# Anti-inflammatory drugs and psychosis

Wijnand Laan

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**Anti-inflammatory drugs and psychosis**

Ontstekingsremmende geneesmiddelen en psychose

(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. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 3 juli 2008 des ochtends te 10.30 uur

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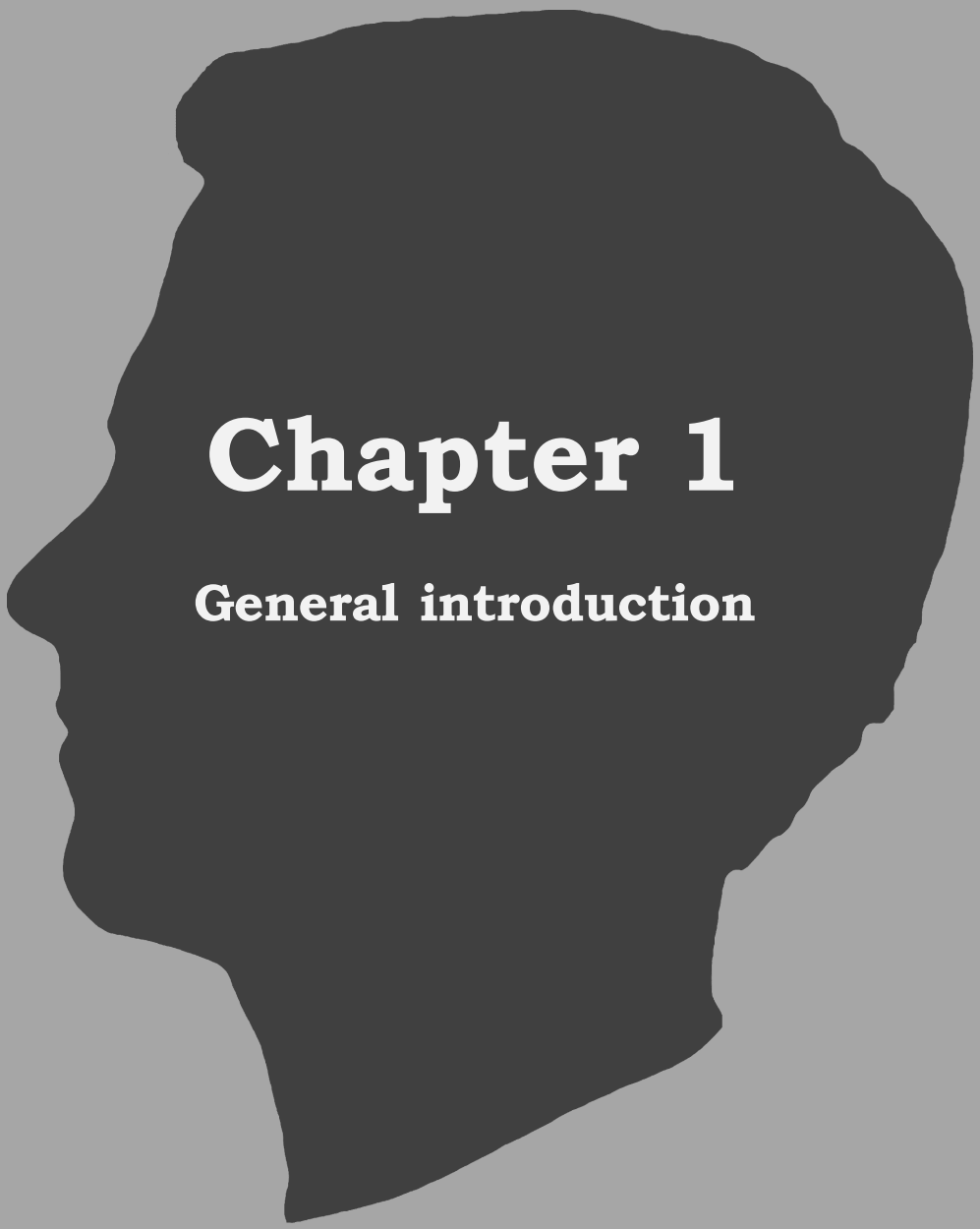
## Table of content

# Chapter 1

## General introduction



# Chapter 1

## General introduction

# General introduction

Schizophrenia is one of the most disabling psychiatric disorders in the world. The age of onset of schizophrenia is relatively low, with first symptoms often arising around twenty years of age [1]. Common symptoms of schizophrenia are delusions (often the paranoid belief that external forces are conspiring against the patient), hallucinations (generally voices that converse with or about the patient), disorganized speech, disorganized or catatonic behaviour and negative symptoms such as affective flattening, alogia, or avolition.[2] Patients with schizophrenia need to decide whether the voices or suspicions they experience are real, or part of their inability to discern relevant information from their surroundings, for most of their life[3]. Schizophrenia was first described by Kraepelin around 1893 as 'dementia praecox', a term later replaced to schizophrenia by Beuler[4]. Schizophrenia would literally translate from Greek to 'split mind', which is probably the cause of the often made mistake of people to think that patients with schizophrenia have a split, or multiple, personality disorder.

## Incidence and prevalence

The reported lifetime prevalence of schizophrenia in the western world ranges from 0.5% to 1.6%, indicating that around one in hundred people will develop schizophrenia in life.[5] The prevalence of schizophrenia in the Netherlands can be estimated at around 100.000 cases.[6] The yearly incidence is estimated at around 11.1 per 100.000 persons, meaning that around 1750 people in the Netherlands develop will this disorder each year.[7] The reported annual incidences range considerably between and within countries.[5] Research by the World Health Organisation indicates that the prevalence of schizophrenia is similar across a wide range of cultures and nations.[8] The prevalence of schizophrenia, however, appears to increase with the level of urbanisation. This might be caused by selective migration, i.e. people at higher risk of psychosis are more inclined to move to a urbanized environment.[9]

## Aetiology

Several risk factors for schizophrenia have been proposed, with genetic susceptibility being one of the strongest. Genetic studies indicate that the heritable component accounts for around 70% of the risk of schizophrenia, although no single genetic factor has yet been found that could fully explain

this disorder.[10] Other suspected risk factors include prenatal maternal infections, obstetric complications, stressful social conditions, family dysfunction[11], high urbanisation environment, cannabis use, and toxoplasma gondii infection.[1,12,13] Whether a person will actually develop schizophrenia is most likely the result of several environmental factors, and the interaction of these with a genetic predisposition to psychosis.

## Pathophysiology

The classical hypothesis of schizophrenia proposes hyperactivity of dopamine transmission as the main pathophysiologic feature. This is supported by findings of a correlation between doses of dopamine receptor blocking anti-psychotics and their potency to inhibit positive symptoms in schizophrenia[14] and the psychosis stimulating properties of dopamine enhancers.[15]

Recently, increasing attention is paid to the possible role of the immune system as several immunological changes were found in patients with schizophrenia.[16,17]

The role of the immune system is also supported by two hypotheses that indicate a potential beneficial effect in the treatment of schizophrenia by the inhibition of the cyclooxygenase enzyme.

Firstly, several studies demonstrated the dysregulation of proinflammatory cytokines such as interleukins and interferons in schizophrenia[18], which are a product of the prostaglandin cascade[19] in which the cyclooxygenase enzyme plays a crucial role. These findings are also indirectly supported by the evidence that many anti-psychotics may act as immuno-modulators[20,21].

Secondly, there is the NMDA receptor dysfunction hypothesis, where it is postulated that in schizophrenia the disinhibition of the glutamatergic projections to hippocampal and cortical areas causes neuronal exitotoxic cell death[22]. The inhibition of the cyclooxygenase enzyme may play an important role here, as prostaglandins are intermediaries in the postsynaptic signal transduction cascade of cells with NMDA-type glutamate receptors, and prostaglandins inhibit the astrocytical reuptake of glutamate.

Also, an inverse relation between schizophrenia and rheumatoid arthritis has long been acknowledged[23]. This inverse relation might be caused by the frequent use of NSAIDs in the treatment of rheumatoid arthritis. Alternatively, it has been suggested that several neuronal membrane phospholipid abnormalities in schizophrenia are responsible for the lower prevalence of rheumatoid arthritis in schizophrenia.[24]

Structural neurobiological findings in schizophrenia are enlarged ventricles accompanied by an overall reduction in brain volume and cortical grey matter. Regions such as the frontal lobes, amygdale and hippocampus also appear to be decreased in patients with schizophrenia. These observations can not be explained by illness duration or treatment as they are also present in newly diagnosed cases and unaffected relatives.[12] One of the hypotheses behind these structural brain changes is that they are the results of abnormal early brain development. The observation that clinically manifest psychosis emerges many years after early structural brain changes led to the hypothesis that schizophrenia is a neurodevelopmental disorder. That the onset of psychosis is delayed until early adulthood is speculated to be the result of excessive synaptic pruning in schizophrenia that leads to psychosis when reaching a certain threshold level. The synaptic elimination that occurs during adolescence may delay the moment this threshold level is reached.[12]

## Prognosis

Without proper treatment it is estimated that the chance of relapse within the first year after the first psychosis is as high as 80%[3]. This chance can be lowered to only 30% during treatment with anti-psychotic drugs[3]. In a Dutch 15-year up follow-up cohort with patients with a first diagnosis of schizophrenia, two-third of all cases had at least one relapse of psychosis. With each relapse one in six patients did not remit from that episode. Patients with schizophrenia are also often impeded in their social functioning and are often not able to maintain their previous employment.[25] Schizophrenic cases are also at a higher risk for a range of somatic disorders notably diabetes[26], obesity, cardiovascular and renal diseases.[27] Patients suffering from schizophrenia also tend to smoke more than the general population[28], increasing their cardiovascular risk even more. Moreover, some anti-psychotics are associated with other metabolic abnormalities such as insulin resistance and hyperglycemia.[29] As much as one in ten patients from the Dutch cohort committed suicide.[30] Each of these findings illustrates the devastating consequences of schizophrenia.

## Burden of disease

Schizophrenia is the nine-most costly disorder in men in the Netherlands.[31] As estimated by the Rijksinstituut voor Volksgezondheid en Milieu (RIVM) the direct costs assigned to schizophrenia are as high as 485.3 billion euros

yearly, a figure that does not include indirect costs such as productivity loss due to disability.

## Treatment options

The pharmacological treatment of schizophrenia is mainly done using anti-psychotics. These drugs can generally be divided into two categories, the typical and the atypical anti-psychotics. The mechanism of action of the typical anti-psychotics is mainly by blocking the dopamine D2 receptor. The atypical anti-psychotics share this property but also block a subtype of the serotonergic receptor[3]. Although being effective in the prevention of new psychosis in the many schizophrenic cases, still around 25% of the treated patients experience a relapse during the first two years of treatment with either typical of atypical antipsychotic drugs[3]. There also remains a large group of schizophrenic patients that responds poorly to anti-psychotic treatment[3,32]. A recent study showed that while symptoms improve during treatment with anti-psychotics, the functional outcome hardly does[33]. Two recent studies, the CATIE and the CUtLASS trials, showed that the newer anti-psychotic drugs were not more effective or better tolerated than the older drugs.[34] Potential side effects of anti-psychotics include weight gain, Parkinsonism, agranulocytosis (clozapine only) and diabetes mellitus.[3]
Other, non pharmacological treatment options for schizophrenia include for example cognitive-behavioural therapy, where the aim is to improve patient's understanding and coping in order to reduce suffering and distress and improve functioning.[35]

## Room for improvement

As can be conceived in view of the persistently unfavourable prognosis of schizophrenia, major research efforts are put into elucidating the pathogenesis of schizophrenia with the ultimate aim to discover new, better treatments.[34]

## History of aspirin

Aspirin is one of the oldest still used medications in the world. The use of the natural form of aspirin, derived from willow leaves, dates back to the Sumerian period. Stone tablets from this period describe how conditions like rheumatoid arthritis and other inflammation were treated by the consumption of the willow leaves[36]. The main problem with this early form of aspirin, salicyclicacid, was the 'unpleasant' side effects it had as it irritated the

stomach and tasted bad. This was partly resolved when in 1897 Felix Hoffman was able to acetylate the phenol group of the salicyclicacid molecule and thus forming acetylsalicylic acid, or Aspirin as it was registered by the Bayer pharmaceutical company on the first of February 1899. Now, over a century later, the same molecule is still widely used with new indications still being discovered such as an anti-platelet agent, and in the prevention of myocardial infarctions, stroke, migraine, dementia, and applications outside the cardiovascular system e.g. colon cancer[36]. It is currently the most widely used drug in the world.[37]

## Mechanism of action of aspirin

The mechanism of action of aspirin is inhibiting the function of cyclooxygenase. The cyclooxygenase enzyme is responsible for the conversion of the arachidonic acid molecule to prostaglandin-G2. This prostaglandin is then further transformed by a number of other enzymes to different substances which play major roles in the human body, like in platelet aggregation, nerve transmission and fever.
Aspirin selectively acetylates the hydroxyl group of the serine residue of the cyclooxygenase enzyme, thereby irreversibly inhibiting its function. A new cyclooxygenase enzyme needs to be synthesised before more prostanoids can be produced.[37]

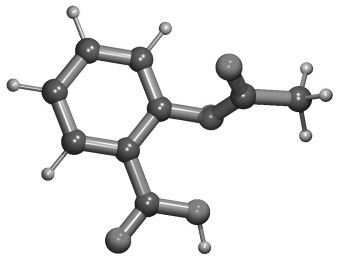


***Figure 1.*** *Aspirin*

## Side-effects of aspirin

In this thesis we will look into the potential beneficial effect of aspirin to see if it is an effective adjuvant for the treatment of schizophrenia. Unfortunately, aspirin is associated with side effects, some of them serious. As aspirin inhibits the synthesis of protective prostaglandins in the stomach it causes the stomach to become more vulnerable to the gastric acids which can lead to gastric ulcers and even bleedings.[38] The inhibition of platelet aggregation by aspirin in the secondary preventing of myocardial infarctions and ischemic stroke, is also the cause of one of the most serious side-effects, severe bleedings, like hemorrhagic stroke.[39] Any prescription of aspirin will need to be carefully evaluated considering its potential side-effects.

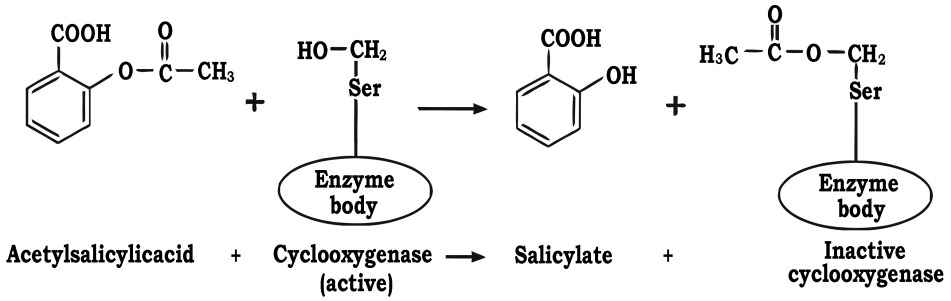



***Figure 2*** *The inhibition of the cyclooxygenase enzyme by aspirin*

## Cyclooxygenase one and two

There are two isoforms of the cyclooxygenase (COX) enzyme, COX-1 and COX-2. The activity of COX-1 is constitutive, present in nearly all cells at a constant level, providing prostaglandins to the stomach and intestines to maintain their mucosal integrity. COX-2 activity is normally absent however and needs to be induced, for example by inflammation.[38] Whereas the newer COX inhibitors such as rofecoxib (Vioxx) and celecoxib (Celebrex) selectively inhibit only the COX-2 enzyme, leading to less gastric side-effects, aspirin unselectively inhibits both the COX-1 and COX-2 enzyme. Recently the selective COX-2 inhibitors have unfortunately been associated with severe cardiovascular side-effects, leading to withdrawal of rofecoxib from the market.[40,41]

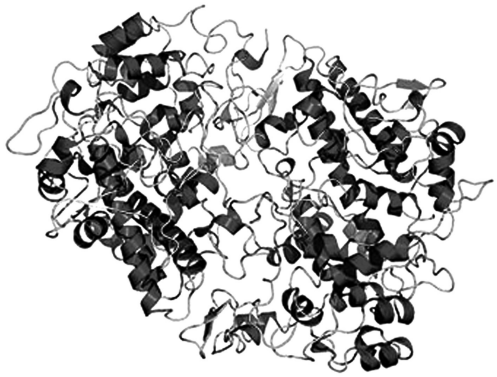


***Figure 3.*** *The cyclooxygenase enzyme*

## Objectives

The aim of the present thesis was to investigate the suspected relation between anti-inflammation agents and schizophrenia. To this end, two observational studies using prescription data from a regional health care insurance

company were performed, investigating the potential inverse relation between anti-inflammatory drugs and psychosis.
At the time the current PhD project was initiated, only one randomized trial had been performed that investigated the relation between a novel anti-inflammatory drug (celecoxib) and schizophrenia[42]. Because celecoxib, among other novel cyclooxygenase inhibitors, is associated with an increased cardiovascular risk[40,43], and it has never been tested whether this effect was modified by immune parameter, we aimed to investigate the relation between the classical and widely used NSAID aspirin (acetylsalicylic acid) and schizophrenia in a randomized placebo controlled double-blind trial. Besides, as aspirin inhibits both the COX-1 and the COX-2 enzyme[38] it has a potential broader range of action. In this trial patients diagnosed with either schizophrenia, schizo-affective- or schizophreniform disorder were recruited at one of several psychiatric hospitals in the Netherlands. After three months of follow-up the change in symptoms severity was evaluated as determined by the Positive And Negative Symptom Scale (PANSS) questionnaire.[44]

## Outline of this thesis

In **chapter two** the burden of psychiatric disorders in Europe is described as determined by various financial measures, sick-leave, early retirement and death. The costs are related to the amount of funding for research on brain disorders in the Netherlands. In **chapter three** results from a case control study are presented investigating the relation between the use of NSAIDs prior to the incident use of anti-psychotics. **Chapter four** describes this relation again using a case control design to determine the effect of another group of anti-inflammatory drugs, glucocorticosteroids, on the risk of a psychotic episode. **Chapter five** describes the rationale and the protocol for the randomized trial performed and described in **chapter six**. Here the results are presented and discussed. In the general discussion in **chapter seven** the main results of this thesis are presented and discussed. Finally in **chapter eight** a summary in both Dutch and English of the results from this thesis are presented.

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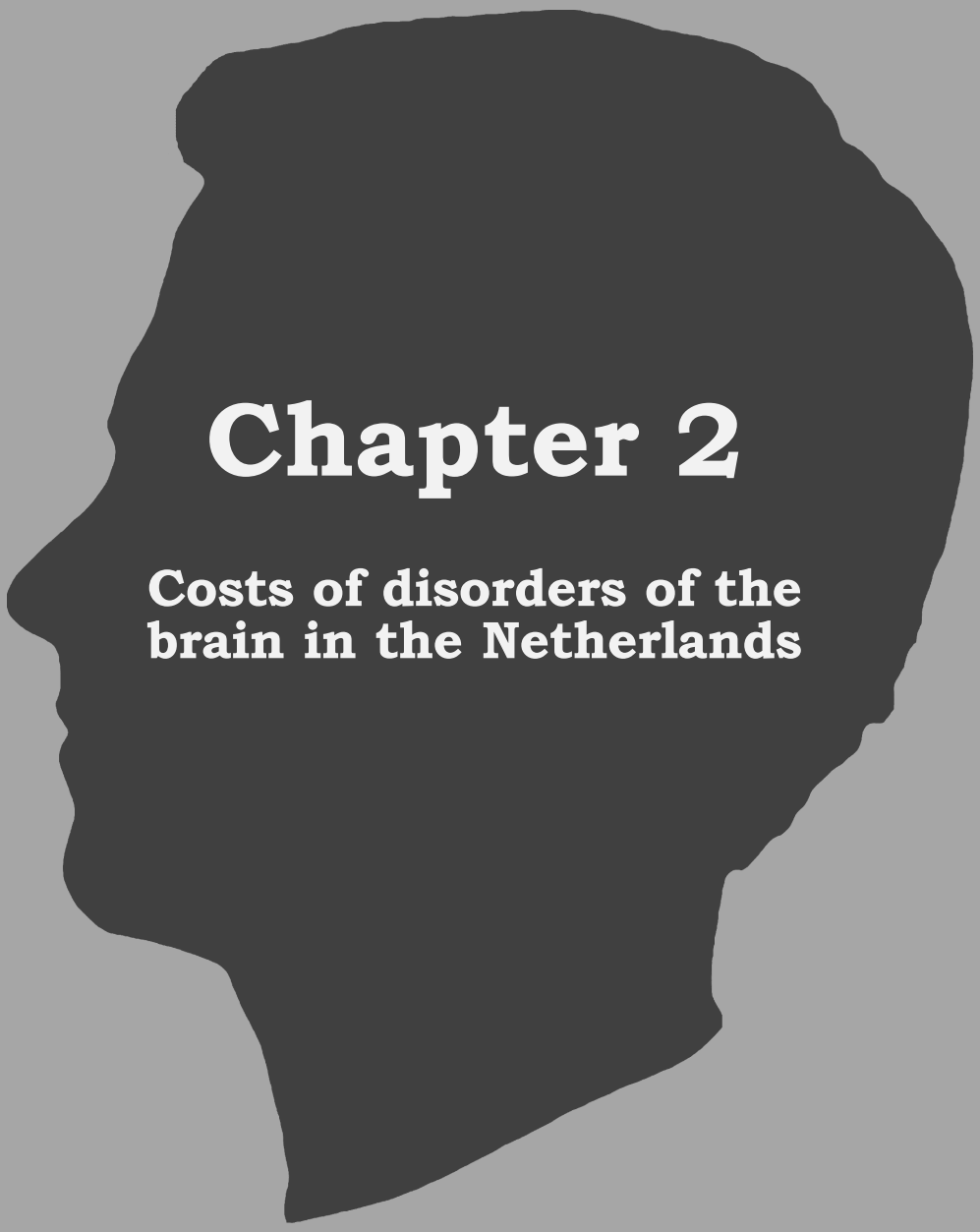
# Chapter 2

## Costs of disorders of the brain in the Netherlands



# Chapter 2

## Costs of disorders of the brain in the Netherlands

The contents of this chapter are based on:
van Ree J.M., Laan W., Burger H., Grobbee D.E., Sobocki P.
Cost of disorders of the brain in the Netherlands
Submitted

# Costs of disorders of the brain in the Netherlands

**Abstract**

This paper presents the results from the "Costs of Disorders of the Brain in Europe" study specifically for the Netherlands in 2004 and discusses them in relation to the available literature. Twelve different disorders of the brain were selected. The cumulative number of cases of disorders of the brain in the Netherlands in 2004 was estimated at 5.9 million, with migraine as the most common one. Affective disorders had the highest attributable financial burden with total costs of 4255 million euros. In total, disorders of the brain cost each Dutch citizen 1109 euros per year. Sick leave was responsible for 36% of total costs, followed by hospitalization with 15% and social services with 13%. With 32.1% costs brain disorders were found to be responsible for the largest part of disease assigned costs, while cardiovascular disease contributed to only 8.1%. Only 0.07% of total costs of brain disorders in the Netherlands is spend on research.

## Introduction

Estimations of the cost of disease are needed for rational health care resource allocation. In these estimations, disorders of the heart, liver, kidneys and other organs are usually grouped according to their site of origin. In contrast, brain disorders have not been viewed as a group. Rather, they are seen as psychiatric or mental disorders, neurological disorders, or neurosurgical disorders. While the medical field is becoming more and more specialized and in many cases further sub-specialisation and disorder-related clinics are desirable, a number of similarities and shared interests between psychiatry and neurology have developed over the last decades. Yet, basic brain research (neuroscience) is equally relevant to neurological and psychiatric disorders. In addition, brain disorders may be viewed together because politicians and other health care decision makers prefer to deal with large fields of activity.

The European Brain Council (EBC) is an example of this new tendency to group brain disorders. It is a co-ordinating council formed by European organisations in psychiatry, neurology, neurosurgery, basic neuroscience, as well as European patient organisations in psychiatry and neurology. The

brain-related branches of the pharmaceutical industry and healthcare insurance are also represented. The EBC has, as its first major task, analysed the burden and cost of brain disorders in Europe. Without knowing the size of the problem, it is difficult to make clear recommendations about initiatives in research, teaching and public awareness.
The "Cost of Disorders of the Brain in Europe" study aims to present estimates of the costs of disorders of the brain in Europe based on the existing literature. Its main results were published in June 2005.[1] The aim of the present study is to report data for the Netherlands and discuss them in relation to the literature.

## Methods

The methodology of the European study that forms the basis of the current publication has been described in detail previously.[1] In brief, 12 different disorders (or groups of disorders) of the brain were selected because they were believed to have the highest cost and because a preliminary survey indicated that at least some relevant data were present for these disorders. Other disorders that might have been equally costly or relevant were left out because they were too heterogeneous and / or too little data were available which for example was the case with mental retardation and eating disorders. The disorders selected were: addiction, affective disorders, anxiety disorders, brain tumours, dementia, epilepsy, migraine and other headaches, multiple sclerosis, Parkinson's disease, psychotic disorders, stroke and brain trauma. A steering committee consisting of Jes Olesen, Hans Ulrich Wittchen, Bengt Jönsson and Patrick Sobocki made this selection and appointed a group of 2-6 neurologists, psychiatrists or neurosurgeons for each of these disorders. These persons were considered to be leading European experts in the epidemiology of the particular disorder. In parallel, the steering committee selected a health economic panel to govern the health economic studies, which were performed by the company Stockholm Health Economics under contract with the EBC. The epidemiology data used were based on a systematic review of published epidemiological data in Europe. These reviews have been published separately.[2-8]
The main source used for the reviews were electronic databases (Medline and Web of Science) complemented by national registries and the internet. Twelve months prevalence data were collected for all disorders by country

and stratified according to age, gender and disorder severity where published evidence allowed it. When no data were available in a country, best possible estimates or extrapolated data were used.
In parallel, the economists collected all available English language publications from Europe using Medline and HEED (Health Economic Evaluation Database). These data are presented in reviews published separately.[9] It was attempted to present all relevant costs including direct medical costs, direct non-medical costs and indirect costs. Indirect costs were defined as the value of the output that is lost because people with a certain illness, disease or disorder are impaired and to ill to work, either short-term or long-term.[10] So-called intangible costs such as suffering, loss of quality of life etc. have not been calculated. All economic data were transformed to euros for 2004.
All healthcare costs are presented in euroPPP: Purchasing Power Parity, an international measure designed to compare economics data between countries while adjusting for their relative purchasing power. For the specific costs of brain disorders in the Netherlands the healthcare costs were adjusted with a factor 1.12 compared to the overall European costs, non-medical costs with a factor of 1.04, pharmaceutical costs with a factor 1.17 and production loss (indirect costs) with a factor of 0.74 compared to the European costs.
The data presented in this paper are the aggregated results for the Netherlands.

## Results

### Prevalence

The cumulative number of brain disorders in the Netherlands amounted to 5.9 million in 2004. This figure is an aggregate of the prevalence estimation for each brain disorder included in the study. The prevalence estimates of mental disorders, migraine and epilepsy are all based on the European patient populations aged 18-65.
The distribution of estimated cases with brain disorders in the Netherlands across specific disorders are presented in figure 1. The most common brain disorder was migraine, with an estimated 2.4 million cases. Affective disorders (depression and bipolar disorder) affected 715 thousand people and anxiety disorders (panic, phobias, obsessive compulsive disorder (OCD) and generalized anxiety disorder (GAD)) 1.8 million. Number of cases with

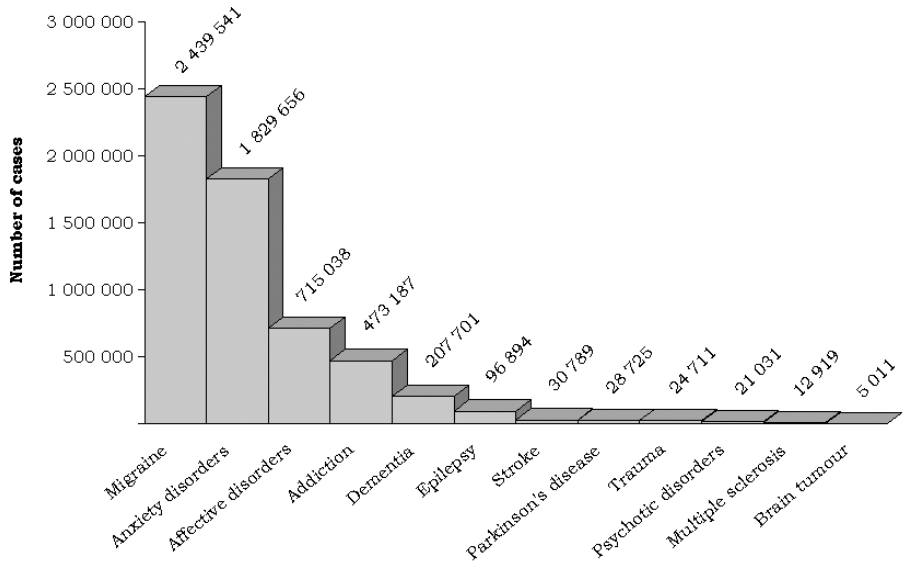



***Figure 1*** *Estimated number of cases of specific brain disorders in the Netherlands in 2004. Please note: The number of cases of stroke and trauma are based on incidence data because of lack of appropriate prevalence data in the literature. Results on addiction omit nicotine dependence. The prevalence estimates of mental disorders, migraine and epilepsy are all based on populations aged 18-65.*

addiction in the Netherlands totalled 473 thousand (including illicit drug dependence and alcohol dependence). If we were to add nicotine dependence to this estimate, the total amount of cases would be 1.5 million. Among the less prevalent brain disorders were multiple sclerosis and brain tumour.

**Cost of brain disorders**

The yearly total costs are the product of the year prevalence and the costs per case. The total cost of all included brain disorders in the Netherlands per year was estimated at 17.9 billion Euros. The distribution of the total costs according to disorder is depicted in figure 2. Affective disorders, as was the case for Europe, were the most costly followed by addiction and dementia. Among the neurological disorders migraine and stroke were the most costly followed by epilepsy and MS. The cost of stroke was based on incidence because of lack of prevalence data and thus grossly underestimated.

**Cost per patient**

Based on this data the cost per case per year for each disorder can be calculated by deviding the total costs of a disorder by the number of cases. As can be calculated by this, brain tumour is the most costly disorder with 55,925 euros per case, followed by multiple sclerosis with 33,483 euros.

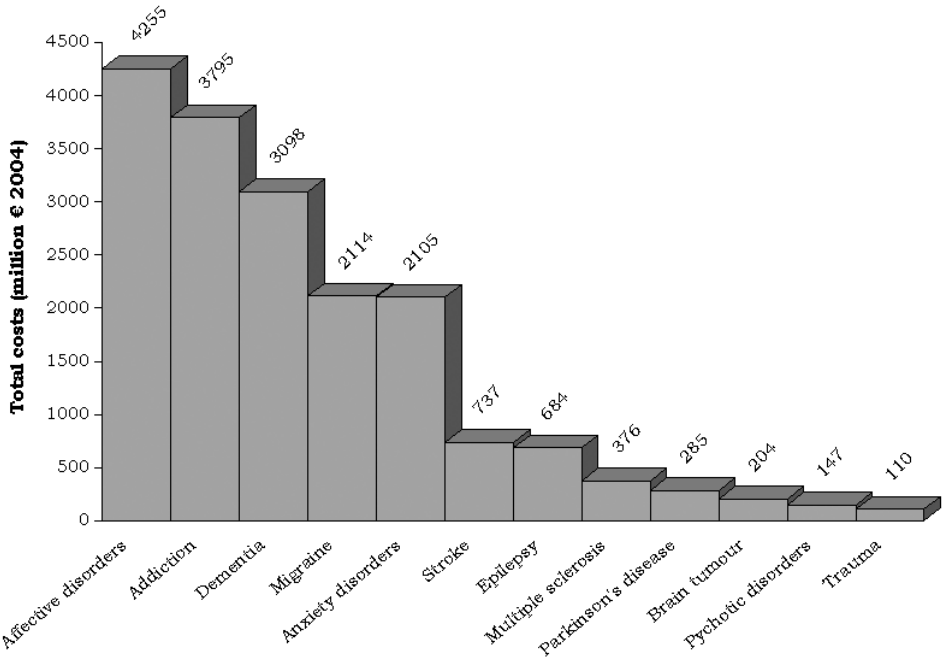



***Figure 2*** *Cost per case of specific brain disorders in the Netherlands (euroPPP 2004)*

**Cost of brain disorders distributed by resource items**

These data are presented in detail in table 1. Direct health care cost amounted to 4.7 billion euros and constituted 26% of total cost, direct non-medical cost totalled 3.5 billion euros, 19%, and indirect cost 9.8 billion euros (55%) and was mainly because of production loss due to sick leave. As previously mentioned, important cost categories are missing for several of the disorders.

| | Costs in million euros | Percentage of total costs |
|---|---|---|
| **Direct healthcare costs** | **4652** | **26 %** |
| Hospitalization | 2742 | 15 % |
| Drugs | 357 | 2 % |
| Outpatient care | 1476 | 8 % |
| Medical devices | 77 | 0 % |
| **Direct non-medical costs** | **3451** | **19 %** |
| Social services | 2328 | 13 % |
| Informal care | 834 | 5 % |
| Adaptations | 218 | 1 % |
| Transportation | 70 | 0 % |
| **Total indirect costs** | **9809** | **55 %** |
| Sick leave | 6441 | 36 % |
| Early retirement | 1649 | 9 % |
| Premature death | 1720 | 10 % |
| **Total costs** | **17913** | **100 %** |

***Table 1*** *Distribution of total cost of specific brain disorders in the Netherlands by resource use components (euroPPP, 2004)*

| | Healthcare costs | Direct non-medical costs | Indirect costs | Total cost |
|---|---|---|---|---|
| **Neurosurgical disorders** | **159** | **12** | **143** | **314** |
| Brain tumour | 49 | 12 | 143 | 204 |
| Trauma | 110 | - | - | 110 |
| **Neurological disorders** | **689** | **780** | **2 728** | **4 197** |
| Epilepsy | 96 | 185 | 403 | 684 |
| Migraine and other headaches | 99 | - | 2 015 | 2 114 |
| Multiple sclerosis | 92 | 169 | 115 | 376 |
| Parkinson's disease | 113 | 172 | - | 285 |
| Stroke | 289 | 254 | 195 | 737 |
| **Neurological/mental disorder** | **687** | **2 411** | **-** | **3 098** |
| Dementia | 687 | 2 411 | - | 3 098 |
| **Mental disorders** | **3 116** | **249** | **6 938** | **10 303** |
| Addiction | 1 016 | 202 | 2 576 | 3 795 |
| Affective disorders | 963 | - | 3 292 | 4 255 |
| Anxiety disorders | 1 036 | - | 1 069 | 2 105 |
| Psychotic disorders | 101 | 47 | - | 147 |
| **All brain disorders** | **4 652** | **3 451** | **9 809** | **17 913** |

***Table 2*** *Cost of specific brain disorders in the Netherlands by disorder area (euroPPP million)*

**Cost of brain disorders per inhabitant**

It may be of interest how much brain disorders cost each individual citizen in the Netherlands. These data can be calculated by deviding the total costs as in table 2 by the total number of Dutch inhabitants in 2004, 16,148,929. As can be calculated, all brain disorders taken together cost each Dutch citizen 1109 euros per year.

**Cost of specific brain disorders distributed by medical speciality and disorder**

Attributing disorders to one speciality is quite artificial. Brain tumour and brain trauma are not only cared for by neurosurgeons but also by neurologists and other specialities. Similarly, stroke, dementia, and most other disorders are cared for by more than one speciality and not the least by general practitioners. However, for certain purposes an attempt to separate into specialities may be useful. We have allocated the different brain disorders to brain specialty in table 2. Dementia has been kept separate, because it is considered to be equally shared between psychiatry and neurology. The most common neurosurgical disorder, herniated disc, was not included in our study.

## Discussion

Brain disorders form a major cost item in the Netherlands. The total costs of the 12 brain disorders selected for the present study amounted to 17.9 billion euros. These disorders consume approximately 4% of gross national product in the Netherlands, resulting in costs of around 1100 euros per head of the population.

The most common brain disorders are migraine and anxiety disorders with respectively 2,439,541 and 1,829,656 cases. However, since the costs per case are relatively low, the total costs for these disorders remain low. The least common brain disorders are multiple sclerosis and brain tumours. These disorders however have the highest costs per case, 33,483 and 55,925 euros respectively. Although affective disorders occupy only the eighth position in the costs per case ranking and a third position on the number of cases ranking, they have the highest financial burden on the Dutch healthcare costs, with a total of 4255 million euros.

**Methodological considerations and previous cost studies**

Only few studies were performed in the Netherlands investigating the costs of brain disorders.
Over the last two decades 'The Institute of Societal Health Care' (Erasmus University) and 'The National Institute for Public Health and Environment' (RIVM) performed a number of studies investigating the total yearly direct healthcare costs. Data are available for the years 1988 [11], 1994 [12], 1999 [13] and 2003.[14] In 1988, 1994, 1999 and 2003 the total direct costs that could be assigned to any disorder were respectively 13.492, 21.909, 29.616 and 47.466 million euros. The total direct costs for brain disorders were respectively 4.471, 7.762, 9.662 and 15.253 million euros (figure 3).

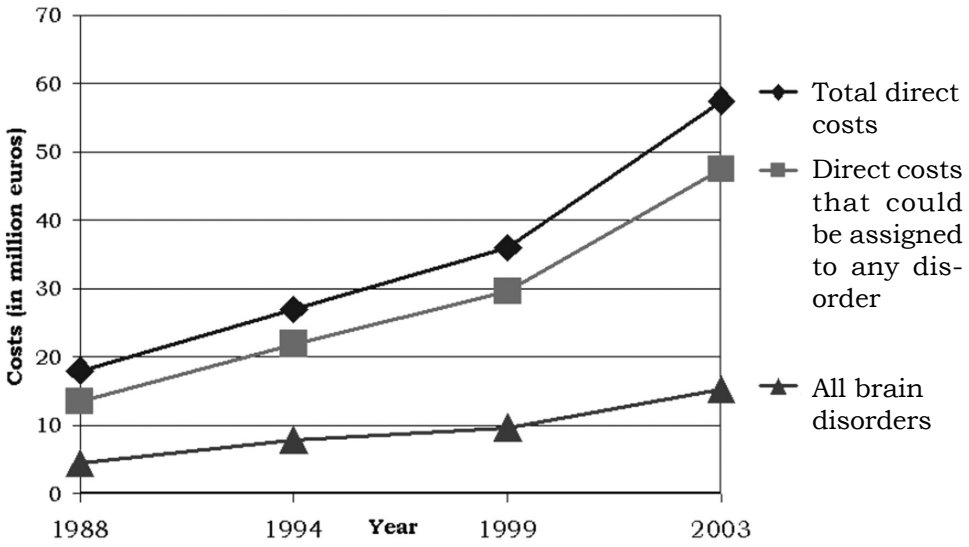



***Figure 3*** *The rise of direct healthcare costs in the Netherlands over the years*[11-14]

Although there is a clear rise in absolute costs of brain disorders there is no rise in percentage of the total direct healthcare costs (respectively 33.1, 35.4, 32.6 and 32.1%). This contradicts the popular view that the costs of brain-disorder are deviating from the trends of the total healthcare costs. These estimates did not include the informal care, which in our study was included. Our estimate of the total direct costs of care for brain disorders was estimated at 8.1 billion euros, but is an underestimation since direct medical costs for

several important disorders (e.g. mental retardation) were not included because of lack of specific data and the limitation to 12 brain disorders.

In the Dutch NEMESIS study the prevalence and incidence of all brain disorders in the Netherlands was estimated over the years 1996 to 1999. The total one-year prevalence for any brain disorder was estimated at 23.5 percent of the Dutch population, which makes a total of 3.8 million cases.[15] In our study we estimated 5.9 million cases of brain disorders, which is substantially higher, most likely because this is an aggregate estimate of all analysed brain disorders. When correcting for co-occurrence of brain disorders our estimate will certainly be substantially lower.

The cost of strokes in the Netherlands in 1993 was estimated at 1148 million euros[16] and in 2003 at 1452 million euros[14], which was about 3% of the yearly healthcare budget. This is a higher figure than the estimated yearly costs of 737 and a percentage of total healthcare costs of 1.23% in our study. This may be explained by the fact that in our study for stroke incidence instead of prevalence data were used.

In 1994 a study was published investigating the burden of typical neurological disorders in the Netherlands, like dementia and multiple sclerosis.[17] The typical 'mental' disorders like affective and psychotic disorders were not taken into account in that study. The financial burden for all neurological disorders was estimated at 14% of the healthcare budget at that time. This is comparable to the current estimate of 15.5% (((314+4197+3098)/49230 (estimated disease assigned costs in the Netherlands)*100) in the present study. The authors concluded that 3-5% of all GP visits, 7% of all hospital visits, 70% of all nursing home stays, 14% of all deaths and 6% of all sick leaves was caused by neurological disorders.

The last published data (2003) on direct healthcare costs per disease in the Netherlands[14] shows that of the disorder-assigned costs 20.1% could be attributed to mental disorders, 5.5% to neurological and neurosurgical disorders and 6.5% to dementia. Similar percentages can be calculated for the data of the present study: 20.9% for mental disorders, 9.2% for neurological / neurosurgical disorders and 6.3% for dementia (data presented in table 2 divided by the estimated disease assigned costs, amounting to 49230). The figures for neurological / neurosurgical disorders are higher in the present study, most probably because of including the indirect costs for migraine and other headaches (4.1% of total costs).

The current estimates may have underestimated the true costs of brain disorders in the Netherlands. This is because a number of important brain disorders like mental retardation, developmental disorders, eating disorders and neuromuscular disorders were not included in the current estimate because of lack of data. Neither included were the costs resulting from addiction related crime. Including this will likely substantially raise the total burden of addictions.
The estimates in dementia and Parkinson's disease were limited to the population aged 65 or older, and stroke on the age group 25 years or older. These estimates were in this respect conservative.
For headache related disorders we were only able to include migraine in the current analysis. Including all other forms of headaches in the current analysis will likely substantially raise the costs of brain disorders. However, most headaches cannot be considered primarily a brain disorder but may be secondary to non-brain disorders.
Berg and Stovner [18;19] reviewed the prevalence and costs of migraine and other headaches. In this review the 1-year prevalence of general headaches was almost 4 times higher than the prevalence of migraine (respectively 51 and 14 percent).

**Comparison with cost and burden of other disorders and implications for research**

The healthcare costs for brain disorders in the Netherlands are by far the highest compared to other groups of diseases. Costs for brain disorders in 2003 in the Netherlands amounted to 32.1% of disorder assigned costs, while for cardiovascular disease (excluding stroke) and cancer this was only 8.1 and 5.0%.[14]
With a total cost of 5251 million euros on drugs in the Netherlands [20], the drugs for brain disorders constitute only 6.8% of all Dutch drug costs. This is remarkable since drugs for brain disorders are often seen as overused and too costly.
From a report by the World Health Organisation it can be concluded that mental disorders have the highest disease burden, responsible for the loss of 25.3 percent of the disability adjusted life-years in the European Union. This burden is almost 10% higher than the burden of cardiovascular disease and cancer, which contribute to respectively 17.1 and 16.7 percent of disability adjusted life-years lost.[21]

Unfortunately it is not clear in the Netherlands how much of the total health care budget is spent on research of brain disorders. However, when the research budgets of the five largest funding sources of brain research in the Netherlands (the Netherlands Brain foundation, Epilepsy foundation, the Parkinson foundation, the Multiple Sclerosis foundation and the specific government funding on brain research (ZONMW)) are accumulated, the amount of funding is approximately 10.4 million euros. Please note that this does not include stroke research, since in the Netherlands this is partly funded by the Netherlands Heart foundation. Discriminating between heart research grants and stroke research grants in this organisation would be very disputable since there is a large overlap in research projects for both disorders. This 10.4 million euro is around 0.07% of the total costs of brain disorders in the Netherlands. Not only is the absolute amount of funding for brain disorder research in the Netherlands quite small, the percentage of funding of brain disorder research compared to the huge financial burden is out of proportion as well.

In the fifth framework program of the European Union only 8% (85 million euros) of the budget was spent on neurosciences.[22] Remarkably, it is estimated that brain disorders account for 23% of the years of healthy life lost, 50% of years lived with disabilities and 35% of disability adjusted life years.[23]

If in the Netherlands only 1% of the total costs of brain disorders was spend on research, the amount of total funding would be multiplied by a factor 15. We conclude that the amount of money spent in the Netherlands on research on brain disorders is small relative to their huge healthcare costs. Although no big breakthrough in the treatment or cure of brain disorders has yet been made, much has been discovered about the functioning of the brain. Several important advances were made in brain disorder treatment in the last decade like the introduction of atypical neuroleptics and the promising 'repetitive transcranial magnetic stimulation' in the treatment of depression. There is nevertheless still a long road of research to go before we actually have lowered the burden of brain disorders to the level of other major diseases like cancer or cardio-vascular disease. The more priority research on brain disorders will get, the shorter this road may be.

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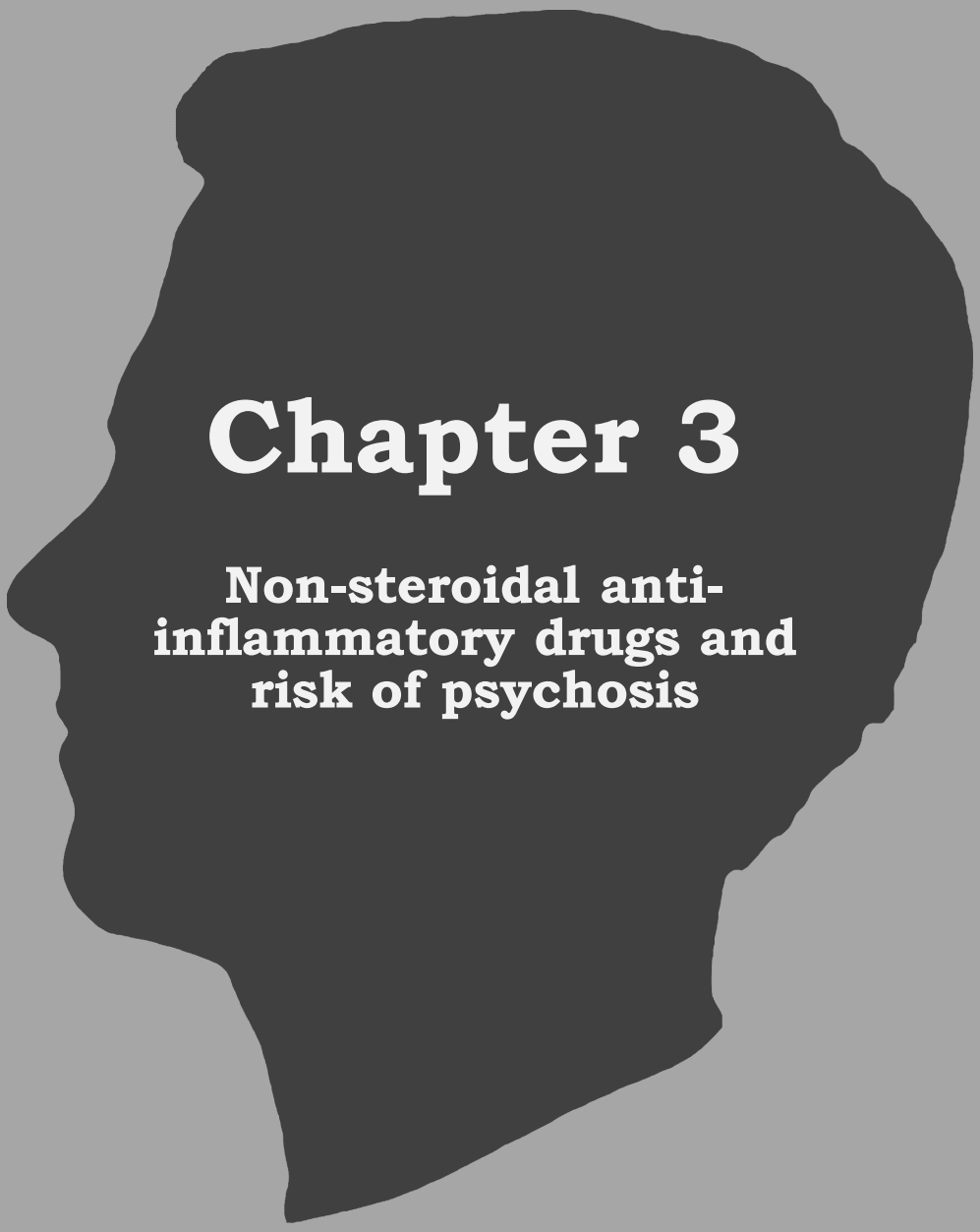
# Chapter 3

## Non-steroidal anti-inflammatory drugs and risk of psychosis



# Chapter 3

## Non-steroidal anti-inflammatory drugs and risk of psychosis

The contents of this chapter are based on:
Laan W., Selten J.P., Grobbee D.E., Smeets H., Kahn R.S., Burger H.
Non-steroidal anti-inflammatory drugs and the risk of psychosis
European Neuropsychopharmacology, volume 17, issue 4, pages 309-311

# Non-steroidal anti-inflammatory drugs and risk of psychosis


## Abstract

The objective of the current research was to examine the relation between non-steroidal anti-inflammatory drugs (NSAID) use and risk of psychosis. To this end we performed a longitudinal case-control study using prescription data from a Dutch health insurance company. Men aged 25 years or over and women aged 30 years or over were excluded to prevent inclusion of non-incident cases. This resulted in eighty-two cases and 359 randomly selected controls from the same population. The overall relative risk of incident antipsychotic use for NSAID users, adjusted for age and prescription frequency, was 0.80 (95%CI: 0.48–1.33). After stratification for gender the risk of psychosis was significantly lower (59%) in male NSAID users only. The relative risks for male and female subjects were 0.41 (95%CI: 0.17–0.97) and 1.31 (95%CI: 0.65–2.64), respectively. These results suggest that in men NSAIDs may lower the risk of psychosis.


## Introduction

A negative association between the occurrence of rheumatoid arthritis and schizophrenia has been known for a long time[1]. This suggests involvement of the immune system in the pathophysiology of schizophrenia. Indeed, immune alterations have been observed in patients with schizophrenia[2-6], although it cannot be excluded that these changes result from long-term neuroleptic treatment[7]. Some of the immunological changes may be counteracted by prostaglandin inhibitors, e.g. non-steroidal anti-inflammatory drugs (NSAIDs). Muller and coworkers showed a beneficial effect of add-on therapy with celecoxib [8]. Improved understanding of the putative relation between NSAID use and risk of psychosis may shed a light on the immunological inflammation hypothesis and may point at new treatment options.

The present study aims to longitudinally investigate the relation between NSAID use and subsequent schizophrenic psychosis. The relation was additionally studied in men and women separately because males are at a

considerably higher psychosis risk than females[9], and because the negative association with rheumatoid arthritis has shown to be modified by gender[1].

## Experimental procedures

We performed a prospective nested case-control analysis using anonymized pharmacy records from the Agis Health Insurance Database (N = 550.000). Data on all prescribed NSAIDs (ATC-codes N02BA(01-to-79) and M01A(A01-to-X68) and anti-psychotics (ATC-code N05A(A01-to-X12) between 1995 and 2002 were extracted.

All study subjects were registered at the insurance company for at least five years. Cases were those insured with first use of anti-psychotics during at least three months in the years 2000 to 2002. To prevent inclusion of non-incident cases, men aged 25 years or over and women aged 30 years or over were excluded. These age cut-offs correspond to the respective mean ages of disease onset[10]. Controls were a random, four times larger sample of non-cases from the same database. We took account of prescription frequency of any medication because cases that were socially withdrawing before disease onset may have been less likely to visit a general practitioner and consequently, to receive any medication, including an NSAID.

For cases, NSAID use and prescription frequency were defined as any prescription for NSAIDs and total number of prescriptions per year in the four years preceding anti-psychotics use. For controls this period was defined by calendar years 1999 to 2002. Subjects using lithium suggesting bipolar disorder, or methotrexate or sulfasalazine suggesting rheumatoid arthritis, were excluded. We calculated odds ratios (OR) with 95% confidence intervals (95% CI) as measures of relative risk of NSAID use for psychosis.

Using logistic regression additional adjustments were made for age and prescription frequency. We repeated the analyses while stratifying for gender.

## Results

Eighty-two cases and 359 controls were included in the analysis. Cases showed the same mean age as controls (21 years) but a higher proportion males (52 versus 30%) and a higher mean prescription frequency (6.5 versus 4.8 per year). The four-year cumulative incidence of NSAID use in the source population, as estimated from the controls, was 41% (95% CI 36 – 46%).

| | Unadjusted | Adjusted for age | Adjusted for age and prescription frequency |
|---|---|---|---|
| **Men** | 0.58 (0.26 - 1.31) | 0.44 (0.19 - 1.05) | 0.41 (0.17 - 0.97) |
| **Women** | 1.47 (0.78 - 2.90) | 1.47 (0.74 - 2.90) | 1.31 (0.65 - 2.64) |
| **Total** | 0.87 (0.53 - 1.42) | 0.85 (0.51 - 1.40) | 0.80 (0.48 - 1.33) |

***Table 1*** *Relative risk of psychosis according to NSAID use (with 95% confidence intervals), for the group as a whole and for men and women separately.*

Among NSAID users mean age was 22 years (range 13 to 30) and 26% was male. For non-NSAID users mean age was 20 years (range 12 to 30) and 40% was male. Mean age for males was 19 years and 22 years for females. Overall, the relative risk of psychosis for NSAID users was 0.87 (95% CI: 0.53 – 1.42). After adjustment for age and prescription frequency the relative risk was similar, i.e. 0.80 (95%CI: 0.48 – 1.33). Further analyses were stratified for gender (table 1). NSAID use was significantly related to a 59% decreased risk of psychosis in men (adjusted relative risk 0.41 (95% CI: 0.17 – 0.97)) while in women, NSAID use was associated with a small and statistically non-significant increase in risk (1.31 (95%CI: 0.65 – 2.64)). The two-tailed p-value for interaction between gender and NSAID use was 0.08.

## Discussion

The results of the present study show a protective effect of NSAIDs on the risk for treated psychosis in men only.
To appreciate this finding, some characteristics of the study need to be addressed. The incident use of anti-psychotics was used in this analysis as a proxy for incident psychosis. In both a Dutch and an Italian study[11,12] a substantial part of anti-psychotics were prescribed for other indications, notably non-schizophrenic psychosis. This could have resulted in a slight overestimation of the true incidence of schizophrenic psychosis. As it is highly unlikely that this overestimation has selectively affected NSAID users, the consequent misclassification has been non-differential, with underestimation of the observed effect as a result. Another potential limitation of the data is that prescription data may not completely cover NSAID use in the population. In the Netherlands certain NSAIDs can be without prescription, i.e. over the counter. Consequently insurance companies will not register these NSAIDs, leading to an underestimation of true NSAID use. If subjects in the prodromal

phase of psychosis were more likely to omit a visit to their general practitioner than healthy subjects and consequently perhaps used more over the counter NSAIDS instead, overestimation of the protective effect may have occurred. To antagonize this potential bias we controlled in the analyses for prescription frequency for any medication. Yet, overall prescription frequency may not fully capture the tendency of cases to visit their GP.

Our findings agree with previous reports from the limited number of studies carried out in this area. In a case report review by Jiang and Chang[13] 5 cases with adverse psychiatric reactions to NSAIDs are described. This suggests that the use of NSAIDs at least may have an effect on the central nervous system. As far as we know only one study addressed the effect of NSAIDS on psychosis directly. In this study, a randomized trial by Muller[8] 25 male and 25 female patients with acute exacerbation of schizophrenia were randomly assigned to either risperidone plus celecoxib (COX-2 NSAID), or risperidone plus placebo. The celecoxib group showed significantly greater improvement in total PANSS (Positive and Negative Syndrome Scale) scores indicating that the addition of NSAIDs to regular anti-psychotic treatment may have beneficial effects on the course of schizophrenia. Unfortunately, no gender-specific results were presented.

A possible effect of NSAIDs on the occurrence and course of psychosis is plausible in view of a number of mechanisms proposed in the literature.

Psychotic symptoms have been described in processes accompanied by a process of inflammation and in several autoimmune disorders involving the CNS[14-16]. Signs of inflammation were found in the post-mortem CNS tissues of some schizophrenic patients[6] Recently, it has been discovered that the cyclo-oxygenase enzyme in platelets, which is inhibited by NSAIDs, is hyperactive in schizophrenia[17]. The observations of our study suggest that the use of NSAIDs might reduce the risk of schizophrenia in males only. An explanation for the absence of a positive effect of NSAIDS in women may be that the supposed protection by estrogens[18] leaves little room for positive effects of NSAIDs.

In conclusion, our findings in a large cohort study with over 80 patients with incident treated psychosis support the view that NSAIDs may reduce the risk of future psychosis, although this effect appears to be restricted to males.

**Acknowledgements**

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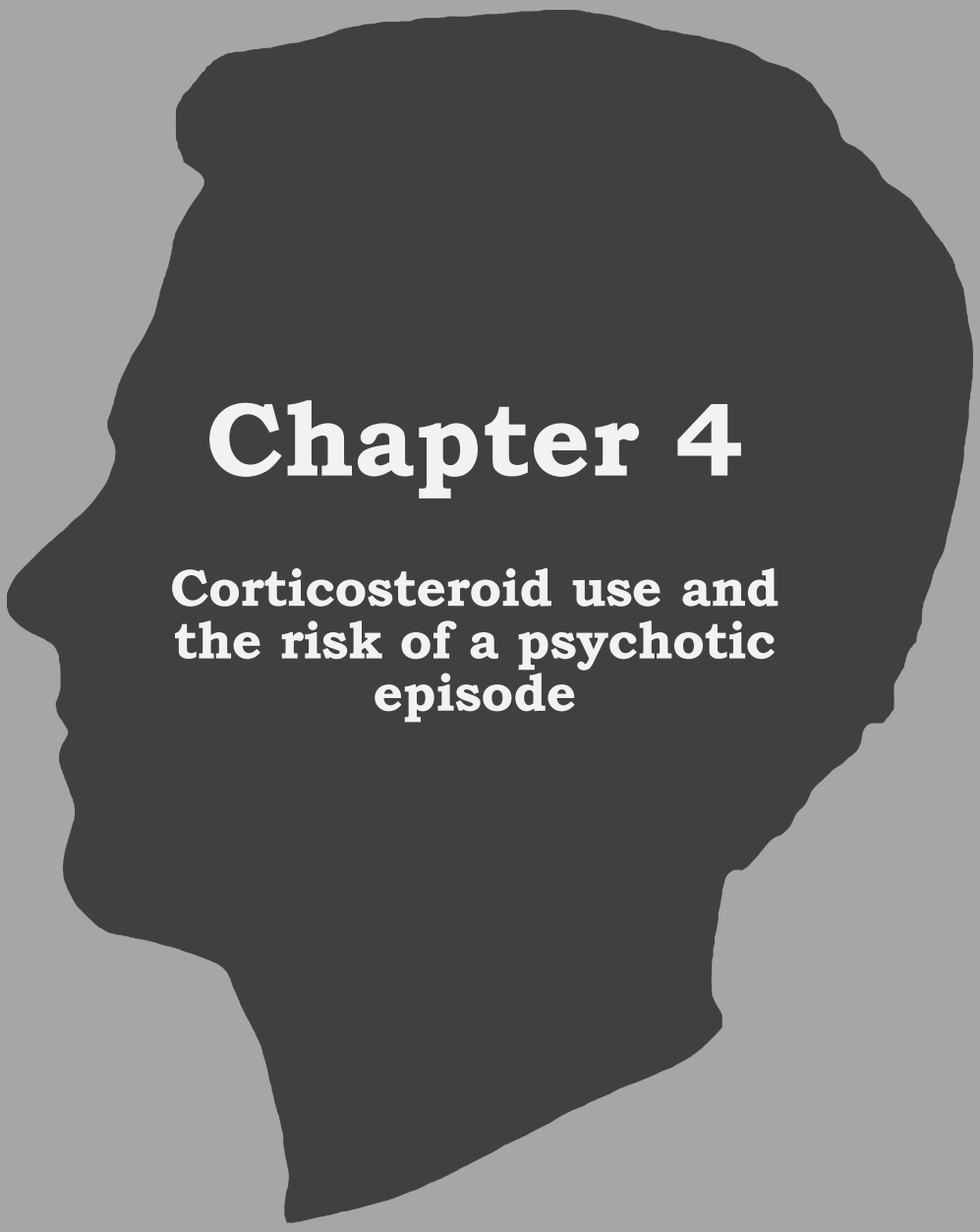
# Chapter 4

## Corticosteroid use and the risk of a psychotic episode



# Chapter 4

## Corticosteroid use and the risk of a psychotic episode

The contents of this chapter are based on:
Laan W., Smeets H., de Wit N.J., Kahn R.S., Grobbee D.E., Burger H.
Corticosteroid use and the risk of a psychotic episode
Submitted

# Corticosteroid use and the risk of a psychotic episode


## Abstract

The hypothesis that chronic inflammation may play a role in schizophrenia receives increasing attention. The best known and oldest evidence for the role of inflammation in schizophrenia is the inverse relation between this disorder and rheumatoid arthritis. More recently there have been a number of randomized trials showing that adjuvant non-steroidal ant-inflammatory drugs inhibit the symptoms of schizophrenia. In this paper we aim to investigate whether use of steroidal anti-inflammatory drugs is associated with a decreased risk for psychosis as well.

A longitudinal nested case-control study with 1363 cases and 4617 controls was performed investigating the association of corticosteroid consumption with a new psychotic diagnosis. The use of inhaled or systemic glucocorticosteroids (GCS) in the year prior to the new diagnoses for the cases and the same year for their age and sex matched controls was examined. Separate analyses took place for the cases and controls in the youngest subgroup. A potential dose-response relation was examined using quartiles of GCS consumption.

A significant reduced relative risks of 0.52 (95% confidence interval (CI) 0.36 – 0.75) was found for any GCS in men only (RR in women: 0.84 (95%CI 0.59 – 1.20)). Similar relative risks were present for the inhaled and systemic GCS and in the youngest subgroup. The relation appeared dose related.

GCS appear to be associated with a lower risk of psychosis in men only. This supports the view that inflammation plays a role in the pathogenesis of psychosis and schizophrenia.


## Introduction

Current treatment in psychosis focuses on the antagonism of the dopaminergic and serotoninergic receptor.[1] Although an effective treatment in a large part of patients, still around two-third of cases will have at least one relapse, and for each relapse one in six will not remit from that episode.[2] Consequently, there is ample interest in other mechanisms than those involving the dopamine and serotonine receptor. One of these mechanisms is inflammation. Over the past few years, evidence for a role of chronic

inflammation in the etiology psychosis and schizophrenia has accumulated. The first evidence for a relationship between inflammatory disease and psychiatric disease was provided by Nissen and Spencer in 1936 (reviewed by Eaton et al.[3]), who found not a single case of arthritis of any of 2200 psychiatric inpatients.

Further research confirmed an inverse relation between rheumatoid arthritis and schizophrenia. Eaton et al.[3] reviewed the literature and concluded that in twelve out of fourteen articles investigating the relation between rheumatoid arthritis and schizophrenia an inverse relation was found. The suggestion has been raised that this inverse relation is caused by the anti-inflammatory medication received for arthritis at first onset prevents the development of the other disorder. A role for chronic inflammation in schizophrenia is also indirectly supported by observation that certain anti-psychotics have an anti-inflammatory effect.[4]

Moreover, Muller et al.[5] and Akhondzadeh et al.[6], in randomized trials, showed that adjuvant treatment with non steroidal anti inflammatory drugs (NSAIDs) attenuates the severity of psychotic symptoms in schizophrenic patients. Support from more basic research has come from Potvin et al. who reported in a recent meta-analysis elevated levels of the inflammatory cytokines Il-1RA, sIl-2R and Il-6 and decreased levels of the T-cell proliferation stimulating interleuking Il-2 in schizophrenic patients.[7] It has also recently been shown that serum cortisol levels are elevated in schizophrenia.[8,9] Cortisol is known to be elevated as a result of inflammation and stress.[10] Finally, we previously showed a protective effect of NSAIDs on incident psychosis in male subjects.[11]

Glucocorticosteroids (GCS), are potent inhibitors of inflammation and other immune processes. They inhibit the access of leukocytes to inflammatory sites, interfere with their function and the function of fibroblasts and endothelial cells at those sites and suppress the production and the effects of humoral factors.[12]

GCS can be classified into two groups according to the way they are administrated. In ATC (Anatomical Therapeutic Chemical) categories, they are classified as [13] systemically (ATC group H02AB), and inhaled GCS (ATC group R03BA)[13]. The main indication of the first group of drugs is chronic inflammatory disorders like Crohns disease, polymyalgia rheumatica and sarcoidosis. As GCS also have severe side-effects, notably osteoporosis, these drugs are usually only prescribed in case of inflammatory exacerbation, also since chronic use of GCS may result in corticosteroid dependency.[14] Inhaled

GCS are used in chronic obstructive pulmonary disease (COPD), like asthma, where treatment with GCS is usually chronic.[15] With an estimated absorption of around 40% into the blood stream, these drugs also have systemic effects.[16] As GCS are strongly anti-inflammatory and inflammations are suspected to play a role in schizophrenia, corticosteroids may lower the risk of a new psychotic episode. We expect this protective effect to be present for both inhaled and systemic GCS. As inhaled GCS are often used chronically, but in a lower dose, we expect the effect in both groups to be about equal. Since we showed in a previous study that the protective effect of non steroidal anti inflammatory drugs was restricted to men, and because men have a considerably higher risk of psychosis[17], we expect to see the largest effect in male subjects.

## Methods

We performed a nested longitudinal case-control study investigating the relation between psychotic episodes and GCS use. This was done by linking the databases of the RIPAG-MWU (Stichting Regionale Informatie Patiënten in de Geestelijke Gezondheidszorg regio Midden Westelijk Utrecht) foundation and the Agis Health Insurance Company for cases with a new psychotic episode.

The RIPAG-MWU is a case-register established in 1998 which collects psychiatric treatment data and diagnoses from the psychiatric healthcare hospitals in the middle western part of the province of Utrecht, the Netherlands. The catchment area of the RIPAG-MWU foundation contains around eight-hundred-thousand inhabitants, mainly from the town of Utrecht and surrounding villages. In this database all visits to psychiatric hospitals, admissions to psychiatric wards, DSM-IV diagnoses and type of care are recorded from 1999 onwards. In total this resulted in over 60.000 recorded cases with a psychiatric disorder over the years 1999 to 2005. These cases had a total of over 380.000 recorded diagnoses, and received over 4.5 million days of inpatient and 6.4 million days of outpatient care.

In the Netherlands every inhabitant is obliged to be insured for healthcare costs.[18] Before January 2006 people earning below 33.000 euros (approximately 48.600 US dollar) a year were obliged to be insured at one of several Dutch national health insurance providers. As the average yearly income in the Netherlands in 2005 was around 21.000 euros, this included a major part of the Dutch population.[19] In the middle-western part of the

province of Utrecht the largest health insurance provider was the Agis Health Insurance Company, with around 1.2 million participants. All medication use and costs except that of inpatients is recorded in the Agis Health Database. In the present study cases were defined as those with a new psychotic episode in the years 2002 to 2005, where no earlier psychotic episode was recorded in the years 1999 to 2001. A psychotic episode was defined as a new DSM-IV diagnosis with codes 293.81, 293.82, 295.1, 295.2, 295.3, 295.4, 295.6, 295.7, 297.1, 297.3, 298.8 or 298.9 (schizophrenia and related psychosis). By linking the two databases a complete representation of healthcare use of the cases with a psychotic episode could be made. Demographics and diagnosis were derived from the RIPAG-MWU database and prescribed medication from the Agis health insurance company. Case data was linked for the years 2002 to 2005. Cases in the both databases were matched on a number of personal data (part if the family name, gender, date of birth) that theoretically identify every unique case. During the matching procedure all personal data was removed, resulting in an anonymous database. However, as not all cases treated by centers in the RIPAG-MWU region live in that same region and therefore were not insured at the Agis insurance company, a part of the cases will not return a positive match in the Agis Health Insurance database.

The control group was selected from the same source population, as represented by records in the Agis Health Insurance database. To increase statistical power, four controls were matched to each case with regard to age and gender. [20]

Pharmacy data were analyzed for the index year only. The index year was defined as the 365 days preceding the first psychotic episode for the cases and the same days for their respective controls.

As social withdrawal is a common symptom of schizophrenia[21] cases might be less likely to visit a physician and with that to be prescribed a GCS. To prevent confounding of results by this tendency we considered the total DDDs (defined daily doses)[13] for any medication prescribed in the calendar year at the beginning of the index year, together with age and gender, as potential confounders. As different prescription behaviour might also have resulted from previous psychosis we will also analyse the youngest subgroup, as delineated by the median age, of cases separately since they are less likely to already have had an earlier episode.

The GCS consumption was defined as any prescription of a GCS during the index year. A potential dose-response relation was examined by the creation of four subgroups, delineated by the quartiles of DDDs consumption in controls.
All analyses were performed using the SAS statistical package (SAS v9.1, SAS Institute Inc., Cary, NC, USA). Relative risks and p-values were calculated using conditional logistic regression analysis.

## Results

A total of 3872 cases from the Ripag-MWU with a psychotic episode between 2002 and 2005 were found eligible for linking to the Agis health insurance data. Of those, an expected percentage of 47.8% (N=1849) could be linked to a record in the Agis health insurance database. Cases that were and were not matched did not materially 56differ on demographic characteristics. The cases were matched 1:4 with 7396 controls from the same source population of Agis insured. Subsequently, 486 cases (26.3%) and 2779 (37.6%) controls were excluded from final analysis as they were not insured at the Agis Health insurance company for the complete, or part of the index year, leaving 1363 cases and 4617 controls to be analysed. The age and gender distribution of the study-population is given in table 1.

| | **Controls** | **Cases** |
|---|---|---|
| N | 4617 | 1363 |
| Age | 46.6 ± 15.8 | 45.1 ± 15.3 |
| Median age | 41.8 | 41.8 |
| Male gender | 2622 / 56.8% | 836 / 61.3% |
| Total prescribed defined daily doses | 609 ± 1985 | 1279 ± 16593 |
| Sytemical glucocorticosteroid users | 212 / 4.6% | 45 / 3.3% |
| Inhaled glucocorticosteroid users | 218 / 4.7% | 40 / 2.9% |
| Any glucocorticosteroid users | 393 / 5.3% | 77 / 4.2% |

***Table 1.*** *Study population characteristics in the index year*

The prevalence of systemic and inhaled GCS use in the control population was 4.6 and 4.7 percent during the index years, respectively. The percentages of use in the group of cases were substantially lower. Cases received around twice the quantity in DDDs of all drugs prescribed during the index year compared to the control population.

| | Sytemic GCS | Inhaled GCS | Any GCS | Youngest subgroup, any GCS |
|---|---|---|---|---|
| **Men** | 0.51 (0.31 - 0.84) | 0.58 (0.36 - 0.94) | 0.52 (0.36 - 0.75) | 0.47 (0.26 - 0.86) |
| **Women** | 1.07 (0.68 - 1.67) | 0.68 (0.41 - 1.11) | 0.84 (0.59 - 1.20) | 0.78 (0.41 - 1.49) |
| **Total** | 0.74 (0.53 - 1.03) | 0.62 (0.44 - 0.88) | 0.65 (0.51 - 0.85) | 0.59 (0.38 - 0.91) |
| **P-value for interaction by gender** | 0.03 | 0.65 | 0.32 | 0.25 |

***Table 2.*** *Relative risk (95% confidence interval) of a psychotic episode for corticosteroid use and p-value for interaction by gender, GCS: Glucocorticosteroids*

| | ddd of any GCS consumption | Any GCS RR |
|---|---|---|
| **No GCS** | 0 | 1 |
| **First quartile** | 0.1 - 20.7 | 0.73 (0.46 - 1.17) |
| **Second quartile** | 20.7 - 50.0 | 0.70 (0.41 - 1.20) |
| **Third quartile** | 50.0 - 192.5 | 0.70 (0.45 - 1.10) |
| **Fourth quartile** | 192.5 - 1401.0 | 0.47 (0.26 - 0.84) |

***Table 3.*** *Dose-response relation of total GCS consumption. ddd: defined daily doses, GCS: Glucocorticosteroids RR: Relative risk of psychosis*

The relative risk of psychosis was 0.74 (95% confidence interval (CI) 0.53 – 1.03) for users of systemic GCS, 0.62 (95% CI 0.44 – 0.88) for the inhaled GCS and 0.65 (95% CI 0.51 – 0.85) for any GCS. Adjustment for potential confounders did not affect the relative risk.
The findings according to increasing use of GCS are shown in table 3.

## Discussion

The results of the present large case-control study show that GCS use is associated with a substantially lowered risk of psychosis. The associations were of equal strength for both systemic and inhaled GCS. In male subjects the relative risks of psychosis were around 0.50, thus indicating a 50% reduction of the risk. In women, no risk reduction associated with systemic GCS use could be demonstrated, the relative risks for both inhaled and systemic corticosteroids were somewhat closer to unity and did not reach statistical significance. The sex difference in response to GCS in the risk of psychosis is substantiated by the significant p-value of 0.03 for interaction. Analysis by quartiles of GCS consumption showed increasing risk reduction with increasing doses.
To appreciate the findings some issues need to be discussed. In this study we used a first recorded diagnosis of a psychotic disorder as the start of psychosis. Prodromal psychotic symptoms may, however, already have been slumbering for years before being treated and diagnosed.[22] The recorded date of the psychotic episode might therefore not truly mark the beginning of psychosis. When the date of psychosis is estimated too long after the actual onset of psychosis this could bias the relative risks, as physicians might treat a psychotic case differently that a non-psychotic case. The cases with a psychosis in this study also appeared to be relatively old, with an average age of 46.6 years at first recorded diagnosis. This might indicate that most cases were not having a first but rather a repeat episode. This could result in different medication consumption in the already prevalent cases. As the relative risks in the youngest subgroup were not substantially different and even slightly lower compared to the complete population there is no reason to suspect that the potential repeated psychotic episodes in the older cases biased the results.
Forty-eight percent of cases with a new psychotic episode over the years 2002 to 2005 gave a positive match with a person from the Agis Health

Insurance database. The cases that did not return a positive result either lived outside the region of middle western Utrecht between 2001 and 2005 and therefore may have had another insurance company, or had a yearly income of over 33.000 euros. Neither of these factors will have biased the findings.

As the RIPAG-MWU dataset covers all major psychiatric hospitals in the region it is highly unlikely that any new case of psychosis in the region will be missed. Moreover, cases and controls were derived from the same source population, i.e. those insured by AGIS between 2001 and 2005.

The chances of cases taking less GCS because of social withdrawal in the prodromal phase of psychosis are very slim. As can be seen in table 1 the cases were prescribed a higher total volume of medication and might therefore even be more likely to have been prescribed a GCS, which was not the case. This higher prescription volume in the cases could, however, have resulted from repeated psychotic episodes. Nevertheless, as including prescription frequency in the model did not substantially alter the relative risks we do not expect any bias to arise from the inclusion of repeated episodes.

For this study all data on medication prescribed to the cases and controls was available for analysis. The only prescription data missing is that what was prescribed during periods of inpatient-care, as this is not directly financed by insurance companies. As cases are probably only admitted after onset of psychotic episodes this will not likely result in any bias.

The protective effects of GCS as observed in this study indicate that the use of these drugs may be associated with the risk psychotic episodes, or at least delay it's onset. This association was less pronounced in the group of female subjects. Previous studies already showed that women have a later onset of psychosis with a better prognosis[22]. These findings could indicate a different pathogenesis of psychosis in men and woman. It can be postulated that the protective effects of GCS is already accounted for by oestrogen in female subjects.[23]

The negative association between GCS use and psychosis as observed in this study can be caused by several pathways. GCS for example activate several anti-inflammatory genes and inhibit the synthesis of several inflammatory proteins through the suppression of their encoding genes. GCS also reduce the transcription of inflammatory enzymes such as nitric oxide synthase and the prostaglandin producing cyclooxygenase-2.[24] Prostaglandins in itself are critical mediators in inflammation.[25] The inhibition of

prostaglandins may also play a role in psychosis by inhibiting the glutamate reuptake in astrocytes. This is because decreased levels of glutamate and other glutamergic abnormalities have repeatedly been shown in for example the cerebrospinal fluid of patients with schizophrenia.[26]
Among the interleukins that are inhibited by GCS are those that were found to be elevated in schizophrenia.[7,24]
GCS, allthough very effective in inhibiting inflammation, are also associated with numerous psychiatric side effects, such as manic symptoms, depressive symptoms, memory impairment and even steroid psychosis.[27] It is not clear what mechanisms are causing these side-effects, but it does suggest that GCS indeed do have an effect on psychiatric functioning.
The hypothesis that inflammations plays a role in psychosis has also been confirmed in trials where patients with schizophrenia received non steroidal anti-inflammatory drugs[5,6] and is again supported by the findings from this observational study. We hope these findings will support further research into the immunological aspects of schizophrenia.

## Conclusion

In conclusion, the results of this large study with 4617 controls and 1363 cases with a new psychotic episode show that GCS use decreases the risk of psychosis. The reduction in risk is most clear for males. The findings lend support to the view that inflammation plays a role in the etiology of schizophrenia.

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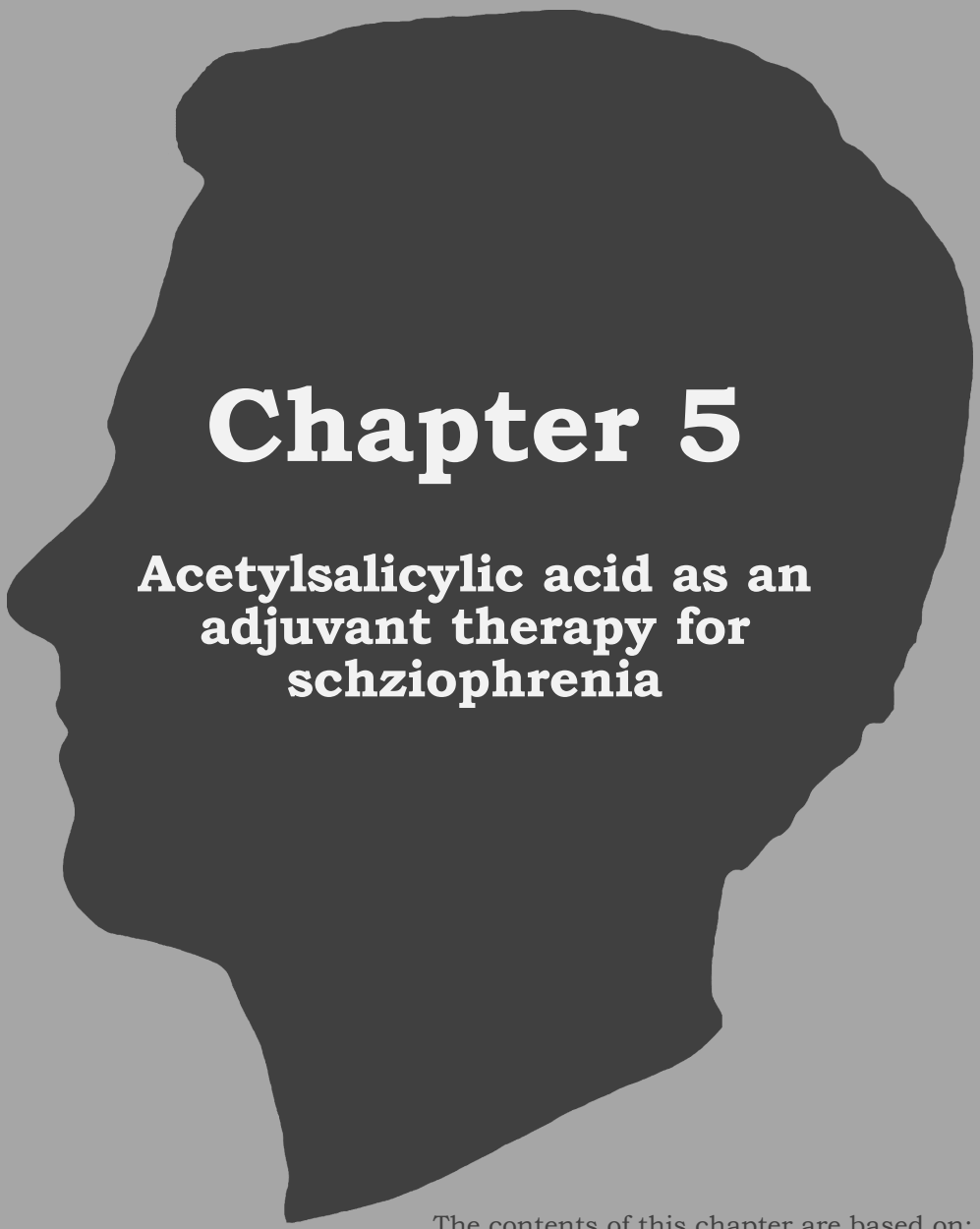
# Chapter 5

## Acetylsalicylic acid as an adjuvant therapy for schizophrenia



# Chapter 5

## Acetylsalicylic acid as an adjuvant therapy for schziophrenia

The contents of this chapter are based on:
Laan W., Selten J.P., Kahn R.S., Huisman A.M.,
Heijnen C.J., Grobbee D.E., Burger H.
Acetylsalicylic acid as an adjuvant therapy for schizophrenia
Trials, volume 7, issue 1, page 31

# Acetylsalicylic acid as an adjuvant therapy for schziophrenia

# Acetylsalicylic acid as an adjuvant therapy for schziophrenia


## Abstract

Findings from both epidemiological and basic research point to the possibility that NSAIDS impede the deterioration in schizophrenia.
To study the efficacy of acetylsalicylic acid we will perform a randomized placebo controlled double-blind add-on trial of 80 inpatients and outpatients with schizophrenia, schizophreniform or schizoaffective disorder. Patients will be 1:1 randomized to either 3 months 1000 mg acetylsalicylic acid per day or 3 months placebo, in addition to their regular antipsychotic treatment. All patients will receive pantoprazole treatment for gastroprotection. The outcomes of this study are 3-month change in psychotic and negative symptom severity, cognitive function, and several immunological parameters. This trial may (1) yield a new (adjuvant) therapy for schizophrenia and (2) add to the knowledge on the pathogenesis of this major psychiatric disorder.

Trial Registration: Current Controlled Trials ISRCTN27745631


## Background

Despite several advances in the treatment of schizophrenia, currently available pharmacotherapy does not change the course of illness or prevent functional deterioration in a substantial number of patients. Therefore, research efforts into alternative or adjuvant treatment options are needed. In this project we will empirically investigate the effect of the anti-inflammatory drug acetylsalicylic acid as an add-on to regular antipsychotic therapy on the symptoms of schizophrenia.

There are several observations and theoretical considerations that support the hypothesis that anti-inflammatory drugs can be effective in antagonizing the process underlying the clinical deterioration in schizophrenia. In numerous epidemiological and clinical studies an inverse relationship between schizophrenia and rheumatoid arthritis has been demonstrated, i.e. these conditions rarely coexist in one person[1,2]. A possible explanation for this relationship implies that the use of anti-inflammatory drugs by patients with rheumatoid arthritis protects them against the development or

progression of schizophrenia. This hypothesis is supported by the observation, made in a recent population-based study, that not only rheumatoid arthritis is far less frequent among patients with schizophrenia, but also other musculoskeletal conditions commonly treated with anti-inflammatory drugs[3]. These conditions were osteoarthritis of the knee, hip and spine, low back pain, and intervertebral disc disorders.

The hypothesis of the effectiveness of anti-inflammatory drugs in schizophrenia is also supported by more basic science findings. A prominent hypothesis concerning the pathogenesis of schizophrenia implicates dysfunction of the N-methyl-D-aspartate acid (NMDA) receptor[4]. This hypothesis suggests that in schizophrenia progressive excitotoxic neuronal cell death occurs via disinhibition of glutamatergic projections to hippocampal and cortical areas[5].In this respect, prostaglandins may play an important role in two ways: (1) because they are intermediaries in the postsynaptic signal transduction cascade of cells with NMDA-type glutamate receptors and (2) by potentiating glutamatergic transmission by inhibiting astrocytic reuptake of glutamate. Both mechanisms can potentiate excitotoxic cell death[6]. As non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis through the inactivation of cyclooxygenase, they may be of therapeutic value in schizophrenia. This mechanism may also play a role in the recently confirmed inverse relation between long-term use of NSAIDs and the risk of Alzheimer's disease[7]. The therapeutic potential of acetylsalicylic acid is further suggested by the results of an experiment performed by Grilli et al., who reported that acetylsalicylic acid and its metabolite sodium salicylate protected against neurotoxicity elicited by the excitatory amino acid glutamate in rat neuronal cultures and hippocampal slices[8].

Also according to the immunological hypothesis of schizophrenia, intervention with acetylsalicylic acid may have favorable effects. Activation of the immune system in schizophrenic patients is evident from many studies demonstrating dysregulated pro-inflammatory cytokines like interleukin (IL)-1, IL-2, and in particular IL-6 and tumor necrosis factor (TNF)-alpha[9]. The importance of the immune system in the pathophysiology of schizophrenia is indirectly supported by the evidence that many antipsychotics can act as immunomodulators[10,11]. Recently, decreased T helper-1 (TH-1) related immune parameters were found in patients with schizophrenia[11] and a shift to TH-2 like immune activity in a subgroup of schizophrenic patients has been

hypothesized[12]. Prostaglandin E2 is known to enhance the production of TH2 cytokines via inhibition of the production of IL-12 by antigen presenting cells such as monocytes[13]. Therefore, it is conceivable that the shift towards TH-2 cytokine production in schizophrenia will be counteracted by inhibition of prostaglandin formation by acetylsalicylic acid. Also because IL-12 enhances production of TH-1 cytokines, we expect that administration of acetylsalicylic acid will also result in more TH-1 activity (e.g. g-interferon production) relative to TH-2 activity (e.g. IL-4 production). The resulting correction of the T-helper cell imbalance may eventually reduce the symptoms of schizophrenia. Accordingly, we postulate that the greatest effect of acetylsalicylic acid will therefore be observed in those individuals with the highest relative TH-2 activity, i.e. the lowest IFN-g/IL-4 ratio. It should be noted that peripheral expression of cytokines may be a reflection of the pattern of cytokine production in the brain, where cytokines are produced by glial cells, astrocytes etc., and that, additionally, anti-inflammatory cytokines of peripheral origin may signal the brain, thereby contributing to the symptoms of schizophrenia. In order to monitor the effect of the proposed immunosuppressive treatment with acetylsalicylic acid and to get more insight in the possible role of cytokines in the clinical symptoms of schizophrenia, we intend to determine TH-1 and TH-2 cytokines as well as IL-6 (general immune activation), produced by peripheral blood cells before, during and after the treatment with acetylsalicylic acid.

Alternatively, NSAIDS may ameliorate symptoms of schizophrenia by affecting neuronal membrane phospholipids. As suggested by Horrobin a decreased incorporation of arachidonic acid and docosahexaenoic acid into membrane phospholipids combined with an increased removal of these essential fatty acids hamper normal neurodevelopment and adult neuronal functioning[14]. Each of these abnormalities may be related to an altered activity of phospholipase $A_2$. As acetylsalicylic acid inhibits phospholipase $A_2$ this NSAID may yield clinical improvement in schizophrenia[1].

Finally, a recent study showed cyclo-oxygenase hyperactivity in platelets of schizophrenic patients[15]. If also present in the brain this further implicates acetylsalicylic acid as a potential therapeutic agent for schizophrenia.

As cyclooxygenase-1 and cyclooxygenase-2 are both constitutively expressed in the brain[16], both the older COX-1 NSAIDS such as acetylsalicylic acid and indomethacin and the newer selective COX-2 NSAIDS such as celecoxib may theoretically impede the pathologic process in schizophrenia. We are aware

of only one clinical trial that examined the potential therapeutic role of NSAIDS in schizophrenia. It demonstrated a beneficial effect of the COX-2 inhibitor celecoxib as an add-on therapy during five weeks on schizophrenia psychopathology in 50 patients[17]. We decided to study the efficacy of the non-selective classical NSAID acetylsalicylic acid because of its neuroprotective effect in rat neuronal cultures and, in view of the epidemiological inverse relation between schizophrenia and rheumatoid arthritis, because of its past widespread use in the treatment of rheumatoid arthritis.

**Research questions**

Does 1000 milligrams of acetylsalicylic acid daily reduce symptoms of schizophrenia? Is this effect modified by initial relative TH-2 activity?

**Study Objectives**

To determine the effect of three months additional treatment with acetylsalicylic acid on positive, negative and cognitive symptoms as well as immunological parameters in patients treated with antipsychotics for schizophrenia. A secondary objective is to examine whether this effect is modified by initial relative TH-2 activity.

## Design and methods

**General**

We will perform a randomized, placebo-controlled, double-blind multicenter trial of 80 inpatients and outpatients with schizophrenia, schizophreniform or schizoaffective disorder.

**Inclusion criteria**

To be included in the study one has to give written informed consent, be diagnosed with schizophrenia, schizophreniform or schizoaffective disorder according to DSM-IV, aged between 18 and 55 years old, with disease duration less than 10 years. All participants have to be clinically stable, meaning no change in dose of antipsychotic drugs 2 weeks before inclusion. At randomisation all participants need to have a score of at least 60 on the total score of the Positive and Negative Syndrome Scale (PANSS) with two scores of at least 4. For safety reasons participants are not allowed to have a

contraindication for, or be hypersensitive to acetylsalicylic acid or pantoprazole, have a significant somatic illness or be pregnant. Participants are not allowed to use corticosteroids or chronically use of nonsteroidal anti-inflammatory drugs (NSAIDs) or platelet inhibitors. Persons with drugs dependencies are not allowed to participate.

**Screening**

Patients will be recruited at the Department of Psychiatry of the University Medical Center Utrecht, 'Symfora Amersfoort', 'Psychiatric Center AMC / de Meren, Amsterdam', 'Spatie Apeldoorn', 'Stichting de Geestgronden', 'Adhesie Deventer', 'RIAGG Amersfoort' and the 'Delta pychiatric hospital'. If the treating responsible psychiatrist considers a patient eligible for study, his diagnosis will be confirmed according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) using the Comprehensive Assessment of Symptoms and History (CASH). The PANSS will be filled out and the remaining inclusion criteria will be checked by taking medical history and performing a general physical examination. Finally, venous blood will be taken for the assessment of immunological parameters.

**Informed consent**

The trial will be conducted in agreement with the principles of the Declaration of Helsinki (Edinburgh 2000). The investigator will explain the benefits and risks of participation in the study to each subject and will provide an informed consent form approved by the ethical review board of the University Medical Center Utrecht. The patient is then asked to sign the form prior to inclusion into the study. Data from this study will be treated confidentially and publication of the results of this study will be performed anonymously.

**Placebo run-in and adherence**

A placebo run-in procedure will be set up to test the participant's adherence behavior in advance of the actual study. Patients meeting the inclusion criteria will be asked to take the add-on study medication (only placebo, no pantoprazole) during two weeks and will be asked to return the empty blisters to the researcher for administrative reasons. Only participants showing greater than 80% adherence (more than 80% of medication taken) will be randomized. During the trial the participants and their close relatives/friends will be informed about the importance of continuation of taking the study

medication and returning the empty blisters to the researcher. Adherence will be checked by counting the returned empty blisters and determining plasma salicylic acid at months two and three. All participants will be kindly asked not to use any drugs such as marijuana or hashish within 24 hours before visit.

**Baseline assessments**

As patients will be randomized in strata of relative TH-2 activity a blood sample will be taken at the beginning of the placebo run-in in order to have the immunological parameters determined by the time of randomization. At most one week before randomization, the severity of baseline psychotic symptoms will be assessed using the PANSS. In addition, a short cognitive test battery focusing on verbal learning and motor performance (e.g. California verbal learning test, Purdue Peg Board test, trail making test, HQ-Continues Performance test) will be administered.

**Randomized intervention**

Patients will be randomized in a 1:1 ratio to either supplementation of acetylsalicylic acid or placebo in addition to their current antipsychotic treatment. Randomization will be performed in strata of psychiatric center (tertiary or non-tertiary) and relative TH-2 activity (high/low), delineated by the median IFN-g/IL-4 ratio. To this end a computer-generated list will be produced with allocation codes in random order, balanced in the four strata by using permuted blocks. The aspirin dose is based on a trade-off between a dose that has a relatively low risk of gastro-intestinal toxicity in young persons, and the dose that is presumed to be anti-inflammatory, the latter being adopted from therapeutic doses used in the treatment of musculo-skeletal disorder[18]. Placebo will be identically packaged, looking and tasting tablets. For optimal gastro protection, all patients (also those randomized to placebo) will be given 40 milligrams of pantoprazole daily[19].

**Concomitant medication**

As an analgesic the patients will be emphatically advised to take acetaminophen instead of acetylsalicylic acid or other NSAIDS. A record of all medication taken will be kept during the entire trial.

**Adverse reactions**

Acetylsalicylic acid use may cause dyspeptic complaints, ulcer disease and gastrointestinal bleeding. However, due to its strong association with high age (odds ratio 1.04 per year[20]), we expect that the risk of ulcer or serious bleeding is considerably lower than 1% per year that was observed in persons over 60 years of age taking similar doses of aspirin[21]. Further, all patients will be given 40 milligrams pantoprazole daily which has shown to reduce the risk of NSAID induced gastrointestinal problems considerably[19]. Nevertheless, at every follow-up visit the participants will be asked about epistaxis, hematemesis, melena, rectal bleeding and hematuria. Further, dyspeptic complaints will be systematically recorded at every visit using an 8-item self-administered questionnaire[22]. Patients will be urged to stop taking study medication one week in advance of molar extractions or similar surgical procedures and to continue not before one week after the procedure. In case of medical emergencies the initial care will be managed by the general practitioner as in usual care, if possible after consultation of the investigator, or the person taking medical responsibility for the participants in this study (Prof. dr R.S. Kahn). At a later stage the investigator will consult the treating psychiatrist and the patient's general practitioner whether continuation in the trial is reliable.

**Study outcomes**

The primary outcome of this trial is the 3-month change in positive and negative symptoms on the total PANSS score. Secondary outcomes are the 3-month change in the PANSS subscales, cognitive symptoms, immunological parameters (g-interferon, IL-4, IL-6 and IL-12), and psychoactive medication taken during the trial.

**Follow-up assessments**

At one, two, and three months, and in case of withdrawal from the study, the severity of positive and negative symptoms will be reassessed using the PANSS. The cognitive tests will be repeated at three months or at study discontinuation. Blood samples will be taken at 2 and 3 months, or at withdrawal, for determination of the Aspirin levels. All assessments will be performed blind to medication status. The overview of the visits can be seen in table 1.

| | Run-in | Baseline | 1 Month | 2 Months | 3 Months* |
|---|---|---|---|---|---|
| Informed Consent | X | - | - | - | - |
| Screening | X | - | - | - | - |
| Pregnancy test | X | - | - | - | - |
| Randomization | - | X | - | - | - |
| Immune parameters | X | - | - | X | X |
| Blood for DNA isolation | X | - | - | - | - |
| Aspirin concentration | - | - | - | X | X |
| PANSS | - | X | X | X | X |
| CASH (+) | X | - | - | - | - |
| Cognitive tests | - | X | - | - | X |
| Adverse events | - | - | X | X | X |
| Co-medication | X | X | X | X | X |
| Compliance | - | X | X | X | X |

***Table 1.*** *Overview of study visits. * or withdrawal; + if previous CASH is longer than 6 months ago.*

**Immunological measurements**

To analyze the effect of the treatment on cytokine production, we will determine the in vitro capacity of peripheral blood mononuclear cells to produce cytokines. Heparinized blood (15 ml) will be drawn before, after two and after three months of treatment, or at earlier withdrawal. Peripheral blood mononuclear cells will be isolated by centrifugation of Ficoll isopaque. T cell cytokine production will be stimulated by incubation of cells with anti-CD28 and anti-CD2 monoclonal antibodies and supernatants will be collected after 48 hours of culture. In addition, adherent cells (monocytes/ macrophages) will be stimulated for 24 hours with lipopolysaccharide to induce IL-6 and IL-12 production. Cytokine levels in culture supernatants will be analyzed by ELISA. In vivo cytokine production will be analyzed by determining cytokine levels in plasma samples obtained at the same time points. In addition, blood will be stored for future research possibilities on the immunological or genetic aspects of schizophrenia, schizoaffective and schizophreniform disorders, after permission of the patients (in the informed consent form).

**Withdrawal from the study**
A patient must be withdrawn from the study when judged necessary by the responsible psychiatrist or when the patient withdraws his/her informed consent. In these instances all outcomes should be assessed.

**Study size**
The planned number of patients to be included in this trial is 80, 40 in each arm. This is sufficient to show a statistically significant difference between the intervention arms of effect size (Cohen's d) ³ 0.66 for the change in total PANSS score from baseline to last follow-up. It is based on an alpha of 0.05, a power (1-beta) of 0.8 and a two-sided unpaired t-test. Further, we accounted for 10% withdrawal. It should be noted that the power of the repeated measures analyses is considerably higher.

**Data analysis**
The statistical significance of the difference in the change in total PANSS score, its subscores, cognitive functions, immunological parameters from baseline to last follow-up between the arms and psychoactive medication will be tested using a two-sided unpaired t-test and its magnitude will be supplied with a 95% confidence interval. In addition, all outcomes will be analyzed as dependent variables in repeated measurements analyses with treatment arm as the independent variable. To study whether the potentially beneficial effect of acetylsalicylic acid is modified by initial relative TH-2 activity, we will repeat the analyses in strata of IFN-g/IL-4 ratio. The analyses will primarily be 'intention-to-treat'. In addition, a per protocol analysis will be performed on those who showed more than 90% adherence. If despite randomization important baseline differences in prognostic factors exist, adjustments will be made by including the corresponding variables as independents in the multivariable models. Finally, the change in psychopathological symptoms will be related to the change in immunological parameters using multivariable regression models. In these analyses adjustments for confounders will be made when appropriate.

**Duration**
We estimate that recruitment of patients will take 1 year. Follow-up will last 3 months. Assuming that data analysis and reporting require around 9 months, the total duration of the trial will be approximately 2 years.

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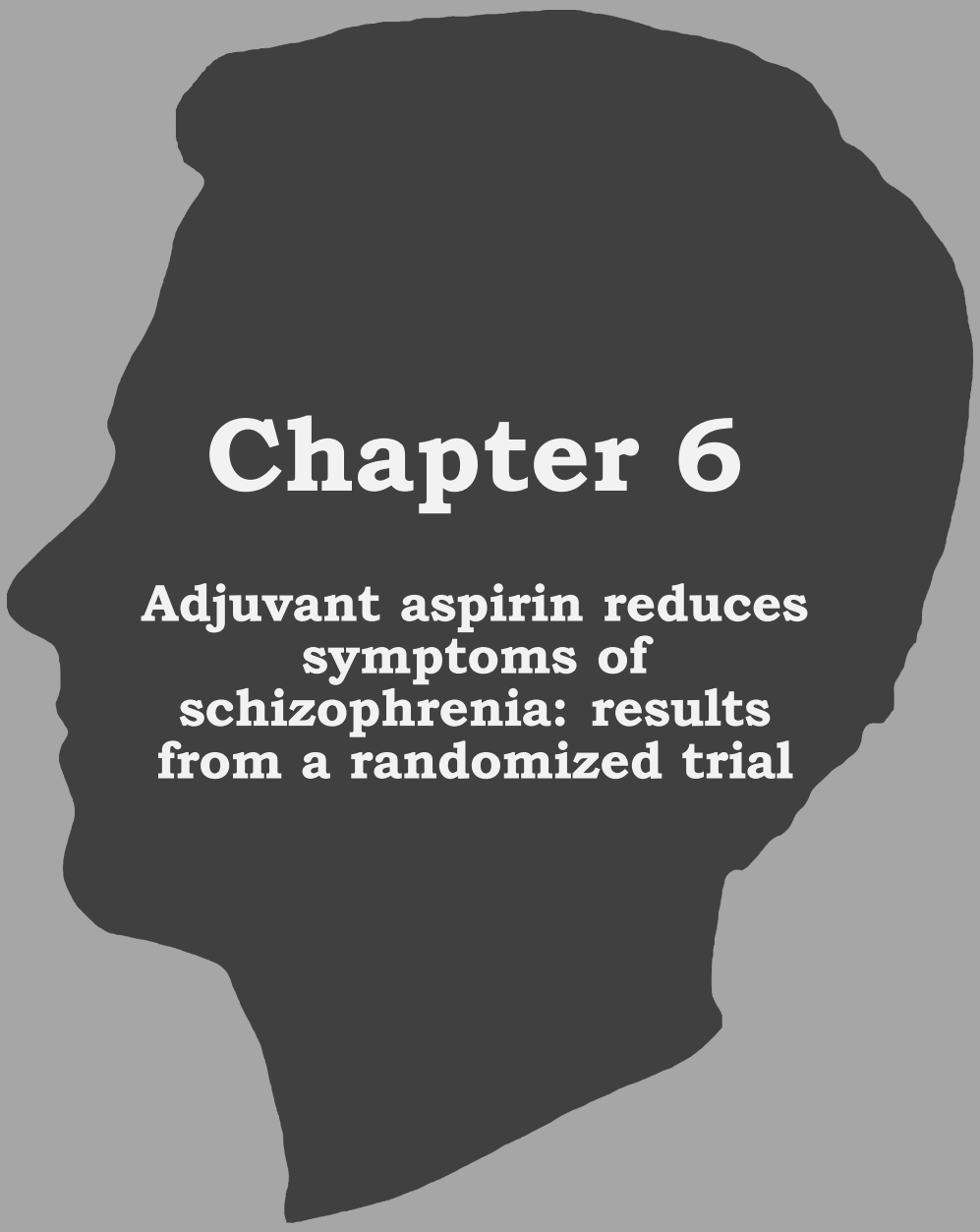
# Chapter 6

## Adjuvant aspirin reduces symptoms of schizophrenia: results from a randomized trial



# Chapter 6

## Adjuvant aspirin reduces symptoms of schizophrenia: results from a randomized trial

The contents of this chapter are based on:
Laan W., Grobbee D.E., Selten J.P., Heijnen C.J., Kahn R.S., Burger H.
Adjuvant aspirin to reduce symptoms of schizophrenia
Submitted

# Adjuvant aspirin reduces symptoms of schizophrenia: results from a randomized trial


## Abstract

It has been suggested that inflammation plays a role in the pathophysiology of schizophrenia. Consequently, aspirin (acetylsalicylic acid) may reduce symptoms of schizophrenia but results from trials are lacking.

We performed a randomized double-blind, placebo-controlled trial including 70 patients diagnosed with schizophrenia, schizoaffective, or schizophreniform disorder. Participants were randomised to aspirin 1000 mg per day or placebo and all received pantoprazole for gastric protection. During three months of follow-up, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). Primary outcome was the change in the total PANSS score. Secondary outcomes were changes in the positive, negative and general symptoms scores on the PANSS and the results from a cognitive test battery. Immunological measurements included T-helper cell 1 (TH1) / T-helper cell 2 (TH2) reactivity.

Mixed effect models showed a significant beneficial effect of the adjuvant therapy on the total PANSS score with a monthly treatment effect of -1.62 (95% confidence interval (CI) -2.93; -0.30). On the positive PANSS sub-score the effect was -0.52 (-1.02; -0.02). Over the total follow-up, the effect sizes were 0.47 and 0.39 for the reduction in total and positive scores, respectively. The effect was substantially larger in patients with the more disturbed immune function, as indicated by TH1/TH2 reactivity (p= 0.018). Trends for the negative and general PANSS subscores were similar to the trends in the total and positive scores, without reaching statistical significance. Aspirin did not affect cognitive function.

Aspirin given as adjuvant therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia. This reduction is more pronounced in those with the more severely disturbed immune function. Immune parameter may therefore be a potential new target for anti-psychotic drugs developement.


## Introduction

Current treatment in psychosis focuses on the antagonism of the dopaminergic and serotoninergic receptor.[1] Although an effective treatment

in a large part of patients, still around two-third of cases will have at least one relapse, and for each relapse one in six will not remit from that episode.[2] The cognitive decline resulting from schizophrenia also is only minimally effected by the current anti-psychotic drugs[3]. The urgent need for discovering new, safe, and effective drugs for chronic schizophrenia was emphasized in a recent editorial on the apparent lack of superiority of second- over first-generation antipsychotics.[4] Consequently, there is ample interest in other mechanisms than those involving the dopamine and serotonine receptor. One of these mechanisms is inflammation. Non steroidal anti-inflammatory drugs (NSAIDs) are candidate adjuvant drugs in schizophrenia for at least two reasons. First, an evolving body of evidence points to altered immune function, in particular T-helper cell (TH) dysbalance with a relative shift to TH-2 activity compared to TH-1 activity[3,5,6]. NSAIDs may restore this balance by inhibition of prostaglandin E2 synthesis[3,6,7]. Also, they may reduce inflammatory cytokines which have shown to be up-regulated in schizophrenia[8]. Second, NSAIDs may ameliorate symptoms through antagonizing dysfunction of the N-methyl-d-aspartate (NMDA)-receptor, a key feature of a well established neuro-chemical model of schizophrenia[9,10]. This is because prostaglandins are intermediates in the postsynaptic signal transduction cascade of cells with NMDA-type glutamate receptors, and prostaglandins inhibit astrocytic reuptake of glutamate. Both mechanisms potentiate glutamatergic transmission and may underlie the excitotoxic neuronal cell death observed in schizophrenia[11]. As NSAIDs inhibit prostaglandin synthesis, they potentially attenuate both mechanisms[12,13].
To date, only three randomized studies with NSAIDs in schizophrenia have been published, all using the selective cycloxygenase-2 (COX-2) inhibitor celecoxib. The first study conducted by Muller et al. in 50 patients treated with risperidone, showed that addition of celecoxib reduced total psychopathology over a five week period as compared to placebo[14]. Subsequently, in 35 patients, Rapaport et al.[15] did not find an effect after eight weeks of celecoxib supplementation, while in a similar study, Akhondzadeh et al.[16] showed a considerable positive add-on effect in 60 patients. Unfortunately, celecoxib and other COX-2 inhibitors have repeatedly been associated with an elevated cardio-vascular risk[17,18]. As cardiovascular disease is a major threat to schizophrenic patients[19], the cardioprotective aselective COX inhibitor aspirin (acetylsalicylic acid) is arguably preferable. Furthermore, because aspirin unselectively inhibits both COX-1 and COX-2

enzymes, it potentially has a wider range of action. It is presently unknown whether unselective COX inhibition reduces psychotic symptoms of schizophrenia, and whether an effect is modified by immune function. It is also unknown whether COX inhibition improves cognitive functioning in schizophrenia. In a randomized double-blind placebo-controlled trial we investigated the effect of aspirin on symptoms of schizophrenia over a three month period, in addition to regular antipsychotic therapy. As the active disease process underlying schizophrenia is thought to cause progressive brain damage[20], we expected to see the largest effect in those with the shortest disease duration. Furthermore, the most pronounced effect was anticipated in patients with the most severe T-helper cell dysbalance.

## Methods

### Participants

Seventy in- and outpatients from 10 psychiatric hospitals in the Netherlands were included. All screened patients gave written informed consent. To be included patients had to be between 18 and 55 years of age, diagnosed with either schizophrenia, schizoaffective, or schizophreniform disorder, and to be at least moderately ill as determined by a minimal total score of 60 on the PANSS with two sub-scores of at least four. Exclusion criteria were illness duration longer than 10 years, contra-indications for aspirin or for pantoprazole, significant somatic illness, chronic NSAID use, corticosteroid use, pregnancy or change of type or doses of anti-psychotic drugs in the last two weeks. The study was approved by the medical ethics review board of the University Medical Center Utrecht, the Netherlands.

### Study settings

The study design and procedures have been described earlier in detail[21]. In brief, we performed a randomized double-blind placebo controlled add-on trial. Participants showing greater than 80% compliance during a placebo run-in entered the 3-month treatment period and were randomized 1:1 to either aspirin 1000 mg or placebo daily. Randomization was done by strata of psychiatric center (referral or non-referral) and relative TH1/TH2 reactivity, the latter defined by the median interferon-gamma (IFN-g) / interleukin-4 (IL-4) ratio. For gastric protection all participants received pantoprazole 40 mg daily.

At each visit the Positive and Negative Syndrome Scale (PANSS) was filled out to assess psychopathology. The PANSS is a well-established and reliable scale for the assessment of severity of symptoms of schizophrenia[22]. Change in total PANSS score from baseline to follow-up was the primary outcome and changes on the positive symptoms, negative symptoms and general psychopathology PANSS subscales were secondary outcomes.
During baseline and final visits patients underwent the following cognitive tests: the Rey auditory verbal learning test assessing memory, the HQ Continuous Performance Test measuring attention, the Purdue Pegboard Test quantifying fine locomotor skills, and the Trail Making Test assessing psychomotor skills. Changes in these tests were additional secondary outcomes. At baseline, months two and three, a blood sample was taken for immunological measurements. Samples were stimulated with anti- CD2/28 for IL-4 and IFN-g measurements, and with lipopolysaccharide (LPS) / recombinant interferon-gamma for Il-12 and Il-6 measurements. Cytokines were analysed using ELISA-essays.
Participants continued their regular antipsychotic treatment. Psychiatrists were requested to delay any change in antipsychotic treatment until after the trial. A record was kept of all medication prescribed. At each visit participants were asked about bleedings and dyspeptic complaints, scored on an eight-item questionnaire[23].
We planned 80 patients to be included in this trial, 40 in each arm. If one assumes 10% loss to follow-up, this is sufficient to show intermediate or larger effect-sizes (Cohen's d of 0.67) with an alpha of 0.05 and power (1-beta) of 0.80. Our sample size agrees with the recommended 40 to 100 patients for drug augmentation studies in schizophrenia[24].

**Data analysis**
Analyses were performed on intention-to-treat basis. If a patient dropped out, all outcome measures were assessed within a week. We first examined baseline differences between the randomized groups. Subsequently, scores on the PANSS and the cognitive tests were analyzed using mixed models for fixed and random effects[25]. In these models all data available at each time point can be used. Dependency of repeated assessments within individuals was accounted for by including random effects for patient. The monthly treatment effect of aspirin compared to placebo was estimated as the group-by-slope interaction for all outcomes. Treatment effects over the total three-

month period were expressed as Cohen's d effect sizes[26]. Cognitive test results were analysed after transformation to z-scores[27], with higher scores indicating better cognition. Since cognitive tests were performed twice, no random slope could be included and only a random intercept was considered.
Multiple imputation techniques were used to estimate values for missing immunological data (N=24)[28].
To demonstrate modification of treatment effect by immune dysfunction, we repeated the analyses in subgroups of patients defined by the median TH1/TH2 reactivity. In addition, analyses were repeated for subgroups according to mean disease duration.
Variations in treatment effect by immune status or illness duration were additionally evaluated by testing the statistical significance of the corresponding continuous interaction terms.
Analyses, blind to treatment status, were done using the SAS statistical package. The two sided level of significance was set at 0.05. Means with corresponding 95% confidence intervals are given where appropriate.

## Results

Eighty-five patients were included in the run-in period (figure 1). Of those, 70 were eligible and were randomized. Baseline characteristics are displayed in table 1. In the placebo group the proportion of males was somewhat higher, the duration of illness slightly shorter and the proportion of clozapine users slightly higher. Other baseline characteristics showed no material differences. Notably, the total PANSS and subscores were equally distributed among the randomized groups. Twelve participants (17%), six in each group, did not complete follow-up. In the placebo group five lacked motivation and one

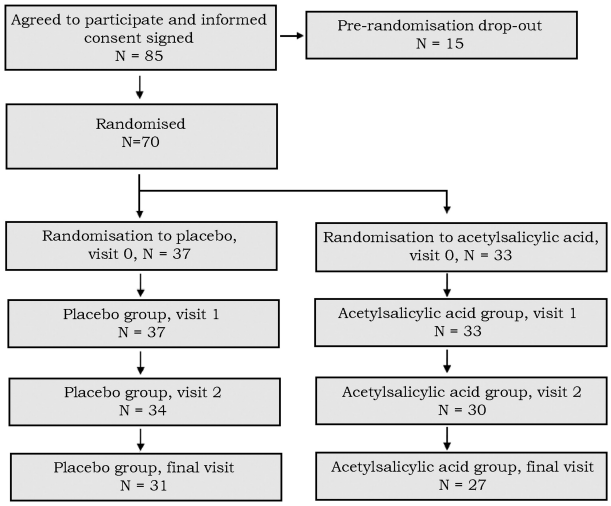


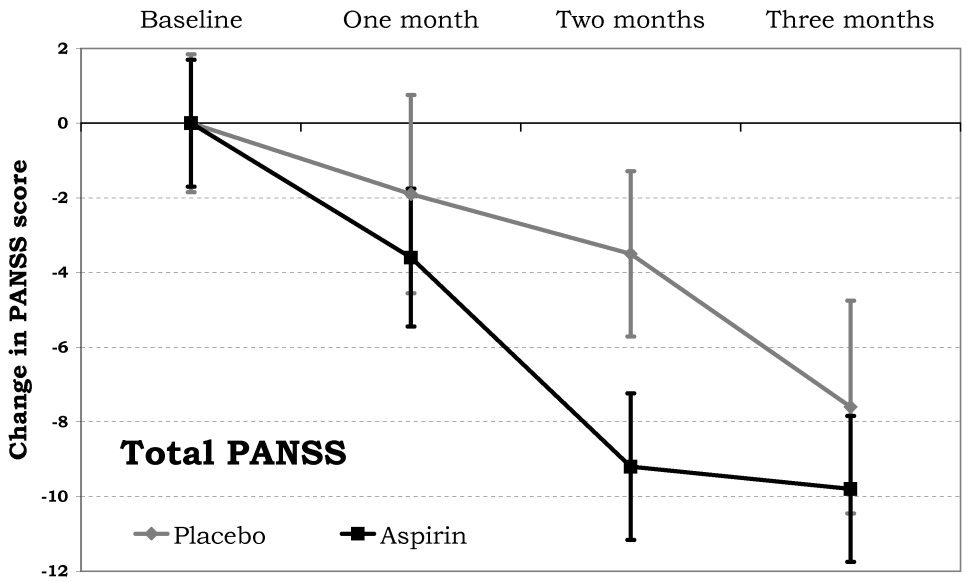

***Figure 1*** *Flow of patients through the trial*

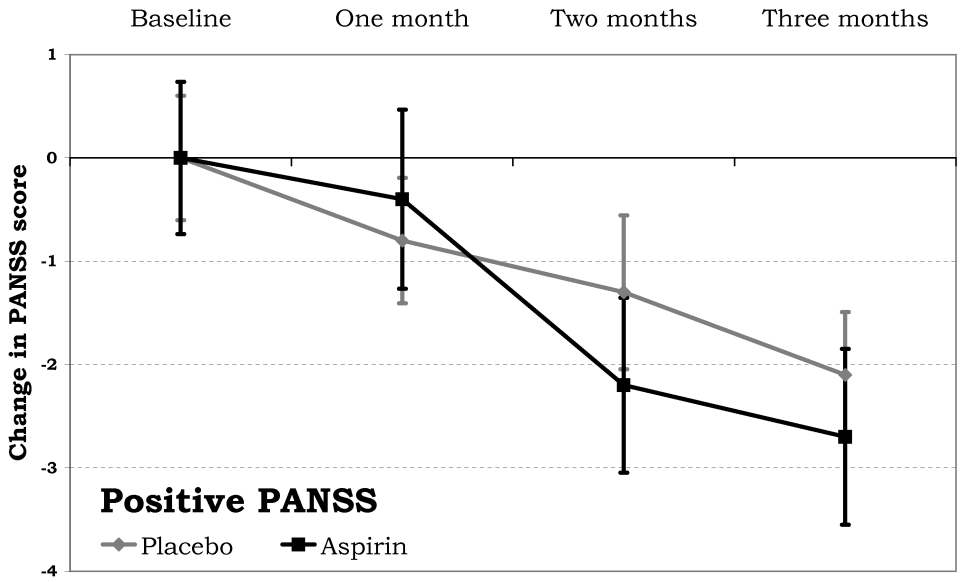
| | **Placebo** (mean ± sd) or (N / %) | **Aspirin** (mean ± sd) or (N / %) |
|---|---|---|
| N / % | 37 / 53% | 33 / 47% |
| Male gender | 33 / 89% | 25 / 75% |
| Age | 30.6 ± 9.2 | 31.6± 8.9 |
| Duration of illness (years) | 3.4 ± 2.5 | 4.1 ± 3.0 |
| Co-medication | | |
| Olanzapine | 7 / 19% | 10 / 30% |
| Clozapine | 11 / 30% | 5 / 15% |
| Risperidone | 9 / 24% | 7 / 21% |
| DDDs of anti-psychotic drugs | 1.04 ± 0.67 | 0.93 ± 0.62 |
| Adherence during run-in | 96.6% | 96.9% |
| PANSS scores | | |
| Total | 73.1 ± 10.3 | 71.1 ± 10.6 |
| Positive | 17.6 ± 3.7 | 16.5 ± 4.2 |
| Negative | 18.8 ± 5.2 | 18.2 ± 4.5 |
| General | 36.6 ± 5.5 | 36.3 ± 5.7 |
| Cognitive tests | | |
| RAVLT cognitive test | 19.2 ± 6.9 | 20.5 ± 7.8 |
| HQCPT cognitive test | 91.6 ± 10.6 | 85.3 ±21.3 |
| PPT cognitive test | 45.1 ± 6.4 | 45.4 ± 8.7 |
| TMT cognitive test | 91.6 ± 45.1 | 82.1 ± 38.0 |
| Blood sample taken | 24 / 65% | 22 / 67% |
| Th1/Th2-ratio | 302.1 ± 268.8 | 290.2 ± 260.2 |

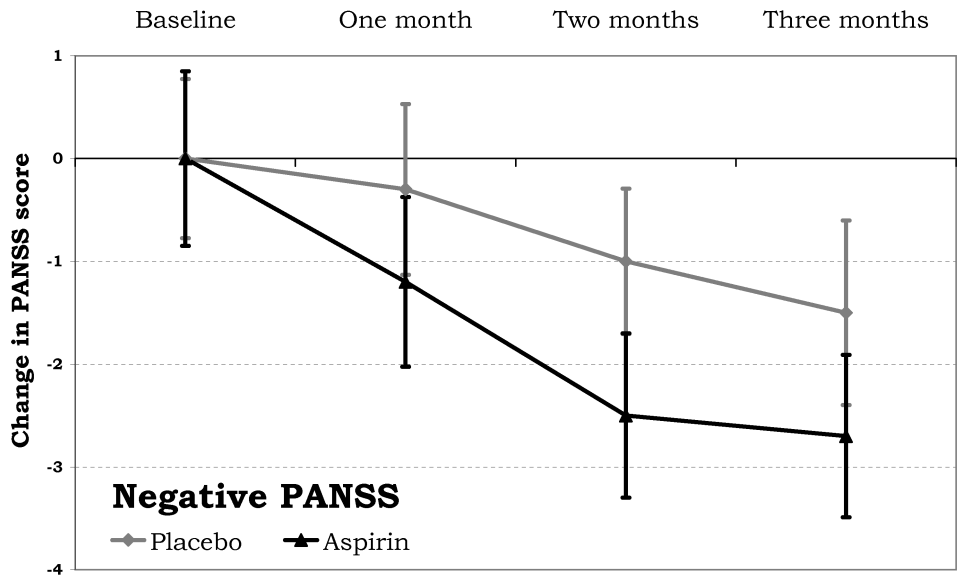
***Table 1*** *Baseline characteristics. DDD: Defined daily dose; PANSS: Positive and negative syndrome scale; RAVLT: Rey auditory verbal learning test; HQCPT: HQ continuous performance test; PPT: Purdue pegboard test; TMT: Trail making test; Th: T-helper cell.*

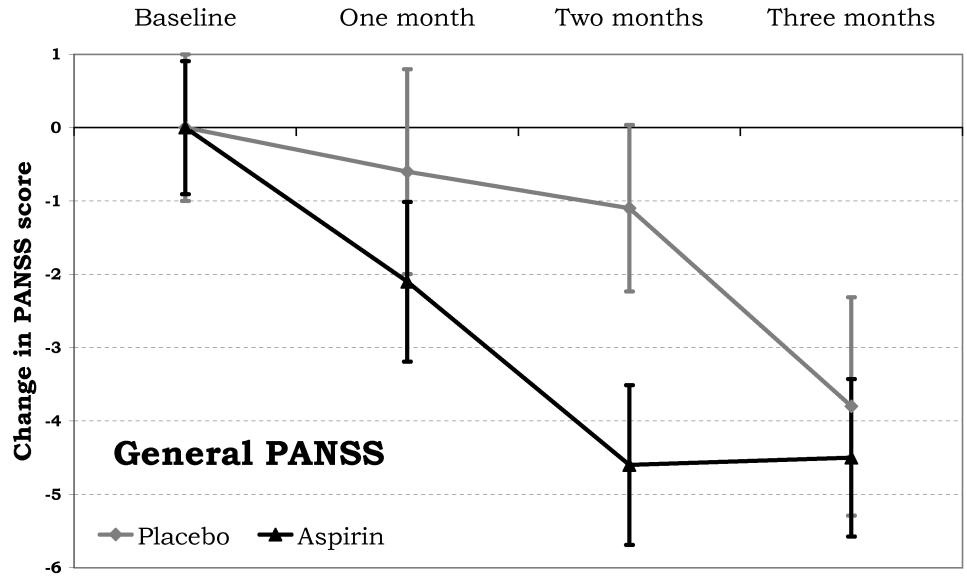
was referred to a non-participating hospital. In the aspirin group three lacked motivation and three stopped because of non severe gastrointestinal side effects.

All PANSS scores significantly dropped during follow-up in both groups ($P < 0.001$). The treatment effects, estimated by the mean monthly change in PANNS score are given in table 2.


Baseline
One month
Two months
Three months
Change in PANSS score
2
0
-2
-4
-6
-8
-10
-12
Total PANSS
Placebo
Aspirin


Baseline
One month
Two months
Three months
Change in PANSS score
1
0
-1
-2
-3
-4
Positive PANSS
Placebo
Aspirin




***Figures 2-5*** *Change in PANSS scores relative to baseline value. Error-bars indicate standard errors.*

The rates of decline of all PANSS scores were consistently larger in the aspirin group than in the placebo group. Differences between the rates of decline, i.e. treatment effects, were most substantial and statistically significant for the total and the positive PANSS scores. On the negative and general symptoms subscale, treatment effects were in the same direction as the effects on the total and positive scale, but did not reach statistical significance. Aspirin borderline-significantly increased TH1/TH2 reactivity during follow-up (p=0.05). In subgroups of T-helper cell dysbalance, treatment effects for total PANSS were -2.32 (95% CI: -4.08; -0.55) in the lowest TH1/TH2, i.e. most disturbed group, and -0.29 (95% CI:-2.58; 2.00) in the highest TH1/TH2 group (p for interaction 0.018). The separate immune values (Il-4, Il-10 and interferon-gamma) did not substantially modify treatment effects.
When analysed in subgroups of duration of disease the overall mean duration (3.8 years) as cut-off point, the treatment effect on total PANSS was -2.30 (95%CI:-4.00;-0.60) in the group with the shortest duration, and -1.21 (95%CI:-3.25; 0.83) in the group with the longer disease duration (p for interaction 0.66).

Aspirin treatment did not affect results of any of the cognitive tests (table 3). Five serious adverse events (SAEs) were registered during the trial, none of them gastro-intestinal. Two participants, one from the placebo and one from the aspirin group, attempted suicide. One participant was admitted to a closed ward before randomization because of relapse of psychotic complaints. One participant from the aspirin group and one from the placebo group were admitted to a closed ward because of suicidal thoughts and one participant from the placebo group was admitted to an open ward for daily routine restructuring. No dyspeptic complaints needing medical attention were observed. In the placebo group eleven participants reported moderate, two reported serious and no participants reported very serious dyspeptic complaints as evaluated by the dyspepsia questionnaire[23]. In the aspirin group these numbers were ten, zero and one, respectively.
During follow-up eight participants from the placebo-arm and five participants from the aspirin-arm changed dose or type of anti-psychotics with no systematic differences between groups. No trend of change to or from a specific anti-psychotic drug was observed.

| | Total Panss | Positive Panss | Negative Panss | General Panss |
|---|---|---|---|---|
| Placebo group final score | 65.5 ± 10.9 | 15.5 ± 3.4 | 17.3 ± 4.4 | 32.8 ± 6.0 |
| Aspirin group final score | 61.3 ± 14.8 | 13.8 ± 4.3 | 15.7 ± 4.7 | 31.8 ± 7.7 |
| Monthly treatment effect | -1.62 (-2.93; -0.30) | -0.52 (-1.02; -0.02) | -0.41 (-0.93; 0.10) | -0.72 (-1.49; 0.05) |
| Treatment p-value | p=0.016 | p=0.042 | p=0.115 | P=0.066 |
| Three months effect size | 0.47 | 0.39 | 0.26 | 0.39 |

***Table 2*** *Final outcome scores, treatment effect estimates (95%-CI), p-values and effect sizes (Cohen's d)*

| | Total | RAVLT | HQCPT | PPT | TMT |
|---|---|---|---|---|---|
| Treatment effect Z-score | 0.060 | 0.178 | -0.243 | -0.003 | 0.122 |
| Treatment effect 95% CI | (-0.593; 0.714) | (-0.142; 0.499) | (-0.624; 0.138) | (-0.290; 0.284) | (-0.230; 0.475) |
| Treatment p-value | 0.854 | 0.271 | 0.208 | 0.983 | 0.490 |

***Table 3*** *Treatment effect estimates, 95%-CI and p-values of treatment on the cognitive tests. For all z-scores a positive value indicates an improvement in cognitive functioning. RAVLT: Rey auditory verbal learning test; HQCPT: HQ continues performance test; PPT: Perdue pegboard test; TMT: Trail making test*

## Discussion

In this randomized placebo-controlled double-blind trial, addition of aspirin to regular antipsychotic treatment substantially reduced symptoms of schizophrenia. The strongest and statistically significant effects were observed for total and positive symptoms. Over the three month treatment period the effect size (Cohen's d) for total PANSS was approximately 0.5 which is considered a medium, nearly large effect[26] The effect was most marked in those with the lowest TH1/TH2 reactivity, suggesting that the reduction of psychotic symptoms is larger among those with the more pronounced immunological disturbances. Cognition was not affected by aspirin.

To appreciate these findings, some aspects of the study need to be addressed. Although groups were well balanced at baseline, the placebo group included more clozapine users than the aspirin group. This need, however, not have affected prognosis. Although clozapine is often prescribed to more therapy resistant patients it is also particularly effective in reducing symptoms in these patients[29]. Moreover, when treatment estimates were adjusted for clozapine use, they did not change.

The present trial had the largest sample size and longest time of follow-up to date but still the effects on the negative, general and perhaps cognitive symptoms are inconclusive, Perhaps, a larger trial or a trial with longer follow-up could show unequivocal effects on these outcomes as well. Finally, the results do not concern the long-term effects of aspirin. Yet, it is in our view very unlikely that the beneficial effects we observed from aspirin would remain limited to three months.

To our knowledge, there are no published trials investigating the effect of a COX inhibitor on cognitive symptoms of schizophrenia. Therefore, we are unable to compare our cognitive findings to other, similar trials.

Studies by Muller et al.[14] and Adzekondah et al.[16] demonstrated significant effects of the NSAID celecoxib on schizophrenic symptoms. Both studies showed a more marked monthly effect of celecoxib than we observed for aspirin. Participants in these studies underwent an anti-psychotics wash-out period of respectively two and seven days prior to administration of risperidone and randomisation to either placebo or celecoxib. Patients in these studies therefore showed considerably higher baseline PANSS score than those in our study. For this reason there was more to gain in the celecoxib studies from the start and comparison with our study is difficult.

Our findings on aspirin agree with those from Müller et al.[30] in that the effect of the NSAID was most pronounced in those with the shortest disease duration. Indeed, the smaller overall treatment effect in our trial could be explained by Muller's study comprising more patients with shorter disease duration.

The larger symptom amelioration we observed in those with the more altered TH1 / TH2 ratio was in accordance with our expectation and supports the hypothesis on the pathophysiologic role of dysbalance in T-helper cells in schizophreniaREF. Besides, aspirin may have reduced symptoms through other mechanisms, e.g. by antagonizing dysfunction of the N-methyl-d-aspartate (NMDA)-receptorREF.

No significant differences in changes in cognition were observed between groups. However, as cognitive functioning appears to be stable over time in schizophrenia[31] and the currenct anti-psychotics hardly improve these functions[3], it may be difficult to actually alter these functions during a relatively short period.

No serious gastric or bleeding events requiring medical attention were observed, thus indicating that the dose of aspirin was safe in combination with pantoprazole. Given the fairly large effect over three months, the refractory character of symptoms while on anti-psychotics alone and the safety of aspirin, this drug is potentially a useful addition to regular treatment.

Finally we cannot exclude the possibility that aspirin exerts its effect in interaction with anti-psychotics. Yet, we view this unlikely as the mechanism of action of aspirin is essentially different from that of antipsychotics, the latter antagonising dopamine receptors. The effect of aspirin as a single treatment cannot be estimated, since it would be unethical to randomize patients with schizophrenia to placebo alone.

Celecoxib has been associated with an elevated cardiovascular risk[17,18]. Because aspirin has well established cardioprotective effects[32] and schizophrenic patients already have a markedly elevated cardiovascular risk[19], aspirin is in our view a better choice than celecoxib.

Further investigations with different doses will need show whether the dose of aspirin chosen in this trial was optimal. Future research may also assess effects of stronger suppression of the cyclooxygenase enzyme in schizophrenia.

## Conclusion

The results of this 3-month randomized trial indicate that aspirin is a potentially useful therapy in combination with antipsychotic drugs for schizophrenia.

## Acknowledgements

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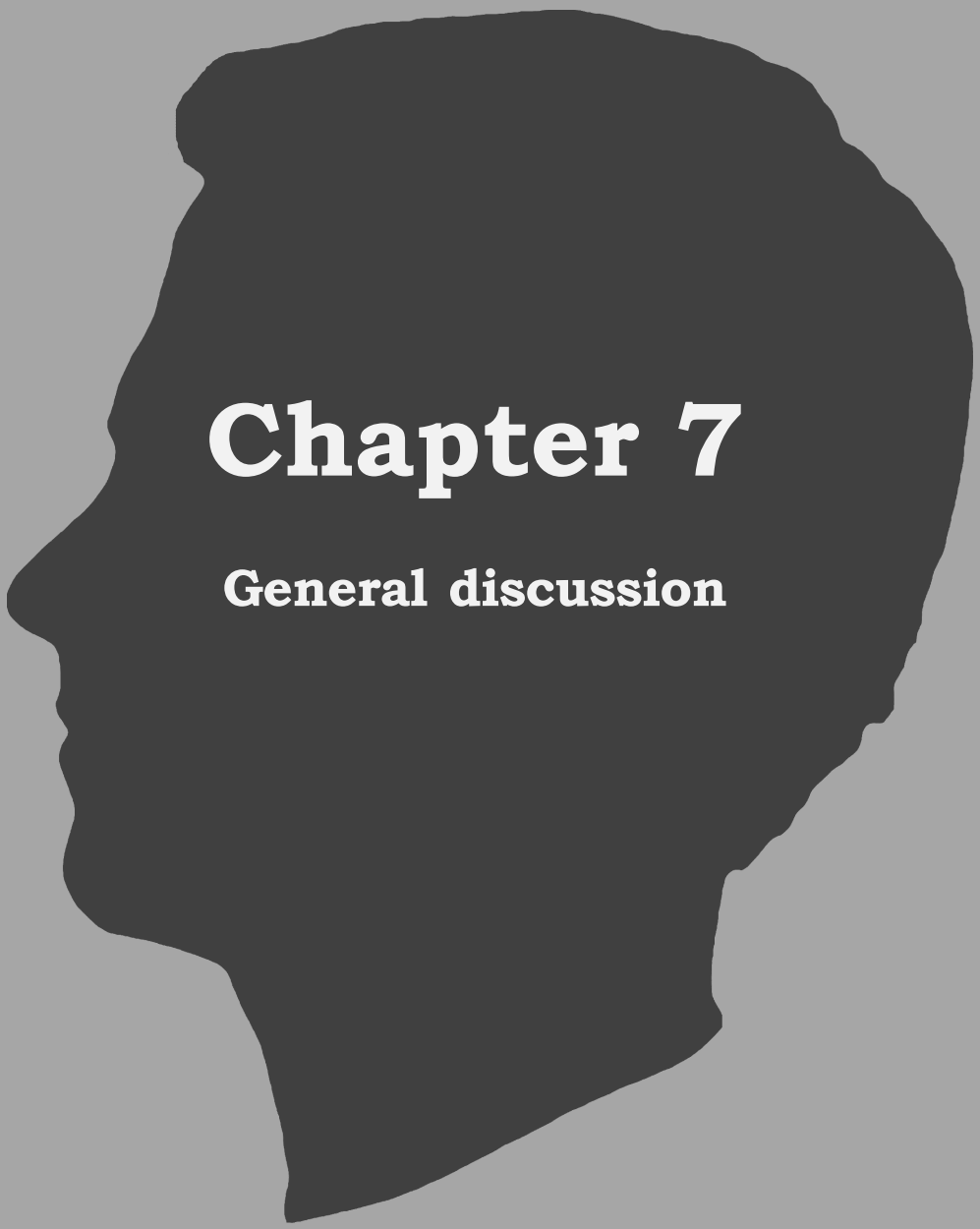
# Chapter 7

## General discussion



# Chapter 7

## General discussion

# General discussion

## Main findings

In the present thesis we aimed to investigate the effect of anti-inflammatory drugs on schizophrenia. Please note that in this chapter we occasionally use the word psychosis rather than schizophrenia as not in all studies described in this thesis we were able to differentiate between a psychosis and a formal diagnosis of schizophrenia.

We performed several studies with varying methodologies in different populations. All studies yielded interesting results essentially pointing in the same direction, i.e. that the use of anti-inflammatory drugs is associated with a decreased risk of psychosis. To address the public health relevance of research into schizophrenia, the chapters describing our studies are preceded by a chapter on the financial burden of brain disorders in Europe. In this chapter it is shown that in the Netherlands an estimated 21.000 people had a psychotic disorder in 2004. Further around 147 million euros of direct, i.e. healthcare costs are spent on this disorder each year. The total direct costs resulting from all psychiatric disorders were estimated to amount at 10.303 million euros.

The use of NSAIDs appeared to be negatively associated with subsequent psychosis in men, as defined by incident anti-psychotics use. In addition, our second observational study on this subject demonstrated that the use of glucocorticosteroids also is inversely associated with future psychosis, again particularly in men. In the latter study, psychosis was defined as a new DSM-IV diagnosis of a psychotic disorder as recorded by a psychiatric case registry. In addition to these observational studies on the potential preventive effects of anti-inflammatory drugs, we performed a randomized placebo-controlled trial investigating the effect of an anti-inflammatory drug on the severity of schizophrenic complaints. In this trial the relation between inflammation and schizophrenia was confirmed as the severity of psychotic complaints declined faster in the group receiving aspirin compared to the group receiving placebo.

This chapter aims to discuss several points worth considering when interpreting the results of this thesis.

## Strengths and limitations to the study on burden of disease

All figures presented in chapter two were based on overall European figures. This implies that the prevalence, incidence and healthcare costs of these disorders would be equally distributed over the different countries, which in fact might not be the case. For example, in the Netherlands a specific ethnic group has a higher prevalence of schizophrenia, where other ethnic groups do not.[1] As the different European countries have different ethnic groups this extrapolation of results to individual countries might not actually reflect the true situation. Besides, several important costs like direct non-medical costs for the common disorders affective and anxiety disorders were not included in the analysis. This could result in a marked underestimation of the actual costs.
Another factor that could result in biased healthcare cost estimates is the way these are reimbursed. Until 2006 all inpatient care was payed as a lump sum to the psychiatric hospitals. The amount was not calculated on a per patient or per diagnosis basis, but was based upon the total yearly costs made by that hospital. Attributing healthcare costs of inpatient care directly to a specific disorder is therefore not possible, and can only be estimated.

## Strengths and limitations of the observational studies

Two of the chapters in this thesis discussed the prescriptions of anti-inflammatory drugs prior to psychosis. In the first we investigated the prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) prior to incident anti-psychotics use. In this study we used the date of incident anti-psychotics use as a proxy for the date of incident psychosis. In the second study we investigated the relation between glucocorticosteroids (GCS) use prior to a first recorded diagnosis of a psychotic disorder. The date of the first recorded diagnosis was used here as a proxy for the date of psychosis. As can be seen we used two different ways of estimating the time of onset of psychosis. It is likely that both estimates are more or less close to the actual date of psychosis, but we can not be sure. Besides, it may be rather artificial to define a starting date for a psychosis. The time between first prodromal signs of a psychosis and the actual first psychotic episode may be as long as five years.[2] A diagnosis may have been made theoretically anytime during

those years, which leaves room for biased estimation of the relation between the exposure to anti-inflammatory drugs and psychosis due to reverse causality.

The Agis health insurance company that supplied the prescription data for the observational studies recorded all prescribed medication of its insurants, except that of inpatients. This gave us a unique overview of the medication used in a large group of cases and controls that could otherwise only have been estimated using retrospective interviews, which are prone to recall bias.

The diagnoses that were used in chapter four were the DSM-IV diagnoses made by the treating psychiatrists. These diagnoses where not only used in treatment, but also by the psychiatric hospitals in their financial declarations to the insurance companies. If a diagnosis was not made or not recorded it would mean it would not be paid for. The chances of diagnoses missing are therefore not very large. As all major psychiatric hospitals in the region of middle western Utrecht participate in the RIPAG-MWU foundation, which we used to detect cases, it is not likely that we missed a material number of diagnoses.

The region of middle western Utrecht had an estimated population of 1.3 million inhabitants in 2006.[3] With an estimated annual incidence of schizophrenia in the Netherlands of 0.4 per 1000 men and 0.3 per 1000 woman it can be estimated that approximately 455 people in the region of middle western Utrecht will develop this disorder in any given year. In the chapter discussing the relation between glucocorticosteroids and a diagnosis of psychosis we found 3872 cases with a new psychotic disorder between 2002 and 2005, being 968 new cases each year. This is about twice the number of cases that was expected given the estimated incidence. Part of this higher incidence in the region can probably be attributed to the fact that it is a highly urbanized region, resulting in a higher risk of psychosis.[4] Besides that, we probably also included a number of non-incident cases as we were only able to look back three years and cases might just not have been treated during that period.

The lower prescriptions of NSAIDs and GCS in the years before the onset of psychosis in cases compared to the controls is in these studies interpreted as evidence of a protective effect of these drugs on psychosis. Although these findings were not substantially confounded by the tendency of cases in the prodromal phase of psychosis to visit a physician, they might still be influenced by other factors that were not taken into consideration. Cases in

the prodromal phase of psychosis may well be treated for symptoms like depression or anxiety disorders. Additional prescriptions of NSAIDs or GCS may not be safe with the already prescribed drugs, thus resulting in lower NSAID or GCS consumption.
In the Netherlands most NSAIDs can also be bought over the counter i.e. without a prescription. These over the counter NSAIDs were not registered by the insurance company and may therefore have resulted in an overall underestimation of the total NSAID consumption. This is, however, not likely to be substantially different in the cases and controls.
GCS and NSAIDs have also been associated with psychotic side-effects.[5,6] This might also make a treating physician reluctant to prescribe one of these drugs to a person on the verge of psychosis, thus resulting in the lower prescription rates of these drugs in cases.
Particularly in observational studies, it is essential to examine potential forms of bias. As cases and controls were not interviewed but all data was obtained from well kept databases the chances of information bias are in our view quite slim. A potentially more serious threat to the validity of the observational studies is for example confounding. This form of bias could arise from factors that influence both the independent variable, being NSAID or GCS consumption and apart from that influence, the dependent variable, being psychosis. The use of lithium could be a confounding factor as this drug cannot be prescribed together with cyclooxygenase-2 inhibitors as they increase the risk of lithium intoxication, and lithium is indicated for schizoaffective disorders. For this reason anyone using lithium was excluded from the analysis in the NSAID article. As rheumatoid arthritis is negatively associated with schizophrenia, possibly by means of the treatment with anti-inflammatory drugs, as patients suffering from rheumatoid arthritis are often prescribed NSAIDs, rheumatoid arthritis was also a potential confounder and cases suffering from this disorder were also excluded from analysis. As far as we can think of there were no other confounding factors that needed to be considered in the analyses. We can, however, never be fully sure.

## Strengths and limitations of the randomized trial.

One of the most time-consuming but also most rewarding and interesting part of this thesis was the randomized trial described in chapters five and six. Here we found that treatment with aspirin on top of antipsychotic

medication had a reducing effect on the severity of psychotic complaints in schizophrenia.

For intervention research, randomized placebo-controlled clinical trials are often seen as the 'gold standard' in evidence based medicine. As participants in randomized placebo controlled clinical trial are randomized to either of the exposure groups, the chances of any prognostic differences between groups are small in case of large samples, and if they are present, they are the result of chance. For that reason confounding is removed by design in randomized trials of sufficient size and any differences in the outcomes can thus be attributed to the randomized intervention.

Still, certain issues need to be addressed regarding the randomized trial conducted and described in this thesis.

When a participant was randomized to either the placebo or the treatment group, the researcher and the patient were blinded as to which group the patient was randomized to. If, however, a patient was presenting gastric or bleeding adverse events, it would suggest that this participant was randomized to the aspirin group. However, as there were no substantial differences in rates of adverse events between the randomized groups, this is not likely to have biased the results. As aspirin is, besides other qualities, also an analgesic, participants might be able to tell whether one was receiving aspirin or not and thus influence the outcome. All participants were asked at the end of the trial to what treatment they thought they were randomized to, which, after deblinding, however did not seem to be related to the actual randomization.

Some remarks concerning the generalizability of the results from our randomized trial need to be made. Patients that agreed to be included might have been those cases with more than average persistence of symptoms. This is because patients showing optimal response on regular anti-psychotic treatment and consequently have few symptoms to be improved, might be unwilling to participate in the trial. Therefore, a patient had to have a minimum level of symptoms while being treated with anti-psychotics in order to be included. Consequently, the positive effect as observed was conditional on an unsatisfactory result of regular anti-psychotic treatment. The results may therefore not be generalizable to patients that respond relatively well to anti-psychotics. However, restriction of the study to subjects with persistent and less treatment responsive symptoms may well have lead to an underestimation of the benefits of aspirin.

We attributed the observed effect in the randomized trial to the anti-inflammatory properties of aspirin, which was based on the observation that the effect was modified by initial immune parameters. It can, however, not be excluded that other mechanism of action of aspirin were in part responsible for this effect. One of the best known effects of aspirin is its analgesic effect.[7] Although the symptoms of schizophrenia are not likely influenced by an analgesic effect, it could be postulated that the participants of the trial randomized to the aspirin group were reporting fewer total symptoms because of a generally increased level of wellbeing due to this analgesic effect.
Just like in the trials by Müller[8] et al. and Akhondzadeh[9] et al. with a COX-2 inhibitor, we found that the adjuvant anti-inflammatory therapy decreases the symptoms in patients with schizophrenia. These first two trials were performed with a selective COX-2 inhibitor. Unfortunately, celecoxib and other COX-2 inhibitors have repeatedly been associated with an elevated cardio-vascular risk[10,11]. As patients with schizophrenia are already at higher risk for cardiovascular disease[12], the non-selective COX inhibitor aspirin, which in contrast has a cardioprotective effect[13], is preferable.
There has been ample discussion whether the group of disorder we call 'Schizophrenia' is one single disorder. The 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV)[14] divides the group of schizophrenia-like-disorder into three categories, schizophrenia, schizophreniform, and schizoaffective disorder. Schizophrenia is then further subcategorized into different subtypes, catatonic, disorganized, paranoid, residual and the undifferentiated subtype. Most research, such as the research described in this thesis, is treating all the subtypes as one disorder with the same basic pathology. Whether this is valid or the grouping of the different subtypes is as artificial as the name itself is not clear.[15]

## The chicken or the egg?

The role of the immune system in schizophrenia has been investigated and described in previous work.[16-20] There appears to be general agreement that the immune system plays an important role in schizophrenia. The immunological disturbances as reported in these papers are hypothesized to have played a role in the pathogenesis of schizophrenia. It remains uncertain, however, whether these findings could as well be a result of psychosis rather than the cause. Antagonizing those immunological disturbances would in

that case not likely do any good. The results from chapter six do not support this theory, but rather support the view that the inhibition of inflammations in schizophrenic patients may result in a reduction of the severity of complaints.

## Clinical implications

In chapter six we found a monthly treatment effect of -1.62 points on the PANSS rating scale[21] (95% confidence interval (CI): -2.93; -0.30), with an effect-size of 0.47, for the adjuvant therapy with aspirin. This effect-size can be seen as medium, nearly large.[22] A conservative view on the pharmacological treatment of schizophrenia holds that treatment is a success when the total PANSS score drops at least 25% in cases with an acute exacerbation.[23] The total reduction of complaints in chapter six was estimated at 4.86 points, or 6.8% over the three months of follow-up. Based on simple application of conventional criteria, the results from the adjuvant therapy with aspirin would therefore not be called a success. However, most patients in our trial were not in a phase of acute exacerbation, but rather were patients that did not respond satisfactory to their current treatment. Reducing these so-called refractory symptoms is probably harder than reducing symptoms in cases with acute exacerbations. Besides, most participants in the trial already received pharmacological anti-psychotic treatment for a substantial period of time. The reduction of symptoms as a result of the adjuvant therapy was therefore over and above the effect of regular treatment. Still, it might be even more interesting to see whether adding aspirin to the start of regular anti-psychotic treatment will increase the treatment success rate compared to the regular anti-psychotic treatment alone.

## What do the results of this thesis mean, and what do they not mean?

The observational studies in chapters three and four show that the use of anti-inflammatory drugs is inversely related to, or negatively associated with, psychotic episodes. It is very tempting to replace the words ‘related’ and ‘associated’ by the word ‘prevent’. This would, however, assume that inflammations play a causal role in the etiology of schizophrenia, without which a psychosis would not be able to occur. This has not at all been

proven yet. The results of the observational studies only indicate that anti-inflammatory drugs may decrease the risk of psychosis, or at least delay its onset, which is a materially different statement. We have no good explanation for our finding that the inverse relation was largely restricted to men. We hypothesized that a protective effect of estrogens in women leaves little room for the protective effects of anti-inflammatory drugs.[24] This is also supported by the observation that the prevalence of schizophrenia in women is only at the same level of that in men after the menopause[2], and that women are more vulnerable to the development of psychosis during phases of low estrogen.[25]

The results of the randomized clinical trial as discussed in chapter six strongly suggest a role for inflammation in the pathophysiology of schizophrenia. The symptoms in the aspirin group decreased significantly more compared to the placebo group and this difference was maximal for those with the most pronounced immunological disturbances. This, however, does not immediately imply that aspirin at this state of research should replace the effective anti-psychotic drugs that are on the market today. Anti-psychotics are a proven effective treatment in psychosis[26]. No one treated with any anti-psychotic drug should stop his or her treatment and replace it by any anti-inflammatory drug without the agreement of the treating psychiatrist. The results only indicate that the addition of aspirin to anti-psychotic drugs may decrease the severity of schizophrenic complaints.

## Directions for future research on inflammation and schizophrenia

Although there were several interesting findings in this thesis neither of these will probably soon alter treatment in schizophrenia without further research. One of the most feasible next steps might be to perform a larger scale double blind placebo controlled randomized trial with aspirin or a more potent non-specific cyclooxygenase inhibitor. It might also be worthwhile, as stated above, to see whether the addition of aspirin will increase the overall treatment success-rate. A next trial may also want to test whether the addition of aspirin to regular treatment in a group of ant-psychotics resistant schizophrenic patients may be beneficial, as these cases might be the most to benefit from additional improvement in treatment. Moreover, there is currently no certainty as to the optimal dose of aspirin. We used a relatively high dose of the drug to be certain that it would suppress

inflammation. Lower dosage may, however, have similar effects with a lower rate of side effects or intolerance.
Pharmaceutical industries might want to investigate novel anti-psychotic drugs that may have a more potent anti-inflammatory effect than the current anti-psychotics.
In addition, the preventive efficacy of aspirin in a population with cases at high risk of psychosis may be studied in the future although this will require the inclusion of a huge study population. Such investigations may, if randomized, yield stronger evidence of a preventive effect of NSAIDS than can be derived from our observational studies.

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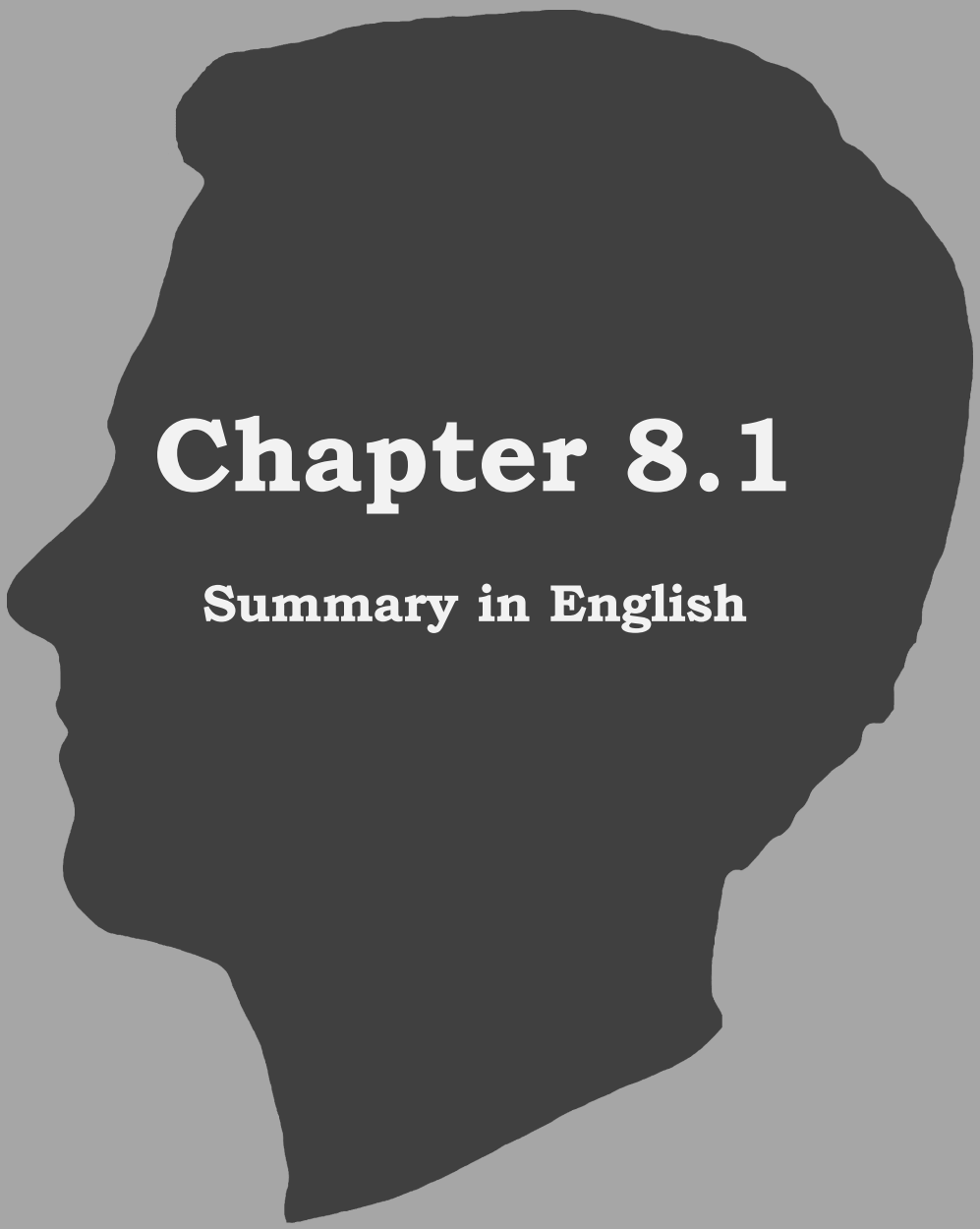
# Chapter 8.1

## Summary in English



# Chapter 8.1

## Summary in English

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In **chapter 1** we discuss the disorder known as schizophrenia. Schizophrenia is a most disabilitating psychiatric disease. Common symptoms of schizophrenia include hallucinations and delusions. Patients suffering from schizophrenia are often unable to determine whether the things they experience are real, or part of their disorder, and need to be ignored. About one in a hundred people in the Netherlands are diagnosed with schizophrenia sometime in their life. Although there is treatment for schizophrenia in the form of anti-psychotic drugs, not all patients respond well to this treatment. A large part of patients will have remaining symptoms for the rest of their lives. A number of hypotheses have been made over the years, trying to explain the pathophysiology of schizophrenia. One of these hypotheses is that inflammations may in part be involved in the disease. Inflammations can be inhibited by a number of drugs, for example by non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and with steroidal anti-inflammatory drugs like prednisone. The aim of this thesis is to investigate the hypothesized relation between anti-inflammatory drugs and schizophrenia.

First, in **chapter 2** we examine the financial burden of psychotic and other psychiatric disorders in the Netherlands. In total there are an estimated 21.000 patients between the age of 18 and 65 with a psychotic disorder in the Netherlands. The associated healthcare costs are estimated at 147 million euros yearly. This results in around 7000 euros healthcare costs per case of schizophrenia per year. In total all psychiatric disorders account for as much as 32% of all disease assigned healthcare costs in the Netherlands, far more than for example cancer, contributing only to an estimated 5% of all disease assigned costs.

**Chapter 3** describes a retrospective case-control study investigating whether the use of NSAIDs is associated with psychosis. The hypothesis was that the use of NSAIDs may be associated with a lower risk of psychosis, as defined by incident anti-psychotic use. We indeed found a decreased risk for incident anti-psychotic use in men, however not in women. The relative risk in men was 0.41 (95% confidence-limits (CI): 0.17 – 0.97) when results were adjusted for age and total prescription volume. The results suggest that the use of NSAIDs is associated with a decrease risk of subsequent psychosis.

In **chapter 4** we report on another observational study investigating the association between an anti-inflammatory drug and psychosis. This time the anti-inflammatory drugs were glucocorticosteroids (GCS), and the psychosis was defined by a new DSM-IV diagnosis of a psychotic disorder as registered by the RIPAG-MWU (Stichting Regionale Informatie Patiënten in de Geestelijke Gezondheidszorg regio Midden Westelijk Utrecht) case-register. The results were comparable to those in chapter 3, we found an association between GCS and a new diagnosis of a psychotic disorder for men only. The crude relative risk for men using either systemic or inhaled GCS was 0.52 (95% CI: 0.36 – 0.75). This association was present also in the youngest subgroup and a dose-response relation appeared to be present. The relation for woman was less pronounced compared to men, indicating a different pathophysiology. Also, the suspected protective effect of estrogens might limit the protective effect of the GCS in women.

We performed a double-blind placebo controlled randomized adjuvant trail investigating the effect of the non steroidal anti-inflammatory drug aspirin. The design and rationale behind this trial are described in **chapter 5**. In brief, during the three months of follow up participants with a schizophrenic disorder were randomized to either aspirin or placebo, together with pantoprazole for gastric protection. The severity of symptoms was estimated using the positive and negative symptom scale (PANSS). The change in total PANSS score was the primary outcome, with secondary outcomes being the changes on its subscales and the changes on a number of cognitive tests. As it is hypothesized that the effect of aspirin on psychotic symptoms is modified by the reversion of an altered TH1 / TH2 immune balance we also included this ratio in the analysis as a moderator of the aspirin effect.

**Chapter 6** then presents the results of this trial. We found a significant monthly treatment effect of -1.62 (95% CI -2.93; -0.30) points on the total PANSS and on the positive PANSS subscale (-0.52 (95% CI -1.02; -0.02). The effect was substantially larger in patients with the lower immune function, as indicated by TH1/TH2 immune balance (p= 0.018). Trends for the negative and general PANSS sub-scores were similar to the trends in the total and positive scores, without reaching statistical significance. Aspirin did not affect cognitive functions. The results of this randomized trial indicate that of aspirin

may be a beneficial therapy in combination with anti-psychotic drugs in schizophrenia.

The main results as presented in this thesis are then put into perspective in the general discussion in **chapter 7**. Here we also discuss the strengths, limitations and implications of the studies performed.

# Chapter 8.2

## Nederlandstalige samenvatting

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Allereerst bekijken we in **hoofdstuk 1** de ziekte die wij kennen als schizofrenie. Schizofrenie is één van de meest invaliderende psychiatrische aandoening die er is. De meest voorkomende symptomen van deze aandoening zijn hallucinaties en wanen. Mensen die aan schizofrenie leiden kunnen vaak niet bepalen of de waarnemingen die zij ervaren onderdeel zijn van de aandoening en daarmee negeert dienen te worden, of echt zijn. Eén op de honderd mensen in Nederland zal ergens in zijn leven gediagnosticeerd worden met schizofrenie. Alhoewel er een farmaceutische behandeling bestaat door middel van anti-psychotica reageren lang niet al de patiënten goed op deze medicatie. Een groot deel van de schizofrenie patiënten zal moeten leren leven met de symptomen die achterblijven. Over de jaren heen zijn er verschillende hypotheses ontstaan die de pathofysiologie van schizofrenie proberen te verklaren. Eén van deze hypotheses is dat ontstekingen in de hersenen een rol spelen in het ontstaan van deze aandoening. Ontstekingen kunnen geremd worden door verschillende vormen van medicatie, bijvoorbeeld door de niet-steroïde ontstekingsremmers zoals aspirine en de steroïde ontstekingsremmers zoals prednison. Het doel van dit proefschrift is de potentiële relatie tussen de genoemde ontstekingsremmers en schizofrenie te onderzoeken.

In **hoofdstuk 2** bekijken we eerst de financiële consequenties van de verschillende psychiatrische aandoeningen in Nederland, waaronder van schizofrenie. Er wordt geschat dat er ongeveer 21.000 mensen in Nederland zijn tussen de 18 en 65 jaar oud die leiden aan deze aandoening. De totale kosten die hiermee gepaard gaan worden geschat op 147 miljoen euros, wat wil zeggen dat de gemiddelde case afgerond 7000 euro per jaar kost. Alle psychiatrische aandoeningen samen zijn verantwoordelijk voor 32% van alle aan ziekte te relateren kosten van de gezondheidszorg, hetgeen een stuk hoger is dan bijvoorbeeld aan kanker, met 5%.

**Hoofdstuk 3** beschrijft een retrospectieve case-controle studie waarin gekeken wordt of er een relatie bestaat tussen niet steroïde ontstekingsremmers (NSAIDs) en psychose. De hypothese daarbij was dat het gebruik van NSAIDs de kans op een nieuwe psychotische episode verkleind. Een nieuwe psychotische episode werd daarbij bepaald aan de hand van het incidente gebruik

van anti-psychotica. In dit hoofdstuk vonden we inderdaad een negatieve associatie tussen NSAID gebruik en psychose, echter, alleen bij mannen. Het gevonden relatieve risico voor mannen bleek 0.41 te zijn (95% betrouwbaarheidsinterval (BI): 0.17 – 0.97), na correctie voor leeftijd en het totale aantal voorschriften. Deze resultaten suggereren dat het gebruik van NSAIDs inderdaad geassocieerd is met een verlaagd risico op een psychose.

In **hoofdstuk 4** rapporteren we over een andere observationele studie waarin we keken naar het verband tussen ontstekingsremmers en psychose. Deze keer waren de ontstekingsremmers de glucocorticosteroïden (GCS), en werd de psychose bepaald aan de hand van een nieuwe DSM-IV diagnose van een psychotische aandoening in het RIPAG-MWU (Stichting Regionale Informatie Patiënten in de Geestelijke Gezondheidszorg regio Midden Westelijk Utrecht) casus register. De resultaten bleken vergelijkbaar te zijn met die uit hoofdstuk 3, we vonden een negatieve associatie tussen GCS gebruik en psychose, maar enkel voor mannen. Het ongecorrigeerde relatieve risico voor ofwel systemische ofwel geïnhaleerde GCS bleek 0.52 (95% BI: 0.36 – 0.75) te zijn. Deze associatie was aanwezig in zowel de jongste als de oudste subgroep, en er bestond een dosis-respons relatie. Het feit dat de relatie in vrouwen minder duidelijk was dan in mannen zou wellicht verklaard kunnen worden door een beschermend effect van oestrogenen bij vrouwen, waardoor de GCS geen toegevoegd effect meer hadden.

De opzet en de rationale achter het belangrijkste onderzoek uit dit proefschrift wordt vervolgens beschreven in **hoofdstuk 5**. In dit onderzoek hebben we een placebo-gecontroleerd dubbel blind gerandomiseerde trial uitgevoerd waarin we keken naar het effect van de niet-steroïde ontstekingsremmer aspirine op de symptomen van schizofrenie. Kort samengevat, in dit onderzoek werden patiënten met een aan schizofrenie gerelateerde aandoening gedurende drie maanden gerandomiseerd naar ofwel aspirine ofwel placebo. Daarnaast kregen alle deelnemers pantoprazol ter bescherming van de maag. De ernst van de klachten werd bepaald aan de hand van de PANSS (positieve en negatieve symptomen score) vragenlijst. De verandering in de totale PANSS score was daarbij de primaire uitkomst, waarbij de secundaire uitkomsten de veranderingen in haar subschalen waren. Additionele secundaire uitkomsten waren bovendien de veranderingen op een aantal cognitieve testen. Omdat

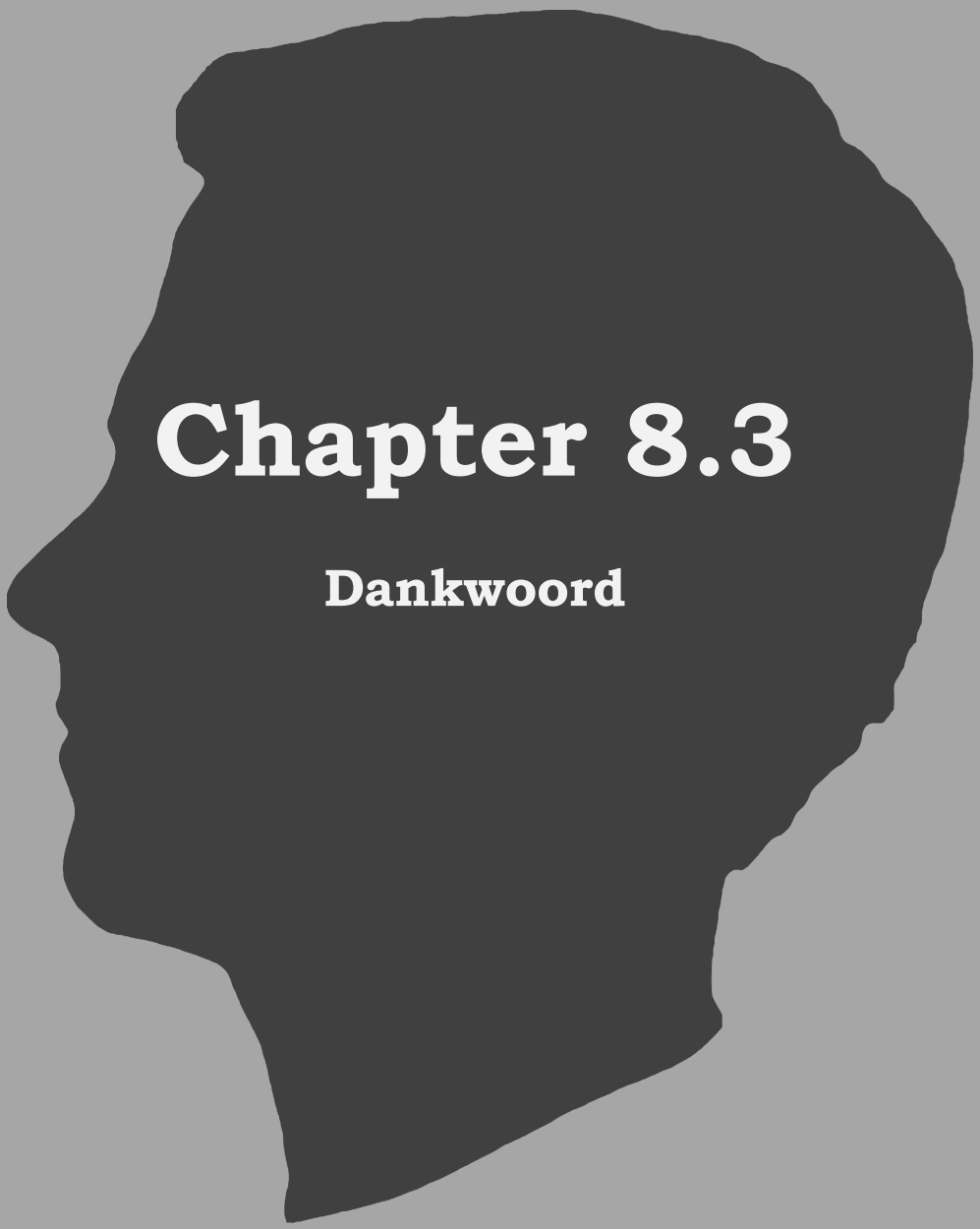
de hypothese achter de afname van de symptomen gerelateerd is aan een belangrijke immuunratio bekeken wij ook of de verhouding tussen T-helpercel-1 (TH1) activiteit en T-helpercel-2 (TH2) activiteit modificator van dit effect zou zijn.

In **hoofdstuk 6** worden vervolgens de resultaten van dit onderzoek besproken. We vonden een significant maandelijks behandelingseffect van aspirine van -1.62 punten (95% BI: -2.93; -0.30), op de totale PANSS score, en -0.52 (95% BI: -1.02; -0.02) op de positieve PANSSS score. Dit effect was substantieel groter in de patiënten met de lagere TH1/TH2 immuun balans (p=0.018). De trends voor de negatieve en algemene PANSS scores waren vergelijkbaar aan de totale en positieve PANSS scores, maar bleken de statistische significantiegrens niet te bereiken. De aspirine bleek geen effect op de cognitieve functies te hebben. De resultaten van dit onderzoek geven aan dat de bijbehandeling met aspirine naast de gebruikelijke anti-psychotica inderdaad een positief effect bij schizofrenie heeft.

Tenslotte worden de implicaties, sterke en zwakke punten van de onderzoeken zoals beschreven in dit proefschrift bediscusieerd in **hoofdstuk 7**.

# Chapter 8.3

Dankwood



# Chapter 8.3

## Dankwoord

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Het boek is af! De onderzoeken uit dit proefschrift waren zeker geen eenmansactie. In dit hoofdstuk zou ik dan ook graag een aantal mensen willen bedanken zonder wiens hulp mijn promotie zeker niet mogelijk zou zijn geweest.

Allereerst, Dr. H. Burger, beste Huib. Zonder jouw inspirerende steun als co-promotor zou hier waarschijnlijk nooit een proefschrift hebben gelegen. Ondanks dat de inclusie van deelnemers in de trial over het algemeen moeizaam ging heb jij me gemotiveerd weten te houden om door te zetten. De afstand tussen Utrecht en Groningen heb ik nooit als een belemmering ervaren in onze samenwerking. Ik denk niet dat ik me een betere co-promotor dan jou had kunnen wensen.

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Prof. Dr. R.S. Kahn, beste René. Jouw kritische blik heeft dit proefschrift zeker voor een deel de vorm gegeven die het nu heeft. Zonder jouw hulp zou dit project bovendien nooit van de grond zijn gekomen.

Misschien wel de belangrijkste personen, de deelnemers aan de trial zoals beschreven in hoofdstuk vijf en zes. Zonder onderzoek is er geen vooruitgang in de medische zorg mogelijk. Bedankt voor het vertrouwen dat jullie mij gaven door deel te nemen aan mijn onderzoek.

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Niek, bedankt dat je mijn onafhankelijke arts wilde zijn aan wie ik mijn patiënten kon voorleggen als ik vragen had. We gaan samen nog even door in de RIPAG.

# Dankwoord

Henk en Hugo, twee hoofdstukken van dit proefschrift hebben Agis-data als bron. De prettige samenwerking bij zowel het verkrijgen van de data als bij het schrijven heb ik als erg plezierig ervaren. Ik zal ook jullie de komende tijd nog veel zien in verband met de RIPAG.

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Daarnaast wil ik uiteraard de rest van al mijn vrienden en vriendinnen bedanken voor de gezellige avondjes samen stappen, praten, borrelen of wat we dan ook deden.

Sander en Soner, mijn paranimfen. Het is mij een eer dat jullie mijn paranimfen willen zijn, we maken er een mooi feestje van!

Beste schoonfamilie, lieve Lia, Theo en Annemarijn. Bij jullie heb ik me vanaf het eerste moment al thuis gevoeld, heel erg bedankt daarvoor. Zoals jullie zien ga ik nou toch echt 'afstuderen' ;-)

Lieve Valentijn, Dorothee en Liedewij. Ik ben heel erg blij met jullie als broer en zusjes! Hoewel we van uiterste oosten naar uiterste westen over het land zijn verspreid zien we elkaar nog zeer regelmatig en geniet ik altijd van ons samen.

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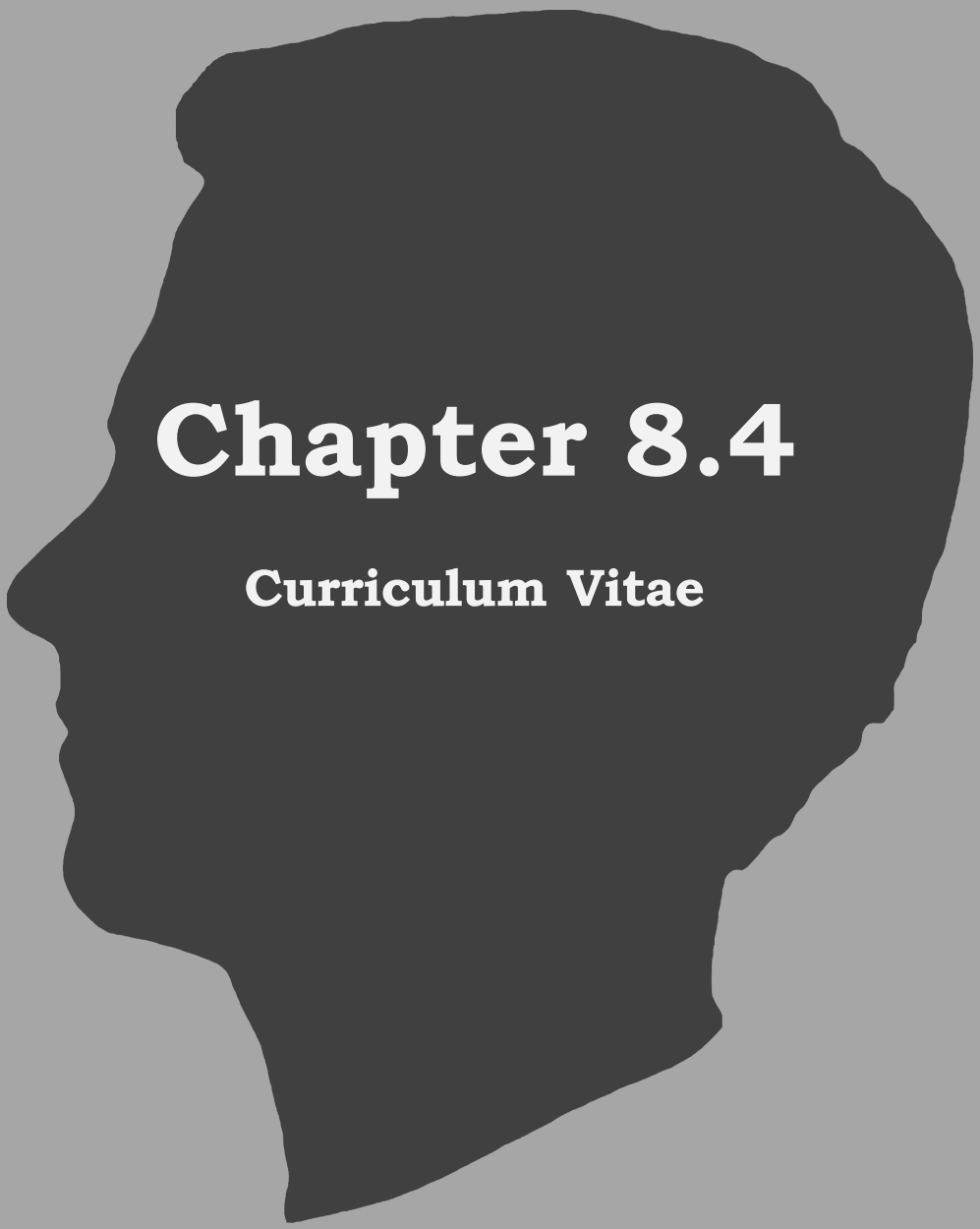
# Chapter 8.4

## Curriculum Vitae



# Chapter 8.4

## Curriculum Vitae

# Curriculum Vitae

Wijnand Laan was born on May the 4th, 1978, in Hengelo OV, The Netherlands. In 1997 he graduated from the secondary school 'Twickel College' and started his university training in Nutrition and Public Health at Wageningen University, with a focus on Human Epidemiology. As a part of his study two research projects were conducted. The first project focused on the effect of a single nucleotide polymorphism in the NAD(P)H:quinone oxidoreductase gene on the relation between smoking and colorectal cancer, the second on the effect of a single nucleotide polymorphism in the alpha1a-adrenoceptor gene on the efficacy of alpha1-adrenoceptor antagonists in benign prostatic hyperplasia treatment. In September 2003 he obtained his Master of Science degree in Nutrition and Health. In January 2004 he started as a PhD student on the projects as described in this thesis, which were supervised by Prof. D.E. Grobbee, Prof. R.S. Kahn and Dr. H. Burger. He obtained his Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences, Erasmus Medical Center Rotterdam in June 2006. As of January 2008 he has a postdoctoral position in the psychiatric case register RIPAG, which is now part of the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.