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Drug Utilization Pattern of Antipsychotics in Norway:

A Registry based study from 2004-2014

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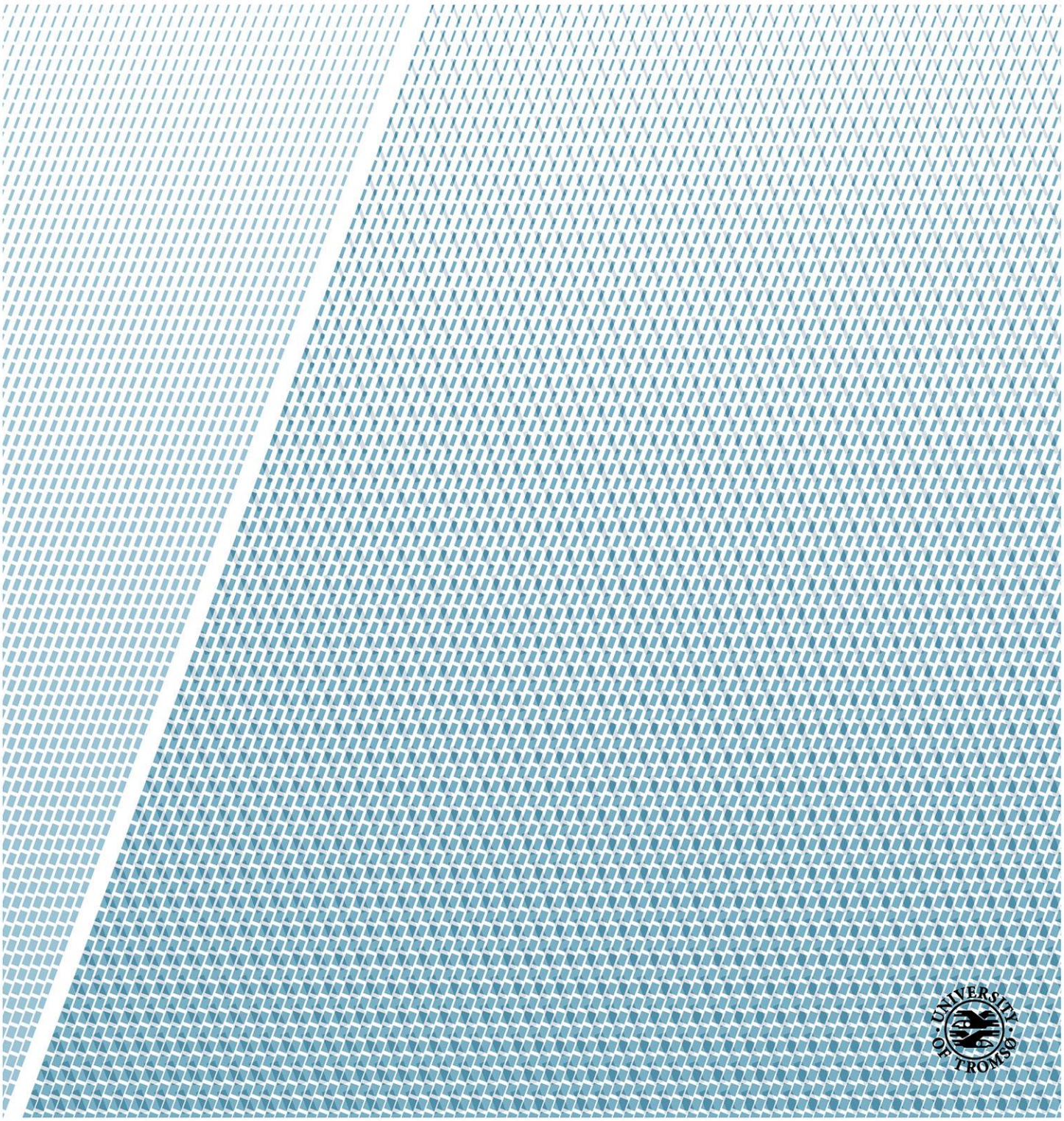

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ABSTRACT

Background: Antipsychotic drugs are primarily used in the treatment of Schizophrenia and bipolar disorder while they are also used in the management of severe depression and anxiety disorder. Despite the prevalent use of the antipsychotic medication in the Scandinavian countries, studies about the prescription pattern are scarce.

Objective: To explore the utilization pattern of antipsychotic drugs in Norway from 2004-2014. In addition, the study aims to compare the prescription pattern of Norway with that of Denmark and Sweden.

Methodology: A descriptive retrospective multi cross-sectional study was carried out to study the utilization pattern. Data were extracted from the National prescription database of Norway, Denmark and Sweden. Study variables were prevalence, cost per user and DDD/user/day. Microsoft excel 2013 was used to carry out the necessary calculations and results were expressed in percentage and mean values. Since, the study was based on population data, no statistical test was done.

Results/Conclusion: Prevalence of antipsychotic use was higher in Norway (21.22), and Denmark (22.56) as compared to Sweden (15.68). In general, women had higher prevalence as compared to men in Norway. Quetiapine, levomepromazine and olanzapine were the most prescribed drugs in Norway and all three countries studied had similar top ten-drug list. In Denmark, nine out of 10 and in Sweden, eight out of 10 drugs were same as that of Norway. Several antipsychotics were found to have low average dose per user per day in Norway, Sweden and Denmark which indicates higher off-label and non-antipsychotic utilization of these medications. Average cost per user of antipsychotics were higher in Denmark (3935 NOK) than in Norway (2896 NOK).

LIST OF ABBREVIATIONS

NHS-UK	National Health Service, United Kingdom
FGA	First Generation Antipsychotic
SGA	Second Generation Antipsychotic
D1, D2, D4	Dopamine Receptors
5-HT2A	5-hydroxytryptamine (serotonin) receptor 2A
NIMH	National Institute of Mental Health
EPSEs	Extrapyramidal side effects
WBC	White Blood Cell
CYP3A4	Cytochrome P450 3A4
IV/IM	Intravenous/Intramuscular
WHO	World Health Organization
DDD	Defined Daily Dose
NorPD	Norwegian Prescription Database
PDR, Sweden	Swedish Prescribed Drug Register
DNPR	Danish National Prescription Registry
NIPH	Norwegian Institute of Public Health
RMPS	Register of Medicinal Product Statistics
OTC	Over the Counter
ATC	Anatomical Therapeutic Classification
NOK	Norwegian Kroner
DKK	Danish Kroner

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1 INTRODUCTION

1.1 Background

According to the National Health Service (NHS), UK, "Psychosis is the mental health problem that causes the people to perceive or interpret the things differently from those around them. Two major symptoms of the psychosis is hallucinations and delusions" (1). Psychosis is a mental state which leads to abnormal perceptions, thought and ideas(2). Psychosis is not a specific illness or disease rather it includes disorders such as schizophrenia, bipolar disorder, acute idiopathic psychotic illness and other conditions marked by serious agitation(2, 3).

1.1.1 Overview of Schizophrenia

Though the psychotic disorder comprises various illnesses, antipsychotics are primarily used in the treatment of schizophrenia(4). According to NHS, "Schizophrenia is a long term mental health condition that causes a range of different psychological symptoms which includes: hallucinations, delusion, and behavioral change.'' Schizophrenia is a severe and chronic disorder of brain which has affected human race throughout the history(5).

People with schizophrenia often do not have any physical symptom of illness. However, there would be common behavioral changes which includes: social withdrawal, depersonalization, loss of appetite, loss of hygiene, delusion, hallucination, sense of control from outside world and disorganized speech(6).

The Merck Manuel has grouped the signs and symptoms of schizophrenia into four categories(7) :

Table 1-1: Symptoms of Schizophrenia

Positive symptoms	**Negative symptoms**	**Cognitive symptoms**	**Disorganized or mood symptoms**
Hallucination	Social withdrawal	Impairment in attention, processing speed, working memory, abstract thinking	Disorganized thinking with rambling, non-goal directed speech
Delusion	Anhedonia	Impair problem solving skills	Childlike silliness, agitation
	Blunted effect	Low social skills	Inappropriate appearance, hygiene, or conduct
	poverty of speech		Catatonia

1.1.2 Epidemiology

Scientific evidence suggests that at any given time as many as 51 million people worldwide suffer from schizophrenia and this disorder primarily develops in people aged between 15-45 years(8). However, it may also occurs before puberty as well as people in their 70s and 80s(2, 9). Schizophrenia affects both genders equally and it has been found to occur in all races and ethnic groups around the world. Conversely, the typical onset of the disorder in male is 23-28 years while in female; it is 28-32 years (2, 5).

Schizophrenia is considered as a common mental health problem having the prevalence of 0.5-1 % worldwide. Nevertheless, there is 10% risk of development in people who have a first-degree relative with the disorder. If both parents are affected, risk for the offspring is 40%. In addition, people with second-degree relatives having the disorder have a higher risk than the normal population. Similarly, if either of the twin has the disorder, there is 40 to 65 percent chances of occurring disorder in other twin(2, 5).

1.1.3 Etiology:

Schizophrenia has a strong genetic component and it is considered a neurodevelopmental disorder meaning that an alteration in brain cells occurs in the utero or during childhood and

adolescence or both. (10, 11) However, the exact cause of the disorder is still unknown. A scientific research has found that the etiology of schizophrenia is related with genetic and perinatal factors. In addition, social and environmental factors are also found to increase the risk of the disorder. Many studies have documented the genetic origin of the schizophrenia but no single genes that may lead to the condition have been identified so far and it is believed that multiple genes are associated with this condition. Similarly, women who are infected to certain virus or who are undernourished during their pregnancy has a greater risk of giving birth to a child having a high risk of schizophrenia(5, 12).

1.1.4 Antipsychotic agents

Antipsychotic medications are a wide range of drugs that are used in the treatment of mental illness primarily schizophrenia and bipolar disorder. However, some of these drugs are also used in the management of severe depression and anxiety disorders (13). Antipsychotic medications have been available since mid-1950s and more than 60 drugs were discovered in last century. Of these 60, about 20 are most widely used in the market for clinical use today (4, 5, 14). Reserpine and chlorpromazine were the first drugs discovered to be beneficial in the treatment of schizophrenia but former was used only for a short period of time and no longer practice as antipsychotic agent(10).

The antipsychotic drugs are classified into two categories: First-generation (FGA) or typical antipsychotics and Second generation (SGA) or atypical antipsychotics. Though, there is no clear distinction between first and second generation drugs, division is primarily based on the receptor profile, incidence of extrapyramidal side effects and efficacy in the treatment(4). Further, FGAs are classified into three groups based on their potency as low potency, mid potency, and high potency drugs. For the purpose of this study, we are using terminology first (FGA) and second-generation antipsychotics (SGA). The classification of antipsychotics is shown in the table 1-2.

Table 1-2: List of Antipsychotic Drugs

First Generation Antipsychotics(FGA)	Second Generation Antipsychotics(SGA)
Low Potency	Clozapine
Chlorpromazine	Risperidone
Thioridazine	Olanzapine
Prochlorpromazine	Quetiapine
Mid potency	Ziprasidone
Triofluperazine	Aripiprazole
Perphenazine	Paliperidone
Loxapine	Iloperidone
Molindone	Asenapine
High potency	Lurasidone
Heloperidol	
Fluphenazine	
Thiothixine	

Source: Lippincott Illustrated Reviews-Pharmacology (11)

1.1.5 Mechanism of action:

The exact mechanism of action of antipsychotic drugs is not known yet, however, it is believed that antagonism of dopamine and/or serotonin receptor is the main determining factor of antipsychotic action. Many of these antipsychotic agents also block the cholinergic, adrenergic and histaminergic receptor. It is unclear if any of this receptor blocking effect alleviates the antipsychotic action, but, they often leads to the side effects(11).

Almost all of the FGAs and most of SGAs have the mechanism of action by blocking dopamine receptors (D2/D3) on the brain and periphery. The clinical efficacy of the FGAs is directly proportional to the relative ability to block the D2 receptor in the mesolimbic system of the brain(15).

Along with the dopamine receptor, most of the SGAs are able to inhibit serotonin receptor, principally 5-HT2A receptors. Clozapine, for example has a higher affinity towards D1,D4, 5-HT2, muscarinic and alpha adrenergic receptor and act as a weak D2 antagonist(11). The table 1-3 summarizes the relative ability of the drugs to the receptors.

Table 1-3: Comparative efficacy of the drugs towards the receptor

Drug	**D2/5-HT2A affinity**
Chlorpromazine	High
Fluphenazine	High
Thiothixene	Very high
Haloperidol	Medium
Clozapine	Very low
Risperidone	Very low
Olanzapine	Low
Quetiapine	Low
Ziprasidone	Low
Aripiprzole	Medium

Source: Basic and Clinical Pharmacology(10)

Some animal studies suggest that antipsychotic agents initially increase and afterwards decrease the electrical activity in midbrain dopaminergic neurons in the substantia nigra and ventral tegmentum, and responsible for the release of the dopamine in regions containing dopaminergic nerve terminals. Thus, effects on mesolimbic or mesocortical dopamine pathways are believed to provide the antipsychotic effect whereas effects on nigrostriatal pathways leads to motor side effects(11).

1.1.6 Action and therapeutic effect:

All antipsychotic drugs can effectively reduce the positive symptoms of schizophrenia i.e. hallucination and delusion through the blockage of dopamine receptor in mesolimbic system. Cognitive impairment and negative symptoms such as anhedia, apathy blunted affect, and impaired attentions are usually not improved with FGAs. SGAs, however, could improve the negative symptoms as well. SGAs also induce the calming effect but do not disturb the intellectual functioning and motor coordination. Normally, antipsychotic drugs have delayed action and usually takes up to several days to weeks to occur a therapeutic effect, meaning that therapeutic effects are dependable to the secondary changes to corticostriatal pathways(11).

Other than the antipsychotic action, these agents also produce several actions in the body such as extrapyramidal effects, antiemetic effects, and anticholinergic effects. Extrapyramidal effects include dystonia, Parkinson like symptoms, akathisia, and tardive dyskinesia.

Though the antipsychotics are effective in the treatment of the schizophrenia, not all the patients respond to the therapy and complete stabilization of the condition rarely observed. Many studies have found that FGAs are usually more effective in the treatment of positive symptoms while SGAs are effective to treat drug resistant cases and the negative symptoms. Nevertheless, effectiveness of SGAs over the FGAs in treating negative symptoms has not been well documented (11).

Antipsychotics have various non-antipsychotic indications as well. For example, the older antipsychotic drugs like prochlorperazine are useful in the treatment of drug-induced nausea. However, these powerful agents should be used with caution for their antiemetic actions. Other use of antipsychotic drugs includes: as a hypnotic agent, and as a co-analgesic used in combination with narcotic analgesic for the treatment of chronic pain with anxiety(11).

1.1.7 Adverse effects:

All antipsychotic drugs have adverse effects and around 80 % of patient taking medication has experienced significant adverse effects. According to the National Institute of Mental health (NIMH) (5), patient with antipsychotic medication should not drive unless their medications are adjusted. NIMH listed general side effects associated with these drugs:

- Drowsiness
- Orthostatic hypotension
- Blurred vision
- Increased heartbeat
- Increased sensitivity to sun
- Skin rashes
- Menstrual problem in women

FGAs are more likely induce extrapyramidal side effects (EPSEs) which includes rigidity, tremor, muscle spasm, restlessness, distress, slurred speech, anxiety, paranoia etc (15). Another problem associated with the long-term use of these medications is muscle movement that the patient cannot control. This commonly occurs in the face and distal extremities and the condition is called as tardive dyskinesia which can be range from mild to severe(5, 15).

Though, SGAs do not tend to induce EPSEs or tardive dyskinesia, they increase the risk of having diabetes and high cholesterol due to their potential of causing weight gain and alter metabolism. Therefore, regular monitoring of glucose and lipid level is recommended while on antipsychotic therapy. Table 1-4 summarizes side effects and sedative profile of different antipsychotic drugs.

Table 1-4: Adverse effects of Antipsychotic

Name	Side effects	Sedation	Comments
First Generation Antipsychotics			
Chlorpromazine (Thorazine)	Anticholinergic side effects; photosensitivity; Orthostatic hypotension; QT prolongation; Cholestasis	+++	EPSEs not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine			
Triofluperazine	Fewer anticholinergic side effects	++	Well tolerated by most patients
Perphenazine	Fewer EPSEs than higher potency drugs	++	Little weight gain
Loxapine	Frequent EPSEs	++	
Molindone	Frequent EPSEs	0	
Heloperidol	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed with the dose that are too high;
Fluphenazine	Frequent EPSEs	0/+	
Thiothixine	Frequent EPSEs	0/+	
Second Generation Antipsychotic			
Clozapine	Agranulocystosis (1%); weight gain; seizures; drooling; hypothermia	++	Requires weekly WBC count for first 6 months, then biweekly if stable
Risperidone	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6mg qd
Olanzapine	Weight gain	++	Mild prolactin elevation
Quetiapine	Sedation; weight gain; anxiety	+++	Bid dosing
Ziprasidone	Orthostatic hypotension	+/++	Minimal weight gain; increase QT interval
Aripiprazole	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist
Paliperidone	Restlessness, EPSEs	+	Active metabolite of risperidone
Iloperidone	Dizziness, hypotension	0/+	Requires dose titration
Asenapine	Dizziness, EPSEs, weight gain	++	Sublingual tablets; bid dosing
Lurasidone	Nausea EPSEs	++	Uses CYP3A4

Source: Harrison's Manual of Medicine, 18e(15)

1.1.8 Comparative efficacy and guidelines:

Various international organization (for e.g., American Psychiatric Association, National Institute of Health and Care Excellence (NICE), Canadian Psychiatric Association) has proposed guidelines for the treatment of schizophrenia. These guidelines offer strategies for the rational use of medications in order to minimize the side effects associated with antipsychotics. Rational use of antipsychotic medications can be considered into three dimensions i.e. FGAs vs SGAs; mono therapy vs combination therapy and optimal dose of the drugs(16).

Although antipsychotics are effective in the management of schizophrenia, patients often responds differently to the medications and no theory has been discovered yet to explain how patients will respond. Therefore, patient may receive several medications before finding a suitable one. Since SGAs, in general, has less side effects, are recommended by most of the guidelines as a first line treatment of schizophrenia(5, 16).

Scientific evidence has found no advantage of combination therapy of antipsychotic drugs. Monotherapy is usually recommended and combination therapy should only be carried out while switching the drugs for short period of time or in drug resistant cases. The choice of medication is highly depended on individual response(16, 17). Table 1-5 shows the therapeutic dose and formulations of different antipsychotic agents.

Table 1-5: Doses of Antipsychotics

Name	Formulations	Minimum effective Therapeutic PO dose (mg)	Average Daily PO Dose (mg)
First Generation Antipsychotics			
Low Potency			
Chlorpromazine	Oral; IV/IM	100	100-1000
Thioridazine	Oral	100	100-600
Mid Potency			
Triofluperazine	Oral	5	2-50
Perphenazine	Oral	10	4-64
Loxapine	Oral	10	30-100
Molindone	Oral	10	30-100
High potency			
Heloperidol	Oral; IV/IM	2	5-20
Fluphenazine	Oral; Inj. Solutions	2	1-20
Thiothixine	Oral	2	2-50
Second Generation Antipsychotic			
Clozapine	Oral	50	150-600
Risperidone	Oral; IM	4	2-8
Olanzapine	Oral; IM	5	10-30
Quetiapine	Oral	150	350-800
Ziprasidone	Oral; IM	40	120-200
Aripiprazole	Oral; IM	10	10-30
Paliperidone	Oral; IM	-	3-12
Iloperidone	Oral	-	12-24
Asenapine	Oral	-	10-20
Lurasidone	Oral	-	40-48

Source: Harrison's Manual of Medicine 18e; Basic and Clinical Pharmacology; Medscape (10, 12, 15)

However, many studies suggest that there is regional and nationwide differences in the prescribing pattern of antipsychotics and it is , therefore, difficult to achieve the uniformity of the pattern(16). In order to achieve the optimal outcomes from the available drugs, it is important to consider individual variation of the disorder. On the other side, schizophrenia often relapses in vast majority of patients. Various studies suggest 95% of five-year relapse rate from the first presentation. Studies also suggest that antipsychotic drugs are central in preventing the relapse of the disorder. In absolute numbers, 50% cases of schizophrenia relapse without treatment while with treatment this figure reduced to 25%(18). Another finding suggests that around 80 % of cases relapse if treatment is stopped within 1 year compared to only 20% relapse in treated cases (12).

Antipsychotic drugs, as a class, have poor tolerability, safety, and acceptability to the patients. In a study from 2005 found that, 74% of cases discontinued their medication within first 18 months of therapy followed by subsequent relapse. Adverse effects are found to be major factor behind the intolerability of treatment and it has been found that about one third of the discontinuation was linked to the patient deciding to stop medication (10, 11). Likewise, children, breastfeeding women, and elderly patient poses special challenges over antipsychotic treatment and medication must be prescribed with the particular caution(12).

Antipsychotic class of drugs do not have uniform pharmacology and has a high degree of variability in terms of relative efficacy and side effects(18). Therefore, treatment of schizophrenia needs the input of medical, psychological, and psychosocial assistance. It should be noted that diabetes, cardiovascular disease, lung disease and obesity are prevalent in schizophrenia cases which should not be neglected (12). Hence, long-term management of schizophrenia should be focused on doctor-patient relationship in selecting, and treatment option that provides the best solutions for the patient. This may include multiple visit and switching the drug over the course until the best possible alternative is found(11, 12).

NHS UK recommends that personalized care should be provided for the effective management of schizophrenia. This can be achieved through by taking account of the following factors:

- Age
- Patient preference
- Lifestyle
- Cultural and religious beliefs
- Allergies and intolerance
- Adverse drug reactions
- Recommended guidelines(18)

Despite the significant use of the antipsychotics in the Norwegian population, research about its prescribing pattern is very limited. Therefore, it is important to do the research in the field of rational use of the antipsychotic medications(16).

1.2 Rationale of the study:

According to the WHO, drug utilization research is defined as marketing, distribution, prescription, and use of the drug in the society, with special emphasis on resulting medical, social, and economic consequences. Thus the principle aim of drug utilization study is to explore the rationale use of medicines in the population(19).

The purpose of this study is to explore the drug utilization pattern of antipsychotic drugs in Norway during the period of 2004 to 2014. This study also aims to compare the actual use of the antipsychotics to the national and international prescription guidelines with the primary focus on the choice of the drug, cost effectiveness, average drug dose and their variation during the study period. In addition, study will also evaluate influence of socio-demographic characteristics over the drug use pattern. Finally, we also wanted to make a comparison of Norwegian antipsychotic prescription pattern with other two Scandinavian countries: Denmark and Sweden.

2 STUDY QUESTIONS:

I. What is the prescription pattern of different antipsychotic drug in Norway in 2014?

- What is the prevalence of overall and individual antipsychotic drug use in Norway in 2014?
  - Prevalence will be stratified according to gender in order to identify any differences.
  - Top ten prescribing antipsychotic drugs will be identified according to the highest number of users
- What is the average cost per user of each drugs?
- What is the turnover by Defined Daily Dose (DDD) per user per day of each drugs?

II. How does the prescription pattern change in Norway from 2004 -2014 with respect to top ten antipsychotic drugs of 2014?

- How does the prevalence change during 2004-2014?
- How does cost per user change during 2004-2014?

III. How does the prescription pattern of antipsychotics in Norway differ from that of Sweden and Denmark?

- What is the prevalence of antipsychotic use in Denmark and Sweden?
- What are the top ten antipsychotic drugs in Denmark and Sweden in comparison to Norway?
- What is the pattern of DDD per user per day in Sweden and Denmark as compared to Norway?
- What is the cost per user of antipsychotic drugs in Denmark and Sweden as compared to Norway?

IV. Is there any difference between the prescription pattern of FGAs and SGAs in Norway, Denmark, and Sweden?

3 METHODOLOGY

3.1 Data source:

Data were extracted from the Norwegian Prescription Database (NorPD), Swedish Prescribed Drug Register (PDR, Sweden), and Danish National Prescription Registry (DNPR). We extracted the antipsychotic prescription data in Norway from 2004-2014, Denmark 2013 and Sweden from 2014.

3.1.1 Norwegian Prescription Database

Norwegian prescription data were retrieved from the Norwegian prescription database that is administered by the Norwegian Institute of Public Health (NIPH). It was established in 2004 and it covers the entire population of Norway. From 1 January 2004, all pharmacies in Norway are obliged to submit data electronically to NorPD on all dispensed prescriptions. NorPD therefore contains all information about prescription (reimbursed or not), which has been dispensed from the pharmacies with the exception of institutions (hospitals and nursing homes). It has a unique patient identification number, patient demographic data, prescriber data, and details of dispensing pharmacy (20, 21).

3.1.2 Danish National Prescription Registry

From 1994, Demark started to record the information about all the drugs sold in Denmark in Register of Medicinal Product Statistics (RMPS). Afterwards, similar national prescription registries were established in other Nordic countries. Since 2003, data in the RMPS were made accessible for the researchers through the sub-registry called as Danish National Prescription Registry (DNPR). DNPR contains complete information on all drugs dispensed from outpatient pharmacies. Each patient is provided with the unique patient identification number and register provides the information about the sex, age, reimbursement, turnover, region, drug information and prescriber's information(22).

This database covers the entire country since it is mandatory to report in Denmark. In addition to the primary sector sale, data from the hospital sector are also included in the database from 1996 (23).

3.1.3 Swedish Prescribed Drug Register

Swedish data were collected from the Swedish Prescribed Drug Register. It was established in 2005 and the register contains data with unique patient identification number for all prescribed drugs dispensed in Sweden. National Corporation of Swedish pharmacies is responsible for data collection and it contains information about patient's age, sex, place of living, drug brand name, formulation, package size, amount, expenditure, reimbursement and prescriber profession and practice. The register covers the entire population of Sweden (patient identity data are missing for less than 0.3% of the dispensed prescription). However, the register does not include the data on OTC medication, drug used in hospitals and only partially, drug used in ambulatory care but administered at day care centers (21, 24).

3.2 Study Drugs

All the drugs in Nordic countries including Denmark, Sweden and Norway are classified according to the Anatomical Therapeutic Chemical (ATC) system and antipsychotics is designated with the code of 'NO5A' in ATC system(25). All antipsychotic drugs from three database were included in the study. NorPD contains 32 antipsychotic drugs whereas Denmark and Sweden contains 34 and 31 drugs respectively (see appendix D).

For the purpose of this study, the term 'drug' refers to all the substances prescribed during the study period regardless of their brands.

3.3 Study Setting

Entire country, Norway, Sweden and Denmark

3.4 Study Design

Descriptive retrospective multi cross-sectional study design.

3.5 Study Variables

The study consists of six variables. Descriptions of all variables are listed in the table below:

Table 3-1 : Description of the variables

Variable	Description	Measurement Scale
Age	It is the person's age at the first time purchase of the medicine on prescription from concerned ATC code/group of medicine in particular year.	Number
Number of User	A user is defined as a person who had at least one prescription dispensed in the pharmacy during the calendar year.	User per 1000 inhabitants
Population	The number of users in a population or number of user per 1000 inhabitants	Number
Gender	Respective sex of drug users	Male/Female
Cost per user	It is defined as an average cost of the antipsychotic drugs per user for a particular year.	Norwegian Kroner (NOK)
DDD per user per Day	DDD stands for average daily dose and defined as an assumed average maintenance dose per day for a drug used for its main indication in adults. DDD/user/day stands for average daily dose per user per day of a particular year.	Per user per day

3.6 Study population

The study population comprised of all individuals who had received at least one prescription of antipsychotic medication dispensed in Norway during the year 2004-2014, Denmark 2013 and Sweden 2014.

3.7 Analysis and Statistics

The statistical calculations were mainly descriptive and mean, standard deviation or percentage was presented as a result. Microsoft Excel 2013 was used for the analysis of the data. Since, the study is based on the population data (not sample data) from the registries, no statistical test is required, and therefore statistical test was not carried out.

Cost per user of each drugs were calculated by dividing total turnover of individual drug by its number of users. Similarly, DDD/user/day for each drug was calculated by dividing total turnover by DDD by its number of users and 365 days.

Similarly, cost per user of Denmark was converted to the NOK from DKK using the annual average of the daily conversion rate from Norges Bank (26).

3.8 Ethical Consideration:

This study is based on the anonymous data from the NorPD, PDR, Sweden, and DNPR. The dataset are available for public use, and there is no restriction on use. Further, all the data extracted for the purpose of this study is aggregated data, which is not person-identifiable. Permission to conduct this study therefore did not required any ethical approval.

4 RESULTS

4.1 Prescription pattern in Norway

4.1.1 Prescription pattern in Norway in 2014

Prevalence of antipsychotic drug use in Norway was 21.22 per 1000 inhabitants and approximately 316 million NOK of all antipsychotic drugs were sold in 2014. Further, prevalence of antipsychotic drug use was found to be higher in female with 23.66 users per 1000 inhabitants compared to men with 18.81 users per 1000 inhabitants.

Table 4-1: Prescription pattern of Antipsychotic agents in Norway in 2014

	ATC Code	Class of Drug	User per 1000	Number of user	DDD/user/Day	Cost per user
1	N05AH04 Quetiapine	2nd	6.51	33462	0.31	2191
2	N05AA02 Levomepromazine	1st	3.64	18704	0.05	361
3	N05AH03 Olanzapine	2nd	3.24	16639	0.74	3133
4	N05AF03 Chlorprothixene	1st	2.94	15097	0.12	458
5	N05AB04 Prochlorperazine	1st	1.82	9339	0.03	205
6	N05AX08 Risperidone	2nd	1.62	8323	0.35	4110
7	N05AN01 Lithium	-	1.47	7557	0.81	1914
8	N05AX12 Aripiprazole	2nd	1.05	5395	0.60	12054
9	N05AF01 Flupentixol	1st	0.81	4182	0.26	507
10	N05AD01 Haloperidol	1st	0.78	4019	0.18	325
11	N05AF05 Zuclopenthixol	1st	0.57	2913	0.58	1131
12	N05AH02 Clozapine	2nd	0.50	2572	1.05	3860
13	N05AB03 Perphenazine	1st	0.33	1715	0.58	2672
11	N05AX13 Paliperidone	2nd	0.16	833	0.97	32495
15	N05AE04 Ziprasidone	2nd	0.15	765	0.98	7764
16	N05AL05 Amisulpride	2nd	0.12	597	0.69	6228
17	N05AA01 Chlorpromazine	1st	0.04	196	0.14	3381
18	N05AG02 Pimozide	1st	0.02	114	0.64	2679
19	N05AE03 Sertindole	2nd	0.02	100	0.79	11759
20	N05AH05 Asenapine	2nd	0.01	50	0.40	12988
21	N05AC02 Thioridazine	1st	0.01	43	0.35	2724
22	N05AB02 Fluphenazine	1st	0.003	16	1.12	3477
23	N05AD03 Melperone	2nd	0.001	6	0.19	1599
24	N05AE05 Lurasidone	2nd	0.001	5	0.14	4464

The table 4-1 shows the prescription pattern of Antipsychotic drugs in 2014 and the table was arranged in descending order of number of users. Quetiapine had the highest prevalence of 6.5

users per 1000 inhabitants followed by levomepromazine (3.64), olanzapine (3.24), chlorprothixine (2.91), and prochlorperazine (1.82).

Paliperidone had highest average cost per user among all antipsychotic drugs with approximately 32500 NOK per user followed by asenapine, aripiprazole and sertindole with approximately 13000, 12000 and 11760 NOK per user respectively. The top prescribing drug quetiapine had average cost of around 2200 NOK and cost per user of levomepromazine and olanzapine was approx. 360 NOK and 3133 NOK respectively.

The top five drugs with highest average dose per user per day were found to be fluphenazine (1.12), clozapine (1.05), ziprasidone (0.98) , paliperidone (0.97) and lithium (0.8) while five drugs with the lowest average dose per user were prochlorperazine 0.03), levomepromazine (0.05), chlorprothixine (0.12), haloperidol (0.18) chlorpromazine (0.142).

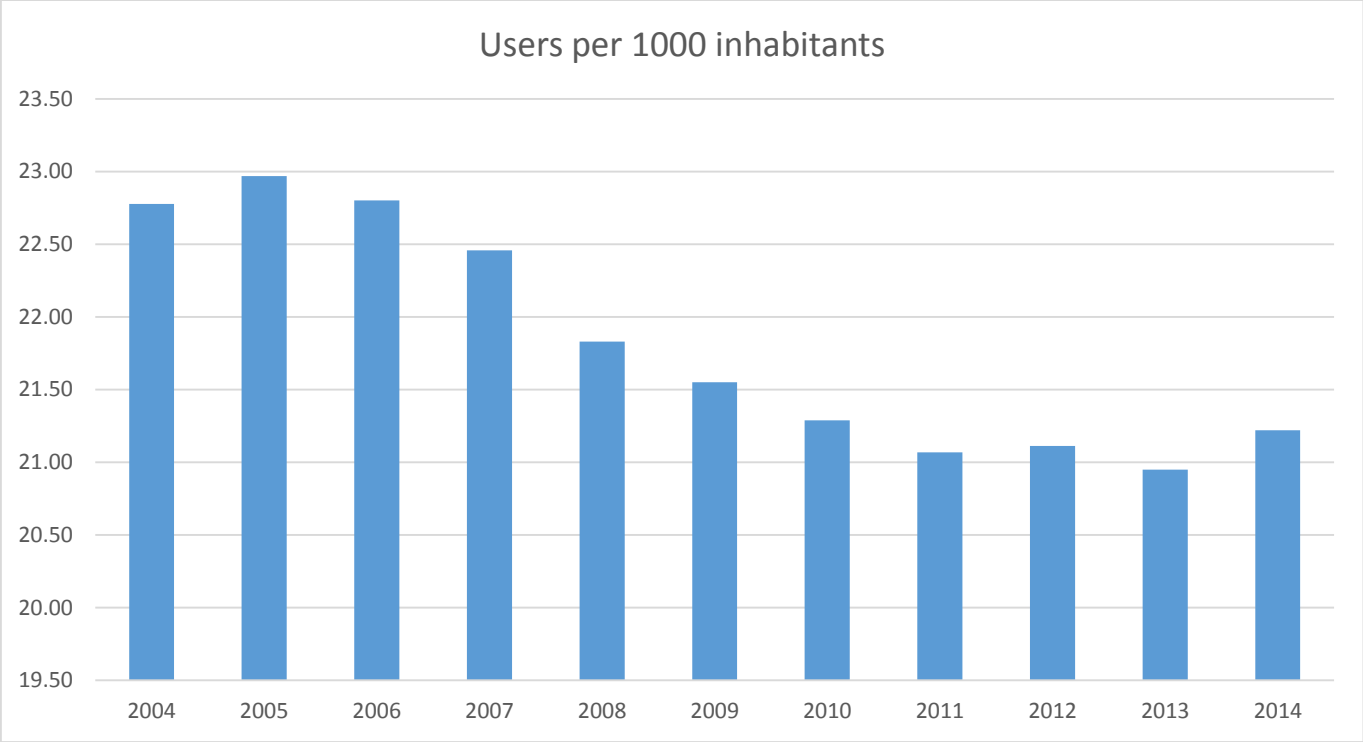
Table 4-2: Prevalence of Antipsychotic agents according to the gender in Norway in 2014

ATC Code	**Class of Drug**	**Male (N=48,582)**	**Female (N= 60473)**
N05AH04 Quetiapine	2nd	5.68	**7.35**
N05AA02 Levomepromazine	1st	3.09	**4.20**
N05AH03 Olanzapine	2nd	**3.39**	3.09
N05AF03 Chlorprothixene	1st	2.68	**3.20**
N05AB04 Prochlorperazine	1st	0.98	**2.67**
N05AX08 Risperidone	2nd	**1.73**	1.51
N05AN01 Lithium	-	1.25	**1.69**
N05AX12 Aripiprazole	2nd	1.02	**1.08**
N05AF01 Flupentixol	1st	0.56	**1.07**
N05AD01 Haloperidol	1st	0.73	**0.84**
N05AF05 Zuclopenthixol	1st	0.55	**0.58**
N05AH02 Clozapine	2nd	**0.62**	0.38
N05AB03 Perphenazine	1st	0.28	**0.39**
N05AX13 Paliperidone	2nd	**0.20**	0.13
N05AE04 Ziprasidone	2nd	0.12	**0.18**
N05AL05 Amisulpride	2nd	**0.12**	0.11
N05AA01 Chlorpromazine	1st	0.03	**0.05**
N05AG02 Pimozide	1st	**0.03**	0.02
N05AE03 Sertindole	2nd	0.02	**0.02**
N05AH05 Asenapine	2nd	0.01	**0.01**
N05AC02 Thioridazine	1st	**0.01**	0.01
N05AB02 Fluphenazine	1st	0.00	0.00

As seen in Table 4-2, women in general had a higher prevalence as compared to men (bold number showing highest prevalence). However, some drugs are used more in men such as olanzapine, risperidone, clozapine, paliperidone, amisulpride, pimozide, and thioridazine.

4.1.2 Change in Prevalence in Norway from 2004 - 2014

Figure 4-1: Change in prevalence from 2004-2014 in Norway



The above figure 4-1 showed that prevalence of antipsychotic drugs was at peak on 2005 with almost 23 users per 1000 inhabitants. After 2005, prevalence was decreased slightly to reach 21.07 in 2011. Finally, prevalence of all antipsychotic drugs in 2014 in Norway was 21.22 users per 1000 inhabitants.

Figure 4-2: Change in prevalence of top ten drugs of Norway from 2004-2014

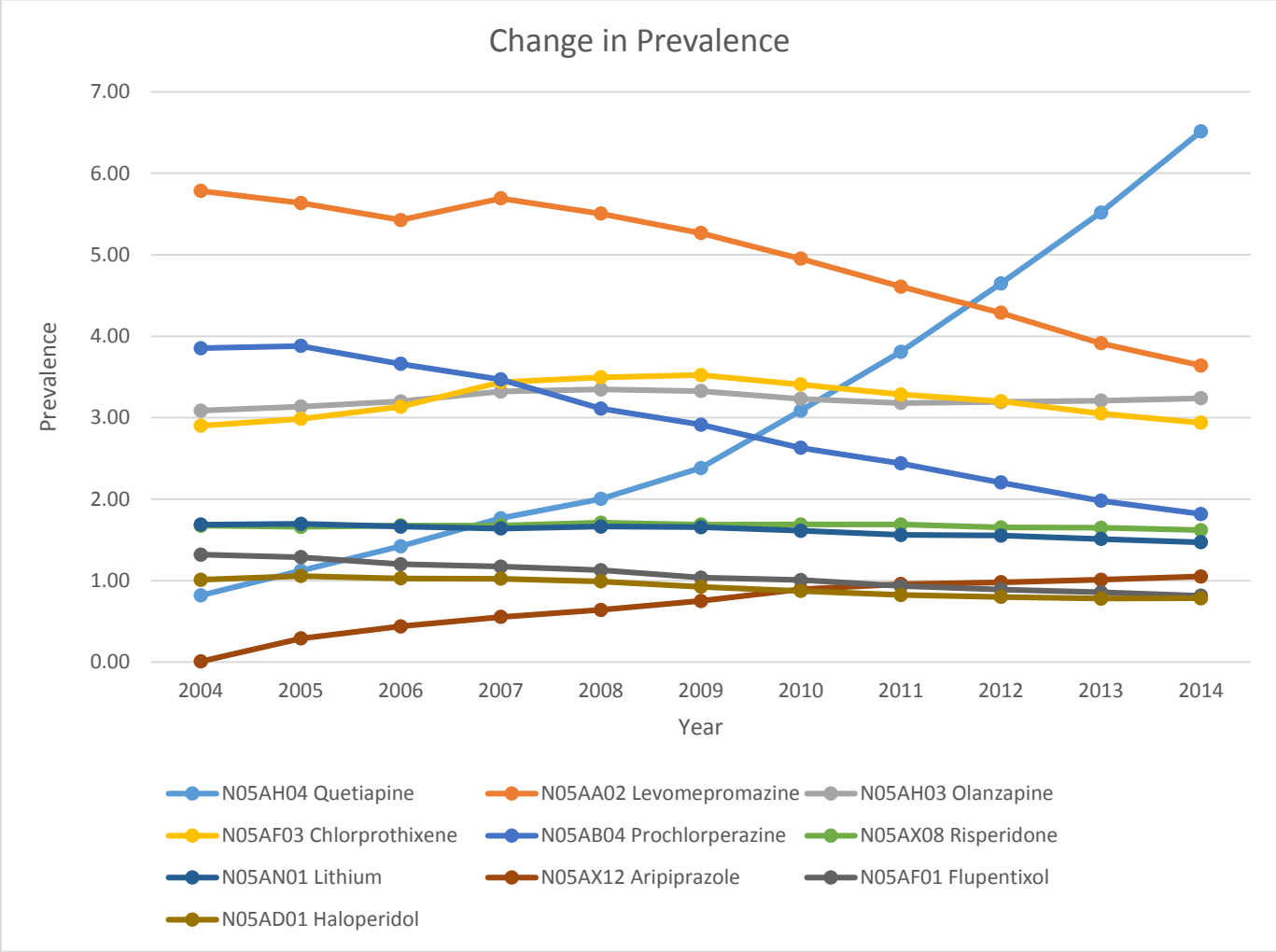


Figure 4-2 shows the differences in the consumption pattern of antipsychotic drugs in Norway over the course of eleven years. The most significant change occurred for Quetiapine. Initially, the use of Quetiapine increased almost three folds from 2004 to 2009 and then went up even more sharply to reach 6.51 users per 1000 inhabitants in 2014. Similarly, aripiprazole had a 105 times increase in the prevalence from 2004 (0.1per 1000 inhabitants) to 2014 (1.05 per 1000 inhabitants).

On the other hand, use of levomepromazine and prochlorperazine was decreased in this period. Prevalence was decreased by 2.14 per 1000 and 2.03 per 1000 for levomepromazine and prochlorperazine from 2004 to 2014 respectively.

4.1.3 Change in cost per user in Norway from 2004-2014

In 2004, average cost per user of antipsychotic was 3950 NOK and in 2014, it was decreased to 2896 NOK. (See appendix E)

Figure 4-3: Change in cost per user from 2004-2014 in Norway

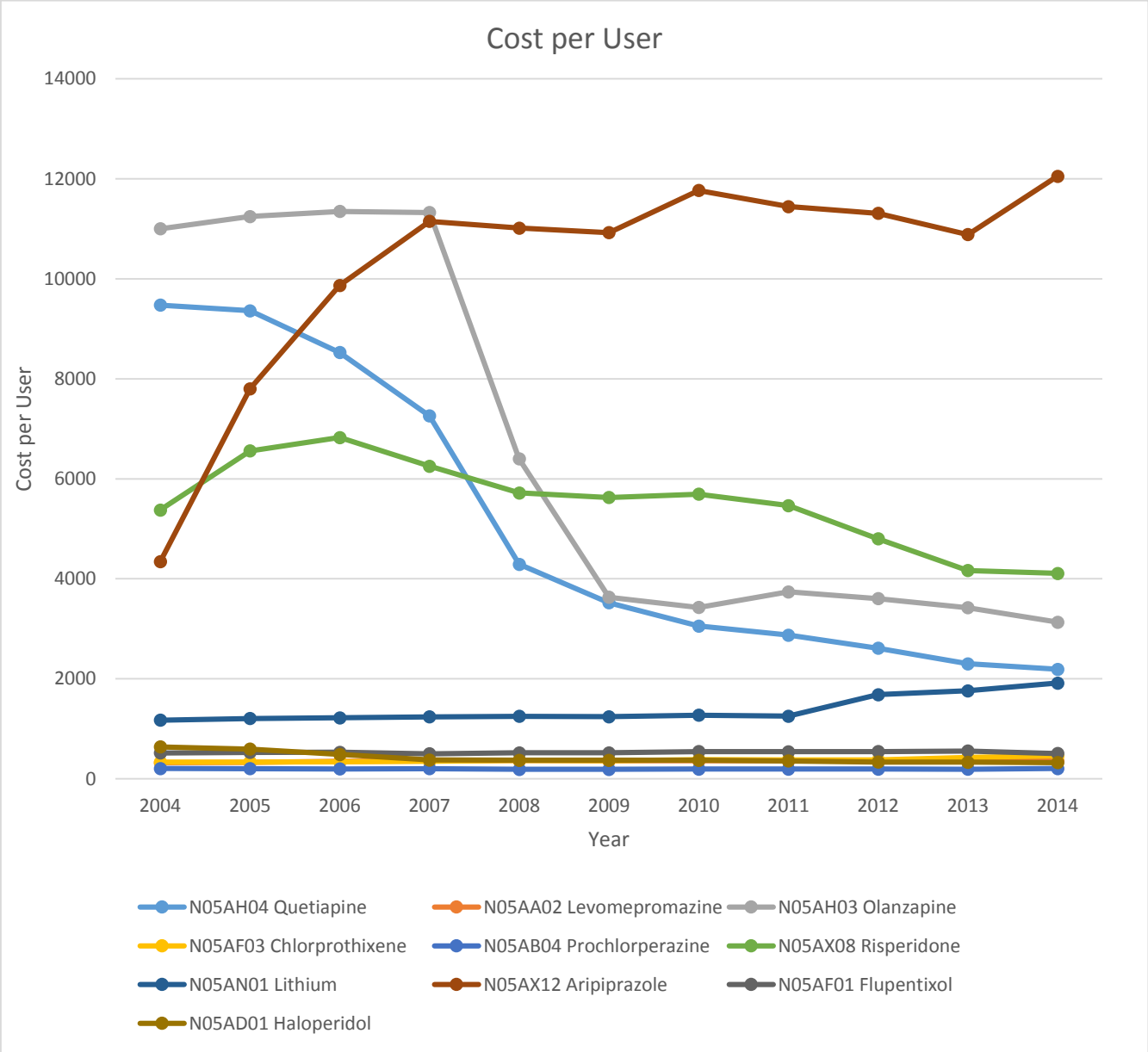


Figure 4-3 suggests that aripiprazole had significant increase in cost per user. Initially, its cost was increased aggressively from 4342 NOK in 2004 to approx. 11150 NOK in 2007 after which it reached to 12054 NOK per user in 2014 with some fluctuations in between. Similarly, Lithium's cost/user was increased from 1252 NOK in 2011 to 1914 NOK in 2014 while it had

almost horizontal movement before 2011. Olanzapine had a minimal increase in cost until 2007, which dropped around 3 times from 2007 to 2009. It continues to fall and reach 3133 NOK in 2014 with fluctuations in between. Quetiapine had continuous decline in cost/user with rapid drop occurring from 2005 to 2008. Its cost/user was decreased from 9474 NOK in 2004 to 2191 NOK in 2014. Risperidone had minimal increase at the beginning but it was quickly decline from 2006. Rest of the drugs did not have significant cost per user change during 2004-2014.

4.2 Top ten drugs in Norway, Sweden, and Denmark:

Table 4-3: Top ten Antipsychotic drugs of Norway, Sweden and Denmark

ATC Code	Class of Drugs	Norway(2014)	Sweden(2014)	Denmark(2013)
N05AH04 Quetiapine	2nd	1	2	1
N05AA02 Levomepromazine	1st	2	6	7
N05AH03 Olanzapine	2nd	3	1	4
N05AF03 Chlorprothixene	1st	4	-	2
N05AB04 Prochlorperazine	1st	5	-	-
N05AX08 Risperidone	2nd	6	3	3
N05AN01 Lithium	-	7	4	6
N05AX12 Aripiprazole	2nd	8	5	5
N05AF01 Flupentixol	1st	9	9	8
N05AD01 Haloperidol	1st	10	7	10
N05AF05 Zuclopenthixol	1st	-	8	9
N05AH02 Clozapin	2nd	-	10	-

Table 4-3 compares the top ten-drug list according to the number of users in three different countries. Nine out of top ten drugs in 2013 in Denmark fell within the range of top ten drugs of Norway. The only exception was zuclopenthixol. Likewise, eight out of top ten drugs in Sweden was on the list of Norway. However, the ranking differed considerably in three countries.

4.3 Prescription pattern in Denmark and Sweden

The total turnover of all antipsychotic drug sale in Denmark was approximately 475 million NOK in 2013. Similarly, prevalence of antipsychotic use in Denmark was 22.56 per 1000 inhabitants in 2013 with female having higher prevalence than male i.e. 24.29 and 20.8 users per 1000 inhabitants respectively. However, Sweden had lower prevalence as compared to

Norway and Denmark. The total prevalence of Sweden was 15.68 with female 16.96 and male 14.40 users per 1000 inhabitants.

Table 4-4: Prevalence of Antipsychotic drug users

	Norway (2014)	**Denmark (2013)**	**Sweden (2014)**
Male	18.81	20.8	14.40
Female	23.66	24.29	16.96
Total	21.22	22.56	15.68

Table 4-5: Prescription pattern of antipsychotic drugs in Denmark in 2013

S.N	ATC code	Number of user	User per 1000 inhabitants	Cost per User (DKK)	Cost per User (NOK)	DDD per User per Day
1	N05AH04 (Quetiapine)	46495	8.3	2598	2721	0.65
2	N05AF03 (Chlorprothixene)	23043	4.11	329	344	0.65
3	N05AX08 (Risperidone)	17937	3.2	3979	4166	0.64
4	N05AH03 (Olanzapne)	17905	3.2	1110	1162	0.49
5	N05AX12 (Aripiprazole)	10093	1.8	14087	14749	0.48
6	N05AN01 (Lithium)	8886	1.59	1270	1329	0.35
7	N05AA02 (Levomepromazine)	7828	1.4	949	993	0.34
8	N05AF01 (Flupentixol)	6506	1.16	517	541	0.33
9	N05AF05 (Zuclopenthixol)	6387	1.14	818	856	0.32
10	N05AD01 (Haloperidol)	5865	1.05	276	288	0.31
11	N05AH02 (Clozapine)	3252	0.58	1140	1194	0.27
12	N05AE04 (Ziprasidone)	1697	0.3	6292	6588	0.18
13	N05AX13 (Paliperidone)	1686	0.3	29174	30546	0.11
14	N05AG02 (Pimozide)	926	0.17	721	755	0.11
15	N05AB03 (Perphenazine)	796	0.14	4156	4351	0.09
16	N05AL05 (Amisulpride)	755	0.13	4807	5033	0.06
17	N05AB04 (Prochlorperazine)	746	0.13	483	505	0.65
18	N05AL01 (Sulpiride)	554	0.1	3699	3872	0.65
19	N05AE03 (Sertindole)	442	0.08	502	526	0.64
20	N05AE03 (Sertindole)	400	0.07	13783	14430	0.49
21	N05AC01 (Periciazine)	283	0.05	1633	1709	0.48
22	N05AD05 (Pipamperone)	269	0.05	1045	1094	0.35
23	N05AH05 (Asenapine)	112	0.02	8786	9199	0.34

Table 4-6: Prescription pattern of antipsychotic drugs in Sweden in 2014

S.N	ATC Code	Number of users	User per 1000 inhabitants	DDD per User per Day
1	N05AH03 Olanzapine	34645	3.59	0.67
2	N05AH04 Quetiapine	34503	3.58	0.35
3	N05AX08 Risperidone	34482	3.58	0.25
4	N05AN01 Lithium	21246	2.2	0.70
5	N05AX12 Aripiprazole	15881	1.65	0.50
6	N05AA02 Levomepromazine	14405	1.49	0.11
7	N05AD01 Haloperidol	14105	1.46	0.30
8	N05AF05 Zuklopentixol	7652	0.79	0.66
9	N05AF01 Flupentixol	6344	0.66	0.28
10	N05AH02 Clozapine	5962	0.62	0.94
11	N05AB03 Perfenazine	2979	0.31	0.88
12	N05AX13 Paliperidone	2213	0.23	0.89
13	N05AF03 Chlorprothixine	1847	0.19	0.14
14	N05AE04 Ziprasidone	1412	0.15	0.79
15	N05AD03 Melperone	1386	0.14	0.12
16	N05AB02 Fluphenazin	210	0.02	1.67
17	N05AB04 Prochlorperazine	101	0.01	0.02
18	N05AC02 Thioridazine	98	0.01	0.00
19	N05AG02 Pimozide	90	0.01	0.00

Tables 4-5 and 4-6 depict prescription pattern in Denmark and Sweden. In Denmark, latest available data was 2013 data and for Sweden, it was 2014.

Like Norway, quetiapine had the largest prevalence (8.3 per 1000) in Denmark. Second in the table was chlorprothixene (4.1 per 1000).Whereas; olanzapine was on top of the table (3.59 per 1000) in Sweden followed by quetiapine (3.58 per 1000). Top ten antipsychotic drugs in Denmark (2013) were quetiapine, chlorprothixene, risperidone, olanzapine, aripiprazole, lithium, levomepromazine, flupentixol, zuclopenthixol and haloperidol respectively. Similarly,

Swedish top ten antipsychotics were olanzapine, quetiapine, resperidone, lithium, aripiprazole, levomepromazine, haloperidol, zuclopenthixol, flupentixol and clozapine respectively.

In Denmark, average cost per user of quetiapine was 2721 NOK and chlorprothixine had 344 NOK. Similarly, risperidone and olanzapine had average cost of 4166 NOK and 1162 NOK respectively.

In Sweden, top drugs with high average dose per user per day were fluphenazine (1.67), clozapine (0.94), and palperidone (0.89) while low average dose drugs were prochlorperazine (0.017), levomepromazine (0.105), and melprone (0.12). Similarly, in Denmark, drugs with high average dose were perphenazine (1.31), ziprasidone (1.12), and clozapine (0.95) while drugs with low average dose per user per day were prochlorperazine (0.059), levomepromazine (0.09), and sertindole (0.105).

5 DISCUSSION

5.1 Prevalence

The prevalence in Norway (21.22) is comparable to that of the Denmark (22.56) whereas Sweden (15.68) has lower antipsychotic use prevalence comparing to these two countries. Studies have found different prevalence rates of antipsychotic drug use around the world. Compared to these studies, all three countries studied have a higher prevalence. J. Alonso et al found out average prevalence of 12 per 1000 inhabitants in a study carried out in seven European countries between 2000 and 2003 (27). ME Domino et al. found 12 antipsychotic users per 1000 inhabitants in United States between 1996 and 2005 (28). In a Norwegian paper by Kjosavik et al. found that, "Prevalence of psychotropic medication is higher in Norway. The same is true for antipsychotics." He reviewed 16 studies on the drug utilization pattern of antipsychotics and found a prevalence between 3 to 13 per 1000 adults and 0.8 to 10.6 per 1000 children and adolescent(29). Similarly, in a nationwide population based study carried out in Italy from the retrospective data during 1995-2002 reported a prevalence of 6.6 per 1000 inhabitants in 2002 (30). Similarly, Percudani et al found out the prevalence of 9 per 1000 inhabitants in general population of Lombardy, Italy (31).

However, there are very few studies based on national data or covering large population. Out of them, recent nationwide studies were even rare. Most of the studies were based on the sample data which are prone to recall bias(29). Our study was based on national data for all age groups while some of the studies were specific to adults and some were specific to the children and adolescent.

Though the two Italian studies were based on the large population of Italy, but only reimbursed prescriptions. Since, SGAs were not reimbursed in Italy until 2000 , it could have significant impact on the prevalence of antipsychotics studied in 2001 and 2002 (29).

Kjosavik et al. in his work, points out that these differences in the antipsychotic use in different countries may explain the national variation to some extent (29).

5.1.1 Gender Difference in Prevalence:

Prevalence was higher in female than male in Norway as well as Denmark and Sweden. This finding was consistent with most of the literature on antipsychotics. Kaye et al. found a higher prevalence in female (15 per 1000) than male (9 per 1000) (32). Similarly, two studies conducted in Italy in 2001 and 2002 found similar results (30, 31).

Though the finding was similar to the other studies, it was quite surprising that female had higher prevalence of antipsychotic use despite the fact that schizophrenia and psychotic illness affects both gender equally (33). J. Alonso et al reported the similar gender differences in all psychotropic medication utilization and pointed out that differences could explained on the basis of socio-cultural differences. One of the plausible explanation could be that women more often seek medical attention with their psychological symptoms. J. Alonso et al cited Mellinger et al. in his work, "use of alcohol is most prevalent among groups of people who are least likely to use medically prescribed mood changing drugs, and vice versa". Studies suggest the inverse relationship between alcohol consumption and psychotropic drug use meaning that people who use or abuse alcohol as self-medication are less likely to take antipsychotic drugs. Since, women are less likely to abuse alcohol compared to men, higher use of antipsychotic in women is obvious (27). However, alcohol as self-medication could further worsen the condition and should be avoided.

5.1.2 Change in Prevalence in Norway

In 11 years period (2004-2014), prevalence was higher in 2005 (23 per 1000) and lowest in 2013 (21 per 1000). The small decrease in overall prevalence of antipsychotics in Norway from 2004-2014 is quite different from previous studies in other countries.

Verdoux et al. reviewed the findings from the studies exploring antipsychotic prescribing trends from 2000. Seventeen studies were included in the review and nearly all of them showed the increase in antipsychotic prescriptions with dramatic rise in SGAs prescriptions (34) . Similarly, Domino et al. (2005) found out the substantial increase in the antipsychotic prescription in US population between 1996/97 and 2004/05 (28).

If we look at the individual drug prevalence pattern over the 11 years of period, quetiapine and aripiprazole showed the significant rise in the number of users while levomepromazine and prochlorperazine had decreased prevalence. On the other hand, use of chlorprothixine and olanzapine fairly remain stable on the either edge of study period while they showed some fluctuations in the middle of the years.

A Canadian study reported an increase in quetiapine use between 2005 and 2012. They highlighted that there was gradual decrease in its utilization for psychosis. Therefore, increased use of quetiapine over other antipsychotic medication is a result of its off-label utilization in a conditions such as. mood disorders, psychotic disorders, anxiety disorders and sleep disturbances (35).

Aripiprazole is considered to be different antipsychotics due to its partial dopamine agonist effects which leads to the fewer side effects while treating schizophrenia and acute bipolar disorder. Bhati et al. believed that this relatively safe profile might lead clinician to try in other off-label indications. It has been used to treat the conditions like psychotic unipolar and bipolar depression, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and pervasive developmental disorders in children and adults(36). Therefore, a good safety profile and various off-label use could be the reason for increased use of aripiprazole in Norway. However, further research should be carried out to explore the reasons for increased use.

In contrast, decreased use of the FGAs, levomepromazine and prochlorperazine could be due to the recommendation of SGAs over FGAs, by most of the guidelines, as a first-line drug in

the treatment of Schizophrenia (37). However, this interpretation could not be verified given the fact that antipsychotics, particularly FGAs, are used for its non-antipsychotic and off-label indications to a large extent and this use could have changed significantly during the study period.

5.2 Top ten antipsychotic drugs:

In Norway, quetiapine was mostly prescribed antipsychotic drug in 2014. Interestingly, top ten-drug list of Sweden and Denmark are quite similar to the Norwegian one. Eight out of top 10 drugs in Sweden (2014) and nine out of 10 drugs in Denmark (2013) were same as that of Norway (2014). In addition, Norway (2014) and Denmark (2013) had four SGAs and 6 FGAs in top ten list whereas Sweden had five drugs in each groups. Though the list of the drug is similar in three countries, their ranking in the table was quite different from each other.

Marston et al. identified three most prescribing SGAs as olanzapine, quetiapine and risperidone and FGAs as haloperidol, chlorperazine and trifluperazine in primary care in United Kingdom (38). This finding was partly similar to our study as three SGAs were also the top prescribing drugs of our studied countries whereas FGAs were different. Statista reported that top prescribing drugs in United States in 2011/12 were quetiapine, Seroquel (quetiapine), Abilify (aripiprazole), quetiapine fumarate, Seroquel XR (quetiapine), olanzapine, haloperidol, Zyprexa (olanzapine), Geodon (ziprasidone) and clozapine. Though the report provided top prescribing list based on the individual drug brand names, it is clear that quetiapine, olanzapine and aripiprazole were the most prescribing drugs in United States (39).

5.3 DDD per User per Day

Seven antipsychotic drugs (out of the top ten drug) in Norway had less than 0.5 DDD/user/day. Similar trend was observed in Denmark (2013) and Sweden. Seven out of 10 in Denmark and six out of 10 in Sweden had lower than 0.5 DDD/user/day. Certain drugs such as prochlorperazine was as low as 0.03 (Norway), 0.06 (Denmark) and 0.02 (Sweden)

DDD/user/day. Similarly, Levomeperazine was 0.05(Norway), 0.09 (Denmark) and 0.1(Sweden) DDD/user/day.

Even though, DDD doesn't necessarily reflect the true prescribed dose, it is considered as a technical unit for measurement which is widely used in drug research and statistics (29). Further, DDD only represent the average dose for its primary indication while antipsychotic are used for various indications other than psychotic illness. The relatively low DDD/user/day of the antipsychotic drugs can be explained in terms of their non-antipsychotic indication, off-label utilization and duration of treatment. For example, prochlorperazine has standard DDD of 100mg whereas it is available in Norwegian market as 5mg tablet meaning that its antipsychotic use is extremely rare(25). Kaye et al observed less than 10% of antipsychotic were used for first time schizophrenia and other psychosis while for bipolar disorder was even less (1%). Nearly 50% of the prescription were indicated for anxiety, depression and panic disorder and 15 % was prescribed to treat agitation and dementia (32). Similarly, a large primary care database based UK study found out that approximately half of the antipsychotics were prescribed to the people who were not diagnosed with serious mental illnesses. Generally, when antipsychotic are off-label prescribed, they were found out to be given at low dose and for short duration (with exception of ADHD and dementia) which leads to the low DDD (38). In addition, patient with psychosis disorder have higher chance of discontinuation of drugs when the symptoms subside as well as there is higher rate of drug switching given its large side effect profile. Similarly, even if a given drug has been exclusively used for its primary indication with recommend dose but with short duration or if the treatment is started somewhere in the middle of the year, it will tend to decrease the average DDD/user/day of that year. Therefore, drug discontinuation, drug switching, time of initiation of drug treatment, and high non-antipsychotic and off-label use could be the major factors behind the low DDD.

On the other hand, certain drugs such as clozapine, palperidone, ziprasidone, perphenazine has higher DDD in all three countries. I believe that these drugs are being prescribed mainly for its primary antipsychotic indication or they are being prescribed at the dose higher than the standard DDD. For example, clozapine had DDD of 300mg but it is mainly prescribed for the drug resistant schizophrenia and has the maximum therapeutic dose of 450mg (25). It means if the drug is prescribed above 300mg, it will certainly have high DDD/user/day.

5.4 Cost per User:

Norway spent approximately 316 million NOK in 2014 for all kinds of antipsychotic drugs whereas Denmark (2013) spent 475 million NOK. However, Swedish data on turnover were not available for the comparison.

On average Norway has lower cost per user compared to Denmark. Cost of antipsychotic per user in Norway was 2896 NOK whereas Denmark (2013) had 3935 NOK per user.

5.4.1 Cost per user change over time in Norway:

During 2004-2014, only four (out of top ten list) SGAs drugs quetiapine, risperidone, olanzapine and quetiapine displayed the significant price change. Out of them aripiprazole exhibited the considerable increase in price whereas average cost of rest three drugs were declined considerably. In addition, these four drugs showed great degree of fluctuation over time.

As the average cost of quetiapine decreased from 2004-2014, its prevalence was increased but with different slope. For aripiprazole, both average cost and prevalence was increased during this period. Though olanzapine displayed sharp decrease in average cost from 2007-2009, prevalence wasn’t changed significantly. In Norway, prevalence of antipsychotics, in general, was not related to the average cost per user of these agents.

The sharp price drop of the olanzapine from 2007-2008 as well as drop of the price of quetiapine and risperidone can be explained by the fact that these drugs lost their patents and included in 'graded pricing model'. One report estimated around 31% of the price were dropped for these three drugs in 2008 as compared to 2007(40).

Though aripiprazole showed the rapid increase in average cost from 2004 to 2007, its cost per DDD was not increased rapidly. The sharp rise in the graph is due to the fact that it was introduced in the European market in 2004 and its use was considerably increased after its introduction (41). The high degree of fluctuations in the cost per users of all four drugs could be due to the reference price system in Norway. Reference pricing was applied in Norway from 1993 until 2003 and a system similar to the reference pricing called as 'index pricing' was introduced in 2003 (42). According to this system, non-prescription drugs price in Norway is determined based on the average of three lowest price of nine reference countries: Sweden, Finland, Denmark, Germany, United Kingdom, Netherlands, Austria, Belgium and Ireland. Therefore, change in the price of drugs in Norway could be due to changes in the European price, changes in exchange rates or a pharmaceutical being withdrawn from one of the above-mentioned nine European countries (43).

5.5 First vs Second Generation Antipsychotic:

Norway (2014) and Denmark (2013) had four SGAs and six FGAs in top ten list whereas Sweden had five drugs in each groups. Although, most of the mental health guidelines recommends SGA as fist-line treatment drugs, my study found the higher utilization of FGAs in all three countries.

Studies on other countries showed mixed results. Marston et al. found that around two third of the antipsychotic prescriptions were SGAs in UK general population (38). Kroken et al. found 40% of the cases were prescribed with at least one FGA at the discharge in Norwegian hospitals(16). One Italian study observed almost equal prescription of both class of

antipsychotics (44). Similarly, a Canadian study found that the FGA use is increasing at a greater rate than SGA (45).

There could be multiple explanation for the higher use of FGA despite the guideline's recommendations on SGAs. E. Johnsen et al. believes that mental illnesses often relapse and both patient and physician known what antipsychotic they used and what worked. In such case, it is rational to choose the well-known old drug which was previously effective in treating the condition (46). Another explanation could be the fact that recent clinical trials showing no differences between FGAs and SGAs. Two large independent clinical trials: CUtLASS in UK and CATIE in North America found that FGAs and SGAs had similar effectiveness in treating most cases of schizophrenia (45). Similarly, antipsychotic drugs have high level of non-antipsychotic and off-label utilization and database provide the aggregated data rather than the data specific to the conditions (schizophrenia). Even if there is less use of FGAs in the psychotic illness or SGAs were preferred to FGAs, it may not be reflected on the finding due to their several indications.

Therefore, further research needs to be carried out to explore the difference in prescription pattern of FGAs vs SGAs.

5.6 Strength

- The study was based on the comprehensive data from three national databases: NorPD, PDR Sweden and DNPR. Therefore, data extrected from these sources were complete and accurate. These database contains all the informations about the prescribing of antipsychotic drugs in Norway, Sweden and Denmark.

- Only the prescriptions, which were actually dispensed from the pharmacy counters, are entered in the database. This will eliminate the primary non-compliance and improve the data validity.
- The data is free from any recall bias which otherwise could arise from survey data.
- To our knowledge, this is the first nationwide study about the individual antipsychotic drug prescription pattern including DDD, prevalence, and turnover.

5.7 Limitations

- Drug dispensed during hospital or nursing home stay was not included in NorPD and PDR Sweden while DNPR contains the hospital data as well. Therefore, hospital data were not included in this study, which will underestimate the total drug use.
- The study aims to compare the findings from Norway to that of Sweden and Denmark. Unfortunately, Swedish database provides data from 2006 only and Danish database was not updated for 2014 data while this study was conducted. This makes the study with limited comparison. Also, Swedish database doesn't provide any information about the total turnover of the individual drugs due to which comparison with the Swedish turnover and cost per user were not carried out (29, 47).

6 CONCLUSION

Prevalence of antipsychotic use was higher in Norway and Denmark (2013) as compared to Sweden. While comparing to other studies, all three studied countries have higher prevalence of antipsychotic use. The prevalence did not change much over time and was around 21 users per 1000 inhabitants during the study period in Norway.

In general, women have higher overall drug prevalence than men in all three countries. However, certain drugs in Norway had exception: Olanzapine, risperidone, clozapine, paliperidone, amisulpride, and pimozide.

Quetiapine, levomepromazine, olanzapine, chlorprothixene, prochlorperazine, risperidone, lithium, aripiprazole, flupentixol and haloperidol were the top ten list of Norway. Sweden and Denmark also had similar list: eight out of 10 and nine out of 10 were same as that of Norway respectively.

Several antipsychotics were found to have a low DDD/user/day for e.g. levomepromazine, prochlorperazine etc. which indicates high non-antipsychotic or off-label utilization. Whereas, certain drugs such as clozapine, palperidone, and ziprasidone had high DDD/user/day, possibly due to prescribing in higher dose than standard DDD.

FGAs were widely used in all three countries regardless of the expert recommendations to prescribe SGAs. This difference could linked to the higher non-antipsychotic and off-label use as well as recent studies showing no differences in efficacy of FGAs vs SGAs.

The average cost per user in Norway was decreased from 2004 (3950 NOK) to 2014 (2896 NOK) and the average cost per user of antipsychotic in Norway is lower than in Denmark. A Danish users had to pay around 1040 NOK higher than Norwegian on average per year for any antipsychotic agents. It is mainly because Norway has a reference pricing system that compares the price of nine countries including Denmark.

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APPENDIX A

Table: Total prevalence of Antipsychotic drug users in Norway

Year	Users per 1000 inhabitants
2004	22.78
2005	22.97
2006	22.80
2007	22.46
2008	21.83
2009	21.55
2010	21.29
2011	21.07
2012	21.11
2013	20.95
2014	21.22

APPENDIX B:

Table: Change in prevalence of Antipsychotic drugs from 2004-2014 in Norway.

	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
N05AH04 Quetiapine	0.82	1.12	1.42	1.77	2.00	2.38	3.09	3.81	4.65	5.52	6.51
N05AA02 Levomepromazine	5.78	5.64	5.43	5.69	5.50	5.27	4.95	4.61	4.29	3.91	3.64
N05AH03 Olanzapine	3.09	3.14	3.20	3.32	3.35	3.33	3.23	3.18	3.19	3.21	3.24
N05AF03 Chlorprothixene	2.90	2.99	3.13	3.44	3.50	3.52	3.41	3.28	3.20	3.05	2.94
N05AB04 Prochlorperazine	3.85	3.88	3.66	3.47	3.11	2.91	2.63	2.44	2.20	1.98	1.82
N05AX08 Risperidone	1.67	1.66	1.68	1.68	1.71	1.69	1.69	1.69	1.65	1.65	1.62
N05AN01 Lithium	1.69	1.70	1.66	1.64	1.66	1.66	1.61	1.56	1.55	1.51	1.47
N05AX12 Aripiprazole	0.01	0.29	0.44	0.55	0.64	0.75	0.90	0.96	0.98	1.01	1.05
N05AF01 Flupentixol	1.32	1.29	1.20	1.17	1.13	1.04	1.01	0.93	0.89	0.86	0.81
N05AD01 Haloperidol	1.01	1.06	1.03	1.02	0.99	0.92	0.87	0.82	0.80	0.78	0.78

APPENDIX C

Table: Change in cost per user of top ten drugs of Norway from 2004-2014

Cost per user											
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
N05AH04 Quetiapine	9474	9361	8526	7258	4290	3520	3057	2875	2611	2300	2191
N05AA02 Levomepromazine	323	330	348	358	368	361	360	361	357	352	361
N05AH03 Olanzapine	11003	11249	11350	11326	6398	3631	3428	3740	3604	3423	3133
N05AF03 Chlorprothixene	332	334	340	348	367	364	382	380	376	430	458
N05AB04 Prochlorperazine	206	202	199	202	189	190	195	195	194	193	205
N05AX08 Risperidone	5375	6560	6825	6252	5719	5628	5694	5464	4800	4167	4110
N05AN01 Lithium	1173	1205	1220	1239	1251	1242	1273	1252	1684	1760	1914
N05AX12 Aripiprazole	4342	7803	9868	11151	11016	10926	11769	11446	11310	10886	12054
N05AF01 Flupentixol	516	527	532	501	520	521	544	541	544	556	507
N05AD01 Haloperidol	638	595	488	375	372	372	371	358	335	332	325

APPENDIX D

Table: Antipsychotic drug available in Norway, Denmark, and Sweden

S.N	**Norway**	**Denmark**	**Sweden**
1	- N05AB02 -Fluphenazine	N05AA01 (Chlorpromazine)	N05AA01 Klorpromazin
2	- N05AB03 -Perphenazine	N05AA02 (Levomepromazine)	N05AA02 Levomepromazin
3	- N05AB04 -Prochlorperazine	N05AA03 (Promazine)	N05AA04 Acepromazin
4	- N05AB06 -Trifluoperazine	N05AA04 (Acepromazine)	N05AA06 Cyamemazin
5	- N05AB08 -Thioproperazine	N05AB01 (Dixyrazine)	N05AB01 Dixyrazin
6	- N05AC01 -Periciazine	N05AB02 (Fluphenazine)	N05AB02 Flufenazin
7	- N05AC02 -Thioridazine	N05AB03 (Perphenazine)	N05AB03 Perfenazin
8	- N05AC04 -Pipotiazine	N05AB04 (Prochlorperazine)	N05AB04 Proklorperazin
9	- N05AD01 -Haloperidol	N05AC01 (Periciazine)	N05AB06 Trifluoperazin
10	- N05AD03 -Melperone	N05AC02 (Thioridazine)	N05AC01 Periciazin
11	- N05AD08 -Droperidol	N05AC04 (Pipotiazine)	N05AC02 Tioridazin
12	- N05AE03 -Sertindole	N05AD01 (Haloperidol)	N05AD01 Haloperidol
13	- N05AE04 -Ziprasidone	N05AD03 (Melperone)	N05AD03 Melperon
14	- N05AE05 -Lurasidone	N05AD05 (Pipamperone)	N05AD05 Pipamperon

15	- N05AF01 -Flupentixol	N05AD06 (Bromperidol)	N05AD08 Droperidol
16	- N05AF03 -Chlorprothixene	N05AD08 (Droperidol)	N05AE03 Sertindol
17	- N05AF05 -Zuclopenthixol	N05AE03 (Sertindole)	N05AE04 Ziprasidon
18	- N05AG02 -Pimozide	N05AE04 (Ziprasidone)	N05AF01 Flupentixol
19	- N05AG03 -Penfluridol	N05AF01 (Flupentixol)	N05AF03 Klorprotixen
20	- N05AH01 -Loxapine	N05AF03 (Chlorprothixene)	N05AF05 Zuklopentixol
21	- N05AH02 -Clozapine	N05AF05 (Zuclopenthixol)	N05AG02 Pimozid
22	- N05AH03 -Olanzapine	N05AG02 (Pimozide)	N05AH02 Klozapin
23	- N05AH04 -Quetiapine	N05AG03 (Penfluridol)	N05AH03 Olanzapin
24	- N05AH05 -Asenapine	N05AH01 (Loxapine)	N05AH04 Kvetiapin
25	- N05AL01 -Sulpiride	N05AH02 (Clozapine)	N05AL01 Sulpirid
26	- N05AL03 -Tiapride	N05AH03 (Olanzapine)	N05AL03 Tiaprid
27	- N05AL05 -Amisulpride	N05AH04 (Quetiapine)	N05AL05 Amisulprid
28	- N05AN01 -Lithium	N05AH05 (Asenapine)	N05AN01 Litium
29	- N05AX07 -Prothipendyl	N05AL01 (Sulpiride)	N05AX08 Risperidon
30	- N05AX08 -Risperidone	N05AL05 (Amisulpride)	N05AX12 Aripiprazol
31	- N05AX12 -Aripiprazole	N05AN01 (Lithium)	N05AX13 Paliperidon
32	- N05AX13 -Paliperidone	N05AX08 (Risperidone)	
33		N05AX12 (Aripiprazole)	
34		N05AX13 (Paliperidone)	

APPENDIX E

Table: Average cost per user of antipsychotic in Norway

Year	**Average Cost per user (NOK)**
2004	3059
2005	3409
2006	3615
2007	3787
2008	2952
2009	2547
2010	2609
2011	2697
2012	2784
2013	2811
2014	2896