuation[22]. The most current NICE guideline on schizophrenia states that the patient should be informed of a high risk of relapse if they stop medication in the 1–2 years after achieving remission. Therefore, it seems that this trial is still up to date with its required 12 month period of stabilisation before considering withdrawal of antipsychotic medication[21].

Comparison to literature

Our findings, in this longterm randomised trial, are in line with the five other published trials in first-episode schizophrenia in that they showed considerably lower one-year[3,18,23] or two-year[5,14] relapse risks after continuation (41%, 0%, 0%, 46%, 43%), than after discontinuation (79%, 41%, 57%, 62%, 64%) of antipsychotic treatment[3,5,14,18,23]. However, the two-year relapse rates in our study were higher in the discontinuation (91%) group. This may have resulted from a lower threshold to detect relapse that was used in our study, or from the longer follow-up time we used.

The primary outcomes of the previous studies were imminent or actual readmission[5,14,23], substantial clinical deterioration[18] potentially leading to marked social impairment. When we analyzed our data using a comparable outcome, i.e. psychiatric hospitalisation, nine month relapse risks were similar with 0% in the continuation group and 36.4% in the discontinuation group.

One study performed later than ours used relapse criteria from questionnaires such as the PANSS and the Clinical Global Impression, with slightly stricter criteria for relapse than this study[3]. They found relapse rates more comparable to our study (41% in the quetiapine and 79% in the placebo group). However, they randomised patients that were stable for at least 8 weeks, after one year of antipsychotic treatment to either placebo or quetiapine, thereby taking them off the antipsychotic regimen the patients had responded to in terms of remission. This may have increased their relapse rate. Their hospitalisation rates were 16% in the placebo versus 6% in the quetiapine group, however not all patients were hospitalised for relapse.

Recently, two more medication discontinuation studies in first-episode schizophrenia patients have been published. A randomised trial with an epidemiological sample of first-episode psychosis patients that were in remission for six months found relapse risks of 21% in a maintenance strategy group and 43% in a discon-

tinuation strategy group[29]. However, patients (with their treating physicians) were allowed to not follow the randomisation strategy if they did not want to, which provides a good explanation for the, compared to this study, low relapse rates in the discontinuation strategy group, and the high relapse rate in the continuation group. Furthermore, they included not only patients with a schizophrenic disorder and allowed for moderate positive symptoms during remission. Also they assessed patients only every 6 months. Interestingly, they did not find a difference in functioning between the patients randomised to the continuation or discontinuation strategy. However, due to the deficits in following through the actual randomisation purpose a bias cannot be ruled out. A relapse rate of 96% in two years was found in recent-onset schizophrenia patients that discontinued fluphenazine, although most of the patients did not need to be hospitalised to achieve a new remission[12]. Unfortunately no control group was available in this study.

Limitations

Patients with a DSM-IV diagnosis of schizophrenia, schizophreniform and schizoaffective disorder were included. The effect of tapering may have been diluted since patients with a schizophreniform or schizoaffective disorders generally have a better prognosis in terms of outcome than patients suffering from schizophrenia[15,16]. However, in clinical practice patients suffering from one of these related disorders are pharmacologically treated as having schizophrenia, unless severe affective symptoms occur[21,22]. Therefore, our study population largely reflects our target population, i.e. those patients in whom antipsychotic discontinuation is considered. In our view this adds to the generalisability of our results. The observation that no patient used mood-stabilisers during the previous year suggests that among the schizoaffective patients a dominant affective component was lacking.

About 2.4 million inhabitants can make use of our included centers. The incidence in the Netherlands of non-affective psychosis is about 2.2 per 10.000[1], constituting, with about 60% of patients likely to achieve remission, a potential number 950 participants. We included 20 subjects, which is only 2.1% of this potential. It may very well be possible that a large number of remitted patients discontinued their medication before reaching one year of remission, and either relapsed, or remained stable and were referred back to the general practitioner. It is difficult to conceive what would have been the effect of including these lost cases, the good-prognosis patients that were referred out, as well as the prematurely discontinued cases.

It might be more effective to collect and follow-up an epidemiological sample of patients with a first episode. Including subjects might be easier in a large early psychosis programme with a lengthy follow-up, continuing after remission of the patients. Since our sample was collected in multiple organisations for mental health the results of this patient group might not generalise entirely to patients coming solely from an early psychosis specialist setting.

Due to the relatively small sample size, the statistical power of our study was limited. Yet, as is evident from the confidence intervals in the primary analysis, equal relapse rates in the continuation and discontinuation group appear very unlikely.

It cannot be excluded that the outcome observations were biased since the researchers were not blind to medication status. However, using the more objective outcome, i.e. hospitalisation, showed a detrimental effect of discontinuation at the time of maximum contrast, although borderline significant.

We failed to define relapse in terms of duration. It cannot be excluded that this might have somewhat inflated the number of relapses since short episodes of psychosis might have been included.

Furthermore we did not monitor treatment other than pharmacological. Thus, we cannot exclude a difference between the groups in received relapse prevention of non-pharmacological character, although randomisation theoretically should have eliminated this problem.

Compliance was assessed with the MARS[26], a 10 item list that is a valid and reliable measure of compliancy for psychoactive medications. Since the scores are well above 50% of the maximum score they seem to be indicative of a good enough compliance. However, since we did not determine plasma levels of antipsychotics we cannot exclude medication non-compliance.

It is clear from the small number of studies available and the small groups investigated, that this particular research question – is it justified to discontinue antipsychotics in the stable and remitted first-episode schizophrenia patient, or not - although clinically very important, is not easily investigated in large groups of patients. The one-year stable and remitted first-episode schizophrenia patient is rare and difficult to find. Then there is the challenge of convincing the patient (and the treating psychiatrist) to agree with randomisation, thereby asking to hand over this emotionally charged and insight related decision of (dis)continuation to fate. These conditions make withdrawal trials in this category of schizophrenia patients very difficult to perform. It might be of importance to take this

into account when weighing the potential of the relatively scarce data to have clinical impact.

Meta-analysis

McCreadie used a placebo-controlled design without a tapering period, while we performed an open trial without placebo use or blinding and a tapering period of 6 to 12 weeks[23]. Although awareness of medication status in our study might have affected the risk of hospitalisation, the placebo controlled study showed a similarly increased risk of hospitalisation associated with medication discontinuation. The risk of relapse in McCreadie's study might have been increased since no tapering period was included. Despite these two differences between the studies we feel that pooling the results is valid since both studies randomised first-episode schizophrenia patients that were stable for at least one year.

The results of the pooled analysis emphasize that the risk of severe relapse requiring hospitalisation is markedly elevated after discontinuation of antipsychotics in stable and remitted first-episode schizophrenia patients, even if discontinuation is effectuated after a period of remission of at least one year.

Conclusion

In conclusion, relapse risk in first-episode schizophrenia patients remitted from a single psychotic episode, who have been clinically stable for at least one year, is markedly increased by discontinuation of antipsychotic therapy. Consequently, advantages of medication discontinuation as presented in current guidelines, may not outweigh the associated increase in relapse risk. In future studies the topics safety monitoring and sampling of patients should receive extra attention.

Acknowledgements

Supported by a grant from ZonMw (Netherlands Organization for Health Research and Development) (2100.0057) and an unrestricted gift from Eli Lilly and Company® (H6U-UT-LRAC). We thank Ingeborg van der Tweel, statistical advisor at the Centre for Biostatistics, University Utrecht.

References

1. Boonstra N., Wunderink L., de Wit P.H. et al. [The administrative incidence of non-affective psychoses in Friesland and Twente]. *Tijdschr Psychiatr* 2008;50(10):637-643.
2. Carpenter W.T., Jr., Hanlon T.E., Heinrichs D.W. et al. Continuous versus targeted medication in schizophrenic outpatients: outcome results. *Am J Psychiatry* 1990;147(9):1138-1148.
3. Chen E.Y., Hui C.L., Lam M.M. et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010;341:c4024.
4. Chrzanowski W.K., Marcus R.N., Torbeyns A. et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology (Berl)* 2006;189(2):259-266.
5. Crow T.J., MacMillan J.F., Johnson A.L. et al. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 1986;148:120-127.
6. Davis J.M., Janicak P.G., Singla A. et al. Maintenance antipsychotic medication. In: Barnes T., editor. Antipsychotic Drugs and Their Side-Effects. 1st ed. London: Academic Press Limited, 1993:183-203.
7. Dellva M.A., Tran P., Tollefson G.D. et al. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatr Serv* 1997;48(12):1571-1577.
8. Engelhardt D.M., Rosen B., Freedman N. et al. Phenothiazines in prevention of psychiatric hospitalization. IV. Delay or prevention of hospitalization--a reevaluation. *Arch Gen Psychiatry* 1967;16(1):98-101.
9. First M.B., Gibbon M., Spitzer R.L. et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Version (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute, 1996
10. Gaebel W., Moller H.J., Buchkremer G. et al. Pharmacological long-term treatment strategies in first episode schizophrenia--study design and preliminary results of an ongoing RCT within the German Research Network on Schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2004;254(2):129-140.
11. Gilbert P.L., Harris M.J., McAdams L.A. et al. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry* 1995;52(3):173-188.
12. Gitlin M., Nuechterlein K., Subotnik K.L. et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry* 2001;158(11):1835-1842.
13. Hogarty G.E., Goldberg S.C., Schooler N.R. et al. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. *Arch Gen Psychiatry* 1974;31(5):603-608.
14. Hogarty G.E. and Ulrich R.F. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiatr Res* 1998;32(3-4):243-250.
15. Iancu I., Dannon P.N., Ziv R. et al. A follow-up study of patients with DSM-IV schizophreniform disorder. *Can J Psychiatry* 2002;47(1):56-60.

16. Jager M., Bottlender R., Strauss A. et al. Fifteen-year follow-up of ICD-10 schizoaffective disorders compared with schizophrenia and affective disorders. *Acta Psychiatr Scand* 2004;109(1):30-37.
17. Kane J.M., Leucht S., Carpenter D. et al. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry* 2003;64 Suppl 12:5-19.
18. Kane J.M., Rifkin A., Quitkin F. et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 1982;39(1):70-73.
19. Kay S.R., Fiszbein A. and Opler L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
20. Kay S.R., Opler L.A. and Lindenmayer J.P. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1988;23(1):99-110.
21. Kuipers E. and Kendall T. Schizophrenia (update). Antoniou J., Barnes T., Bhui K. et al., eds. Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). 1-399. 2009. London, National Institute for Health and Clinical Excellence . Clinical guidelines CG82.
22. Lehman A.F., Lieberman J.A., Dixon L.B. et al. Practice Guideline for the Treatment of Patients With Schizophrenia. Second Edition. 1-184. 2004.
23. McCreadie R.G., Wiles D., Grant S. et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. *Acta Psychiatr Scand* 1989;80(6):597-602.
24. Pocock S.J. The Size of a Clinical Trial. In: Pocock S.J., editor. Clinical trials: A practical approach. 1st ed. Chicester: John Wiley & Sons Ltd., 1983:129-130.
25. Ram R., Bromet E.J., Eaton W.W. et al. The natural course of schizophrenia: a review of first-admission studies. *Schizophr Bull* 1992;18(2):185-207.
26. Thompson K., Kulkarni J. and Sergejew A.A. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res* 2000;42(3):241-247.
27. van Loenen A.C., de Boer J.E., Beckeringh J.J. et al. Pharmacotherapeutical Compass. van Loenen A.C. and de Boer J.E., eds. 28th, 1-1272. 2009. Utrecht, Commissie Farmaceutische Hulp van het College voor zorgverzekeringen. Pharmacotherapeutical Compass. van, L.A.C.
28. Wiersma D., Nienhuis F.J., Slooff C.J. et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 1998;24(1):75-85.
29. Wunderink L., Nienhuis F.J., Sytema S. et al. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry* 2007;68(5):654-661.

Chapter 3

Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia

Geartsje Boonstra, Neeltje E.M. van Haren, Hugo G. Schnack, Wiepke Cahn, Huibert Burger, Maria Boersma, Bart de Kroon, Diederick E. Grobbee, Hilleke E. Hulshoff Pol, René S. Kahn.

Journal of Clinical Psychopharmacology 2011;31(2):146-153

Abstract

The influence of antipsychotic medication on brain morphology in schizophrenia may confound interpretation of brain changes over time. We aimed to assess the effect of discontinuation of atypical antipsychotic medication on change in brain volume in patients. Sixteen remitted, stable first-episode patients with schizophrenia, schizoaffective or schizophreniform disorder and twenty healthy controls, were included. Two magnetic resonance imaging brain scans were obtained from all subjects with a one year interval. The patients either discontinued (N=8) their atypical antipsychotic medication (olanzapine, risperidone or quetiapine) or did not (N=8) during the follow-up period. Intracranial volume and volumes of total brain, cerebral gray and white matter, cerebellum, third and lateral ventricle, nucleus caudatus, nucleus accumbens and putamen were obtained. Multiple linear regression analyses were used to assess main effects for group (patient-control) and discontinuation (yes-no) for brain volume (change), while correcting for age, gender and intracranial volume. Decrease in cerebral gray matter and caudate nucleus volume over time was significantly more pronounced in patients relative to controls. Our data suggested decreases in the nucleus accumbens and putamen volumes during the interval in patients who discontinued antipsychotic medication while increases were found in patients who continued their antipsychotics. We confirmed earlier findings of excessive gray matter volume decrements in patients with schizophrenia as compared to normal controls. We found evidence suggestive for decreasing volumes of the putamen and nucleus accumbens over time after discontinuation of medication. This might suggest that discontinuation reverses effects of atypical medication.

Introduction

Schizophrenia is a chronic disorder, characterised by recurrent psychotic episodes and a decline in functioning. Treatment typically involves long-term antipsychotic use.

Increasing evidence suggests that the often replicated brain volume decrease in schizophrenia[63] is progressive over time[3,13,23,30,32,50]. Although some of the progressive brain changes appear related to the course of illness[1,3,4,26,32,42] it has been an issue of debate what, if any, is the influence of medication. Some argue, based

on research in monkeys, that the loss of grey matter in schizophrenia can be attributed to the use of typical or atypical antipsychotic medication[15]. In contrast, in studies in schizophrenia patients, loss of grey matter (GM) volume appears to be attenuated by atypical antipsychotics, but not by haloperidol[27,43,47].

One of the best replicated findings in schizophrenia is the increase in caudate nucleus (NC) volume being related to intake of typical antipsychotics[37,38]. It has been suggested that changing treatment to atypical antipsychotics appears to 'normalise' this effect[10,40,53]. However, investigated longitudinally, the use of atypical antipsychotic medication has been related to stable[22,28,60], increasing[22,44] and decreasing[6,11,17,20,40,53] volumes of basal ganglia.

Differentiating between antipsychotic-induced changes and those inherent to the disease would be most valid through randomisation of antipsychotic-naïve first-episode patients to treatment or placebo in comparison to healthy controls. However, this design is clearly coupled with ethical issues. One alternative design is to longitudinally study brain volumes in patients who discontinue their medication, or not. Guidelines offer the psychiatrist the possibility to discontinue antipsychotic medication in remitted and stable first-episode schizophrenia patients[41]. The National Institute for Health and Clinical Excellence (NICE) guideline[39] states that "it is uncertain whether maintenance drug treatment is required for all people with schizophrenia. Around 20% of individuals will only experience a single episode". To assess medication-related changes in brain volume over time we compared remitted and stable schizophrenia patients in whom atypical antipsychotic medication was either discontinued or continued in a one-year follow-up magnetic resonance imaging (MRI) study.

Materials and methods

Subjects

After complete description of the study, written informed consent was obtained from all participants. The Medical Ethics Review Board of the University Medical Centre Utrecht approved the study. Sixteen patients were included. They were aged 16 to 55 years and diagnosed with schizophrenia, schizophreniform or schizoaffective disorder as assessed with the Structured Clinical Interview for DSM-IV Axis-I disorders[19]. They were treated in a tertiary or secondary psychiatric centre in The Netherlands. Furthermore, only clinically remitted and stable

first-episode patients with scores of three or less over the previous year on each core psychosis item (delusions, conceptual disorganisation, hallucinatory behaviour and suspiciousness or persecution) of the Positive and Negative Syndrome Scale (PANSS)[36] were included. Exclusion criteria were medication non-compliance during the past year, use of mood-stabilisers, severe neurological illness, current suicidal ideation, or a history of a serious suicide attempt. Duration of remission, suicidal ideation and compliance were assessed by interviewing patients and their treating physician. Of the included patients MRI brain-images were acquired at baseline (T0) and 12 months follow-up (T12) or, if possible, at relapse before T12 and before medication restart. To assess the influence of discontinuation of atypical antipsychotics on brain volume change (corrected for time-interval: [Volume T12-Volume T0)/T12-T0)]) the included patients were divided in two subgroups: patients who tapered (in 6-12 weeks) and discontinued antipsychotic treatment (N=8) and patients who continued antipsychotics (N=8) between T0 and T12. A proportion of the participating patients (N=10) were selected from a randomised trial investigating the effect of discontinuation versus continuation of antipsychotics on relapse risk (First author, Chapter 1). Half of the patients in this study were originally randomised to continuation (N=4) or discontinuation (N=4) and remained in that group. Two patients in the discontinuation group were originally randomised to continuation but tapered and discontinued after 6 months in the study. The remainder of the patients (N=6) chose to continue or discontinue their antipsychotics. All subjects participating in this study were on atypical antipsychotic medication at inclusion. The type of drug had been determined by the treating clinician, and not the researcher, and remained the responsibility of the treating clinician during the study. In retrospect, none of the patients changed their type of antipsychotic medication during the current study. During follow-up, patients were evaluated every two months by a trained researcher with extra visits in case of impending relapse. Each visit the PANSS, the Global Asessment of Functioning[34] (GAF) and the Clinical Global Impression[18,25] (CGI) were administered and medication status was assessed. Haloperidol dose-equivalences (HEQ) for quantification of antipsychotic exposure were calculated using patient charts as follows (ratio haloperidol: other antipsychotic): risperidone 1:1, olanzapine 1:2.5, quetiapine 1:100[35].

Additionally 20 controls were included and scanned twice with an interval of one year on average. The controls were group-matched for age and gender to the patients. The control sample has been described previously[3]. Baseline character-

istics are shown in Table 1. Controls had no mental (history) or physical illness at both baseline and follow-up measurement.

MRI data acquisition

Magnetic resonance images (MRIs) were acquired using a 1.5 Tesla Philips NT scanner. A T1-weighted three-dimensional fast field echo (3D-FFE: echo time (TE)=4.6 milliseconds, repetition time (TR)=30 milliseconds, flip angle=30 degrees, field of view (FOV)=256/80% mm) with 160–180 contiguous coronal 1.2-mm slices and a T2-weighted dual echo turbo spin-echo (DE-TSE: TE1=14 milliseconds, TE2= 80 milliseconds, TR=6350 milliseconds, flip angle=90 degrees, FOV=256/80% mm) with 120 contiguous coronal 1.6-mm slices of the whole head were used for the quantitative measurements. In addition, a T2-weighted DE-TSE (TE1=9 milliseconds, TE2=100 milliseconds, TR=2200 milliseconds, flip angle=90 degrees, FOV=250/100% mm) with 17 axial 5-mm slices and 1.2-mm gap of the whole head was acquired for clinical neurodiagnostic evaluation. The scans were processed on the neuro-imaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. Before quantitative assessments, 10 randomly chosen images were cloned for calculation of inter-rater reliability using the intraclass correlation coefficient (ICC). All images were coded to ensure blindness for subject identification. Scans were put into Talairach frame (no scaling)[58] and corrected for inhomogeneities in the magnetic field[56].

Volume measures of the intracranium, total brain (TB), cerebral gray (GM) and white matter (WM), cerebellum, third (V3) and lateral ventricles (LV) were determined. Quantitative assessment of the intracranial volume was performed with use of a fully-automated computer program based on histogram analyses followed by mathematical morphological operators in the DE-TSE image. Quantitative assessment of the TB, GM, WM, cerebellar, V3 and LV volumes were performed based on histogram analyses followed by mathematical morphological operators in the 3D-FFE image, using the intracranial volume as mask[54,55]. In addition, for the cerebellum and V3 and LV volumes, anatomical knowledge-based selection principles were used. For the cerebellum, this included a plane perpendicular to the sagittal plane through the aquaduct. For the V3, this included the coronal slices through the anterior commissure (AC) as anterior border, the coronal slice through the posterior commissure (PC) as posterior border and a manually outlined roof to prevent leaks into the transverse cistern, drawn in the midsagittal reconstructed slice from a point superior to the thalamus and just in-

ferior to the plexus choroideus. For the LVs, this included automated computer-incorporated anatomical knowledge of the anatomical location of the LVs in the brain (e.g., they are surrounded by WM). All segmentations were checked after measurements and corrected manually if necessary. The interrater reliabilities of the volume measurements, determined by the Intraclass Correlation Coefficient (ICC) were 0.95 and higher.

Basal ganglia structures were traced manually by a single experienced rater (BK). Nucleus caudatus (NC), putamen and nucleus accumbens (NA) were outlined in contiguous coronal slices in an anterior-posterior direction. The sagittal and axial planes were used for reference. Segmentation procedures are based on previously described guidelines[53,57].
In the first segmentation slice the NC had to be visible infero-lateral of the LVs, in the last slice either the PC appeared or the NC was still clearly discernible in the coronal view. Medially, the frontal horn and body of the LV bordered the NC and laterally the internal capsule. The interconnecting GM striae between the NC and putamen visible in the internal capsule were not included in the NC or putamen volumes. At the inferior border the NC and the NA were separated by a horizontal line from the most basal extent of the LV to the most lateral point of the NC.
Putamen segmentation commenced in the first slice where the structure was clearly distinguishable while it ended in the last slice where the boundaries were still clearly discernible. The anterior limb of the internal capsule and the globus pallidus formed the medial border and the external capsule the lateral border. Infero-medially, the putamen and the NA were separated by a vertical line from the most latero-inferior point of the internal capsule to the inferior border of the putamen/NA. In slices where the AC was visible, the most lateral point of the AC was used as the starting point of the vertical line separating the putamen and the NA.
In the first slice containing both NC and putamen segmentation of the NA started, while it ended in the slice where the boundaries for the NA were still clearly discernible. Supero-laterally, the putamen and NC bordered the NA and infero-medially the surrounding WM.
Ten scans were duplicated and randomly intermixed with the data set to allow for an estimation of intrarater reliability using (ICCs). ICC scores were 0.99 for NC, 0.97 for NA and 0.90 for putamen volume.

Data-analysis

To investigate the effect of illness and antipsychotic treatment on brain volume (change) multiple linear regression analyses were performed using SPSS15. Volumes of the total brain, cerebral grey and white matter, lateral and third ventricle, nucleus accumbens, nucleus caudatus and putamen were added as dependent variable. A group variable (patient-control) and a medication variable (on-off medication at follow-up) were added as independent variables. Age, intracranial volume and gender were added as covariates. In case of significant group differences in (change in) basal ganglia volumes baseline TB volume instead of the intracranial volume was added as a covariate. In addition, it was tested if baseline volume of the basal ganglia structures were correlated with volume change over time using Pearson correlations. If this were the case, baseline volume was added as a covariate.

As the patients and controls differed significantly on abuse of drugs and/or abuse of alcohol at baseline and the patient groups differed significantly on parental education these variables were added separately as a covariate in case of significant findings. This will only be mentioned if it led to differences in the results.

The patient groups also differed significantly on duration of illness since the first start of antipsychotics, but due to the high correlations with age ($r=0.92$, $p<0.001$) adding this as a covariate would lead to the problem of multicollinearity. All statistical tests were two-tailed. For the comparisons of volume (change) between the two patient groups confidence interval, range and median were given for significant results.

Results

Demographic and clinical comparison of groups

Baseline characteristics were comparable between the patients and controls and between patient groups. There were four exceptions (**Table 1**, data-analysis). The one year relapse rate was 50% in the discontinuation and 13% in the continuation group.

Illness effect

Baseline

At baseline V3 and putamen volume of patients was significantly larger than that of controls (**Table 2**). V3 remained larger after exclusion of one outlier. Correction for TB instead of intracranial volume did not change these results.

Change

GM and NC volume change during the interval differed significantly between patients and controls (**Table 3**, **Figure 1a** and **1d**). While controls showed an increase in GM and NC volume, patients showed decreases over time. Additionally, NA volume increase over time was more pronounced in controls as compared to patients (**Table 3**, **Figure 1c**). Furthermore, WM volume in patients showed a larger increase over time as compared to controls (**Table 3**, **Figure 1b**). The significant changes in the basal ganglia remained significant after correction for baseline TB volume and baseline volume of the structure concerned. However, after exclusion of the largest outlier in the patients the difference in NA change was not significant (p=0.18) and after correction for having a positive history of alcohol or drug abuse or dependency the difference in NA change was trend level significant (p=0.06).

Table 1. Baseline characteristics of normal controls (NCS), all patients (PTS), patients who were medication-free at follow-up (OFF) and patients on medication at follow-up (ON)[a].

Variables, N or mean (sd)	NCS	PTS	P-value	PTS OFF	PTS ON	P-value
Gender, male/female	15/5	12/4	n.s.	6/2	6/2	n.s.
Age, years	27.97 (5.63)	28.8 (6.9)	n.s.	27.97 (8.24)	29.56 (5.72)	n.s.
Handedness (right/left/ambidexter)	16/4/0	13/2/1	n.s.	7/1/0	6/1/1	n.s.
Patient level of education (years)	14.40 (2.30)	12.94 (2.49)	n.s.	13.75 (2.12)	12.13 (2.70)	n.s.
Parental level of education (years)	12.60 (2.14)	12.13 (3.00)	n.s.	13.93 (1.84)	10.56 (3.02)	0.02
Diagnosis: Schizophrenia / Schizoaffective / Schizofreniform	-	8 / 6 / 2	-	4 / 3 / 1	4 / 3 / 1	n.s.
Scan interval (weeks)	53.76 (5.09)	55.63 (6.11)	n.s.	57.27 (8.55)	54.00 (0.84)	n.s.
Age at onset of illness	-	25.49 (7.04)	-	25.84 (8.16)	25.14 (6.27)	n.s.
Antipsychotic type: olanzapine/risperidone/quetiapine	-	11/3/2	-	6/2/0	5/1/2	n.s.
Duration of psychosis before remission (years)	-	1.19 (1.87)	-	0.96 (1.26)	1.42 (2.41)	0.02
Dosage of antipsychotics in H-EQ	-	3.38 (2.39)	-	3.50 (2.00)	3.25 (2.87)	n.s.
H-EQ taken during interval corrected for interval duration	-	856.55 (863.85)	-	547.37 (548.28)	1156.73 (1039.22)	0.005
Drugs/alcohol abuse or dependency ever before T0 (no/yes)	19/1	8/8	n.s.	4/4	4/4	n.s.
Drugs/alcohol abuse/dependency at T0 (no/yes)	17/3	14/2	0.03	7/1	7/1	n.s.
PANSS Positive scale	-	10.13 (2.66)	-	9.00 (1.60)	11.25 (3.11)	n.s.
PANSS Negative scale	-	12.75 (3.15)	-	13.13 (3.72)	12.38 (2.67)	n.s.
PANSS General scale	-	24.69 (5.34)	-	23.75 (2.61)	25.63 (7.23)	n.s.
GAF	-	61.31 (11.61)	-	58.13 (11.93)	64.50 (11.11)	n.s.
CGI	-	1.56 (0.63)	-	1.38 (0.52)	1.75 (0.71)	n.s.

Sd: standard deviation. H-EQ: Haloperidol Equivalents, n.s.: non significant, PANSS: Positive and Negative Syndrome Scale, GAF: Global Assessment of Functioning, CGI: Clinical Global Impression. [a] All differences for baseline characteristics were checked with the Pearson's Chi-Square test for nominal variables, ANOVA for normally distributed continuous variables and Mann-Whitney U test for not normally distributed continuous variables.

Table 2. Raw baseline brain volume, comparison between normal controls (NCS) and all patients (PTS) with schizophrenia and between patients who continued (PTS-C) and stopped antipsychotic medication (PTS-S)[a].

	Normal controls versus patients						Discontinuation of antipsychotics versus continuation in patients					
Brain structure	**Baseline volume NCS in ml (sd)**	**Baseline volume PTS in ml (sd)**	**b**	**SE[b]**	**t df=31**	**p**	**Baseline volume PTS-S in ml (sd)**	**Baseline volume PTS-C in ml (sd)**	**b**	**SE[b]**	**t df=31**	**p**
Total Brain	1 181.44 (127.39)	1 146.84 (139.89)	-3.16	15.32	-0.21	0.84	1 141.88 (133.94)	1 151.80 (154.73)	-19.08	18.31	-1.04	0.31
Cerebral Gray Matter	681.49 (60.04)	657.41 (79.91)	-12.08	14.56	-0.83	0.41	654.65 (71.40)	660.17 (92.57)	-0.09	17.40	-0.01	0.99
Cerebral White Matter	499.95 (81.16)	489.43 (64.30)	3.91	12.19	0.32	0.75	487.23 (65.39)	491.64 (67.63)	-8.77	14.57	-0.60	0.55
Lateral Ventricles	15.67 (12.43)	18.10 (8.06)	2.35	3.66	0.64	0.53	16.15 (8.69)	20.04 (13.33)	1.39	4.38	0.32	0.75
Third Ventricle	0.65 (0.28)	0.99 (0.53)	0.43	0.14	3.05	<0.01	1.04 (0.61)	0.93 (0.48)	-0.17	0.17	-1.00	0.33
Cerebellum	148.07 (13.52)	147.52 (18.69)	5.92	4.58	1.29	0.21	151.18 (19.53)	143.86 (18.35)	-8.96	5.47	-1.64	0.11
N. Accumbens	2.09 (0.45)	2.01 (0.45)	0.07	0.16	0.46	0.65	2.10 (0.55)	1.92 (0.32)	-0.20	0.19	-1.07	0.29
N. Caudatus	7.92 (1.10)	7.60 (0.94)	-0.08	0.35	-0.24	0.81	7.65 (1.07)	7.55 (0.86)	-0.23	0.41	-0.55	0.59
Putamen	9.11 (0.73)	9.61 (1.60)	1.41	0.31	4.61	<0.01	10.32 (1.40)	8.90 (1.54)	-1.49	0.37	-4.07	<0.01

Sd: standard deviation, SE: standard error, p: p-value, ml: milliliter, df: degrees of freedom. [a] Difference between groups expressed as unstandardised regression coefficients b ± SE. [b] Corrected for gender, age and intracranial volume, in which b represents the corrected volume difference in milliliters.

Table 3. Raw change in brain volume over one year, comparison between all patients with schizophrenia and normal controls and between patients who continued (PTS-C) and stopped antipsychotic medication (PTS-S)[a].

	Normal controls versus patients						Discontinuation of antipsychotics versus continuation in patients					
Brain structure	**Change NCS in ml (sd)**	**Change PTS in ml (sd)**	**b**	**SE(b)**	**t df=31**	**p**	**Change PTS-S in ml (sd)**	**Change PTS-C in ml (sd)**	**b**	**SE(b)**	**t df=31**	**p**
Total Brain	7.98 (12.15)	5.77 (17.75)	0.12	7.12	0.00	0.99	9.73 (19.8)	1.80 (15.70)	-10.13	8.51	-0.26	0.24
Cerebral Gray Matter	7.35 (19.72)	-7.17 (13.92)	-16.02	7.50	-2.14	0.04	-9.73 (14.6)	-4.61 (13.63)	3.97	8.95	0.44	0.66
Cerebral White Matter	0.63 (17.58)	12.94 (17.27)	18.05	7.32	2.46	0.02	19.46 (15.2)	6.41 (17.67)	-12.74	8.75	-1.46	0.16
Lateral Ventricles	0.07 (1.05)	-0.11 (0.90)	-0.43	0.43	-1.00	0.33	-0.38 (0.71)	0.16 (1.04)	0.55	0.52	1.07	0.30
Third Ventricle	0.00 (0.08)	-0.01 (0.10)	-0.05	0.04	-1.46	0.15	-0.06 (0.07)	0.03 (0.12)	0.08	0.04	1.88	0.07
Cerebellum	1.05 (2.89)	0.44 (2.70)	0.66	1.17	0.57	0.58	1.68 (2.2)	-0.80 (2.70)	-2.67	1.40	-1.91	0.07
N. Accumbens	0.05 (0.14)	0.01 (0.14)	-0.12	0.06	-2.07	0.05	-0.07 (0.11)	0.08 (0.13)	0.14	0.07	2.12	0.04
N. Caudatus	0.04 (0.21)	-0.04 (0.21)	-0.19	0.09	-2.23	0.03	-0.13 (0.22)	0.06 (0.15)	0.19	0.10	1.89	0.07
Putamen	-0.17 (0.37)	0.28 (0.65)	0.02	0.17	0.13	0.89	-0.11 (0.27)	0.67 (0.70)	0.77	0.21	3.72	<0.01

Sd: standard deviation, SE: standard error, p: p-value, ml: milliliter, df: degrees of freedom. [a] Difference between groups expressed as unstandardised regression coefficients b ± SE. [b] Corrected for gender, age and intracranial volume, in which b represents the corrected volume difference in milliliters.

Medication effect

The two patient groups did not differ significantly on any of the volumes at baseline except for putamen volume (**Table 2**, b=-1.49, 95%CI (-2.23, -0.74), discontinuation group: range (8.52, 13.12), median=10.07, continuation group: range (6.75, 11.08), median=8.88).

Figure 1. One year (raw) volume change in controls and patients.

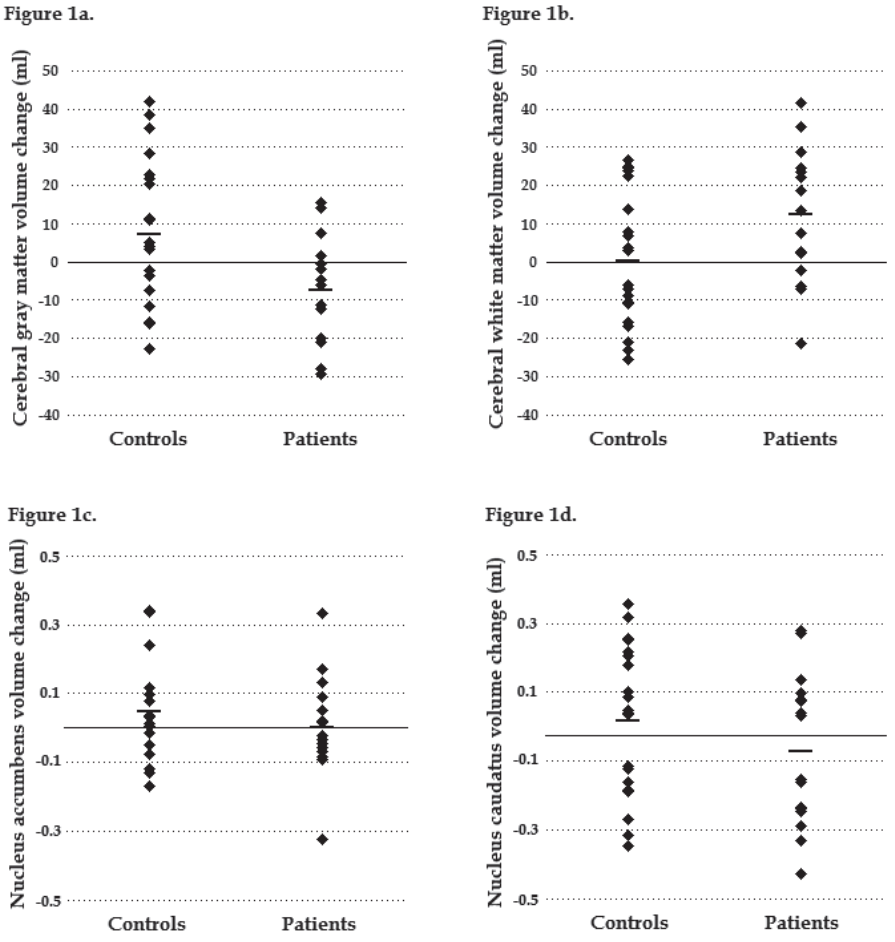
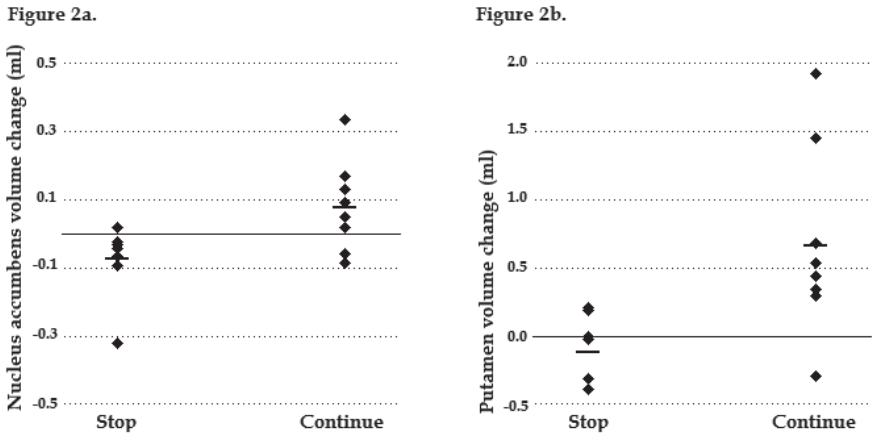


Figure 2. One year (raw) nucleus accumbens (2a) and putamen (2b) volume change in patients who either stopped or continued antipsychotic treatment before a second MRI scan. Note the differences in range of the y-axis.



Over time, a decrease in NA and putamen volume was found in patients who discontinued medication, while increases were found in patients who continued their antipsychotics (**Table 3**, **Figure 2a** and **2b**, NA: b=0.14, 95%CI (0.01, 0.28), discontinuation group: range (-0.32, 0.02), median=-0.04, continuation group: range (-0.09, 0.33), median=-0.07, putamen: b=0.77, 95%CI (0.35, 1.20), discontinuation group: range (-0.53, 0.21), median= -0.03, continuation group: range (-0.29, 1.93), median=0.49). Correction for TB volume did not change these findings. However, after exclusion of the largest outlier in the patients the difference in NA change was no longer significant (p=0.12).

Discussion

This study examined the effect of discontinuation of atypical antipsychotic medication on brain volume change during a one-year interval in remitted and stable first-episode schizophrenia patients. We replicated earlier findings of excessive decrease in cerebral gray matter volume in patients relative to controls. In addition, our results suggest that discontinuation or continuation of atypical antipsychotics does not influence GM volume change in patients. If anything, cerebral GM volume decrease over time seemed more pronounced in patients who dis-

continued than in patients who continued antipsychotic medication, although this difference was not significant. Thus, our results suggest that the excessive reduction of GM volume occurs irrespective of atypical antipsychotic treatment continuation or discontinuation. This might indicate that the excessive loss of GM volume in schizophrenia patients cannot be explained by the intake of atypical antipsychotic medication.

To date, only a limited number of longitudinal studies has been done that looked directly at the influence of atypical antipsychotic treatment on brain volume in a controlled manner. This is especially the case if one excludes studies in which pre-study treatment was unknown, consisted of both atypical and typical antipsychotics, or where patients were analyzed together independently of being antipsychotic-naïve, or not, prior to the study[9,11,12,14,21,29,43,45,46,61]. Findings so far, indicate that GM volume increases after starting atypical antipsychotic treatment in antipsychotic-naïve patients[3,13,23,30,32,50], but also after changing from typical to atypical antipsychotic treatment[47]. One randomised study identified GM loss after one year of treatment with haloperidol compared to olanzapine[43]. Unfortunately, it was not mentioned what type of antipsychotics (typical/atypical) the patients used before the start of the study medication. Together, these findings suggest that atypical antipsychotics might prevent the loss of GM tissue. Indeed, in a large longitudinal study in a sample of both first-episode as well as chronically ill patients cumulative intake of atypical medication was associated with less loss of GM tissue[26].

That GM tissue loss is most likely associated with the effects of the illness and is not a consequence of (atypical) antipsychotic medication intake, is also supported by evidence that cerebral GM deficits in patients appear to be present before the start with antipsychotic medication[8,31,49,62] or even before the start of the first symptoms[32]. However, some studies report no differences between normal controls and medication naïve patients[2,24,33,47,52].

In contrast to our findings in humans, a randomised study in Macaque monkeys found that chronic treatment with atypical (N=6, for 1.2 years) and typical (N=6, for 2.2 years) antipsychotics resulted in a reduction of parietal GM volume, compared with placebo [15]. However, it is difficult to extrapolate these regional post-mortem animal findings to those occurring in vivo in the brains of patients with schizophrenia.

Antipsychotics may exert their effect in focal areas of the brain[48]. Here, we focused on the basal ganglia. At baseline all patients were on atypical antipsychotic medication. Patients discontinuing atypical antipsychotics seemed to decrease in NA and putamen volume over time. This is of particular interest since putamen volume appeared to increase in patients as compared to controls at baseline. Moreover, the two patient groups did not differ on baseline brain volumes, except for the putamen, which was larger in patients who discontinued their antipsychotic regimen as compared to patients who continued their antipsychotic medication. Outcome of the illness might be a possible explanation for this as Buchsbaum identified a larger putamen in patients with good outcome schizophrenia in comparison to those with a poor outcome and healthy controls[1]. Indeed, the patients who stopped tolerated tapering and were able to not use medication without experiencing a relapse for a certain period of time. Whether this would have been the case in those that continued their antipsychotics is unknown.

It might be that the increase in putamen volume at baseline in patients relative to controls is an effect of taking atypical antipsychotic medication (although this cannot be tested in our study, but see[22]). If this were the case our findings suggest that discontinuation reverses the effects of atypical medication, at least in the putamen and possibly to some extend in the NA.

Indeed, starting atypical antipsychotics in antipsychotic-naïve patients resulted in volume increases in the NC[44], NA[44] and putamen[22] compared to baseline[22] or compared to controls[44], although some studies found no volume changes[22,28,44]. In contrast, starting atypical antipsychotics after discontinuing typical antipsychotic medication has been associated with caudate[6,20,53] and putamen volume reductions[40], while other studies found no caudate[40] or putamen volume change[20]. These data implicate that the consequences of atypical medication are dependent on the state of the brain, being either medication-naïve or being on typical medication.

Suggestive evidence was found for an excessive increase over time in cerebral WM volume in patients as compared to controls, which, in patients, did not appear to be influenced by either continuation or discontinuation of antipsychotics. Cerebral WM volume in antipsychotic-naïve patients was reported to be similar to normal controls[2,31,33,47,52] (but see for decreased WM[8]). Although initiation of atypical antipsychotics in antipsychotic-naïve[47] or antipsychotic-free schizophre-

nia[7] did not result in WM volume changes, WM volume did decrease significantly in haloperidol-treated patients who were changed to clozapine treatment[47].

Strengths and limitations

Studies like this one are complicated to carry out, resulting in a small number of included patients. Consequently, type II errors cannot be ruled out. To our knowledge this is the first MRI study that compared brain volume change between patients who discontinued or continued atypical antipsychotic medication. Therefore, we are convinced that, despite the small sample sise it is important data to present. In addition, this serves as the rationale for not applying a correction for multiple testing. The majority of our findings would not have survived such a correction.

Half of the patients in this study were randomised to continuation (n=4) or discontinuation (n=4). In the continuation group the remaining 4 patients chose to continue their medication because of fear of relapse which is a sign of good insight. In contrast, in the discontinuation group 4 patients decided to stop their antipsychotic treatment despite risk of relapse. Since insight is a predictor of good outcome[16], the continuation group might have consisted of patients with a better outcome than the discontinuation group. However, all patients were clinically stable enough to allow for discontinuation at inclusion in the study.

In this study the patients used olanzapine, risperidone or quetiapine which are grouped among the atypical antipsychotics[41] and have less binding potential for the dopamine 2 (D2) receptor than typical antipsychotics[64]. However, risperidone is known to have a more firm grip on the D2 receptor than the other second generation antipsychotics[5,51,59]. This differential effect of binding potential for the three antipsychotics used in this study might have diluted the volume changes in the discontinuation group in the basal ganglia structures.

The exclusion of more severe patients (at risk or history of suicide, abandonment of previous treatment) and the inclusion of patients with, a priori, better prognosis than schizophrenia such as schizoaffective disorder and schizophreniform disorder, made this sample one with a better prognosis than the general population of first psychotic episodes, as indicated by the values of the PANSS, the GAF and the CGI at baseline. This is a consequence of the design of the study as guidelines offer the psychiatrist the possibility to discontinue antipsychotic medication only in remitted and stable first-episode schizophrenia patients[41].

Conclusions

We confirmed earlier findings of gray matter volume decrements in patients with schizophrenia in comparison to normal controls. Our main conclusion is that the excessive cerebral gray matter volume decrease found in patients with schizophrenia is unlikely to be explained by atypical antipsychotic treatment. However, the increase in putamen volume at baseline appears to be (at least partly) a medication effect as putamen (and possibly also nucleus accumbens) volume decreased in patients after discontinuation with atypical antipsychotics

Acknowledgements

We want to thank the Netherlands Organization for Health Research and Development (ZonMw, No. 2100.0057) and Eli Lilly and Company® (H6U-UT-LRAC) for their unrestricted financial support.

References

1. Buchsbaum M.S., Shihabuddin L., Brickman A.M. et al. Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophr Res* 2003;64(1):53-62.
2. Cahn W., Hulshoff Pol H.E., Bongers M. et al. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. *Br J Psychiatry Suppl* 2002;43:s66-s72.
3. Cahn W., Hulshoff Pol H.E., Lems E.B. et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry* 2002;59(11):1002-1010.
4. Cahn W., van Haren N.E., Hulshoff Pol H.E. et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006;189:381-382.
5. Catafau A.M., Penengo M.M., Nucci G. et al. Pharmacokinetics and time-course of D(2) receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients. *J Psychopharmacol* 2008;22(8):882-894.
6. Chakos M.H., Lieberman J.A., Alvir J. et al. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995;345(8947):456-457.
7. Christensen J., Holcomb J. and Garver D.L. State-related changes in cerebral white matter may underlie psychosis exacerbation. *Psychiatry Res* 2004;130(1):71-78.
8. Chua S.E., Cheung C., Cheung V. et al. Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. *Schizophr Res* 2007;89(1-3):12-21.
9. Chua S.E., Deng Y., Chen E.Y. et al. Early striatal hypertrophy in first-episode psychosis within 3 weeks of initiating antipsychotic drug treatment. *Psychol Med* 2009;39(5):793-800.
10. Corson P.W., Nopoulos P., Miller D.D. et al. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. *Am J Psychiatry* 1999;156(8):1200-1204.
11. Crespo-Facorro B., Roiz-Santianez R., Perez-Iglesias R. et al. Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(8):1936-1943.
12. Degreef G., Ashtari M., Wu H.W. et al. Follow up MRI study in first episode schizophrenia. *Schizophr Res* 1991;5(3):204-206.
13. DeLisi L.E., Sakuma M., Tew W. et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 1997;74(3):129-140.
14. Deng M.Y., McAlonan G.M., Cheung C. et al. A naturalistic study of grey matter volume increase after early treatment in anti-psychotic naive, newly diagnosed schizophrenia. *Psychopharmacology (Berl)* 2009;206(3):437-446.
15. Dorph-Petersen K.A., Pierri J.N., Perel J.M. et al. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology* 2005;30(9):1649-1661.

16. Drake R.J. Insight into illness: impact on diagnosis and outcome of nonaffective psychosis. *Curr Psychiatry Rep* 2008;10(3):210-216.
17. Ebdrup B.H., Glenthoj B., Rasmussen H. et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci* 2010;35(2):95-104.
18. Endicott J., Spitzer R.L., Fleiss J.L. et al. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33(6):766-771.
19. First M.B., Gibbon M., Spitzer R.L. et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Version (SCID-I/P, Version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute, 1996
20. Frazier J.A., Giedd J.N., Kaysen D. et al. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 1996;153(4):564-566.
21. Garver D.L., Holcomb J.A. and Christensen J.D. Cerebral cortical gray expansion associated with two second-generation antipsychotics. *Biol Psychiatry* 2005;58(1):62-66.
22. Glenthoj A., Glenthoj B.Y., Mackeprang T. et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. *Psychiatry Res* 2007;154(3):199-208.
23. Gur R.E., Cowell P., Turetsky B.I. et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 1998;55(2):145-152.
24. Gur R.E., Maany V., Mozley P.D. et al. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatry* 1998;155(12):1711-1717.
25. Guy W. Clinical Global Impressions: ECDEU Assessment Manual for Psychopharmacology, Revised. Bethesda Md: National Institute of Mental Health, 1976
26. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 2008;63(1):106-113.
27. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Focal Gray Matter Changes in Schizophrenia across the Course of the Illness: A 5-Year Follow-Up Study. *Neuropsychopharmacology* 2007;2057-2066.
28. Heitmiller D.R., Nopoulos P.C. and Andreasen N.C. Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. *Schizophr Res* 2004;66(2-3):137-142.
29. Ho B.C., Andreasen N.C., Nopoulos P. et al. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry* 2003;60(6):585-594.
30. Hulshoff Pol H.E. and Kahn R.S. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34(2):354-366.

31. Jayakumar P.N., Venkatasubramanian G., Gangadhar B.N. et al. Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naive schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29(4):587-591.
32. Job D.E., Whalley H.C., Johnstone E.C. et al. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 2005;25(4):1023-1030.
33. John J.P., Burgess P.W., Yashavantha B.S. et al. Differential relationship of frontal pole and whole brain volumetric measures with age in neuroleptic-naive schizophrenia and healthy subjects. *Schizophr Res* 2009;109(1-3):148-158.
34. Jones S.H., Thornicroft G., Coffey M. et al. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry* 1995;166(5):654-659.
35. Kane J.M., Leucht S., Carpenter D. et al. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry* 2003;64 Suppl 12:5-19.
36. Kay S.R., Fiszbein A. and Opler L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
37. Keshavan M.S., Bagwell W.W., Haas G.L. et al. Changes in caudate volume with neuroleptic treatment. *Lancet* 1994;344(8934):1434.
38. Keshavan M.S., Rosenberg D., Sweeney J.A. et al. Decreased caudate volume in neuroleptic-naive psychotic patients. *Am J Psychiatry* 1998;155(6):774-778.
39. Kuipers E., Kendall T., Antoniou J. et al. Schizophrenia (update). National Clinical Practice Guideline Number 82. Update, 1-399. 2009. London, National Collaborating Centre for Mental Health. National Clinical Practice Guideline.
40. Lang D.J., Kopala L.C., Vandorpe R.A. et al. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *Am J Psychiatry* 2004;161(10):1829-1836.
41. Lehman A.F., Lieberman J.A., Dixon L.B. et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161(2 Suppl):23.
42. Lieberman J., Chakos M., Wu H. et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry* 2001;49(6):487-499.
43. Lieberman J.A., Tollefson G.D., Charles C. et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 2005;62(4):361-370.
44. Massana G., Salgado-Pineda P., Junque C. et al. Volume changes in gray matter in first-episode neuroleptic-naive schizophrenic patients treated with risperidone. *J Clin Psychopharmacol* 2005;25(2):111-117.
45. McClure R.K., Carew K., Greeter S. et al. Absence of regional brain volume change in schizophrenia associated with short-term atypical antipsychotic treatment. *Schizophr Res* 2008;98(1-3):29-39.
46. Milev P., Ho B.C., Arndt S. et al. Initial magnetic resonance imaging volumetric brain measurements and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. *Biol Psychiatry* 2003;54(6):608-615.

47. Molina V., Reig S., Sanz J. et al. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr Res* 2005;80(1):61-71.
48. Navari S. and Dazzan P. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med* 2009;39(11):1763-1777.
49. Ohrmann P., Siegmund A., Suslow T. et al. Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. *J Psychiatr Res* 2007;41(8):625-634.
50. Pantelis C., Yucel M., Wood S.J. et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005;31(3):672-696.
51. Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. *J Clin Psychiatry* 1996;57 Suppl 11:4-11.
52. Salgado-Pineda P., Baeza I., Perez-Gomez M. et al. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. *Neuroimage* 2003;19(2 Pt 1):365-375.
53. Scheepers F.E., de Wied C.C., Hulshoff Pol H.E. et al. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology* 2001;24(1):47-54.
54. Schnack H.G., Hulshoff Pol H.E., Baare W.F. et al. Automated separation of gray and white matter from MR images of the human brain. *Neuroimage* 2001;13(1):230-237.
55. Schnack H.G., Hulshoff H.E., Baare W.F. et al. Automatic segmentation of the ventricular system from MR images of the human brain. *Neuroimage* 2001;14(1 Pt 1):95-104.
56. Sled J.G., Zijdenbos A.P. and Evans A.C. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 1998;17(1):87-97.
57. Staal W.G., Hulshoff Pol H.E., Schnack H.G. et al. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *Am J Psychiatry* 2000;157(3):416-421.
58. Talairach J. and Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Propositional System: An Approach to Cerebral Imaging. Stuttgart: Thieme, 1988:1-122.
59. Tauscher J., Kufferle B., Asenbaum S. et al. Striatal dopamine-2 receptor occupancy as measured with [123I]iodobenzamide and SPECT predicted the occurrence of EPS in patients treated with atypical antipsychotics and haloperidol. *Psychopharmacology (Berl)* 2002;162(1):42-49.
60. Tauscher-Wisniewski S., Tauscher J., Christensen B.K. et al. Volumetric MRI measurement of caudate nuclei in antipsychotic-naive patients suffering from a first episode of psychosis. *J Psychiatr Res* 2005;39(4):365-370.
61. Tauscher-Wisniewski S., Tauscher J., Logan J. et al. Caudate volume changes in first episode psychosis parallel the effects of normal aging: a 5-year follow-up study. *Schizophr Res* 2002;58(2-3):185-188.

62. Venkatasubramanian G., Jayakumar P.N., Gangadhar B.N. et al. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. *Psychiatry Res* 2008;164(3):215-222.
63. Wright I.C., Rabe-Hesketh S., Woodruff P.W. et al. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 2000;157(1):16-25.
64. Zipursky R.B., Meyer J.H. and Verhoeff N.P. PET and SPECT imaging in psychiatric disorders. *Can J Psychiatry* 2007;52(3):146-157.

Chapter 4

Resolution of side-effects after discontinuation with antipsychotic treatment: a small observational study

Geartsje Boonstra

Unpublished results

Abstract

Although the relapse rate, even after a single episode of psychosis in schizophrenia, necessitates extreme care for relapse after discontinuation, many patients wish to stop their antipsychotic treatment because of the burden of side-effects. The reversibility of side-effects after discontinuation has not often been investigated prospectively in comparison to continuation of antipsychotic treatment. Two groups of first-episode schizophrenia patients, each with 8 subjects, were followed for a year. Both groups were treated with atypical antipsychotics at baseline. One group subsequently continued their medication and the other group discontinued. At baseline and at follow-up the Barnes akathisia rating scale (BARS), the abnormal involuntary movement scale (AIMS), the unified Parkinson disease rating scale (UPDRS) and the Approaches to Schizophrenia rating scale (ASC-self report) were taken off, and body mass index (BMI) was measured. We found a significant and substantial decrease in BMI in patients that withdrew from their antipsychotic regiment in comparison to patients that continued. We found no differences in change over time between groups in BARS, AIMS, UPDRS and ASC-SR scores. It seems that weight gain is, at least partially, reversible after discontinuation of antipsychotic treatment.

Introduction

In schizophrenia antipsychotic treatment is necessary to overcome or prevent psychosis, certainly after more episodes[11,27], and most probably also after one psychosis[5,7,12,16,18,31]. However, in clinical practice patients often wish to discontinue their antipsychotic regimen, sometimes because of lack of insight in the recurrent nature of their disease and sometimes because of side-effects.
These side-effects are common, sometimes dangerous and mostly unpleasant. Among the most troublesome effects are the neurological: extrapyramidal symptoms including Parkinsonism, akathisia, dystonia and tardive dyskinesia[3]. Although less frequent and often less intense than with typical antipsychotics, atypical antipsychotics do induce extrapyramidal symptoms[35,43], but see Miller[32]. A degree of extrapyramidal symptoms is present in almost all patients treated with antipsychotics. The 5-year cumulative incidence of tardive dyskinesia is estimated at 25%[19]. Most induced extra dyramidal side-effects appear to be revers-

ible upon discontinuation, although tardive dyskinesia can (partially) persist after discontinuation[13]. Atypical antipsychotic drugs induce more weight gain than typical antipsychotic drugs[14,38,45]. Weight gain leads to increases in triglycerides and cholesterol, and may induce insulin resistance and diabetes[1,28]. The weight gain induce by atypical antipsychotics seems to be associated with dosage[25,34,39,41]. The combination of weight gain, hypercholesterolaemia and diabetes, as well as a risk of undertreatment, increases the cardiovascular risk in schizophrenia patients[36,42]. Other side-effects are drowsiness, dizziness, sedation, constipation, tachycardia and sexual side-effects[24,35], this list is not exhaustive.

Careful discontinuation, under frequent monitoring of early relapse signs, of antipsychotic medication in first-episode patients can be considered since approximately 15% of first-episode schizophrenia patients will never experience another psychotic episode after withdrawal of medication[37,44]. However, it would be useful to know what the actual gain in terms of reversal of side-effects might be, before venturing discontinuation and risking a relapse with all its possible concomitant loss of functioning. This study aimed to compare the change in side-effects over one year between first-episode schizophrenia patients that continued their atypical antipsychotic medication and patients that discontinued it.

Methods:

Subjects

After complete description of the study, written informed consent was obtained from all participants. The Medical Ethics Review Board of the University Medical Centre Utrecht approved the study. Sixteen patients were included. They were aged 16 to 55 years and diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder as assessed with the Structured Clinical Interview for DSM-IV Axis-I disorders (First, 1996). They were treated in a tertiary or secondary psychiatric centre in The Netherlands. Furthermore, only clinically remitted and stable first-episode patients with scores of three or less over the previous year on each core psychosis item (delusions, conceptual disorganisation, hallucinatory behaviour and suspiciousness or persecution) of the Positive and Negative Syndrome Scale (PANSS) were included[20,21]. Exclusion criteria were medication non-compliance during the past year, use of mood-stabilisers, severe neurological illness, current suicidal ideation, or a history of a serious suicide

attempt. Duration of remission, suicidal ideation and compliance were assessed by interviewing patients and their treating physician. To assess the influence of medication discontinuation on side-effects the included patients were divided into two subgroups: patients who tapered (in 6-12 weeks) and discontinued antipsychotic treatment (N=8) and patients who continued antipsychotics (N=8) between baseline and one year follow-up. A proportion of the participating patients (N=10) were selected from a randomised trial investigating the effect of discontinuation versus continuation of antipsychotics on relapse risk (First author, Chapter 1). Half of the patients in this study were originally randomised to continuation (N=4) or discontinuation (N=4) and remained in that group. Two patients in the discontinuation group were originally randomised to continuation but tapered and discontinued after 6 months in the study. The remainder of the patients (N=6) chose to continue or discontinue their antipsychotics. All subjects participating in this study were on atypical antipsychotic medication at inclusion. The type of drug had been determined by the treating clinician, and not the researcher, and remained the responsibility of the treating clinician during the study. In retrospect, none of the patients changed their type of antipsychotic medication during the current study. During follow-up, patients were evaluated every two months by a trained researcher with extra visits in case of impending relapse. Each visit the medication status and the weight was assessed. Weight was measured with the same weighing scale (electronic), with shoes and jacket off, and clothes on. At baseline and every six months, we measured extrapyramidal symptoms, dystonia and akathisia with the Unified Parkinson Disease Rating Scale (UPDRS)[30], the Barnes Akathisia Rating Scale (BARS)[4] and the Abnormal Involuntary Movement Scale (AIMS)[15,26,33]. Furthermore we used the Approaches to Schizophrenia Communication Self Report (ASC-SR) tool[9] to assess other side-effects frequently associated with the use of antipsychotics. This latter questionnaire is used in clinical practice to facilitate the discussion about side-effects and contains 22 items. We scored 1 for report of problems on a specific item, and 0 for no problems, the maximum score thus being 22. Items measured with this tool: change in energy, slowness or problems with movement, restlessness or feeling the need to move, muscle tightness, tremor, muscle contractions, dizziness when rising up or fainting, nausea, faster heart rate, hyper salivation, weight change, drowsiness, sleeping to long, dry mouth, blurred vision, constipation, difficulty with urinating, memory problems, concentration problems, worries about sex life and (only for women) changes in menstruation or breasts. Haloperidol dose-

Table 1. Baseline characteristics of patients who were medication-free at follow-up (OFF) and patients on atypical antipsychotic medication at follow-up (ON)[a].

Variables, N or mean (sd)	PTS OFF	PTS ON	p
Gender, male/female	6/2	6/2	n.s.
Age, years	27.97 (8.24)	29.56 (5.72)	n.s.
Diagnosis: Schizophrenia / Schizoaffective / Schizofreniform	4 / 3 / 1	4 / 3 / 1	n.s.
Age at onset of illness	25.84 (8.16)	25.14 (6.27)	n.s.
Antipsychotic type: olanzapine/risperidone/quetiapine	6/2/0	5/1/2	n.s.
Duration of psychosis before remission (years)	0.96 (1.26)	1.42 (2.41)	0.02
Dosage of antipsychotics in H-EQ at baseline	3.50 (2.00)	3.25 (2.87)	n.s.
H-EQ taken during interval corrected for interval duration	547.37 (548.28)	1156.73 (1039.22)	0.005
Weight (kg)	86.75 (17.15)	86.70 (16.26)	n.s.
Length (cm)	1.81 (0.11)	1.82 (0.10)	n.s.
Body mass index	26.47 (4.37)	26.18 (4.12)	n.s.
BARS	0	.13 (.35)	n.s.
AIMS	0	0	-
UPDRS	8.50 (4.59)	5.38 (3.34)	n.s.
ASC-SR	5.63 (2.67)	4.63 (2.88)	n.s.
PANSS Positive scale	9.00 (1.60)	11.25 (3.11)	n.s.
PANSS Negative scale	13.13 (3.72)	12.38 (2.67)	n.s.
PANSS General scale	23.75 (2.61)	25.63 (7.23)	n.s.

Sd: standard deviation, H-EQ: Haloperidol Equivalents, n.s.: non significant, BARS: Barnes akathisia rating scale, AIMS: abnormal involuntary movement scale, UPDRS: unified Parkinson disease rating scale, ASC-SR: Approaches to Schizophrenia Communication tool – Self Report, PANSS: Positive and Negative Syndrome Scale. [a] All differences for baseline characteristics were checked with the Pearson's Chi-Square test for nominal variables, ANOVA for normally distributed continuous variables and Mann-Whitney U test for not normally distributed continuous variables.

equivalences (HEQ) for quantification of antipsychotic exposure were calculated using patient charts as follows (ratio haloperidol: other antipsychotic): risperidone 1:1, olanzapine 1:2.5, quetiapine 1:100[17].

Data-analysis
The significance of differences in change over time and baseline measurement of Body Mass Index (BMI: weight (kg)/(length (m) x length (m)), BARS total score, AIMS total score, UPDRS total score and ASC-SR total score was calculated with the Student t-test for independent samples.

Results:

Baseline characteristics were comparable between patient groups except for cumulative haloperidol equivalents used in the study interval which were significantly lower for patients that discontinued than for patients that continued (See **Table 1**).

We found a significant and substantial decrease in body mass index (BMI) in patients that discontinued their antipsychotics in comparison to patients that continued (p=0.003). We found no other differences in change over time in side-effects between patients that continued their antipsychotics and patients that discontinued these medications (See **Table 2**).

Table 2. Difference in one year change in side-effects between first-episode schizophrenia patients that either continued or discontinued their antipsychotic medication.

Variables (mean, sd)	Change continuation group (N=8)	Change withdrawal group (N=8)	t (df)	p	95% CI
Body mass index	0.04 (0.86)	-1.93 (1.24)	-3.7 (14)	<0.01[a]	-3.12, -0.82
BARS	0	0	-	-	-
AIMS	0	0.13 (0.35)	1.0 (14)	0.35	-0.17,0 .42
UPDRS	-2.00 (3.16)	-2.00 (3.74)	0	1.0	-3.72, 3.72
ASC-SR	-0.57 (3.82)	-0.57 (5.00)	0	1.0	-5.18, 5.18

Sd: standard deviation, n: number of subjects, df: degrees of freedom, BMI: body mass index, BARS: Barnes akathisia rating scale, AIMS: abnormal involuntary movement scale, UPDRS: unified Parkinson disease rating scale, ASC-SR: Approaches to Schizophrenia Communication tool - Self Rating. [a] The difference in body mass index change over time was significant (p=0.003).

Discussion

The decrease in body mass index that patients experienced after withdrawal differed significantly and substantially from that in patients that continued their antipsychotic regimen. However, no differences in change in extrapyramidal side-effects and akathisia over time were detected between patients that continued and discontinued antipsychotic treatment.

Comparison to literature

A substantial increase in weight (±10kg) after initiation of antipsychotic therapy has frequently been reported[14,34,38,45]. Weight gain during antipsychotic treatment is difficult to fight; either exercise[10] with of without medication[29] is needed. However, exercise is thwarted by negative symptoms in schizophrenia. Furthermore, extra medication intake is mostly not appreciated by patients with schizophrenia, and on top of that, new medications may involve new unwanted side-effects. Another strategy might be dose reduction[25,34,39,41] or switching to typical antipsychotic medication[2] or aripiprazole since atypical antipsychotic medication leads to more weight gain than does typical medication[14,38,45] and aripiprazole may lead to weight loss[40]. An alternative method to decrease in weight seems to be to dis-

continue antipsychotic medication, as is shown in this study. However, a dangerous concomitant relapse risk is involved[5,7,11,12,16,18,31].

In medication-naïve schizophrenia patients there is a baseline prevalence of EPS[23]. This, in combination with the low dosages (and thus lower percentage of dopamine 2 receptor binding), might be the reason that the level of extrapyramidal symptoms (EPS) was not found to be different between discontinuing and continuing patients. Furthermore, atypical antipsychotics have a less rigid binding to dopamine receptors than typical antipsychotics, and medication particles are bound to the dopamine receptors for a smaller percentage of the time, thereby decreasing the risk on EPS. Also, it might be that EPS was not detectable with the questionnaires we used since these questionnaires might be not sensitive enough. There are physical instruments available to measure EPS objectively, it might be that they prove to be more sensitive than questionnaires in the future[6,8,22].

Limitations

The number of patients included in this study is small. This increases the risk of both type I and type II errors. This is the reason we included 95% confidence intervals in **Table 2**. As can be seen from these, the difference BMI change appears to be a robust finding.

The study is observational, it cannot be excluded that a selection bias occurred in forming the groups, and this might have influenced the results. As can be seen from **Table 1**, the baseline characteristics were not different between patients except for duration of psychosis. Since the BMI was comparable at baseline we feel that this has not influenced our results.

The ASC-SR questionnaire is not validated. Therefore it could be that the results are not trustworthy or not a reflection of true side-effects. Also, we asked the patients per item whether they were troubled by it, instead of making the patient fill in the questionnaire themselves. However, we do not feel this change in procedure is a problem since it was the same for all patients.

Conclusion

An advantage of discontinuation of atypical antipsychotics may be a loss of weight. Other advantages were not objectified in this small observational study. A disadvantage of discontinuation is the risk of relapse; this may not outweigh the advantages.

References

1. Ananth J., Parameswaran S. and Gunatilake S. Side effects of atypical antipsychotic drugs. *Curr Pharm Des* 2004;10(18):2219-2229.
2. Andersen T.H., Bech P. and Larsen N.E. Switching patients from olanzapine or risperidone to a combination treatment using perphenazine plus buspirone: evaluation of antipsychotic efficacy and side-effects, including extrapyramidal effects and weight loss. *Nord J Psychiatry* 2005;59(3):205-208.
3. Arana G.W. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry* 2000;61 Suppl 8:5-11.
4. Barnes T.R. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989;154:672-676.
5. Boonstra G., Burger H., Grobbee D.E. et al. Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: Results from an aborted randomised trial. *International Journal of Psychiatry in Clinical Practice* 2010;E-Pub online publication.
6. Caligiuri M.P., Teulings H.L., Filoteo J.V. et al. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Hum Mov Sci* 2006;25(4-5):510-522.
7. Chen E.Y., Hui C.L., Lam M.M. et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010;341:c4024.
8. Chung K.A., Lobb B.M., Nutt J.G. et al. Objective measurement of dyskinesia in Parkinson's disease using a force plate. *Mov Disord* 2010;25(5):602-608.
9. Dassori A.M., Miller A.L. and Weiden P.J. The Approaches to Schizophrenia Communication (ASC) Tool: Including the Patient Perspective in Treatment. *Disease Management and Health Outcomes* 2003;11(11):699-708.
10. Ganguli R. Behavioral therapy for weight loss in patients with schizophrenia. *J Clin Psychiatry* 2007;68 Suppl 4:19-25.
11. Gilbert P.L., Harris M.J., McAdams L.A. et al. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry* 1995;52(3):173-188.
12. Gitlin M., Nuechterlein K., Subotnik K.L. et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry* 2001;158(11):1835-1842.
13. Glazer W.M., Morgenstern H., Schooler N. et al. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. *Br J Psychiatry* 1990;157:585-592.
14. Green A.I., Lieberman J.A., Hamer R.M. et al. Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res* 2006;86(1-3):234-243.
15. Guy W. Abnormal Involuntary Movement Scale (AIMS). In: Psychopharmacology Research Branch N., editor. *ECDEU Assessment Manual for Psychopharmacology*, revised.Rockville, Maryland: National Institute of Mental Health, 1976:534-7.
16. Hogarty G.E. and Ulrich R.F. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiatr Res* 1998;32(3-4):243-250.

17. Kane J.M., Leucht S., Carpenter D. et al. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *J Clin Psychiatry* 2003;64 Suppl 12:5-19.
18. Kane J.M., Rifkin A., Quitkin F. et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 1982;39(1):70-73.
19. Kane J.M., Woerner M. and Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. *J Clin Psychopharmacol* 1988;8(4 Suppl):52S-56S.
20. Kay S.R., Fiszbein A. and Opler L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
21. Kay S.R., Opler L.A. and Lindenmayer J.P. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1988;23(1):99-110.
22. Koning J.P., Tenback D.E., Kahn R.S. et al. Instrument measurement of lingual force variability reflects tardive tongue dyskinesia. *J Med Eng Technol* 2010;34(1):71-77.
23. Koning J.P., Tenback D.E., van O.J. et al. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* 2010;36(4):723-731.
24. Lader M. Some adverse effects of antipsychotics: prevention and treatment. *J Clin Psychiatry* 1999;60 Suppl 12:18-21.
25. Lane H.Y., Chang Y.C., Cheng Y.C. et al. Effects of patient demographics, risperidone dosage, and clinical outcome on body weight in acutely exacerbated schizophrenia. *J Clin Psychiatry* 2003;64(3):316-320.
26. Lane R.D., Glazer W.M., Hansen T.E. et al. Assessment of tardive dyskinesia using the Abnormal Involuntary Movement Scale. *J Nerv Ment Dis* 1985;173(6):353-357.
27. Lehman A.F., Lieberman J.A., Dixon L.B. et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161(2 Suppl):23.
28. Lindenmayer J.P., Czobor P., Volavka J. et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry* 2003;160(2):290-296.
29. Maayan L., Vakhrusheva J. and Correll C.U. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010;35(7):1520-1530.
30. Martinez-Martin P., Gil-Nagel A., Gracia L.M. et al. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Mov Disord* 1994;9(1):76-83.
31. McCreadie R.G., Wiles D., Grant S. et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. *Acta Psychiatr Scand* 1989;80(6):597-602.
32. Miller D.D., Caroff S.N., Davis S.M. et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry* 2008;193(4):279-288.
33. Munetz M.R. and Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. *Hosp Community Psychiatry* 1988;39(11):1172-1177.
34. Perry P.J., Argo T.R., Carnahan R.M. et al. The association of weight gain and olanzapine plasma concentrations. *J Clin Psychopharmacol* 2005;25(3):250-254.

35. Potkin S.G., Gharabawi G.M., Greenspan A.J. et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophr Res* 2006;85(1-3):254-265.
36. Raedler T.J. Cardiovascular aspects of antipsychotics. *Curr Opin Psychiatry* 2010;23(6):574-581.
37. Ram R., Bromet E.J., Eaton W.W. et al. The natural course of schizophrenia: a review of first-admission studies. *Schizophr Bull* 1992;18(2):185-207.
38. Saddichha S., Manjunatha N., Ameen S. et al. Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in India: a randomized, double-blind, controlled, prospective study. *J Clin Psychiatry* 2007;68(11):1793-1798.
39. Sahoo S., Mishra B. and Akhtar S. Dose-dependent acute excessive weight gain and metabolic changes in a drug-naive patient on risperidone are reversible with discontinuation: a case report. *Br J Clin Pharmacol* 2007;64(5):715-716.
40. Schorr S.G., Slooff C.J., Postema R. et al. A 12-month follow-up study of treating overweight schizophrenic patients with aripiprazole. *Acta Psychiatr Scand* 2008;118(3):246-250.
41. Simpson M.M., Goetz R.R., Devlin M.J. et al. Weight gain and antipsychotic medication: differences between antipsychotic-free and treatment periods. *J Clin Psychiatry* 2001;62(9):694-700.
42. Stahl S.M., Mignon L. and Meyer J.M. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand* 2009;119(3):171-179.
43. Weiden P.J. EPS profiles: the atypical antipsychotics are not all the same. *J Psychiatr Pract* 2007;13(1):13-24.
44. Wiersma D., Nienhuis F.J., Slooff C.J. et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 1998;24(1):75-85.
45. Zipursky R.B., Gu H., Green A.I. et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. *Br J Psychiatry* 2005;187:537-543.

Chapter 5

Duration of untreated illness in schizophrenia is not associated with 5-year brain volume change

Geartsje Boonstra, Wiepke Cahn, Hugo G. Schnack, Tanca C. Minderhoud, Hilleke E. Hulshoff Pol, René S. Kahn, Neeltje E.M. van Haren.

Submitted and in revision

Abstract

Objectives: Evidence for an association between duration of untreated illness (DUI) with clinical and functional outcome or brain volume (change) in schizophrenia patients is inconclusive. We aimed to investigate the relationship between DUI, outcome and brain volume at illness onset or brain volume change during the first five years of the illness in first-episode patients.
Methods: Magnetic resonance images were acquired at baseline (T0) and after 5-year (T5) of 57 schizophrenia patients. Correlations were calculated in patients between brain volume (change), DUI and outcome variables.
Results: We found no significant correlation between DUI and brain volume (change) in schizophrenia patients. A longer DUI was significantly correlated with higher PANSS scores at T0 and T5, and with higher scores on the Camberwell Assessment of Need scale at T5. Baseline volume of the cerebrum, lateral ventricles and cerebellum volume (change) were associated with PANSS scores at T0 and T5.
Conclusion: Although clinical outcome is associated with both brain volume (change) and DUI, we found no evidence for a relationship between DUI and brain volume (change). DUI and baseline brain volume or 5-year brain volume (change) seem to explain different parts of the variation in clinical outcome.

Introduction

Schizophrenia is, in the majority of cases, characterised by an insidious onset which is often preceded by a decline in functioning. Duration of untreated psychosis (DUP), duration of prodrome (DPD) and duration of untreated illness (DUI) have all been used to characterise the duration of the period before the start of treatment or the onset of psychosis. DUP is the period between the onset of psychosis and the moment the patient receives treatment. In this context treatment is generally defined as hospitalisation[4,49,63] or (adequate) antipsychotic treatment[15,18,23,63,70]. Onset of psychosis is usually determined retrospectively and is defined as the onset of first positive psychotic symptoms[4,15,23,46,63,70].
The start of the duration of prodrome is usually defined as a persistent deviation from the individual's normal premorbid functioning, behaviour or personality

and/or the emergence of prodromal psychiatric symptoms that do not fulfill the criteria for psychosis[4,15,18,22,48,60]. It ends at the emergence of psychotic symptoms. Finally, duration of untreated illness is defined as the sum of DUP and DPD.
Clinical and social outcome variables have been found to be associated with DUI[18,48,61] and DPD[25,34,51] in that longer DUI or DPD was associated with poorer outcome. However, others could not replicate such a relationship[5,14,27,34,38,39,51,59,70]. In contrast, a small to moderate effect of DUP on outcome in schizophrenia, including symptom remission and functional rehabilitation has been established in two reviews[53,63].
Interestingly, poorer outcome has also been associated with smaller brain volumes[8,56], larger ventricles[20] and excessive brain volume loss over time[9,10,33], for review see[40,43]. Therefore, one could hypothesise that DUP, DUI or DPD through their effect on outcome, are associated with (change in) brain volume abnormalities in schizophrenia patients or vice versa. Indeed, cross-sectional studies provide evidence for an association between brain abnormalities and a longer DUP, DUI or DPD[3,4,15,16,37,45,46,49,62,72,74]. So far, only one longitudinal study investigated the relationship between DUP, outcome and global brain volume change over time using computed tomography (CT), and found no evidence for such a relationship[49].
The present study aimed to investigate the relationship between DUI, global brain volume after a first episode and brain volume change during a 5-year interval (as measured with MRI), and outcome (both at baseline as well as after about 5 years of illness) in first-episode schizophrenia patients.

Materials and methods

Subjects and design

Patients, aged 17 to 40 years, with a maximum exposure of 6 months to antipsychotic medication, were recruited from The First Episode Schizophrenia Research Program at the University Medical Centre Utrecht, the Netherlands. After complete description of the study written informed consent was obtained from all participants. The Medical Ethics Review Board of the University Medical Centre Utrecht approved the study. This study was performed in accordance with the Declaration of Helsinki. Patients who had an MRI scan at inclusion (T0) and who were diagnosed according to DSM-IV criteria with schizophrenia at follow-up

(T5) were included. Diagnosis was assessed with the Comprehensive Assessment of Symptoms and History Schizophrenia[2]. The Positive and Negative Syndrome Scale (PANSS) was performed at T0 and T5[41,42]. At T5 both the Global Assessment of Functioning (GAF) and the Camberwell Assessment of Need (CAN) were performed[24,26,64]. Course of illness data to determine DUI were collected retrospectively using patient reports prompted by key data and all other possible sources of information, including data from a shortened version of the Interview for the Retrospective Assessment of the Onset of schizophrenia (IRAOS) at T5[31]. Furthermore, a careful examination of the medical records was carried out and the treating psychiatrist and/or key worker were interviewed.

The duration of illness (DUI) was defined as the period from onset of prodrome to the start of antipsychotic treatment. Criterion B from the DSM-III was used to define onset of prodrome (when one or more major areas of functioning such as work, interpersonal relations, or self care are markedly below the level achieved prior to the onset). Consensus was reached between two independent researchers (WC and TCM) about the date the prodrome started.

To calculate the lifetime cumulative dosage of antipsychotic medication up to T0 and T5, a careful examination of the medical records was carried out, and a table from the Dutch National Health Service was used to derive the haloperidol equivalents for typical antipsychotics[58] (conversion rates: broomperidol 1:1, droperidol 1:1, haloperidol 1:1, penfluridol 1:1, perfenazine 5:1, pimozide 0.85:1, pipamperon 50:1, zuclopentixol 5:1). For atypical antipsychotic medication, the respective pharmaceutical companies suggested conversion rates into haloperidol equivalents (H-EQ) (clozapine, 40:1; olanzapine, 2.5:1; quetiapine, 50:1; risperidone, 1:1; sulpiride, 170:1).

In addition, 56 controls were included, group-matched for age, gender and handedness, in order to assess whether this patient sample shows the expected brain abnormalities (i.e., smaller cerebral (gray matter) volume at baseline, and excessive gray matter volume loss over time in patients relative to controls).

MRI data acquisition

Magnetic resonance images (MRIs) were acquired using a 1.5 Tesla Philips NT scanner. A T1-weighted three-dimensional fast field echo (3D-FFE: echo time (TE)=4.6 milliseconds, repetition time (TR)=30 milliseconds, flip angle=30 degrees, field of view (FOV)=256/80% mm) with 160–180 contiguous coronal 1.2-mm slices, and a T2-weighted dual echo turbo spin-echo (DE-TSE: TE1=14 mil-

liseconds, TE2=80 milliseconds, TR=6350 milliseconds, flip angle=90 degrees, FOV=256/80% mm) with 120 contiguous coronal 1.6-mm slices of the whole head were used for quantitative measurements. In addition, a T2-weighted DE-TSE (TE1=9 milliseconds, TE2=100 milliseconds, TR=2200 milliseconds, flip angle=90 degrees, FOV=250/100% mm) with 17 axial 5-mm slices and 1.2-mm gap of the whole head was acquired for clinical neurodiagnostic evaluation. The scans were processed on the neuro-imaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. Before quantitative assessments, 10 randomly chosen images were cloned for calculation of interrater reliability using the intraclass correlation coefficient (ICC). All images were coded to ensure blindness for subject identification. Scans were put into Talairach frame[73] (no scaling) and corrected for inhomogeneities in the magnetic field[71].

Volume measures of the intracranium, total brain (TB), cerebral gray (GM) and white matter (WM), cerebellum (CB), third (V3) and lateral ventricles (LV) were determined. Quantitative assessment of the intracranial volume was performed using a fully-automated computer program based on histogram analyses followed by mathematical morphological operators in the DE-TSE image. Quantitative assessment of the cerebrum, GM, WM, CB, V3 and LV volumes were performed based on histogram analyses followed by mathematical morphological operators in the 3D-FFE image, using the intracranial volume as mask[68,69]. In addition, for CB and V3 and LV volumes, anatomical knowledge-based selection principles were used. For CB, this included a plane perpendicular to the sagittal plane through the aquaduct. For V3, this included the coronal slices through the anterior commissure (AC) as anterior border, the coronal slice through the posterior commissure (PC) as posterior border, and a manually outlined roof to prevent leaks into the transverse cistern, drawn in the midsagittal reconstructed slice from a point superior to the thalamus and just inferior to the plexus choroideus. For the LVs, this included automated computer-incorporated anatomical knowledge of the anatomical location of the LVs in the brain (e.g., they are surrounded by WM). All above segmentations were checked and corrected manually if necessary. The interrater reliabilities of the volume measurements, determined by the ICC were 0.95 and higher.

Data-analysis

Differences in baseline characteristics were checked with the Pearson's Chi-Square test for nominal variables, ANOVA for normally distributed, and Mann-Whitney U test for abnormally distributed continuous variables (**Table 1**). Brain volume (change) was corrected for intracranial volume, age and gender using multiple regression analyses. Unstandardised residuals were saved and used in the main analysis. The difference in volume (change) between patients and controls was tested using ANOVA for normally distributed, and Mann-Whitney U test for abnormally distributed volume variables. Pearson's correlation coefficients, or Spearman Rank correlation coefficients in not-normally distributed variables, were calculated to investigate the association between 1) DUI and corrected brain volume (change) 2) clinical outcome measures (PANSS total and subscores at T0 and T5, GAF and CAN professional total score at T5) and DUI, and 3) clinical outcome measures and corrected brain volume (change).

At baseline, 36 patients were medication-naïve and correlation analyses on baseline measures of outcome, brain volume and DUI were performed in this subgroup to exclude the influence of potential medication effects. SPSS18 was used for all analyses. Only findings that exceeded the threshold of $p=0.01$ are presented.

Table 1. Baseline characteristics for all patients, and those patients with both a baseline and a 5-year follow-up scan, as well as for all controls and those controls with both a baseline and a 5-year follow-up scan.

Variables, mean (sd)	T0, N=57	T0 + T5, N=42	T0, N=56	T0 + T5, N=37
Age	24.7 (5.8)	24.0 (5.3)	24.8 (5.9)	25.0 (6.7)
Gender (male/female) (n)	51/6	37/5	49/7	31/6
Total education of the subject (yr)	12.0 (2.6)	12.1 (2.6)	14.3 (2.6)[a]	14.6 (2.6)[a]
Highest level of parental education(yr)	12.9 (3.6)	13.7 (3.4)[a]	12.3 (5.0)[b]	13.7 (2.8)
Handedness (percentage right/left/ ambidexter/missing) (n)	49/2/5/1	35/2/4/1	40/5/2/9	28/4/0/5
Naïve/T/AT/Both (n)	36/12/5/4	27/8/4/3	-	-
Abuse of drugs within 3 months before the first MRI (no/yes)	31/25	22/19	-	-
Abuse of drugs ever before the first MRI (no/yes)	23/34	16/26	-	-
PANSS total score at T0	73.4 (16.8)	74.3 (17.6)	-	-
PANSS positive symptom score at T0	18.0 (5.8)[c]	17.7 (5.5)	-	-
PANSS negative symptom score at T0	19.6 (5.3)	19.1 (5.4)	-	-
PANSS general symptom score at T0	37.2 (9.4)	38.0 (9.7)	-	-
Duration of untreated illness, weeks	313.4 (316.8)	270.6 (238.8)	-	-

T0: baseline, T5: follow-up at 5 years, T0+T5: baseline and follow-up measurement present, T: typical antipsychotics, AT: atypical antipsychotics, PANSS: positive and negative syndrome scale. [a] Mean total education was higher in controls compared to patients, both in groups with only a scan at T0 ($p<0.01$) and groups with T0+T5 ($p<0.01$). [b] Parental education was significantly higher in patients with T0+T5 MRI scan compared to patients with only a T0 scan ($p<0.01$). [c] The PANSS positive score was significantly higher in medication naïve patients as compared to medicated patients ($p=0.02$). Mean total education in years was significantly higher in controls compared to medication naïve patients ($p<0.01$). The PANSS positive score was significantly higher in medication-naïve patients compared to medicated patients ($p=0.02$).

Results

Brain volume (change) in patients and controls

At baseline third ventricle volume was larger in patients compared to controls. Patients, compared to controls, showed a more pronounced loss of cerebral gray matter volume over a five year interval (See **Table 2**).

Table 2. Mean baseline brain volumes and mean 5-year change in brain volume in patients and controls.

Brain volume, mean (sd)	Baseline N=57	Change, (T5-T0) N=42	Baseline N=56	Change, (T5-T0) N=37
Total brain	1324.63 (110.13)	-2.72 (6.29)	1350.93 (122.62)	-1.16 (3.74)
Cerebral gray matter	810.28 (67.00)	-6.61 (6.44)[b]	698.36 (68.52)	-2.60 (4.6)
Cerebral white matter	514.35 (62.43)	3.29 (4.84)	489.10 (66.11)	0.95 (4.4)
Cerebellum	147.21 (12.84)	0.45 (0.75)	49.03 (12.69)	0.16 (0.53)
Third ventricle	0.85 (0.40)[a]	0.02 (0.04)	0.72 (0.31)	0.00 (0.02)
Lateral ventricles	14.73 (8.28)	0.33 (0.65)	14.88 (8.78)	0.14 (0.24)

T0: baseline, T5: follow-up at 5 years. [a] The difference between baseline third ventricle volume in patients and controls was significant (p=0.001). [b] The difference in cerebral gray matter change was significant between controls and patients (p=0.01). In medication-naïve patients we found a larger baseline cerebral gray matter than in medicated patients (data not shown).

DUI and brain volume (change).

No significant correlations were found between brain volume (change) and DUI, see **Table 3**.

DUI and clinical outcome

Significant associations were found between DUI and clinical and functional outcome, indicating larger DUI to be related to poorer outcome (**Table 3**). DUI was found longer with higher PANSS total scores at T5 (rho=0.42, p=0.003), PANSS positive score at T0 and T5 (T0: rho=0.37, p=0.008, T5: rho=0.53, p=0.00009) and

the PANSS general score at T5 (rho=0.37, p=0.01). Furthermore, there was a positive correlation between DUI and the CAN total score at T5 (rho=0.41, p=0.004).

Brain volume (change) and clinical outcome

Significant correlations were found between brain volume (change) and level of symptoms both at baseline as well as follow-up measurement (**Table 3**). There was a negative correlation between baseline total brain volume and the negative PANSS score at T0 and T5 (T0: r=-0.44, p=0.002; T5: rho=-0.40, p=0.005). Cerebellum volume change was negatively correlated with the PANSS general score at T0 (r=-0.43, p=0.01). These correlations suggest that the presence of more symptoms is related to more CSF and less brain tissue. In contrast, positive PANSS score at T5 was negatively correlated to baseline lateral ventricle volume (r=-0.34, p=0.009) and positively to cerebellar volume (r=0.36, p=0.01).

Medication naïve patients

Medication naïve patients (N=36) showed no significant correlations between baseline brain volume and DUI or outcome. In medication-naïve patients DUI was significantly longer in patients with a higher baseline PANSS general score (rho=0.49, p=0.01).

Table 3. Pearsons correlation or Spearman's (ρ) coefficients between brain volume (change), duration of untreated illness (DUI) and functional and clinical outcome.

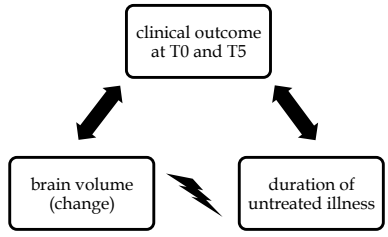
Baseline brain volume	**N=57**	**N=42**	**N=49**	**N=49**	**N=42**	**N=48**	**N=48**	**N=48**	**N=48**	**N=41**	**N=48**
	DUI	**T0 PANSS total score**	**T0 PANSS positive score**	**T0 PANSS negative score**	**T0 PANSS general score**	**T5 PANSS total score**	**T5 PANSS positive score**	**T5 PANSS negative score**	**T5 PANSS general score**	**T5 GAF score**	**T5 CAN score**
Total brain	.08 (ρ)	-.31	-.06	-.44#	-.22	-.13	.03	-.40[a] (ρ)	-.23 (ρ)	.19	.03
Cerebral gray matter	-.05 (ρ)	-.20	-.07	-.26	-.15	-.11	-.10	-.20 (ρ)	-.13 (ρ)	.10	.08
Cerebral white matter	-.05 (ρ)	-.18	-.01	-.23	-.13	-.08	.01	-.18 (ρ)	-.12 (ρ)	.18	-.07
Cerebellum	.25 (ρ)	.08	.03	-.17	.08	.09	.36#	-.08 (ρ)	.13 (ρ)	-.11	.03
Third ventricle	-.09 (ρ)	.16	-.01	.33	.13	-.01	-.19	.32 (ρ)	.11 (ρ)	-.09	-.06
Lateral ventricles	-.09 (ρ)	-.20	-.06	.06	-.16	-.17	-.37#	-.13 (ρ)	-.30 (ρ)	.13	.03
Brain volume change	**N=42**	**N=35**	**N=38**	**N=38**	**N=35**	**N=41**	**N=41**	**N=41**	**N=41**	**N=36**	**N=41**
Total brain	-.30 (ρ)	-.03	-.10	.17	-.10	-.13	-.10	-.17 (ρ)	-.11 (ρ)	.34	-.29
Cerebral gray matter	-.08 (ρ)	.00	.08	.10	-.04	-.04	-.02	-.20 (ρ)	-.15 (ρ)	.31	-.16
Cerebral white matter	-.16 (ρ)	-.01	-.22	.09	-.04	-.07	-.12	.08 (ρ)	12 (ρ)	.04	-.13
Cerebellum	-.20 (ρ)	-.37	-.25	-.14	-.43#	-.16	-.22	-.32 (ρ)	-.25 (ρ)	.26	-.20
Third ventricle	.10 (ρ)	-.14	-.01	-.22	-.11	-.08	-.00	.10 (ρ)	.01 (ρ)	-.29	.22
Lateral ventricles	.17 (ρ)	-.16	.14 (ρ)	-.13 (ρ)	-.00	.04	.02	.10 (ρ)	.01 (ρ)	-.23 (ρ)	.32
DUI	**-**	**N=42**	**N=49**	**N=49**	**N=42**	**N=48**	**N=48**	**N=48**	**N=48**	**N=41**	**N=48**
DUI (ρ)	-	.33	.37#	.10	.35	.42#	.53#	.18	.37#	-.29	.41#

Sd: standard deviation, ml: milliliters, PANSS: Positive And Negative Syndrome Scale, GAF: Global Assessment of Functioning, CAN: Camberwell Assessment of Need. [a] p≤0.01 (significant). Correlations are Pearsons correlations coefficients unless indicated otherwise.

Discussion

We investigated for the first time the association between duration of untreated illness (DUI), brain volume at baseline and 5-year brain volume change as measured with MRI, and clinical outcome at baseline and 5-year follow-up in first-episode schizophrenia patients. Our main finding was the lack of association between DUI and brain volume at illness onset or brain volume change during the first five years of illness. We did identify correlations of symptom scores at illness onset and after 5-year follow-up with both DUI and brain volume (change). It seems that DUI and brain volume explain different parts of the variance in clinical outcome in first-episode schizophrenia patients (**Figure 1**).

Figure 1. Associations (arrow) between clinical outcome, brain volume (change) and duration of untreated illness.



DUI and brain volume (change)

Our finding is in line with the only longitudinal (CT) study that found no relationship between DUP and 5-year change in frontal brain atrophy in 24 first-episode schizophrenia patients[49]. Two cross-sectional MRI studies, using either a volumetric or a voxel-based morphometry (VBM) approach did show associations between longer DUI and decreased volume or gray matter density in small areas in the brain in first-episode schizophrenia patients, i.e., superior temporal gyrus, fusiform gyrus, lingual and parahippocampal gyrus[4,45]. However, other cross-sectional region-of-interest or VBM studies found no associations between DUI and (partial) brain volume of the thalamus, caudate nucleus, hippocampus, (lateral) ventricles, temporal lobe and cerebral hemispheric volumes[15,16,22,39]. Considering the above, if there is a relation between DUI and brain volume (change), it might be restricted to focal areas of the brain.

In this sample, patients only differed from controls in that they had a significantly larger third ventricle volume. This might explain the lack of association between DUI and baseline volume. Any brain abnormality might have been too subtle to pick up. In contrast, we did find excessive loss of gray matter volume over time in first-episode patients as compared to controls. These findings are in line with earlier studies using subjects from this cohort of first-episode patients[9,10].

DUI and clinical outcome

The association between DUP, DUI and DPD and the course of schizophrenia is well established[53,63], amongst others in studies with a follow-up of 5 year or more[7,18,19,29,35,76]. Consistent with the above, we found DUI to be significantly longer with higher scores on measures of functional and symptomatic outcome both at baseline and at follow-up measurement. Most convincing was the association between DUI and positive symptoms.

Clarke showed that longer DUI predicted more severe PANSS positive symptoms at 4-year follow-up in first-episode schizophrenia patients[12]. However, other studies failed to find a correlation between positive symptom scores and DUI in first-episode schizophrenia[5,6,27,38].

At follow-up, the GAF score and DUI were not correlated. This is interesting as several studies did identify a correlation between DUI and GAF at follow-up measurement, with intervals ranging from one to four years[10,12,25,44].

However, all of these studies investigated patients that were already on medication, which obviously affects the outcome measures of symptomatology. Importantly, we included 36 medication-naïve patients in whom correlations between symptomatic and functional outcome at baseline and DUI were all in the same direction and of similar (or larger) magnitude compared to the total sample. However, due to the smaller magnitude of this sample these correlations did not all reach significance. In summary, we replicated the associations between DUI and psychiatric symptomatology at baseline, and after five years in medicated as well as medication-naïve patients.

Brain volume (change) and outcome

Showing more positive symptoms at follow-up was related to a smaller baseline lateral ventricle volume and a larger baseline cerebellum volume.

These correlations seem counterintuitive. In support of our finding a similar positive association between white matter of the cerebellar vermis and positive

symptoms in chronic schizophrenia was reported[47]. In contrast, an association between smaller cerebellum volume and spending more weeks per year in a psychotic syndrome in chronic schizophrenia was found[75]. Also, in a meta-analysis Kempton et al. reported a consistent correlation between ventricular volume enlargement over time and poorer outcome or higher symptom scores[43] (but see[20]). However, evidently, confounding by antipsychotic medication use is unavoidable in longitudinal studies or studies with chronic schizophrenia patients, such as the above. Interestingly, some studies found no associations of positive or negative syndrome scores with brain volume (change) in first-episode schizophrenia patients[9,21], or even medication-naïve patients[22].

We also showed that lower total brain volume was associated with more negative symptoms both at illness onset as well as at follow-up measurement which is in line with earlier studies from our group including overlapping samples[9,10,33]. These findings also corroborate with findings in antipsychotic-naïve first-episode patients that showed reduced temporal and frontal baseline volumes to be associated with less improvement of negative symptoms over 30 months[30], while (progressive) gray matter deficits identified in a VBM study in chronic schizophrenia patients were found to be associated with negative symptoms[55].

However, in contrast, other research by our group did not identify associations between baseline volume and outcome at follow-up[32]. One other first-episode study found the volume of focal areas (with VBM) to be inversely related to the GAF score[52]. In medication-naïve patients we found equally large correlations, although not significant because of the smaller number of patients, between PANSS total and negative score and baseline TB and third ventricle volume.

Strengths and limitations

We included patients with ages ranging from 17 to 40 years. Of the included subjects, 12 patients had an age of 30 or more at inclusion. Although the agespan of 30 to 40 is late to develop schizophrenia, it can be the case that patients are ill for a long time before being introduced to mental health care. This seems to have been the case since there was a long DUI in these patients compared to the rest of the patient group, namely 11.6 years (standard deviation (sd) 5.3) versus 3.9 (sd 3.8) years.

Unfortunately, the IRAOS, which aims to measure the onset of schizophrenia was only completed at follow-up measurement, thereby increasing the possibility of inaccurate data because of memory bias. It is important to realise that it is dif-

ficult to determine DUI, DUP or DPD prospectively, since prediction of psychosis and prodrome is not yet feasible in clinical practice[11]. Furthermore, problems related to memory exist in studies investigating DUI, DUP and DPD[1,13,17,28]. To ensure internal validity we obtained consensus between two investigators about the time of onset of prodrome.
The mean DUI determined in our study (313 weeks), is higher than previously reported DUIs that vary from 119 to 227 weeks[50,67]. This might be a consequence of the large variation in defining onset of illness, which differs from "first behavioural changes related to the illness"[36,48,65,67] or "first personality and behavioural changes[5]" to "first non-specific (psychiatric) symptom related to psychosis"[27,51] or a combination of these[12,25,44,60]. The definition we used is well described and has been used before, however, without reporting a mean or median DUI[70].
A number of our patients used alcohol or drugs either in the past, or, less often, at the time of scanning at baseline or follow-up measurement. This might have influenced our results[54,57,66].

Conclusion

We hypothesised that through a shared association with outcome DUI would be associated with (change in) brain volume. However, although associations of baseline and 5-year follow-up symptom scores with both DUI as well as cerebral volume (change) were identified in first-episode patients, no associations were found between DUI and brain volume (change). Therefore, it seems that brain volume at illness onset and excessive tissue loss over time during the first years of the illness and DUI explain a different part of the variation in symptomatic and functional outcome.

Acknowledgements:

We want to thank the patients that participated in this lengthy study for their willingness to return each time to our center for research. Furthermore we want to thank Monica Rais for her work in determining the cumulative medication exposure.

References

1. Aleman A., Hijman R., de Haan E.H. et al. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry* 1999;156(9):1358-1366.
2. Andreasen N.C., Flaum M. and Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* 1992;49(8):615-623.
3. Angelopoulos E.K., Markianos M., Daskalopoulou E.G. et al. Changes in central serotonergic function as a correlate of duration of illness in paranoid schizophrenia. *Psychiatry Res* 2002;110(1):9-17.
4. Bangalore S.S., Goradia D.D., Nutche J. et al. Untreated illness duration correlates with gray matter loss in first-episode psychoses. *Neuroreport* 2009;20(7):729-734.
5. Barnes T.R., Hutton S.B., Chapman M.J. et al. West London first-episode study of schizophrenia. Clinical correlates of duration of untreated psychosis. *Br J Psychiatry* 2000;177:207-211.
6. Barnes T.R., Leeson V.C., Mutsatsa S.H. et al. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br J Psychiatry* 2008;193(3):203-209.
7. Bottlender R., Sato T., Jager M. et al. The impact of duration of untreated psychosis and premorbid functioning on outcome of first inpatient treatment in schizophrenic and schizoaffective patients. *Eur Arch Psychiatry Clin Neurosci* 2002;252(5):226-231.
8. Buchsbaum M.S., Shihabuddin L., Brickman A.M. et al. Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophr Res* 2003;64(1):53-62.
9. Cahn W., Hulshoff Pol H.E., Lems E.B. et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry* 2002;59(11):1002-1010.
10. Cahn W., van Haren N.E., Hulshoff Pol H.E. et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006;189:381-382.
11. Cannon T.D., Cadenhead K., Cornblatt B. et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008;65(1):28-37.
12. Clarke M., Whitty P., Browne S. et al. Untreated illness and outcome of psychosis. *Br J Psychiatry* 2006;189:235-240.
13. Coughlin S.S. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43(1):87-91.
14. Craig T.J., Bromet E.J., Fennig S. et al. Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *Am J Psychiatry* 2000;157(1):60-66.
15. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. *Schizophr Res* 2007;91(1-3):87-96.
16. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. *Neuroimage* 2007;35(4):1613-1623.

17. Croyle R.T., Loftus E.F., Barger S.D. et al. How well do people recall risk factor test results? Accuracy and bias among cholesterol screening participants. *Health Psychol* 2006;25(3):425-432.
18. Crumlish N., Whitty P., Clarke M. et al. Beyond the critical period: longitudinal study of 8-year outcome in first-episode non-affective psychosis. *Br J Psychiatry* 2009;194(1):18-24.
19. de H.L., Linszen D.H., Lenior M.E. et al. Duration of untreated psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. *Schizophr Bull* 2003;29(2):341-348.
20. DeLisi L.E., Sakuma M., Maurizio A.M. et al. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res* 2004;130(1):57-70.
21. DeLisi L.E., Sakuma M., Tew W. et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 1997;74(3):129-140.
22. Ebdrup B.H., Glenthoj B., Rasmussen H. et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci* 2010;35(2):95-104.
23. Emsley R., Chiliza B. and Schoeman R. Predictors of long-term outcome in schizophrenia. *Curr Opin Psychiatry* 2008;21(2):173-177.
24. Endicott J., Spitzer R.L., Fleiss J.L. et al. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33(6):766-771.
25. Fusar-Poli P., Meneghelli A., Valmaggia L. et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry* 2009;194(2):181-182.
26. Goldman H.H., Skodol A.E. and Lave T.R. Revising axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry* 1992;149(9):1148-1156.
27. Gonzalez-Blanch C., Crespo-Facorro B., varez-Jimenez M. et al. Pretreatment predictors of cognitive deficits in early psychosis. *Psychol Med* 2008;38(5):737-746.
28. Guay M. Long-term retention of temporal information. *Percept Mot Skills* 1982;54(3):843-849.
29. Gunduz-Bruce H., McMeniman M., Robinson D.G. et al. Duration of untreated psychosis and time to treatment response for delusions and hallucinations. *Am J Psychiatry* 2005;162(10):1966-1969.
30. Gur R.E., Cowell P., Turetsky B.I. et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 1998;55(2):145-152.
31. Hafner H., Riecher-Rossler A., Hambrecht M. et al. IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophr Res* 1992;6(3):209-223.
32. Haren v.N.E., Cahn W., Hulshoff Pol H.E. et al. Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. *Schizophr Res* 2003;64(1):41-52.

33. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 2008;63(1):106-113.
34. Harrigan S.M., McGorry P.D. and Krstev H. Does treatment delay in first-episode psychosis really matter? *Psychol Med* 2003;33(1):97-110.
35. Harris M.G., Henry L.P., Harrigan S.M. et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. *Schizophr Res* 2005;79(1):85-93.
36. Harrison G., Amin S., Singh S.P. et al. Outcome of psychosis in people of African-Caribbean family origin. Population-based first-episode study. *Br J Psychiatry* 1999;175:43-49.
37. Ho B.C., Alicata D., Ward J. et al. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *Am J Psychiatry* 2003;160(1):142-148.
38. Ho B.C., Andreasen N.C., Flaum M. et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 2000;157(5):808-815.
39. Hoff A.L., Sakuma M., Razi K. et al. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *Am J Psychiatry* 2000;157(11):1824-1828.
40. Hulshoff Pol H.E. and Kahn R.S. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34(2):354-366.
41. Kay S.R., Fiszbein A. and Opler L.A. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
42. Kay S.R., Opler L.A. and Lindenmayer J.P. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1988;23(1):99-110.
43. Kempton M.J., Stahl D., Williams S.C. et al. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophr Res* 2010;120(1-3):54-62.
44. Keshavan M.S., Haas G., Miewald J. et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr Bull* 2003;29(4):757-769.
45. Keshavan M.S., Haas G.L., Kahn C.E. et al. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res* 1998;32(3-4):161-167.
46. Lappin J.M., Morgan K., Morgan C. et al. Gray matter abnormalities associated with duration of untreated psychosis. *Schizophr Res* 2006;83(2-3):145-153.
47. Levitt J.J., McCarley R.W., Nestor P.G. et al. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *Am J Psychiatry* 1999;156(7):1105-1107.
48. Loebel A.D., Lieberman J.A., Alvir J.M. et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* 1992;149(9):1183-1188.

49. Madsen A.L., Karle A., Rubin P. et al. Progressive atrophy of the frontal lobes in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. *Acta Psychiatr Scand* 1999;100(5):367-374.
50. Malla A., Norman R., Schmitz N. et al. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. *Psychol Med* 2006;36(5):649-658.
51. Malla A.K., Norman R.M., Manchanda R. et al. One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophr Res* 2002;54(3):231-242.
52. Mane A., Falcon C., Mateos J.J. et al. Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. *Schizophr Res* 2009;114(1-3):136-143.
53. Marshall M., Lewis S., Lockwood A. et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005;62(9):975-983.
54. Mathalon D.H., Pfefferbaum A., Lim K.O. et al. Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. *Arch Gen Psychiatry* 2003;60(3):245-252.
55. Mathalon D.H., Sullivan E.V., Lim K.O. et al. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 2001;58(2):148-157.
56. Molina V., Hernandez J.A., Sanz J. et al. Subcortical and cortical gray matter differences between Kraepelinian and non-Kraepelinian schizophrenia patients identified using voxel-based morphometry. *Psychiatry Res* 2010;184(1):16-22.
57. Nesvag R., Frigessi A., Jonsson E.G. et al. Effects of alcohol consumption and antipsychotic medication on brain morphology in schizophrenia. *Schizophr Res* 2007;90(1-3):52-61.
58. No authors listed. Farmacotherapeutisch Kompas* (Pharmacotherapeutical Compass). Hoofdstuk (Chapter): Centraal zenuwstelsel (psychische aandoeningen) / Antipsychotica (Central nervous system (psychiatric disorders) / Antipsychotics (*in Dutch). Loenen v.A.C., Boer d.J.E., Danz M. et al., eds. 2007, 1-1216. 2007. Amstelveen, Commissie Farmaceutische Hulp van het College voor zorgverzekeringen. Farmacotherapeutisch Kompas. Loenen, v.A.C. and Boer, d.J.E.
59. Norman R.M., Townsend L. and Malla A.K. Duration of untreated psychosis and cognitive functioning in first-episode patients. *Br J Psychiatry* 2001;179:340-345.
60. O'Callaghan E., Turner N., Renwick L. et al. First episode psychosis and the trail to secondary care: help-seeking and health-system delays. *Soc Psychiatry Psychiatr Epidemiol* 2010;45(3):381-391.
61. Owens D.C., Johnstone E.C., Miller P. et al. Duration of untreated illness and outcome in schizophrenia: test of predictions in relation to relapse risk. *Br J Psychiatry* 2010;196:296-301.
62. Penttila M., Jaaskelainen E., Haapea M. et al. Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophr Res* 2010;123(2-3):145-152.

63. Perkins D.O., Gu H., Boteva K. et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005;162(10):1785-1804.
64. Phelan M., Slade M., Thornicroft G. et al. The Camberwell Assessment of Need: the validity and reliability of an instrument to assess the needs of people with severe mental illness. *Br J Psychiatry* 1995;167(5):589-595.
65. Rabiner C.J., Wegner J.T. and Kane J.M. Outcome study of first-episode psychosis. I: Relapse rates after 1 year. *Am J Psychiatry* 1986;143(9):1155-1158.
66. Rais M., Cahn W., Van H.N. et al. Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *Am J Psychiatry* 2008;165(4):490-496.
67. Robinson D., Woerner M.G., Alvir J.M. et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999;56(3):241-247.
68. Schnack H.G., Hulshoff Pol H.E., Baare W.F. et al. Automated separation of gray and white matter from MR images of the human brain. *Neuroimage* 2001;13(1):230-237.
69. Schnack H.G., Hulshoff H.E., Baare W.F. et al. Automatic segmentation of the ventricular system from MR images of the human brain. *Neuroimage* 2001;14(1 Pt 1):95-104.
70. Selten J.P., Veen N.D., Hoek H.W. et al. Early course of schizophrenia in a representative Dutch incidence cohort. *Schizophr Res* 2007;97(1-3):79-87.
71. Sled J.G., Zijdenbos A.P. and Evans A.C. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 1998;17(1):87-97.
72. Takahashi T., Suzuki M., Tanino R. et al. Volume reduction of the left planum temporal gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. *Psychiatry Res* 2007;154(3):209-219.
73. Talairach J. and Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Propositional System: An Approach to Cerebral Imaging. Stuttgart: Thieme, 1988:1-122.
74. Théberge J., Al-Semaan Y., Drost D.J. et al. Duration of untreated psychosis vs. N-acetylaspartate and choline in first episode schizophrenia: a 1H magnetic resonance spectroscopy study at 4.0 Tesla. *Psychiatry Res* 2004;131(2):107-114.
75. Wassink T.H., Andreasen N.C., Nopoulos P. et al. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. *Biol Psychiatry* 1999;45(1):41-48.
76. White C., Stirling J., Hopkins R. et al. Predictors of 10-year outcome of first-episode psychosis. *Psychol Med* 2009;39(9):1447-1456.

Chapter 6

Initiation of antipsychotic treatment by general practitioners: a case-control study

Geartsje Boonstra, Eelko Hak, Diederick E. Grobbee, René S. Kahn, Huibert Burger.

Journal of Evaluation in Clinical Practice 2011;17(1):12-17

Abstract

Objective: Antipsychotics are approved treatment for severe conditions and have serious side-effects. Antipsychotics are often prescribed off-label. Although a substantial proportion of antipsychotics is prescribed in primary care it is largely unknown what motivates the general practitioner (GP) to *initiate* antipsychotic treatment. Therefore we sought to examine the relation between predefined, licensed as well as off-label, reasons for antipsychotic treatment and the initiation of this treatment by the GP as well as report registration and incidence of antipsychotic treatment in general practice.

Methods: In a case-control study 723 patients selected from an electronic database and with a new antipsychotic prescription were compared with 3,615 controls receiving any other new prescription. Using logistic regression six predefined categories of International Classification of Primary Care (ICPC)-codes ('psychosis', 'depression and anxiety', 'sleeping disorders', 'acute stress and surmenage', 'dementia', 'somatic indications') were associated with initiating antipsychotic treatment.

Results: All, including off-label, categories were significantly related to intitiating antipsychotic treatment. The incidence of initiating antipsychotic therapy was 1.28 per 1,000 persons per year (95% CI:(1.09, 1.48). GPs registered an ICPC-code in 50% and prescribed typical antipsychotics in 90% of the cases. Prescription of atypical antipsychotics increased almost threefold over the study period.

Conclusions: The results suggest that GPs prescribe antipsychotics off-label. Despite serious side-effects and relatively infrequent occurrence in Dutch general practices GPs seem imprecise in underpinning and registrating the initiation of antipsychotic treatment. GPs increasingly prescribe atypical antipsychotics although the prescription of typical antipsychotics still dominates.

Introduction

Up to 80% of all antipsychotics are reported to be prescribed in primary care[5,7,8,13,17]. Furthermore, 1-3.2% of general practice patients receives antipsychotic drugs when investigated cross-sectionally and approximately 10% of the general practitioner-patient encounters in which a psycho-active drug is prescribed involves an antipsychotic[1,5,8,14,16]. Thus, prescription of antipsychotics seems relatively

common in general practice. Antipsychotics may induce serious side-effects such as tardive dyskinesia, Parkinsonism, akathisia, weight gain and sedation and enhance the risk of cerebrovascular incidents in some patient groups. Consequently, there has been concern about off-label use (off-label use defined as the use of a drug outside the licensed indication) of antipsychotics[4,6,14,17,18,20]. Although off-label use can partly be attributed to following guidelines based on proof from large randomised controlled trials, minimal evidence may support other off-label use. It is estimated that 30-50% of all prescriptions of antipsychotics is for off-label use[4,14,17,20]. However, it is largely unknown which conditions give rise to off-label antipsychotic prescribing by general practitioners (GPs). To investigate possible motives for off-label prescription, we associated six predefined diagnostic categories, four of them being off-label indications for antipsychotic treatment in the Netherlands, with new antipsychotic use in a case-control study using anonymous electronic medical records and pharmacy prescription data from a large population of GP patients in The Netherlands.

Methods

Database

Data was derived from the Almere Health Care Medical database, consisting of patients registered with approximately 110 GPs in 20 general practices in Almere in The Netherlands. Between 1999 and 2003 the population contributing to the database increased from 109,946 to 164,008 patients, thus representing a growing, large, and dynamic population. GPs received training in systematic data entry and were financially compensated for providing data. Health problems and diagnoses were coded according to the International Classification of Primary Care (ICPC), version I with Dutch subtitles (2000)[11]. Linkage to pharmacy data from 17 pharmacies in the form of Anatomical Therapeutical Chemical Classification System-codes (ATC-codes) enabled the study of prescribing in relation to diagnosis.

Cases

Cases had to be registered in the database between 1 February 1999 and 31 December 2003 and be prescribed an antipsychotic by a GP, after a minimum of twelve months in which no antipsychotics were prescribed. By doing so, we selected cases of new antipsychotic prescribing, with new being arbitrarily defined.

Controls

Random selection of controls was done likewise. Only patients with whatever new medication prescription, except for antipsychotic prescriptions, were eligible. Like in cases, new medication prescribing was defined as the absence of a prescription of the same medication in the preceding twelve months. We aimed at selecting five controls per case to enhance precision of the association measure.

Exposure assessment

Prior to the analyses, health problems and diagnoses were selected that were hypothesized to be reasons for antipsychotic prescribing. This was done on content grounds while consulting two GPs. Subsequently, we clustered the selected ICPC-codes in six diagnostic categories (see **Table 1**). 'Depression and anxiety', 'sleeping disorders', 'acute stress and surmenage' and 'dementia' are the four diagnostic categories that are off-label reasons for antipsychotic treatment. 'Somatic indications' is a diagnostic category consisting of three somatic symptoms that may or may not constitute an approved indication for antipsychotic therapy, depending on the symptoms' severity and lack of earlier response to other than antipsychotic treatment. 'Psychosis' is the obvious on-label indication for the use of antipsychotics. This category was invoked to validate our data as it was expected to be highly associated with antipsychotic prescribing. Only ICPC-codes recorded within an arbitrary time frame of minus seven to plus seven days around the prescription date were included. In case of two concurrent ICPC-categories detected at one prescription occasion, the ICPC-category diagnosed closest to the prescription date was selected.

Data-analysis

Data was processed and analysed using SPSS 12.0 and Microsoft ® Excel SR-2. The yearly incidence of new antipsychotic prescribing was estimated as the number of cases in a particular year, divided by the number of persons in the database at the midpoint of that year. The incidence estimates per year were subsequently averaged over the total study period.

Logistic regression was used to calculate odds ratios (ORs) as measures of relative risk (RR) of the prescribing of antipsychotics for the diagnostic categories, while correcting for the potentially confounding variables age, gender and insurance status[9,12]. The reference category consisted of patients for which only ICPC-codes other than the codes belonging to diagnostic categories under study were

recorded or no ICPC-code at all. The ORs were supplied with a 95% confidence interval (95%CI) as a measure of precision.

Table 1. The six diagnostic categories of International Classification of Primary Care-codes of interest.

Diagnostic Category	ICPC-2 codes	Full ICPC Description
Psychosis	P20.4, P72.2	Hallucinations/delusions, delusional disorders
	P71.0, P71.3	Other organic psychosis
	P71.1	Organic amnestic syndrome (excl. alc.)
	P72.0, P72.1	Schizophrenia all forms, Schizophrenia
	P72.3	Non-organic psychoses
	P72.4, P73.0	Schizo-affective disorder, affective psychoses
	P72.5	Other schizophrenic disorders
	P73.1, P73.2	Manic disorder, bipolar disorder
	P98.0, P98.2	Other not specified psychoses
	P99.0	Puerperal psychoses
Depression and anxiety	P01	Feeling anxious/nervous/tense
	P03	Feeling depressed
	P74	Anxiety disorder/anxiety state
	P76.0, P76.1	Depressive disorder, Reactive depression
	P76.2	Other depressive disorder
Sleeping disorders	P06	Sleep disturbance
Acute stress and surmenage	P02.0, P02.3	Acute stress reaction, other acute stress reaction
	P02.1, P02.2	Reaction to bereavement, reaction to violence
	P78.0	Neuraesthenia/surmenage
	P78.1	Hyper aesthetic emotional syndrome
	P78.2	Other form of neuraesthenia/surmenage
Dementia	P70.0	Senile dementia/Alzheimer
	P70.1	Alzheimer's disease
	P70.2	Arteriosclerotic/multi-infarct dementia
	P70.3	Dementia as a consequence of another specific disorder
	P70.4	Other dementia
	P20.1	Orientation in time/place/person disturbed
	P20.2	Attention/concentration disorders
	P20.3	Amnesia all forms
Somatic indications	D09, D10, R29.1	Nausea, Vomiting, Hiccups

Results

A total of 2,809 patients were identified as users of antipsychotics in the database. We excluded 1,279 patients with less than twelve months of antipsychotic-free follow-up since 1 February 1999 and 789 patients because the new prescription was not performed by a GP. The remaining 723 cases were all included. Subsequently 3,615 controls were selected.

The incidence of initiating antipsychotic therapy was 1.28 per 1,000 persons per year (95%CI:1.09, 1.48). A frequency distribution of the different antipsychotic medications is shown in **Figure 1**. It demonstrates that typical antipsychotics represent the vast majority of newly initiated antipsychotic therapies (90.7%). The proportion of atypical antipsychotics increased over time from 4.7% in 2000 to 14.4% in 2003. **Table 2** shows that the proportions of female gender and private insurance status are larger in controls than in cases. It further shows that mean age was substantially higher in the cases. In 47.7% and 47.6% of cases and controls, respectively, no ICPC-code was registered in the 14 days time interval (-7 days, +7 days) around the prescription date. The logistic regression analysis showed substantially elevated probabilities of prescription for each diagnostic category compared to the reference category (**Table 3**). The ORs were all statistically significant, also after adjustment for the potential confounders. Changes in the ORs after adjustment were largely attributable to age. As expected, the OR for the validation category 'psychosis' was the highest. Excluding cases and controls in which no ICPC-codes were registered resulted in slightly higher ORs for all categories (data not shown).

Figure 1. Bar chart showing the percentages antipsychotics newly prescribed by the general praetitioners in the cases. Different combinations (N=7) of up to three different typical antipsychotics (N=10), clozapine (N=2), penfluridol (N=6), periciazine (N=6), perphenazine (N=1), quetiapine (N=1), sulpiride (N=6), tetrabenazine (N=1) and tiapride (N=1) were combined to the category "other (<1 %)" since they were each prescribed in less than 1% of the cases.

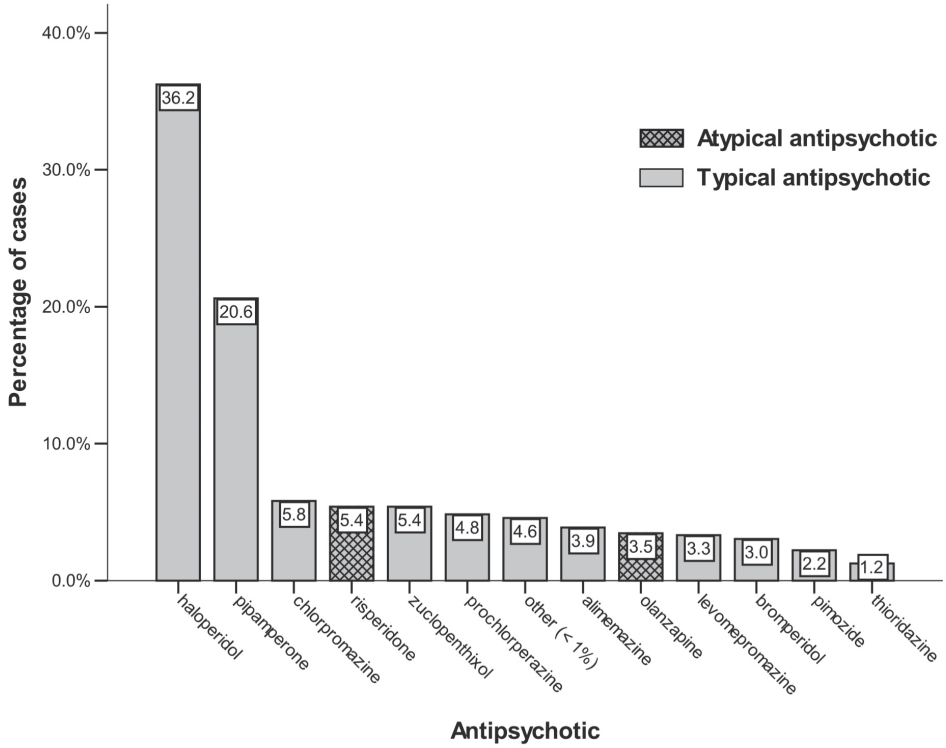


Table 2. Characteristics of cases and controls

Variables	Controls (N=3,615)	Cases (N=723)
Age, mean (range)	40,2 (1-101)	56,3 (0, 101)
Gender, no. (%)		
Female	2,234 (61.8)	353 (48.8)
Insurance status, no. (%)		
Private insurance	1,068 (29.5)	151 (20.9)
State insurance	2,547 (70.5)	572 (79.1)
Diagnostic categories, no. (%)		
Psychosis	2 (0.1)	69 (9.5)
Depression and anxiety	46 (1.3)	30 (4.1)
Sleeping disorders	16 (0.4)	9 (1.2)
Acute stress and surmenage	15 (0.5)	7 (1.0)
Dementia	2 (0.1)	29 (4.0)
Somatic indications	16 (0.4)	40 (5.5)
Other ICPC-codes diagnosed[a]	1,799 (49.8)	203 (28.1)
No ICPC code diagnosed	1,719 (47.6)	345 (47.7)

[a] International Classification of Primary Care

Table 3. Crude and adjusted odds ratio's with 95% confidence intervals (95%CI) for antipsychotic prescribing according to diagnostic category.

Diagnostic Categories	Crude Odds Ratio (95%CI)	Adjusted[a] Odds Ratio (95%CI)
Psychosis	225.2 (55.0, 921.2)	170.7 (41.3, 705.9)
Depression and anxiety	4.3 (2.7, 6.8)	4.5 (2.8, 7.4)
Sleeping disorders	3.7 (1.6, 8.4)	3.5 (1.4, 8.4)
Acute stress and surmenage	3.0 (1.2, 7.5)	3.6 (1.4, 9.1)
Dementia	94.6 (22.5, 397.8)	42.9 (9.7, 190.5)
Somatic indications	16.3 (9.1, 29.3)	17.5 (9.4, 32.6)

[a] Adjusted for age, gender and insurance status.

Discussion

Summary of main findings

Four ICPC diagnostic categories that are no approved indications for antipsychotic treatment in The Netherlands, i.e. 'anxiety and depression', 'acute stress and surmenage', 'sleeping disorder', and 'dementia', were moderately to strongly associated with initiating antipsychotic therapy. In approximately half of the patients that was prescribed antipsychotics no ICPC-code was registered. The overall incidence of new antipsychotic prescribing was low, i.e. 1.28 per 1,000 person-years. Furthermore GPs mainly prescribed typical antipsychotics, however the incidence of initiating treatment with an atypical antipsychotic increased almost threefold over the study period.

Strengths and limitations

The high relative risk of prescription for the psychosis category supports the validity of our results. A further strength is that despite the relatively small numbers of patients in the diagnostic categories, the associations observed were fairly strong and all statistically significant.

The limitations of this study are largely inherent to the use of retrospectively collected health-care data. The database did not provide information explicitly stating that the recorded ICPC-codes were the reasons for prescribing antipsychotics, nor did it provide information about the past evolution and severity of the recorded problems, or about unregistered co-existing problems. Therefore, there could be other relevant reasons for general practitioners to prescribe antipsychotics explaining the association between the prescription and the analyzed ICPC-codes. However, we feel that the relations are likely to be largely real as in 84.6% of cases and controls where an ICPC-code was registered, the day of registration coincided with the date of antipsychotic prescribing. Furthermore, a sensitivity analysis excluding all none-coinciding ICPC-codes yielded higher risks for all categories in both adjusted and non-adjusted analyses.

The twelve-month antipsychotics-free period prior to prescription, defining initiation of antipsychotic therapy, may have been too short. However, it seems unlikely that intermittent antipsychotic use was materially classified as new use since in only 4.8% of the cases a subsequent second antipsychotic-free period of at least twelve months was identified within the study period. Nonetheless, a source of bias may be that in 18 cases (2.5%) and in 253 controls (7.1%) the GP

indicated it was a repeat prescription, even though there was a 12-month antipsychotic-free period preceding it. Because of lack of clarity regarding the rules for registration of the indication "repeat" by the GP we ignored it in the selection of our cases and controls. A sensitivity analyses excluding these as "repeat" marked prescription instances in cases and controls yielded similar ORs for all categories (data not shown).

Some of the approved indications for antipsychotics in The Netherlands, i.e. agitation and restlessness and severe and treatment refractory anxiety, do not have a separate ICPC-codes in the Dutch ICPC-registration systems. Obviously, the ICPC-registration system is not designed specifically for registration of approved indications for antipsychotic treatment, but has to cover, mostly in more general terms, the entire spectrum of diagnoses and symptoms that can be encountered in the general practice. However, as the two mentioned approved indications for prescription of antipsychotics could coincide with any of the aforementioned four off-label diagnostic categories, especially 'dementia' and 'depression and anxiety', the relative risks for these categories may have been overestimated. Other reasons for recording one of the off-label categories could be reluctance to diagnose psychosis or incomplete skills or confidence for diagnosing and treating mental disorders[2,15].

In view of the above, it seems likely that our results reflect, at least partially, either off-label prescribing or incomplete registration and probably a combination of these factors.

A clear preference for prescribing typical antipsychotics, as opposed to atypical antipsychotics, was observed. This is in line with the guidelines of the Dutch College of General Practitioners (NHG) recommending typical antipsychotics as a first line of treatment[19].

Comparison with existing literature

The estimated incidence of the GP initiating antipsychotic treatment in the present study was 1.3 per 1,000 person years. Previously published studies reported higher rates of initiation of antipsychotic therapy by the GP, 3.3, and 10.1 per 1,000 person years respectively[9,10,18]. When we included new antipsychotic prescriptions registered by any physician, and not only by the GP, a higher incidence of 2.7 new prescriptions per 1,000 person-years (95%CI: 2.40, 2.97) was found.

The population in Almere is relatively young in comparison with the general population in The Netherlands (source: Statistics Netherlands, Voorburg/Heerlen) while antipsychotics are more often prescribed to elderly people, as is reflected in the mean age in Table 2[1]. When we projected our incidence rate to the age distribution of the general population in The Netherlands the rate of new antipsychotic prescription by GPs, was 1.69 per 1,000 person-years (95%CI: 1.48, 1.91).

Our finding of considerable off-label prescribing of antipsychotics by GPs is consistent with previous work. A study by Mortimer showed that in the majority of cases it was impossible to ascertain a diagnosis that suggested the need for antipsychotic treatment, despite professionals scrutinizing case notes and performing personal enquiries of the GPs[14]. A small retrospective Dutch study using questionnaires found that in 11% of the cases that used antipsychotics, in six general practices, the diagnosis was unkown[17]. The latter study also found that at least 76.9% of women and 40% of the men were prescribed antipsychotics for approved indications, in case the GP made the diagnosis and initiated antipsychotic drug therapy, while in our study in 15.1% of all cases an on-label diagnosis was registered. In this study the percentage increased to 28.8 if those cases were included where any ICPC code was registered and to 33.6 if additionally the date of registration and the prescription date coincided. One study performed in the U.K., including 200 randomly selected first-time users of antipsychotics of 10-99 years old, found that more than half of all incident antipsychotic use in the general practice was for non-approved indications such as depression, anxiety states and panic disorder, 15% for agitation and dementia, and less than 10% for the treatment of schizophrenia and other psychoses[10]. This study excluded less frequently prescribed antipsychotics. In agreement with our study Trifiró et al.[18] reported that anxiety disorders were the most common off-label reason to prescribe typical antipsychotics in a general practice database. The preference of the GP for prescribing typical antipsychotics in the present study (90% of the prescriptions) is consistent with a finding of Hamann et al., who found 77% of typical antipsychotic first prescriptions, while, unlike the present study, prescription of low-potency antipsychotics and depot administrations were excluded from the analyses[7]. A UK study concerning the years 2000 and 2001 found that olanzapine and risperidone were the most frequently prescribed atypical medications, 45% and 38%, respectively (37.3% and 58.2% in our study, respectively)[3]. The proportion of ini-

tiated therapy with atypical antipsychotics by the GP increased almost threefold over the years 2000 (4.7%) to 2003 (14.4%) in the present study, consistent with incidence-rates in Italy that increased similarly from 0.4 per 1,000 person years in 1999 to 1.3 per 1,000 person-years in 2002[18].

Implications for future research or clinical practice

Our results enforce the need for future prospective studies in general practice to prompt GPs to enter a diagnosis and an ICPC-code at the moment of each prescription of antipsychotics, and simultaneously indicate any problem experienced in allocating proper ICPC-codes to the patient. This will provide more robust data to confirm or disprove off-label prescribing of antipsychotics by the GP.

Conclusion

General practitioners do not often initiate antipsychotic therapy. In this study it seemed that, when initiating such treatment, the general practitioner partially did this for off-label indications. Furthermore, at initiation of antipsychotic therapy there was no registration of an ICPC code in 50% of the cases, despite the rareness of the occasion and the severity of the approved indications for antipsychotic treatment. GPs preferred to prescribe typical rather than atypical antipsychotics, yet the proportion of initiated atypical antipsychotic therapy increased threefold from 2000 to 2004.

Acknowledgements

We would kindly like to thank J.H. Boonstra, MD and A. Boels, MD for their highly appreciated input. Furthermore, we would like to thank all the 110 GPs of the Almere Health Care group as well as A. Prins, MS and P. van Steenwijk, MS. Also, we want to express our gratitude for the work done by Nicole Boekema as the datamanager of the database. Lastly, we want to thank Foundation Quadraet, a collaboration between the UMCU and Almere Health Care, for funding the Almere Health Care Medical Database.

References

1. Alonso J., Angermeyer M.C., Bernert S. et al. Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004;(420):55-64.
2. Andersen S.M. and Harthorn B.H. Changing the psychiatric knowledge of primary care physicians. The effects of a brief intervention on clinical diagnosis and treatment. *Gen Hosp Psychiatry* 1990;12(3):177-190.
3. Ashcroft D.M., Frischer M., Lockett J. et al. Variations in prescribing atypical antipsychotic drugs in primary care: cross-sectional study. *Pharmacoepidemiol Drug Saf* 2002;11(4):285-289.
4. Barbui C., Danese A., Guaiana G. et al. Prescribing second-generation antipsychotics and the evolving standard of care in Italy. *Pharmacopsychiatry* 2002;35(6):239-243.
5. Beardsley R.S., Gardocki G.J., Larson D.B. et al. Prescribing of psychotropic medication by primary care physicians and psychiatrists. *Arch Gen Psychiatry* 1988;45(12):1117-1119.
6. Chen H., Reeves J.H., Fincham J.E. et al. Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia medicaid enrollees in 2001. *J Clin Psychiatry* 2006;67(6):972-982.
7. Hamann J., Ruppert A., Auby P. et al. Antipsychotic prescribing patterns in Germany: a retrospective analysis using a large outpatient prescription database. *Int Clin Psychopharmacol* 2003;18(4):237-242.
8. Hohmann A.A., Larson D.B., Thompson J.W. et al. Psychotropic medication prescription in U.S. ambulatory medical care. *DICP* 1991;25(1):85-89.
9. Joukamaa M., Sohlman B. and Lehtinen V. The prescription of psychotropic drugs in primary health care. *Acta Psychiatr Scand* 1995;92(5):359-364.
10. Kaye J.A., Bradbury B.D. and Jick H. Changes in antipsychotic drug prescribing by general practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. *Br J Clin Pharmacol* 2003;56(5):569-575.
11. Lamberts H W.M. ICPC. International Classification of Primary Care. Oxford: Oxford University Pres, 1987
12. Linden M., Lecrubier Y., Bellantuono C. et al. The prescribing of psychotropic drugs by primary care physicians: an international collaborative study. *J Clin Psychopharmacol* 1999;19(2):132-140.
13. Mond J., Morice R., Owen C. et al. Use of antipsychotic medications in Australia between July 1995 and December 2001. *Aust N Z J Psychiatry* 2003;37(1):55-61.
14. Mortimer A.M., Shepherd C.J., Rymer M. et al. Primary care use of antipsychotic drugs: an audit and intervention study. *Ann Gen Psychiatry* 2005;4:18.
15. Oakley B.M., Lee A. and Prabhu R. Self-reported confidence and skills of general practitioners in management of mental health disorders. *Aust J Rural Health* 2007;15(5):321-326.
16. Osborn D.P., Levy G., Nazareth I. et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Rsearch Database. *Arch Gen Psychiatry* 2007;64(2):242-249.

17. Rijcken C.A., Boelema G.J., Slooff C.J. et al. Off-label use of antipsychotics in the community pharmacy: the sex differences. *Pharmacopsychiatry* 2003;36(5):187-191.
18. Trifiro G., Spina E., Brignoli O. et al. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999-2002. *Eur J Clin Pharmacol* 2005;61(1):47-53.
19. Wiersma T. and Goudswaard A.N. NHG-standaarden voor de huisarts. First ed. Houten: Bohn Stafleu van Loghum, 2005:0-1314.
20. Zitman F.G. [Neuroleptics as anxiolytics and antidepressive agents]. *Ned Tijdschr Geneeskd* 1988;132(9):378-379.

Chapter 7

General discussion







Aim

This thesis addresses the necessity of prophylactic antipsychotic treatment in first-episode schizophrenia patients and the effect of discontinuation of antipsychotics on brain volume and side-effects as well as the usage of these medications in general practice. Furthermore, the influence of the delay of antipsychotic treatment during the prodromal and psychotic phase of schizophrenia on brain volume and outcome in first-episode schizophrenia patients is researched and discussed.

Summary of methods and findings

Chapter 2 describes a study in which remitted first-episode schizophrenia patients were randomised to discontinuation, or continuation of their antipsychotic treatment. These patients had been clinically stable for at least one year before participation. Additionally a pooled analysis was performed of our study and the only other studies that researched discontinuation in a randomised fashion in one-year remitted and stable first-episode schizophrenia patients. We found a markedly increased risk of a psychotic relapse after gradual discontinuation and subsequent stopping of antipsychotic medication compared to continuation. In **Chapter 3** we studied the effect of discontinuation of atypical antipsychotic medication on brain volume change (using magnetic resonance imaging (MRI) during a one-year interval in remitted and stable first-episode schizophrenia patients. Patients discontinuing atypical antipsychotics decreased in nucleus accumbens and putamen volume over time, but did not change in gray matter (GM) volume compared to continuation. **Chapter 4** describes the decrease in body mass index (BMI) found after stopping with antipsychotic treatment, while no decrease in extrapyramidal symptoms was identified. In **Chapter 5** we investigated the association between duration of untreated illness (DUI), brain volume at baseline and 5-year brain volume change as measured with MRI, and clinical outcome at baseline and 5-year follow-up in first-episode schizophrenia patients. Our main finding was the lack of association between DUI and brain volume at illness onset or brain volume change during the first five years of psychotic illness. We did identify correlations of symptom scores at illness onset and after 5-year follow-up with both DUI and brain volume (change). It seems that DUI and brain vol-

ume explain different parts of the variance in clinical outcome in first-episode schizophrenia patients.
In **Chapter 6** a case control study in an electronic database is described, in which initiation of antipsychotic therapy in the general practice was associated to International Classification of Primary Care (ICPC) diagnostic categories. We found that general practitioners (GPs) did not often initiate antipsychotic therapy and in 50% they failed to register the reason for it in terms of an ICPC-code. We found initiation of antipsychotics to be associated with four ICPC diagnostic categories that are no approved indications for antipsychotic treatment in The Netherlands, i.e. 'anxiety and depression', 'acute stress and surmenage', 'sleeping disorder', and 'dementia'. As expected, GPs mainly prescribed typical antipsychotics, however the incidence of initiating treatment with an atypical antipsychotic increased almost threefold over the study period.

Discussion

Supporting the results in **Chapter 2**, a markedly increased risk after discontinuation compared to continuation was also found in four earlier trials in first-episode schizophrenia[11,16,31,36,48]. However, these studies had a lack of a tapering period, a short (or non-existent) duration of remission before tapering, with consequent uncertain stability of patients or a switch of antipsychotics just before the trial[11]. We performed an 'open' pragmatic trial, which means that patient and psychiatrist were aware of the allotted intervention (tapering or continuation). The treating psychiatrist managed the actual pattern of tapering of the antipsychotic treatment (within predefined time limits) as well as concomitant treatments. This strategy was chosen to enhance generalisation to clinical practice. The results indicate that there is a markedly increased risk of relapse after discontinuation of antipsychotic therapy. This risk may not outweigh advantages, in terms of resolution of side-effects, of medication discontinuation. This conclusion is supported by Beasley et al., who found that discontinuation of olanzapine in stable patients with chronic schizophrenia compared to continuation led to a decrease in quality of life, even if the patients did not experience psychotic relapse[5]. Our findings will need to be replicated, preferably with a larger sample. Considering the ardent wish of most schizophrenia patients to discontinue their antipsychotics, certainly after remission of a first psychotic episode, it will not be possible

to avoid withdrawal in clinical practice. Nonetheless, the clear and present risk of relapse should be discussed elaborately, a crisis prevention and action plan containing early signs of relapse should be written, and there should be regular contacts with a skilled mental health care worker that knows the patient well.
In possible counterpoise to the conclusion of **Chapter 3**, we found evidence for the putamen, which is associated with side-effects caused by antipsychotics, and the n. accumbens, to react to antipsychotic medication withdrawal with shrinkage over time. This is of particular interest since putamen volume appeared to be increased in patients as compared to healthy controls at baseline, while at that time all patients still used antipsychotics. However, the putamen volume was larger at baseline in patients who discontinued their antipsychotic regimen as compared to patients who continued. Since it concerns a cohort study, and not a randomised study, clinical outcome of the illness might be a possible explanation for the latter finding, as Buchsbaum identified a larger putamen in patients with good outcome schizophrenia in comparison to those with a poor outcome and healthy controls[6]. Indeed, the patients who stopped antipsychotics in this study were apparently able to tolerate tapering and not using medication for a period without experiencing a relapse into psychosis. This might be a sign of a better outcome. Whether the patients that continued their antipsychotics would have been able to tolerate this is of course unknown. It might also be that the increase in putamen volume at baseline in patients relative to controls is an effect of taking atypical antipsychotic medication (although this cannot be tested in our study, but see Glenthoj et al. 2007[23]. If this were the case our findings might mean that discontinuation reverses the effects of atypical medication, at least in the putamen. Interestingly, a review on the mechanism of atypical antipsychotic medications relates increase in activation levels (as represented by increase in Fos-protein levels) in the nucleus accumbens to decrease in positive symptoms, while increases in extra-pyramidal symptoms (side-effects of antipsychotics) are related to increases in Fos levels (and activation) in the putamen and caudate nucleus[1]. Extrapolating from the assumption of reversibility, discontinuation of atypical antipsychotics might decrease the level of activation of Fos levels in both the putamen and the nucleus accumbens, accompanied with volume decrease in both structures, and leading to less EPS and more positive symptoms respectively. Additionally, volumetric data implicate that the consequences of atypical medication for putamen, n. accumbens or n. caudatus are dependent on the state of the brain, being either medication-naïve or being on typical antipsychotic

medication[10,19,20,23,41,46,56], although some studies reported (partially) negative findings[20,23,28,41,46].

Importantly, our results suggest that the excessive reduction of GM volume occurs irrespective of atypical antipsychotic treatment use. To date, only a limited number of controlled longitudinal studies investigated the influence of atypical antipsychotics on brain volume. One randomised study identified GM loss after one year of treatment with haloperidol compared to olanzapine[43]. Together, brain volumetric findings indicate that atypical antipsychotics seem to prevent the loss of GM tissue[7,18,26,32,34,49,53]. Indeed, in a large longitudinal study in a sample of both first-episode as well as chronically ill patients cumulative intake of atypical medication was associated with less loss of GM tissue[27].

However, cerebral GM deficits in patients appear to be present before the start with antipsychotic medication[12,33,52,58] or even before the start of the first symptoms[34]. This supports the likelihood of GM volume loss being associated with the effects of the illness, and not with medication. On the other hand, some studies report no differences in GM between normal controls and medication-naïve patients[7,26,35,49,55]. It would be useful to perform a study like this in a larger sample.

In the same patient groups investigated in **Chapter 2** and **3**, we regularly monitored signs of extrapyramidal side-effects (EPS) such as dystonia, Parkinsonism, (tardive) dyskinesia and akathisia with several questionnaires, and measured weight change over time. This is reported in **Chapter 4**, as unpublished results. The only significant difference between patients discontinuing and patients continuing their antipsychotics was a decrease in BMI of about 2 points after withdrawal. This is a clear advantage of discontinuation of antipsychotic therapy since methods to lose weight during antipsychotic therapy are all time- and effort-consuming[22] or involve medication use[44]. No changes in EPS were identified after withdrawal of antipsychotics. Interestingly, the clinical impression (GB) was that patients discontinuing their antipsychotic medication subsequently had more expression on their face (disappearance of a "mask-like" face) and moved more supple. They appeared more 'alive'. Unfortunately, these observations were not measurable objectively and systematically because of their subtlety. Nonetheless, patients often complain of feeling 'trapped' as if they reside in a 'suit-of-armour' in clinical practice. This might be explained by the EPS they experience using antipsychotic medication. These are serious side-effects since human interaction is impaired when facial and body mime is diminished because of side-effects. It would be interesting to have a more objective way of measuring subtle forms

of Parkinsonism. An explanation for not finding a decrease of side-effects with questionnaires might be the relatively low dosages of antipsychotics that were used in this study, the fact that only atypical antipsychotics were used or the lack of sensitivity of the questionnaires.

In **Chapter 5** we found no association between duration of untreated illness (DUI) and brain volume (change). This is in line with the only longitudinal CT (Computed Tomography) study on this subject, that found no relationship between duration of untreated psychosis and 5-year change in frontal brain atrophy in first-episode schizophrenia [45]. Two cross-sectional MRI studies did show correlations between longer DUI and decreased volume or GM density in small areas in the brain in first-episode schizophrenia patients[2,40], in contrast to other studies[14,15,30]. Considering the above, if there is a relation between DUI and brain volume (change), it might be restricted to focal areas of the brain.

Consistent with the literature, we found DUI to be significantly longer with higher scores on measures of functional and symptomatic outcome both at baseline and at follow-up measurement. Most convincing was the association between DUI and positive symptoms as measured with the Positive and Negative Syndrome Scale (PANSS). Although in previous literature such an association has been reported[13], lack of association was also found[3,4,24,29]. Lastly, there was a positive correlation between DUI and the Camberwell Assessment of Need total score at T5, although the Global Assessment of Functioning (GAF) score and DUI were not correlated. The latter is interesting as several studies did identify a correlation between DUI and GAF at follow-up measurement, with intervals ranging from one to four years[9,13,21,39]. However, all of these studies investigated patients that were already on medication, which obviously affects the outcome measures of symptomatology. Importantly, we included 36 medication-naïve patients in whom correlations between symptomatic and functional outcome at baseline and DUI were all in the same direction and of similar (or larger) magnitude compared to the total sample. However, due to the smaller magnitude of the sample these correlations did not all reach significance. In summary, we replicated the associations between DUI and psychiatric symptomatology at baseline and after five years of illness in medicated as well as medication-naïve patients.

Brain volume (change) and outcome were also found to be correlated. The relation between more PANSS positive symptoms at 5-year follow-up and a smaller baseline lateral ventricle and larger baseline cerebellum volume seems counterintuitive. We found some support[17,42], contradiction[38,59] and also lack of replication

of our findings[8,18,19]. Importantly, confounding by usage of antipsychotic medication is unavoidable in longitudinal studies or studies with chronic schizophrenia patients, such as the above.
We also showed that lower total brain volume was associated with more PANSS negative symptoms both at treatment onset as well as at follow-up measurement which is in line with earlier studies from our group including overlapping samples[8,9,27]. These findings corroborate results from previous studies[25,47]. In medication-naïve patients we found equally large correlations, although not significant because of the smaller number of patients, between PANSS total and negative score and baseline TB and third ventricle volume.
The final study, in **Chapter 6** in this thesis describes an electronic database study in which initiating antipsychotic therapy in the general practice was associated to ICPC diagnostic categories. The validity of the results is supported by the high relative risk of prescription for the "psychosis category". The limitations of this study are largely inherent to the use of retrospectively collected health-care data, which were not specifically collected for this specific study. Our finding of considerable off-label prescribing of antipsychotics by GPs is consistent with previous work[37,50,54]. In agreement with our study Trifiró et al[57] reported that anxiety disorders were the most common off-label reason to prescribe typical antipsychotics in a general practice database.

Conclusions

It appears that there is a markedly increased risk of relapse after discontinuation of antipsychotic therapy in remitted and stable first-episode schizophrenia patients, which may not outweigh advantages of medication discontinuation in terms of resolution of side-effects. However, antipsychotic medication withdrawal in this patient group might be associated with decrease over time in the volume of the putamen, in which increase has been associated with extra-pyramidal side-effects. Nonetheless, we could not identify differences with questionnaires in movement disorders in patients that continued versus patients that discontinued antipsychotics. Nevertheless, the body mass index of patients that discontinued their medication decreased significantly and substantially compared to continuation. Importantly, the results presented in this thesis suggest that the gray matter deficits that were identified in these schizophrenia patients are not a medication

effect. Furthermore, we found that although symptomatic and functional outcome was associated with both duration of illness and (change in) brain volume, there was no correlation between DUI and brain volume (change) in first-episode patients. Therefore, it seems that brain volume at treatment onset and excessive tissue loss over time during the first five years of the illness and DUI explain a different part of the variation in symptomatic and functional outcome.
Additionally our results suggest that general practitioners prescribe antipsychotics off-label in part of their patients. However, general practitioners do not often initiate antipsychotic treatment, and in the large majority of cases they start with typical antipsychotics as prescribed in their guidelines. Importantly, in 50% of the first prescriptions they do not enter an ICPC-code as a diagnosis into their electronic patient dossier.

Future perspectives

The main caveat of the studies described in **Chapter 2, 3 and 4** is the small number of patients.
An other important problem is that we have probably not identified all patients eligible for participation in these studies. Furthermore, we would have liked to first see the (change) in brain volume of these patients after their initial start with antipsychotic treatment.
In planning and executing a discontinuation study a difficulty lies in the precision with which the patients should be followed in order to truly be able to establish a relapse at the moment it occurs. Also, it's a challenge to motivate the patients to undergo MRI scanning 4 or 5 times in two years, and making them travel the distance to the hospital.
Missing eligible patients, and also being able to investigate their initial reaction to antipsychotic medication, might be solved by using an epidemiological sample, including every first-episode psychosis patient. However, it is almost impossible to randomise someone to starting with antipsychotics or not at the first psychosis. To withhold treatment would be unethical if it were longer then one or two observational weeks for diagnostic purposes. Also the suffering of the patient should allow it and permission of both the patient and the judicial representative is required. Fortunately, it has been shown that a one week medication period is long enough to identify brain morphologic differences between medication-

naive and recently medicated patients[51]. However, most acutely admitted psychotic patients need antipsychotic treatment as soon as possible. Wunderink et al. did investigate an epidemiological sample which they already randomised at baseline, when the patients were still in the middle of their first-episode, to continuation of discontinuation of antipsychotic therapy[60]. The randomisation was only executed at the moment the patient had reached remission for 6 months. However, the participation in such a trial would be prolonged with the duration it takes the patient to become stable. This might cause an extra burden on the patient. On the other hand, it would be possible to implement duration of illness research, as described in **Chapter 5** in this period, and to implement a study of the reaction of the brain to initiation of antipsychotic therapy.

In the case of Wunderink et al. the actual execution of the (dis)continuation strategy was left to the treating psychiatrist and patient[60]. Perhaps this arose from the larger anonymity in this bigger trial, leading to less control in the individual case. Since patients and treating psychiatrists differ in wishes and insights from researchers, the actual execution of the withdrawal or continuation was impaired: there was discontinuation in the continuation strategy, and the other way around. This dilution might have been prevented if the randomisation had only been activated in those cases where patient (and treating psychiatrist) truly wished to participate in a trial in which both continuation and discontinuation were possibilities, after reaching remission. However, a more intensive research contact at the moment of remission would have been necessary to assess and discuss the will to, and consequences of, participation to a strict protocol. Also the follow-up would have had to be more intensive. Perhaps this could be avoided if a more robust relapse criterion such as hospitalisation would be used. However, in clinical practice hospitalisation occurs at different places by different psychiatrists for different reasons and at different levels of psychosis or discomfort. Taking off a validated questionnaire by trained researchers can prevent such idiosyncrasies, but requires more intensive follow-up.

In the Netherlands, a relatively small country, with about 3200 first-episodes of psychosis per year, it would be best to develop a well-known maze of referral facilities for everybody that comes into contact with first-episode psychosis patients. This should be coupled to a large research project. There should be the possibility to immediately (within hours) refer to a facility that is relatively close to the patient. In this facility, research should be combined with care at a high level to provide an excellent reason for both the patient and the referring party

for the referral. The research should subsequently come to the patient instead of the other way around. Preferably, a patient would have a manager for his or her treatment, and one for the research. There should be a close connection between these two. A research manager should be able to manage 20-25 patients. The manager for the research should not only be aware of the research projects the patient can participate in, and arrange for these to happen if the patient should want to participate, but should also be able to accompany the patient and be resourceful in doing parts of the research his- or herself after instruction. Also, the research manager should prospectively and anonymously collect pre-defined general research data in a pre-defined anonymous way, such as medication exposure, physical data (i.e. length, weight, extrapyramidal side-effects), dates of hospitalisation and discharge, blood sampling (i.e. prolactin, blood levels of antipsychotics), etc. In this way a maximum of participation in research should lead to a minimum of stress and exposure for the patient. There should be supervision top-down as too how many research projects are running and how feasible it is to create a good sample for each project. A supervisor should have contact with the research-managers to assess the possibility of starting a new research-project. Of course, an organisation as described above would cost a lot of effort and money. Fortunately, a number of large projects regarding first-episode psychosis have already been ongoing in the Netherlands. For example: GROUP (Genetic Risk and OUtcome in Psychosis) and before that: MESIFOS (MEdication Strategies in First Onset Schizophrenia).

With regard to **Chapter 6**, and future research of indications for initiating antipsychotic therapy by the general practitioner it would be wise to ensure the fusion of the start of antipsychotic therapy with the structured registration of the reason for it. Such stricter coupling of action and reason would provide more robust data to confirm or disprove off-label prescribing of antipsychotics by the general practitioner.

References

1. Ananth J., Burgoyne K.S., Gadasalli R. et al. How do the atypical antipsychotics work? *J Psychiatry Neurosci* 2001;26(5):385-394.
2. Bangalore S.S., Goradia D.D., Nutche J. et al. Untreated illness duration correlates with gray matter loss in first-episode psychoses. *Neuroreport* 2009;20(7):729-734.
3. Barnes T.R., Hutton S.B., Chapman M.J. et al. West London first-episode study of schizophrenia. Clinical correlates of duration of untreated psychosis. *Br J Psychiatry* 2000;177:207-211.
4. Barnes T.R., Leeson V.C., Mutsatsa S.H. et al. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br J Psychiatry* 2008;193(3):203-209.
5. Beasley C.M., Jr., Sutton V.K., Taylor C.C. et al. Is quality of life among minimally symptomatic patients with schizophrenia better following withdrawal or continuation of antipsychotic treatment? *J Clin Psychopharmacol* 2006;26(1):40-44.
6. Buchsbaum M.S., Shihabuddin L., Brickman A.M. et al. Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophr Res* 2003;64(1):53-62.
7. Cahn W., Hulshoff Pol H.E., Bongers M. et al. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. *Br J Psychiatry Suppl* 2002;43:s66-s72.
8. Cahn W., Hulshoff Pol H.E., Lems E.B. et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry* 2002;59(11):1002-1010.
9. Cahn W., van Haren N.E., Hulshoff Pol H.E. et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006;189:381-382.
10. Chakos M.H., Lieberman J.A., Alvir J. et al. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995;345(8947):456-457.
11. Chen E.Y., Hui C.L., Lam M.M. et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010;341:c4024.
12. Chua S.E., Cheung C., Cheung V. et al. Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. *Schizophr Res* 2007;89(1-3):12-21.
13. Clarke M., Whitty P., Browne S. et al. Untreated illness and outcome of psychosis. *Br J Psychiatry* 2006;189:235-240.
14. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. *Schizophr Res* 2007;91(1-3):87-96.
15. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. *Neuroimage* 2007;35(4):1613-1623.
16. Crow T.J., MacMillan J.F., Johnson A.L. et al. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 1986;148:120-127.
17. DeLisi L.E., Sakuma M., Maurizio A.M. et al. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res* 2004;130(1):57-70.

18. DeLisi L.E., Sakuma M., Tew W. et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 1997;74(3):129-140.
19. Ebdrup B.H., Glenthoj B., Rasmussen H. et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci* 2010;35(2):95-104.
20. Frazier J.A., Giedd J.N., Kaysen D. et al. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 1996;153(4):564-566.
21. Fusar-Poli P., Meneghelli A., Valmaggia L. et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry* 2009;194(2):181-182.
22. Ganguli R. Behavioral therapy for weight loss in patients with schizophrenia. *J Clin Psychiatry* 2007;68 Suppl 4:19-25.
23. Glenthoj A., Glenthoj B.Y., Mackeprang T. et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. *Psychiatry Res* 2007;154(3):199-208.
24. Gonzalez-Blanch C., Crespo-Facorro B., varez-Jimenez M. et al. Pretreatment predictors of cognitive deficits in early psychosis. *Psychol Med* 2008;38(5):737-746.
25. Gur R.E., Cowell P., Turetsky B.I. et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 1998;55(2):145-152.
26. Gur R.E., Maany V., Mozley P.D. et al. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatry* 1998;155(12):1711-1717.
27. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 2008;63(1):106-113.
28. Heitmiller D.R., Nopoulos P.C. and Andreasen N.C. Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. *Schizophr Res* 2004;66(2-3):137-142.
29. Ho B.C., Andreasen N.C., Flaum M. et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 2000;157(5):808-815.
30. Hoff A.L., Sakuma M., Razi K. et al. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *Am J Psychiatry* 2000;157(11):1824-1828.
31. Hogarty G.E. and Ulrich R.F. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiatr Res* 1998;32(3-4):243-250.
32. Hulshoff Pol H.E. and Kahn R.S. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34(2):354-366.

33. Jayakumar P.N., Venkatasubramanian G., Gangadhar B.N. et al. Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naive schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29(4):587-591.
34. Job D.E., Whalley H.C., Johnstone E.C. et al. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 2005;25(4):1023-1030.
35. John J.P., Burgess P.W., Yashavantha B.S. et al. Differential relationship of frontal pole and whole brain volumetric measures with age in neuroleptic-naive schizophrenia and healthy subjects. *Schizophr Res* 2009;109(1-3):148-158.
36. Kane J.M., Rifkin A., Quitkin F. et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 1982;39(1):70-73.
37. Kaye J.A., Bradbury B.D. and Jick H. Changes in antipsychotic drug prescribing by general practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. *Br J Clin Pharmacol* 2003;56(5):569-575.
38. Kempton M.J., Stahl D., Williams S.C. et al. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophr Res* 2010;120(1-3):54-62.
39. Keshavan M.S., Haas G., Miewald J. et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr Bull* 2003;29(4):757-769.
40. Keshavan M.S., Haas G.L., Kahn C.E. et al. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res* 1998;32(3-4):161-167.
41. Lang D.J., Kopala L.C., Vandorpe R.A. et al. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *Am J Psychiatry* 2004;161(10):1829-1836.
42. Levitt J.J., McCarley R.W., Nestor P.G. et al. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *Am J Psychiatry* 1999;156(7):1105-1107.
43. Lieberman J.A., Tollefson G.D., Charles C. et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 2005;62(4):361-370.
44. Maayan L., Vakhrusheva J. and Correll C.U. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010;35(7):1520-1530.
45. Madsen A.L., Karle A., Rubin P. et al. Progressive atrophy of the frontal lobes in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. *Acta Psychiatr Scand* 1999;100(5):367-374.
46. Massana G., Salgado-Pineda P., Junque C. et al. Volume changes in gray matter in first-episode neuroleptic-naive schizophrenic patients treated with risperidone. *J Clin Psychopharmacol* 2005;25(2):111-117.
47. Mathalon D.H., Sullivan E.V., Lim K.O. et al. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 2001;58(2):148-157.

48. McCreadie R.G., Wiles D., Grant S. et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. *Acta Psychiatr Scand* 1989;80(6):597-602.
49. Molina V., Reig S., Sanz J. et al. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr Res* 2005;80(1):61-71.
50. Mortimer A.M., Shepherd C.J., Rymer M. et al. Primary care use of antipsychotic drugs: an audit and intervention study. *Ann Gen Psychiatry* 2005;4:18.
51. Narr K.L., Toga A.W., Szeszko P. et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. *Biol Psychiatry* 2005;58(1):32-40.
52. Ohrmann P., Siegmund A., Suslow T. et al. Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. *J Psychiatr Res* 2007;41(8):625-634.
53. Pantelis C., Yucel M., Wood S.J. et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005;31(3):672-696.
54. Rijcken C.A., Boelema G.J., Slooff C.J. et al. Off-label use of antipsychotics in the community pharmacy: the sex differences. *Pharmacopsychiatry* 2003;36(5):187-191.
55. Salgado-Pineda P., Baeza I., Perez-Gomez M. et al. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. *Neuroimage* 2003;19(2 Pt 1):365-375.
56. Scheepers F.E., de Wied C.C., Hulshoff Pol H.E. et al. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology* 2001;24(1):47-54.
57. Trifiro G., Spina E., Brignoli O. et al. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999-2002. *Eur J Clin Pharmacol* 2005;61(1):47-53.
58. Venkatasubramanian G., Jayakumar P.N., Gangadhar B.N. et al. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. *Psychiatry Res* 2008;164(3):215-222.
59. Wassink T.H., Andreasen N.C., Nopoulos P. et al. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. *Biol Psychiatry* 1999;45(1):41-48.
60. Wunderink L., Nienhuis F.J., Sytema S. et al. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry* 2007;68(5):654-661.

Hoofdstuk 8

Nederlandse samenvatting

Doel

Dit proefschrift behandelt de noodzaak tot profylactische antipsychotische behandeling in eerste-episode schizofrenie patiënten, evenals het effect van stoppen met antipsychotica op zowel hersenvolume als bijwerkingen. Daarnaast werd het gebruik van antipsychotica in de huisartsenpraktijk onderzocht. Verder werd de invloed van uitstel van antipsychotische behandeling gedurende de prodromale en psychotische fase van schizofrenie op hersenvolumeverandering en uitkomst in eerste-episode schizofrenie patiënten onderzocht en besproken.

Samenvatting van de methoden en bevindingen

Hoofdstuk 2 beschrijft een studie waarin eerste-episode schizofrenie patiënten werden geloot naar stoppen of doorgaan met hun antipsychotische medicatie. Deze patiënten waren klinisch hersteld en stabiel gedurende tenminste het voorgaande jaar. De enige andere studie die ook het stoppen met antipsychotica gerandomiseerd onderzocht in sinds 1 jaar herstelde en stabiele patiënten met eerste-episode schizofrenie werd samengevoegd met onze studie. We vonden een fors vergroot risico op psychotische terugval bij geleidelijke afbouw en vervolgens stoppen van antipsychotica, in vergelijking met doorgaan. In **Hoofdstuk 3** bestudeerden we het effect van stoppen met atypische antipsychotica op hersenvolumeverandering gedurende een interval van 1 jaar in herstelde en stabiele eerste-episode schizofrenie patiënten. In de patiënten die stopten met antipsychotica verkleinde de nucleus accumbens en het putamen over tijd, maar trad geen verandering op in grijze stof (GS) in vergelijking met doorgaan. **Hoofdstuk 4** beschrijft de afname van de "body mass index" (BMI, een maat voor gewicht) na stoppen met antipsychotica. Er werd geen afname in extrapyramidale bijwerkingen gevonden na stoppen. In **Hoofdstuk 5** onderzochten we in eerste-episode schizofrenie patiënten de associatie tussen 1. de duur van de onbehandelde ziekte (DOZ), 2. hersenvolume tijdens de nulmeting (T0, kort na de start met antipsychotica), en hersenvolumeverandering in 5 jaar. en 3. klinische uitkomsten op T0 en na vijf jaar follow-up. Onze belangrijkste bevinding was het gebrek aan relatie tussen DOZ en hersenvolume op T0 of hersenvolumeverandering na 5 jaar follow-up. Er waren wel correlaties tussen symptoomscores op T0 en na 5 jaar follow-up met zowel DOZ als hersenvolume (verandering). Het lijkt erop

dat DOZ en hersenvolume ieder een ander deel van de variantie van klinische uitkomst bij eerste-episode schizofrenie patiënten verklaren.
In **Hoofdstuk 6** werd een "case-control" studie in een elektronische database beschreven. In deze studie werd het initiëren van antipsychotische behandeling in de huisartsenpraktijk geassocieerd met diagnostische categoriën die werden samengesteld uit de International Classification of Primary Care (ICPC). Huisartsen startten niet vaak met antipsychotica en in 50% van de gevallen registreerden ze geen reden voor het starten, dat wil zeggen, geen ICPC-code. Het starten met antipsychotica was geassocieerd met vier diagnostische ICPC-categoriën die allen geen goedgekeurde indicaties vormen voor antipsychotische behandeling in Nederland, namelijk 'angst en depressie', 'acute stress en overspannenheid', 'slaapstoornis' en 'dementie'. Zoals verwacht schrijven huisartsen voornamelijk typische antipsychotica voor, hoewel de incidentie van het initiëren van behandeling met atypische middelen bijna drievoudig toenam tijdens de studieperiode.

Discussie

De resultaten in **Hoofdstuk 2** ondersteunend werd ook in 4 eerdere trials in eerste-episode schizofrenie een fors verhoogd risico gevonden na stoppen met antipsychotica in vergelijking met doorgaan[11,16,31,36,48]. Echter, in deze studies was er geen afbouwperiode, een korte (of ontbrekende) remissietijd alvorens afbouw plaatsvond met daardoor een onzekere stabiliteit van de patiënten, of een wisseling in type antipsychoticum net voor de trial[11]. Wij hebben een 'open' pragmatische trial uitgevoerd. Dit betekent dat zowel patiënt als behandelend psychiater zich bewust was van de gelootte interventie (afbouwen of doorgaan). De behandelend psychiater bepaalde hoe de antipsychotica werden afgebouwd (binnen van te voren gedefinieerde tijdslimieten) en of er andere therapiën werden ingezet. We hebben deze opzet gekozen om de generalisatie naar de algemene praktijk te vergroten. De resultaten wijzen erop dat er een ernstig verhoogd risico is op terugval in psychose na stoppen met antipsychotica. Dit weegt mogelijk niet op tegen de voordelen van stoppen, zoals het verdwijnen van bijwerkingen. Deze conclusie wordt ondersteund door Beasley et al., die vonden dat het stoppen met olanzapine in patiënten met chronische schizofrenie in vergelijking met doorgaan aanleiding gaf tot afname van de kwaliteit van leven, zelfs als de

patiënten geen psychotische terugval doormaakten[5]. Onze bevindingen zullen moeten worden gerepliceerd met een groter patiëntenaantal.
Gezien de vurige wens van de meeste schizofrenie patiënten om te stoppen met hun antipsychotica, zeker na herstel van een éerste psychose, zal het niet mogelijk zijn om het afbouwen van antipsychotica te vermijden in de klinische praktijk. Desalniettemin moet het duidelijk aanwezige risico op terugval uitvoerig worden besproken, moet er een crisis preventie- en actieplan met daarin vroege waarschuwingssignalen worden geschreven, en moet er regelmatig contact zijn tijdens en na afbouw met een ervaren medewerker in de geestelijke gezondheidszorg die de patiënt liefst goed kent.
Mogelijk als tegenhanger voor de conclusie in **Hoofdstuk 3** vonden we bewijs voor verkleining van het putamen, welke wordt geassocieerd met de bijwerkingen veroorzaakt door antipsychotica, en de nucleus accumbens na het stoppen met antipsychotica. Dit is extra interessant omdat het putamen volume vergroot leek te zijn in patiënten vergeleken met gezonde controles op de nulmeting (T0) op het moment dat alle patiënten nog medicatie gebruikten. Echter, het putamen volume was groter op T0 in patiënten die stopten met antipsychotica in vergelijking met hen die doorgingen. Aangezien dit een cohort studie betreft, en geen gerandomiseerde studie, zou dit verklaard kunnen worden door de uiteindelijke klinische uitkomst van de ziekte, daar Buchsbaum een groter putamen vond in patiënten met schizofrenie met een goede uitkomst in vergelijking met zowel patiënten met een slechte uitkomst als gezonde controles[6]. Inderdaad was het zo dat de patiënten die in deze studie stopten blijkbaar de afbouw en ook een periode zonder medicatie konden verdragen zonder een psychose te krijgen, dit kan een teken van goede uitkomst zijn. Het is natuurlijk niet bekend of de patiënten die doorgingen dit ook zouden hebben kunnen verdragen. Het zou zo kunnen zijn dat de vergroting in het putamen volume in patiënten in vergelijking met controles een effect is van de inname van atypische medicatie (hoewel dit niet getest kan worden in onze studie, maar zie Glenthoj et al. 2007[23]). Als dit het geval zou zijn dan zouden onze bevindingen kunnen betekenen dat het stoppen met atypische antipsychotica het effect ervan omkeert, in elk geval in het putamen. Een interessante review over de mechanismen van atypische antipsychotische medicatie relateert een toename in activatie niveau (gerepresenteerd door een toename in Fos-eiwit activatie) in de nucleus accumbens aan een afname in positieve symptomen, terwijl een toename in extrapyramidale bijwerkingen gerelateerd werd aan een toename in activatie (van Fos-eiwit) in het putamen en de nucleus

caudatus.[1] Extrapolerend vanuit de aanname van omkeerbaarheid zou het afbouwen van atypische antipsychotica het activatie niveau van het Fos-eiwit juist kunnen verminderen in zowel het putamen als de nucleus accumbens en dan gepaard kunnen gaan met een volume vermindering in beide structuren, en zowel minder extrapyramidale als positieve symptomen. Verder impliceren volumetrische data dat de gevolgen van atypische medicatie voor het putamen, de nucleus accumbens en de nucleus caudatus afhankelijk zijn van de staat waarin het brein verkeerd, namelijk in antipsychotica naieve, of gemediceerde staat (gemediceerd met typische antipsychotica)[10,19,20,23,41,46,56], hoewel sommige studies (gedeeltelijk) geen invloed vinden van antipsychotica[20,23,28,41,46].

Het is van belang dat onze resultaten suggereren dat de excessieve reductie van GS optreedt onafhankelijk van het gebruik van atypische antipsychotica. Tot op heden hebben slechts een klein aantal gecontroleerde longitudinale studies gekeken naar de invloed van atypische medicatie op hersenvolume. Eén gerandomiseerde studie vond GS verlies na 1 jaar behandeling met haloperidol, in vergelijking met olanzapine [43]. Tezamen laten hersenvolumetrische bevindingen zien dat atypische antipsychotica GS verlies lijken te voorkomen[7,18,26,32,34,49,53]. Inderdaad was de cumulatieve inname van atypische medicatie in een grote longitudinale studie zowel in eerste-episode als in chronisch zieke patiënten geassocieerd met minder verlies van GS[27]. Echter, cerebrale GS tekorten in patiënten lijken al aanwezig te zijn voor de start met antipsychotica[12,33,52,58] of zelfs voor ontstaan van de eerste symptomen van psychose[34]. Dit ondersteunt de hypothese dat GS verlies is geassocieerd met de effecten van de ziekte, en niet met medicatiegebruik. Van de andere kant zijn er ook studies die geen verschil rapporteren in GS tussen gezonde controles en medicatie-naieve patiënten[7,26,35,49,55]. Het zou nuttig zijn om een studie als de onze in een grotere groep te herhalen.

In dezelfde patiënten groep beschreven in **Hoofdstuk 2** en **3** hebben we regelmatig extrapyramidale bijwerkingen (EPS) zoals dystonie, Parkinsonisme (tardieve) dyskinesie en akathisie vastgelegd met verschillende vragenlijsten. Ook maten we regelmatig het gewicht. Dit wordt beschreven in **Hoofdstuk 4**, als niet-gepubliceerde resultaten. Het enige significante verschil tussen patiënten die stopten en patiënten die doorgingen met hun antipsychotica was een afname van het BMI met ongeveer 2 punten na afbouw. Dit is een duidelijk voordeel van stoppen met antipsychotische behandeling. Immers, gewicht verliezen tijdens antipsychotica gebruik kost veel tijd en moeite[22], of omvat medicatie gebruik[44]. Er werden geen veranderingen in EPS gevonden na stoppen met antipsychotica. Desondanks

was de klinische impressie (GB) dat patiënten na afbouw meer gezichtsexpressie lieten zien (verdwijnen van een 'maskergelaat') en soepeler bewogen. Ze maakten daarbij een levendiger indruk. Helaas zijn deze observaties niet objectief en systematisch te meten door hun subtiliteit. Het is het zo dat schizofrenie patiënten in de klinische praktijk vaak klagen over zich 'gevangen' voelen alsof ze in een 'harnas' zitten bij gebruik van antipsychotica. Dit zou verklaard kunnen worden door de extrapyramidale bijwerkingen die worden veroorzaakt door de antipsychotica. Dit zijn ernstige bijwerkingen omdat de menselijke interactie wordt belemmerd als subtiele gezichts- en lichaamstaal verminderen. Het zou interessant zijn om een meer objectieve manier te hebben om deze subtiele vormen van Parkinsonisme te kunnen meten. Een verklaring voor het met vragenlijsten niet kunnen vinden van afname van de bijwerkingen zou kunnen zijn dat er relatief lage doseringen antipsychotica werden gebruikt en doordat er alleen atypische antipsychotica werden gebruikt. Ook zouden de vragenlijsten niet gevoelig genoeg kunnen zijn.

In **Hoofdstuk 5** vonden we geen associatie tussen de duur van de onbehandelde ziekte (DOZ) en hersenvolume (verandering). Dit komt overeen met de resultaten van de enige longitudinale CT (Computed Tomography) studie over dit onderwerp, die geen verband vond tussen de duur van de onbehandelde psychose en verandering in frontale hersenatrofie in 5 jaar bij eerste-episode schizofrenie[45]. Twee cross-sectionele MRI studies lieten wel correlaties zien tussen langere DOZ en verkleind grijze stof (GS) volume of GS dichtheid in kleine gebieden in het brein in eerste-episode schizofrenie[2,40], in tegenstelling tot andere studies[14,15,30]. Het bovenstaande in overwegende lijkt het zo te zijn dat als er een relatie is tussen DOZ en hersenvolume (verandering) dit beperkt is tot kleine gebieden in het brein.

In overeenstemming met de literatuur vonden we dat DOZ significant langer was bij hogere scores op maten voor functionele en symptomatische uitkomst zowel op T0 als bij 5 jaar follow-up. Het meest overtuigend was de associatie tussen DOZ en de met de Positive And Negative Syndrome Scale (PANSS) gemeten positieve symptomen. Hoewel in de literatuur zo'n associatie eerder is gevonden[13], zijn er ook negatieve bevindingen geweest[3,4,24,29]. Tenslotte was er een positieve correlatie tussen DOZ en de Camberwell Asessment of Need totaalscore bij 5 jaar follow-up, hoewel de Global Assessment of Functioning (GAF) score en DOZ niet gecorreleerd waren. Dit laatste is interessant omdat verschillende studies wel een correlatie tussen DOZ en GAF bij follow-up hebben gevonden, met een

interval wat varieerde tussen de één en de vier jaar[9,13,21,39]. Echter, al deze studies onderzochten patiënten die al op medicatie ingesteld waren. Dit beïnvloedt uiteraard de symptoomuitkomsten. Belangrijk is dat wij 36 medicatie-naieve patienten hebben geïncludeerd en dat de correlaties tussen uitkomst op T0 en DOZ bij hen allemaal in de zelfde richting en van (ongeveer) gelijke grootte waren als in de totale groep. Deze correlaties waren niet allemaal significant door het kleinere aantal patiënten. Samenvattend hebben we de associatie tussen DOZ en psychiatrische klachten op T0 en na 5 jaar behandeling zowel in gemediceerde als in medicatie-naieve patiënten gerepliceerd. Hersenvolume(verandering) en uitkomst waren ook gecorreleerd. De relatie tussen meer PANSS positieve symptomen bij 5 jaar follow-up en een kleinere laterale ventrikel en groter cerebellum op T0 lijken tegennatuurlijk. We vonden hiervoor ondersteunende[17,42], tegensprekende [38,59] en neutrale bevindingen[8,18,19]. Belangrijk is dat verstoring van resultaten door het gebruik van antipsychotische medicatie onvermijdelijk is in longitudinale studies of in studies met chronische schizofrenie patiënten, zoals de bovenstaande.

We hebben ook laten zien dat een kleiner totaal hersenvolume geassocieerd was met meer PANSS negatieve symptomen, zowel op T0 als bij follow-up. Dit komt overeen met eerdere studies van onze groep die overlappende patiëntengroepen includeerden[8,9,27]. Deze bevindingen onderschrijven de resultaten van eerdere studies[25,47]. In medicatie-naieve patiënten vonden we correlaties van dezelfde grootte, hoewel ze niet significant waren door het kleinere aantal patiënten, tussen de PANSS totale en negatieve score en het totale brein en derde ventrikelvolume.

Het laatste hoofdstuk, **Hoofdstuk 6** van dit proefschrift, beschrijft een studie in een elektronische database waarin het starten met antipsychotische behandeling in de huisartsenpraktijk geassocieerd werd met ICPC diagnostische categoriën. De validiteit van de resultaten wordt ondersteund door het hoge relatief risico van voorschrijven van antipsychotica voor de "psychose" catagorie. De beperkingen van deze studie zijn grotendeels inherent aan het gebruik van retrospectief verzamelde gezondheidszorgdata uit een database die niet is opgezet voor dit specifieke onderzoek. Onze bevinding dat huisartsen in een aanzienlijk deel van de patiënten startten met antipsychotica voor indicaties die off-label zijn is consistent met eerder werk[37,50,54]. In overeenstemming met onze studie rapporteerden Trifiró et al[57] dat angststoornissen de meest algemene reden zijn om typische antipsychotica off-label voor te schrijven.

Conclusies

Het lijkt waarschijnlijk dat er een fors verhoogd risico op terugval is na stoppen met antipsychotische therapie in herstelde en stabiele eerste-episode schizofrenie patiënten. Het zou goed kunnen dat dit risico niet opweegt tegen de voordelen van het stoppen met medicatie, namelijk het verdwijnen of verminderen van bijwerkingen. Echter, het afbouwen van antipsychotica in deze patiënten groep zou geassocieerd kunnen zijn met een afname over de tijd in putamen volume, terwijl putamen volume toename geassocieerd is met extrapyramidale bijwerkingen. Desondanks konden we met vragenlijsten geen verschil vinden in bewegingsstoornissen tussen patiënten die stopten of doorgingen. Wel nam de 'body mass index', ofwel het gewicht, substantieel af in patiënten die stopten in vergelijking met patiënten die doorgingen met atypische antipsychotica. Belangrijk is dat onze resultaten suggereren dat de grijze stof tekorten die worden gezien in deze schizofrenie patiënten geen medicatie effect lijken te zijn. Naast deze bevinding vonden we geen correlatie tussen DOZ en hersenvolumeverandering in eerste-episode patiënten, hoewel uitkomst (functioneel en symptomatisch) wel was geassocieerd met zowel DOZ als hersenvolumeverandering. Het lijkt er dus op dat zowel hersenvolume gemeten rond het starten met behandeling en extra hersenvolumeverlies tijdens de eerste vijf jaar van behandeling als duur van de onbehandelde ziekte een verschillend deel van de variantie in symptomatische en functionele uitkomst verklaren.
Als laatste suggereren onze resultaten dat huisartsen antipsychotica in een deel van hun patiënten voor off-label redenen initiëren. Echter, huisartsen startten niet vaak met antipsychotische behandeling, en in de overgrote meerdereheid van de gevallen beginnen ze met typische antipsychotica zoals voorgeschreven in hun richtlijnen. Belangrijk is dat ze in ongeveer 50% van de gevallen geen ICPC-code in het elektronische patiënten dossier zetten bij het voorschrijven van deze middelen.

Toekomst perspectieven

De grootste tekortkoming van de studies beschreven in **Hoofdstuk 2, 3** en **4** is het kleine aantal patiënten. Een hieraan verbonden belangrijk probleem is dat we niet alle patiënten hebben gevonden die aan deze studies mee hadden kunnen

doen. Daarnaast hadden we graag de volumeverandering willen zien veroorzaakt door de start met antipsychotische medicatie.
Bij het plannen en uitvoeren van een stop-studie is het moeilijk om de precisie en frequentie van follow-up vast te stellen die nodig is om een terugval betrouwbaar vast te stellen op het daadwerkelijke moment dat deze gebeurt. Ook is het een uitdaging om de participerende patiënten te motiveren voor alle visites, en om 4 tot 5 keer een MRI scan te ondergaan, met daaraan gekoppeld een reis naar een ziekenhuis. Het missen van includeerbare patiënten, en mogelijkheid hun initiële reactie op antipsychotische medicatie te onderzoeken kan opgelost worden door een epidemiologische groep, waarin iedere eerste-episode patiënt is opgenomen, te onderzoeken. Het is echter bijna onmogelijk om iemand te randomiseren naar wel of niet starten met antipsychotica bij een eerste psychose. Behandeling ontzeggen is onethisch zijn als het langer is dan één of twee observatie weken ter diagnostiek, en zou ook dan alleen mogelijk zijn als het lijden van de patiënt het zou toestaan, in combinatie met toestemming van de wettelijk vertegenwoordiger en de patiënt zelf. Gelukkig is reeds aangetoond dat 1 week medicatie voldoende is om een verschil aan te tonen in hersenmorfologie tussen medicatie-naieve en recent gemediceerde patiënten[51]. De meeste acuut opgenomen psychotische patiënten hebben zo snel mogelijk antipsychotische medicatie nodig. Wunderink et al. hebben inderdaad een epidemiologische onderzoeksgroep bekeken die zij al op T0, toen de patiënten nog midden in hun eerste psychose zaten, hebben gerandomiseerd naar stoppen of doorgaan met antipsychotica [60]. De randomisatie werd pas uitgevoerd op het moment dat de patiënt 6 maanden was hersteld. Echter, de deelnametijd wordt met een dergelijke onderzoeksopzet verlengd met de tijd die het kost om te herstellen, dit is een extra belasting. Hier tegenover staat dat het wel mogelijk zou zijn om dan ook onderzoek te doen naar de invloed van de duur van de onbehandelde ziekte en de eerste hersenmorfologische reactie op antipsychotica, zoals beschreven in **Hoofdstuk 5**.
In de studie van Wunderink et al. werd de uiteindelijke uitvoering van het stoppen of doorgaan overgelaten aan de behandelend psychiater en de patiënt[60]. Misscien kwam dit voort uit de grotere anonimiteit in deze grotere trial leidend tot minder controle in het individuele geval. Omdat patiënten en behandelaars andere doelen, wensen en inzichten hebben dan onderzoekers werd de actuele uitvoering van het stoppen, en ook het doorgaan, belemmerd. Er waren namelijk stoppers in de doorgaan groep, en andersom. Wellicht had deze verdunning voorkomen kunnen worden als de randomisatie alleen was gactiveerd in die ge-

vallen waarin de patiënt (en behandelaar) ook daadwerkelijk wilde participeren in een trial waarin zowel doorgaan als afbouwen een mogelijkheid zou zijn, na het optreden van herstel. En waarbij de strategie veel getrouwer was uitgevoerd bij participatie. Dan was intensief onderzoekscontact nodig geweest op het moment van remissie om de wil om, en consequenties van, meedoen met een dergelijk strict protocol in te schatten en te bespreken. Ook de follow-up had intensief moeten zijn. Misschien zou het minder nodig om intensief te volgen als een meer robuust terugval criterium zoals hospitalisatie wordt gebruikt. Van de andere kant vindt hospitalisatie plaats op verschillende plekken door verschillende psychiaters om verschillende redenen en bij verschillende niveaus van psychose en ongemak. Het afnemen van een gevalideerde vragenlijst kan dit soort problemen voorkomen, maar vergt dus meer intensieve follow-up.
In Nederland, een relatief klein land, met ongeveer 3200 eerste-episoden van psychose per jaar, zou de beste strategie zijn om een goed bekend netwerk van verwijzingsinstanties op te zetten voor iedereen die in aanraking komt met eerste-episode psychose patiënten. Dit zou gekoppeld moeten worden aan een groot onderzoeksproject. Er zou de mogelijkheid moeten zijn om meteen (binnen uren) te verwijzen naar een dichtbijzijnde faciliteit. In deze faciliteit zou onderzoek gecombineerd moeten worden met zorg op een hoog niveau om in een goede reden voor verwijzing te voorzien voor zowel de patiënt als de verwijzende partij. Het onderzoek zou naar de patiënt toe moeten komen, in plaats van andersom. Het zou de voorkeur hebben dat de patiënt naast een casemanager voor de begeleiding bij de ziekte ook een onderzoeksmanager zou hebben voor het onderzoek, met een nauwe samenwerking tussen de twee. Een onderzoeksmanager zou 20-25 patiënten moeten kunnen begeleiden. Deze manager zou niet alleen zich bewust moeten zijn van alle onderzoeken waar een patiënt aan mee kan doen, en regelen dat deze ook plaatsvinden als de patiënt dit wil, maar zou ook de patiënt moeten kunnen vergezellen. Ook zou de manager zelf delen van het onderzoek moeten kunnen uitvoeren, eventueel na instructie. Daarnaast zou de onderzoeksmanager prospectief algemene anonieme onderzoeksdata moeten verzamelen in een van te voren gedefinieerde format, zoals medicatie gebruik, fysieke data (lengte, gewicht, bijwerkingen), data van opnamen en ontslag, laboratoriumuitslagen, etc.. Op deze manier zou een maximum aan participatie tot een minimale hoeveelheid stress en blootstelling aan onderzoek moeten leiden voor de patiënt. Er zou top-down supervisie moeten zijn op het aantal onderzoeksprojecten, met inzicht in de haalbaarheid van voldoende grote onder-

zoeksgroepen per project. Deze supervisor zou contact moeten hebben met de researchmanagers om te kijken of er de mogelijkheid is om een nieuw project te starten. Natuurlijk zou een organisatie zoals hierboven beschreven een heleboel geld en energie kosten. Deze inzichten zijn niet nieuw, en het is fortuinlijk dat Nederland al een aantal grote samenwerkingsprojecten met eerste-episode patiënten heeft gekend, en nog kent. Voorbeelden hiervan zijn GROUP (Genetic Risk and OUtcome in Psychosis) en daarvoor MESIFOS (MEdication Strategies in First Onset Schizofrenie).

Met betrekking tot **Hoofdstuk 6** bij het in de toekomst onderzoeken van indicaties voor het beginnen met antipsychotica door de huisarts de start van antipsychotica gekoppeld moeten worden aan een gestructureerde registratie van de reden ervan. Een dergelijke stictere associatie tussen actie en reden zou meer robuuste data leveren om al of niet off-label voorschrijven te bewijzen.

References

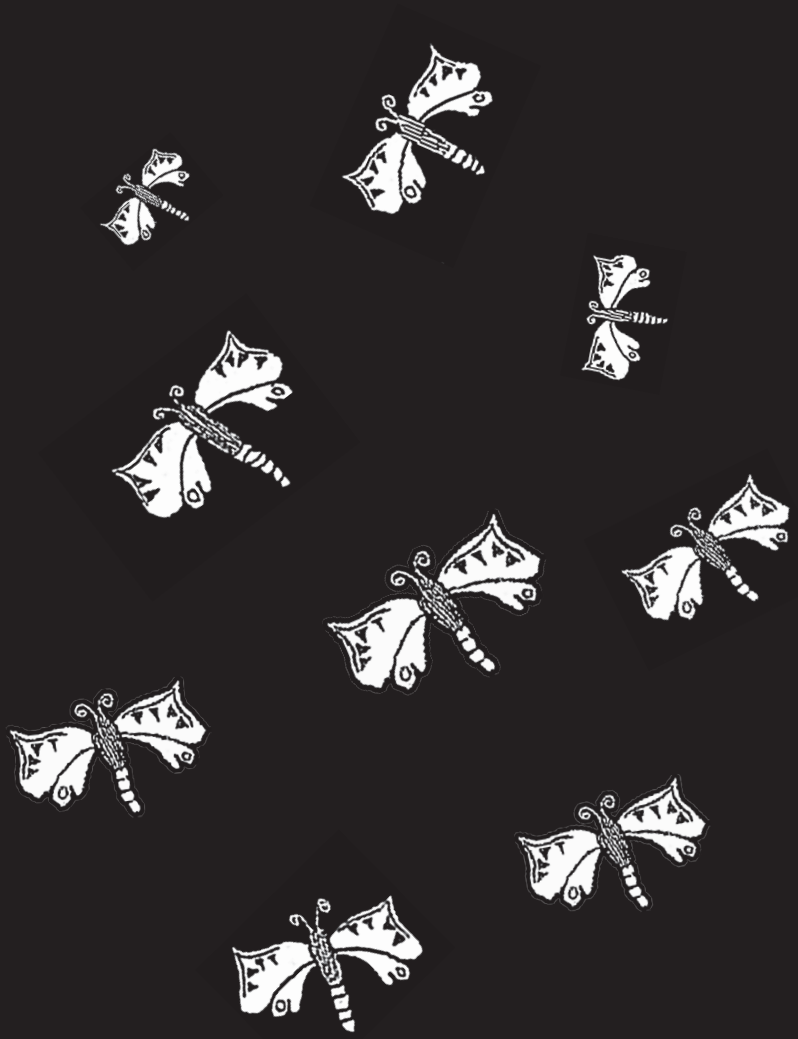
1. Ananth J., Burgoyne K.S., Gadasalli R. et al. How do the atypical antipsychotics work? *J Psychiatry Neurosci* 2001;26(5):385-394.
2. Bangalore S.S., Goradia D.D., Nutche J. et al. Untreated illness duration correlates with gray matter loss in first-episode psychoses. *Neuroreport* 2009;20(7):729-734.
3. Barnes T.R., Hutton S.B., Chapman M.J. et al. West London first-episode study of schizophrenia. Clinical correlates of duration of untreated psychosis. *Br J Psychiatry* 2000;177:207-211.
4. Barnes T.R., Leeson V.C., Mutsatsa S.H. et al. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br J Psychiatry* 2008;193(3):203-209.
5. Beasley C.M., Jr., Sutton V.K., Taylor C.C. et al. Is quality of life among minimally symptomatic patients with schizophrenia better following withdrawal or continuation of antipsychotic treatment? *J Clin Psychopharmacol* 2006;26(1):40-44.
6. Buchsbaum M.S., Shihabuddin L., Brickman A.M. et al. Caudate and putamen volumes in good and poor outcome patients with schizophrenia. *Schizophr Res* 2003;64(1):53-62.
7. Cahn W., Hulshoff Pol H.E., Bongers M. et al. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. *Br J Psychiatry Suppl* 2002;43:s66-s72.
8. Cahn W., Hulshoff Pol H.E., Lems E.B. et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry* 2002;59(11):1002-1010.
9. Cahn W., van Haren N.E., Hulshoff Pol H.E. et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006;189:381-382.
10. Chakos M.H., Lieberman J.A., Alvir J. et al. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995;345(8947):456-457.
11. Chen E.Y., Hui C.L., Lam M.M. et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010;341:c4024.
12. Chua S.E., Cheung C., Cheung V. et al. Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. *Schizophr Res* 2007;89(1-3):12-21.
13. Clarke M., Whitty P., Browne S. et al. Untreated illness and outcome of psychosis. *Br J Psychiatry* 2006;189:235-240.
14. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. *Schizophr Res* 2007;91(1-3):87-96.
15. Crespo-Facorro B., Roiz-Santianez R., Pelayo-Teran J.M. et al. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. *Neuroimage* 2007;35(4):1613-1623.
16. Crow T.J., MacMillan J.F., Johnson A.L. et al. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 1986;148:120-127.
17. DeLisi L.E., Sakuma M., Maurizio A.M. et al. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res* 2004;130(1):57-70.

18. DeLisi L.E., Sakuma M., Tew W. et al. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res* 1997;74(3):129-140.
19. Ebdrup B.H., Glenthoj B., Rasmussen H. et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci* 2010;35(2):95-104.
20. Frazier J.A., Giedd J.N., Kaysen D. et al. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 1996;153(4):564-566.
21. Fusar-Poli P., Meneghelli A., Valmaggia L. et al. Duration of untreated prodromal symptoms and 12-month functional outcome of individuals at risk of psychosis. *Br J Psychiatry* 2009;194(2):181-182.
22. Ganguli R. Behavioral therapy for weight loss in patients with schizophrenia. *J Clin Psychiatry* 2007;68 Suppl 4:19-25.
23. Glenthoj A., Glenthoj B.Y., Mackeprang T. et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. *Psychiatry Res* 2007;154(3):199-208.
24. Gonzalez-Blanch C., Crespo-Facorro B., varez-Jimenez M. et al. Pretreatment predictors of cognitive deficits in early psychosis. *Psychol Med* 2008;38(5):737-746.
25. Gur R.E., Cowell P., Turetsky B.I. et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 1998;55(2):145-152.
26. Gur R.E., Maany V., Mozley P.D. et al. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. *Am J Psychiatry* 1998;155(12):1711-1717.
27. Haren v.N.E., Hulshoff Pol H.E., Schnack H.G. et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol Psychiatry* 2008;63(1):106-113.
28. Heitmiller D.R., Nopoulos P.C. and Andreasen N.C. Changes in caudate volume after exposure to atypical neuroleptics in patients with schizophrenia may be sex-dependent. *Schizophr Res* 2004;66(2-3):137-142.
29. Ho B.C., Andreasen N.C., Flaum M. et al. Untreated initial psychosis: its relation to quality of life and symptom remission in first-episode schizophrenia. *Am J Psychiatry* 2000;157(5):808-815.
30. Hoff A.L., Sakuma M., Razi K. et al. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *Am J Psychiatry* 2000;157(11):1824-1828.
31. Hogarty G.E. and Ulrich R.F. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiatr Res* 1998;32(3-4):243-250.
32. Hulshoff Pol H.E. and Kahn R.S. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34(2):354-366.

33. Jayakumar P.N., Venkatasubramanian G., Gangadhar B.N. et al. Optimized voxel-based morphometry of gray matter volume in first-episode, antipsychotic-naive schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29(4):587-591.
34. Job D.E., Whalley H.C., Johnstone E.C. et al. Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 2005;25(4):1023-1030.
35. John J.P., Burgess P.W., Yashavantha B.S. et al. Differential relationship of frontal pole and whole brain volumetric measures with age in neuroleptic-naive schizophrenia and healthy subjects. *Schizophr Res* 2009;109(1-3):148-158.
36. Kane J.M., Rifkin A., Quitkin F. et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiatry* 1982;39(1):70-73.
37. Kaye J.A., Bradbury B.D. and Jick H. Changes in antipsychotic drug prescribing by general practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. *Br J Clin Pharmacol* 2003;56(5):569-575.
38. Kempton M.J., Stahl D., Williams S.C. et al. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophr Res* 2010;120(1-3):54-62.
39. Keshavan M.S., Haas G., Miewald J. et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr Bull* 2003;29(4):757-769.
40. Keshavan M.S., Haas G.L., Kahn C.E. et al. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res* 1998;32(3-4):161-167.
41. Lang D.J., Kopala L.C., Vandorpe R.A. et al. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *Am J Psychiatry* 2004;161(10):1829-1836.
42. Levitt J.J., McCarley R.W., Nestor P.G. et al. Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *Am J Psychiatry* 1999;156(7):1105-1107.
43. Lieberman J.A., Tollefson G.D., Charles C. et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 2005;62(4):361-370.
44. Maayan L., Vakhrusheva J. and Correll C.U. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010;35(7):1520-1530.
45. Madsen A.L., Karle A., Rubin P. et al. Progressive atrophy of the frontal lobes in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. *Acta Psychiatr Scand* 1999;100(5):367-374.
46. Massana G., Salgado-Pineda P., Junque C. et al. Volume changes in gray matter in first-episode neuroleptic-naive schizophrenic patients treated with risperidone. *J Clin Psychopharmacol* 2005;25(2):111-117.
47. Mathalon D.H., Sullivan E.V., Lim K.O. et al. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 2001;58(2):148-157.

48. McCreadie R.G., Wiles D., Grant S. et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. *Acta Psychiatr Scand* 1989;80(6):597-602.
49. Molina V., Reig S., Sanz J. et al. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr Res* 2005;80(1):61-71.
50. Mortimer A.M., Shepherd C.J., Rymer M. et al. Primary care use of antipsychotic drugs: an audit and intervention study. *Ann Gen Psychiatry* 2005;4:18.
51. Narr K.L., Toga A.W., Szeszko P. et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. *Biol Psychiatry* 2005;58(1):32-40.
52. Ohrmann P., Siegmund A., Suslow T. et al. Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. *J Psychiatr Res* 2007;41(8):625-634.
53. Pantelis C., Yucel M., Wood S.J. et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005;31(3):672-696.
54. Rijcken C.A., Boelema G.J., Slooff C.J. et al. Off-label use of antipsychotics in the community pharmacy: the sex differences. *Pharmacopsychiatry* 2003;36(5):187-191.
55. Salgado-Pineda P., Baeza I., Perez-Gomez M. et al. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. *Neuroimage* 2003;19(2 Pt 1):365-375.
56. Scheepers F.E., de Wied C.C., Hulshoff Pol H.E. et al. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. *Neuropsychopharmacology* 2001;24(1):47-54.
57. Trifiro G., Spina E., Brignoli O. et al. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999-2002. *Eur J Clin Pharmacol* 2005;61(1):47-53.
58. Venkatasubramanian G., Jayakumar P.N., Gangadhar B.N. et al. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. *Psychiatry Res* 2008;164(3):215-222.
59. Wassink T.H., Andreasen N.C., Nopoulos P. et al. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. *Biol Psychiatry* 1999;45(1):41-48.
60. Wunderink L., Nienhuis F.J., Sytema S. et al. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry* 2007;68(5):654-661.

Dankwoord



Hoera! Het boek is af.

Deze promotie is de afronding van mijn opvoeding tot arts. Het was een hele uitdaging. Als klein meisje wilde ik pas leren fietsen zodra ik zeker wist dat ik het kon. Eerst wachtte ik het overzicht over de activiteit af, en het overwinnen van de angst om te vallen. En binnen een dag was het toen geleerd.
Dat zat er dus niet in bij promoveren.
Na 3237 dagen mag ik zeggen dat ik het hele proces heb doorlopen. En de angst om te vallen steekt nog steeds af en toe de kop op.
Wat het al die moeite waard maakte waren de patiëntencontacten, het proces en, niet in de laatste plaats, alle fijne mensen die ik erdoor ben tegengekomen. Het volhouden lukte door de combinatie met de opleiding en mijn liefhebberijen waarbij ook veel inspirerende en leuke mensen mijn pad kruisten. Ik kan helaas niet iedereen noemen die heeft bijgedragen aan dit werk, immers, soms zit steun in hele kleine dingen.

Zonder coaching geen vooruitgang:
Lieve Neeltje; vrolijk, energiek, en altijd klaar voor overleg. We spraken vaak zelfs in de avonden af. Wat is het ontzettend fijn om met je te werken, dank voor alles.
Huib, de eerste jaren hebben we samen geploeterd aan de de STOP-trial; protocol, amendementen, inclusie; the works. Ik: een groentje, jij: ervaren. Het ligt alweer een poos achter ons, ik ben blij dat we dat wat we zaaiden nu mogen oogsten (een zin die het niet gehaald had in een artikel).
René Kahn, je bent bijna 10 jaar lang mijn baas geweest. Duidelijk, charmant, humoreus en soms zorgend; je was mijn klinisch opleider, wetenschappelijk opleider en ook een beetje een extra vader, en je vond die combinatie, naar het scheen, ook verder geen probleem. Dank je wel voor alles.
Rick Grobbee, je was al die jaren mijn tweede promotor. Het verassingselement was soms groot, zeker in de laatste fase. Zo hoog als ik me voelde als zingende nimf op Heidestein in de boom, zo klein voelde ik me in januari. Ik heb onze contacten erg gewaardeerd.
Hilleke Hulshoff Pol, hoogleraar worden is geen akelige reden om geen co-promotor meer te zijn, dank voor je vrolijke humeur en comments.
Mijn fellow researchers, wat een slimme, behulpzame en fijne mensen zijn jullie toch. Maartje Aukes (keihard werken, en heel bescheiden), Maria Boersma

(geen dag zonder Brahms), Heleen Boos (zelf kersverse doctor, fijn dat ik nog even bij je af mocht kijken), Judith Bosman (dank voor de ontroerende kans om op een hele speciale manier vast een beetje te wennen in het academiegebouw), Rachel Brans (helemaal op je plek na je promotie in je nieuwe baan), Martijn van den Heuvel (weet alles, kan alles, doet alles en helpt altijd), Mechteld Hoogendoorn (dank voor je humor en troost in moeilijke momenten), Gerry Jager (heerlijk die combinatie van jou en Frank, minischapen, vers gras, stapels katten, hard werken en dan lekker eten), Joost Jansen (jouw informeren naar de voortgang kwam altijd onverwacht en als kadootje), Kuan Kho (samen zijn we begonnen in het UMCU, wie had op dag 1 kunnen bedenken hoe het allemaal zou gaan lopen?), Cédric Koolschijn (er moet meer gespeeld worden, dank voor je beschikbaarheid), Bart de Kroon (een succesvolle zoektocht door de universiteit, wat zou je gaan kiezen?), Marieke Langen (lachen is gezond), René Mandl (de grote vriendelijke reus), Jiska Peper (superslim, grappig en vlug als water), Tamar van Raalten (temperamentvol en vasthoudend), Thomas Scheewe (zo'n onderzoek zet je lekker in beweging), Astrid van der Schot (het is inderdaad een kwestie van volhouden, en het komt allemaal goed), Hugo Schnack (jij bent mijn natuurkundige onderzoekersslotakkoord).

(Ex)- Collegae assistenten psychiatrie, heel erg bedankt voor jullie collegialiteit, eigenheid en enthousiasme. Ahmet Akdeniz, Steven Bakker (je act als dwangmatige was onvergetelijk), Veerle Bergink, Mori van den Bergh (zingen is heerlijk), Elemi Breetvelt, Hilgo Bruining (er is nog zoveel te doen), Geraud Dautzenberg, Peter-Jan van Eeten, Kim Ekkelenkamp, Maaike van der Erf, Monique Fikse, Sjoerd Fluitman (dank voor het lachen, en: the Spark.com's personality test heeft gelijk gekregen: we zijn straks, zonder overleg, in dezelfde maand gepromoveerd), Miranda Fredriks, Babette de Graeff, Coby Groenendijk, Femke van Hattum (lekker zwemmen in een ven op een zomeravond, wanneer gaan we weer?), Sander Haijma, Wendela Hoen, Jet van der Jagt, Martijn Klein-Gebbink, Saskia Knapen, Marjan Kromkamp (we blijven af en toe wijn slobberen!), David Krol, Daphne Kuijpers, Justine Lamberts, Indrag Lampe (samen klassieke muziek bezoeken is leuk!), Ellen Landeweer (blij dat ik je weer ben tegengekomen, jammer dat je onmiddellijk bent weggevlucht over de oceaan), Max de Leeuw, Adriaan Lemmers, Jeroen Lijmer, Jurjen Luykx (hoe stabiel opgewekt kan een mens zijn), Arija Maat, Bastiaan Meijers, Jantien Meinardi (heerlijk, die humoreuze shopping frenzies in Amersfoort), Sanne de Metz (en toen waren we weer

collega's, leuk!), Emma van der Meulen, Saskia Palmen (jij zet 'druk zijn' in een ontnuchterend perspectief), Emke Plomp, Marjet Polman, Monica Rais, Ariane de Ranitz, Sanne van Rhijn, Marije Rozendal, Anne-Marije Schat (je bent een bron van inspiratie), Floor Scheepers, Chris Schubart, Renate Siebelink, Metten Somers, Iris Sommer, Wouter Staal (over karakter gesproken), Jeroen Terpstra, Afke Terwischa–van Scheltinga, Natalie Veen, Janine van Venrooij, Marjolein de Vette (wat ben je toch integer en zorgvuldig), Laura Vos, Leon Vos, Marrit de Vries, Nienke Vulink (jij en Eric maken dat een mens durft te dromen), Nanouschka van Waart en Zhida Xu (I like chinese).

In de kliniek werd ik voortgedreven door de ambitie alles zorgvuldig te doen. Supervisoren: bedankt voor het overbrengen van het principe 'less is more'. Het is nog niet helemaal gelukt, maar...ik blijf proberen. Nicoletta van Veelen en Wiepke Cahn (ik heb veel gelachen op A3), Rob van Ojen, Arnold Franken, Marco Boks (dank voor de vrijheid), Sina Roelfs, Marko van Gerven (er zit (inderdaad) muziek in samenwerking, dank voor je begeleiding), Just Wernand (één van de vreemdste overgangen ooit om op mijn eerste dag als psychiater jouw hele kamer en klinische functie voor een paar maanden over te nemen).

Lief secretariaat en onderzoeksondersteuners, en in het bijzonder Paula Ywema, Jeanette Sopacua, Emmy Drost, Elly Schreurs, Joyce van Baaren, Esther Caspers, Nicole Boekema en Susanne van Hemert. Voor een praatje, een theetje, een liedje, een vraag, een klus, een afspraak of wat dan ook, ik kon altijd terecht. Dank daarvoor!

Zingen en spelen gaf me energie om de promotie vol te houden, of dat nou 1 week per jaar, 1 avond per week of af en toe een project was. Ik kan helaas niet iedereen noemen. Doesjka Nijdeken (bij jou kon ik op mijn 18e eindelijk echt beginnen met zingen), Mathilde Boers, Lingua Musica (twee jaren zangplezier in mijn eerste 'echte' koor), Maria van Nieukerken (jij hoort altijd alles), Marjan Boonen (dol op je zangles, jou en je katten), Chris Pouw (I Romantici verzorgde 1 week per jaar een feestje middenin de muziek), Joukje Jurjens (vrouw van de wereld), Anne-Lien van den Berg (muziek en dokterschap zijn toch een prachtige combinatie), Marlies Egging (we blijven elkaar (gelukkig) maar tegenkomen), Bastiaan de Haan (mijn lievelingsbas), Florianne Bauer (afgestudeerd wetenschapper met noten op haar zang), Pelle van Mansvelt (zingen is maar 1 van alle leuke dingen, neem nu bijvoorbeeld het pompoen-tatoueren), MaNOj Kamps (muzikaal elfje), Hannie Slingerland (geen dag zonder opera), Jeroen de Wildt (lang leve de smartlap), Yvonne Kok, Marieke Steenhoek (Romantische zangcoach), Marije

van Duijne-Strobosch, Jos Vloemans, Henk Abma (humor is leuk), Haye Bij De Weg (wanneer komt Friesland nou eens dicht bij Utrecht te liggen?).
En natuurlijk mijn geliefde zomerkampers die met elkaar iedere week die ik meemaakte in Beekbergen weer tot een groot feest maakten. Dat verschafte weer voer voor een half jaar hard werken. Marucha Scholten, Ilona Holewijn, Jan de Vast, Maaike Pekelharing, Merel van Strijen, Barry van Strijen, Ramon van Beusichem, George van Bohemen, Gert van der Houwen, Barbara Rozing, Danielle Stolk, Monica Keuning, Reina Cornelisse, Charlotte de Vast, Maaike van der Zwan en nog veel meer mensen die ik allemaal niet kan opnoemen, ontzettend bedankt voor die prachtige tijden.

Jetty Maltha, ik ben very happy dat je weer in Nederland bent, hoewel de pubs in Essex ook buitengewoon aantrekkelijk waren. Natasja de Groot, mijn boekje past 3 keer in dat van jou, en DAT stond al geschreven in de sterren, wat mooi dat we zijn zoals we zijn. Simone Mulder, je bent dokter, OF je bent ineens flying docter, en dat is slechts 1 fantastisch verschil tussen Nederland en Australië. Merel van Strijen-Louët, van interrail tot zomerkamp en van trouwen, via zomerkamp, tot promoveren, wat hebben we veel meegemaakt. Martine Hoogbruin, jij, en je 'floepies' zijn en blijven altijd van harte welkom. Merlijn van Hasselt, even onze vriendschap hier vereeuwigen, dat moet je zeker aanspreken. Iris de Vries, bij jou heb ik pas echt leverpastei leren eten, en natuurlijk liggen krioelen van het lachen op de grond. Anniek Werner, no matter what evil at hand, wij vierden samen feest, in Groningen en in de Schotse bergen. Theo Bosboom, het leven is prachtig, als je er oog en een lens voor hebt. Lina van't Wout, lekker wandelen en praten over promoveren en dingen leren.

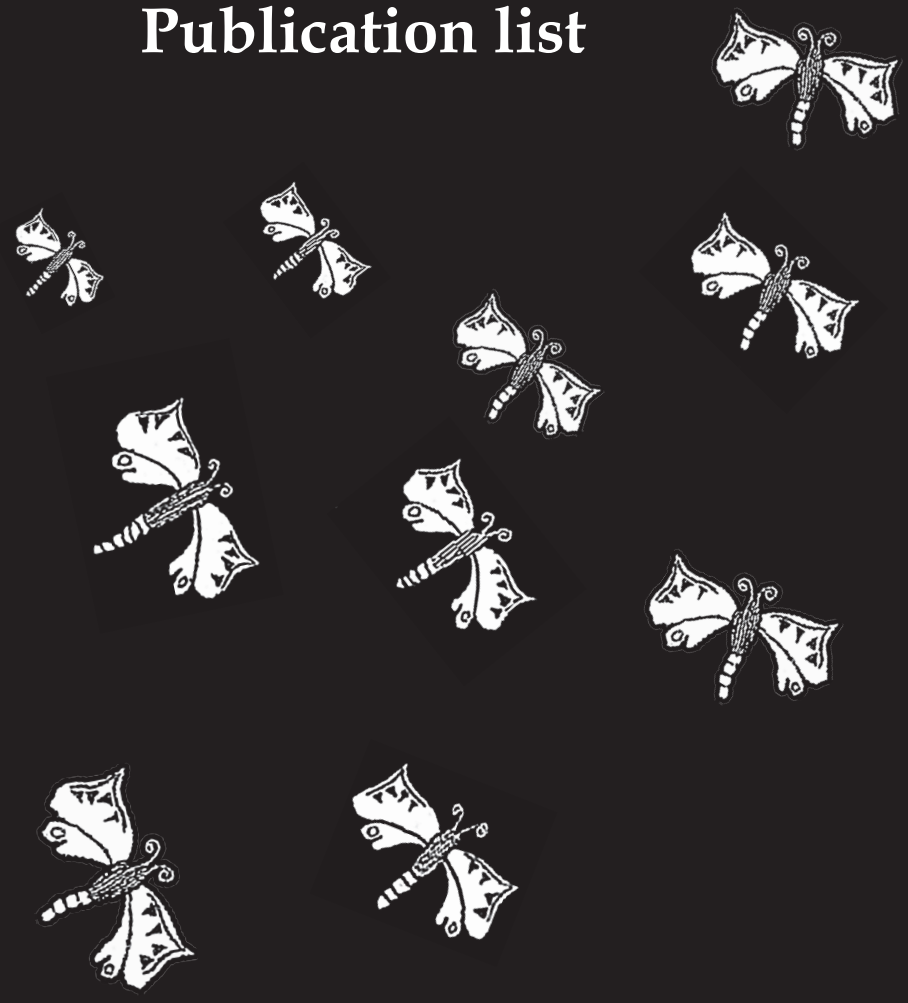
Papa en mama, door overerving van pragmatisch en empathisch dokterschap, en mam's liefde en (dan toch nog een beetje) geduld ben ik psychiater geworden. Met onderzoek hebben jullie niet veel, met hard werken en volhouden wel. Dank dat ik dat alles heb meegekregen van jullie.
Hinse, Ritsert en Anne; mijn gebroertjes. Altijd goed voor lol en energie, met rare fratsen. Ik ben dol op jullie. Hinse, je mildheid van de laatste jaren was voor mij een heel fijn voorbeeld, en je doelgerichtheid is bewonderingswaardig. Ritsert, ik heb nog jaren plezier gehad om je letterplakactie op de snelweg: "geef ritser(t) de ruimte". Wat werk je hard en ben je lief met je tweeling. Anne, het kan je niet mooi of goed genoeg zijn voor iedereen. Je beweeglijkheid en creativiteit zijn

super om te zien. Yomi, Luan en Marjolein, mijn drie slimme schoonzussen. Eindelijk wat vrouwelijk tegenwicht in die mannenfamilie van ons. Josephine, Thijmen, Pepijn, Jonatan, Isabelle, Jildau, Jelte en Mia; wat zijn jullie ieder bijzonder. Hopelijk is het mij gegeven om ook zo'n lekker mollig knuffelding op de wereld te zetten. Pake, bij alle mijlpunten in de levens van je kinderen, kleinkinderen en achterkleinkinderen ben je er, en ik ben dol op je groentesoep. Ria Huiden, mijn lieve tante, dank je wel voor je verwarmende woorden en steun in tijden van nood en plezier. Tante Annie, pas na jaren van opleiding en onderzoek besefte ik welke invloed jij op mijn keuzes hebt gehad. Ik ben best heel tevreden met die keuzes, en trots op jou. Feike en Lydia, dank jullie wel voor de welkome interesse en inzicht in mijn promotieproces. Jakob en Susan, dank voor het geregeld opladen van Martijn's batterij en voor de steun en gezelligheid.

Martijn, mijn liefsteling, zonder jou was dit boekje niet tot stand gekomen. Jij schepte met jouw ruimte de voorwaarde voor mijn schrijven. En, hierbij dan ook eindelijk de officiële erkenning als 'Hij, Die De Schrijfster Gevoed Heeft'. Wonderbaarlijk genoeg bleef je humeur goed en wij samen worden alsmaar beter. Laten we vooral vrolijk doorgaan met samen in de wereld rond te stappen, te beginnen in het hoge Noorden.

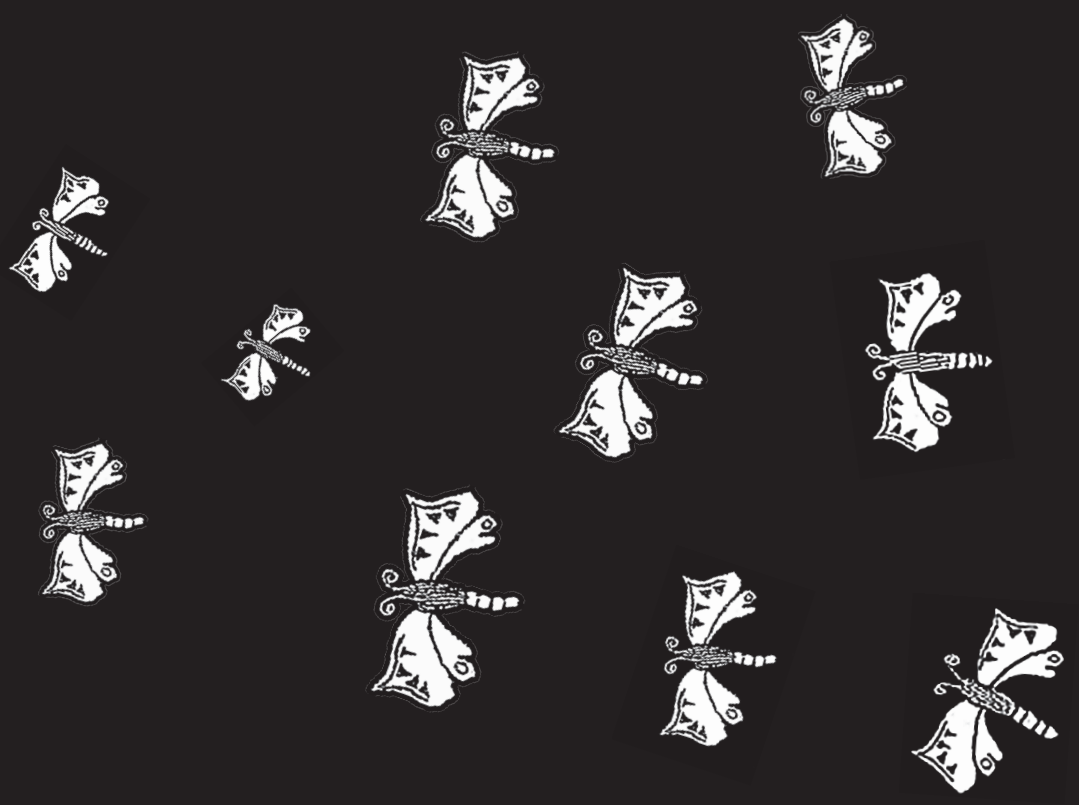
There's more to explore.

Publication list



1. Boonstra G., Burger H., Grobbee D.E. et al. Poster (and abstract) at the XIIIth Biennial Winter Workshop on Schizophrenia Research, Davos, Switzerland, February 4-10, 2006. Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: results from a randomized trial. *Schizophr Res* 2006;81 Suppl:228-229.
2. Boonstra G., Hulshoff Pol H.E., van Haren N.E.M. et al. Poster (and abstract) at the International Congress on Schizophrenia Research 28 March-1 April 2007, Colorado Springs. Does brain volume change after withdrawal of antipsychotic medication in first-episode schizophrenia? *Schizophrenia Bulletin* 2007;33(2):251-252.
3. Boonstra G., Hak E., Burger H. et al. [Poster (and abstract) at the 35th Congress of the Netherlands Society of Psychiatry, 11-13 April 2007, Maastricht. Het starten van behandeling met antipsychotica door de huisarts. Een patiënt-controleonderzoek.] Starting antipsychotic treatment in general practice. A case control study. *Tijdschr Psychiatr* 2007;49(Suppl 1):221.
4. Boonstra G., Burger H., Grobbee D.E. et al. Antipsychotic prophylaxis is needed after remission from a first psychotic episode in schizophrenia patients: Results from an aborted randomised trial. *International Journal of Psychiatry in Clinical Practice* 2010;E-Pub online publication:1-7.
5. Boonstra G., van Haren N.E.M., Schnack H.G. et al. Poster (and abstract) at the 2nd Biennial Schizophrenia International Research Conference, Florence, Italy, 10-14 April 2010. Brain volume changes after withdrawal of atypical antipsychotics in first-episode schizophrenia patients. *Schizophr Res* 2010;117(2-3):223.
6. Boonstra G., Grobbee D.E., Hak E. et al. Initiation of antipsychotic treatment by general practitioners. A case-control study. *J Eval Clin Pract* 2011;17(1):12-17.

Curriculum Vitae



Geartsje Boonstra was born on December 28th, 1973 in Amersfoort, the Netherlands. In 1986 she started secondary school at the Bogerman College in Sneek, the Netherlands and finished her secondary school in 1992, by graduating at the Alkwin Kollege in Uithoorn, the Netherlands. She studied Medicine at Leiden University, the Netherlands. In 1996 she performed epidemiological research in Bolgatanga, Ghana with the Department of Parasitology under supervision of dr. A. M. Polderman. She did her internship Neurology in Edinburgh at the Western General Hospital, Scotland. In 1999 she obtained the title of Medical Doctor. She worked in the Groene Hart Ziekenhuis in Gouda as a resident Internal Medicine and subsequently as a resident Pediatrics at the Maaslandziekenhuis in Sittard, the Netherlands. She began a PhD program in Neurosciences and a specialisation in Psychiatry in 2001 at the University Medical Centre Utrecht under the supervision of Prof. dr. R. S. Kahn. For the PhD program she was also supervised by Prof. Dr. D.E. Grobbee. She finished a Master of Science in Clinical Epidemiology in 2005 at the Erasmus University in Rotterdam. She finished her specialisation in Psychiatry on the 1st of March 2010. She currently works as teampsychiatrist at Altrecht GGZ in an Assertive Community Treatment team in Utrecht, the Netherlands.

Geartsje Boonstra is geboren op 28 december 1973 te Amersfoort. Ze deed 4 jaar gymnasium aan het Bogerman Collega in Sneek en behaalde in 1992 haar V.W.O. diploma aan het Alkwin Kollege te Uithoorn. Ze studeerde Geneeskunde aan de Universiteit Leiden en behaalde in 1999 haar artsexamen. Tijdens de doctoraal fase van haar studie deed ze epidemiologisch en parasitologisch onderzoek in Bolgatanga, Ghana onder supervisie van dr. A. M. Polderman. Ze deed haar co-schap neurologie in Edinburgh, in het Western General Hospital. Ze werkte na haar artsexamen als basisarts bij de Interne Geneeskunde in het Groene Hart Ziekenhuis te Gouda en bij de Kindergeneeskunde in het Maaslandziekenhuis te Sittard. Ze startte met haar promotieonderzoek en specialisatie tot psychiater in 2001 aan de Universiteit Utrecht onder supervisie van Prof. Dr. R. S. Kahn en voor de promotie tevens Prof. Dr. D.E. Grobbee. Ze verkreeg de titel Master of Science in de Klinische Epidemiologie in 2005 aan de Erasmus Universiteit te Rotterdam. Ze rondde haar specialisatie tot psychiater met succes af op 1 maart 2010. Op dit moment werkt ze als teampsychiater bij Altrecht GGZ bij een Assertive Community Treatment team in Utrecht stad.