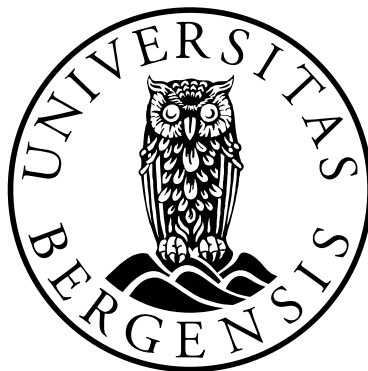


Prescribing and Prescribers of Psychotropic Drugs in Norway

A population based pharmacoepidemiological study

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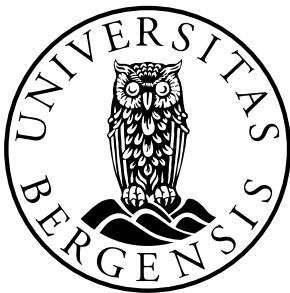
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Scientific environment

This project was conducted during the years 2006 to 2011 at the Research Group for General Practice, Department of Public Health and Primary Health Care, University of Bergen, and the Research Unit for General Practice in Bergen, Uni Health, Bergen.

The second article was accomplished in cooperation with the Regional Center for Age-Related Medicine, Stavanger University Hospital, Stavanger.

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Preface

In 1995, the municipal medical officer in Sandnes, Hans Petter Torvik, asked me to represent the local health authorities in the advisory board of a research project. The project, called “Legal drugs gone astray”, was conducted at the International Research Institute of Stavanger, and investigated the black market and the illegal distribution of legally prescribed drugs in our municipality. Through the work of the committee, my interest in research grew, and after one year I left the committee and joined the research team, as part-time employee at the institute.

Due to my wife’s work, our family moved to Madagascar in 2001. Returning back after a two-year stay in a developing country, I perceived the daily life in Norway and my work at a primary health care center with a different mind.

This thesis was inspired by my first project, my renewed experience of the Norwegian culture, and the day to day work as a GP in the primary health care system.

Acknowledgements

I am honored that *Steinar Hunskår*, Professor at the Department of Public Health and Primary Health Care at the University of Bergen, accepted to be my principal advisor. He has shared his extensive scientific expertise in a pedagogical manner, and I want to thank him cordially for his encouragement, patience and considerate boundary settings through my educational journey. His belief in the project has given me the energy to stay the difficulties, and made this thesis a reality.

Sabine Ruths, Professor at the Department and in the Research Unit for General Practice in Bergen, has been co-supervisor of the study. She has a considerable knowledge in pharmacoepidemiology, current prescription practices and challenges with regard to psychotropic drug use. I am deeply grateful for her commitment, continuous support, and fast feedback during the project period. In addition, her excellent language skills have improved my work a lot.

Dag Årsland, Head of the research group at the Regional Center for Age-Related Medicine at Stavanger University Hospital, has been a second co-supervisor, mainly for the second article of the study. He has been an important discussion partner with the point of view of a specialist in psychiatry. In addition to his skills and knowledge, he has an extraordinary energy and ability to energize others, which I appreciated very much.

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Thanks also to *Guri Rørtveit*, Professor and Head of the Research Unit for General Practice in Bergen and all my colleagues in both the research group and the research unit for all support, encouragement and useful discussions along the way.

I am very grateful for the financial support from the Norwegian Medical Association's *Fund for Research in General Practice*, which enabled the project.

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They have all been very helpful and assisted me to gain and merge the data needed for this project. In addition, *Solveig Sakshaug* at the Department of Pharmacoepidemiology at the Norwegian Institute of Public Health has helped me with data about wholesale figures.

It is especially nice to thank *Hans Petter Torvik*, municipal medical officer in Sandnes. He led me into research in 1995. Later, he has encouraged me to continue my research, and benevolent granted me necessary leave of absence.

Marie Smith-Solbakken, Dr. art and former senior researcher at International Research Institute of Stavanger, now Head of Department of Cultural Studies and Languages, University of Stavanger, headed the first research project in which I took part. I am deeply grateful to her and her colleagues for how they welcomed me, and all I learned. The project gave me a lot of motivation and high job satisfaction. That experience was the main reason why I continued with research.

Sverre Nesvåg, former Research Manager at International Research Institute of Stavanger, now Head of research, Centre for Alcohol and Drug Research, Stavanger University Hospital, challenged me and convinced me to develop a PhD project. *Stein Tore Nilsen*, Research Director at Stavanger University Hospital, pushed me gently further, and facilitated the inception of my project. I owe them both warm thanks for their faith in me and the help they gave me at the start of the PhD project.

I also need to thank the staff, colleagues and substitutes at *Skeiane healthcare center* in Sandnes for their patience and support during my leave. I will apologize for any inconvenience my absence may have caused.

I want to express my deep gratitude and love to my wife, *Bente*, for her patience and encouragement through periods of frustrations and her rejoice at joyful moments. Without her support, my thesis was never written. I also want to thank our children *Einar*, *Andreas*, *Sigrid* and *Lars* who have been more proud than frustrated about their father, studying for a doctoral degree.

Svein R. Kjosavik

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Abstract

Background

One out of three persons in Norway had a mental illness during 2008, and about half of the population will be affected during their lifetime, according to the Government. Although mental health care comprises many other aspects than pharmacotherapy, drugs are widely used to treat psychiatric problems. In this project, the current use of psychotropic drugs in various parts of the health care system is analyzed. No detailed scientific information exists about the relative contribution from different physician groups as regards the prescribing of psychotropic drugs.

Aims

The main aims of this study were to examine prevalence rates, incidence rates and distribution of psychotropic drug use, i.e. antipsychotics, antidepressants, anxiolytics and hypnotics, with special emphasis on the pattern of prescribing in primary and secondary health care.

Material and methods

Data on all prescriptions of psychotropic drugs dispensed from all Norwegian pharmacies from 1 January 2004 until 31 August 2009 were extracted from the Norwegian Prescription Database and merged with data about all general practitioners (GPs) in Norway in the same period from the General Practitioner Database, and information about the general Norwegian population from Statistics Norway.

Prevalence rates were based on all redeemed prescriptions of these drugs in 2005, while new users of antipsychotics and antidepressants in 2008 or of anxiolytics and hypnotics in 2005 were used to calculate incidence rates. The course of the treatment with anxiolytics and hypnotics was analyzed using a 3.5-year period of follow-up.

Results

The prevalence rates per 1,000 inhabitants were 153 for any psychotropic drug, or 24 for antipsychotics, 60 for antidepressants, 62 for anxiolytics and 79 for hypnotics (*Paper I*). The incidence rates were 3.4 for antipsychotics and 8.6 for antidepressants (*Paper II*), and 18.2 for anxiolytics, 24.5 for hypnotics, or 35.4 per 1,000 for anxiolytics and hypnotics combined (*Paper III*). Both prevalence rates and incidence rates were higher for women than men, and increased by age.

Psychiatrists prescribed an important part of drug treatment to children and adolescents. GPs prescribed the vast majority, but also initiated psychotropic drug treatment to most patients, and the proportion increased by patients' age. The average treatment duration declined with increased age of the patients in all four drug classes. The duration was longest for hypnotics and anxiolytics, and only every third patient received short-term treatment, as recommended. The total drug volume of anxiolytics and hypnotics redeemed during the first quarter emerged as the strongest predictor of both long-term and heavy use of such drugs.

Conclusions

Prevalence and incidence rates for psychotropic drug use in Norway are among the highest in Europe. GPs initiate and maintain the drug treatment to the majority. Hence, the quality of psychotropic drug treatment is mainly dependent on the knowledge and practice of each GP. Psychiatrists contribute mainly among children and adolescents and their share of prescriptions decreased significantly with increasing patient age. An increased focus from psychiatrists towards the increasingly ageing part of the population seems requisite.

The study confirms that GPs have a key function in the Norwegian health care system, also when it comes to treatment of mental disorders. Improving mental health care is only achieved in a cost effective manner if GPs are a major part of the effort. Implementation of relevant guidelines and systems for structured clinical audit are recommended, especially in general practice.

Sammendrag på norsk (Norwegian summary)

Bakgrunn

En av tre personer hadde en psykisk lidelse i Norge i 2008, og omkring halvparten vil bli rammet av en slik lidelse i løpet av livet, i følge regjeringen. Selv om psykisk helsetjeneste omfatter mye mer enn medikamentell behandling, er psykofarmaka mye brukt i behandling av psykiske lidelser. I dette prosjektet analyseres dagens bruk av psykofarmaka i ulike deler av helsetjenesten. Det finnes i dag ingen detaljert vitenskapelig informasjon om det relative bidraget fra ulike legegrupper når det gjelder forskrivningen av psykofarmaka.

Studiens formål

Hovedmålene for denne studien var å analysere omfanget av psykofarmaka forskrivning (prevalens), dvs. antipsykotika, antidepressiva, beroligende og sovemedisiner, antall nye brukere (insidens), med spesiell vekt på fordelingen av forskrivningen av slike legemidler i første og andrelinjetjenesten.

Materiale og metode

Data fra Reseptregisteret vedrørende alle resepter på psykofarmaka innløst ved norske apotek fra 1. januar 2004 til 31. august 2009 ble koblet sammen med informasjon fra Fastlegedatabasen om alle fastleger i perioden, og data vedrørende den generelle befolkning fra Statistisk sentralbyrå.

Analysen av prevalensrater baserte seg på resepter innløst i 2005, mens nye brukere av antipsykotika og antidepressiva i 2008 og av beroligende og sovemedisiner i 2005 ble brukt til å beregne insidensrater. Forløpet av behandlingen med beroligende og sovemedisiner ble analysert over en periode på 3,5 år.

Resultat

Prevalensraten per 1000 innbyggere var 153 for psykofarmaka samlet, og 24 for antipsykotika, 60 for antidepressiva, 62 for beroligende og 79 for sovemedisin (*Paper I*). Insidensratene per 1000 innbyggere var 3,4 for antipsykotika, 8,6 for antidepressiva (*Paper II*), 18,2 for beroligende, 24,5 for sovemedisiner eller 35,4 om beroligende og sovemedisiner beregnes samlet (*Paper III*). Andelen som begynte med eller brukte slike legemidler økte med alderen, og var høyere for kvinner enn for menn.

Psykiaternes forskrivning utgjorde en betydelig andel av psykofarmakabehandlingen til barn og unge. Fastlegene både startet behandlingen og skrev ut resepter til videre behandling til de fleste pasientene, og andelen økte med pasientenes alder.

Gjennomsnittlig behandlingstid ble redusert ved økende pasientalder for alle de fire legemiddelgruppene. Varigheten var lengst for sovemedisiner og beroligende, og kun en tredjedel av pasientene fikk korttidsbehandling slik retningslinjene anbefaler. Totalvolumet pasienten mottok i første behandlingskvartal var den sterkeste prediktor for utvikling av langtidsbruk eller storforbruk av beroligende eller sovemedisiner.

Konklusjon

Prevalens- og insidensratene for psykofarmaka i Norge er blant de høyeste i Europa. Fastlegene både starter og vedlikeholder behandlingen til de fleste. Kvaliteten på psykofarmaka behandlingen er derfor i hovedsak avhengig av den enkelte fastlege sin kunnskap og praksis. Psykiaterne bidrar i hovedsak blant barn og unge, og deres andel av reseptene reduseres raskt med økende pasientalder. Et økt engasjement fra psykiatere overfor den stadig mer aldrende del av befolkningen synes nødvendig.

Studien bekrefter at fastlegene har en nøkkelfunksjon i norsk helsevesen, også når det gjelder psykiske lidelser. Et bedre psykisk helsevern kan bare oppnås på en kostnadseffektiv måte hvis fastlegene er en viktig del av satsningen. Implementering av relevante retningslinjer og systemer for strukturert kvalitetsforbedring anbefales, spesielt i allmennpraksis.

Abbreviations

ATC	Anatomical Therapeutic Chemical classification system
BZD(s)	Benzodiazepine(s)
CI	Confidence Interval
DDD	Defined Daily Dose
DSM	The Diagnostic and Statistical Manual of Mental Disorders
EMA	The European Medicine Agency
FDA	Food and Drug Administration
GP(s)	General practitioner(s)
ICD	The International Statistical Classification of Diseases and Related Health Problems
ICPC	The International Classification of Primary Care
NorPD	The Norwegian Prescription Database
OR	Odds Ratio
OTC	Over-The-Counter, i.e. without prescription
SD	Standard deviation
SSRI	Selective serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant
UK	United Kingdom
UN	United Nations
WHO	World Health Organization
WONCA	World Organization of Family Doctors or The World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians
Z-hypnotic(s)	Benzodiazepine related hypnotic(s)

List of publications

The thesis is based on the following papers, which will be referred to by their Roman numerals.

Paper I

Kjosavik SR, Ruths S, Hunnskaar S. Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database. *Pharmacoepidemiology and Drug Safety* 2009;18:572-8.

Paper II

Kjosavik SR, Hunnskaar S, Aarsland D, Ruths S. Initial prescription of antipsychotics and antidepressants in general practice and specialist care in Norway. *Acta Psychiatrica Scandinavica* 2011;123:459-65.

Paper III

Kjosavik SR, Ruths S, Hunnskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *European Journal of Clinical Pharmacology* 2011 Sep 18. [E-pub ahead of print]

1. Introduction

Mental health is crucial to the well-being of individuals, societies and countries. Physical health affects mental health, and mental health inherently affects physical health (1-2).

1.1 Mental health

The World Health Report in 2001 (1) stated that globally, one out of four persons will be affected by a psychiatric disorder at some stage of life. Major depression was ranked as the leading course of years of life lived with disabilities, with schizophrenia and bipolar affective disorder as number seven and nine, respectively. Depression was number four of leading causes of global burden of disease in 2001, measured by the disability-adjusted life years, but anticipated to be number two in 2020. Anxiety and insomnia are among the most prevalent psychological symptoms, ranging from mild disturbances to severe disorders, and often as comorbidity in other psychiatric disorders (3-4). Only a minority of the many millions of people with mental disorders receives treatment, and unnecessary suffering, stigmatization and discrimination are often the result. Thus, mental health problems are among the main challenges for health care systems worldwide.

To improve the situation, the World Health Report 2001 recommended ten actions to be adapted by every country, according to their needs and resources;

1. Provide treatment in primary care
2. Make psychotropic drugs available
3. Give care in the community
4. Educate the public
5. Involve communities, families and consumers
6. Establish national policies, programs and legislation
7. Develop human resources
8. Link with other sectors
9. Monitor community mental health
10. Support more research

The first, second and sixth recommendation are of particular interest to this project. According to the report, management and treatment of mental health in primary care enables the largest number of patients to get help, and cuts wastage from unnecessary investigation and inappropriate and non-specific treatments at higher health care levels. The WHO list of essential drugs (5) includes psychotropic drugs which should be provided in all countries, and made constantly available at all health care levels. Drugs recommended as the most appropriate treatment for various disorders should be made available whenever possible. National policies, programs and legislations are of similar importance to secure sustained actions, reduce burden of mental disease, and counteract discrimination against persons with mental disorders.

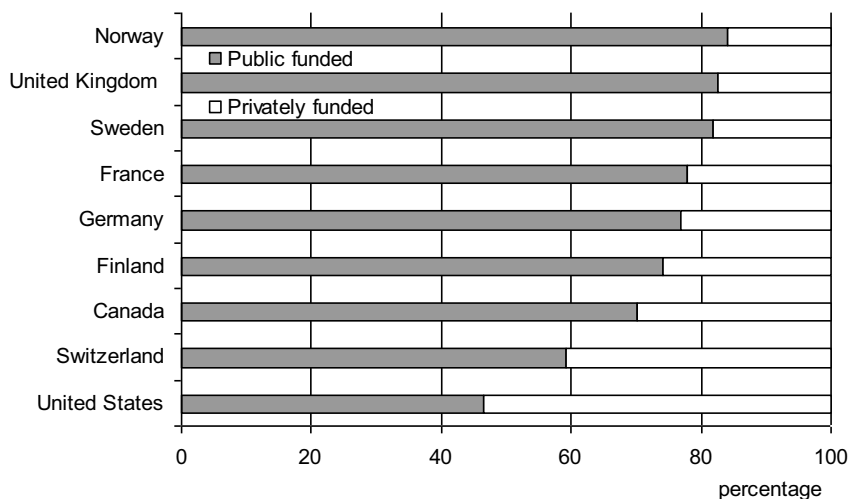
Patients referred from a GP to a specialist represent a selection of the general population, and the probability of disease is higher in this sample than among patients in primary care. Consequently, symptoms, signs and test results among referred patients have a higher predictive value than in general practice (6). Psychological problems are more likely to be caused by a mental disorder in a patient who consults a psychiatrist, while similar symptoms in primary care may be only a nuisance. As an example, the probability that insomnia may be a symptom of mania is much higher in a patient at the psychiatric outpatient clinic than at the GP's office.

These differences are reflected by the distinctions between diagnostic classification systems. In Norway, The International Classification of Primary Care (ICPC) was introduced in family medicine in 1992 (7). ICPC covers symptoms, ailments and functional ability as well as diagnoses. This is suitable in primary care, where all kinds of health phenomena, problems and disorders may be on patients' agenda. The diagnostic classification system in specialist health care is more focused on diseases, their subtypes and severity. Two systems are in use in specialized mental health care, The International Statistical Classification of Diseases and Related Health Problems (ICD) and The Diagnostic and Statistical Manual of Mental Disorders (DSM). The current version, ICD-10, is the main system in Norway, and considered most suitable for clinical use, but DSM (current version IV) is valued in research (8).

1.2 The health care system in Norway

Norway has a strong and well-developed public health service, grounded on a concept of equality, and with the provision to reach out to everyone regardless of their financial situation, social status, age, gender and ethnicity (9). In 2008, Norway spent 8.6 % of the Gross Domestic Product on health care, and the government paid 84 % of the expenditure. In comparison, figure 1 shows the proportions of expenditure that were covered by the public in some countries, based on information from the Organization for Economic Co-operation and Development, OECD (10).

Figure 1 Public and private funding of expenditure on health in 2008



As in other Western European countries, the demographic situation in Norway is changing, and the proportion of the population aged 60 and older is estimated to increase from 20 % in 2006 to 30 % in 2050 (11). Such changes will be a major challenge to the society and the health care system. Older people need more health care and use more medications than younger ones, both for somatic and mental reasons.

Mental health is an important public health issue among older people, and treatment with psychotropic drugs increases by age (12-15). Dementia increases nearly exponentially with age from about 60 years (16). Behavioral and psychological symptoms are often prominent problems in dementia, and use of psychotropic drugs, is pronounced (17). Mental problems as well as medication may increase the risk of falls and other comorbidity. Psychological and social factors are important determinants of health outcomes in older patients, such as duration of hospital admission or the risk of loss of independent living / admission to a nursing home (16).

Increased number of senior citizens and people with chronic and complex illnesses leaves a smaller proportion employable to pay the public bill in years to come, and the ratio of population aged 15 to 64 to the population aged 65 and older will change from 4 to 2 (11).

A National Regular General Practitioner Scheme was implemented in Norway in 2001, giving all inhabitants the right to choose a GP as their regular doctor (18). The reform aimed at improving the quality and availability of health care for all inhabitants, but especially for patients with chronic conditions, including mental health problems. The scheme is provided by the municipalities, and the local health authorities have the responsibility to ensure adequate capacity. The GPs are mainly working in private practice, contracted by the health authorities in each municipality, although some are employed by the municipality on fixed salary. More than 99 % of the population is contracted to a GP (19), and both patients and GPs are mainly satisfied with the reform (20-21). GPs provide medical care for a wide range of somatic and mental health problems. According to the statistics from the Norwegian Labour and Welfare Services, 10 % of consultations in primary care were labeled with a mental diagnostic code in 2006, both for men and women (22). For service in secondary care, including psychiatric and psychological health care, referral from a GP is mandatory. The patients are normally re-allocated to primary health care for further follow-up, when necessary diagnostics and treatment at the secondary care level are completed.

Specialized mental health services comprise psychiatric hospitals and smaller decentralized institutions called district psychiatric centers. Both types of institutions usually provide in- and outpatients' services. Most psychiatrists work in these institutions in the public health care system. In addition, some psychiatrists and psychologists run private specialist practices, based on a contract with the health authorities. Visits to GPs, private specialists or outpatient departments are charged with a Governmental regulated user fee, while hospital admission is free.

Some psychiatrists and psychologists run private practices without a contract with the authorities, especially in the larger cities. Such treatment is fully paid for by the patients or their employer, and no referral is needed.

A national plan to strengthen mental health care was initiated by the Government in 1997 (23). A general political agreement stated that mental health care should be prioritized. This was followed-up by a national mental health reform aiming to improve the availability, the capacity, and the quality of the mental health care (24).

The recommendations in the World Health Report 2001 may be perceived as already implemented in Norway. Still, the impact of mental health problems in Norway is pronounced. The patients' loss of working capacity and the governmental expenses to disability pensions ranks the economical consequence of mental health problems as number one of health problems, in Norway. The government assessed that one in every three persons had a mental illness or disorder during 2008, and approximately one of two will be affected during their lifetime (25). Different professions with different qualifications are involved in mental health care, and a number of non-pharmacological and psychotherapeutic strategies are available to treat and support the patients. Psychotropic drugs are, however, widely used. The second recommendation from WHO emphasizes the importance by making the most efficient drugs available, whenever possible, e.g. in Italy, second generation antipsychotics were not covered by the reimbursement system until 2001.

1.3 Psychotropic drugs

Psychotropic drugs are in this thesis defined as antipsychotics, anxiolytics, hypnotics and antidepressants. Other drugs may also be used for treatment of psychiatric conditions, as for instance psychostimulants, drugs used to treat dementia, and anticonvulsants for use in bipolar disorder, but such drugs are beyond the scope of this project.

1.3.1 Brief history

The introduction of chlorpromazine in psychiatry by Delay et al. in 1952 may be perceived as the inauguration of modern clinical psychopharmacology (26). It was a pharmacological therapy with a specific indication for treatment of psychosis, and became the first approved antipsychotic drug. In 1957, the Swiss psychiatrists Kuhn showed that imipramine improved the symptoms of depression (27). Imipramine together with similar antidepressant drugs became of similar vital importance for the treatment of depression as antipsychotics were for psychosis.

Drugs used for mental problems prior to 1950 were mostly barbiturates which had narrow therapeutic windows with high risk of adverse side effects, overdose, respiratory depression and even death. The introduction of diazepam as treatment for anxiety in the early 1960s soon made barbiturates obsolete. Other benzodiazepines (BZDs) followed and have ever since been widely used as anxiolytics but also as hypnotics and anticonvulsants.

Lithium has a different story (28). It was introduced in psychiatry in the mid-19th century, but soon forgotten. In 1949 it was reintroduced, and accomplished by a randomized controlled trial for mania in 1954. Maintenance and prophylactic therapy to avoid manic and depressive periods in bipolar disorders became evident in the 1960s, but the use in clinical practice developed slowly, and lithium achieved its current status with difficulties.

Research in the 1950s and 1960s resulted in better understanding of the central nervous system and the function of neurotransmitters, but the drugs brought to the market until the 1980s were mainly based on development from already known chemical substances. During the 1990s and the first years of this millennium, many new drugs were brought to the market, and the overall use of psychotropic drugs increased in most high income countries and in all ages, also in children (29-30).

Earlier, antipsychotics were mainly used to treat patients with severe mental illness, often in a mental health care setting. This practice has changed. The newer atypical or second generation antipsychotics are approved for some other conditions than non-affective psychosis, as with bipolar disorder, but off-label prescribing has also been much more common (31), especially for behavioral and psychological symptoms of dementia (32). The second generation antipsychotics induces less sedative and anticholinergic effects than first generation antipsychotics (33), but all antipsychotics may induce serious side effects, and physicians need to balance the potential risks and benefits of using them. In Norway, the wholesale of antipsychotics has been rather stable, but a shift from first generation to second generation drugs has increased the expenses considerably (34).

The introduction of selective serotonin reuptake inhibitors (SSRIs) and other new antidepressants have dramatically increased the use of antidepressants. The number of persons treated with antidepressants were nearly doubled in the United States between 1996 and 2005, and antidepressants became the most commonly prescribed drug class in the United States in 2005 (35). The increase has been considerable also in Europe and other high-income countries (36). In Norway, the wholesale of antidepressants has changed from less than 15 DDD per 1,000 inhabitants per day before 1992 to more than 55 DDD per 1,000 inhabitants per day from 2007 and later (34).

Antidepressants are used with other problems than depression. SSRIs are recommended as first-line treatment of panic disorders, but also approved for treatment of generalized anxiety disorder, obsessive compulsive disorders and some phobias. In addition, studies have shown that SSRIs are effective in premenstrual

dysphoric disorder (37). Older antidepressants are often used for non-psychiatric indications as musculoskeletal conditions, different pain conditions and for sleep disturbances. According to a Canadian study, about one-third of antidepressants are prescribed for other reasons than depression (38) high-income countries.

As regards anxiolytics, BZDs have dominated the market since the 1960s, and still do, while the new generation of hypnotics, Z-hypnotics, is now the drug of choice (39). The long-term consequences of use of Z-hypnotics are still unknown, but they are regarded to be safer than BZD in terms of risk for adverse events (40).

Other drugs such as the antihistamines hydroxyzine and alimemazine are approved for treatment of anxiety and insomnia, respectively, but the use is confined. The newer anxiolytics include buspirone and alprazolam. Buspirone is useful in treatment of anxiety, particularly for those patients who have not used BZD (41). Alprazolam has been shown to be effective in treatment of anxiety, but alprazolam is not recommended as first-line therapy. More than other BZDs, alprazolam cause withdrawal and rebound effects, and may be abused (42).

In Norway, the total use of anxiolytics has been rather stable during the last twenty years. The use of hypnotics decreased during the early 1990s, but has then increased again, year by year since 1995 (34).

1.3.2 Classification of Drugs

The need for an internationally accepted classification system for drug consumption studies was addressed at a symposium in Oslo in 1969 entitled *The Consumption of Drugs*. Norwegian researchers developed the system known as *the Anatomical Therapeutic Chemical (ATC) classification system* (43) by modifying and extending the classification of the European Pharmaceutical Market Research Association.

In the ATC system, drugs are classified into five different levels, according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The system has 14 anatomical main groups (level 1), each with

therapeutic subgroups (level 2), and a pharmacological subgroup (level 3), followed by chemical subgroups (level 4) and each chemical substance (level 5) (44).

Table 1 demonstrates the first three levels in the ATC system for psychotropic drugs included in this thesis, while table 2 shows the different psychotropic drugs marketed in Norway and approved before 2005 and their full ATC codes.

Table 1 The first, second and third level in the ATC system for psychotropic drugs included in this study

N	Nervous system	1. level, anatomical main group
05	Psycholeptics	2. level, therapeutic subgroup
A	Antipsychotics	3. level, pharmacological subgroup
B	Anxiolytics	3. level, pharmacological subgroup
C	Hypnotics	3. level, pharmacological subgroup
06	Psychoanaleptics	2. level, therapeutic subgroup
A	Antidepressants	3. level, pharmacological subgroup

In addition, a unit called the Defined Daily Dose (DDD) was developed. It is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (43). DDD does not necessarily reflect the recommended or prescribed daily dose, but is a technical unit for measurement often used in research and drug statistics. The WHO Regional Office for Europe recommended the ATC / DDD system in 1981, and the WHO Collaborating Center for Drug Statistics Methodology was established in Oslo in 1982. The center is now located at the Norwegian Institute of Public Health, and responsible for the maintenance and further development of the ATC / DDD system (44). In 1996, WHO recognized the ATC / DDD system as an international standard for drug utilization studies.

1.3.3 Authorities and legislation

Until 1995 drugs had to be approved by national authorities in each and every country in Europe. Today the European Medicines Agency (EMA) approves drugs for the countries in the European Union and in The European Economic Area as Food and Drug Administration (FDA) do in the United States.

Table 2 Psychotropic drugs marketed in Norway in 2005-2008

ATC code	Substance	Approved	ATC code	Substance	Approved
Antipsychotics			Antidepressants		
N05A A01	Chlorpromazine	1954	N06A A04	Clomipramine	1970
N05A A02	Levomepromazine	1960	N06A A06	Trimipramine	1966
N05A B01	Dixyrazine	1965	N06A A09	Amitriptylin	1961
N05A B02	Fluphenazine	1964	N06A A10	Nortriptyline	1965
N05A B03	Perphenazine	1958	N06A A12	Doxepin	1969
N05A B04	Prochlorperazine	1957	N06A B03	Fluoxetine	1995
N05A C02	Thioridazine	1960	N06A B04	Citalopram	1995
N05A D01	Haloperidol	1961	N06A B05	Paroxetine	1993
N05A E03	Sertindole	1997	N06A B06	Sertraline	1996
N05A E04	Ziprasidone	2002	N06A B08	Fluvoxamine	1990
N05A F01	Flupentixol	1966	N06A B10	Escitalopram	2002
N05A F03	Chlorprothixene	1959	N06A G02	Moclobemide	1990
N05A F05	Zuclopenthixol	1977	N06A X03	Mianserin	1982
N05A H02	Clozapine	1990	N06A X11	Mirtazapine	2000
N05A H03	Olanzapine	1997	N06A X16	Venlafaxine	1996
N05A H04	Quetiapine	2000	N06A X18	Reboxetine	1999
N05A L05	Amisulpride	1999	N06A X21	Duloksetin	2004
N05A N01	Lithium	1970			
N05A X08	Risperidone	1994			
N05A X12	Aripiprazole	2004			
Anxiolytics			Hypnotics		
N05B A01	Diazepam	1963	N05C D02	Nitrazepam	1965
N05B A04	Oxazepam	1966	N05C D03	Flunitrazepam	1977
N05B A12	Alprazolam	1994	N05C D08	Midazolam	1986
N05B B01	Hydroxyzine	1957	N05C F01	Zopiclone	1994
N05B E01	Buspirone	1992	N05C F02	Zolpidem	1996
			N05C M02	Clomethiazole	1968

Norway joined the EMA system in 2000, and hence abandoned the former principle that new drugs had to demonstrate an *"added value"* in relation to already approved drugs to gain approval. Thus, the number of drugs marketed in Norway has increased.

The Norwegian Medicines Agency is the national regulatory authority for new and existing medicines and the supply chain in Norway (45). The agency has assigned all prescription drugs to three classes; ordinary prescription drugs, such as antipsychotics and antidepressants, are placed in class C, and those prescriptions are allowed to be reiterated for one year. Drugs that are potentially abused or may be addictive are either classified in class B, such as BZDs and Z-hypnotics, or in class A, such as opioids, central stimulants and other drugs regarded as narcotics. Class A prescriptions need special forms. Due to the potential risk for abuse of drugs in class A and B,

prescriptions can only be redeemed once, and prescription forms are kept at the pharmacies for 5 years (A) or 1 year (B) to secure the authorities a possibility for control or investigation of the handling of such drugs.

An electronic prescription system is developed. It will be implemented in primary care in Norway during 2011-2013. The handling of prescriptions will be changed, but the main principle in prescribing legislations will be continued.

A governmental reimbursement system covers prescriptions of drugs for prolonged or chronic treatment, including antipsychotics and antidepressants. Patients normally have to pay themselves for short-time treatment and for addictive drugs, including anxiolytics and hypnotics. Exceptions exist for some anxiolytics when used to treat epilepsy and for anxiolytics and hypnotics used by patients with advanced cancer. Physicians with or without a specialty, dentists as well as veterinarians are authorized to prescribe psychotropic drugs.

1.4 Pharmacoepidemiology

According to the WHO (46), Drug Utilization is defined as the “marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”. Consequently, effects of drug utilization at all levels of the health care system are included in the term, and both quantitative and qualitative methods are used for drug utilization studies. Quantitative studies are used to quantify the current state, trends and the course of drug use over time, while qualitative methods are valuable tools to gain knowledge about attitudes, beliefs, and preferences among patients, physicians or other health care providers.

Pharmacoepidemiology emerged at the intersection between epidemiology and clinical pharmacology. Clinical pharmacology investigates the effects of drugs in humans, and epidemiology studies the distribution and determinants of health-related states and events in the population. Pharmacoepidemiology applies the methods from epidemiology to study the clinical use of drugs in populations, i.e. studies of the use, effects or side effects of drugs in a large number of people (47).

The main purpose of pharmacoepidemiological research is to support efficient and cost-effective use of medicines in the population and thus improve health outcomes. Pharmacoepidemiological studies may use descriptive, analytical as well as experimental design. Descriptive studies include case reports, case series, and cohort or register analyses without a control group (47). Such studies may reveal age and gender specific prevalence or incidence rates, distribution and trends in drug use, frequencies of adverse drug reactions etc. They may focus on different levels of the health care system or different populations. Descriptive studies are usually unable to determine causation, but useful for generating hypotheses for further research.

Analytical studies have the ability to test specific hypothesis, often by using a control group. Typical designs in analytical studies are case-control studies, cohort studies, nested case-control studies, and case-crossover analyses (47).

In experimental studies, the researcher controls the intervention that is given each participant, normally to randomly allocate patients among study groups as in randomized controlled trials. Randomized clinical trials are the study design with best control of bias, as selection bias and confounding, and thereby giving the highest evidence of causality (47).

1.4.1 Sources of information

The ideal source of information for pharmacoepidemiological studies would be a database covering a stable population over a lifetime, with a population large enough to discover rare events, including records from both inpatients and outpatients in primary and specialized health care, covering both somatic and mental health problems, and information about all laboratory and imaging results, prescribed and over the counter drugs, and alternative therapies (47). Such a database does not exist, but the development of large computerized databases has facilitated the evolvement of drug utilization and pharmacoepidemiological studies.

In Sweden, prescriptions to outpatient have been recorded in the database of the county Jämtland and in the small town of Tierp since the early 1970s. The health

service databases in Saskatchewan in Canada were established in 1975 (48). It was one of the first public databases collecting prescription data at the individual level for the entire population of a province, and similar databases are established also in Manitoba, Quebec, and British Columbia. In the United States, several individual based prescription databases have existed since the 1980s, but most are claim databases connected to insurance companies, covering samples not representative for the entire population (47).

The General Practice Research Database in United Kingdom was established in 1987. It is a database of anonymised medical records linked with other health care data, including information about prescriptions (49). Now the database collects information from more than 5 million patients from more than 600 general practices (50).

Other European countries have established databases as well, some more like the claims databases in the United States, as for instance in Germany, and some more similar to the Canadian types as the provincial databases in Italy. In the Netherlands, the PHARMO institute links hospital data with prescription data based on the patients' birth day, gender and GP code (51). The IA-database in Groningen is also a well-known research database in pharmacoepidemiology and pharmacoconomics (52).

Pharmacoepidemiological research has a long tradition in Scandinavian countries. In addition to WHO collaborating center for drug statistics in Oslo, the WHO Global Drug Surveillance program is located in Uppsala in Sweden (53). The main aim of the latter is to detect potential side effects of drugs as early as possible, based on case reports about suspected adverse drug reactions from more than 80 countries.

Since the 1970s, the Nordic countries have assessed trends in drug use based on wholesale information. However, data at the individual person level are essential to assess drug exposure of the population, and to make it possible to link information from different sources together. During the late 1980s, most pharmacies were computerized in the Nordic countries, making automated collection of prescription data at the individual level possible.

The Pharmacoepidemiological Prescription Database of North Jutland in Aarhus and the Odense University Pharmacoepidemiological Database (OPED) were established in 1989 and 1990, respectively. The data were based on the unique and permanent identification number for each citizen, and made it possible to monitor the medication for each person over time, and linking data from different registries together (54). The sample comprised by the two databases has been rather stable and is recognized as representative for the general population, covering around 18 % of the Danish population (54). National prescription database were established in Finland in 1993, in Denmark in 1994, in Sweden in 2005 and in Iceland in 2006 (55).

The Norwegian Prescription Database (NorPD) commenced collection of prescription data from all pharmacies in Norway from 1 January 2004. A unique pseudonym identification code is made for each patient, based on but different from each person's social security number. Similarly, a pseudonym code is made for each prescriber based on the authorization code. The codes relate prescription data to each person and prescriber over time, and provide opportunities for linking data from different databases for research purposes, while personal anonymity is ensured (56).

1.4.2 Previous studies

Of special interest to this thesis are studies revealing prevalence rates, incidence rates and distribution of psychotropic drug prescriptions among different prescriber groups. Comparisons of different studies are hampered by methodological differences with regard to data sources, sampling procedures and time frames, but women use much more psychotropic drugs than men, and the use increases with patients' age (57-59).

Prevalence rates

The prevalence rate of overall psychotropic drug use revealed in the referred articles ranged from 56 to 192 per 1,000 adults, and from 3.4 to 48.7 per 1,000 children and adolescents (table 3). The studies are based on different methods and age groups, and psychotropic drugs are defined differently.

A Danish study (58) included antidepressants, anxiolytics and hypnotics, but not antipsychotics due to few users in the material. Ohayon (59) included all drugs regarded as psychotropic by the patients, including some OTC drugs. The European Study of the Epidemiology of Mental Disorders (57) and the National Health and Nutrition Examination Survey from the United States (60) included antipsychotics, antidepressants, anxiolytics, hypnotics, and mood stabilizers, while a Canadian study (61) also included psychostimulants. Regarding children, the Italian studies (62-63) included antipsychotics, antidepressants and stimulants, while the study from Iceland (64) also included anxiolytics and hypnotics. The studies from the United States (30, 63) covered the same groups as well as anticonvulsants.

Table 3 Prevalence rates of psychotropic drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Adults					
Nielsen (58)	Denmark	2000	Representative sample of 22,486 aged 16 or older	Danish Health and Morbidity Survey 2000	56 men 39 women 72
Ohayon (59)	France, Italy Germany, UK	1993- 1997	Representative sample of 18,679 aged 15 or older	Telephone survey	64
Beck (61)	Canada	2002	Representative sample of 36,984 aged 15 or older	The Canadian Community Health Survey Medication the last two days	72 men 50 women 95
Paulose-Ram (60)	USA	1999- 2002	Representative sample of 12,060 aged 17 or older	Detailed in-person home interview (National Health and Nutrition Examination Survey)	111
Alonso (57)	Germany, The Netherlands, Belgium, Italy, Spain, France	2001- 2003	Representative sample of 21,425 aged 18 or older	Detailed in-person home interview with computer-assisted techniques	123
	Germany				59
	The Netherlands				74
	Belgium				132
	Italy				137
	Spain				156
	France				192
Children and adolescents					
Clavenna (62)	Italy	2004	1,484,770 aged 17 or younger	ARNO, a multiregional prescription database	3.0
Bonati (63)	Italy	2002	Review of 15 articles	MEDLINE and EMBASE	3.4
	USA	2000			35.5
Olfson (30)	USA	1996	6,490 aged 18 or younger	Medical Expenditure Panel Survey	39.0
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	48.7

Studies evaluating the use of antipsychotics revealed prevalence rates ranging from 3 to 13 per 1,000 adults, and from 0.8 to 10.6 per 1,000 children and adolescents (table 4). A trend analysis has documented an increased use of antipsychotics in most high-income countries since the early 1990s until more recent years (31).

Table 4 Prevalence rates of antipsychotic drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Adults					
Ohayon (59)	France, Italy Germany, UK	1993- 1997	Representative sample of 18,679 aged 15 or older	Telephone survey	3
Alonso (57)	Germany, The Netherlands, Belgium, Italy, Spain, France	2001- 2003	Representative sample of 21,425 aged 18 or older	Detailed in-person, computer-assisted, home interview	12
Beck (61)	Canada	2002	Representative sample of 36,984 aged 15 or older	The Canadian Community Health Survey Medication the last two days	5
Mirandola (12)	Italy	2002	2,640,379 residents, Province of Veneto	Data from prescription database of reimbursed drugs	men 6 women 7
Percudani (65)	Italy	2001	9,121,714 residents, Province of Lombardy	Data from prescription database of reimbursed drugs	9 men 9 women 10
Paulose-Ram (60)	USA	1999- 2002	Representative sample of 12,060 aged 17 or older	Detailed in-person home interview (National Health & Nutrition Examination Survey)	10
Mortimer (66)	UK	2003	Patients from seven GPs, 53,000	The Eastern Hull Primary Care Trust	10
Domino (67)	USA	2005	Randomly selected annual sample of 23,000–35,000	Medical Expenditure Panel Survey	12
Kaye (68)	UK	2000	Patients from GPs 1.4-1.7 million aged 10 or older	The General Practice Research Database	12 men 9 women 15
Trifiro (69)	Italy	2002	465,061 patients from 320 GPs	Sample from the Health Search Database	13
Children and adolescents					
Rani (70)	UK	2005	789 467 patients aged 19 or younger	The General Practice Research Database	0.8
Clavenna (62)	Italy	2004	1,484,770 aged 17 or younger	ARNO multiregional prescription database	men 0.9 women 0.5
Olfson (30)	USA	1996	6,490 children aged 18 or younger	Medical Expenditure Panel Survey	2.0
Bonati (63)	Italy	2002	Review of 15 articles	MEDLINE and	0.8
	USA	2000		EMBASE	2.8
	The Netherlands	1999			3.4
Kalverdijk (71)	Canada	1999			3.8
	The Netherlands	2005	119,612 patients aged 19 or younger	The Inter-Action database	6.8
Zoega (64)	Iceland	2007	Residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	10.6

The prevalence rates for antidepressant drug use ranged from 10 to 101 per 1,000 adults, (table 5 a) and from 1.1 to 23.7 per 1,000 children and adolescents (table 5 b); trend analyses have demonstrated a remarkable increase in the use of antidepressants since the introduction of the SSRIs (35-36).

Table 5a Prevalence rates of antidepressant drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Adults					
Ohayon (59)	France, Italy Germany, UK	1993- 1997	Representative sample of 18,679 aged 15 or older	Telephone survey	10
Alonso (57)	Germany, The Netherlands, Belgium, Italy, Spain, France	2001- 2003	Representative sample of 21,425 aged 18 or older	Detailed in-person, computer- assisted, home interview	37
Isacsson (72)	Sweden	1996	Representative sample, 18,000	The prescription database of the county of Jämtland	13 men 11 women 16
Meijer (73)	The Netherlands	2001	Representative sample, 850,000	The PHARMO database	SSRI 17 TCA 6
Olson (74)	USA	1997	Representative sample of 32,636	Medical Expenditure Panel Survey	23
Nielsen (58)	Denmark	2000	Representative sample of 22,486 aged 16 or older	Danish Health and Morbidity Survey 2000	26 men 18 women 33
Rosholm (75)	Denmark	1997	Population of Fünen, 470,000	The Odense Pharmaco- epidemiological Database	41
Percudani (65)	Italy	2001	9,1 million residents, Province of Lombardy	Data from prescription database of reimbursed drug	44 men 29 women 59
Beck (61)	Canada	2002	Representative sample of 36,984 aged 15 or older	The Canadian Community Health Survey Medication the last two days	47
Trifiro (76)	Italy	2003- 2004	142,346 patients from 119 GPs	Data from the Arianna database	60
Bramness (77)	Norway	2004	The Norwegian population 4.6 million	The Norwegian prescription database	Men 50 women 93
Raymond (78)	Canada	2004	4.1 million residents, British Columbia	The British Columbia PharmaNet system	72
Poluzzi (79)	Italy	2002	4.6 million residents in the province	The Emilia Romagna Regional Health Authority Database	78
Paulose-Ram (60)	USA	1999- 2002	representative sample of 12,060 aged 17 or older	Detailed in-person home interview (National Health and Nutrition Examination Survey)	81
Exeter (80)	New Zealand	2007	Residents (n not stated) aged 15 or older	Pharmaceutical Management Agency of New Zealand	94
Olson (35)	USA	2005	Representative sample of 32,320 aged 6 or older	Medical Expenditure Panel Surveys	101

Table 5b Prevalence rates of antidepressant drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Children and adolescents					
Zito (81)	Germany	2000	480,680 aged 19 or younger	Gmuender ErsatzKasse	1.1
	Denmark	2000	111,452 aged 19 or younger	The Odense Pharmaco- epidemiological Database	1.8
	The Netherlands	2000	72,570 aged 19 or younger	The Inter-Action database	5.4
	USA	2000	125,383 aged 19 or younger	The State-Children's Health Insurance program	16.3
Bonati (63)	Italy	2002	Review of	MEDLINE and	2.8
	The Netherlands	1999	15 articles	EMBASE	4.4
	UK	1999			6.0
	USA	2000			15.8
	Canada	1999			16.2
	USA	2002			23.7
Clavenna (62)	Italy	2004	1.5 million aged 17 or younger	ARNO, multiregional prescription database	men 2.6 women 2.7
Olfson (30)	USA	1996	6,490 aged 18 or younger	Medical Expenditure Panel Survey	10.0
Zoega (64)	Iceland	2007	Residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	23.4

Studies focusing on anxiolytics and hypnotics combined revealed prevalence rates ranging from 29 to 106 per 1,000 (table 6). One study revealed the rates for each drug group separately with a mean prevalence rate of 43 per 1,000 for anxiolytics and 15 per 1,000 for hypnotics in France, Germany, Italy, and UK together.

A Norwegian study on hypnotic drug use in 2006 showed rates of 48 and 90 per 1,000 as regards Z-hypnotics and 8 and 10 per 1,000 for BZD hypnotics, for men and women respectively.

Only three studies were found assessing the use of anxiolytics and hypnotics among children and adolescents, with prevalence rates from 1.8 to 6.9 per 1,000 (table 6).

Table 6 Prevalence rates of anxiolytic and hypnotic drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Adults			Anxiolytics / Hypnotics combined		
Nielsen (58)	Denmark	2000	22,486 aged 16 or older	Danish Health and Morbidity Survey 2000	29 men 19 women 39
Beck (61)	Canada	2002	36,984 aged 15 or older	The Canadian Community Health Survey Medication the last two days	31
Paulose-Ram (60)	USA	1999-2002	12,060 aged 17 or older	Detailed in-person home interview (National Health and Nutrition Examination Survey)	38
Lagnaoui (82)	France	2001	4007 aged 18 or older	National cross-sectional telephone survey	75 men 52 women 97
Magrini (14)	Italy	1992-1993	2803 patients aged 18 or older from 62 GPs	A questionnaire survey	86 men 50 women 118
Alonso (57)	Germany, the Netherlands, Belgium, Italy, Spain, France	2001-2003	21,425 aged 18 or older	Detailed in-person computer-assisted home interviews	98
van Hulst (83)	The Netherlands	1993	13,500 patients from 6 GPs	Data from the local pharmacy	100 men 69 women 131
Isacson (84)	Sweden	1976	Population of Tierp, 20,000	Local research database	106 men 71 women 144
			Anxiolytics		
Ohayon (59)	France, Italy, Germany, UK	1993-1997	Representative sample of 18,679 aged 15 or older	Telephone survey	43
	UK	1994			6
	Germany	1996			7
	Italy	1997			58
	France	1993			90
			Hypnotics		
Ohayon (59)	France, Italy, Germany, UK	1993-1997	Representative sample of 18,679 aged 15 or older	Telephone survey	15
	Germany	1996			7
	Italy	1997			7
	UK	1994			16
	France	1993			25
Hausken (15)	Norway	2006	All inhabitants 4.6 million aged 18 to 69	The Norwegian Prescription Database	Z-hypnotics men 48 women 90 BZD men 8 hypnotics women 10
Children and adolescents			Anxiolytics / Hypnotics combined		
Bonati (63)	USA	2000	Review of 15 articles	MEDLINE and EMBASE	2.5
	USA	1996			4.9
	The Netherlands	1999			6.9
Olfson (30)	USA	1996	6,490 children aged 18 or younger	Medical Expenditure Panel Survey	3.0
			Anxiolytics		
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	1.8
			Hypnotics		
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	2.6

Incidence rates

Only a few publications were found that revealed incidence rates of psychotropic drug use. For adult users, one study from the United Kingdom (68) and two studies from Italy (12, 69) calculated incidence rates for antipsychotics (table 7). Both Italian studies evaluated the year 2002, even though the results were quite different. The study based on the whole population in a province revealed an incidence rate per 1,000 inhabitants of 2.6, while the study based on the population in a GP database had 10.9. In the study from United Kingdom, the rates were 3.3 for men and 5.0 for women.

Studies from five different countries revealed incidence rates for antidepressants ranging from 4.2 to 30.6 per 1,000 adults. The Italian study (76) with the highest incidence rate used a GP based database probably not representative of the general population. The other studies were based on representative samples, or the entire population. In addition to methodological differences, real differences may explain some of the variations between the study results.

No study was found on incidence rates of anxiolytic drug use in adults.

A Norwegian study (15) revealed incidence rates for hypnotics of 18.4 and 1.3 per 1,000 adult men for Z-hypnotics and BZD hypnotics, respectively, and 29.6 and 1.3 per 1,000 adult women, respectively.

Only three studies were found focusing on incidence rates for some of these drug groups in children. The incidence rates for antipsychotics ranged from 0.3 to 3.7, while the other rates were all from one Icelandic study with incidence rates of 8.0 for antidepressants, 1.3 for anxiolytics and 2.5 for hypnotics per 1,000 children (table 7). The incidence rates for children in Iceland are probably not representative for other countries as prevalence rates from Iceland differ from the figures in other countries.

Table 7 Incidence rates of psychotropic drug use per 1,000 inhabitants in different countries and years

Author	Country	Year	Population	Method / Material	Rate
Adults			Antipsychotics		
Mirandola (12)	Italy	2002	2,6 million, all ages Province of Veneto	Prescription database of reimbursed drugs	2.6 men 2.2 women 2.9
Trifiro (69)	Italy	2002	465,000 from 320 GPs aged 15 or older	The Health Search Database	10.9
Kaye (68)	UK	2000	Patients from GPs 1.4- 1.7 million aged 10 or older	The General Practice Research Database	men 3.3 women 5.0
			Antidepressants		
Raymond (78)	Canada	2004	4.1 million citizens, British Columbia	The British Columbia PharmaNet system	4.2
Rosholm (75)	Denmark	1997	Population of Fünen, 470,000 aged 20 or older	The Odense Pharmaco - epidemiological Database	13.0
Isacsson (72)	Sweden	1996	Representative sample, 18,000	The prescription database of Jämtland	13.3 men 10.9 women 15.7
Hansen (13)	Denmark	1998	Population of Fünen, 470,000 aged 18 or older	The Odense Pharmaco - epidemiological Database	17.0
Meijer (73)	The Netherlands	2001	850,000 aged 18-85	The PHARMO database	SSRI 14.5 TCA 5.8
Trifiro (76)	Italy	2003- 2004	142,346 patients from 119 GPs in Italy aged 15 or older	The Arianna database	30.6
			Hypnotics		
Hausken (15)	Norway	2006	All inhabitants 4.6 million aged 18 to 69	The Norwegian Prescription Database	Z-hypnotics men 18.4 women 29.6 BZD-hypnotics men 1.3 women 1.3
Children and adolescents			Antipsychotics		
Rani (70)	UK	2005	789 467 patients aged 19 or younger	The General Practice Research Database	0.3
Kalverdijk (71)	The Netherlands	2005	119,612 patients aged 19 or younger	The Inter-Action database	1.6
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	3.7
			Antidepressants		
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	8.0
			Anxiolytics		
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	1.3
			Hypnotics		
Zoega (64)	Iceland	2007	All residents (n not stated) aged 17 or younger	The Medicines Registry on prescribed drugs in Iceland	2.5

Distribution among physicians

Some studies have analyzed various physician groups' proportions of psychotropic drug prescribing. GPs issued the vast majority of prescriptions in all but one study (table 8), while psychiatrists prescribed from 5.7 to 22.5 %.

Some studies discussed the differences in choice of drug types, showing that GPs more often prescribed first generation antipsychotics (85-86) than psychiatrists, and that psychiatrists more often prescribed higher doses of antidepressants than GPs (73, 87).

A French study compared patients identified as depressed by GPs and psychiatrists. Psychiatrists' patients were younger, more often urban, educated, met DSM-IV criteria for depression, had been hospitalized for depression and were younger at onset of depressive problems than the GPs' patients. No difference was found for psychiatric and somatic comorbidity, suicide attempt or severity of current depression. Compared to GPs, psychiatrists more often prescribed tricyclic and non-SSRI non-tricyclic antidepressants, and used more prolonged treatment duration. GPs' patients received less psychotherapy and more non-conventional treatment as homeopathy, acupuncture, herbal medicine etc. The authors concluded that the differences between practices of GPs and psychiatrists appeared to reflect the organization of the French health care system more than the competence of the providers (88).

A study from Sweden found an increased use of antidepressants and fewer suicides in the county of Jämtland, after a primary care educational program on treatment of depression (89), repeating an earlier study from Gotland (90).

An American study comparing the care given by primary care providers and psychiatrists to patients with anxiety concluded that nearly half the primary care patients with anxiety disorders were not treated. However, when they were treated, the care received from primary care physicians and psychiatrists was rather similar (91).

Another American study about the prescribing practices of physicians caring for children with mental illness found no significant differences between psychiatrists and primary care physicians in psychotropic prescribing practices (92).

Table 8 Proportion of dispensed prescriptions of psychotropic drugs, by prescriber group

Author	Country	Year	Population	Method / Material	% of dispensed prescriptions		
					GPs	Psychiatrists	Others
Psychotropic drugs			(prevalence data)				
Ohayon (93)	UK	1994	4,972, aged 15 or older	Telephone survey	> 80		
Antipsychotics			(prevalence data)				
Hamann (86)	Germany	1999-2001	25 million customers	The statutory health insurance	60	34*	6
Ohayon (59)	France, Italy, Germany, UK	1993-1997	18,679 aged 15 or older	Telephone survey	31.7	22.5	45.8
Antidepressants			(prevalence data)				
Ohayon (59)	France, Italy, Germany, UK	1993-1997	18,679 aged 15 or older	Telephone survey	55.8	15.4	28.8
Percundani (94)	Italy	2001	9 million residents, Lombardy	The Regional Administrative Database	84.9 – 91.2		
McManus (87)	Australia	2000	88 % of dispensed antidepressant in Australia (n not stated)	Health Insurance Commission claim records	86	10	4
Antidepressants			(incidence data)				
Verdoux (95)	France	2005-2007	19,975 aged 18 or older	Social Security Insurance database	80.9	5.8	13.3
Henriksson (96)	Sweden	1995	18,000 Representative sample	The prescription database of Jämtland	76	14	10
Anxiolytics			(prevalence data)				
Ohayon (59)	France, Italy, Germany, UK	1993-1997	18,679 aged 15 or older	Telephone survey	69.8	6.1	24.1
Hypnotics			(prevalence data)				
Ohayon (59)	France, Italy, Germany, UK	1993-1997	18,679 aged 15 or older	Telephone survey	81.5	5.7	12.8

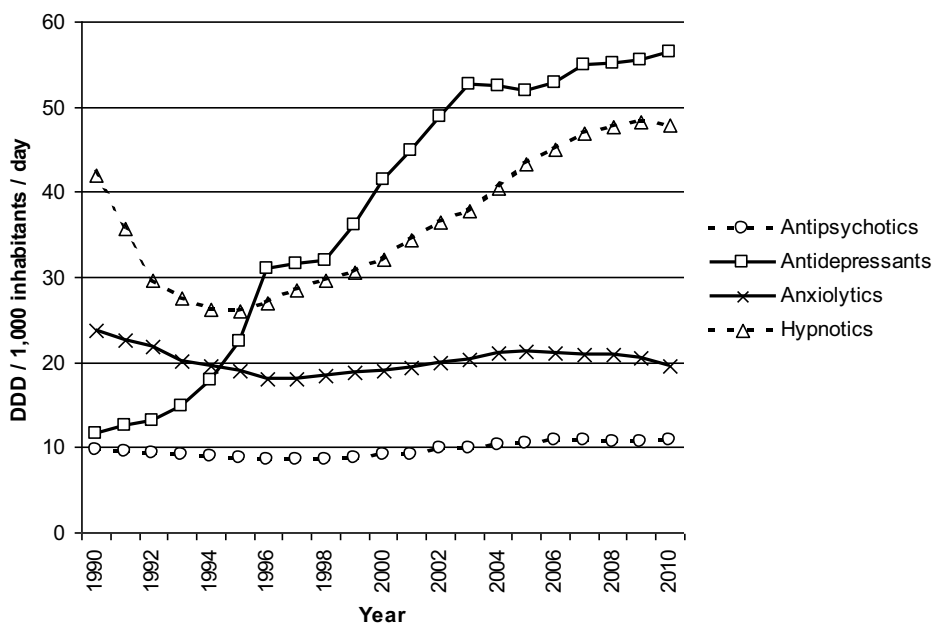
* Psychiatrists, neurologists and psychotherapists

The cited studies confirm extensive use of psychotropic drugs. Especially the use of antidepressants has increased substantially in most high-income countries since the early 1990s. The choice of drugs has changed from older and cheaper to newer and more expensive drugs. The studies have shown that most of the psychotropic drugs are prescribed by GPs, but no detailed scientific information exists about the extent to which GPs initiate psychotropic drug treatment. Neither is any detailed analysis found regarding the relative contribution of different prescribing groups when it comes to the different drug groups for patients of different ages. Such information is relevant because drugs are widely used to treat psychiatric problems.

It is important to examine the situation in Norway since prescription practices are likely to differ between countries, and few studies have been performed with this focus. The four psychotropic drugs groups included in this study constituted 7.7 % of expenses for drug use in Norway in 2005 (97). The wholesale figures in Norway, measured as DDD per 1,000 inhabitants per day are shown in figure 2.

(Department of Pharmacoepidemiology at the Norwegian Institute of Public Health, personal information).

Figure 2 Wholesale figures for psychotropic drugs in Norway 1990-2010



The quality and the capacity of the health care system for handling mental problems are prioritized areas in the health services.

Knowledge about prescribing patterns in different parts of the healthcare system is a prerequisite to improve the quality of psychotropic drug treatment. The impact from different parts of the health care system on the psychotropic drug use is essential information for the authorities to manage the health services in a proper way, and the government has requested more research on the subject of pharmacotherapy (98).

2. The present study

This study examines the use of psychotropic drugs in the general Norwegian population during the years from 2005 to 2008.

2.1 Aims of the papers included in the thesis

The more specific objectives of the study were to examine the incidence and prevalence rates, and the distribution of psychotropic drugs in general practice versus specialist care.

The aims of each paper were as follows;

- **Paper I** To analyze psychotropic drug use in the general population of Norway in 2005, with special emphasis on prescribing patterns in primary and secondary care.
- **Paper II** To examine the incidence rates for antipsychotic and antidepressant drug treatment in the general population of Norway, and to explore to what extent the treatment was initiated by GPs, psychiatrists or other physicians, respectively.
- **Paper III** To examine incidence rates for treatment with addictive anxiolytics and hypnotics in Norway, the proportions initiated by GPs, psychiatrists or other physicians, and the course of the treatment among incident users during a 3.5 year period of follow up.

2.2 Material and methods

2.2.1 Data sources and study population

The research is based on data from the Norwegian Prescription Database (NorPD), the General Practitioner Database at Norwegian Social Science Data Services, and information about the general Norwegian population from Statistics Norway.

The Norwegian Prescription Database, NorPD

The Norwegian Prescription Database was established in 2004 and is maintained at the Norwegian Institute of Public Health (99). It is a national health register with the aim to collect and process data on drug consumption by humans and animals in Norway. The data is used to map usage and monitor trends in the Norwegian drug consumption. Health authorities receive statistical information needed for quality control of drug use and for management and planning of the health care system. In addition, the NorPD is an important resource for research, especially for pharmacoepidemiological studies.

The register contains information on all prescriptions fully paid for by patients, as well as those reimbursed by the government, dispensed at all Norwegian pharmacies to community-dwelling individuals from 1 January 2004. Detailed information about the dispensed drugs and basic demographic information about patients and prescribers are included (97). The information is clearly connected to each physician and patient by a unique pseudonym code. Dispensed prescriptions from each physician and redeemed prescriptions to each patient can thus be followed over time. The privacy of the individual is strictly protected, and it is illegal to try to reverse the information to reveal the identity of patients or physicians.

The database contains no information about drugs purchased without prescription (over the counter, OTC), or the medications dispensed to institutionalized individuals in hospitals and nursing homes, or those who are in prison.

The Regular General Practitioner Database

When the national regular GP scheme was implemented in 2001, the Regular General Practitioner Database was established at the Norwegian Social Science Data Services (50). The Regular GP Database contains monthly updated information on individual GP's patient population, derived from the Norwegian Labour and Welfare Services, Statistics Norway and the Norwegian Social Science Data Services.

Statistics Norway

Statistics Norway is the central bureau of statistics in Norway and was established in 1876. The Agency has primary responsibility for meeting the need of statistics in the Norwegian society. In this project, statistics on the general population were obtained from Statistic Norway and used to establish denominators in the analysis of the different rates concerning gender and various age groups.

Variables

The variables extracted from NorPD included data from all prescriptions of antipsychotics (ATC group N05A), anxiolytics (N05B), hypnotics (N05C) and antidepressants (N06A) from 1 January 2004 until 31 August 2009.

GPs' unique pseudonym codes and information about their enlisted patient populations in February, May, August and November in each year were collected from the Regular GP Database.

Data from NorPD and from the Regular GP Database were merged by Statistics Norway, using each patient's and prescriber's pseudonym code, enabling us to analyze the data at the individual level, while personal anonymity was ensured. The variables extracted from the different registers and included in the study database are shown in table 9.

Table 9 Variables extracted to the study database

The Norwegian Prescription Database			
Drugs	ATC code	Trade name	Generic name
Redeemed prescriptions	Dispensing date	Volume (DDD)	Drug formulation
Patients	Pseudonym code	Gender	
	Birth year and month	Death year and month	
Prescribers	Pseudonym code	Gender	Birth year
	Profession	Specialties	
The Regular General Practitioner Database			
Prescribers	Pseudonym code		
Enlisted population	Date	Number of women	Number of men
	Patient age groups (<10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80)		
Statistics Norway			
General population	Date	Birth year	
	Population of men	Population of women	

2.2.2 Statistical analysis

The chi-square test was used to compare proportions. P values of < 0.05 were considered statistically significant. Logistic regression analyses were used to analyze the associations between binary outcome variables and several independent variables. Effect estimates were presented as odds ratios (OR) with 95 % confidence intervals (CI).

In *Paper I*, the whole population is included, and therefore the results are shown without confidence intervals or p-values.

Logistic regression analyses were performed to examine associations between selected variables; *Paper II*: gender, age groups, prescriber groups, and the use of older antipsychotics or antidepressants and *Paper III*: gender, age groups, drug volume in first quarter, drug redeemed at index day, prescriber groups, prescribers gender, prescribers age groups and prescribers prescribed volume in total, and the risk of being long-term or heavy user of addictive anxiolytics and hypnotics, respectively.

A follow-up analysis of the cohort of new users was carried out in *Paper III*, presented as percentages of the enrolled patients who redeemed at least one prescription in each subsequent quarter (91 days), assigned to the prescriber group that initiated the

treatment. Patients who died in one quarter were excluded from the analysis of the next quarter, i.e. the denominator was the number of patients who were still alive at the beginning of each quarter.

STATA software version 9.2 (Stata Corp., College Station, TX, USA) and the Vassar Stats website for statistical computation (100) were used.

2.2.3 Ethics

The Regional Committee for Medical and Health Research Ethics, the Directorate of Health, the Norwegian Labour and Welfare Services, and the Norwegian Data Inspectorate all approved the study.

2.3 Synopsis of papers

Paper I

Kjosavik SR, Ruths S, Hunskaar S. Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database.

Pharmacoepidemiology and Drug Safety 2009;18:572-8.

Objectives:

To determine the prevalence rates of psychotropic drug use and the distribution of the prescribing among GPs, psychiatrists and other physicians in Norway.

Material and methods:

Information about all prescriptions to community-dwelling persons of antipsychotics, anxiolytics, hypnotics and antidepressants redeemed at all pharmacies in Norway in 2005 was extracted from the Norwegian Prescription Database and merged with data about all GPs in the same period from the Regular GP Database at the Norwegian Social Science Data Services. Information about the general population was collected from Statistics Norway.

Results:

One year prevalence rates per 1,000 inhabitants were 153 for use of any psychotropic drugs, 24 for antipsychotics, 60 for antidepressants, 62 for anxiolytics, and 79 for hypnotics. The rates increased with patients' age and were considerably higher for women than men. GPs prescribed 80 % of the medications, psychiatrists 5 % and other physicians 15 %. Psychiatrists prescribed 32 % of the psychotropic drugs to patients younger than 20. The proportion prescribed by psychiatrists declined rapidly with patients' age and was about 2 % of the prescriptions to patients aged 60 or older.

Conclusions:

GPs issued the majority of prescriptions of antipsychotics, anxiolytics, hypnotics and antidepressants, and the proportion increased with patients' age. Consequently, the quality of pharmacological treatment for mental health problems for adults relies mainly on GPs.

Paper II

Kjosavik SR, Hunskaar S, Aarsland D, Ruths S. Initial prescription of antipsychotics and antidepressants in general practice and specialist care in Norway. *Acta Psychiatrica Scandinavica* 2011;123:459-65.

Objectives:

To reveal the incidence rates of antipsychotic and antidepressant drug use and to what extent such treatment is initiated by GPs, psychiatrists or other physicians in Norway.

Material and methods:

Information on all prescriptions of antipsychotics and antidepressants redeemed at all pharmacies in Norway from 1 January 2004 until 31 August 2009 was extracted from the Norwegian Prescription Database and merged with data about all GPs in the same period from the Regular GP Database. The study population included all patients who redeemed at least one prescription of an antipsychotic and/or antidepressant drug during 2008, provided that they did not release drugs from the same therapeutic subgroup during the 4 year period from 2004 to 2007. Information about the general population was collected from Statistics Norway.

Results:

One year incidence rates per 1,000 inhabitants were 3.4 for antipsychotics and 8.6 for antidepressants. The rates increased with patients' age, except for the age group 60-69 years. Women had higher incidence rates than men but the differences between genders were less pronounced for antipsychotics.

GPs initiated the treatment with antipsychotics for 58 % of the patients, and with antidepressants for 73 %, while the figures for psychiatrists were 15 % and 6 %, respectively. Patients younger than 20 years got their first prescription of antipsychotics from a psychiatrist in 47 % and of antidepressants in 26 % of the cases. The proportion of patients who got started their treatment by a psychiatrist declined rapidly with patients' age, while the GPs' contribution to initial prescribing increased considerably with patients' age.

Psychiatrists issued second generation antipsychotics to 65 % while the other groups of physicians prescribed first generation antipsychotics to more than 70 % of the patients. As regards antidepressants, other specialists provided older antidepressants to 63 %, while physicians without specialty and GPs prescribed newer antidepressants to more than 65 %, whereas psychiatrists issued newer antidepressants in 88 %.

Of the new users of antipsychotics, 57 % redeemed only one prescription during 2008 and a follow-up period of 8 months. The corresponding figure for antidepressants was 33 %. Patients were more likely to release more than one prescription if the initial drug was a second generation antipsychotic or antidepressants, and if the treatment was initiated by a psychiatrist.

Conclusions:

GPs initiated the treatment of both antipsychotics and antidepressants to a majority of the patients, except for antipsychotics to patients younger than 20. Psychiatrists' share was limited, especially among older patients. Consequently, efforts for quality improvement of pharmacotherapy in mental health need to involve GPs, and an increased focus from psychiatrists towards the increasingly ageing part of the population seems requisite.

Paper III

Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway.

European Journal of Clinical Pharmacology 2011 Sep 18. [E-pub ahead of print]

Objectives:

To examine the incidence rates of treatment with addictive anxiolytics and hypnotics in Norway, the percentage initiated by GPs, psychiatrists or other physicians, and the effect of selected variables on the risk among new users of becoming long-term or heavy users during a 3.5 years follow-up period.

Material and methods:

Information on all prescriptions of anxiolytics and hypnotics redeemed at all pharmacies in Norway from 1.January 2004 until 31.August 2009 was extracted from the Norwegian Prescription Database and merged with data about all GPs in the same period from the Regular GP Database at the Norwegian Social Science Data Services. The study comprised only anxiolytics and hypnotics that are considered addictive by the Norwegian Medicines Agency, and prescribed as oral formulations. Included in the study were all patients who redeemed one or more prescriptions of such drugs in 2005, provided that they did not redeem any of these drugs during 2004. The day of the first redeemed prescription of anxiolytics or hypnotics was defined as the index day for each person, and all prescriptions redeemed in the next 14 quarters (3.5 years) were included in the follow up analysis. Patients who redeemed prescriptions only during the first quarter and received a total volume of ≤ 30 DDD were defined as short-term users. In addition, we defined patients as long-term users if they redeemed prescriptions in ≥ 3 quarters in a row and received > 180 DDD in total during the three quarter period, and heavy users if they received an average of ≥ 3 DDD/day during the quarter with highest redeemed drug volume.

Results:

One-year incidence rates per 1,000 inhabitants were 18.2 for anxiolytics, 24.5 for hypnotics, and 35.4 for anxiolytics and hypnotics combined. The incidence rates increased considerably with patients' age and were higher for women than men in all age groups, except those aged 80 years and older who received hypnotics.

Patients aged 19 or younger received their first prescriptions of anxiolytics and hypnotics from a GP in 37.5 % and 64.9 % of the cases, while psychiatrists provided 5.0 % and 9.8 %, respectively. Adults aged 20 to 39 years received their first prescription of anxiolytics and hypnotics from a GP in 72.2 % and 72.0 % of the cases, and from a psychiatrist in 5.0 % and 5.5 %, respectively, but psychiatrists' share declined rapidly with increased patients' age, and accounted for less than 2 % in patients aged 60 and older.

Of the cohort of new users, 30.8 % received short-term treatment, 11.8 % became long term-users, and 1.4 % became heavy users.

When adjusted for other variables, the strongest predictor of both long-term and heavy use emerged to be the total drug volume redeemed during the first quarter. Most long-term users and heavy users received their first prescription from a GP, but the individual risk of both long-term use and heavy use were highest if the treatment was initiated by a psychiatrist. The risk of heavy use was highest among males aged 20 – 39 years and declined with higher age, while the risk of long-term use increased with patients' age.

Conclusions:

The prescribing strategy towards incident users seems to be crucial to prevent long-term or heavy use. In order to prevent inappropriate drug use, there is a need for implementation of relevant guidelines, and systems for structured clinical audit, especially in general practice.

2.4 Discussion

The three papers have different objectives, but are based on a common comprehensive research database and closely related. To our knowledge, this is the first study that analyzes different physician groups' contribution to the prescription of various psychotropic drugs in more detail. Combining the results from the sub-studies reveals even more understanding of the prescribing of these drugs. The relative proportions of the four drug groups dispensed to new users by GPs, psychiatrist and other physicians are revealed by combining *Paper II* and *Paper III*. Combinations of results from all the papers make it possible to estimate average treatment duration of the four drug classes by age.

2.4.1 Discussion of each main finding

Prevalence rates

The prevalence rates per 1,000 were 153 for psychotropic drugs, 24 for antipsychotics, 60 for antidepressants, 62 for anxiolytics and 79 for hypnotics in the Norwegian population in 2005 (*Paper I*).

This study is based on the entire Norwegian population and covers all age groups, while many other studies focus on either children and adolescents or adults. It is important that results from different papers must be considered according to the ages they cover to be compared in a proper manner.

Comparison with other studies in adults

The prevalence rate of psychotropic drug use in adults in Norway is higher than in other countries (57-61). The same is true for antipsychotics (12, 57, 59-61, 65-68) and hypnotics (15, 59), while higher prevalence rates for anxiolytics has been shown in France (59), and for antidepressants in the United States (35) and in New Zealand (80).

Several aspects may explain some of the differences. Many studies were based on surveys of sampled cases (14, 35, 57-61, 67, 72, 74, 82). Such studies may be affected of bias, e.g. recall bias in interview surveys or selection bias of the sample. In addition,

some studies estimated point prevalence rates while our study analyzed one-year prevalence rates, and higher figures may then be anticipated.

In the case of antipsychotics, two Italian studies (12, 65) were based on databases covering large populations in provinces, but only reimbursed prescriptions. Second generation antipsychotics were not covered by the reimbursement system in Italy until 2001, and the studies analyzed data from the year of 2001 and 2002. An impact of this legislation is likely.

GPs' populations were the basis for some studies (14, 66, 68-69, 76). Such samples may be biased compared to the general population, as healthy individuals do not necessarily see a GP, and more seriously ill patients may in some countries be treated in secondary health care only.

Databases covering the whole population of counties or provinces were used in six studies focusing on use of antidepressants (65, 75, 77-80). The differences between these studies may reflect the trend in use of antidepressants, as the older ones have lower rates (65, 73, 75), while the three studies from 2002 to 2004 (77-79) are in line with the Norwegian results, and the newest from 2007 (80) found higher rates.

In addition, real differences in use of psychotropic drugs between countries are probable, and may explain variations to some extent.

Comparison with other studies in children and adolescents

Studies of psychotropic drug use among children and adolescents included different drug groups and made comparisons difficult.

As regards antipsychotics, prevalence rates in Norway were higher than in Italy and the United Kingdom (62, 70), and lower than in Iceland and the Netherlands (64, 71). Lower rates were found in Italy, Germany, and Denmark than in Norway for antidepressants (62-63, 81), while rates were higher in the Netherlands, Iceland, Canada and in the United States (30, 63-64, 81). The prevalence rates for anxiolytics and hypnotics were in line with the Netherlands when analyzed together (63), but higher than the rates in the United States (30). Separately, the Norwegian rate of

anxiolytic use was higher than the Icelandic, while the opposite was the case for hypnotics (64).

Morbidity and treatment gap

Reviews on prevalence rates of mental disorders in Europe in 2005 and 2010 (101-102) show similar results as regards the main psychiatric disorders, i.e. no substantial increase or decrease were identified. According to the “best estimate” from the latest report, anxiety disorders were most frequent, with a one-year prevalence of 14 %. Mood disorders were the second with a 6.9 % prevalence of major depression and 0.9 % of bipolar disorder. Non-organic insomnia had an estimated prevalence of 7.0 %, but insomnia is often a major symptom of other disorders, and the authors assumed that this figure was substantially overestimated. Somatoform disorders had a prevalence of 4.9 %, psychosis 1.2 %, and eating disorders 0.4 %.

According to WHO (103), the treatment gap between patients with various psychiatric disorders and the share that received treatment in Europe was estimated to 18 % for schizophrenia, 25 % for obsessive compulsive disorder, between 40 and 50 % for major depression, dysthymia, bipolar disorder, and panic disorder, above 60 % for generalized anxiety disorder, and more than 90 % for alcohol abuse and dependence disorder.

Interpretation

Clinical and diagnostic information were not available in the study, and yet the results have led to some thoughts about the prescribing practice. Compared to the prevalence estimates of psychosis and bipolar disorders, the prevalence rate for antipsychotic use of 2.4 % seems high. One explanation would be that a higher percentage of patients with psychosis or other severe psychiatric disorders receive treatment in Norway than estimated for Europe. However, the 57 % proportion of patients who redeemed only one prescription of antipsychotics supports the assumption that antipsychotics often are used for non-psychotic or less severe mental problems. Such an explanation is supported by trends in antipsychotic drug use in other countries, revealing expansion of indication for use and increased off-label prescribing of these drugs (31).

The proportion of the patients who redeemed several prescriptions of antipsychotics is more in line with the prevalence rate of psychosis.

According to a Canadian study (38), a third of antidepressants were prescribed for reasons other than depression, as generalized or other anxiety disorder, sleep problems, musculoskeletal conditions, migraine, and chronic pain. Assuming similar prevalence of major depression in Norway as estimated for Europe, and a corresponding prescribing practice in Norway as in Canada, i.e. two-thirds of the antidepressants used for depression, the gap in drug treatment for depression in Norway is close to the WHO-estimated value for Europe.

The difference between the prevalence rate for use of anxiolytics (6.2 %) and the estimated rate for anxiety disorders (14 %) is much larger. Anxiety may range from mild complaints to disabling mental illness, and perhaps some persons included in studies have confirmed anxiety problems although they would deny a need for treatment. Regarding treatment, other drugs than anxiolytics and non-pharmacological treatment are primarily recommended for these disorders, since patients often need long-term treatment, while anxiolytics are recommended for short-term treatment only (104). Since this study lacks clinical information and it is impossible to use the figures from this study to assess the treatment provided patients with anxiety disorders in Norway.

Insomnia is a common symptom of various mental disorders. In such cases, the sleep disturbances may wane when the primary disorder is treated properly, although residual sleep problems are relatively common. Non-pharmacological treatment of insomnia has shown better results than drugs in some studies (4), and hypnotics are only recommended for short-term use. The prevalence for use of hypnotics was 7.9 %, the highest rate among the four drug groups, and it seems evident that hypnotics are used too widely.

Incidence rates

The incidence rates per 1,000 were 3.4 for antipsychotics and 8.6 for antidepressants (*Paper II*), and 18.2 for anxiolytics, 24.5 for hypnotics, or 35.4 for anxiolytics and hypnotics combined (*Paper III*). The studies were based on the entire Norwegian population and covered all ages.

Few papers were found revealing incidence rates for psychotropic drug use, and most were focused on either children and adolescents, or adults.

Comparison with other studies in adults

Two Italian studies analyzed the incidence rates of antipsychotic drug use, with quite different results; 2.6 per 1,000 and 10.9 per 1,000 (12, 69). Both studies used a one-year baseline period to exclude prevalent users, and analyzed prescriptions to new users in 2002. The first study was based on the whole population of a province, but only reimbursed prescriptions were included. The other used a GP based database of patients aged 15 or older. Differences in the databases and in the age of enrolled patients might explain the variation in the results, and clearly demonstrate the importance of such methodological differences.

A study from the United Kingdom, also based on a GP database, used a two year baseline period to exclude prevalent users. Patients aged 10 or older were included, and the results were rates of 3.3 per 1,000 for men, and 5.0 per 1,000 for women (68).

Incidence rates of antidepressants were found in six studies of which four used large population based databases (13, 73, 75, 78), one was a representative sample of a county (72), and one used a GP based database (76). The incidence rates ranged from 4.2 per 1,000 to 30.6 per 1,000. The highest rate was from a GP based database in Italy (76), and as discussed for antipsychotics, the results are probably not representative for the general population. The Canadian study (78) included all ages, and analyzed the incidence rates year by year during the period from 1998 to 2004. The results show a maximum incidence rate in 1999 of 12.4 per 1,000, which declined to 4.2 in 2004, although the prevalence rates increased in the period.

A Dutch study has estimated separate incidence rates for tricyclic antidepressants and SSRI, making comparison more difficult as the information about the combined rate is lacking. The incidence rates in the other studies conducted between 1996 and 2001 ranged from 13.0 to 17.0 per 1,000 among adults. Based on adults aged 20 or older, the Norwegian incidence rate in 2008 was 11.4. The difference in incidence may be related to different years of observation, but differences in the prescribing trends in the countries are probable.

As regards anxiolytics and hypnotics, only one Norwegian study was found assessing incidence rates, but for hypnotics only (15). It was based on the same database as this project, but included only patients between 18 and 69 years with data collection from 2006. This study used data from 2005, but when comparing the same ages, the results were in line.

Comparison with other studies in children and adolescents

Only three studies were found, assessing the incidence rates of such drug use in children and adolescents. In a Dutch study of antipsychotic use based on a large database representative for the general population (71), the rate was twice the Norwegian rate, while a study from the United Kingdom based on GP data (70), had half the Norwegian rate. An Icelandic study (64) revealed incidence rates for all the four classes of psychotropic drugs. The rates were nearly five times higher than the Norwegian results for antipsychotics and antidepressants, while the rates for anxiolytics and hypnotics combined were in line with our study.

Interpretation

The studies revealed that new users were introduced to anxiolytics and/or hypnotics four times as often as to antidepressants and ten times as often as to antipsychotics. Anxiolytics and hypnotics relieve symptoms effectively, but with uncertain long-term treatment effect. Patients, who have experienced benefit of these drugs, often demand extended use even though the drugs are potentially addictive. As only 30.8 % received short-term treatment as recommended, our study confirms sustained use for a majority of patients. Despite the lack of clinical information, it seems likely that too many patients use them in a too long period.

Clinical information is needed to assess the appropriateness of drug treatment. However, the share of the patients who redeemed only one prescription were 57 % for antipsychotics, and 33 % for antidepressants, even though longer treatment periods are recommended for most indications. Increased off-label prescribing and use in other indications than psychosis and depression may be the reason. Consequently, it seems to be a potential for quality improvement also regarding the use of antipsychotics and antidepressants.

A large treatment gap is estimated by WHO between patients with different psychiatric disorders and the portion who are treated (103). To improve the situation, patients in need for treatment should be diagnosed and treated in an appropriate manner. GPs are closest to the patients and have the best opportunity to do so, but the large gap for most mental disorders verify a potential for improvement.

Distribution by age and gender

Prevalence rates (*Paper I*) and incidence rates (*Paper II* and *Paper III*) increased by age. Women used more psychotropic drugs than men at most ages and for all four drug classes, even though the differences were less regarding antipsychotics.

Comparison with other studies

Our findings are in line with age and gender distribution in other studies of prevalence of psychotropic drug use (57-59, 61, 68, 75), and confirm the same trend among new users. The gender differences reflect the morbidity in men and women, as the ratio women / men are estimated to be ≥ 2 for major depression, anxiety disorders, somatoform disorders and eating disorders (102). The prevalence was higher for men than for women only for psychotic disorders and substance dependence disorders, mainly alcohol but also narcotic dependence, in line with two Norwegian studies (105-106). No age group was more susceptible to mental disorders than others in the rural area in Norway (106), while the age group of 30-39 years was most at risk in the city of Oslo (105). The European review (102) found double rates for general anxiety disorder among patient aged 65 or older (3.4 %) compared to the age group 14-65 years (1.7 %), while post-traumatic stress disorder and eating disorders declined by age.

Interpretation

More women than men visit GPs, and do so more often than men in all age groups, except for children aged 10 or younger, and the oldest aged 80 years or older. In addition the number of visits increases by age (22). Thus, increased contact with the health care system may explain some of differences by age and gender. Another important difference between genders is the marked preponderance of males with alcoholic dependence disorders and the treatment gap is estimated to be above 90 % in this group. (103). It is documented that men with mental disorders may use alcohol as self-medication (107-109). Men with mental problems, hidden in the group of dependence disorders, may partly explain the differences between men and women regarding rates for mental disorders.

Older age

Data about individual drug use in nursing homes is not included in NorPD, and thereby unavailable in the study. The number of patients in nursing homes are approximately 41,000 (110) with a mean age of 86 years, and 71 % are women (111). Accordingly, the counter is too small in the analyses of drug use among older people as the patients in nursing homes are included in the denominator. Thus, the real incidence and prevalence rates among older people are even higher than shown.

The increased use of psychotropic drugs by age is of concern. Older people are more susceptible to adverse side effects of drug use (47). Studies have shown that drug related problems caused more than 10% of hospitalizations (112). Women were more prone to side effects of drugs than men (113), and two third were patients aged 60 or older (114). Of the patients admitted to hospital due to adverse side effects, psychotropic drugs caused a minor but significant part. Patients often use psychotropic drugs together with other drugs and poly-pharmacy was shown to be an important risk factor by itself (114).

Behavioral and psychological symptoms are prevalent among patients with dementia (115), and antipsychotics are often used to treat such symptoms, especially in nursing homes (17). Our study shows that such drugs is also commonly given to community-dwelling older people, with the highest incidence rate in the group 80 years and older.

The significant use of older antipsychotics and antidepressants is especially of concern. First generation antipsychotics have stronger dopamine-blocking effects and have a higher risk for parkinsonism and tardive dyskinesias than the second generation antipsychotics. Antipsychotics have other important adverse effects too, and have been shown to increase morbidity and mortality among patients with dementia (116-117). Thus, the extensive use of antipsychotics, especially first generation antipsychotics among older patients, is in contrast to current recommendations (32, 118). The reasons for behavioral and psychological symptoms in dementia are multi-factorial. As shown in a recent study, proper treatment of pain may reduce the symptoms effectively among many patients (119). Thus, thorough clarification of the causes of such symptoms is important to avoid inappropriate use of psychotropic drugs.

Antidepressants have been associated with several severe adverse reactions in older people. Tricyclic antidepressants are usually considered to be particularly harmful to elderly due to anticholinergic, anti-histaminergic, and antiadrenergic effects. In contrast with current recommendations, the incidence rate for receiving older antidepressants increases with age (120). It is also shown an increased use of antidepressants with proximity to death in patients aged 65 or above (121).

A recent study suggests that antidepressants in the elderly are associated with increased mortality, attempted suicide or self-harm, stroke and transient ischemic attack, seizures and more (122), and that the risks are higher in SSRIs compared with tricyclic antidepressants. Increased frequency of falls and fractures has also been revealed among people using antidepressants, but also in patients using anxiolytics and hypnotics (123-124).

The high prevalence and incidence rates for psychotropic drug use among older people confirm a substantial potential for quality improvement of drug use in the geriatric population. Proper management and dosage of drugs are of great importance in these patients, and other therapeutic strategies and psychosocial interventions should be considered instead of or in addition to psychotropic drugs, whenever possible.

Distribution by prescriber

One of the main objectives in this research was to analyze the distribution of the prescribers of psychotropic drugs. The results clearly demonstrate a difference between patients aged 19 and younger compared to the adults. Psychiatrists initiate (*Paper II*) and maintain (*Paper I*) an important part of the treatment with antipsychotics and antidepressants to children and adolescents. Pediatricians and neurologists have similar shares of the anxiolytic prescribing to these patients (not shown in tables), probably due to the use of BZD for somatic conditions, e.g. epilepsy and convulsions.

In adults, the contribution of the GPs is striking, increasing from approximately 70 % to 80 % of the prescriptions of antidepressants, anxiolytics and hypnotics in patients aged 20-39 up to above 80 years, and slightly lower percentages for antipsychotics. Psychiatrists' share declines rapidly with increasing age of the patients. Regarding antipsychotics and antidepressants the percentage decline from 44 % and 26 % to patients aged 19 or younger, to less than 6 % and 3 % to patients above 60, respectively. The psychiatrists' share of prescriptions of anxiolytics and hypnotics was less than 8 % in the youngest, and declined to less than 1 % in patients above 60.

Another interesting finding is the impact from *other physicians*. This group comprised more than 15,000 physicians compared to approximately 4,000 GPs and 1,350 psychiatrists. *Other physicians* include all physicians in other fields than general practice and psychiatry, together with residents in psychiatry not approved as specialists during the studied period. They were responsible for the first prescription in approximately 20 % of the cases receiving antidepressants, anxiolytics and hypnotics, and around 25 % for antipsychotics among adults, regardless of age. The proportion in total is also remarkably constant, with around 12 % of the total dispensed prescriptions of antipsychotics and antidepressants and around 15 % of anxiolytics and hypnotics.

Comparison with other studies

A telephone survey from the United Kingdom (93) found the GPs' proportion of dispensed psychotropic drugs to be above 80 % in 1994. Another telephone survey, analyzing the prescribing to approximately 19,000 patients in four countries from 1993

to 1997 (59), found the share from GPs to be 31.7 % for antipsychotics, 55.8 % for antidepressants, 69.8 % for anxiolytics and 81.5 for hypnotics, while the figures for psychiatrists were 22.5 %, 15.4 %, 6.1 % and 5.7 %, respectively. In a study from Germany (86) based on an insurance database covering 25 million people in 1999-2000, the proportion of antipsychotics issued by GPs was 60 %, while psychiatrists and neurologists prescribed 34 %. As regards antidepressants, an Australian study (87) based on 88 % of dispensed prescriptions of antidepressants in 2000 revealed that GPs issued 86 % of the prescriptions while psychiatrists prescribed 10 %. The percentage from GPs was in line with this in an Italian study (94) based on a provincial database of 9 million inhabitants in 2001. The results above are all based on prevalence studies, and only two papers were found to analyze the distribution by prescribers of initial prescribing. A Swedish study of new users of antidepressants in 1995 based on a database of approximately 18,000 inhabitants (96), revealed the proportions to be 76 % by GPs and 14 % by psychiatrists, while a French study from 2005-2007 (95) analyzing the incidence of antidepressants to a population of around 20,000 aged 18 or older found the share to be 81 % from GPs and 6 % from psychiatrist.

No other studies were found that analyzed the distribution in detail by age and gender, nor any that analyzed which prescribers who initiated treatment with antipsychotics, anxiolytics or hypnotics.

Interpretation

It seems reasonable that the patients with primarily mental health problems are mainly treated by GPs and psychiatrists, while the patients with mental problems secondary to somatic disorders are mainly treated by GPs and other physicians. From such a view, the difference between *other physicians* and *psychiatrists* is interesting. The proportion of psychotropic drugs prescribed by other physicians was quite stable regardless of age, while the share from psychiatrists decline rapidly with age, even though both prevalence rates and incidence rates for use of all the four psychotropic drug classes increased by age.

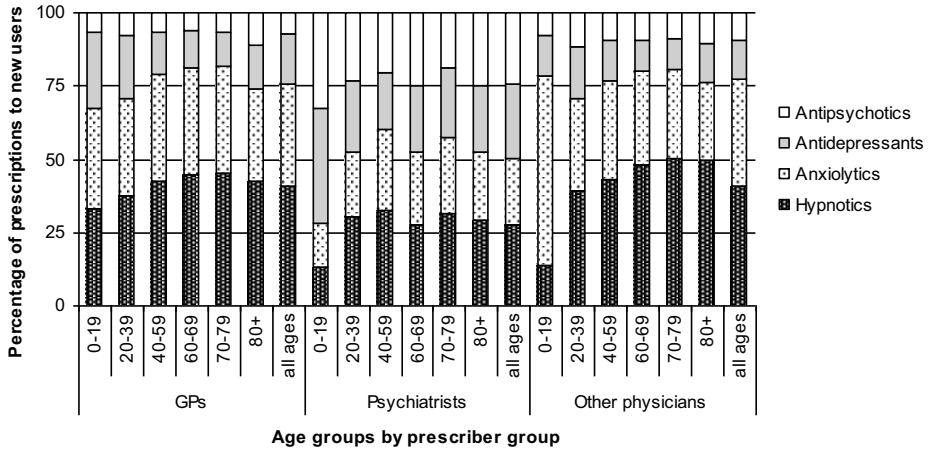
It is not known how this distribution has been earlier, or if there has been a shift between different prescriber groups after the introduction of the new psychotropic drugs during the last two decades. However, in the national mental health reform (24), the government underlined a higher priority for children and young people in secondary health care. The inverse relation shown between the incidence and prevalence rates at different ages, and the share of patients who got their prescriptions from a psychiatrist, may reflect a high concordance to this priority. It also indicates a limited admission to secondary mental health care for older people. Drugs should not be a simple solution to mental problems. Improved collaboration between GPs and specialists, particularly regarding older patients, seems crucial, and the psychogeriatric field needs a higher priority in specialist health care. This is going to be even more urgent as the demographic situation in Norway is changing, and the proportion of older people increases.

Relative distribution of the drug classes prescribed for new users

The results from *Paper II* and *Paper III* can be combined. Then a new perspective is revealed regarding physicians' prescribing practice. By summarizing the number of new users of antipsychotics, antidepressants, anxiolytics and hypnotics initiated by GPs, psychiatrists and other physicians, the relative distribution of the drug classes provided by the different physician groups to new users can be calculated (figure 3).

Even though GPs issued the vast majority of psychotropic drugs to new users, and *other physicians* prescribed a small proportion, the distribution between the drug classes provided was similar. GPs and other physicians issued anxiolytics or hypnotics in three fourths of the cases when all ages were combined. GPs prescribed a slightly higher proportion of antidepressants and a correspondingly lower share of antipsychotics than other physicians, but the differences were minor. Psychiatrists' contribution of redeemed prescriptions of anxiolytics and hypnotics to new users were less than 3 %, while the percentage for antipsychotics and antidepressants were 14.9 % and 6.3 %, respectively. However, the relative distribution of the drug groups provided by psychiatrists to new adult users was fairly evenly distributed between the four classes.

Figure 3 Relative distribution of the drug classes provided by the different physician groups to new users



The distribution was quite different among children and adolescents. Psychiatrists provided mainly antipsychotics and antidepressants, while other physicians prescribed mostly anxiolytics to this group. The latter is probably due to non-psychiatric indications of anxiolytics, i.e. epilepsy.

No other study that had analyzed this distribution was found, so comparison with other studies was impossible.

Interpretation

The differences between the physician groups' prescribing practices were smaller than one might expect. The epidemiology is quite different among patients visiting GPs compared to the patients referred to psychiatrists. The latter consist of patients with higher prevalence of mental disorders. Thus, it was expected that psychiatrists issued a higher proportion of antipsychotics and antidepressants to new patients than GPs and other physicians. The figures confirm such a difference, although it might have been expected to be even greater. The most unexpected result was perhaps the equally large proportion of new adult patients receiving anxiolytics, hypnotics, antipsychotics and antidepressants issued by psychiatrists. *Paper III* revealed that the risk for long-term or heavy use of anxiolytics and hypnotics were highest if treatment was initiated by a

psychiatrist, but the results gave the impression that psychiatrist prescribed anxiolytics and hypnotics to few new patients. Although the percentage was low, the total amount of new users of these drugs were much higher than for antipsychotics and antidepressants, and the actual number of new patients who received drugs from psychiatrists were rather similar regarding the four drug classes.

Another unexpected result was the similarity in the proportion of anxiolytics and hypnotics issued by GPs and other physicians to new users. GPs are dealing with all kind of problems affecting the patients, both somatic and mental as well as social. Other physicians are mainly specialists and residents in somatic departments in hospitals, and mental health is secondary to their main tasks. It would be reasonable to expect that GPs had a practice more similar to psychiatrists than to other physicians, but the results show that this is not the case. Physicians perceiving mental problems as less important tasks may use less effort to uncover the underlying diagnoses, and be content with providing symptomatic treatment.

Another assessment of the high share of symptomatic treatment with anxiolytics and hypnotics provided by GPs may be that the overall outcome is dominated by a high number of patients with mental symptoms caused by somatic or social problems, compared to patients with psychiatric disorders. However, GPs issued a larger proportion of antidepressants than *other physicians*, and prescribed mainly newer types, more like psychiatrists, while *other physicians* provided mainly older antidepressants, which may indicate that the treatment more often was given for other reasons than depression (*Paper II*).

When data are aggregated in this way, it seems that physicians in Norway are trained in a similar manner and appear to give fairly similar treatment to their patients in average.

Distribution of treatment duration

The study lacks clinical information. Even information about prescribed dosage was unavailable. The ability to assess the duration of the treatment to each patient was thus limited, and subject to much uncertainty and interpretation.

Paper I revealed the prevalence rates and *Paper II* and *Paper III* the incidence rates of the four drug classes. By combining these results a new perspective is revealed, the average treatment duration.

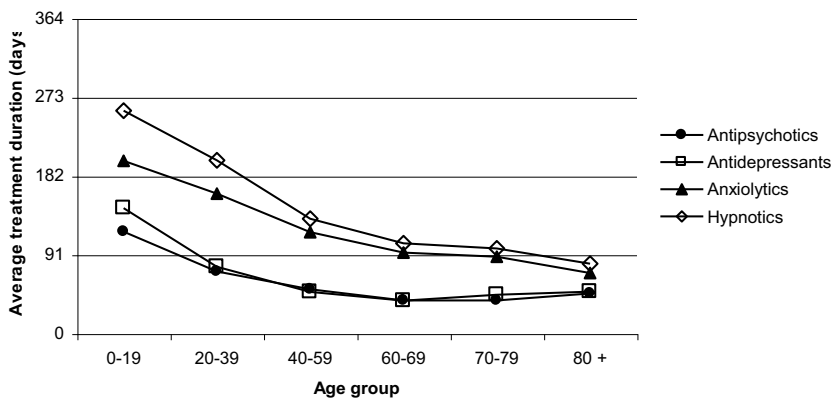
When the situation is in a *steady state*, the relation between incidence rate, prevalence rate, and average duration of treatment may be expressed as:

$$\text{Average duration} = \frac{\text{Incidence rate}}{\text{Prevalence rate}}$$

Wholesale figures were rather stable between 2005 and 2008 regarding antipsychotics and anxiolytics, while antidepressants and hypnotics had some increase (34). By assuming a stable situation during the project period, the mean duration of the treatment given to each age group for each drug class could be estimated (figure 4).

The average treatment duration has a rather similar and marked reduction with increased age in all four drug classes. The exact figures should be considered with some uncertainty, but the assumption seems acceptable, since the estimated average treatment duration is quite similar for anxiolytics and hypnotics, and for antipsychotics and antidepressants.

Figure 4 Estimated average treatment duration for each drug class by age



A striking result of this analysis is the similar trend in all the four curves. Even though the recommended treatment duration for anxiolytics and hypnotics are less than four weeks, while antipsychotics and antidepressants normally are recommended as more prolonged treatment, the reality seems to be quite different. Comparison with other studies were impossible, as no similar results was found.

Interpretation

The decreased average treatment duration with increased age may be a result of a more cautious attitude among physicians to provide psychotropic drugs to young people. If only the more severe cases are treated among younger patients, the average treatment duration may be more prolonged. Conversely, if more people get drugs for less severe symptoms with increasing age, shorter average treatment duration will be understandable and expected. The high proportion of patients who redeemed only one prescription of antipsychotics (> 50 %) and antidepressants (> 30 %) (*Paper II*) may explain the shorter average treatment duration for these drugs. The share of the patients with long-term use may increase the figures for average treatment duration considerable. No clinical consensus has been found as regards definition of long-term or heavy use of anxiolytics and hypnotics, but variables of importance for the risk of long-term or heavy use of such drugs has been analyzed and discussed in several studies (83-84, 125-127). Both international and national guidelines recommend short-term use only, e.g. less than four weeks (39, 128-131), but this study (*Paper III*) shows that only a third of the patients are treated in accordance with these recommendations, even in new users of today.

The big difference between clinical practice and academic recommendations may question the appropriateness of the recommendations as in a paper from psychiatric practice in Italy (132). But other studies conclude that non-addictive drugs and non-pharmacological treatment may give as good or better results than the addictive drugs in a longer perspective (4, 133), so short-time use of these drugs are still the recommended approach. Thus, the estimated average treatment duration is certainly not in accordance with the recommendations, and the analysis confirms a substantial potential for quality improvement regarding these drugs.

2.4.2 Methodological strengths and limitations

The study is based on comprehensive information from three national data sources. The Norwegian Prescription Database delivered data about all prescriptions of psychotropic drugs from all pharmacies in the country dispensed to community-dwelling inhabitants from 1. January 2004 to 31. August 2009. Less than 1 % of prescriptions were excluded due to missing data of some variables. The Regular GP Database provided complete information about all GPs and patients enlisted at each physician. Merging data from these universal databases together with information about the general population from Statistics Norway enabled us to create a comprehensive research database, capable of analyzing prevalence rates and incidence rates as well as the course of drug use regarding anxiolytics and hypnotics. Merging data from NorPD and the Regular GP Database also provided a unique opportunity to differentiate between prescriptions issued by GPs, psychiatrists and other prescribers.

A rather strict definition was used to reveal one-year incidence rates for antipsychotic and antidepressant drug use, excluding patients receiving treatment during a 4-year baseline period. A less strict definition was used as regards new users of anxiolytics and hypnotics, but thus the course during a follow up period of 3.5 year could be analyzed.

To our knowledge, this is the first nation-wide study analyzing the distribution of psychotropic drug utilization, i.e. use of antipsychotics, antidepressants, anxiolytics, and hypnotics, by different prescriber groups in more detail. This was completed regarding both prevalent users (*Paper I*) and incident users (*Paper II* and *Paper III*). No other studies were identified revealing incidence rates for anxiolytics, and few studies had shown incidence rates for other psychotropic drugs. No studies was found who analyzed the different prescriber groups' practice as regard the relative distribution between the four drug classes issued to new users.

However, several limitations should be taken into consideration.

Dispensed prescriptions were used as a proxy for drugs prescribed by the physicians, as well as for drugs consumed by the patients. The patients' compliance is unknown, and may differ between patients treated by various physician groups.

Limitations regarding the existing databases include the lack of individual information about medications prescribed for institutionalized patients. Nursing home residents and inpatients constitute a smaller part of the total population but their consumption of psychotropic drugs is significantly higher than among patients receiving home nursing services (134). Accordingly, the counter is too small and the denominator too large in the analysis, and the real incidence and prevalence rates among older people even higher than shown.

The prescribed dosage of the dispensed prescriptions is not available in NorPD, as it is in the Swedish prescription database (135). NorPD includes information about prescribers' specialties, but no information about physicians' working field.

Information from the Regular GP Database solved the problem to separate GPs from other physicians, but the distribution of physicians not working as GPs had to be based on assumptions. Physicians were defined as psychiatrists if they were approved as a specialist in psychiatry or child and adolescent psychiatry during the period covered by the study period, although this assumption may include some psychiatrists not working in clinical practice or in other fields. In addition, residents in psychiatry who did not fulfilled their specialty during the observed period, could not be distinguished from residents in other departments.

Prescriptions covered by the national reimbursement system require diagnostic codes. However, the codes are considered to be quite inaccurate, and thus not included in the analysis in this study. Hopefully the quality improves so that the codes will be more useful in the future. Other clinical information was not available in NorPD, and according to current legislation, it is very difficult to achieve permission from the authorities to merge such information with data from NorPD. The lack of diagnoses and indications for drug treatment hampers investigation of patients' morbidity, comparison between patient groups treated in different parts of the health care system,

as well as the assessments of prescribing quality. Thus, differences in prescribing patterns between the different prescriber groups may be confounded by indication.

In lack of clinical information, examination of co-prescribing could be a source for more information about each patient. Such analyses have not been done in this project, but should be conducted in the future.

A change in the legislation in 2009 allowed the Norwegian patient registry to collect data at the individual level. This register collect some information about all patients referred to secondary health care. The register may improve the possibilities in research, but still clinical data from primary care is unavailable.

Researchers' access to information from NorPD is strictly regulated. Researchers must just assume that the delivered data is correct, and have few opportunities to assess the quality correctness and of delivered information.

In *Paper I*, lithium and prochlorperazine were included in the calculation of prevalence rates for antipsychotics. This was logical from a pharmacoepidemiological view as both the drugs are classified in the N05A group in the ATC system. Yet it may be otherwise from a clinical point of view, as the use of these drugs differs from the rest of the antipsychotics. It is also important to take this aspect into consideration when comparing the results with other papers.

In *Paper III*, the incidence rate for anxiolytics and hypnotics may be overestimated due to a baseline period of only one year. Patients may have used anxiolytics or hypnotics earlier, but not during baseline. If the treatment was re-activated during our inclusion period, the patients were incorrectly recognized as new users. The same possibility exists for antipsychotics and antidepressants, but with a baseline period of four years, such an effect should be of little significance.

No information was available about patients who have bought drugs legally abroad or illegally on the black market. Neither do we know the extent of false prescriptions.

2.5 Concluding remarks and implications

This project has demonstrated that GPs not only prescribe the majority of psychotropic drugs, but also initiate the treatment to the majority of patients with mental health problems in Norway. Although mental health care comprises many other aspects than pharmacotherapy, it is apparent that GPs have a key function in the Norwegian mental health care services. The first recommendation from WHO to improve the mental health care, *provide treatment in primary care*, may be perceived as fulfilled.

The second recommendation from WHO, *make psychotropic drugs available*, may also be perceived as fulfilled, as the project has proved that prevalence rates and incidence rates for psychotropic drug use are in line with or higher than in other high-income countries.

Through the mental health reforms initiated in 1997-1998 (23-24), the Norwegian government was in advance of WHO's sixth recommendation from 2001, *to establish national policies, programs and legislation*. Thus this recommendation may also be perceived to be met.

The demographic changes will result in a higher proportion of older inhabitants, and the demand for health care services will increase. The need for better working methods and improved use of resources is already a political issue and focused in the new health care reform, The Coordination Reform (136). It will be implemented in 2012, and the results remain to be seen.

As this study confirms, the quality of the service to adults and older inhabitants depends on the GPs' knowledge and practice. A cost effective improvement of mental health care can only be achieved if GPs are an essential part of the effort. Accordingly, the government should have been concerned to ensure the quality of services provided to these patients in primary care. However, GPs were barely mentioned in the improvement reform of mental health services (24).

Thus, improved collaboration between GPs and specialists, particularly regarding older patients, seems crucial. In Sweden, short courses of GPs has reduced the suicide rate as well as the frequency of sick-leave due to depression in two different projects (89-90), and thereby confirmed the substantial potential for improvement of mental care in general practices. In Australia, new approaches with expanding roles for psychiatrists as educators and clinical mentors for GPs have been attempted (137-138). Different strategies should be tried out and evaluated to find cost-effective measures to successfully empower GPs to deal with mental problems in the best possible way.

Prior to the establishment of the Norwegian prescription database, the Norwegian Medical Association, the Norwegian Pharmacy Association, the Norwegian Dental Association and the Norwegian Veterinary Association proposed jointly to establish a program for structured clinical audit to improve quality of drug prescribing in Norway. The proposal was aimed at a national prescription database, together with personal audit and counseling of prescribers.

The NorPD was founded by the government in 2004, and the aims were determined to be: a) Map drug usage in Norway and monitor trends, b) Be a resource for research in order to see positive and negative effects of drug consumption, c) Give health authorities a statistical base for quality control of drug use and for steering and planning and d) Give prescribers a basis for internal control and quality improvements.

NorPD is established as a provider of information about dispensed prescriptions in Norway, and has met the first three purposes, even though the Norwegian prescription database has important limitations regarding research. Development of systems to obtain individual drug use in institutions and hospitals are highly desirable. In addition it is important to solve the need of clinical information, while personal anonymity is ensured. Clinical information is essential for further improvement and development of the research in this field.

Another interesting new resource for information is the new electronic prescription program. Such information can easily be incorporated in the NorPD while personal privacy is assured. It can be a unique possibility to gain some more knowledge about

patients' compliance with physicians' recommendations, as figures can be obtained about prescriptions not redeemed. Such data are unavailable today.

NorPD has cooperated with researchers in some quality improvement projects (139-140), but an ongoing system for structured clinical audit and quality improvement of drug use has not been established. Although NorPD has credibility, it is unlikely that NorPD is suitable for such a task, as the impact of such an organization will depend on clinical knowledge, and close cooperation and communication with the physicians.

This project reveals a relatively high use of first generation antipsychotics in primary care, a high proportion of patients who redeemed only one prescription of antipsychotics and antidepressants, and low correspondence between international and national guidelines and actual prescribing of addictive anxiolytics and hypnotics.

GPs prescribe the vast majority of psychotropic drugs in all ages. Hence, the quality of pharmacological treatment is mainly dependent on the knowledge and practice of each GP. Improving mental health care is only achieved in a cost effective manner if GPs are a major part of the effort.

Clinical information has not been available in the project, and consequently, the clinical impact is not known. However, the results support the proposal to establish a continuous program for clinical audit and quality improvement of drug use. If such a scheme is established, it will meet the seventh recommendation from WHO; *develop human resources*.

In addition, it would be a great opportunity to improve research in primary health. If clinical information aimed for audit and quality improvement can be made available for researchers, pharmacoepidemiological studies and clinical research can make major advances. Such a system will thus provide a longed basis for clinical research in general practice, and meet the tenth recommendation by WHO, *support more research*.

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