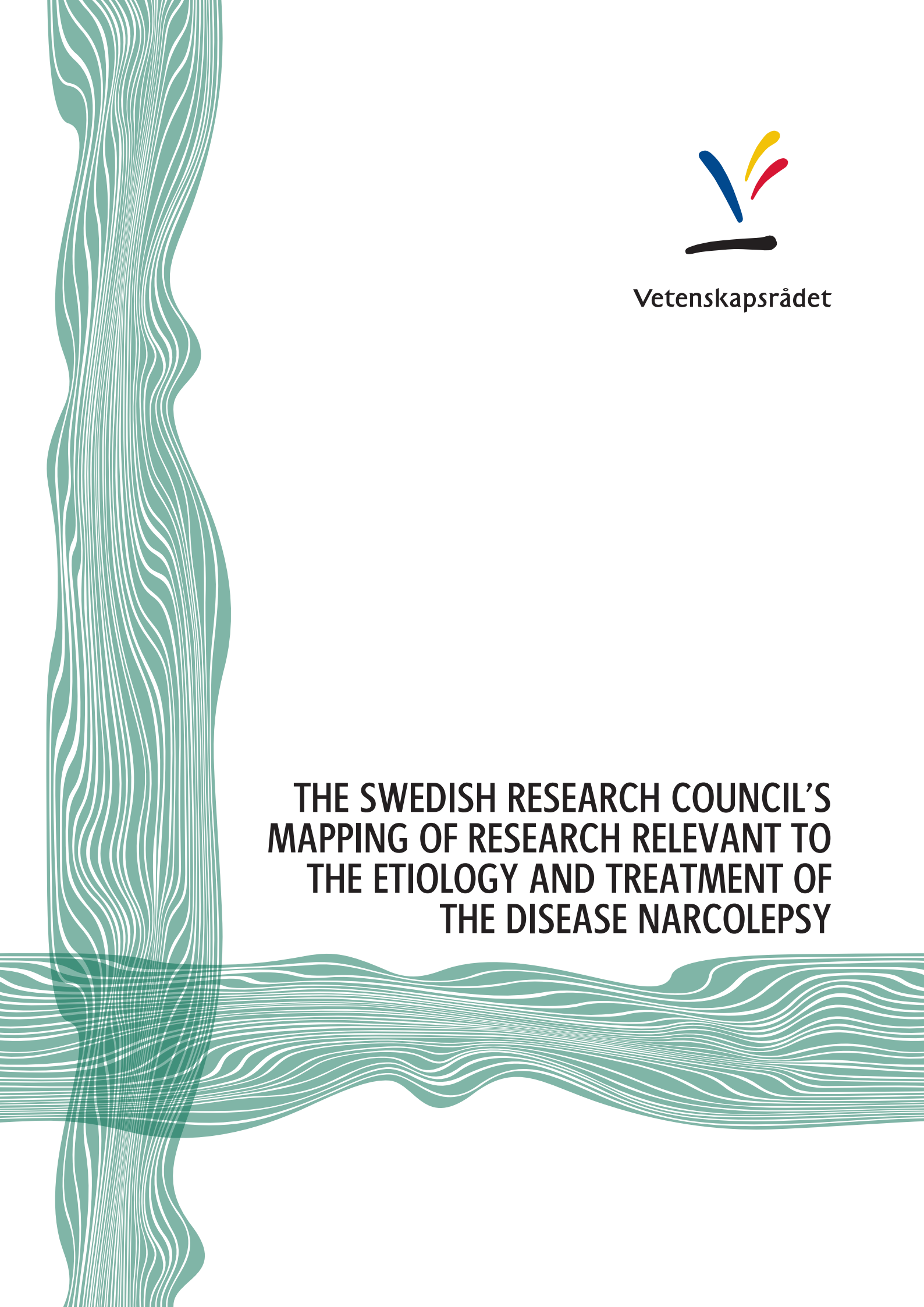

Vetenskapsrådet

THE SWEDISH RESEARCH COUNCIL'S MAPPING OF RESEARCH RELEVANT TO THE ETIOLOGY AND TREATMENT OF THE DISEASE NARCOLEPSY

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SWEDISH RESEARCH COUNCIL
VETENSKAPSRÅDET
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SE-101 38 Stockholm, SWEDEN

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PREFACE

The Swedish Research Council is a government agency with the responsibility to support basic research of the highest scientific quality in all academic disciplines. It is also part of the Council's remit to evaluate research and assess its academic quality and success.

This report is the response to a government assignment given to the Swedish Research Council on the 3rd of November 2011 to map research with relevance to etiology and treatment of the disease narcolepsy. The council was also assigned to analyze the knowledge gaps in the field, based on the mapping of the research. The report is based on input from five different activities; a bibliometric analysis, studies of relevant literature, interviews with international and Swedish researchers, a workshop with selected researchers and consultations with relevant Swedish authorities and organizations.

The Swedish Research Council would like to express its sincere gratitude to the consulted experts for devoting their time and expertise to this important task.

Stockholm 12-12-18

Mats Ulfendahl
Secretary General for Medicine and Health
The Swedish Research Council

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SAMMANFATTNING

Denna rapport är svaret på ett regeringsuppdrag till Vetenskapsrådet att kartlägga forskning med relevans för uppkomst och behandling av sjukdomen narkolepsi, samt att analysera kunskapsbristerna inom området. Till grund för rapporten ligger fem olika aktiviteter; en bibliometrisk analys, studier av relevant litteratur, intervjuer med internationella och svenska forskare, en workshop med utvalda forskare samt konsultationer med relevanta svenska myndigheter och organisationer.

Forskning om narkolepsins uppkomst har gjort stora framsteg de senaste åren. Man har funnit gener som är associerade med sjukdomen, utlösande faktorer har föreslagits och nervceller som är påverkade i hjärnan har identifierats. Trots dessa framsteg så är sjukdomens underliggande mekanismer fortfarande okända och behandlingsalternativen som finns idag fokuserar på att lindra symptomen. Även om behandlingarna är effektiva för vissa patienter så är den i många fall inte tillräcklig för att helt lindra narkolepsisymptomen. Behandlingarnas bieffekter är ofta besvärande och många gånger påverkas patientens livskvalitet negativt. Det finns även socioekonomiska konsekvenser förknippade med sjukdomen på såväl individ- som samhällsnivå.

Forskning om hur patienter kan behandlas på bästa möjliga sätt är värdefull i ett kortsiktigt perspektiv. I ett längre perspektiv är det övergripande målet att förstå sjukdomens underliggande mekanismer för att diagnosticera, förebygga eller bota sjukdomen så snart som möjligt. Ett antal kunskapsbrister har identifierats angående uppkomst och behandling av narkolepsi. Dessa har delats in i fem olika teman:

Orsak bakom nervcellsförlust
- Genetisk predisponering
- Andra riskfaktorer
- Immunologiska mekanismer

Effekter av nervcellsförlusten
- Omfattning av cellförlusten
- Nervcellsnätverkens funktion

Kartläggning av symptom
- Skillnad mellan Pandemrix-inducerade fall och andra fall
- Icke-sömnrelaterade symptom

Behandlingsstudier
- Longitudinella studier på behandling, bieffekter och livskvalitet
- Kliniska studier på barn
- Sjukdomsbörda och sjukvårdens hantering av sjukdomen

Nya behandlingsalternativ
- Symptomatiska behandlingar
- Immunmodulerande behandlingar
- Terapier baserade på ersättning av hypocretin

En stor del av forskningen sker i USA och Europa. Vid sidan av detta sker relevant forskning även i Japan och Kina. Narkolepsiforskningen i Sverige är begränsad, även om vissa studier har påbörjats de senaste åren. Generellt sett har de experter som konsulterats framhävt behovet av internationellt samarbete för att belysa kunskapsbristerna. Gemensamma diagnoskriterier och standardiserade tillvägagångssätt för insamlande av data behövs för att göra databaser internationellt kompatibla så att data

kan delas mellan länder. Experterna rekommenderar även nationella center med ett begränsat antal läkare som behandlar patienterna. Detta kan underlätta och stimulera forskning inom området.

Svensk forskning skulle kunna belysa en del av kunskapsbristerna genom att ta tillvara på den omfattande erfarenheten av databaser och register som finns i Sverige och övriga nordiska länder. För att stimulera forskning om narkolepsi skulle Sverige också kunna initiera och främja internationellt samarbete på en nordisk eller Europeisk nivå. Detta kan öka studiernas vetenskapliga genomslagskraft, samt främja den svenska forskningens kvalitet inom området.

SUMMARY

This report is the response to a government assignment given to the Swedish Research Council (SRC), to map research relevant to the etiology and treatment of the disease narcolepsy, and to analyze the knowledge gaps in the field. The report is based on input from five different activities; a bibliometric analysis, studies of relevant literature, interviews with international and Swedish researchers, a workshop with selected researchers and consultations with relevant Swedish authorities and organizations.

Research on the etiology of narcolepsy has made considerable progress during recent years. Genes associated with the disease have been identified, triggering factors have been suggested and neurons affected in the brain have been identified. Despite this progress, the mechanisms underlying the disease are still uncertain. The treatment options available today focus on relieving the symptoms of narcolepsy. Although efficient for some, the treatments are in many cases not sufficient to counteract the symptoms, the side effects are often troublesome and the patient's quality of life is many times affected. There are also socioeconomic consequences associated with the disease on an individual and societal level.

In a short-term perspective, research on how already affected patients can be treated in the best way will be valuable. In a longer perspective, the goal is to understand the underlying mechanisms of the disease to be able to diagnose, prevent or cure the disease as early as possible. In the report, a number of knowledge gaps have been identified concerning the etiology and treatment of narcolepsy. These have been subdivided into five different topics:

Cause of neuronal cell loss
- Genetic predisposition
- Other risk factors
- Immunological mechanism

Effect of neuronal cell loss
- Extent of cell loss
- Function of the neural circuitry

Mapping of symptoms
- Difference between Pandemrix-induced cases and others
- Non-sleep related symptoms

Treatment studies
- Longitudinal studies on treatments, side-effects and quality of life
- Clinical studies in children
- Disease burden and health-care management of disease

New treatment options
- Symptomatic treatments
- Immunomodulatory treatments
- Hypocretin replacement therapies

A large part of the research on narcolepsy is conducted in the USA and Europe. Outside of these, Japan and China also have relevant research. Narcolepsy research in Sweden is limited, although some studies have been initiated in recent years. In a general perspective, the consulted experts emphasize the need for international collaboration in addressing many of the knowledge gaps. Common diagnose criteria and standardized procedures for collection of data are essential for making databases internationally

compatible to allow for sharing of data. National centers with a limited number of clinicians treating patients are also recommended by the consulted experts in order to facilitate and stimulate research in this field.

Swedish research may have the opportunity to address some of the knowledge gaps by making use of the extensive experience and infrastructure in Sweden and other Nordic countries concerning databases and registries. To stimulate research, Sweden could also initiate and promote international collaboration on a Nordic or European level. This may elevate the scientific impact of the studies, as well as advance and improve the quality of Swedish research in this field.

1 INTRODUCTION

1.1 THE GOVERNMENTAL ASSIGNMENT

On the 3rd of November 2011, The Swedish Research Council (SRC) was given an assignment by the Swedish government to map research with relevance to etiology and treatment of the disease narcolepsy. The council was also assigned to analyze the knowledge gaps in the field, based on the mapping of the research.

The assignment was to be performed after consultation with authorities concerned, such as the Medical Products Agency (MPA, Läkemedelsverket) in Sweden and the Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet). Further, individual experts and authorities were to be consulted on a national and international level.

The governmental assignment, which is enclosed as Appendix 4.1, was to be handed in to the Government offices (Ministry of Education and Research, and Ministry of Health and Social Affairs) by the 31st of December 2012.

The background to the assignment was two studies performed by the Swedish Medical Products Agency in 2011 showing a connection between the Pandemrix vaccine and the risk of developing narcolepsy. Pandemrix vaccination was used during the swine influenza (H1N1) pandemic in 2009 and 2010, and around 60% of the Swedish population was vaccinated. The studies could not explain the reason for the increased risk to develop narcolepsy, and against this background, the Swedish government assigned the SRC to map research relevant to the etiology and treatment of narcolepsy and to analyze the knowledge gaps in the field.

1.2 WORK PROCEDURE

The work at the Swedish Research Council has been performed by a project group containing six members: Anna Vallstedt Haeger (project manager), Anders Hellström (deputy project manager), Sten Söderberg, Mattias Petersson, Marianne Wikgren and Teresa Ottinger. In addition, Staffan Karlsson performed the bibliometric analyses. The work has been planned and conducted by the project group under the supervision of a steering group consisting of the Secretary General for Medicine and Health Mats Ulfendahl and the Executive Director Mariann Samuelsson, whom was replaced by the Director General Mille Millnert in the last two months of the project.

The work has included consultation with a number of Swedish authorities and organizations; the MPA, the Swedish Institute for Communicable Disease Control, The Pharmaceutical Insurer (Läkemedelsförsäkringen), the Swedish Association of Local Authorities and Regions (Sveriges Kommuner och Landsting) and the National board of Health and Welfare (Socialstyrelsen). The consultation partners have given input on the progress and contents of the report throughout the process. A list of the representatives from these organizations can be found in Appendix 4.2.

In order to map research relevant to etiology and treatment of narcolepsy, a number of approaches have been used. A bibliometric analysis has been performed to identify where in the world the relevant research is conducted. The available literature in the publication database Medline has been studied in order to get an overview of the field and to identify international researchers. A number of interviews with international and Swedish researchers have been conducted. A workshop with international and Swedish researchers within the field was organized in order to confirm the results of the mapping exercise and to further discuss knowledge gaps and future directions. For workshop participants, see Appendix 4.5.

The eight international researchers interviewed were chosen to ensure geographical spread and coverage of different research areas within the narcolepsy field, such as basic and clinical science. The aim

of these interviews was to get a picture of the research field in terms of focus of the current research efforts, where they are conducted, the knowledge gaps and the research needed to address these gaps. A number of questions were also designed with the aim to carry out a SWOT (Strength, Weaknesses, Opportunities and Threats) analysis of the research field. The interviews were performed in person or by videoconference. The interviewed researchers and their affiliations can be found in Appendix 4.3.

A total of nine Swedish researchers were interviewed to map current and planned research efforts in Sweden, to get their view on what the Swedish research should focus on and needed prerequisites to carry out this research. The interviews were performed in person or by telephone. The researchers and their affiliations can be found in Appendix 4.4.

1.3 STRUCTURE OF THE REPORT

Section 2 of the report presents the main findings from the SRC's literature overview and the interviews performed with experts in the field: a presentation of the current knowledge concerning etiology and treatment of narcolepsy, as well as the knowledge gaps and the need for future research efforts. This section also contains an analysis of where the relevant research is conducted from a global perspective, performed by using Bibliometric analysis and Large Network Analysis. One of the aims of section 2 is to provide a knowledge base on which to build the understanding of the knowledge gaps.

Section 3 summarizes the findings in section 2 in terms of the most important knowledge gaps. Based on the needs and gaps identified in the analysis, the SRC has also found it relevant to discuss future directions of narcolepsy research from a general and Swedish perspective.

As stated above, the background to the assignment was the connection between Pandemrix influenza vaccination and narcolepsy, although this has not been the main focus of this report. A brief overview of the current knowledge on the connection between narcolepsy and Pandemrix is provided in section 1.5. A more thorough mapping of international and national initiatives concerning this issue can be found in Appendix 4.6. Where appropriate, discussions on research related to narcolepsy in connection to Pandemrix can be found in the other sections.

1.4 AN INTRODUCTION TO NARCOLEPSY [1]

Narcolepsy is a chronic neurological disorder characterized by the brain's inability to control sleep-wake cycles. In most cases, symptoms first appear in individuals between the ages of seven and 25. In rare cases, narcolepsy may appear at a younger age or in older adults. Excessive daytime sleepiness is the most prominent symptom and is usually also the first symptom to occur, along with sudden bouts of sleep that cannot be prevented. Other major symptoms include: sudden loss of voluntary muscle tone (cataplexy) that may be triggered by strong emotions, vivid dream-like images/hallucinations (hypnagogic hallucinations) or paralysis during sleep onset or when waking (sleep paralysis). Disturbed nocturnal sleep and memory problems are also frequent. Secondary effects, primarily in children, are loss of ability to concentrate, learning disabilities, depression, obesity and disturbed metabolism. The disease often has major effects on the social life of the affected individuals, due to the nature of the symptoms. The variety and severity of symptoms in patients often differ from case to case, where some are only affected by excessive daytime sleepiness while others may display the whole range of symptoms.

Narcolepsy generally occurs spontaneously and is thus referred to as primary narcolepsy. It is believed that narcolepsy is caused by a combination of genetic and other risk factors such as environmental factors. The most common hypothesis is that there is a lack of the brain neurotransmitter hypocretin (also called orexin) in the hypothalamus in these individuals, caused by degeneration of the hypocretin-producing cells following an autoimmune reaction. Loss of hypocretin then results

[1] The text is based on information obtained from the literature (references can be found in Appendix 4.6) as well as from interviews and a workshop with researchers in the narcolepsy field.

in an inability to regulate sleep. Cataplexy is almost always present in these individuals. Secondary narcolepsy also occurs, and is the result of direct effects on the hypothalamus following head trauma, neurological injury or tumors.

Narcolepsy is generally viewed as an underdiagnosed condition. Thus, the exact prevalence is not known although international studies indicate that 270-500 individuals out of one million are affected by some form of narcolepsy. The prevalence of narcolepsy with cataplexy is around 0.02-0.05% (200-500 affected out of one million individuals) and although it appears throughout the world, there is some variance. For instance, the disease appears to be more frequent in Japan (0.16-0.18%). Males and females are equally affected. The prevalence of narcolepsy without cataplexy is largely unknown, and these patients are more likely to be underdiagnosed.

Diagnosis of narcolepsy is made from the typical symptoms of excessive sleepiness and sudden loss of muscle tone. Normally, diagnosis is often late - the average time between symptom onset and final diagnosis is more than 10 years - since none of the described symptoms are exclusive to narcolepsy and may be found in other more common conditions. However, diagnosis of patients obtaining narcolepsy in connection to Pandemrix has been considerably faster in comparison. Cataplexy is the most specific symptom and is rarely present outside narcolepsy. Tests specialized for sleep disorders are usually required before a diagnosis can be confirmed, particularly when cataplexy is not present. Measuring the levels of hypocretin in a sample of cerebrospinal fluid may also be helpful when other diagnostic methods are not sufficient.

1.5 PANDEMRIX AND NARCOLEPSY

Pandemrix is one of eight vaccines for the H1N1 2009 influenza pandemic (swine flu), licensed within the EU/EEA area. The vaccine was developed by GlaxoSmithKline and patented in September 2006. The European Commission approved the vaccine for use in September 2009, upon the recommendations of the European Medicines Agency (EMA). Based on national reports the EMA estimated that as of the beginning of August 2010, at least 38.6 million people in EU/EEA countries had been vaccinated, of them more than 30.5 million with Pandemrix.

In August 2010, after reports of increasing numbers of narcolepsy cases, the Swedish MPA and The Finnish National Institute for Health and Welfare (THL) began investigations about narcolepsy as a possible side effect to Pandemrix flu vaccination in children, and found at least 6.6 times increased risk among children and youths, or at least 3.6 additional cases of narcolepsy per 100.000 vaccinated subjects. In Finland, Sweden and Norway influenza vaccine was offered schoolchildren through their school health system, explaining why high coverage rates were obtained in these age groups.

As a result of these and other findings, EMA concluded in July 2011 that in persons under 20 years of age, the vaccine should be used restrictively. The EMA noted that the vaccine was likely to have interacted with genetic or environmental factors that might raise the risk of narcolepsy, and that other factors may have contributed to the results. The results of the VAESCO [2] epidemiology study of narcolepsy and pandemic vaccines, which was conducted in nine EU member states, was published in September 2012. A more detailed review of these and other studies on the association between narcolepsy and Pandemrix is given in Appendix 4.6.

[2] Vaccine Adverse Events Surveillance and Communication http://vaesco.net/vaesco.html

2 MAPPING OF RESEARCH RELEVANT TO THE ETIOLOGY AND TREATMENT OF NARCOLEPSY

2.1 THE ETIOLOGY OF NARCOLEPSY

The following text describes the current knowledge and the proposed focus of future research efforts regarding the etiology of narcolepsy, based on information obtained from the literature (references can be found in Appendix 4.7) as well as from interviews and a workshop with researchers active in the narcolepsy field.

2.1.1 CURRENT KNOWLEDGE

Research on the etiology of narcolepsy has made considerable progress during the last decade. Genetic studies have found several genes predisposing for the disease, environmental factors that trigger the onset of the disease have been suggested and specific neurons affected in the brain (hypocretin neurons) have been identified. These findings are discussed in more detail below. Current knowledge points to an autoimmune origin of the disease. However, despite of this progress, the specific mechanism by which the disease occurs is still uncertain.

Genetic predisposition

It is believed that narcolepsy is caused by a combination of genetic and other risk factors such as environmental factors. The role of genetics in humans with narcolepsy is not completely understood, and no consistent pattern of heredity has been recognized in families so far. The majority of narcolepsy cases occur sporadically, i.e. the disease is not inherited and there is no history of the disease in the family. However, studies have shown that the risk of narcolepsy among first-degree relatives (parents, sibling, and children) is 1-2%, as compared to 0.02% in the general population, showing that the genetic predisposition can be inherited to some extent. If the cause for narcolepsy was purely genetic, one would expect that in the case where one monozygotic twin has the disease, the other twin would also develop it. However, studies on twins have shown that the other twin will be affected in 25-35% of the cases. This further reinforces the idea that genetics do play a role in the development of human narcolepsy, but that in most cases the influence of other risk factors is required for the disease to develop.

The underlying genetic predisposition is complex and has been extensively studied. Several studies have revealed that more than 90% of the narcolepsy patients with cataplexy carry one specific gene variant of the human leukocyte antigen (HLA) termed HLA-DQB1*0602. This association is remarkably conserved across different ethnic populations. HLA is a key player in the immune system and different HLA gene variants are linked to autoimmune diseases like psoriasis, type 1-diabetes and multiple sclerosis. The strong association between this gene variant and narcolepsy shows that in most cases it is required in order to develop the disease. However, this gene variant is common in the population, where ~20-30% carry it without any symptoms of narcolepsy. This means that the gene variant itself does not cause narcolepsy; one or several other factors are needed to trigger the onset of disease. In combination with HLA-DQB1*0602, other HLA-DQB1 gene variants have been shown to modulate the risk of narcolepsy, where some increase the risk and some reduce it. This supports the general notion that genetic predisposition is necessary for developing narcolepsy.

Genetic factors other than HLA-DQB1 are likely to be involved in narcolepsy predisposition, since the increased risk in first-degree relatives cannot be solely explained by the HLA subtypes. Recent technical advances in reading and analyzing the genetic code have contributed to the identification of the association of narcolepsy with cataplexy, and gene variants of the T-cell receptor alpha (TRA@), and the purinergic receptor P2Y (P2Y11). To date, the association with TRA@ is unique to narcolepsy

since other presumable autoimmune diseases often have an association to the T-cell receptor beta (TRB@) instead. However, it should be stressed that the two gene variants TRA@ and P2Y11 only explain a fraction of the genetic predisposition, since they are frequent also in individuals without any symptoms of narcolepsy. In contrast to the strong correlation between patients with narcolepsy and the HLA-DQB1*0602 gene variant, the association of the disease and the gene variants TRA@ and P2Y11 is considerably weaker. These two gene variants increase the predisposition, but are on the other hand not necessary to have in order to develop the disease. Similar to HLA, TRA@ and P2Y11 have important functions in the immune system. This association could indicate an interaction between these genes, and further exploration of this may lead to a better understanding of the biology behind narcolepsy. Additional gene variants that have been suggested to increase the risk of developing narcolepsy are; TNF-alpha, CPT1b/CHKB, COMT, MAOA. The biological mechanisms of these gene variants in relation to narcolepsy have not been studied further.

Risk factors, environmental triggers and autoimmunity

Since genetics cannot solely explain the development of narcolepsy, other factors have to be involved. A risk factor is something that can be statistically associated with an increased risk of disease, although it does not necessarily have a direct causal relationship with the development of the disease. Risk factors can be of a different nature, such as behavioral, biomedical, environmental or demographic (such as age and gender). The risk factors for narcolepsy are largely unknown. Environmental factors such as infections have been suggested to be more directly involved in triggering the onset of a possible autoimmune reaction leading to the disease, and these will be referred to as trigger factors.

The nature of the environmental trigger factors is still uncertain, although recent studies have shed some light on this issue. Some studies have suggested an association with *Streptococcus pyogenes* bacterial infection in conjunction with the onset of disease, demonstrating that upper airway infections might be a trigger. In a large study in China the onset was shown to be cyclical. The number of cases significantly increased 5-7 months subsequent of the seasonal flu/cold. In the same study, a three-fold increase in disease onset was observed following the 2009-2010 H1N1 swine flu pandemic compared to other years. This observation suggests that the H1N1 influenza could trigger the onset of the disease. It is important to note that even if some studies indicate an involvement of infections such as *Streptococcus pyogenes* and H1N1 influenza in triggering narcolepsy, these infections are fairly widespread and only a very small fraction of the infected individuals would develop narcolepsy. It is therefore likely that several different risk factors in combination are required for the disease to develop.

The most compelling evidence for an environmental trigger is the significant increase (4 to 13- fold increase) of narcolepsy noted in Sweden, Finland, and Ireland among children and adolescents vaccinated with Pandemrix (containing the adjuvant ASO3) during the H1N1 swine flu pandemic. This suggested that the vaccine in combination with the adjuvant triggered the development of narcolepsy. However, the risk to develop narcolepsy after Pandemrix vaccination is still very small, again suggesting that several factors are needed in order to develop the disease.

In Sweden, the incidence rates per 100 000 persons varied with the latitude of the region. The regions in the south showed the highest rates of 2.31-2.99, the regions in the middle of the country 0.99-1.88, and the region in the north the lowest rate of 0.25. Possible explanations for this are being looked into by the MPA, such as the spread of the H1N1 swine flu infection throughout the country, the timing of vaccination and possible batch-related effects. A detailed report on current international studies regarding the connection between Pandemrix and narcolepsy is available in Appendix 4.6 of this report.

The association between infections, vaccines and the onset of narcolepsy points to the involvement of the immune system in the cause of the disease. In autoimmune diseases there is an inappropriate immune response against substances and tissues normally present in the body. In other words, the immune system interprets a part of the body as foreign and attacks and kills its own cells. Autoimmune diseases are often strongly associated with specific HLA gene variants, as the HLA genes encode proteins which present parts of foreign substances called antigens (e.g. viruses or bacteria) to the immune system. This presentation is a signal to the body to start an immune response, and antibodies are synthesized against

the foreign protein to kill all similar substances in the body. An autoimmune response can be initiated if the HLA protein presents a bodily-specific protein by mistake or a part of a virus or bacteria that resembles a body protein (molecular mimicry). The strong association with the HLA-DQB1*0602 gene variant, in combination with the association with specific variants of the TRA@ and P2Y11 genes, support the theory of an autoimmune response. TRA@ is a well-studied gene and is known to interact with HLA in the immune system. It is therefore possible that these two gene variants interact and for some reason trigger an autoimmune response towards the affected cells in the brain.

However, there is no solid evidence to confirm that narcolepsy is an autoimmune disease. From a clinical point of view, the presence of an autoimmune disease is often associated with other autoimmune diseases in the patient or in family members of the patient. This association has not yet been documented in families with narcolepsy. In addition, the autoantibodies typical to an autoimmune disease have not been detected and common markers indicating inflammation are absent.

The orexin/hypocretin system

A major breakthrough in understanding the cause of narcolepsy was the discovery of the involvement of the hypocretin system in the brain. Hypocretin signaling molecules (also called orexins) are present in a distinct part of the brain called hypothalamus. In 1999, it was found that naturally occurring narcolepsy in dogs is caused by a mutation in the gene expressing one of the receptors for hypocretin in the brain. This was the starting point of a number of studies looking at the hypocretin system in human narcoleptic patients.

Human narcoleptic patients do not normally display any mutations in these genes. However, hypocretin has been found to be undetectable in the cerebrospinal fluid of almost all patients with narcolepsy and cataplexy. Postmortem analysis has further suggested that patients with narcolepsy and cataplexy have around 10% of the normal amount of hypocretin cells in the brain. Genetically engineered mice that lack the hypocretin peptides or the hypocretin-producing neurons display symptoms of narcolepsy such as sleepiness and cataplexy. Therefore, it appears likely that the specific destruction of hypocretin cells in human narcolepsy with cataplexy is responsible for a large part of the symptoms of the disorder. It is important to note that narcoleptic patients without cataplexy often have detectable amounts of hypocretin in cerebrospinal fluid, and most likely a much less dramatic loss of hypocretin neurons, as suggested by studies showing an approximate 30% reduction of hypocretin cells. It remains to be determined whether the disease mechanisms are the same, and whether different levels of hypocretin can explain differences in symptoms.

Only around 70, 000 of the billions of neurons in the brain contain hypocretin-signaling molecules. These hypocretin neurons have been found in the hypothalamus, from where they send projections to numerous parts of the brain to affect other neurochemical systems. Through the effect on these other systems of the brain, hypocretin neurons are thought to sustain wakefulness and suppress REM (Rapid Eye Movement) sleep.

Wakefulness and sleep is regulated by numerous neurochemical systems in the brain, such as acetylcholine, norepinephrine, dopamine, serotonin, histamine and hypocretin. These systems interact in a variety of ways to ensure rapid and complete transitions between sleep/wake states. The hypocretin neurons project towards many brain regions that are involved in arousal/wake states and they are mainly active during wakefulness and are silent during NREM (non-Rapid Eye Movement) sleep and REM sleep. Although the mechanism by which the different systems interact is still uncertain, a general theory is that hypocretin neurons stabilize wakefulness by enhancing activity in the arousal systems and thereby ensuring alertness and sustained wakefulness over long periods of time.

The amount of wakefulness in people with narcolepsy during a 24 h period is almost normal. However they have great problems with maintaining long periods of wakefulness and often have fragmented sleep during nighttime. In addition, the occurrence of cataplexy and hypnagogic hallucinations suggests that elements of REM sleep mix into wakefulness. Thus, it is possible that hypocretins have a stabilizing role on the neural circuits that regulate transitions between sleep and wake states. In this scenario, the loss of hypocretins would destabilize this mechanism and lead to frequent transitions

between wakefulness and sleep. However, this hypothesis is not proven and the pathways underlying cataplexy and other narcolepsy symptoms remain elusive.

Besides their primary role as regulators of sleep-wake cycles, the hypocretin neurons have been implicated in several other functions such as metabolism, food-intake and pleasure-seeking behavior.

2.1.2 KNOWLEDGE GAPS AND THE NEED FOR FUTURE RESEARCH EFFORTS

When it comes to understanding the biological mechanisms behind narcolepsy, one may think of this as consisting of two sub-questions. One is why and how the hypocretin neurons die and the mechanisms involved in this process, the other is how the loss of these neurons causes narcolepsy. Both questions are important to unravel in order to truly understand the disease. To date, the mechanism behind the death of the cells is unknown and the knowledge of which neural circuits that are affected and their function is limited. The knowledge gaps and the research needed to fill these gaps will be discussed below.

Cause of neuronal cell loss

The current hypothesis is that environmental factors may trigger the onset of the disease in genetically predisposed individuals. The previously mentioned gene variants explain a large portion of the genetics behind narcolepsy. However, there are probably several additional gene variants that have not yet been identified, which could be involved in the genetic predisposition. New techniques in the field have been developed during the last decade and are now frequently used to sequence and analyze the genic code in a fast and cost efficient way. To reach a statistically significant result, thousands of samples (e.g. blood) need to be collected from patients. More extensive collaboration among researchers in the field and contribution of samples to genetic studies would undoubtedly be helpful. The genetic studies are important to increase the knowledge and understanding of the etiology of narcolepsy. It is also important to follow up the findings of new gene variants with functional biological studies.

Studies aimed at finding risk factors aside from genetic involved in narcolepsy have so far yielded limited results. For instance, 30% of the Swedish population carries the HLA gene variant predisposing for narcolepsy and only a small number of these individuals developed narcolepsy subsequent to vaccination with Pandemrix. Other risk factors involved in the process of developing this disease have to exist, and there is an overall need for more epidemiological studies addressing these issues. As a first step, epidemiological studies can map the incidence of the disease to find plausible correlations with for example geographic location or seasonal disease onset. These studies can be the basis of further studies pinpointing risk factors. Even in such studies it will be difficult to identify risk factors for narcolepsy, as there is a low incidence of the disease in the population and a delay (often of several years) in diagnosing these patients. These studies would benefit from international collaboration.

Many findings point to an autoimmune cause of the disease; the presumably selective loss of hypocretin neurons, the complex genetic susceptibility with an association to HLA and TRA@, and the recent findings of the increased risk for narcolepsy with the H1N1 vaccination Pandemrix. However, the evidence at this point is more circumstantial in nature.

Substantial efforts have been made to prove that narcolepsy is an autoimmune disease, but no conclusive evidence like autoantibodies, antigens, or evidence of cell destruction by an autoimmune attack have been identified. Antibodies against the Tribbles homolog (Trib2) protein, which is expressed in the hypocretin neurons, were identified in some (˜20%) patients with narcolepsy. It remains to be determined whether these antibodies are involved in the autoimmune process, or if they are a consequence of the process. If the hypocretin neurons are destroyed by means of an autoimmune process, it has been proposed that it is a transient event, much of which might be over by the time when symptoms of the disease have started to occur. This scenario would make an on-going autoimmune attack very hard to detect. Therefore, it is essential to have access to blood and serum samples taken during, or close to, onset of the disease to be able to detect markers of autoimmunity. The research community continuously put efforts into finding the evidence for an autoimmune mechanism. This includes

screening for antibodies in patient sera and searching for immune cells reactive towards the hypocretin cells. Although difficult to accomplish, these studies are an important step towards understanding the underlying cause of the disease.

To further investigate an autoimmune origin of the disease, animal models are also valuable tools and recapitulating the human disease process in an animal model such as mice would greatly enhance the understanding of the disease. This could be attempted for example by using mice engineered to express the human HLA-DQB1*0602 gene variant, possibly in combination with other predisposing genes such as TRA@, then injecting human immune cells or exposing these mice to triggering events such as H1N1 vaccine and H1N1 influenza virus.

One of the stronger indications that narcolepsy is an autoimmune disease comes from the association with the H1N1 influenza vaccine Pandemrix. Research focusing on the process by which this vaccine could trigger narcolepsy may give important clues on the etiology of narcolepsy. This research is also valuable when considering issues of vaccine safety.

Studies addressing the loss of neurons in deceased narcolepsy patients have been performed on a limited number of brains. The evidence points to that the absence of hypocretin peptides is due to the selective death of the hypocretin neurons. However, more studies should be performed to firmly establish this. In other diseases where cells of the brain selectively die (called neurodegenerative diseases), such as Parkinson's and Alzheimer's, the disease is progressive and there are clear signs of inflammation when the cells die. No conclusive data has been shown to demonstrate inflammation in narcolepsy. Since most of the cell-death is likely to occur before the clinical onset of the disease, looking at brains of newly diagnosed patients would be informative. However, since the onset of the disease often occurs during adolescence and the patient's life expectancy is normal, these studies are unlikely to be realized to any large extent. Also, the common lag time between occurrence of symptoms and diagnosis is a complicating factor.

Since there is no firm evidence that an autoimmune disease causes the loss of hypocretin cells, it is important to consider other pathophysiological mechanisms such as an infectious or toxic reaction affecting the hypocretin system. Interestingly, the HLA-association is exceptionally strong in narcolepsy with cataplexy compared to other autoimmune diseases. Possible pathophysiological mechanisms with a more direct effect of HLA and/or TRA@ should be considered for further research.

Effect of neuronal cell loss

Current studies suggest that a large part of the symptoms of narcolepsy can be explained by the loss of hypocretin signaling. However, there is still a possibility that other neuronal cell groups are affected and future studies should be able to address this. The difference between narcolepsy with or without cataplexy and whether this could be attributed to difference in hypocretin signaling should also be further explored.

Provided that hypocretin cell loss is the major cause of the disorder, one important question to address is how this loss gives rise to the symptoms of narcolepsy. This entails understanding the neurobiology of the circuits that regulate sleep-wake cycles, and what effect the loss of hypocretin input has on these circles. This knowledge is also valuable in developing and refining pharmaceutical agents to treat the disease.

Understanding how neural circuits control bodily functions in humans is a very difficult task. The techniques available to do research on humans, such as neuroimaging, are useful although they have limitations in how the circuits can be studied in detail. These techniques will hopefully be further developed in the future to allow for more functional studies in humans. Research using animal models has the potential to provide knowledge in understanding the circuits in a more detailed fashion. There are now several mouse models available where hypocretin signaling in the brain has been blocked; such as mice lacking the hypocretin genes, mice lacking the hypocretin receptors and mice where the hypocretin neurons selectively die in grown-up mice. These mice all display various degrees of the classical symptoms of narcolepsy, and experiments using these mice have provided many new insights into the sleepiness of narcolepsy.

However, much more work is needed to get to the fundamental causes of the symptoms. New upcoming techniques, such as optogenetics, are likely important tools in order to outline the neural circuits that control sleep and wakefulness. Optogenetics is a technique where specific neurons or proteins are genetically targeted to allow for the imaging and/or manipulation of these targets in intact neural circuits, even in living moving animals. These techniques are relevant for the entire neuroscience community interested in understanding neural circuits, and are not being developed specifically to understand narcolepsy, although they can be used in this field in the future. The hope is to pinpoint the influence of hypocretin neuron signaling on various systems and how the lack of hypocretin gives rise to symptoms of sleep fragmentation, cataplexy, hypnogogic hallucinations and so forth.

Furthermore, narcolepsy is often accompanied by a variety of metabolic symptoms, including obesity and depression. The cause of these symptoms is unknown, although hypocretin has been suggested to be involved in food-seeking behavior. Further studies are needed to elucidate the neurobiology behind these symptoms.

2.2 TREATMENT OF NARCOLEPSY

The following section describes the treatment options available today and the proposed focus of future research efforts, based on information obtained from the literature (references can be found in Appendix 4.7), as well as from interviews and a workshop with researchers active in the narcolepsy field.

2.2.1 TREATMENT OPTIONS

At present, there is no curative treatment for narcolepsy. When cataplexy is present, the loss of hypocretin is believed to be irreversible and life-long. Treatment is therefore focused on managing and alleviating the symptoms and their effects. Personalized treatment is always necessary, depending on the symptoms of the affected individual.

Excessive daytime sleepiness and cataplexy can be addressed with prescribed drug treatment. At present two different drugs, Modafinil and Sodium oxybate (Xyrem) have been awarded marketing authorization for the treatment of narcolepsy in adults. Sodium oxybate is a sedative also known as gamma hydroxybuturate (GHB) and can be used to reduce daytime sleepiness and cataplexy while enhancing night sleep. Drugs that have been developed to treat other disorders are also used by clinicians to manage narcolepsy, such as different central stimulating agents and antidepressants. Agents stimulating the central nervous system (e.g. amphetamine-like stimulants) may alleviate excessive sleepiness and antidepressants (tricyclics and serotonin-enhancing drugs, SSRI-drugs) show effect in preventing attacks of cataplexy.

Besides drug therapy, various behavioral strategies are usually applied according to the needs of the affected individual. Daytime naps and improving the quality of nighttime sleep (so called sleep hygiene; exercising before bed-time, dietary restrictions, sleep schedules etc.) are a few examples. Modifications of the physical environment to accommodate resting or sleeping may be necessary, as are safety precautions due to the nature of the symptoms. Social and psychological support in order to maintain a functional life can be offered not only to the affected individual but also his or her family.

Potential drugs under development or evaluation

This report focuses on academic research, and an extensive description of drugs in development is outside our scope. However, a search of publicly available databases regarding clinical trials and orphan drug [3] designation yields some results. In the EU and USA, narcolepsy is classified as an orphan disease (rare medical condition).

[3] An orphan drug is a pharmaceutical substance that has been developed to treat a rare medical condition (called an orphan disease). Orphan drug status is assigned by FDA (USA Food and Drug Administration) in the USA and COMP (Committee for Orphan Medicinal Products) in the EU.

The EudraCT (European Union Drug Regulating Authorities Clinical Trials) database contains all clinical trials that have been initiated in the EU since May 2004. In terms of new drugs not yet available on the market, there are two histamine H3-receptor antagonists/inverse agonists that are registered as having clinical trials in several European countries. One is GSK-189254 developed by GlaxoSmithKline and the other one is Tiprolisant (BF2.649) from the French company Bioprojet. Tiprolisant has progressed to phase III clinical testing and has received orphan drug status in the USA and EU for narcolepsy. Histamine is thought to have important wake promoting properties, and drugs directed against the H3-receptor increase synaptic histamine. These agents are mainly targeting excessive daytime sleepiness, but may have some effect on cataplexy as well.

Another company, Aerial BioPharma, plans to begin phase II testing of their drug ADX-N05 as a treatment for narcolepsy. The drug has also received orphan drug status in the USA. According to the company, preclinical data, clinical data and toxicology show promise in treating excessive daytime sleepiness as well as cataplexy. The agent is thought to activate multiple neurotransmitters including dopamine and noradrenalin, which may explain its effects since several neurotransmitter systems are thought to be affected by the loss of hypocretin.

During the compilation of this report, it was noted that another company, A Carlsson Research AB in Sweden, is preparing an application for a clinical trial of a new drug in treatment of narcolepsy. Their compound has previously shown promising results in clinical trials of mental fatigue, a condition that may accompany a variety of brain disorders such as traumatic brain injury. The hope is that it will prove efficient in treating narcolepsy as well.

A simple web-search identified two companies; Reset therapeutics and Ontochem, which pursue research aimed at developing hypocretin agonists (see discussion around hypocretin replacement therapies below). The status of this research is uncertain. It is possible that also other companies are also working along this line, although not advertising it in public.

2.2.2 KNOWLEDGE GAPS AND THE NEED FOR FUTURE RESEARCH EFFORTS

Targeting the underlying cause or preventing the disease is the ultimate goal for treatment of any disorder. However, the current treatment options for narcolepsy are purely symptomatic in nature. They often require a combination of non-medication based changes of behavior and life style as well as one or several pharmaceutical agents to reach results. Research needed to improve treatment options include mapping of symptoms and quality of life, long-term follow up of treatment efficiency and side effects, and the development of new drugs.

Mapping of symptoms

In order to treat narcolepsy effectively, it is important to have a thorough understanding of the different symptoms of the disease. The range of symptoms when it comes to sleep-related difficulties can vary substantially in different patients, where some suffer only from excessive daytime sleepiness and fragmented night sleep, while others also display cataplectic behavior, hypnogogic hallucinations and sleep paralysis.

Aside from the most prominent sleep-related symptoms, studies show that many patients have problems with obesity, and there have been indications of an accelerated puberty age, suggesting that metabolic and hormonal systems are affected too. Some studies have suggested a possible presence of an autonomic imbalance as well as attention and cognition deficits, although there is no conclusive data. There may also be a higher prevalence of other sleep disorders such as obstructive sleep apnea as well as depression.

Thus, there is a need for additional studies where the symptoms and problems associated with narcolepsy are mapped in a systematic way. This is especially important in regard to the new cases where patients may have acquired narcolepsy as a consequence of the H1N1-vaccine Pandemrix (these will be referred to as Pandemrix-induced narcolepsy in the text). Several of the interviewed clinicians suggest that these patients display a more abrupt disease onset as compared to other narcolepsy patients, as well as more severe symptoms. It will be important to investigate these aspects and compare the Pandemrix-induced cases with other cases.

Formally, there is a possibility that the patients developing narcolepsy in connection to Pandemrix vaccination would have developed the disease at a later time point as a response to another triggering event had they not been subjected to the vaccine at a young age. It is therefore important to study the incidence of new cases of narcolepsy in the following years to see if the number will decrease.

Treatment studies

Overall, there is a need for more longitudinal follow-up studies, where affected individuals are followed over a long period of time. In such studies, symptoms, treatment effects, side-effects as well as health-related quality of life can be addressed. In this work, the establishment of clinical databases will be very important.

Studies have shown that individuals with narcolepsy report having a reduced health-related quality of life. Health-related quality of life may include physical and mental health perceptions, socioeconomic status and social support and relationships. In affected children, the symptoms often cause a substantial decrease in the child's well-being and function. Further studies are needed to elucidate the effects on health-related quality of life of the disease in order to design and implement support measures as well as treatment schemes.

In recent studies the socioeconomic consequences of narcolepsy for individuals as well as for society has been shown to be considerable. Health-care management and interventions may have an effect on quality of life for the patients as well as on the socioeconomic consequences. There are indications that these parameters differ between countries with different health care structures. These issues could be further explored in studies assessing the individual and societal burden of the disease in relation to health-care management. These studies could also include a health economic approach.

There are no drugs approved for the treatment of narcolepsy in children as of yet and no established guidelines for the treatment of the disease in children, due to the lack of clinical studies. However, physicians prescribe drugs off-label to children based on experience. Many clinicians advocate the use of Sodium oxybate (Xyrem) for treatment of narcolepsy in children and would welcome a double-blind controlled trial to evaluate the efficacy and safety of this drug in children. In general, there is a need for well-designed clinical trials to improve treatment in children and adolescents.

New treatment options

Symptomatic treatments

Many of the drugs used to alleviate the symptoms in narcolepsy patients, such as central stimulants and antidepressants, may induce adverse reactions. This is a consequence of their targeting of neurotransmitter systems involved in multiple brain circuits. Some patients also develop a tolerance towards certain drugs, while some drugs have varying effects on different patients. This makes the development of drugs with less adverse side effects, and the development of expanded treatment options, an urgent priority. As researchers understand more about the systems that interact to regulate sleep and wakefulness, and especially the importance of the disrupted hypocretin signaling, the development of tailored drugs for narcolepsy and other sleep disorders will be aided. The development of new drugs is likely to involve academia for the identification of drug targets, the pharmaceutical industry for drug development and drug agencies to provide regulatory advice.

Immunomodulatory treatments

Ultimately, a better understanding of the process that destroys the hypocretin neurons should result in strategies for prevention of the disease. Current evidence suggesting an autoimmune cause of narcolepsy opens up for the possibility to investigate whether treatments to modulate or suppress the immune system at the early stages of the disease can prevent it from progressing. Several studies have attempted to address this by administrating intravenous high-dose immunoglobulin (IVIg) and/or corticosteroids; however the results have not been conclusive and the patient number has been low. Other immune-modulatory treatments could also be an option. The patients need to be treated as soon

as possible after the disease on-set, as it is believed that symptoms appear only after the majority of cells have been destroyed. Thus, the usefulness of these treatments is uncertain; however if successfully combined with earlier diagnosis of the disease they could provide a real opportunity to improve the condition of newly diagnosed patients and decrease the need for symptomatic treatments on a long-term basis. Randomized controlled trials would be valuable to evaluate the efficacy and safety of immunomodulatory treatments.

Hypocretin replacement therapies

From a theoretical viewpoint, an optimal therapy for narcolepsy would be to substitute the missing hypocretin. Experiments administrating hypocretin in animal models of narcolepsy where hypocretin neurons are silenced or destroyed have shown positive results, although there are several challenges with hypocretin-based therapies in humans. The hypocretin peptides themselves do not pass the blood-brain-barrier, which would rule out an oral administration. One approach is to develop small molecular agonists that could pass the blood-brain-barrier and activate the receptors. One issue is the potential loss of hypocretin receptors in the absence of stimulation by hypocretin in humans, and whether the activation of remaining receptors would be able to reverse the symptoms in hypocretin replacement therapies. If hypocretin replacement therapy could be successfully developed, it would be likely to make a substantial improvement of the treatment of narcolepsy.

If administered hypocretin receptor agonists reduce the symptoms of narcolepsy, gene therapy and stem cell transplantation of hypocretin-producing cells could possibly lead to a long-term replacement of hypocretin. These techniques are still under development and have several safety issues to consider, which indicates that these treatments will not be available in the near future.

2.3 MAPPING OF RELEVANT RESEARCH ENVIRONMENTS

2.3.1 BIBLIOMETRIC ANALYSIS

The research area of narcolepsy is relatively small and the research is conducted in a limited number of research environments around the globe. In this report, we have used two approaches to map the geographical spread of research relevant to narcolepsy. Firstly, a bibliometric analysis was performed to systematically identify peer-reviewed articles, leading research groups, and scientific networks through a quantitative and statistical approach. Secondly, the findings from the bibliometric and network analyses were discussed and confirmed in dialogue with the consulted researchers active in the narcolepsy research field.

The bibliometric analysis was carried out using the Swedish Research Council's publication database, which is based on data records licensed from the company Thomson Reuters. The database approximately corresponds to the data available in the Thomson Reuters web service Web of Science. The search is based on fractionized statistics (i.e. the number of co-authors on a publication affects the power of the hit) with a citation window of three years, without self-citations.

The analysis is based on peer-reviewed publications where the search term "NARCOLEPSY" is mentioned in the title, abstract, or as one of the key words. An analysis where the keywords "HYPOCRETIN" and "OREXIN" were included gave twice the amount of publications, showing that in parallel to more specific narcolepsy research a substantial amount of research relating to these peptides has been done since their discovery in 1998. However, in order to analyze research more directly related to narcolepsy, orexin and hypocretin has not been included in the results presented below.

The bibliometric analysis has been used to provide an overview of the research field in terms of where the research is conducted. The picture is not an absolute reflection of the reality, as there are limitations to this technique. Depending on the search criteria (included key words, years and so on) the picture might vary slightly between countries and organizations. In addition, not all journals are included in the database even though it does contain the vast majority of the leading journals in the world.

Volume and citations

The number of scientific publications per year 1982-2011 is presented in Figure 1. As mentioned, the narcolepsy research field is relatively small. However, it is obvious that the research field has advanced between 1998-2000, after the increased knowledge of the hypocretin system and the proofs of reduced levels of hypocretin in narcolepsy patients. Since then, approximately 180 scientific articles have been published each year and the trend is rising.

According to the graph in Figure 1, the Swedish contribution to the narcolepsy research field is limited. Between the years of 1982-2011 Swedish researchers have published only a few publications per year, and no positive effect on the understanding of the hypocretin system can be detected. Sweden's proportion of the total production of narcolepsy publications from the year 2000 is 0.9%, in relation to 1.1% of all publications in the database.

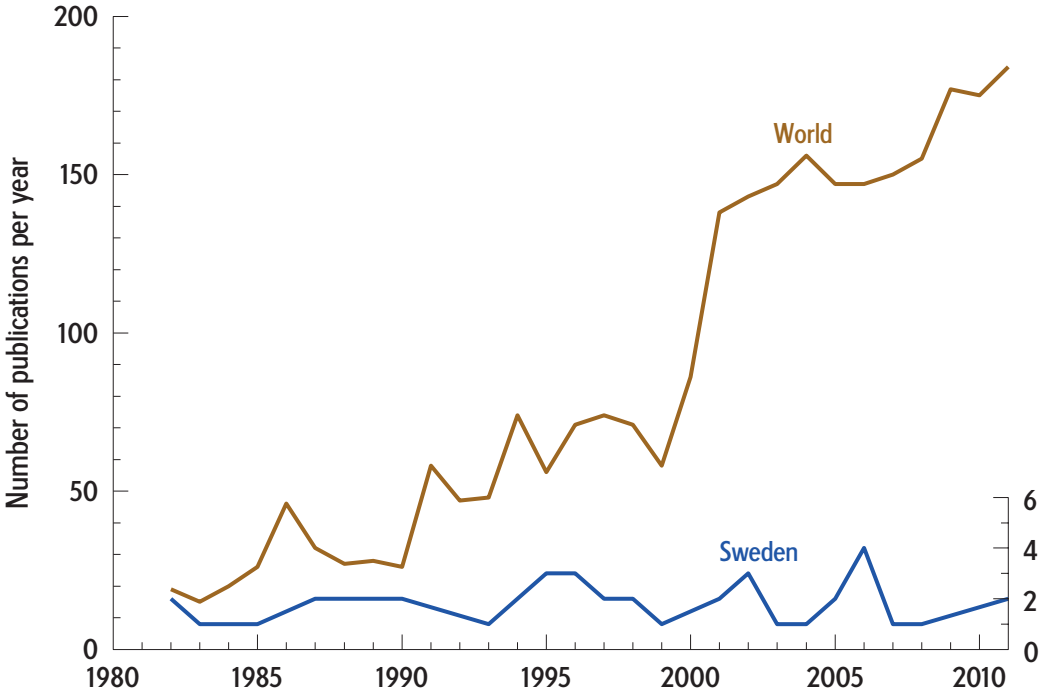

Figure 1. Number of narcolepsy publications per year between 1982-2011 in the world (left y-axis) and in Sweden (right y-axis). There is a high increase in publications in the end of the 20th century due to the discovery of the hypocretin involvement. The Swedish contribution to the narcolepsy literature is constant and relatively low.

The mean citation rate of narcolepsy publications peaked at 2.7 during the years 2000-2001, due to the discovery of hypocretin (Figure 2). For unknown reasons, there was also a peak in citation around 1986. The strong increase in 2000-2001 could mainly be explained by two specific publications. The first was written by two groups at Stanford University and University of Leiden, and the other by several groups at Harvard University and University of Texas. Subsequently, the mean citation value has been around 1.3. The Swedish production is too small to permit any significant conclusions to be drawn, but the mean citation value for the period 2001-2010 is around 1.4, comparable to the world mean citation value.

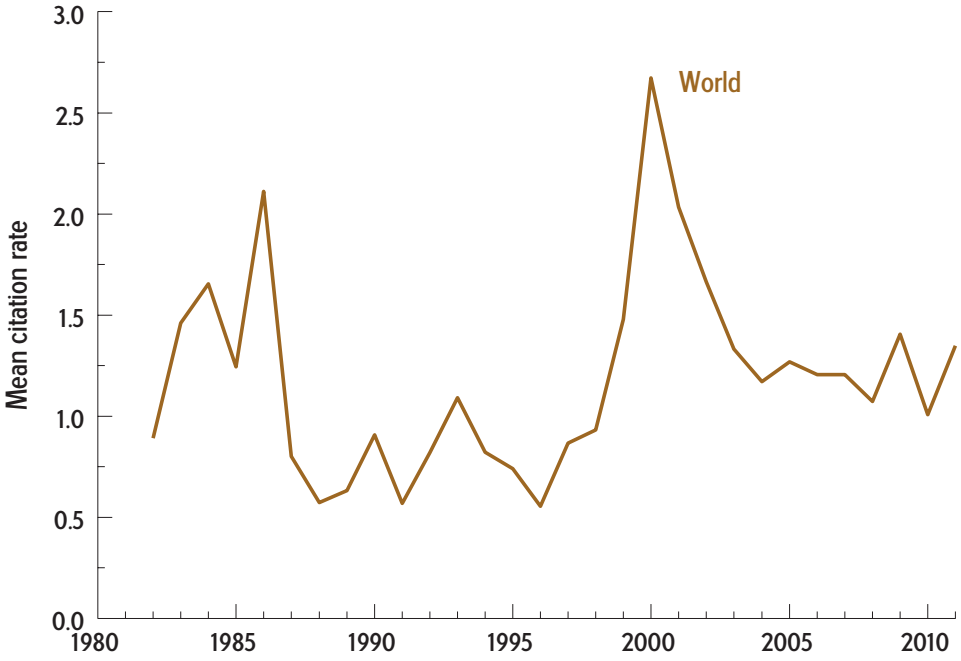

Figure 2. Mean citation rate 1982-2011 of publications relevant to narcolepsy research in the world.

According to the bibliometric analysis, narcolepsy research is dominated by researchers in the USA. (Table 1 shows the top 15 countries). 38% of the publications are written by researchers in the USA, compared to 20% of all research areas. The articles published by the researchers in the USA are cited 60% higher than the world mean citation. The USA is followed by Japan, which publishes 9% of the articles. Thereafter follows Germany, France, United Kingdom, and Italy with 5-6% of the total production. The publications from Japan, France, and United Kingdom are relatively frequently cited (mean citation value ˜1.3), whilst the German and Italian publications are cited less (0.95). The Scandinavian countries are further down the list, with Denmark at position 18 (14 publications), followed by Finland (position 21, 9 publications), Sweden (position 23, 8 publications) and Norway (position 24, 6 publications).

Table 1. Number of published narcolepsy articles by the leading countries 2002-2011.

Country	*Number of publications*	*Ratio of the total production*	*Mean citation value*
USA	637	38.1%	1.6
Japan	157	9.4%	1.2
Germany	105	6.3%	0.9
France	97	5.8%	1.4
United Kingdom	83	5.0%	1.1
Italy	82	5.0%	0.7
Switzerland	73	4.4%	1.3
Canada	56	3.4%	1.2
Netherlands	49	2.9%	1.2
Spain	47	2.8%	0.7
Australia	28	1.7%	1.2
Korea	24	1.5%	0.9
Mexico	23	1.4%	0.3
China	20	1.3%	1.0
Brazil	20	1.2%	0.3

The USA is world leading in the narcolepsy research field in terms of publications and the top two universities in the world are located in the USA (Stanford and Harvard) (Table 2). This is further demonstrated by the fact that ten of the universities/companies on the top 20 list are located in the USA. Stanford contributes 13% of the publications in the USA, and 5% of the publications in the world. Outside of the USA, University of Bologna is the most productive research center, followed by Leiden University and the University hospital in Zürich. The presence of one company (Cephalon Inc, the producer of Modafinil) and one private non-profit research institute (Scripps) on the list is noteworthy.

Table 2. The organizations which published most articles in the narcolepsy field 2002-2011.

Country	*Organization*	*Number of publications*	*Mean citation value*
USA	Stanford Univ	85	1.6
USA	Harvard Univ	31	1.6
Italy	Univ Bologna	29	0.7
USA	Univ Calif Los Angeles	25	2.1
Netherlands	Leiden Univ	22	1.1
Switzerland	Univ Zurich Hosp	19	1.3
USA	Univ Penn	17	1.8
Japan	Univ Tsukuba	15	2.5
USA	Yale Univ	14	1.9
USA	Univ Texas	14	2.2
USA	Mayo Clin	12	0.9
USA	Scripps Res Inst	11	1.4
Czech Republic	Charles Univ Prague	10	1.1
USA	Cephalon Inc	10	1.2
Japan	Akita Univ	10	1.0
United Kingdom	Univ Oxford	10	1.6
Canada	McGill Univ	9	2.6

Collaboration networks

Figure 3, displays the collaboration network of the leading organizations during the period 2006-2011 (the layout is created in Pajek [4]). Figure 3 and Table 3 are based on whole counts of articles and not fractionalized statistics, as compared to Table 2. In addition, Table 2 display results from 2002-2011. This explains why Table 2 and Table 3 display small differences. The network is limited to organizations with at least eight publications during this period. No Swedish organization fulfilled this criterion.

Stanford's position in the field is confirmed by the network analysis, where a large collaboration pattern is displayed, especially with Bologna, but also with a large number of other groups around the globe. It is also clear that some European countries collaborate extensively and that collaborations within a country are more frequent than groupings between countries.

[4] V. Batagelj, A. Mrvar: Pajek – Program for Large Network Analysis. http://vlado.fmf.uni-lj.si/pub/networks/pajek

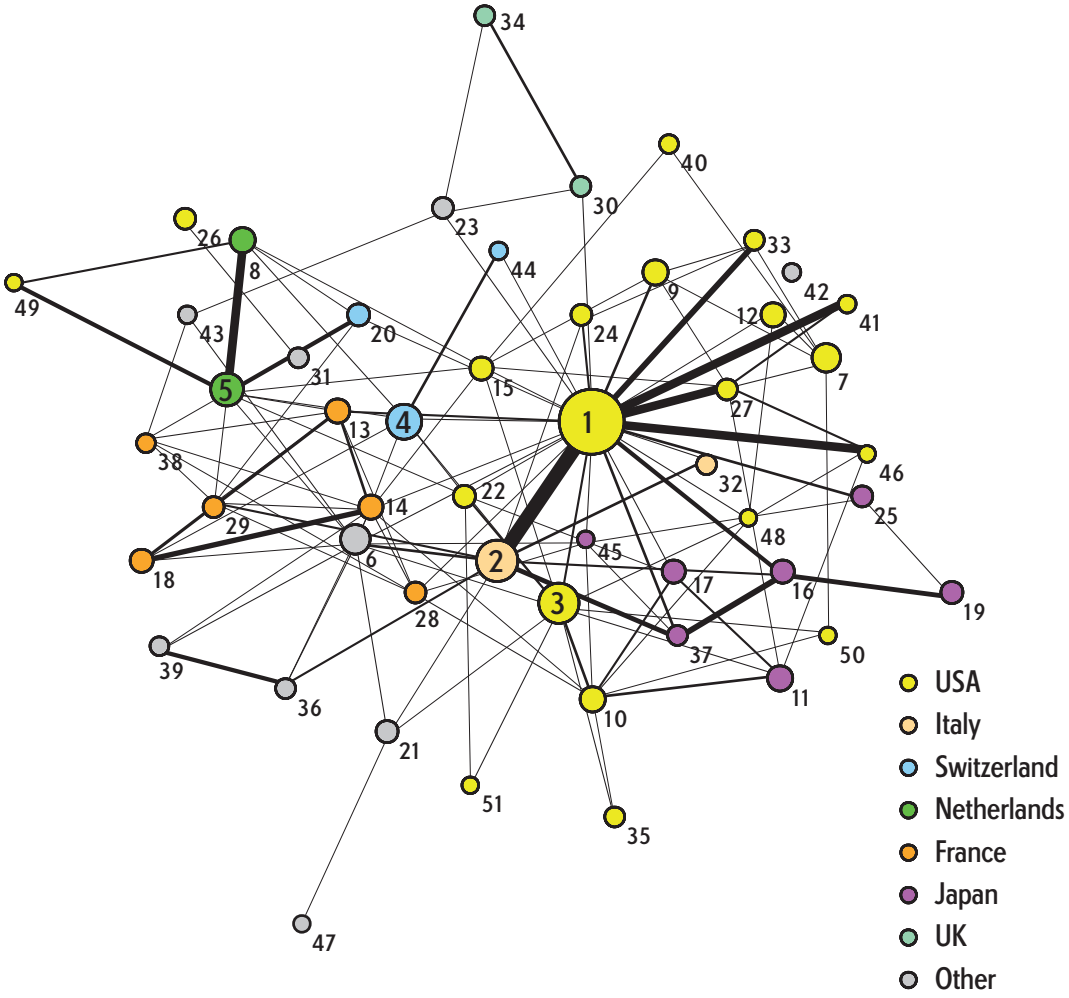

Figure 3. Collaboration network of organizations producing at least eight publications in the field of narcolepsy during the period 2006-2011. The color of the circle indicates the country of the organization and the number indicates the name (see Table 3). The area of the circle corresponds to the number of publications, and the thicknesses of the lines are related to the number of collaborations between the two organizations.

Table 3. The numbers correspond to the organizations in Figure 3.

Code	*Name*	*Code*	*Name*
1	Stanford Univ, USA	27	Univ Washington, USA
2	Univ Bologna, Italy	28	Univ Lyon 1, France
3	Harvard Univ, USA	29	Chu Montpellier, France
4	Univ Zurich Hosp, Switzerland	30	Univ Oxford, United Kingdom
5	Leiden Univ, Netherlands	31	Univ Fed Sao Paulo, Brazil
6	Charles Univ Prague, Czech Republic	32	Univ Roma La Sapienza, Italy
7	Univ Penn, USA	33	Univ Texas, USA
8	Radboud Univ Nijmegen, Netherlands	34	Univ Cambridge, United Kingdom
9	Univ Calif Los Angeles, USA	35	Merck Res Labs, USA
10	Univ Texas Sw Med Ctr Dallas, USA	36	University of Copenhagen, Denmark
11	Kanazawa Univ, Japan	37	Univ Tokyo, Japan
12	Cephalon Inc, USA	38	Hop Gui de Chauliac, France
13	Inserm, France	39	Glostrup, Denmark
14	Hop La Pitie Salpetriere, France	40	Johns Hopkins Univ, USA
15	Mayo Clin, USA	41	Univ Wisconsin, USA
16	Tokyo Inst Psychiat, Japan	42	Sungkyunkwan Univ, Korea, Republic of
17	Univ Tsukuba, Japan	43	Univ Montreal, Canada
18	Univ Paris 06, France	44	Univ Zurich, Switzerland
19	Japan Somnol Ctr, Japan	45	Tohoku Univ, Japan
20	Univ Lausanne, Switzerland	46	Univ Calif San Francisco, USA
21	Univ Marburg, Germany	47	Univ Nacl Autonoma Mexico, Mexico
22	Beth Israel Deaconess Med Ctr, USA	48	Yale Univ, USA
23	Mcgill Univ, Canada	49	Netherlands Inst Neurosci, Netherlands
24	Univ Minnesota, USA	50	Med Univ S Carolina, USA
25	Akita Univ, Japan	51	Univ Michigan, USA
26	Univ Toronto, Canada		

2.3.2 CONCLUSIONS ON INTERNATIONAL RESEARCH ENVIRONMENTS

The bibliometric analysis shows that much of the narcolepsy research is carried out in the USA, which is confirmed in the interviews with researchers from several different laboratories in the world. Japan also has a considerable amount of research in this area, as do several countries in Europe. It appears that much of the basic research concerning the etiology and basic science of narcolepsy is performed in the USA, while a major part of the clinical research is conducted in Europe. The higher citation values of the articles from the USA could be explained either by a higher impact of the science or that basic research is in general more cited than clinical science.

The narcolepsy research community agrees that Stanford is the leading research center, with a large number of collaborations. The large number of DNA samples, which have to be collected in order to perform genetic screens to identify new gene variants predisposing for narcolepsy, could partly explain the frequent associations with other labs. The bibliometric analyses and interviews indicate that collaboration is fairly extensive, both between organizations within countries and internationally. The interviewed researchers also mentioned a number of centers in Europe with strong research in the narcolepsy field in Italy, France, the Netherlands and Switzerland. This was largely confirmed by the bibliometric analysis. An association of European narcolepsy researchers has been formed, the European Narcolepsy Network, with the goal of supporting European narcolepsy research, optimizing patient care and facilitating the development of databases.

China is ranked fairly low in the analysis, but numerous researchers agree that the research in China is expanding especially due to a big narcolepsy center in Beijing that collects all narcolepsy patient samples from the north part of the country.

2.3.3 SWEDISH NARCOLEPSY RESEARCH

Narcolepsy research conducted in Sweden appears very limited, as verified by the bibliometric analysis and the interviews with Swedish and international researchers. However, it is complicated to perform a relevant mapping of current Swedish research in a quantitative way since the bibliometric analysis relies on peer-reviewed scientific publications. The results of the Swedish research performed today will not be visible in the statistics until a few years from now.

Compared to many other European countries, there has been a lack of neurologists in Sweden with a specific research focus on narcolepsy. However, after the extensive increase of narcolepsy cases after the vaccination with Pandemrix during the H1N1 flu 2009/2010, some clinicians who have met an increasing number of patients have started up research in this area. In discussion with the Swedish Medical Products Agency (MPA) and looking at the projects applying for grants from the Swedish Research Council, a small number of groups have been identified residing in Gothenburg, Linköping, Örebro and Stockholm. Representatives from these groups have been interviewed regarding their planned research.

The Swedish Research Council and the Academy of Finland made a joint effort in 2012 to support clinical research. In this call, one Finnish/Swedish collaboration project on narcolepsy was supported among the four granted projects. The narcolepsy project was funded with a total amount of 1 million €, where 486 000 € was assigned the Swedish collaboration partner from the Swedish Research Council.

Research projects initiated by The Medical Products Agency

The MPA in Sweden has initiated a research effort to elucidate the association between Pandemrix and narcolepsy. The studies are carried out by the MPA and a number of groups at the Karolinska institute and the Swedish Institute for Communicable Disease Control. The MPA has funded these projects with approximately 1 million €. Part of the research is carried out in collaboration with Finnish researchers. Researchers with strong backgrounds in several different disciplines with focus on neuroimmunology and infectious immunology have been connected to this initiative, which is carried out during 2012 and 2013.

The main focal points of this research are to:

1. Perform a case-control study by interviewing patients and healthy individuals. The patients will be characterized and possible associations with Pandemrix, the flu, other infections and diseases in the family etc. will be mapped.
2. Collect blood samples from patients in order to study the genetic (e.g. HLA variants) and immunological factors (e.g. auto-antibodies, antigens etc.) that are of importance for developing narcolepsy. The role of vaccines and the flu in triggering the disease will also be investigated.
3. Execute a register-based study to follow up seven counties/health-care regions in Sweden in order to compare 3-4 million vaccinated individuals to 2-3 million unvaccinated individuals, and their risk of developing neurological and autoimmune diseases. This study will be performed using a larger number of patients and a longer observation period compared to a previous study in Stockholm County performed by the MPA.
4. A study where possible associations of narcolepsy cases in Sweden, the epidemiological incidence of the H1N1 flu 2009, and the vaccination status during the pandemic will be performed and analyzed by SMI in collaboration with the MPA. The aim of this study is to try to understand the large regional differences of affected narcolepsy individuals in Sweden after the vaccination.

Swedish national quality narcolepsy register

The MPA has worked together with clinical neurologists to establish a national quality register, to include all Swedish narcolepsy patients regardless of whether their disease was triggered by the vaccination or not. The register will make it possible to follow patients and the results of their treatments over time and increase the understanding of the disease. At present, the register is not linked to a biobank. However, samples are being collected within the MPA initiated studies, and may be connected to the register in the future. The Swedish Association of Local Authorities and Regions fund the register.

3 CONCLUSIONS

This section summarizes the knowledge gaps and discusses possible future directions in narcolepsy research, based on the information received from the interviewed researchers, workshop participants and consulted authorities and organizations, which will all be referred to as the consulted experts in the below sections.

3.1 THE MAJOR KNOWLEDGE GAPS

A number of knowledge gaps have been identified concerning the etiology and treatment of narcolepsy. These have been subdivided into five different topics; cause of neuronal cell loss, effect of neuronal cell loss, mapping of symptoms, treatment studies and new treatment options. Some of the knowledge gaps could be addressed and answered within a fairly short time perspective, while others may take a long time to resolve. In a long-term perspective, the goal is to understand the underlying mechanisms of the disease to be able to diagnose, prevent and cure the disease as early as possible. In a shorter time perspective, research on how affected patients can be treated in the best way will be valuable.

3.1.1 ETIOLOGY

Although significant advances have been made during the past decade, the cause of narcolepsy is still unknown. There are a number of knowledge gaps that needs to be filled in order to pinpoint the specific mechanisms underlying the cause of the disease. Future research should be aimed at understanding the specific cause of the neuronal cell loss and what effect the cell loss has on the neuronal circuits in the brain giving rise to the symptoms of the disease.

Cause of neuronal cell loss

- ***Genetic predisposition***

Further genetic studies are needed in order to identify additional gene variants that can give further insights into the underlying mechanism of the disease. To be able to perform these large-scale genetic studies, it is essential for researchers to collaborate on an international basis, where samples and patient data can be shared in databases and biobanks.

- ***Other risk factors***

Current knowledge regarding risk factors other than genetic does not explain why some individuals develop the disease and some do not. Large-scale epidemiological studies are needed to address this issue. These studies are important as a first step to map the incidence of the disease to find plausible correlations that further studies can build on to pin point risk factors. It should be noted however that the low number of individuals affected and the delay in time of the diagnosis will make it difficult to identify risk factors for narcolepsy.

- ***Immunological mechanism***

Further basic immunological studies are needed with the aim to identify autoantibodies, antigen or cells reactive against the hypocretin cells to firmly prove the autoimmune origin of the disease. In addition, studies exploring signs of inflammation in tissue obtained from autopsy material are needed, as the current studies are few and inconclusive. To further prove an autoimmune origin of narcolepsy and to understand the disease process, it would be valuable to be able to re-create the disease events in animal models such as mice. These mice could for example be engineered to express human predisposing genes and exposed to triggering events such as Pandemrix. These may also be used to evaluate new treatment options.

Effect of neuronal cell loss

- ***Extent of cell loss***
  In order to thoroughly address the extent of hypocretin cell death in narcolepsy patients and whether other cell populations in the brain are affected, there is a need to perform studies on autopsy material. Such studies would provide detailed information on the cellular changes occurring in patients with and without cataplexy.
- ***Function of the neural circuitry***
  In order to elucidate how the loss of neurons can give rise to the symptoms of narcolepsy, there is a need to understand the neural circuitry involved. Neuroimaging (visualization of information processing in centers of the brain) in humans can provide some information on this; however this technique has its limitations on how much detail that can be visualized. In order to study neural circuits in a more detailed fashion, studies using animal models such as mice are valuable. In these models, new upcoming techniques such as optogenetics, with which specific neurons can be activated or inhibited, may contribute to the understanding of which neural circuits that are affected and their function.

3.1.2 TREATMENT

The treatment options available for narcolepsy patients are focused on relieving the symptoms of the disease. In many cases, they are not enough for the patient to experience normalization and the side effects are often troublesome. Therefore, there is a need to expand the treatment options for patients with narcolepsy as well as to further refine the existing treatments. In addition, mapping the symptoms in a more systematic way will be helpful in designing future treatments.

Mapping of symptoms

- ***Difference between Pandemrix-induced cases and others***
  The most compelling evidence of an environmental factor having triggered narcolepsy is the recent connection between Pandemrix vaccine and the onset of the disease. It is therefore of interest to investigate the symptoms of these cases and compare with other cases to see whether the symptoms and the progress of the disease appear similar. In connection to this, genetic studies can be performed to look at the genetic predisposition of these individuals. It is also important to study the incidence of narcolepsy cases over a long time period to see if the number of new cases will decrease.
- ***Non-sleep related symptoms***
  There is a need for additional studies on non-sleep related symptoms, such as obesity, earlier puberty onset, metabolic changes, hormonal changes, attention and cognition deficits and depression in narcolepsy patients.

Treatment studies

- ***Longitudinal studies on treatments, side-effects and quality of life***
  In general more longitudinal follow-up studies, where individuals are followed during a long period of time, are needed to address questions such as treatment effects, side effects and health related quality of life. There is a lack of systematic studies on this, especially in children who are treated with drugs that have only been tested on adults. Studies to elucidate the effects on health-related quality of life of the disease will be important in order to design and implement support measures as well as treatment schemes.
- ***Clinical studies in children***
  There is a need for well-designed clinical trials to improve treatments in children and adolescents. Since these studies are lacking, there are no established guidelines for the treatment of the disease in children and various drugs are prescribed off-label based on experience. It would be valuable if

new pharmaceutical treatments would be evaluated by the licensing company also in children when introduced to the market through applying the regulation of Pediatric Investigational Plans (PIPs) [5].

- ***Disease burden and health-care management of disease***
  There is a need for further studies on health-care disease management of narcolepsy and the effects on quality of life as well as socioeconomic consequences. Improving and evaluating health-care management of the disease can potentially reduce the burden of the disease on an individual and societal level. These studies could also include a health economics approach.

New treatment options

- ***Symptomatic treatments***
  As many of the current drugs have problems with adverse side effects, there is a need to develop new symptomatic treatments of narcolepsy. This work is likely to be aided by advances in the understanding of sleep-wake regulation. Collaboration with regulatory agencies could facilitate the development of new drugs and other therapeutic interventions, possibly by the use of the orphan drugs or advanced therapies regulations.
- ***Immunomodulatory treatments***
  Double-blind randomized controlled trials with larger number of patients would be valuable to investigate whether immunomodulatory treatments could prevent the disease from progressing in early-diagnosed patients. If the treatment turns out to be successful it could improve the condition of newly diagnosed patients and decrease the need for symptomatic treatments on a long-term basis. However, collaborations between research groups are needed to collect a high enough number of patients which have been diagnosed close to disease on-set.
- ***Hypocretin replacement therapies***
  Since the most common hypothesis is that hypocretin appears to be responsible for symptoms associated with narcolepsy with cataplexy, a potential future treatment would be to replace the missing hypocretin. An extensive pharmaceutical drug development approach is needed, probably involving the development of hypocretin receptor agonists (small synthetic molecules able to bind and activate the receptors). In a longer perspective, gene-therapy or stem cell transplantation of hypocretin-producing cells could possibly ensure a long-term replacement of hypocretin. However, these techniques are still in their infancy and further basic research is needed to demonstrate an effect.

3.2 DISCUSSION ON FUTURE DIRECTIONS FOR NARCOLEPSY RESEARCH

3.2.1 THE GENERAL PERSPECTIVE

A large part of the research in the narcolepsy field appears to be conducted by a limited number of groups in the world. It is clear that a considerable amount of the research is performed in the USA, especially regarding basic research related to the etiology of narcolepsy. In terms of clinical narcolepsy research, there are a number of prominent groups in Europe as well as in the USA. Japan and China also has strong research in the field. In general, although narcolepsy is a rare disease, the research field has made considerable progress during the last decades.

Many of the consulted experts emphasize the importance of national centers with centralized health-care to give the patient the best possible care, and to facilitate research on narcolepsy patients as well as patients with other rare diseases. In some countries, such as France and Italy, health care is organized in

[5] A development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorization of a medicine for children. To be filed to the European Medicines Agency.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&mid=WC0b01ac0580025b91

this fashion and often involves both child and adult neurologists, as well as psychologists, who are able to give their patients a common diagnose procedure in all centers. According to the consulted experts, such an organization should facilitate registration and storage of samples in a uniform way and the build-up of reliable clinical databases with patient information in connection with biobanks.

Even though national centers might be a step towards a more organized research on narcolepsy, there are a limited number of patients in every country. Therefore, international collaboration is a key issue in addressing many of the knowledge gaps in the field and to reach a high enough patient number in many of the studies involving narcolepsy patients. Such studies include treatment studies in children, follow-up studies of treatment effects and of health-related quality of life and immunomodulatory trials. International collaboration is also needed in epidemiological studies addressing the incidence of the disease, as comparing different regions and countries can give valuable clues concerning risk factors and triggers.

International collaboration can be facilitated by common diagnose procedures and similar procedures for collection of data. The consulted experts have expressed that information in national databases should be comparable and exchangeable between countries. Another option is a common European database for all narcolepsy patients. The European Narcolepsy Network has been formed with the goal to develop standardized core databases and improving diagnostic and therapeutic measures. Since narcolepsy is a rare disease, collecting the limited biological material for storage in biobanks would also be valuable, especially if this can be done in connection to international databases.

The consulted experts have conveyed the need for funding to stimulate international collaboration and to facilitate the work towards standardization of data and creation of databases. One suggestion that has been brought up is that research councils in different countries could co-fund a common call in urgent areas in need of collaboration.

One weakness that the researchers identify in this research field is the shortage of immunological competence needed to address the presumable autoimmune cause of the disease. However, narcolepsy research has come into focus due to the recent association with Pandemrix, which might open up for more collaboration across fields. One suggestion raised by the consulted experts is some kind of fellowship program (such as post-docs, clinicians and guest researchers) where the exchange of research competence between fields and countries could be facilitated as well as general collaboration between research groups.

3.2.2 THE SWEDISH PERSPECTIVE

The bibliometric analyses and interviews with researchers show that Sweden has had a limited amount of research on narcolepsy. This may be partly due to a lack of Swedish neurologists with a specific research focus on narcolepsy and that the disease is relatively rare. Current research that has not been published yet is difficult to evaluate technically. However, some research projects have started recently, but the scientific outcome of this research cannot be assessed yet. The MPA in Sweden has initiated a number of studies in collaboration with researchers at the Karolinska Institute and the Swedish Institute of Communicable disease in an effort to address the reason for the association between Pandemrix vaccine and narcolepsy. Some of these studies are aimed at understanding the immunological aspects of this issue. The studies are planned to be completed during 2013. The researchers involved in the MPA-initiated studies are specialized in other fields of research, making it uncertain whether they will continue with these studies without the financial support of the MPA. However it is possible that if these studies generate important information relating to more general issues in immunology and genetics there will be an interest to explore this further. Thus, when these studies are finalized a discussion with involved stakeholders on how to proceed would be valuable.

As the current research efforts in Sweden are few, Sweden has limited possibilities to address the knowledge gaps in the narcolepsy research field. However, the opportunity in Sweden to address some specific research questions involving narcolepsy has been emphasized by the consulted experts, particularly in relation to the recent increase in the number of narcolepsy patients. There is a need to

map the symptoms in Pandemrix-induced patients compared to other narcolepsy patients, especially since clinicians have indicated that Pandemrix-induced patients might display more severe symptoms. Furthermore, long-term follow-up studies of treatment effects, side effects and of quality of life could be addressed.

The discussion on prerequisites and opportunities for Swedish research below is based on input from the consulted experts.

National registries

Sweden has an advantage due to its many registries and databases with information on the population. These are based on the social security number of each individual in the population, making it possible to link different databases and registries within different fields, such as health care and demographics. This unique infrastructure makes Sweden, and other Nordic countries with similar systems, especially suitable for epidemiological studies and there are strong researchers within this field. One opportunity to make use of the strengths in Sweden and the Nordic countries could be to perform epidemiological studies to systematically map the incidence of narcolepsy, to find correlations that can be further explored in order to identify risk factors for the disease. Few studies have addressed this issue as of yet. Due to the rareness of the disease, international collaboration would be of value in these studies.

National quality registries within the Swedish health care system have been established during the last decades. A national quality registry is a database that contains individualized data concerning patient problems, medical interventions, and outcomes after treatment. These are built by specialists within the Swedish health care system and often concern a specific disease. The MPA has initiated the establishment of a registry to include all Swedish narcolepsy patients, regardless of their disease being triggered by vaccination or not. This registry can be used to perform long-term follow-up studies of treatment effects, side effects and of quality of life, in particular in the follow-up and monitoring of the Pandemrix-induced narcolepsy cases. This would require adequate commitment and resources in order to develop and maintain the registry.

Also, the consulted experts have emphasized the importance of connecting registries and databases with biobanks, where biologic material could be stored. This would in a long-term perspective enable research involving for example genetics or immunology.

Organization of care and research

It is clear that the research on narcolepsy has been limited in Sweden. The consulted experts have therefore conveyed that structural interventions might stimulate and facilitate Swedish research in this field.

Many of the internationally established research groups in the narcolepsy field work in close connection with the national centers for care of narcolepsy patients. Within the region or country, care of many of the patients is centralized to a limited number of centers. The consulted experts have expressed the value of such an organization to facilitate research within this field, as the patients are relatively few and many of the studies require a large patient material. Care of narcolepsy patients in Sweden is not organized in such a fashion today, and future research efforts in this field might benefit from a similar structure. In such a structure, a limited number of clinicians are responsible for the care and treatment of patients in a certain region. Of interest in this context is that the National board of Health and Welfare (Socialstyrelsen) has recently handed in a proposal for a national strategy on rare diagnoses to the government. This has been issued as a response to a European project named Europlan, which has outlined recommendations for the development of national plans for rare diseases [6].

Studies addressing issues such as long-term follow-up of treatments that require documentation of patients in a national registry could also benefit from a smaller number of specialists being responsible

[6] Sällsynta sjukdomar - En slutrapport om nationell funktion och förslag till strategi (2012-10-31) http://www.europlanproject.eu/_newsite_986987/Resources/docs/2008-2011_2.EUROPLANRecommendations.pdf

for the treatment and documentation of patients in Sweden. Additionally, the collection of biobank material might be easier if the patients are handled by a smaller number of clinicians and centers.

The establishment of organized centers with clinicians responsible for treatment and research related to narcolepsy could also improve the collaboration between research groups in Sweden. This may also facilitate the flow of information to patients in regard to care and research on narcolepsy, as well as promoting the understanding of research in this field. Regional centers might also facilitate the recruitment of patients to clinical trials of new drugs.

Although the commitment and interest in doing research on narcolepsy has to stem from the researchers, increasing the number of patients treated by specific clinicians may improve the possibilities to pursue research in this field. However, the consulted experts generally express the need for funding and time dedicated to research in this field. The few research groups that have started doing research in this area in Sweden have also expressed a need for increased coordination of the efforts, such as a forum where they can meet and exchange ideas and experiences.

International collaboration

Sweden, along with Finland and Ireland, has the most cases of Pandemrix-induced narcolepsy patients, while other countries in Europe mostly have narcolepsy cases that lack this connection. Sweden could contribute to the advancement of narcolepsy research by making samples and data from Swedish Pandemrix-induced narcolepsy patients accessible for international collaboration, and participate in the work towards making data more internationally comparable to allow for sharing of data. The experts also conveyed that increasing Swedish collaboration with researchers in other countries may advance and improve the quality of Swedish research. One possibility could be to earmark funding for collaborative narcolepsy research efforts between Swedish and international researchers. This may also be achieved by funding of joint calls with funding agencies in other countries on an international, European or Nordic level, or by the funding of international exchange programs.

Another point that has been emphasized is that Nordic countries generally apply common procedures and have similar national registries. One opportunity is to increase collaboration on the Nordic level, for instance by performing parallel analyses of patient material and databases to increase the scientific impact of the studies. The consulted experts have suggested that a Nordic symposium with narcolepsy researchers and clinicians could be a good starting point for such collaboration.

4 APPENDICES

APPENDIX 4.1 THE GOVERNMENTAL ASSIGNMENT

REGERINGEN

Regeringsbeslut **I:5**

2011-11-03 U2011/6112/F

Utbildningsdepartementet

Vetenskapsrådet
Box 1035
101 38 Stockholm

VETENSKAPSRÅDET
Ink 2011 -11- 22
Dnr: 111-2011-7704
Handl: Mats Ulfendahl

Kopia: Marianne Samuelsson
Agnetha Curtsdt
Elisabet Rosdahl

Kartläggning av forskning med relevans för uppkomst och behandling av sjukdomen narkolepsi

Regeringens beslut

Regeringen uppdrar åt Vetenskapsrådet att kartlägga forskning med relevans för uppkomst och behandling av sjukdomen narkolepsi. Vetenskapsrådet ska också med utgångspunkt från kartläggningen analysera kunskapsluckor inom området.

Vetenskapsrådet tilldelas 600 000 kronor för att påbörja kartläggningen. Kammarkollegiet ska utbetala medlen 2011 engångsvis efter rekvisition från utgiftsområde 9 Hälsovård, sjukvård och social omsorg, anslag 1:6 Bidrag till hälso- och sjukvård, anslagspost 14 Patientsäkerhet. Rekvisitionen ska hänvisa till bidragsbeslutets diarienummer.

En redovisning av uppdraget ska lämnas till Regeringskansliet (Utbildningsdepartementet och Socialdepartementet) senast den 31 december 2012.

Uppdraget ska utföras efter samråd med berörda myndigheter såsom Läkemedelsverket och Smittskyddsinstitutet. Uppdraget ska vidare ske efter samråd med enskilda experter och myndigheter på såväl nationell som internationell nivå.

Ärendet

Läkemedelsverket har genomfört två studier om ett eventuellt samband mellan vaccination med Pandemrix och insjuknande i narkolepsi. Resultaten från studierna visar att risken att insjukna i narkolepsi är högre för vaccinerade barn och ungdomar än för ovaccinerade. Utfallet är i linje med resultaten från liknande finska studier. Studierna kan emellertid inte förklara orsaken till den ökade risken för narkolepsi som observerats. Det finns därför behov av att kartlägga forskning med relevans för uppkomst och behandling av sjukdomen narkolepsi och

Postadress 103 33 Stockholm
Besöksadress Drottninggatan 16
Telefonväxel 08-405 10 00
Telefax 08-21 68 13
E-post: registrator@education.ministry.se

genomföra en analys av kunskapsluckor på området, samt med hänsyn till det i analysen framkomna kunskapsluckorna prioritera framtida fortsatta insatser. Med hänsyn härtill får Vetenskapsrådet i uppdrag att kartlägga forskning med relevans för uppkomst och behandling av sjukdomen narkolepsi samt att med utgångspunkt från kartläggningen analysera kunskapsluckor inom området.

På regeringens vägnar

Jan Björklund

Maria Wästfelt

Kopia till

Kammarkollegiet
Läkemedelsverket
Smittskyddsinstitutet
Socialstyrelsen
Sveriges Kommuner och Landsting
Narkolepsiföreningen Sverige

APPENDIX 4.2 THE SWEDISH RESEARCH COUNCIL'S CONSULTATION PARTNERS

ORGANISATIONS AND REPRESENTATIVES

Läkemedelsverket (the Medical Products Agency, MPA): **Nils Feltelius**
Smittskyddsinstitutet (the Swedish Institute for Communicable Disease Control): **Annika Linde**
Läkemedelsförsäkringen (The Pharmaceutical Insurer): **Anders Öhlén**
Sveriges Kommuner och Landsting (the Swedish Association of Local Authorities and Regions): **Åsa Åkerman**
Socialstyrelsen (the National board of Health and Welfare): **Susanne Bergman**

APPENDIX 4.3 LIST OF INTERVIEWED INTERNATIONAL RESEARCHERS

Claudio Bassetti, The Neurology department, University Hospital of Bern, Switzerland
Yves Dauvilliers, Department of Neurology, Hôpital Gui de Chauliac, INSERM, France
Poul Jennum, Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, University of Copenhagen, Denmark
Emmanuel Mignot, Stanford Center for Sleep Sciences and Medicine, Stanford University Medical School, the USA
Seiji Nishino, Sleep and Circadian Neurobiology Laboratory, Stanford University, the USA
Guiseppe Plazzi, Department of Neurological Sciences, University of Bologna, Italy
Thomas Scammell, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, the USA
Masashi Yanagisawa, Howard Hughes Medical Institute, University of Texas, the USA

APPENDIX 4.4 LIST OF INTERVIEWED SWEDISH RESEARCHERS

Peter Bergman, Department of Laboratory Medicine, Karolinska Insitutet, Stockholm
Karin Blomberg, School of Health and Medical Sciences, Örebro University, Örebro
Maria Engström, Department of Medical and Health Sciences, Linköping University
Tove Hallböök, Pediatric Neurology, Queen Silvia Children´s Hospital, Gothenburg
Tomas Hökfelt, Department of Neuroscience, Karolinska Institutet, Stockholm
Krister Kristensson, Department of Neuroscience, Karolinska Insitutet, Stockholm
Tomas Olsson, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm
Lars Palm, Department of Pediatrics, Skåne University Hospital, Malmö
Attila Szakacs, Children's clinic, Halmstad Hospital Halland, Gothenburg

APPENDIX 4.5 WORKSHOP PARTICIPANTS

Yves Dauvilliers, Department of Neurology, Hôpital Gui de Chauliac, INSERM, France
Poul Jennum, Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, University of Copenhagen, Denmark
Gert Jan Lammers, Department of Neurology, Leiden University Medical Center, The Netherlands

Guiseppe Plazzi, Department of Neurological Sciences, University of Bologna, Italy
Mehdi Tafti, Center for Integrative Genomics, University of Lausanne, Switzerland
Markku Partinen, Department of Clinical Neurosciences, University Central Hospital, Helsinki, Finland
Tomas Olsson, Department of Clinical Neuroscience, Karolinska Institutet, Sweden
Tove Hallböök, Pediatric Neurology, Queen Silvia Children´s Hospital, Gothenburg, Sweden
Nils Feltelius, the Medical Products Agency, Sweden

APPENDIX 4.6 PANDEMRIX AND NARCOLEPSY – MAPPING OF INTERNATIONAL STUDIES

During the swine flu (H1N1) pandemic 2009 and 2010, around 31 million individuals in 47 countries were vaccinated with the flu vaccine Pandemrix. The use of Pandemrix was authorized within the EU in September 2009.

In August 2010, following reports of a higher than expected number of narcolepsy cases in connection with swine flu vaccination in Sweden and Finland, the European Medicines Agency (EMA) initiated a review of reported data on the association of narcolepsy with the Pandemrix vaccination. On July 21 2011 EMA, through its Committee for Medicinal Products for Human Use (CHMP), gave the recommendation that administration of Pandemrix to individuals below 20 years of age should be restricted to risk groups and only when seasonal flu vaccine was not available. EMA considered that the epidemiological studies in Sweden and Finland indicated that administration of Pandemrix increased the risk of narcolepsy with six to thirteen times the average risk in children and adolescents below 20 years of age.

EMA based its recommendation on available data on the association of narcolepsy and Pandemrix and the overall risk-benefit balance for the vaccine. The data included the results of epidemiological studies carried out in Sweden and Finland, together with risk assessments and case reports from several EU countries. Epidemiological studies of vaccination and narcolepsy in eight member countries (Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden and the UK) were coordinated by the European Centre for Disease Prevention and Control (ECDC) with data from the international network Vaccine Adverse Events Surveillance and Communication (VAESCO).

The final VAESCO narcolepsy study, published in September 2012 [7] confirmed the association between vaccination with Pandemrix and an increased risk of narcolepsy in children and adolescents (5 to 19 years of age) in Sweden and Finland (the signaling countries). In the non-signaling countries (Denmark, France, Italy, the Netherlands, Norway and the UK), the strictest primary analysis (an assessment designed to avoid most biases like media and diagnostic awareness biases) found no significant risk to children and adolescents. However, the report also includes comments and disclaimers from Finland, France, and Norway, addressing concerns about the overly strict exclusion criteria, and the pooling of data from the non-signaling countries which is misleadingly expressed as a representative result from six countries. In France, a follow-up study presents results (see below) which are not included in the VAESCO report.

Since July 2011 additional data from several countries have become available. A study conducted by the Irish Medicines Board (IMB) was published in April 2012. The association between narcolepsy and Pandemrix is being investigated by several European research groups, also in Sweden and Finland.

[7] European Centre for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation) Stockholm: ECDC; September 2012: http://www.ecdc.europa.eu/en/publications/Publications/Vaesco%20report%20FINAL%20with%20cover.pdf

Sweden

During the outbreak of swine flu in Sweden, Pandemrix was administrated to over five million individuals in the period between October 2009 and March 2010, which accounts for about 60% of the entire population.

The Swedish Medical Products Agency/Läkemedelsverket (MPA) reported on March 28, 2011 the results from a registry based comparative cohort study [8] in four Swedish regions with a population corresponding to 57% of the entire population. The incidence of narcolepsy in vaccinated and non-vaccinated individuals was compared, and the study indicates a four-fold risk for narcolepsy in children and adolescents vaccinated with Pandemrix, compared to non-vaccinated individuals.

For a more comprehensive picture of the development of narcolepsy in Sweden, the MPA conducted a case inventory study [9] which was published on June 30, 2011. Data on confirmed and suspected cases of narcolepsy were collected from clinical departments and sleep laboratories. The journals were scrutinized by clinical experts to estimate the occurrence of the first symptoms of narcolepsy and to confirm the diagnosis. Data on vaccination were obtained from vaccination journals.

The inventory resulted in 87 confirmed cases of narcolepsy with cataplexy with the onset of symptoms during the study period January 2009 to December 2010. Of these cases, 69 (85%) had been vaccinated with Pandemrix before the onset of symptoms.

The occurrence of narcolepsy with cataplexy in the whole population during the two year study period shows that the incidence peaked during the last quartile of 2009 and the first quartile of 2010, and thus co-occurred with the pandemic and the national vaccination campaign.

The incidence of narcolepsy with cataplexy was almost seven-fold in those vaccinated compared to those who were not vaccinated. The incidence rates were measured to be 4.2 per 100 000 in the vaccinated cohort, compared to 0.64 per 100 000 in the non-vaccinated cohort, yielding a relative risk of 6.6 and an absolute risk of 3.6 additional cases per 100 000 vaccinated children and adolescents. The incidence was substantially higher within three months of the vaccination, 14.1/100 000 compared to 1.3/100 000 in the later time window.

The registry study and the case inventory study together confirm the causal relationship between an increased risk of narcolepsy and vaccination with Pandemrix. During 2012, the MPA is conducting a more detailed registry study to follow up important safety aspects of the vaccine [10].

Further research is needed to increase the understanding of genetic and environmental factors behind the increased incidence of narcolepsy, and MPA has initiated additional research projects [11]. The geographical co-occurrence of the swine flu and vaccination could be one factor, another is genetic disposition. In March 2011 MPA was assigned the task of coordinating national research in the field, through cooperation with external research groups, e.g. in Finland.

In June 2012 the Swedish Narcolepsy Association stated an overview of the administration of different batches of Pandemrix associated to narcolepsy cases. According to this statement, 12 of a total of 35

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8 A registry based comparative cohort study in four Swedish counties of the risk for narcolepsy after vaccination with Pandemrix - A first and preliminary report, by the Medical Products Agency
http://www.lakemedelsverket.se/upload/nyheter/2011/PandemrixRegReport110328.pdf

9 Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations-Results of a case inventory study by the MPA in Sweden during 2009-2010
http://www.lakemedelsverket.se/upload/nyheter/2011/Fallinventeringsrapport_pandermrix_110630.pdf
Svensk sammanfattning: Förekomst av narkolepsi med kataplexi hos barn/ungdomar i samband med H1N1-pandemin och vaccinationer med Pandemrix http://www.lakemedelsverket.se/upload/nyheter/2011/Sammanfattning_fallstudie_narkolepsi.pdf

10 Nyheter från Läkemedelsverket den 21 december 2011:
http://www.lakemedelsverket.se/Alla-nyheter/NYHETER-2011/Ytterligare-registerstudier-av-Pandemrix-planeras-under-2012/

11 Nyheter från Läkemedelsverket den 1 februari 2012:
http://www.lakemedelsverket.se/Alla-nyheter/NYHETER-2012/Lakemedelsverket-samordnar-forskning-kring-vaccinsakerhet-och-narkolepsi-/

batches were administered to children and adolescents that later developed narcolepsy [12]. MPA will analyze these findings in more detail in order to verify whether the previous analysis performed by the MPA is still valid.

Finland

During 2009 and 2010, 2.76 million individuals were vaccinated with Pandemrix, which is over half of the population (30% of the adolescents and 82% of the children). In August 2010 vaccination with Pandemrix was stopped after observations of a sudden increase of narcolepsy cases among vaccinated children and adolescents. The simultaneous media attention most likely contributed to put focus on the issue.

In September 2010 the Finnish National Institute for Health and Welfare (THL) set up a national narcolepsy work group to conduct a retrospective cohort study in order to investigate the association between narcolepsy and Pandemrix. Simultaneously, immunogenetic and virological studies were initiated. In an intermediate report [13] from January 2011 the work group considered that vaccinated children and adolescents between four and 19 years of age ran a much higher risk of contracting narcolepsy compared to non-vaccinated individuals in the same age group.

By August 2011 98 cases of narcolepsy following vaccination with Pandemrix were reported. Of these 79 individuals were in the 4-19 years age group. In its final report [14] the work group confirmed the earlier estimation that vaccination with Pandemrix in 2009-2010 contributed to the increased incidence rate of narcolepsy. The study showed that the increase of narcolepsy cases was six per 100 000 vaccinated individuals within eight months after vaccination, which corresponds to a 12.7 higher risk in vaccinated than in non-vaccinated individuals. Two Finnish papers on the narcolepsy-Pandemrix relationship have been published in the open access journal PLoS ONE [15], [16].

In all studied cases of narcolepsy following vaccination with Pandemrix was observed in individuals with a genetic predisposition of contracting narcolepsy (the HLA DQB1*0602 allele). The researchers behind the report believe that the increased risk of narcolepsy could be explained by the vaccine in combination with other factors.

Ireland

In Ireland, Pandemrix was administered to some 900 000 individuals in 2009 and 2010. The vaccination rate against swine flu in the entire population was not as high as in Sweden, but 40% of children and adolescents were vaccinated.

A retrospective population based cohort study was initiated by the Irish Medicines Board (IMB) and the Health Service Executive (HSE), comparing the incidence of narcolepsy in vaccinated and non-vaccinated individuals.

From April 2009 to December 2010, 32 cases of narcolepsy were identified in Ireland. 28 cases were children aged 5 to 19 years, and of these 22 had been vaccinated with Pandemrix. In 17 of these children

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[12] http://www.mynewsdesk.com/se/pressroom/lakemedelsverket/pressrelease/view/pandemrix-och-narkolepsi-768199

[13] Finland: Lägesrapport av den nationella arbetsgruppen för narkolepsi 31.1.2011.
http://www.thl.fi/thl-client/pdfs/85b88efc-b6a4-4cb3-b22e-4a2536eb021e
Nyheter från THL 1.9 2011: http://www.thl.fi/sv_SE/web/sv/meddelande?id=26352

[14] Final Report from the National Work Group for Narcolepsy 31.8.2011 (in Finnish) Rapport 58/2011. Loppuraportti Pandemrix-pandemiarokotteen epäilystä haittavaikutuksista [Slutrapport över misstänkta biverkningar av pandemivaccinet Pandemrix]. Ulpu Elonsalo, Hillevi Tikkanen och Nanna Nohynek.
http://www.thl.fi/thl-client/pdfs/c02a3788-a691-47a4-bca8-5161b6cff077

[15] Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, et al. (2012) AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland. PLoS ONE 7(3): e33536. doi:10.1371/journal.pone.0033536: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0033536

[16] Partinen M, Saarenpää-Heikkilä O, Ilveskoski I, Hublin C, Linna M, et al. (2012) Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland. PLoS ONE 7(3): e33723. doi:10.1371/journal.pone.0033723: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0033723

the same genetic predisposition (HLA DQB1*0602 allele) as found in the Finnish study was observed (the rest of the narcolepsy cases were not tested for the allele).

The study indicates that children vaccinated with Pandemrix were at 13 times higher risk of contracting narcolepsy than non-vaccinated children (5.8 cases per 100 000 individuals for vaccinated compared to 0.5 for non-vaccinated). The median delay between the vaccination and the first symptom of narcolepsy was 2.2 months. A case study was conducted to ascertain that the number of reported cases was not influenced by the media coverage following the reports from Sweden and Finland.

In its final report [17] (published in April 2012) the Irish National narcolepsy study concluded that the increased incidence of narcolepsy in children vaccinated with Pandemrix and adolescents mirrored a real increased risk for developing narcolepsy. The report stresses the importance of further studies into the underlying factors contributing to the connection.

Observations from other countries

Preliminary passive observation reports from several countries indicate a higher than expected incidence of narcolepsy in children and adolescents following vaccination with Pandemrix.

Almost half of the population in Iceland was vaccinated with Pandemrix against swine flu in 2009 and 2010. A total of five individuals under 19 years of age contracted narcolepsy in 2010, which was a significant increase, but only three of these cases could be connected to vaccination [18].

The health authorities in Norway are following all suspected cases of narcolepsy associated with the Pandemrix vaccination in 2009-2010. By May 2012, 42 cases of narcolepsy in children aged 4-19 years have been reported and several others are still under investigation [19]. A number of studies are currently being carried out in Norway.

In Germany, where only eight per cent of the total population was vaccinated against swine flu, the Paul-Ehrlich Institute reported (April 2012) a total of 29 cases of narcolepsy following vaccination with Pandemrix. Of these, 19 were children and adolescents (8-17 years of age).

The French medical agency Afssaps (now L'Agence nationale de sécurité du médicament et des produits de santé – ANSM) reported in April 2011 an increased incidence of narcolepsy in vaccinated children (10-15 years of age). Swine flu vaccine was administered to 5.7 million individuals in France, of these 4.1 million were vaccinated with Pandemrix and 1.6 million with Panenza. A total of 25 narcolepsy cases were observed, and of these 23 cases were found in the group vaccinated with Pandemrix. In this study, which formed the French part in the VAESCO study, no increased incidence was observed in other age groups. But in a later follow-up study [20], published in September 2012, a total of 51 cases of narcolepsy following vaccination with Pandemrix were reported, and of these 22 were persons over 16 years of age. These new findings are the first to demonstrate an increased incidence of narcolepsy also in higher age groups.

In the Netherlands a mass vaccination in November 2009 targeted children in the age group six months to five years of age. The Pharmacovigilance Centre Lareb reported in July 2011 three confirmed cases of narcolepsy associated with vaccination with Pandemrix.

Results from studies in Canada and UK are still pending.

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[17] Investigation of an increase in the incidence of narcolepsy in children and adolescents in 2009 and 2010.Final Report of National Narcolepsy Study Steering Group: http://www.dohc.ie/publications/Nat_Narcolespy_Study_SC_Report.html

[18] ECDC March 2, 2011: http://www.ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f-77d4-4ad8-b6d6-bf0f23083f30&ID=1028&MasterPage=1

[19] Statens Legemiddelverk 2012-06-01: http://www.legemiddelverket.no/templates/InterPage____83622.aspx?filterBy=

[20] Etude NarcoFlu-VF (NarcoFlu VAESCO-France) : Grippe, vaccination antigrippale et narcolepsie : contribution française à l'étude cas-témoins européenne. Août 2012. (20/09/2012) (1854 ko)

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