Pharmacological Drug use of Healthy Controls and Psychiatric Patients in a Case-Control Study using the National Norwegian Prescription Database

Credit hours:60

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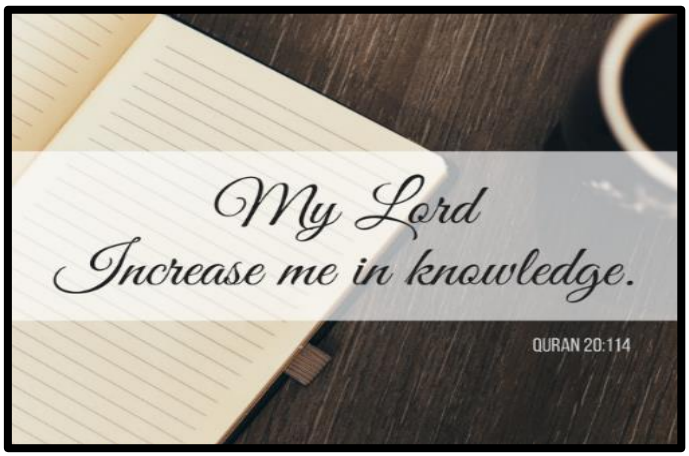
I will always remain grateful to all of you and will end this writeup with the below beautiful pray!



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Abstract:

Background:

Mental disorders are considered among the highest-ranking causes of non-fatal burden globally (GBD, 2016). Psychiatric patients not only use psychotropic medications, but they are also frequent users of somatic medications (Abdullah-Koolmees, 2013). This requires advancements in recommendations of psychiatric medicines due to psychiatric and somatic comorbidities (Leung BM, 2019). However, there is less research done to find realistic prevalence estimates of drug use in these patients in comparison with healthy volunteers. This lack of information became even more attractive with the availability of powerfully built data source in the form of Prescription Registers in some western countries, for example Norway.

Objectives:

To evaluate what extent healthy participants in a psychiatric research setting were prescribed medication, the total prescription pattern of medication among patients with severe psychiatric disorders and to compare them.

Methodology:

Clinically diagnosed participants from the TOP study were investigated by linkage with information for prescriptions of medication registered in the Norwegian Prescription database (NorPD) one year before and one year after inclusion to the TOP study. The NorPD data was extracted on the basis of ATC codes of drugs and obtained from all the pharmacies between 2004 -2017 while TOP study is a cross-sectional naturalistic study conducted in psychiatric departments of five major hospitals in the catchment areas of Oslo, where the diagnosis was made by DSM-IV through Structural Clinical interview IV (American Psychiatric Association, 1995).

Both data sources were linked together by the unique personal number assigned to every resident in Norway. Then we investigated the medication use by them in a case-control cohort study pattern. Statistical analyses were performed using SPSS version 25. Significance threshold was set as $p < 0.05$. Variables were presented as percentages. Chi-square test was performed to compare use of medications acting on nervous system and medications used for somatic disorders between patient and control groups during the time intervals one year before and one year after inclusion in the TOP study. The strength of differences in this medicine use between patients and controls was then evaluated by logistic regression controlling for age and gender.

Results:

There was a similar gender distribution between the groups, while there were a larger proportion of young adults (68% vs 62%), fewer middle-aged adults (28% vs 37%) and more elderly (3.6 vs 1.3%) among patients than controls. Patients usually used both nervous system acting medications and somatic medications more frequently than controls. On the other side, the controls were also found prescribed some medications more often than the investigated patients' group. However, this pattern is less frequently seen but has significance findings which we discussed in this research project.

Conclusion:

The overall medication use was higher among patients than controls. The control group did not represent completely healthy and medicine free volunteers, as was often expected when comparing them with patients' group. These findings directed attention of scientific society towards vigorous and trustworthy control screening.

Key words: Controls, healthy volunteers, somatic disorders, ATC codes, psychiatric patients, prescription register

Conflict of Interest:

There is no conflict of interest to declare.

Declaration:

I hereby declare that this master thesis has been my independent work and has not been aided with any prohibited means. I declare, to the best of my knowledge and belief, that the literature taken from published and unpublished sources or documents have been reproduced in my own words and throughout citations are mentioned in references.

This work has not been submitted for evaluation to any other examination authority and not been published yet.

Dur-e-Shahnaz Shafi

10.02.2021

Abbreviations:

ATC codes= Anatomical Therapeutic Chemical Codes

ATC-N = Drugs within ATC category N (Nervous System)

ATC-S = Drugs within ATC categories indicated for somatic disorders.

CG= Controls' group

HV= Healthy volunteers

NorPD= Norwegian Prescription Database

NPR= Norwegian Patient Registry

NPbR=Norwegian Population Register

PG= Patients' group

TOP study=Thematically Organized Psychosis study

WHOCCDSM=WHO's Collaborating Centre for Drug Statistics Methodology

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1: INTRODUCTION:

1:1: Background:

Magnitude of The Problem (Global Burden of Mental Diseases):

Mental disorders are considered among the highest-ranking causes of non-fatal burden globally (GBD, 2016). Global Burden of Diseases is presented as a report which is also called "Mortality and Causes of Death Collaborators Report" and considered as the most trustworthy statistics. According to a prior study of 1996, Mental disorders have already contributed an increase of about 15% in the global disease burden many decades ago as compare to global burden of somatic diseases (Mazziotta JC, 1996)

There are numerous studies done on the global burden of mental disease. Although most of their findings illustrate the growing burden of mental disorders in terms of disability rather than mortality. Collectively, these disorders claim for about one third of all years lived with disability (YLD) worldwide, YLDs contributing to significant increment in disability-adjusted life years (DALYs) (WHO, 2011) (fig.1). While measuring non-fatal burden, depressive disorders and anxiety disorders ranked as the 3rd and 9th leading contributors respectively to years lived with disability. Psychiatric disorders were reported to contribute to 5% of global DALYs and 15.7% of global YLDs (Kassebaum et al. 2016). One DALY represents the loss of one healthy year of life and aggregates the YLDs with the years of life lost (YLLs) due to premature mortality (fig.2).

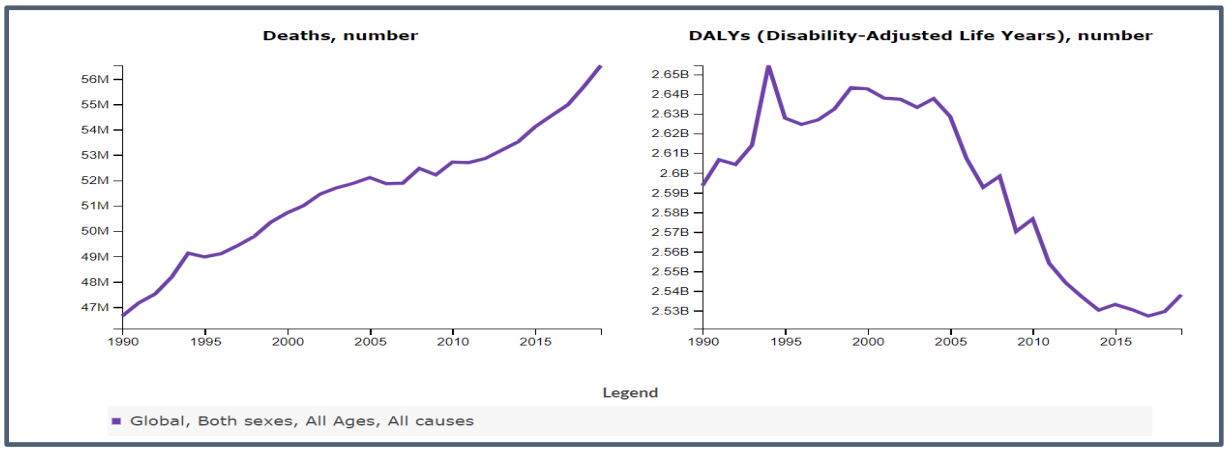

Fig.1 (Kassebaum et al. 2016)

Fig. 2 (Colton CW, 2006)

Mortality Rate:

In spite of the above-mentioned fact that global burden of mental disorders is reported mostly as disability and not mortality, even then this mortality is significant than other causes of deaths in general population (Whiteford HA, 2013). This association of higher mortality and mental disorders has many complications right from molecular levels like physiological factors, endocrine level, neurotransmitters involve as well as on behavioural and socio-economical levels. This is the reason such patients often do not die of their mental illness directly but because of other somatic complications, infectious diseases or suicides (Colton CW, 2006). All the schools of health sciences agreed that whatever be the reason of this mortality, the ultimate burden of psychiatric diseases can be reduced by prevention and better treatment of comorbidities (Walker ER, 2015).

The most alarming aspect with mental disorders is the increased mortality rate which is significantly higher in mentally compromised individuals than general population (Vos T et al, 2013). In comparison with normal population, patients of this group die approximately 15-20 years earlier. The death causes are both natural and unnatural deaths, including suicides, accidents as well as deaths due to comorbidities.

The estimates of a large meta-analysis found that mental disorders attribute as the major reasons of deaths in the world. They account for 14.3% of deaths worldwide, which is approximately equal to 8 million deaths yearly. (Walker ER, 2015).

There are many reasons behind the high mortality rate among individuals with mental disorders (Skurtveit et al., 2005). In recent years there has been a dramatic change in lifestyle with changes in diet, physical activity and smoking habits, which has negatively affected patients

with severe mental disorders in particular. These patients do not seek medical care as often as people in the general population because of poor insight into their own somatic illnesses and negligence from health care providers may add to this lack of adequate use of health service. In addition, side effects of the psychopharmacological treatment, including increase in body weight and subsequently many life-threating disorders, may influence the high mortality rate as well as effects of the psychiatric disorder itself. So, for example, diabetes mellitus type 2 is more common among patients with schizophrenia and bipolar disorders than the rest of the population and recent studies indicate a partly common genetic background between somatic diseases and psychiatric disorders.

Prevalence:

Besides causing significant disability, globally psychiatric disorders are recognized to exceed highly prevalent diseases like HIV or cancer in terms of numbers affected (Ustün TB,1999).

The prevalence of psychiatric disorders is overwhelming almost all over the world and estimated to be 13.4% worldwide (Polanczyk GV, 2015). This eventually accounts for a significant contribution in the global burden of disease (Whiteford HA, 2010) with a proportion of 9.8% in low- and middle-income countries (Patel V, 2007).

If we focus on Asian countries like China (Shen YM, 2018), the precise current prevalence is not known yet, but according to the epidemiological studies conducted 10 years ago in Hunan, Liaoning, and Sichuan provinces, revealed prevalence of mental illness of 16.22% (Guan B, 2010), 15.24% (Wen P, 2008) and 9.15% (Qu Y, 2015) respectively.

In the same area, The Eastern Mediterranean region (EMR), is a very heterogeneous area in terms of their gross domestic income, sociodemographic profiles, health conditions, lifestyles, health system and medical coverage (Mandil et al. 2013). About 85% of population in this area has been suffering from depression, anxiety, and post-traumatic stress disorder in the past 25 years (Ghosh et al. 2004). Over the past two decades, this region has gone through tremendous development in health sector resulting in longer life expectancy and better quality of life (Memish 2014; Mokdad et al. 2014, 2016). In spite of all these advancements, there is no decrease in burden of psychiatric diseases seen in past quarter century (Mokdad AH, 2018).

Prevalence studies of psychiatric disorders done in Australia have shown very interesting results. The findings of meta-analysis have revealed that indigenous Australians has triple burden of psychological distress than the non-indigenous population (Black EB,2015).

Prevalence of mental disorders in American older adults remained high and is seemed increasing with the passage of age till 85 years and at this point of age there is seen some stability or declined. The authors claim this as a low participation in the research studies after this age (Reynolds K,2015)

Bebbington and McManus, in a latest work done in 2020 also observed this persistent prevalence in British general population collected on the basis of structured surveys, called The British Adult Psychiatric Morbidity Survey (APMS). These are regularly repeated survey programmes based on validated procedures for observing mental illness in randomly chosen samples from general population (Ginn S, 2012). Bebbington and McManus established this authentic prevalence by the previously conducted surveys in 2000, 2007 and 2014 and this well-defined methodology gives the prevalence of one in four when they took all types of mental disorders under consideration of this inference.

This rising prevalence of mental disorders is seen in all age groups even in children because of an early onset of mental disorders, for example ADHD and Autism (La Maison C, 2018).

Efforts done by WHO:

The World health organization (WHO) has special concerns to study prevalence of mental disorders and disability caused by it among different regions of the world. That's why WHO is putting efforts in many developing countries, as well as in developed countries in the form of world mental health (WMH) surveys. These surveys will help participating countries to carry out epidemiological studies through systematic strategies. This will help many countries to establish high quality community epidemiological research by providing standardized research instruments, training of researchers, and data analysis advancements. All the proposed instructions were given at:(www.hcp.med.harvard.edu/wmh).

One of the main findings of WMH surveys was that only few people with severe psychiatric disorders get treatment at all and even fewer get optimal or high-quality treatment. This data emphasizes the provision of standard treatments and prevention measures to general population in order to minimise the global burden of mental disorders (Wang et al., 2007).

Expectations and Challenges in mental health care:

Mental health had been neglected for many decades. Advancements are needed in public health practice and understandings of psychiatric disorders among the general population. In addition, attitude of society towards psychiatric patients should also been changed in course of these years, but there is still a stigma associated with psychiatric disorders and often these individuals are still isolated and considered as wired, pretending and untreatable and even sometimes haunted (Ustün TB,1999)

Severe psychiatric disorders like schizophrenia, bipolar disorders and major depression are among the main reasons of disability in the whole world and has lowered the life quality for patients as well as their caregivers and/or family members (Von Korff M, 1998). The cost of treatment is higher than all cancer treatment. That is the reason psychiatric disorders are considered as big challenges for public health (Vos T, 2015).

On the other hand, one could easily observe continuous advancement in other fields of biomedical sciences. As a result, mortality rate of heart disease and several types of cancers has declined since the 1970s (Jemal A,2005 and Hashim D, 2016). In the past few decades there has been significant increase in quality of life and life expectancy in the general population, which has given better prospects of life for a number of patients (Laursen TM, 2014).

This development is unfortunately not seen in patients with psychiatric disorders, presumably because mental health science is lagging behind in this advance technology marathon. Comparatively fewer improvements are seen in diagnostic or prognostic tools for psychiatric illnesses and this situation with unavailability of diagnostic biomarkers results in chronicity and ultimately severity of psychiatric disorders (Sawa A, 2002).

This lack of diagnostic biomarkers becomes even more demanding when mental disorders tend to arise with other comorbidities. The overall health condition of an individual can be explained as a complex originating from several internal and environmental factors. Such complications have kept the reasonable drug development as a big challenge in the mental science field (Sawa A, 2002).

Limitations of Psychiatric medications:

Despite of this high demand of rational treatment, there are only slight upgrade in psychiatric medications in past decades (Insel TR, 2010). Pharmaceutical companies claim that new drug development is a big challenge, especially because mental illnesses are complicated phenomena comprised of many internal and environmental factors, stating that there is a prior need of new research approaches in diagnostic areas before we can expect new drug development (Miller G, 2010).

However, the advancements in computational neurosciences have provided opportunity to better understand the causes of psychiatric disorders at the cellular level (Huys QJ, 2016). If appropriate research is done on neuron modelling, then drug development would be easier because of better understanding of neuronal circuits and neurotransmitter signalling mechanisms involved in psychiatric disorders and brain networks responsible for behavioural patterns (Einevoll GT, 2019). In short, this biophysical psychiatry approach could help to understand detailed pathophysiology of brain functions and how it is affected by mental disorders (Mäki-Marttunen T et al, 2019).

Consumption of Psychiatric medications:

Almost half of the people face mental health issues at some stage in their lives and use psychotropic medicines for shorter or for longer periods of times (WHO report, 2001). Overall use of psychotropic drugs has increased in the whole world, but levels of use vary from country to country. This consumption is relatively lower in Nordic countries as compared to the USA (Zito et al., 2006). At the same time findings of coexisting medical complications with psychiatric disorders brought importance to combination treatments and introduction of medicines with broader effectiveness. The psychiatric and somatic comorbidities require advancements in recommendations of psychiatric medicines (Leung BM, 2019).

Psychiatric and Somatic Comorbidities:

Psychiatric disorders are rarely found alone but often seen with many comorbidities. Clinical studies have shown a higher prevalence of comorbidities than non-clinical studies and chronic psychiatric disorders display a higher frequency of comorbidities (Kessler RC, 2005). The same results were found later on among adolescents (Merikangas KR, 2010). This psychiatric co-morbidity is highly prevalent with cardiovascular diseases (CVD) and infectious diseases. A

study concluded that depression leads to 50% greater risk of CVD (De Hert M, 2015). In the same way hepatitis is seen 5-11 times higher in mentally ill people as compared to healthy populations (Rosenberg SD et al, 2001). Presence of comorbidities with psychiatric disorders worsen the diagnosis process, and many potentially effective treatments remain incompetent (Polanczyk G, 2007).

Prevalence of Somatic Diseases and medication use in Psychiatric Patients:

Psychiatric patients do not only use psychotropic medications, but they are also more frequent users of somatic medications as compared to the general population (Abdullah-Koolmees, 2013). Psychiatric patients often report co-existing diabetes mellitus, obesity, stomach problems, cardiac issues, respiratory and skin diseases (Iacovides A, 2008). This comorbidity could also be explained by the association between psychiatric illnesses and medically unexplained physical symptoms (MUPS) (Katsamanis M et al, 2011). In past studies 30% of psychiatric patients had prescriptions for somatic diseases, which increased to 60% by 2007 (De Hert M et al, 2010). In other studies, it was documented that the high use of somatic medications by psychiatric patients was also to manage or minimize the side effects caused by psychiatric medications (Shim J C, 2007) (Bendz H, Serretti A, 2009) (Maayan L, Stoklosa J, 2011) (Crews M P, 2012), such as anticholinergic medication to control extrapyramidal side effects (Abdullah-Koolmees, 2013).

In later studies, where interactions between psychiatric and somatic medications were investigated it was reported that unfavourable interactions reduced quality of life remarkably (Haueis P et al, 2011).This can be understood by a study, where approximately 42% of psychiatric patients used antidepressants in combination with non-steroidal anti-inflammatory drugs (NSAIDs) to treat side effects of generalized pain, but because of this co-use they reported complications of gastrointestinal bleeding (Mort JR et al 2006).

These previous findings have declared higher prevalence of somatic medications by psychiatric patients, however there is still acute need to do further research in this area to increase the patients' compliance and improving quality of life (Baumeister H, 2005).

Norwegian population, psychiatric disorders, co-morbidities and medicines use:

Solberg BS did a nationwide study on Norwegian population in 2019, mainly addressing ADHD and Autism. He discussed comorbidities of these psychiatric disorders and associated factors contributing to such comorbidities in details. He noticed that ADHD and Autism were highly prevalent comorbidities among Norwegian population as they were formerly profound in other populations of the world.

Despite high co-prevalence of psychiatric and somatic diseases, researches have shown that somatic diseases more often remain undiagnosed and untreated among psychiatric patients than in the general population (De Hert M, 2011). In Europe, including Norway, psychiatric patients less often use somatic health care services (Norredam M 2009, Abebe Ds 2018). However, information about psychotropic drug use in Norway by the general population still needs vigorous research. Data is already available about drug use by the general population in the form of prescription registry, and some research is done in pharmaco-epidemiology to investigate prescription patterns or trends in drugs use over the time. But still there is an opportunity to connect all the resources to make well-grounded conclusions, and rich information about the real-life patterns of drug use may inform the clinical field as well as future research. We therefore felt compelled to link the accessible information rich data bases together to investigate what is not known yet about pharmacological drugs, specifically psychotropic drugs, their usage by the clinically diagnosed patients as well as by the healthy individuals who are generally considered as healthy controls in research studies. What is special for our research context is that we have a sample of patients diagnosed with mental disorders and a sample of screened healthy control subjects (TOP study). We examined the realistic use of pharmacological medicines by these participants in comparison with national prescription register.

Psychiatric research and Healthy controls:

Epidemiology research has been used to see the prevalence of psychiatric disorders among a particular population. This is the same pool from where healthy volunteers are taken and used as a control to compare the presence of a certain psychiatric illness among the suffering people.

As this prevalence is drawn from the extent to which a population is diseased as compared to the healthy individuals, so that standard group should be disease free. (Shtasel DL et al, 1991).

The research work done previously in psychiatric studies has uncovered many interesting facts through contrast with healthy controls. This comparison helped scientists to see the difference between healthy brain anatomy and physiology with patients who have mental disorders. However, it was observed that healthy controls were surprisingly having higher prevalence of psychopathology than their comparative patients' group when investigated at biochemical level, while it was expected that controls will be healthier (Pavletic AJ, 2017). This leads to the idea that selection of controls at the initial stage, was not refined enough to see the underlying health conditions. It was concluded that in psychiatric research in general and precisely in biological psychiatry, there is a need of establishing proper standards for the selection of healthy controls as they exist for the selection of patients. Such findings emphasized the importance of using equally vigilant measures at the time of controls' selection as were used while recruiting patients and recommendations were made to do further research in this direction (Gibbons, 1990).

This has been pointed out for about 3 decades ago, but unfortunately studies were been done in mental health sciences without any predefined criteria for healthy volunteers and research community kept psychiatric investigations continued without paying attention towards this crucial topic of selecting healthy volunteers. As a result, the attitude towards inspection of healthy volunteers and patients became less serious (Pavletic, 2020). It was a common practice in neurosciences that healthy volunteers have often participated without being rigorously screened. This ended up sometimes in visible biases and sometimes influence the quality of research latently (Pavletic, 2020).

The significance of effective controls selection in psychiatry was explored in 1991, when 50% of potential healthy volunteers had to leave the study because of present or past psychiatric sufferings. This filtered the healthy sample many times from 1607 to 312 and finally from 312 to just 157 participants after going through a number of screening interviews as well as laboratory tests (Shtasel et, 1991). Later on, a metanalysis is done in 2009 which provides evidence that out of 474 studies performed in the field of neuroimaging, only 7% studies had verified their healthy volunteer by a physical vetting. Approximately 75% of brain imaging studies had self-reported controls or without mentioning any screening technique for controls (Mazziotta et al, 2009). In the same analysis when the development of an MRI- atlas for healthy

human brain was under process, the researchers found that almost 48% of participants who were claiming themselves healthy, were excluded. The interesting finding was their older age where most prominent exclusion factors were underlying neurological abnormalities and hypertension which affect brain drastically without showing any symptom. Many groups of scientists meant that exclusion of both healthy volunteers and patients is seen with robust screening (Pavletic AJ, 2008)

After discussing all the challenges related to mental health science and current advancements, we come closer to the conclusion that the existing gaps between different factors should be diminished, specially between what is known by the science and how that can be implemented to serve the humanity in reasonable ways. The preventive and treatment strategies should be practicable enough in the real world, so that they can combat the constantly recurring nature of mental disorders (Lehman AF, 1998)

At the primary care settings, combination of both psychosocial counselling and psychotropic medications will minimize the intensity of psychiatric disorders (Malt UF, 1999). Introducing new feasibility settings for the patient care will provide accessible platform for early diagnosis and favourable treatments (Von Korff M, 1998).

Possible reasons of selecting unhealthy controls:

After getting the understanding about immense need of robust screening methods for controls, this is also important to see the factors which are resulting in false positive controls. In a couple of studies, attention is brought to the possible mediators like monetary charm in the form of incentives. This may play a crucial role to attract participants in the study without fulfilling the inclusion criteria (Resnik DB, 2015). This biasness is quite common in poor countries. Because of these incentives, some healthy volunteers do not disclose their compromised mental health. As mental disorders are often symptomless and remain unidentified because they do not have relevant biomarkers, this overall scenario ends up in a non-ideal control group (Dickert NW, 2013).

Secondly, there are many apparently healthy people who have some dormant psychiatric issues, and they are not comfortable to disclose them under a short interaction with a research team. This was evident in another study conducted on 121 healthy volunteers. They went through structured screening by trained researchers. The results revealed 16.5% had current mental disorder, 35.6% had a personal history of mental disorder and 39.4% had a family history of

mental disorders (Halbreich U, 1989). Another inaccuracy is seen with forgetfulness. This volunteer-provided personal history remains insufficient when it comes to reliability. Hence, this imprecision of might having poor memory, could be a source of discussable bias (Pavletic AJ, 2017)

All these dialogues confirm that self-reporting method was inadequate to confirm the eligibility of healthy volunteers. Hence, reliable screening tests are needed to establish health condition of study participants. Biological markers have been frequently used as the most precise evidence in almost all diagnosis, but psychiatry is the only field of medical science where researchers continue to diagnose by psychological and physical symptoms only (Kapur S, 2012). The development of biomarkers is still in progress, and when eventually successful, they can further help doctors to make correct diagnosis and eventually reasonable selection of effective medicine. (Abi-Dargham A, 2016).

Note: The same argument is discussed in ***challenges*** above, which supports that invention of biomarkers and diagnostic measures will help to find better pharmacological treatment as well as true diagnosis of unreported or overreported psychiatric illnesses.

Possible screening methods for healthy controls:

We are convinced by the above statements that mental health studies need to apply screening methods for the selection of healthy volunteers (HVs). Unfortunately, we are lacking studies, which can help us regarding such methods. However, scientists are agreed to develop inert procedures which can be used without causing any risk to aim of the study, resources of research and study population. As well as they should be cost-effective to avoid extra expense to conduct the study. We can explain that with the findings of a research done in 2014 by Pavletic AJ et al. According to which electrocardiogram screening brought false positive anxiety results among HVs. Therefore, such screening tools should be chosen cautiously without affecting aim, sources, population and cost of the study as mentioned above.

Challenges in screening of HVs:

This selection of healthy volunteers is a big challenge because of undiscovered psychological problems. Extra precautions are needed with a protocol demanding biomedical invasive testing. Studies showed the fact that psychological compromised individuals had volunteered themselves as a control group within no time after knowing some extraordinary testing is

involved. Findings declared that this participation was associated with impulsiveness and tough-mindedness, which has a direct link with behavioural disorders (Gustavsson JP, 1997)

Work done by Eufemia R in 1985 discussed advantages and disadvantages of publicity strategies for recruitment process. Despite the fact that we can effortlessly formulate standards for screening of HVs, the availability of funds and time are the common challenges faced by almost all the researchers (as mentioned above).

One possibility that can be made by the research institutions, is to establish a common pool of well-screened HVs. This will not increase the budget of individual studies and researchers could have readily available healthy controls for a quality work.

When the collected research data is based on comparison with the healthy controls, then this group should have the characteristics truly representing HVs. Otherwise, the interpretations are not well grounded and having hidden selection bias (Pavletic AJ, 2020).

Reliability of National registers:

National health registers provide high quality data with generally high reliability. They have played constructive role in improving quality of health services (Nesvåg R, 2017). In unique epidemiological studies like psychiatric disorders, these data sources are considered gold standards because of their wide population coverage (Dalman C, 2002). National registers are commonly found in developed countries, where patients automatically get registered in national databases while they are in contact with any primary, secondary, or tertiary health system. We can take an example of Israel, where 93% of clinically diagnosed schizophrenic patients were found in the national register (Weiser M, 2012). However, a Swedish study in 2011, show some uncertainties in psychiatric diagnosis (Ludvigsson JF, 2011). To address this riskiness and to understand how important role these data bases could play in mental health studies, there is still a lot of research which can be done with these registers. Hence our work is based on Norwegian national prescription register (NorPD). The core purpose of this research is to understand prevalence of diseases, to investigate the medicine use and to find other related factors which can help in better health management in future.

Norwegian prescription register (NorPD) is a centralized database where all the delivered prescriptions are collected and stored under high confidentiality and safety. Since 2008 all the pharmacies are obliged to send this information to NorPD. This prescription data is linked with

Norwegian patients' register (NPR) where all the information from every health sectors is received. All the health care systems, whether they are completely or partially funded by the government, have obligatory duty to send the patients' data over to NPR. This covers almost all the data for psychiatry medications because all the psychiatric treatment is given by the help of government. All the persons registered in Norwegian Public register (NPbR) have a unique 11 digits personal number. This identification number was incorporated in NPR in 2008 which as a result provides the possibility for linking any enormously large data correctly by using this assigned ID number. By doing this it is easy to keep track for every registered person across all treatment vicinity (Nesvåg R, 2017).

2: METHODOLOGY:

2.1: Study organization:

This study was performed with the support of The Norwegian Centre for Mental Disorders Research (NORMENT). NORMENT is a Centre of Excellence (CoE) in The Faculty of Medicine, established in 2013 and funded by the Research Council of Norway. The centre is based on a collaboration between four partners: The University of Oslo (host institution), the University of Bergen, Oslo University Hospital, and Haukeland University Hospital. The aim of the research at NORMENT is to understand the underlying mechanisms of severe mental disorders and find answers to why some people develop perceptual disturbances, delusions, depressions, or manic phases. To achieve its aims, NORMENT is working on four main areas, as below:

1: Genetics: To disclose the complete genetic architecture of psychotic disorders and determine their functional impact on human health.

2: Brain imaging: To identify novel brain imaging phenotypes which are linking genes and clinical phenotypes in certain mental disorders.

3: Outcome Prediction: To use genetic, environmental and clinical factors to predict disease progress and their outcomes.

4: Clinical Intervention: To translate pathophysiological discoveries into clinical and pharmacological interventions.

This master's project is to explore pharmacological aspects of psychiatric medication used by patients and healthy controls from the Norwegian Population. To get the authentic data of medication used, national data registries are the best sources for providing true information. For this research project we got access to two main data sources, one is the national Norwegian prescription register (NorPD), which was established in 2004 and the other is information retrieved from the Thematically organized psychosis (TOP) study which is one of the research projects run by NORMENT institute. The leader of the TOP study, Professor Ole A. Andreassen has given the approval of this master's thesis under the supervision of Professor Erik Gunnar Jönsson and Dr. Kjetil Nordbø Jørgensen in affiliation with Faculty of Medicine, University of Oslo.

2.2: Objectives:

To study the use of psychotropic and somatic medications in clinically investigated patients with psychiatric disorders and healthy control individuals using the Norwegian prescription database (NorPD).

2.3: Aims of study:

The aims of the study were:

1: to evaluate what extent healthy individuals in a demanding psychiatric research setting were prescribed medication and

2: to investigate the total prescription pattern of medication among patients with severe psychiatric disorders.

3: to compare the pattern of medication use between patients and healthy controls.

2.4: Participants & Study Area:

Study participants were recruited from the Oslo region, Norway and contacted to take part in TOP study between 2004-2017. Patients were recruited from psychiatric hospitals and treatment facilities in this region. Healthy controls from the same region were randomly drawn from the Norwegian Population Register and asked to participate. They were then recruited by the above-mentioned inclusion and exclusion criteria. Then the same population after their consent was studied from NorPD. This study focuses on prescribed medications for psychiatric and/or somatic patients and healthy volunteers.

Hence, we studied a specific cohort group of people categorized as patients and controls. Both were sharing same characteristics and studied in a definite period of time frame. As such, the study is a cross-sectional study.

2.5: Data Sources:

All the original research data resources will be stored under strict ethical rules and regulations at research server by Oslo university hospitals and by National institute of public health. The Top study has a license from the Data Inspectorate for the storage of information till 2050. Furthermore, this project got license from birth register, death reasons register and prescription register. Prescription register demands that data should be non-identifiable. Therefore, the merged data sets were pseudonymized.

2.6: Ethical considerations:

The TOP study has already been approved by REK; Regional Committees for Medical and Health Research Ethics (2009/2485-91). All subjects gave their written informed consent to participate in the study. This master's project got adjoint approval in TOP study by formal procedure in May 2019.

2.7: TOP study:

It is a cross-sectional naturalistic study where subjects have been recruited consecutively since 2004. Data analysed in this master thesis include subjects recruited to the TOP study between 2004 and 2017 from psychiatric departments of five major hospitals in the catchment areas of Oslo. The TOP study is a collaborative project between researchers' groups in university-hospitals in Oslo, the university of Oslo and the Norwegian Institute of Public health. TOP study is a long-term commitment on research investigating causes, treatment and duration of mental disorders. All the participants in TOP study have given consent to make use of their information from Norwegian Prescription Database (NorPD). After providing a written informed consent, participants were recruited by inclusion criteria for the TOP study as:

Inclusion criteria for patients in TOP study:

a) Age between 18 to 65 years.
b) Ability to give written consent.
c) Diagnosis of schizophrenia, other psychotic disorders and bipolar spectrum disorders according to DSM-IV.
d) Ability to understand and speak a Scandinavian language.

Exclusion criteria for patients in TOP study:

a) Individuals with a history of moderate or severe head injury
b) Neurological disorders
c) Autoimmune disease
d) Mental retardation (defined as IQ<70)

Inclusion criteria for controls in TOP study:

a) Age between 18 to 65 years.
b) Ability to give written consent.
c) Ability to understand and speak a Scandinavian language.

Exclusion criteria for controls in TOP study:

a) Individuals with a history of moderate or severe head injury
b) Current symptoms of psychiatric disorder in need of treatment
c) History of severe mental disorder or severe mental disorder among first-degree relatives
d) Neurological disorders or other somatic illness thought to affect brain function.
e) Mental retardation (defined as IQ<70)
f) Use of cannabis within the last 3 months.

2.8: Clinical assessments of TOP study:

As mentioned before, the patients with psychotic disorders in Oslo, Norway were approached through psychiatric departments of 5 major hospitals to be included as participants of the TOP study. The interested subjects were contacted for further information collection. In addition, demographical and clinical data were obtained by clinical interviews and from medical records. Diagnosis was made according to the Diagnostic and statistical Manual of Mental Disorders, fourth edition (DSM-IV) based on the Structural Clinical interview for DSM-IV (SCID) (American Psychiatric Association, 1995) and reviews of medical case notes. Patients with a diagnosis of schizophrenia spectrum, bipolar spectrum and patients with other non-organic psychotic disorders were included in the patients' group. Controls were recruited separately through population register of the Oslo region. Controls were screened for exclusion criteria and those who fulfilled the requirements was included as controls. However, the controls were

neither interviewed with the SCID, nor were their medical case notes reviewed. All the selected patients were assessed with comprehensive biochemical assessments. Patients' levels of symptoms were assessed using Global Assessment of Functioning Symptom scale (GAF-s) (Pedersen et al., 2007), the Positive and Negative Syndrome Scale Total Score (PANSS) (Kay et al., 1987), the Inventory of Depressive Symptomatology-Clinician rated (IDS-C) (Thrivedi et al., 2004), and the Young mania rating scale (YMRS) (Young et al., 1978).

Main variables from the TOP study in the present database were:

1. Date for inclusion (reference date)
2. Sociodemographic information (age, gender, education, etc)
3. Diagnosis
4. Symptoms
5. Compliance to medication
6. Side-effects of medication.
7. Somatic diseases (diabetes, hypertention, etc)
8. Lifestyle (Smoking, Diet, exercise, etc)
9. Medicines used
10. Biochemical results (glucose levels, C-reactive protein, hormone markers, inflammation markers, etc)

2.9: The Norwegian Prescription Database (NorPD):

It is a national register containing records of prescriptions filled to patients who are not admitted in any institution. This register is maintained from 1st January 2004 and contains information from pharmacies all over Norway, including information about physicians, patients and medicine for every received prescription (Furu et al., 2008). All pharmacies in Norway are legally obliged to submit all electronic data on prescriptions to the Norwegian Institute of Public Health. The medicines are classified according to their Anatomical Therapeutic Chemical (ATC) classification system. For this research work, the data about the medication use by the TOP study participants between 2004 -2017 was drawn from NorPD.

2.10: Data extraction from NorPD:

Data was extracted through linkage between selected variables from the TOP study dataset and selected variables from the NorPD. Due to pseudonymization requirements the date of study inclusion and the dates of prescriptions being filled were removed from the dataset. To preserve information about when a prescription was filled relative to study inclusion, these were converted into difference dates. We were therefore able to investigate drug use in defined periods before and after study inclusion.

This calculation helps us to see the medicine use both before and after the inclusion of TOP study. To evaluate this use, we analysed the data for 6 months, 1 year and 2 year both before and after inclusion phase. As the results were almost the same and 1 year's period is a reasonable duration to observe any possible findings, we worked on data which was 1 year before and 1 year after inclusion in TOP study.

Main variables from prescription register (NorPD) are:

A: Physician License number
B: Patient number, birth year, gender, death year, death month.
C: prescription data: All ATC codes

2.11: Data handling procedure:

After getting access to data resources, the master's project was started by merging TOP-study data with data from the prescription register (NorPD). These are large data sets with a large number of variables including ATC codes of prescriptions, from all the Norwegian pharmacies between 2004 -2017.

On the other hand, data from TOP study was identified by personal ID number and then merged with the corresponding person in prescription register by the same ID number while the patients remain anonymous.

Then according to TOP study classification, 1531 participants were patients diagnosed with severe mental disorders and 1036 were healthy controls which gave a total sample of 2567 participants. From this large number, there were more than 200 participants with lack of records

in prescription register and incomplete questionnaires. The final samples with complete data sets consisted of 1406 patients and 920 controls, giving a total participant number of 2326.

2.12: Anatomical Therapeutic Chemical Codes (ATCs):

WHO's Collaborating Centre for Drug Statistics Methodology (WHOCCDSM) describes the definition of ATC codes. These are tools helping in research and monitoring of medicine consumption, which then can improve quality of drug utilization. This coding has been successfully applied to present and compare drug consumptions statistics at many international and other high-profile platforms (WHOCCDSM, 2018).

Structure of ATCs:

In the general ATC classification system, we see active substances in categories and their sub-categories at five different levels. At the first level, drugs are grouped into 14 main anatomical groups. It indicates the body part where the drug is targeted to produce effects. Each main ATC group is further categorised at 2_{nd} level giving therapeutic groups. It explains indication of drug use. The 3_{rd} and 4_{th} levels are either chemical or pharmacological and the 5_{th} group often shows chemical name of the drug. As a simple explanation, we can say that the 2_{nd}, 3_{rd} and 4_{th} levels are often used to identify therapeutic, pharmacological and chemical group of the drug, respectively, while 5^{th} level identifies chemical nature (WHOCCDSM, 2018).

We took metformin as an example to explain the structure of ATC code:

A	1st level, anatomical main group	Alimentary tract and metabolism
A10	2nd level, therapeutic subgroup	Drugs used in diabetes
A10B	3^{rd} level, pharmacological subgroup	Blood glucose lowering drugs, excluding insulins
A10BA	4th level, chemical subgroup	Biguanides
A10BA02	5th level, chemical substance	Metformin

(WHOCCDSM, 2018).

Every country has its own department which works on these prespecified ATC codes by WHOCCDSM. These authorities in a country, are responsible to classify available market medicines as per their therapeutic indications. Because the indication of a certain medicine could be different in different countries, there may be some differences between ATC systems of different countries. The WHO Collaborating Centre in Oslo works on ATC classification in Norway and make new entries in the system upon requests from the drug manufacturers.

The ATC codes we worked upon in this project are taken from Norwegian drugs formulary, called Felleskatalogen. This is a collective source of information about available medicines in Norway and available both as a book and in digital form (Felleskatalogen, 2020)

Categorization of selected ATCs:

For the sake of easiness to study use of pharmacological drugs in healthy controls and psychiatric patients, we categorised medicines into two groups: Drugs within ATC category N (Nervous System) = **ATC-N**, see table 3 and Drugs within ATC categories indicated for somatic disorders =**ATC-S**, see table 8.

2:13: Statistical analysis:

The data were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics version 25) (SPSS Inc., Chicago, IL, USA/IBM, New York, USA). The level of statistical significance was set to $p < 0.05$. Variables were presented as percentage and mean. Chi-square test was used to compare use of psychiatric medications between patients and controls groups one year before and after the inclusion in TOP study (table 4 & 6 respectively) and then to compare use of other somatic medications between patient and control group one year prior and after inclusion (table 9 & 11 respectively). To investigate the association between patients and controls with psychiatric and somatic medications taking age and gender into account, we performed Logistic regression (table 5,7 and table 10,12 respectively).

3: RESULTS:

3:1: Demographic Data:

3:1a: Gender distribution:

Demographic data about gender and age in the study sample is shown in table 1 & 2. There were greater number of patients (n=1406) than controls (n=920), but both the groups have similar gender distributions, with a small excess of men (52% and 54%, respectively) in both groups.

Table 1: Gender distribution				
	Patients		**Controls**	
Gender	Frequency	Percentage	Frequency	Percentage
Male	729	51.8	495	53.8
Female	677	48.2	425	46.2
Total	1406	100	920	100

Table 1

This gender distribution can also be seen with the help of bar graph presentation below (fig 3).

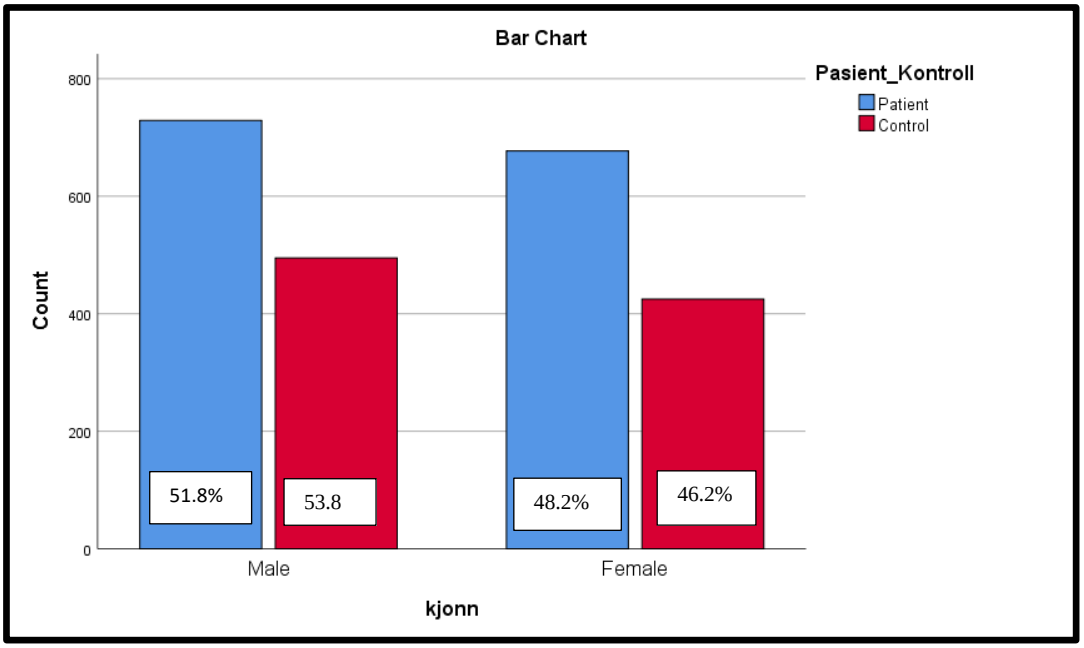

Fig3(SPSS generated)

3:1b: Age distribution:

Table 2: Age distribution:				
categorized into 3 groups	**Patients**		**Controls**	
	Frequency	Percentage	Frequency	Percentage
1=18-36 years	956	68%	569	61.8%
2=37-55 years	400	28.4%	339	36.8%
3=56-65 years	50	3.6%	12	1.3%
Total	1406	100%	920	100%

Table 2

Table 2 shows the age distribution of the sample when divided into three equal time-interval. The highest number of participants were in the youngest age group (18-36 years), representing 68% of the patients and 62% of the controls. The middle age category (37-55 years) was the second largest comprising 28% of patients and 37% of the controls. The third category having participants from 56 to 65 years of age had least number of participants with 4% in patients and 1% in controls. The graphical presentation is given as bar graph (figure 4) and normal distribution graph (figure 5). Figure 5 clearly indicates that patients' group has a majority of younger population, whereas the controls have majority of middle age participants.

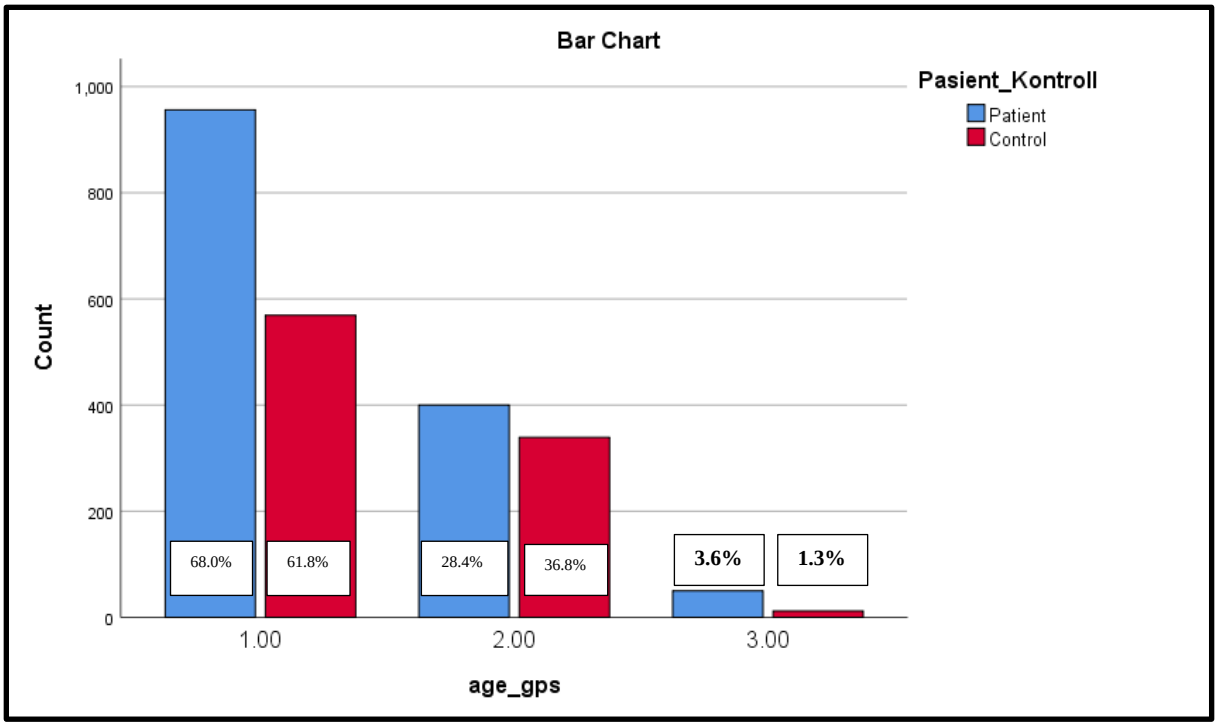

Fig4 (SPSS generated)

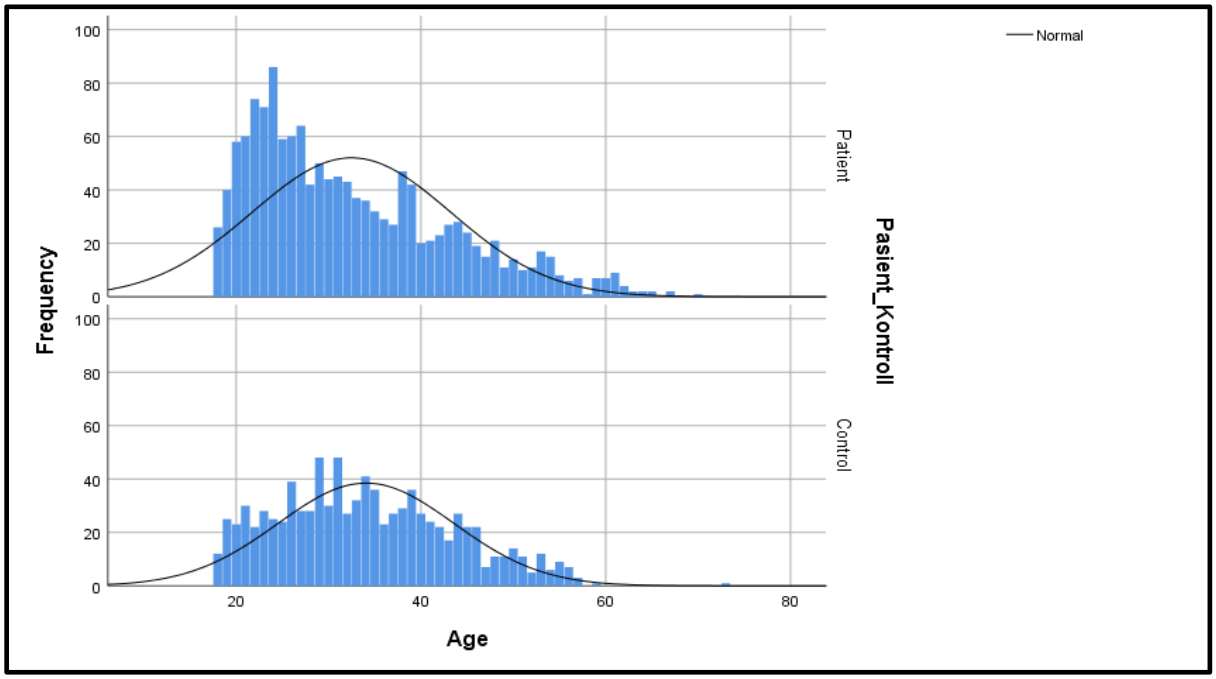

fig 5(SPSS generated)

3:2: Clinical Data:

3:2:1 Use of Drugs within ATC category N (Nervous System):

To see any difference in usage of ATC-N medication between patients and control group, we ran chi-square analysis on 16 ATC codes within category N (Nervous System) (Table 3).

Table 3: ATC-N = Drugs within ATC category N (Nervous System)	
N01A	General anaesthetics
N01B	Local anaestetics
N02A	Opioids
N02B	Other analgesics and antipyretics
N02C	Anti-migraine
N03A	Anti-epileptics
N04A	Anti cholinergics
N04B	Dopaminergic agents
N05A	Anti-psychotics
N05B	Anxiolytics
N05C	Hypnotics og sedatives
N06A	Antidepressives
N06B	Psyco-stimulants, ADHD and nootropic agents
N06D	Dementia treatments
N07B	Drugs for addiction disorders
N07X	Other drugs working on nervous system.

Table 3

3:2:1a: Use of ATC-N the year before inclusion in TOP Study:

We compared use of ATC-N among patients and controls using NorPD data in the last year before the inclusion in the TOP study (Table 4).

Patients used significantly more drugs than controls from nine of the 16 ATC-N, including other analgetics and antipyretics (N02B), antiepileptics (N03A), anticholinergics (N04A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), psychotropics, ADHD and nootropic agents (N06B) and drugs for addiction disorders (N07B). Neither patients, nor controls had been prescribed general anaesthetics (N01A), drugs for dementia treatment (N06D) or other drugs working on the nervous system (N07X) and only very few (5 or less in each group) had been prescribed local anaesthetics (N01B) or dopaminergic agents (N04B). Relatively few of both patients (2.2%) and controls (1.3%) used antimigraine drugs (N02C). Opioids (N02A) were slightly more common in patients (9.8%) than controls (8.7%) . None of these latter differences were statistically significant.

Table 4: Drugs within ATC-N the year before inclusion in TOP Study:

ATC-codes (nervous system)		Patients		Control		Total		P-value
		Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
N01A	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	
N01B	Using	5	0.4	0	0	5	0.2	0.070
	Not using	1401	99.6	920	100	2321	99.8	
N02A	Using	138	9.8	80	8.7	218	9.4	0.365
	Not using	1268	90.2	840	91.3	2108	90.6	
N02B	Using	50	3.6	19	2.1	69	3	0.038
	Not using	1356	96.4	901	97.9	2257	97	

N02C	Using	31	2.2	12	1.3	43	1.8	0.115
	Not using	1375	97.8	908	98.7	2283	98.2	
N03A	Using	318	22.6	2	0.2	320	13.8	<0.0001
	Not using	1088	77.4	918	99.8	2006	86.2	
N04A	Using	24	1.7	0	0	24	1	<0.0001
	Not using	1382	98.3	920	100	2302	99	
N04B	Using	3	0.2	0	0	3	0.1	0.161
	Not using	1403	99.8	920	100	2323	99.9	
N05A	Using	931	66.2	2	0.2	933	40.1	<0.0001
	Not using	475	33.8	918	99.8	1393	59.9	
N05B	Using	282	20.1	14	1.5	296	12.7	<0.0001
	Not using	1124	79.9	906	98.5	2030	87.3	
N05C	Using	402	28.6	27	2.9	429	18.4	<0.0001
	Not using	1004	71.4	893	97.1	1897	81.6	
N06A	Using	561	39.9	8	0.9	569	24.5	<0.0001
	Not using	845	60.1	912	99.1	1757	75.5	
N06B	Using	27	1.9	0	0	27	1.2	<0.0001
	Not using	1379	98.1	920	100	2299	98.8	
N06D	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	
N07B	Using	18	1.3	3	0.3	21	0.9	0.017
	Not using	1388	98.7	917	99.7	2305	99.1	
N07X	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	

Table 4: (p-value=* shows that none of the two groups uses that analysed ATC code)

Logistic regression (table 5) showed significant prescription rate of "Other analgetics and antipyretics (N02B)", antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and drugs for addiction disorders (N07B) to patients (Table 5). These relationships were significant both with or without adjusting for age and gender.

Table 5: Logistic Regression ATC category N Before One Year								**95% C.I.for EXP(B)**	
ATC-code	**Log. Regression**	**B**	**Std. Error**	**Wald**	**Degree of freedom**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
N01A	Unadjusted	**							
	Adjusted								
N01B	Unadjusted	15.567	1325.123	0.000	1	0.000	5765434.773	*	*
	Adjusted	15.347	1288.566	0.000	1	0.000	4623520.990	*	*
N02A	Unadjusted	0.133	0.147396	0.819	1	0.365	1.142744	0.856	1.525
	Adjusted	0.151	0.147891	1.047	1	0.306	1.163386	0.871	1.555
N02B	Unadjusted	0.559	0.273	4.192	1	0.041	1.749	1.024	2.985
	Adjusted	0.566	0.274	4.284	1	0.038	1.762	1.030	3.012
N02C	Unadjusted	0.534	0.343	2.430	1	0.119	1.706	0.871	3.340
	Adjusted	0.539	0.344	2.451	1	0.117	1.713	0.873	3.362
N03A	Unadjusted	4.900	0.711	47.511	1	0.000	134.156	33.314	540.250
	Adjusted	4.942	0.711	48.315	1	0.000	140.055	34.762	564.283
N04A	Unadjusted	17.150	1325.123	0.000	1	0.999	28054558.860	*	*

	Adjusted	17.165	1307.254	0.000	1	0.990	28481088.305	*	*
N04B	Unadjusted	15.055	1325.123	0.000	1	0.100	3454329.690	*	*
	Adjusted	14.966	1180.574	0.000	1	0.990	3158918.800	*	*
N05A	Unadjusted	6.802	0.710	91.751	1	0.000	899.640	223.674	3618.453
	Adjusted	6.794	0.710	91.522	1	0.000	892.190	221.813	3588.619
N05B	Unadjusted	2.790	0.277	100.934	1	0.000	16.236	9.426	27.966
	Adjusted	2.808	0.277	102.238	1	0.000	16.578	9.619	28.572
N05C	Unadjusted	2.583	0.204	160.283	1	0.000	13.243	8.877	19.755
	Adjusted	2.608	0.205	162.461	1	0.000	13.578	9.091	20.278
N06A	Unadjusted	4.327	0.359	145.041	1	0.000	75.685	37.429	153.041
	Adjusted	4.330	0.359	145.110	1	0.000	75.931	37.538	153.593
N06B	Unadjusted	17.270	1325.123	0.000	1	0.990	31630039.109	*	*
	Adjusted	17.171	1309.721	0.000	1	0.989	28633337.064	*	*
N06D	Unadjusted	**							
	Adjusted								
N07B	Unadjusted	1.377	0.625	4.855	1	0.028	3.964	1.164	13.495
	Adjusted	1.473	0.627	5.531	1	0.019	4.364	1.278	14.900
N07X	Unadjusted	**							
	Adjusted								

Table 5 (logistic regression could not be performed as one (*) or two (**) of the groups had less than one case)

3:2:1b: Use of ATC-N the year after inclusion in TOP Study:

We also compared use of ATC-N medicines among patients and controls using NorPD data in the year after inclusion to the TOP study (Table 6).

Patients used significantly more drugs than controls from 10 out of the 16 ATCs, including opioids (N02A), antimigraine medication (N02C), antiepileptics (N03A), anticholinergics (N04A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), psychotropics, ADHD and nootropic agents (N06B) and drugs for addiction disorders (N07B). Neither patients, nor controls had been prescribed general anaesthetics (N01A), drugs for dementia treatment (N06D) or other drugs working on the nervous system (N07X) and only very few (7 or less in each group) had been prescribed local anaesthetics (N01B) or dopaminergic agents (N04B). Relatively few of both patients (2.4%) and controls (2.3%) used other analgesics and antipyretics (N02B) and this difference was not statistically significant.

Table 6: Use of ATC-N the year after inclusion in TOP Study								
ATC-codes (nervous system)		**Patients**		**Control**		**Total**		
		Frequency	**Percentage**	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**P-value**
N01A	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	
N01B	Using	7	0.5	1	0.1	8	0.3	0.117
	Not using	1399	99.5	919	99.9	2318	99.7	
N02A	Using	136	9.7	67	7.3	203	8.7	0.046
	Not using	1270	90.3	853	92.7	2123	91.3	
N02B	Using	34	2.4	21	2.3	55	2.4	0.833
	Not using	1372	97.6	899	97.7	2271	97.6	
N02C	Using	43	3.1	14	1.5	57	2.5	0.019
	Not using	1363	96.9	906	98.5	2269	97.5	
N03A	Using	447	31.8	5	0.5	452	19.4	<0.0001
	Not using	959	68.2	915	99.5	1874	80.6	
N04A	Using	28	2.0	0	0	28	1.2	<0.0001
	Not using	1378	98.0	920	100	2298	98.8	
N04B	Using	2	0.1	0	0	2	0.1	0.252
	Not using	1404	99.9	920	100	2324	99.9	
N05A	Using	1099	78.2	4	0.4	1103	47.4	<0.0001
	Not using	307	21.8	916	99.6	1233	52.6	
N05B	Using	268	19.1	14	1.5	282	12.1	<0.0001
	Not using	1138	80.9	906	98.5	2044	87.9	
N05C	Using	401	28.5	25	2.7	426	18.3	<0.0001
	Not using	1005	71.5	895	97.3	1900	81.7	
N06A	Using	536	38.1	21	2.3	557	23.9	<0.0001

	Not using	870	61.9	899	97.7	1769	76.1	
N06B	Using	24	1.7	1	0.1	25	1.1	<0.0001
	Not using	1382	98.3	919	99.9	2301	98.9	
N06D	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	
N07B	Using	23	1.6	3	0.3	26	1.1	0.003
	Not using	1383	98.4	917	99.7	2300	98.9	
N07X	Using	0	0	0	0	0	0	*
	Not using	1406	100	920	100	2326	100	

Table 6: (p-value=* shows that none of the two groups uses that analysed ATC codes)

Logistic regression (table 7) showed a significant excess of prescribed opioids (N02A), antimigraine medication (N02C), antiepileptics (N03A), anticholinergics (N04A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), psychotropics, ADHD and nootropic agents (N06B) and drugs for addiction disorders (N07B) to the patients. These relationships were significant both with or without adjusting for age and gender.

Table 7: Logistic Regression: ATC-N Year After One Year								95% C.I.for EXP(B)	
ATC-codes	**Log. Regression**	**B**	**Std. Error**	**Wald**	**Degree of freedom**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
N01A	Unadjusted	**							
	Adjusted								
N01B	Unadjusted	1.526	1.070	2.034	1	0.154	4.598	0.565	37.436
	Adjusted	1.439	1.073	1.799	1	0.180	4.217	0.515	34.528
N02A	Unadjusted	0.310	0.156	3.964	1	0.046	1.363	1.005	1.850
	Adjusted	0.317	0.156	4.115	1	0.043	1.373	1.011	1.864
N02B	Unadjusted	0.059	0.281	0.044	1	0.833	1.061	0.612	1.840
	Adjusted	0.078	0.281	0.078	1	0.781	1.082	0.623	1.877
N02C	Unadjusted	0.714	0.311	5.278	1	0.022	2.042	1.111	3.753
	Adjusted	0.720	0.312	5.312	1	0.021	2.054	1.114	3.789
N03A	Unadjusted	4.446	0.452	96.727	1	0.000	85.298	35.167	206.894
	Adjusted	4.501	0.453	98.923	1	0.000	90.131	37.123	218.828
N04A	Unadjusted	17.307	1325.123	0.000	1	0.990	32825327.948	*	*
	Adjusted	17.324	1323.991	0.000	1	0.990	33399241.677	*	*
N04B	Unadjusted	14.649	1325.123	0.000	1	0.991	2301246.153	*	*
	Adjusted	14.453	1217.545	0.000	1	0.991	1891824.533	*	*
N05A	Unadjusted	6.709	0.505	176.335	1	0.000	819.775	304.538	2206.727

	Adjusted	6.704	0.505	176.047	1	0.000	815.762	303.021	2196.109
N05B	Unadjusted	2.724	0.278	96.184	1	0.000	15.240	8.843	26.267
	Adjusted	2.758	0.278	98.265	1	0.000	15.772	9.142	27.211
N05C	Unadjusted	2.659	0.211	158.525	1	0.000	14.284	9.442	21.609
	Adjusted	2.691	0.212	161.541	1	0.000	14.745	9.737	22.328
N06A	Unadjusted	3.272	0.227	206.944	1	0.000	26.375	16.887	41.192
	Adjusted	3.284	0.228	207.899	1	0.000	26.689	17.079	41.708
N06B	Unadjusted	2.770	1.022	7.353	1	0.007	15.959	2.155	118.175
	Adjusted	2.700	1.023	6.971	1	0.008	14.886	2.005	110.497
N06D	Unadjusted	**							
	Adjusted								
N07B	Unadjusted	1.626	0.615	6.983	1	0.008	5.083	1.522	16.979
	Adjusted	1.660	0.616	7.259	1	0.007	5.260	1.572	17.600
N07X	Unadjusted	**							
	Adjusted								

Table 7(logistic regression could not be performed as one (*) or both (**) of the groups had less than one case)

3:2:2 Use of Drugs within ATC categories indicated for somatic disorders (ATC-S):

The same study samples were again evaluated to see the use of most prescribed ATC codes of somatic diseases as mentioned in table 8 below. We selected 26 somatic ATC-S and investigated their prescription pattern among population of Oslo, Norway.

Investigated ATC-S	Table 8: Therapeutic Indications
A02.	Remedies for acid-related disorders
A03.	Remedies for functional gastrointestinal disorders
A05.	Bile and liver therapy
A07.	Antidiarrheal, intestinal antiseptics and anti-inflammatory drugs
A08.	Anti-obesity agents, excluding dietary supplements
A10.	Drugs for diabetes treatment
B01.	Antithrombotic agents
C01.	Cardiac therapy
C02.	Antihypertensives
C03.	Diuretics
C05.	Vasoprotectors
C07.	Beta blockers
C08.	Calcium antagonists
C09.	Agents having an effect on the renin-angiotensin system
C10.	Lipid modifiers
H02.	Corticosteroids for systemic use
H03.	Thyroid therapy
L02.	Endocrine therapy
L03.	Immuno-stimulants
L04.	Immuno-suppressants
M01.	Anti-inflammatory and anti-rheumatic drugs
M02.	Topical preparations for muscle and joint pain
M03.	Muscle relaxants
M04.	Gout remedies
M05.	Agents for the treatment of bone diseases
R03.	Remedies for obstructive pulmonary disease

Table 8

3:2: 2a: Use of ATC-S the year before inclusion in TOP Study:

Drugs from 8 ATC-S including, Remedies for acid-related disorders (A02), Remedies for functional gastrointestinal disorders (A03), Drugs for diabetes treatment (A10), Antithrombotic agents (B01), Diuretics (C03), Beta blockers (C07), Lipid modifiers (C10), and Thyroid therapy (H03) were significantly more used by the patients, whereas drugs from Cardiac therapy (C01) and Corticosteroids for systemic use (H02) were more used by the controls (table 9) before inclusion in the TOP study. Drugs from the remaining 16 ATCs did not show any significant difference ($p < 0.05$) between the patients' and the controls' groups. Among controls, anti-inflammatory and anti-rheumatic drugs (M01), remedies for obstructive pulmonary disease (R03), remedies for acid-related symptoms (A02) corticosteroids for systemic use (H02) and agents having effect on the renin-angiotensin system (C09) were prescribed to 136, 57, 33, 33 and 16 individuals, respectively, and for all drugs of the remaining ATCs the numbers never exceeded than 10 individuals (table 9).

Table 9: ATC-S the year before inclusion in TOP Study

ATC-S		Patients		Controls		P value
		frequency	Percent	Frequency	Percent	
A02.	Using	81	5.8	33	3.6	0.018
	Not using	1325	94.2	887	96.4	
A03.	Using	28	2	7	0.8	0.017
	Not using	1378	98.0	913	99.2	
A05.	Using	0	0	1	0.1	0.216
	Not using	1406	100	919	99.9	
A07.	Using	14	1	4	0.4	0.131
	Not using	1392	99.0	916	99.6	
A08.	Using	11	0.8	8	0.9	0.819
	Not using	1395	99.2	912	99.1	
A10.	Using	31	2.2	0	0	<0.0001

	Not using	1375	97.8	920	100	
B01.	Using	30	2.1	8	0.9	0.019
	Not using	1376	97.9	912	99.1	
C01.	Using	3	0.2	7	0.8	0.048
	Not using	1403	99.8	913	99.2	
C02.	Using	0	0	1	0.1	0.216
	Not using	1406	100	919	99.9	
C03.	Using	19	1.4	3	0.3	0.012
	Not using	1387	98.6	917	99.7	
C05.	Using	18	1.3	10	1.1	0.676
	Not using	1388	98.7	910	98.9	
C07.	Using	31	2.2	9	1	0.026
	Not using	1375	97.8	911	99.0	
C08.	Using	14	1	4	0.4	0.131
	Not using	1392	99.0	916	99.6	
C09.	Using	28	2	16	1.7	0.662
	Not using	1378	98.0	904	98.3	
C10.	Using	34	2.4	8	0.9	0.006
	Not using	1372	97.6	912	99.1	
H02.	Using	21	1.5	33	3.6	0.001
	Not using	1385	98.5	887	96.4	
H03.	Using	54	3.8	3	0.3	<0.0001
	Not using	1352	96.2	917	99.7	
L02.	Using	1	0.1	3	0.3	0.147
	Not using	1405	99.9	917	99.7	
L03.	Using	2	0.1	1	0.1	0.826
	Not using	1404	99.9	919	99.9	
L04.	Using	4	0.3	2	0.2	0.755
	Not using	1402	99.7	918	99.8	
M01.	Using	193	13.7	136	14.8	0.475
	Not using	1213	86.3	784	85.2	
M02.	Using	12	0.9	3	0.3	0.120

	Not using	1394	99.1	917	99.7	
M03.	Using	9	0.6	2	0.2	0.146
	Not using	1397	99.4	918	99.8	
M04.	Using	1	0.1	1	0.1	0.762
	Not using	1405	99.9	919	99.9	
M05.	Using	2	0.1	1	0.1	0.826
	Not using	1404	99.9	919	99.9	
R03.	Using	93	6.6	57	6.2	0.688
	Not using	1313	93.4	863	93.8	

Table 9

Description of the logistic regression in table 10 below, indicates significant results for ATC-S as Antithrombotic agents (B01), Beta blockers (C07), Lipid modifiers (C10), Thyroid therapy (H03), Muscle relaxants (M03), Corticosteroids for systemic use (H02) with their p-values < α=0.05. This states that ATC-S of these somatic medications are being used largely by the patients' group and not by their respective controls. This shows stronger association between patients' group and these 6 ATC-S for somatic medications table 10. Whereas we left with remaining 20 ATC-S with insignificant results with p-value > α=0.05, proving that no significant association is found between patients' group and their use of Somatic medications with these 20 ATC-S.

Table 10: Log. Reg. of ATC-S the year before inclusion in TOP Study								95% C.I. for EXP(B)	
ATC-code	**Log. regression**	**B**	**Std. Error**	**Wald**	**Degree of freedom**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
A02	unadjusted	0.315	0.234	1.814	1	0.178	1.371	0.866	2.169
	adjusted	0.350	0.235	2.228	1	0.136	1.420	0.896	2.249
A03	unadjusted	0.859	0.430	3.997	1	0.046	2.361	1.017	5.482
	adjusted	0.805	0.432	3.483	1	0.062	2.237	0.960	5.213
A05	unadjusted	-14.380	1071.908	0.000	1	0.989	0.000	0.000	*
	adjusted	-14.289	955.850	0.000	1	0.988	0.000	0.000	*
A07	unadjusted	0.759	0.573	1.755	1	0.185	2.137	0.695	6.575
	adjusted	0.714	0.576	1.536	1	0.215	2.041	0.660	6.310
A08	unadjusted	0.271	0.502	0.292	1	0.589	1.311	0.490	3.506
	adjusted	0.243	0.504	0.233	1	0.629	1.275	0.475	3.422
A10	unadjusted	17.150	1325.123	0.000	1	0.990	28054558.210	0.000	*
	adjusted	17.124	1302.036	0.000	1	0.990	27344212.809	0.000	*
B01	unadjusted	1.021	0.499	4.176	1	0.041	2.775	1.043	7.385
	adjusted	1.071	0.506	4.483	1	0.034	2.918	1.083	7.864
C01	unadjusted	-1.528	0.818	3.492	1	0.062	0.217	0.044	1.077
	adjusted	-1.454	0.823	3.119	1	0.077	0.234	0.047	1.173
C02	unadjusted	**							
	Adjusted								
C03	unadjusted	0.969	0.561	2.989	1	0.084	2.636	0.878	7.910
	adjusted	0.938	0.565	2.759	1	0.097	2.555	0.845	7.731
C05	unadjusted	-0.430	0.356	1.459	1	0.227	0.650	0.324	1.307
	adjusted	-0.438	0.358	1.501	1	0.221	0.645	0.320	1.301
C07	unadjusted	1.068	0.497	4.611	1	0.032	2.909	1.098	7.709
	adjusted	1.120	0.499	5.029	1	0.025	3.064	1.152	8.153
C08	unadjusted	0.679	0.579	1.374	1	0.241	1.971	0.634	6.131
	adjusted	0.607	0.588	1.065	1	0.302	1.834	0.579	5.808
C09	unadjusted	0.088	0.329	0.072	1	0.789	1.092	0.573	2.083
	adjusted	0.116	0.336	0.120	1	0.729	1.123	0.581	2.170
C10	unadjusted	1.198	0.492	5.933	1	0.015	3.313	1.264	8.685

	adjusted	1.259	0.501	6.313	1	0.012	3.523	1.319	9.407
H02	unadjusted	-0.534	0.256	4.361	1	0.037	0.586	0.355	0.968
	adjusted	-0.530	0.257	4.261	1	0.039	0.589	0.356	0.974
H03	unadjusted	2.742	0.724	14.365	1	0.000	15.525	3.759	64.112
	adjusted	2.743	0.725	14.292	1	0.000	15.527	3.746	64.354
L02	unadjusted	-15.480	1071.908	0.000	1	0.988	0.000	0.000	*
	adjusted	-15.326	957.691	0.000	1	0.987	0.000	0.000	*
L03	unadjusted	**							
	Adjusted								
L04	unadjusted	-0.137	0.765	0.032	1	0.858	0.872	0.195	3.906
	adjusted	-0.1100	0.766	0.021	1	0.886	0.896	0.199	4.023
M01	unadjusted	-0.135	0.120	1.264	1	0.261	0.874	0.691	1.106
	adjusted	-0.121	0.121	1.006	1	0.316	0.886	0.698	1.123
M02	unadjusted	-0.749	0.467	2.576	1	0.108	0.473	0.189	1.180
	adjusted	-0.753	0.468	2.593	1	0.107	0.471	0.188	1.178
M03	unadjusted	1.665	0.751	4.910	1	0.027	5.283	1.212	23.033
	adjusted	1.693	0.752	5.073	1	0.024	5.438	1.246	23.734
M04	unadjusted	-1.119	1.225	0.833	1	0.361	0.327	0.030	3.608
	adjusted	-1.027	1.235	0.691	1	0.406	0.358	0.032	4.028
M05	unadjusted	0.676	1.155	0.342	1	0.559	1.965	0.204	18.920
	adjusted	0.708	1.157	0.374	1	0.541	2.030	0.210	19.601
R03	unadjusted	0.259	0.193	1.813	1	0.178	1.296	0.889	1.890
	adjusted	0.277	0.193	2.058	1	0.151	1.319	0.904	1.925

table 10 (logistic regression could not be performed as one (*) or both (**) of the groups had less than one case)

3:2:2b: Use of ATC-S the year after inclusion in TOP Study:

Summary of chi-square results for somatic medication categories are given in table 11. The total of 26 ATC-S were evaluated and drugs from seven ATC-S, including "Remedies for functional gastrointestinal disorders (A03)", Drugs for diabetes treatment (A10), Antithrombotic agents (B01), Beta blockers (C07), Lipid modifiers (C10), Corticosteroids for systemic use (H02), Muscle relaxants (M03) were significantly more used by the patients group as compare to control group ($p < 0.05$), whereas drugs from three ATC-S, including Cardiac therapy (C01), Endocrine therapy (L02), Corticosteroids for systemic use (H02) were more used by CG. Among controls anti-inflammatory and anti-rheumatic drugs (M01), remedies for obstructive pulmonary disease (R03), corticosteroids for systemic use (H02), remedies for acid-related symptoms (A02), vaso-protectors (C05) and agents having effect on the renin-angiotensin system (C09) were prescribed to 141, 43, 33, 28, 16 and 15 individuals, respectively, and for all other drugs of the remaining ATC-S the numbers never exceeded 10 individuals (table 11).

This one year after evaluation gives a slight change in the use of ATC-S groups when observed them with the same study groups one year before the inclusion in TOP study. Whereas rest of the 16 ATCs have insignificant difference between both patients' and controls' groups. These include Bile and liver therapy (A05), Antidiarrheal, intestinal antiseptics and anti-inflammatory drugs (A07), Anti-obesity agents, excluding dietary supplements (A08), Antihypertensives (C02), Vasoprotectors (C05), Calcium antagonists (C08), Agents having an effect on the renin-angiotensin system (C09), Endocrine therapy (L02), Immunostimulants (L03), Immunosuppressants (L04), Anti-inflammatory and anti-rheumatic drugs (M01), Topical preparations for muscle and joint pain (M02), Muscle relaxants (M03), Gout remedies (M04), Agents for the treatment of bone diseases (M05), Remedies for obstructive pulmonary disease (R03). Such groups show p-values are $> \alpha=0.05$ and explains that both comparative groups have no significant difference in the use of particular somatic ATCs.

ATC-S		Table 11: ATC-S the year after inclusion in TOP Study:				P value
		Patients		Controls		
		Frequency	Percent	frequency	Percent	
A02.	Using	58	4.1	28	3	0.176
	Not using	1348	95.9	892	97.0	
A03.	Using	25	1.8	7	0.8	0.039
	Not using	1381	98.2	913	99.2	
A05.	Using	0	0	1	0.1	0.216
	Not using	1406	100	919	99.9	
A07.	Using	13	0.9	4	0.1	0.175
	Not using	1393	99.1	916	99.9	
A08.	using	12	0.9	6	0.7	0.588
	Not using	1394	99.1	914	99.3	
A10.	using	24	1.7	0	0	<0.0001
	Not using	1382	98.3	920	100	
B01.	using	21	1.5	5	0.5	0.033
	Not using	1385	98.5	915	99.5	
C01.	using	2	0.1	6	0.7	0.040
	Not using	1404	99.9	914	99.3	
C02.	using	0	0	0	0	0.216
	Not using	1406	100	920	100	
C03.	using	16	1.1	4	0.4	0.072
	Not using	1390	98.9	916	99.6	
C05.	using	16	1.1	16	1.7	0.224
	Not using	1390	98.9	904	98.3	
C07.	using	22	1.6	5	0.5	0.025
	Not using	1384	98.4	915	99.5	

C08.	using	12	0.9	4	0.4	0.232
	Not using	1394	99.1	916	99.6	
C09.	using	25	1.8	15	1.6	0.789
	Not using	1381	98.2	905	98.4	
C10.	using	25	1.8	5	0.5	0.010
	Not using	1381	98.2	915	99.5	
H02.	using	30	2.1	33	3.6	0.035
	Not using	1376	97.9	887	96.4	
H03.	using	46	3.3	2	0.2	<0.0001
	Not using	1360	96.7	918	99.8	
L02.	using	0	0	3	0.3	0.032
	Not using	1406	100	917	99.7	
L03.	using	0	0	0	0	0.826
	Not using	1406	100	920	100	
L04.	using	4	0.3	3	0.3	0.858
	Not using	1402	99.7	917	99.7	
M01.	using	192	13.7	141	15.3	0.261
	Not using	1214	86.3	779	84.7	
M02.	using	8	0.6	11	1.2	0.101
	Not using	1398	99.4	909	98.8	
M03.	using	16	1.1	2	0.2	0.013
	Not using	1390	98.9	918	99.8	
M04.	using	1	0.9	2	0.2	0.337
	Not using	1405	99.9	918	99.8	
M05.	using	3	0.2	1	0.1	0.551
	Not using	1403	99.8	919	99.9	
R03.	using	84	6	43	4.7	0.177
	Not using	1322	94.0	877	95.3	

Table 11

Findings of logistic regression are given in table 12, which show significant results ($p < 0.05$) for ATC-S, including Remedies for acid-related disorders (A02), Remedies for functional gastrointestinal disorders (A03), Antithrombotic agents (B01), Diuretics (C03), Beta blockers (C07), Lipid modifiers (C10), Corticosteroids for systemic use (H02), and Thyroid therapy (H03), indicating higher use among patients with the exception of Corticosteroids for systemic use (H02). According to which the patients' group used drugs from these ATC codes of somatic medications more often than controls. This shows stronger association between patients' group and these 8 ATCs for somatic medications after one year of their inclusion. On the other hand, rest of the 18 ATCs have insignificant regression values with a p-value > α=0.05. This indicates no significant difference is found between patients and controls when the use of these 18 ATCs during the year after inclusion is assessed. This reveals that a greater number of ATC-S are used in both patients and healthy controls.

TABLE 12: LOGISTIC REGRESSION OF ATC-S THE YEAR AFTER INCLUSION IN TOP STUDY								**95% C.I. for EXP(B)**	
ATC-S	**Log. regression**	**B**	**Std. Error**	**Wald**	**Degree of freedom**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
A02	Unadjusted	0.497	0.211	5.538	1	0.019	1.643	1.087	2.485
	Adjusted	0.544	0.212	6.592	1	0.010	1.723	1.137	2.611
A03	Unadjusted	0.975	0.425	5.266	1	0.022	2.650	1.153	6.093
	Adjusted	0.957	0.426	5.059	1	0.024	2.605	1.131	6.000
A05	Unadjusted	-14.380	1071.908	0.000	1	0.989	0.000	*	*
	Adjusted	-14.220	964.331	0.000	1	0.988	0.000	*	*
A07	Unadjusted	0.834	0.569	2.153	1	0.142	2.303	0.756	7.019
	Adjusted	0.852	0.569	2.240	1	0.134	2.344	0.768	7.150
A08	Unadjusted	-0.107	0.467	0.052	1	0.819	0.899	0.360	2.243
	Adjusted	-0.127	0.468	0.074	1	0.786	0.881	0.352	2.204
A10	Unadjusted	17.411	1325.123	0.000	1	0.990	36421623.962	*	*
	Adjusted	17.397	1307.067	0.000	1	0.989	35937348.539	*	*

B01	Unadjusted	0.910	0.400	5.176	1	0.023	2.485	1.134	5.446
	Adjusted	0.927	0.405	5.239	1	0.022	2.526	1.142	5.585
C01	Unadjusted	-1.277	0.691	3.411	1	0.065	0.279	0.072	1.081
	Adjusted	-1.264	0.692	3.336	1	0.068	0.283	0.073	1.097
C02	Unadjusted	-14.380	1071.908	0.000	1	0.989	0.000	*	*
	Adjusted	-14.229	975.372	0.000	1	0.988	0.000	*	*
C03	Unadjusted	1.432	0.623	5.288	1	0.021	4.187	1.236	14.190
	Adjusted	1.399	0.626	4.998	1	0.025	4.050	1.188	13.807
C05	Unadjusted	0.166	0.397	0.174	1	0.676	1.180	0.542	2.568
	Adjusted	0.166	0.399	0.173	1	0.678	1.180	0.540	2.577
C07	Unadjusted	0.825	0.381	4.689	1	0.030	2.282	1.081	4.816
	Adjusted	0.884	0.383	5.344	1	0.021	2.422	1.144	5.126
C08	Unadjusted	0.834	0.569	2.153	1	0.142	2.303	0.756	7.019
	Adjusted	0.810	0.579	1.960	1	0.162	2.248	0.723	6.989
C09	Unadjusted	0.138	0.316	0.191	1	0.662	1.148	0.618	2.134
	Adjusted	0.156	0.326	0.230	1	0.632	1.169	0.617	2.214
C10	Unadjusted	1.039	0.395	6.903	1	0.009	2.825	1.302	6.130
	Adjusted	1.127	0.402	7.853	1	0.005	3.086	1.403	6.787
H02	Unadjusted	-0.898	0.282	10.100	1	0.001	0.408	0.234	0.709
	Adjusted	-0.873	0.283	9.512	1	0.002	0.418	0.240	0.728
H03	Unadjusted	2.502	0.595	17.701	1	0.000	12.209	3.806	39.164
	Adjusted	2.514	0.596	17.764	1	0.000	12.351	3.837	39.755
L02	Unadjusted	-1.525	1.155	1.743	1	0.187	0.218	0.023	2.095
	Adjusted	-1.613	1.163	1.925	1	0.165	0.199	0.020	1.946
L03	Unadjusted	0.269	1.225	0.048	1	0.826	1.309	0.119	14.458
	Adjusted	0.309	1.234	0.063	1	0.802	1.362	0.121	15.305
L04	Unadjusted	0.270	0.867	0.097	1	0.756	1.310	0.239	7.164
	Adjusted	0.312	0.872	0.128	1	0.720	1.367	0.248	7.545
M01	Unadjusted	-0.086	0.121	0.510	1	0.475	0.917	0.724	1.163
	Adjusted	-0.061	0.122	0.249	1	0.618	0.941	0.741	1.195
M02	Unadjusted	0.967	0.647	2.237	1	0.135	2.631	0.741	9.350

	Adjusted	1.012	0.648	2.438	1	0.118	2.750	0.772	9.795
M03	Unadjusted	1.084	0.783	1.918	1	0.166	2.957	0.637	13.717
	Adjusted	1.111	0.784	2.008	1	0.157	3.037	0.653	14.114
M04	Unadjusted	-0.425	1.415	0.090	1	0.764	0.654	0.041	10.470
	Adjusted	-0.326	1.423	0.052	1	0.819	0.722	0.044	11.753
M05	Unadjusted	0.269	1.225	0.048	1	0.826	1.309	0.119	14.458
	Adjusted	-0.401	1.338	0.090	1	0.765	0.670	0.049	9.225
R03	Unadjusted	0.070	0.174	0.162	1	0.688	1.072	0.763	1.508
	Adjusted	0.088	0.174	0.257	1	0.612	1.092	0.776	1.537

table 12 (logistic regression could not be performed as one (*) of the groups had less than one case)

4: DISCUSSION:

4:1: Clinical findings:

4:1:1 USE OF DRUGS WITHIN ATC-N CATEGORY:

As expected, the patients of the present study, comprising of patients with severe mental illnesses, used more psychiatric medications than controls. This can also be seen in the treatment of psychotic disorder like schizophrenia and bipolar disorder where the neuroleptic drugs and lithium (N05A), are used as principal drugs (Jönsson et al. 2011). Antiepileptics (N03A) and antidepressants (N06A) are used as important mood stabilizers and to cure depression in patients with bipolar disorders but also patients with schizophrenia are sometimes depressed (Jönsson et al. 2011).). Anticholinergics (N04A) are used to minimize extrapyramidal side effects caused by some antipsychotics (Abdullah-Koolmees, 2013). Anxiolytics (N05B) and sedatives (N05C) are used to cope with certain disturbing symptoms in psychotic disorders, whereas use of psychostimulants (N06B) and drugs against addiction disorders mirrors co-morbidity with other psychiatric disorders (Vares et al. 2011).

However, there were seen some ATC-N which were also been used by controls' group frequently and they were N02A (opioids) and N02C (antimigraine medication). This N02A category comprises of CNS acting pain relievers and considered stronger treatments than commonly available pain killers. Mostly healthy people used these opioids because of dental treatment or acute pains for short-termed use. These are also widely used by older people because of chronic backpains, gout or arthritis treatment (O'Brien T et al, 2017). This may be because of CG had higher percentage of people with age group 37-55 years (table 6). On the other side, antimigraine (N02C) category was used largely by healthy individuals in our study groups. This also indicates that people with migraine had considered themselves healthy volunteers and not patients at the time of participating as healthy volunteers. As a conclusion, we cannot say that CG is free from medication use by ATCs-N category

Drugs from local anaesthetics (N01B), anticholinergics (N04A), dopaminergic agents(N04B) and psychostimulants (N06B), including ADHD drugs, were only seldom used by patients as (5,0.4%), (24, 1.7%), (3, 0.2%) and (27, 1.9%) respectively and none of the controls used them (table 4). This likely reflects a difference in patterns of use. However, due to no cases among healthy controls, we could not analyse logistic regression (table 5)

While general anaesthesia (N01A), antidementia (N06D) and other CNS acting drugs, for example those which are indicated for MS treatment (N07X) were not been used by any individual in both groups.

The overall consumption of ATCs-N after one year, seemed higher in PG but there were few exceptions (table 6). In case of local anaesthetics (N01B), antipyretic (N02B) and dopamine acting drugs (N04B), their use in patients VS controls is seen respectively as (0.5% vs 0.1%), (2.4% vs 2.3%) and (0.1% vs 0%), showing poor association between PG and local anaesthetics (N01B) and antipyretic(N02B). However, no use of dopamine acting drugs(N04B) among controls made it impossible to see any association between the study groups in table 5. Antipyretic (N02B) prescription frequency in PG, which was 3.6% before one year, had been prescribed lesser 2.4% after one year. Whereas the controls had about similar prescription rate of 2.1% and 2.3% before and after one year respectively. It is difficult to really know the difference between patients and controls for this ATC-N, giving that these drugs are often bought without prescription.

The antimigraine drugs (N02C) which were significantly used by controls before one year, have switched their prevalence group from control to patients after one-year investigation. This shift has not given any major change within the groups as patients were prescribed 2.2% before and 3.1% after one year inclusion in TOP study while controls used 1.3% and 1.5% before and after study respectively. This means patients used more antimigraine drugs than controls after one year analysis.

There is a unique exception of N04A(anticholinergic) which was significantly been used by PG but logistic regression cannot be performed because of no cases in Controls.

4:1:2: USE OF DRUGS WITHIN ATC-S CATEGORY:

We evaluated the 26 most prescribed ATC-S (table 8) and will discuss first the summary of one year before inclusion time (table 9).

We found that 10 of the ATC-S were significantly used by CG than PG. Their therapeutic indication supports that CG were suffering from acute and/or chronic somatic diseases, including antidiabetics (A10), Antithrombotic (B01), Heart treatments (C01), Betablockers (C07), Lipid modifying agents (C10), Thyroid treatments (H03), Endocrine treatment (L02), Muscle relaxant agents (M03), gastrointestinal agents (A03), systematic corticosteroids (H02).

Further this use is confirmed by the strong association (table 10) between CG and some ATC-S as Antithrombotic (B01), Betablockers (C07), Lipid modifying agents (C10), Thyroid treatments (H03), Muscle relaxant agents (M03), and systematic corticosteroids (H02). This strong associations remains unchanged after adjustments for confounding agents that is age and gender. These findings reassure that these 6 ATC-S were largely used with a significant difference by controls than the patients. Hence proving that apparently seen healthy volunteers were not completely healthy even one year before their inclusion in TOP study.

The same data sets were again evaluated after one year to recheck the health status of CG (table 11). The results again showed that CG used 10 particular ATC-S frequently than their comparative patients, which are mostly same as used by these controls in previous data collected one year before the inclusion of study with the addition of two new ATC-S namely GI agents (A02) and Diuretics (C03) and removal of two previously used ATC-S which were Muscle relaxant agents (M03) and Endocrine treatment (L02). To reconfirm any association of this consumption, we interpret data of logistic regression and found that CG has strong association (table 12) with the use of above mentioned 10 ATC-S which was not attenuated by controlling them against confounding factors of age and gender.

One interesting finding was of Corticosteroids for systemic use (H02), which were prescribed at a rate of 3.6% both one year before and after inclusion for controls and at a rate of 1.5% one year before and 2.1% one year after in patients' group respectively.

4:2: Demographic findings:

4:2:1: Age distribution:

We will discuss findings from two main study groups: Patients' group having 1406 individuals and controls' group having 920 individuals. Let's see our confounding factors in detail; the first one is age and the other one is gender. The participants of TOP study were included from an age of 18 years to 65 years. This ended up in a huge data set and in order to present this data in a more understandable way, we categorized it in 3 groups see table 2. While working on age variables, it was seen that individuals in Patients' group have younger population ranging from 18-36 years of age. This group includes young subjects with a maximum age of 36 years, where physical activities were on their top for most of the candidates and young population mostly do

not have somatic health issues, but this group is seen more prone to many mental issues. The participants of 37 to 55 years of age are grouped together in category 2. This is the middle phase of an average human life where most of the people are exposed to somatic disorders. Here we see larger percentage of controls suffering from somatic disorders with a medication use of 37% as compared to the same age group of patients.

While the last and third category has participants over 56 years of age till 65 years of age. This late phase of human life has fewer number of participants. The point to consider is the chronicity of many health issues in this group of age and we observed that patients have 3.6% of consumers in contrast with the control group having just 1.3%.

4:2:2: Gender distribution:

With reference to table 1, we can document that both the genders equally represent both study groups. In our study groups both males and females are equal consumers of medicine regardless of their gender type. There is no finding of any extraordinary medicine use by any of the two genders. This reason of no difference in medicine use between the genders, could be broad spectrum of disorders which are investigated. On the contrary, past studies reported that there are certain diseases and their comorbidities which have extraordinary incline towards specific gender (Solberg BS, 2018)

5: STRENGTH OF THE STUDY:

This naturalistic study will give the more relevant information about the utilization of medications in clinical practice. Here we are able to compare a large control group with a large patient sample investigation group over a period of time without drop out. Because participants were just being investigated without intervening them by any tool. Whereas in previous randomized controlled trials, we have most likely fewer selected patients, limited time period and often high dropout rate (Lieberman et al., 2005)

Another strength is the use of national prescription registry data (NorPD) with excellent reliability. This furnishes new research approaches in mental health sciences, especially in psychopharmacology where the utilization of such trustworthy data is a great advantage.

6: LIMITATIONS OF THE STUDY:

One limitation could be inadequacy of available data. NorPD is a strong data base which is covering almost all the prescribed medications around the Norway but there is a discussion about missing information in case of hospitalized patients. One could say that healthy controls are rarely hospitalized, thus patients' group could be biased because of hospitalization period. Because the treatment given to patients under this hospitalization period is not registered in NorPD till now. On the other hand, we observe that psychiatric patients report shorter hospital stays in the past decades and mostly get treated in outpatients' clinics. This new finding outweighs any expected hospital stay bias.

One limitation could be inadequacy of available data. NorPD is a strong data base which is covering almost all the prescribed medications around Norway, but information is missing when patients are hospitalized. On the contrary, healthy controls are rarely hospitalized, thus the comparison with the patients group could be biased because of hospitalization period. However, we observe that psychiatric patients report shorter hospital stays in the past decades and mostly get treated in outpatients' clinics. Thus, we do not consider this limitation as this represents any major concern and could outweighs the strengths of this study.

7: CONCLUSION:

Clinical findings: How healthy are the controls actually?

One main purpose of this study is to carefully evaluate how healthy are the control participants and we managed to successfully investigate this too. The above detailed results and discussion have precisely elaborated the health status of clinically investigated healthy controls. This study provides a new approach and shows that screening tools should be used to select healthy individuals in any study, especially in psychiatric research, where knowing of underlying sicknesses is a big challenge for researchers.

The healthy participants of the TOP study were using a large number of medicines against many somatic disorders and a few medicines which are categorized as ATCs for nervous system. Although this control group has minimum or no use of such ATC-N medicines but in comparison with the patient's group, they showed significant results for example, Antipyretic (N02B), Opioids (N02A) and Antimigraine (N02C). In spite of the fact that these ATC-N medicines were not used for severe psychiatric disorders of chronic nature, but they were been used by the control participants within one year before and/or after the inclusion in the TOP study. Hence, we can state that our control group was not disease or medication free.

As a conclusion of our study, we summarised that although patients used both types of ATC-N and ATC-S largely than their compared controls but there is a strong evidence that control group was not completely healthy nor medicine free. Thus, the control group was not an ideal sample consisting of disease-free healthy volunteers, as researchers expected while considering them as control groups for comparison with patient group.

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