Project proposal for the PhD project:

Psychiatric comorbidity in Back Pain Disorders
– Risk, treatment and pharmaco-epidemiological analysis

Applicant

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Introduction

Chronic pain is a common health problem negatively affecting sleep, work ability and socialization[1-4]. Chronic pain also increases morbidity, mortality and health care costs and has a direct and severe impact on the quality of life[3 5-8]. The prevalence of chronic pain is up to 46,5% in the general population[5]. Musculoskeletal back and neck pain are one of the most common pain conditions[2 9] with a lifetime prevalence of low back pain in the range of 51%-84%[6]. Variation in prevalence estimates can be explained by a difference in the definition of pain, research methodologies and differences in study samples[10].

Several different diagnostic classifications systems for back pain disorders (BPD) exist, but most frequently these are divided into specific and non-specific BPD[11]. This study chooses to establish two subgroups for specific BPD based on the presumed cause of illness and available treatment options and one group for unspecified BPD (UBD). The specific subgroups consists of inflammatory back diseases (IBD) and degenerative back diseases (DBD)[12].

Clinical guidelines recommend that treatment consists of a combination of medical, surgical and non-pharmacological interventions such as patient education, physical- and occupational therapy, cognitive-behavioral therapy, nutritional counseling and self-management strategies[13-16]. The most frequent treatment of BPD is pharmacological[17]. Despite not being generally recommended for treatment of back pain disorders[18], opioids are prescribed in up to 66% of patients[19]. The prevalence of concomitant substance abuse disorder in BPD patients receiving opioid treatment is up to 43%[19]. Previous studies fail to establish, which type of back pain patients are prescribed opioids and which specific other psychiatric comorbidities than substance abuse are linked to higher opioid consumption. It does seem, that patients with a high burden of psychiatric comorbidity, have a higher rate of opioid misuse, although studies are old, small and heterogenic[20-23] Several studies on the association between back pain and psychiatric disorders, focusing on depression and anxiety disorders, have been conducted. However, these studies have several limitations: they do not include other types of psychiatric comorbidity[24-29] and they are often based on questionnaires. Including nationwide data sources might minimize potential selection bias. Furthermore, many studies have focused on large heterogeneous groups of patients with nonspecific back pain symptoms instead of being based on BPD diagnosis as defined by the ICD-10[30]. The majority of studies do not compare different BPD-diagnosis when assessing psychiatric comorbidity. [24 27 31-33]

To more accurately assess the risk of psychiatric comorbidity in patients with back pain disorders, population-based registry data could be utilized. The Danish health registries are generally considered to have a high validity, however there are limitations to consider, as described in previous studies on each registry[34 35 36 37], which has to be taken into consideration when interpreting results based on data from these registries.
When investigating psychiatric comorbidity in BPD patients, focusing on anxiety and depression, has been the norm. However, important information on the relationship between other types of mental illness and back pain disorders might be identified, if a dataset of sufficient size and quality, is used for analysis. A population-based set of registry data as the ones available in Denmark provides this. By grouping psychiatry comorbidity according to ICD-10, mental illnesses with common pathways are analyzed together. In the ICD-10 system psychiatric diagnosis are grouped according to symptomology and common etiology[30]. All psychiatric diagnoses are considered relevant in the chosen population, as any psychiatric disorders represents a vulnerably patient with possible complicating factors when treating back pain. The limitation of Danish registry-based data is, that it does not provide complete data from the primary care sector selecting only severe psychiatric diagnosis.
In conclusion, back pain disorders and the association with psychiatric comorbidity has primarily been investigated using symptomology, not ICD-10 diagnoses and with a focus on anxiety and depression. The studies are small, heterogeneous and of varying quality. The use of pharmacological treatment, including opioids, in back pain disorders complicated by psychiatric comorbidity is unknown.

Aim of the thesis

The aim of this PhD thesis is to use population-based registry data to:
1) to estimate the prevalence of psychiatric comorbidity in patients with back pain disorders (BPD) compared to patients with no back pain in the time period 2010-2014; 2) Investigate whether presence of psychiatric comorbidity affects utilization of pharmacological, surgical and other types of treatment for patients with BPD 3) Investigate whether presence of psychiatric comorbidity affects utilization and dosages of pharmacological treatment for patients with BPD.

Clinical contributions of this PhD

This PhD study will contribute with new knowledge on the association between different types of BPD and psychiatric comorbidity. As BPD affects a large part of the population, this is a very important area of research from a public health and clinical perspective. Access to nationwide registries facilitates a comprehensive and population-based dataset, ensuring the ideal circumstances for investigating the association between BPD and potential psychiatric comorbidity. Furthermore, the results can be used to increase clinical awareness of vulnerable patients in the intersection between rheumatology and psychiatry and subsequently improve prevention and clinical management for a complex and resource-demanding patient population.

Materials and methods

Setting and study population

This PhD project includes a population-based nationwide cohort based on data from Danish health registries. Danish health registries, including The Danish National Patient Registry (DNPR), a subdivision of the DNPR, the National Patient Registry – Psychiatry (NPD-Psych), The Danish National Prescription Database and The Danish National Health Service Register, contains complete data on hospital contacts, prescription drug use and services provided by health contractors. By using the Danish Civil Registry and the unique personal identification number assigned to all Danish citizens at birth, data across registries can be linked on an individual level[34 35 36 37].

The study population will be defined as all adult patients (18+) identified in the DNPR[34], covering all inpatient and outpatient services in Denmark, in the time period 1th of January 2010 to 31th of December 2014 with a diagnosis of BPD according to the ICD-10 Classification of Disease (DM*). [30]

Psychiatric comorbidity will be defined as the presence of any of the following diagnosis, according to ICD-10 classification[30], obtained from the National Patient Registry – Psychiatry (NPD-Psych), covering all inpatient and outpatient psychiatric services in Denmark in the time period 1th January 2007 to 31th December 2017: Organic, including symptomatic, mental disorders (F00-DF09), Mental and behavioral disorders due to psychoactive substance use (F10-F19), Schizophrenia, schizotypal and delusional disorders (F20-F29), Mood [affective] disorders (F30-F39), Neurotic, stress-related and somatoform disorders (F40-F48), Behavioral syndromes associated with physiological disturbances and physical factors (F50-F59), Disorders of adult personality and behavior (F60-F69), Mental retardation (F70-F79), Disorders of psychological development (F80-F89), Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90-F98) and, Unspecified mental disorder (F99). To qualify as a psychiatric comorbidity to back pain disorder, we define that the psychiatric diagnosis must be given no earlier than three years prior to back pain disorder diagnosis and no later than three years after.

Study 1) Prevalence of psychiatric comorbidity in back pain disorders

Psychiatric comorbidity in Back Pain Disorders

Risk, treatment and pharmaco-epidemiological analysis

Aim: 1) To estimate prevalence of psychiatric comorbidity in patients with BPD compared to patients without BPD and 2) To estimate prevalence of psychiatric comorbidity in patients with unspecific back pain (UBP) compared to the background population and to patients with a specific back pain (SBP) in a Danish nationwide cohort from 2010-2014.

Hypothesis: 1) There is a higher risk of psychiatric comorbidity in BPD patients compared to the background population and 2) UBP patients have a higher risk of psychiatric comorbidity compared to patients with specific BPD.

Design: The study will be a nationwide register-based matched cohort study.

Procedure: Selected BPD patients with the following diagnosis will be identified via the DNPR: Spondylopathies DM45-49, Other dorsopathies DM 50-54 and Segmental and somatic dysfunction DM99. Each patient will be matched 1:5 on age and sex with patients without back disorders by random at Statistics Denmark[38]. The selection of diagnosis is to be able to match the population with non-BPD patients in the Danish registries.
Information on somatic comorbidity for calculation of Charlson Comorbidity index[39] (CCI) at time of BPD diagnosis, will be retrieved from the DNPR. Data on psychiatric comorbidity will be identified using NPD-Psych. Information on marital status, vital status, and immigration status will be retrieved from the Civil Registration System (CPR)[35]. Patients that are not alive or have emigrated within three years after BPD diagnosis are considered lost to follow-up and excluded from the cohort. Descriptive data on the socioeconomic status, education level and equivalent available income will be retrieved from Statistics Denmark[38]. All data comprising each variable will be retrieved from 1th of January 2007 to 31th of December 2017 (three years before and after study period).

Measures of outcome: Primary outcome is to estimate prevalence of psychiatric comorbidity in patients with BPD compared to the Danish background population. Secondary outcome is to estimate prevalence of psychiatric comorbidity stratified by type of BPD (SBP UBP) compared to the Danish background population. We will use a presence of psychiatric comorbidity as outcome.

Statistics: We will use Fisher's exact test and t-test to compare baseline characteristics with 95% confidence intervals (CI) and p-values. Crude risks of psychiatric comorbidity will be calculated and logistic regression model will be used, to investigate differences between the distribution of risk in BPD patients and the background population. A logistic regression model will also be used to investigate differences between the distribution of psychiatric comorbidity in the IBD, DBD and UBP group compared to the background population. The logistic regressions will be reported using 95% CI and adjusted for the following confounders: age, sex, equivalent available income, educational level, CCI, marital status.

Study 2) The effect of psychiatric comorbidity on type of treatment for BPD

Aim: 1) To investigate whether treatment of BPD in patients with psychiatric comorbidity differ from treatment of patients with BPD without psychiatric comorbidity; 2)To investigate whether treatment of BPD differs in the following subgroups: a) specific BPD and no psychiatric comorbidity; b) specific BPD with psychiatric comorbidity; c) unspecific BPD with no psychiatric comorbidity; d) unspecific BPD with psychiatric comorbidity. Investigation will be performed in a nationwide Danish cohort in 2010-2014.

Hypothesis: 1) Psychiatric comorbidity affects type of treatment in BPD patients and 2) psychiatric comorbidity affects type of treatment in subgroups of BPD.

Design and study population: The study will be a nationwide register-based cohort study. The study population consists of patients with BPD and in the sub-analysis the study population consists of patients with BPD and psychiatric comorbidity.

Procedure: BPD patients will be identified via the DNPR. Surgical treatment will be defined as the presence of any procedure code for back surgery retrieved from DNPR (NOMESCO: KNA-W)[34 40]. Pharmacological treatment of BPD will be defined as any treatment with the following drugs: NSAID (ATC: N01A*), acitomenophen (ATC: N02BE01), opiods (N02A*), antiepileptica (ATC: N03A) and tricyclic antidepressants (ATC: N06AA)[13] identified using the Register of Medicinal Products Statistics[7]. Data on other types of treatment (defined as any treatment not surgical or pharmacological) such as physiotherapist, psychologist, chiropractor or occupational therapist (covered via tax-funded health insurance) will be obtained via The Danish National Health Insurance Service Register (SSR)[37]. All BPD treatment-related information will be retrieved up to three years after the date of BPD diagnosis.
Information on somatic comorbidity for calculation of Charlson Comorbidity index[39] (CCI) at time of BPD diagnosis, will be retrieved from the DNPR. Data on psychiatric comorbidity will be identified using NPD-Psych. Information on psychiatric comorbidity will be used to define whether each patient had a psychiatric diagnosis prior to BPD diagnosis, after BPD diagnosis or no psychiatric diagnosis. If a psychiatric diagnosis occurs both prior to and after BPD diagnosis, the patient will be defines as having a psychiatric comorbidity prior to BPD diagnosis.
Information on marital status, vital status, and immigration status will be retrieved from the Civil Registration System (CPR)[35]. Patients that are not alive or have emigrated within three years after BPD diagnosis are considered lost to follow-up and excluded from the cohort. Descriptive data on the socioeconomic status, education level and equivalent available income will be retrieved from Statistics Denmark[38]. All data comprising each variable will be retrieved from 1th of January 2007 to 31th of December 2017 (three years before and after study period).

Measures of outcome: The outcome is type of treatment for BPD (surgical, pharmacological and other types of treatment)

Statistics: We will use Fisher's exact test and t-test to compare patients' baseline characteristics with 95% confidence intervals (CI) and p-values. For each treatment type we will use logistic regression model to investigate differences in outcome distribution between patients with and without psychiatric comorbidity.The logistic regressions will be performed with 95% CI adjusted for the following confounders: age, sex, CCI, level of education, equivalent available income, type of BPD (IBD, DBD or UBP) and marital status.

Study 3) Effect of psychiatric comorbidity in pharmacological treatment of BPD.

Aim: 1) To compare dosages of pharmacological treatment in BPD patients with and without the presence of psychiatric comorbidity in a nationwide Danish cohort study in 2010-2014. 2) To compare high vs. low dosages of pharmacological treatment for BPD in patients with BPD and psychiatric comorbidity.

Hypothesis: 1) Patients with BPD and psychiatric comorbidity are prescribed a higher dosage of pain medication for BPD compared with BPD patients without psychiatric comorbidity. 2) BPD patients with a psychiatric comorbidity with a high (defined as above the 50th percentile) vs. low (defined as below the 50th percentile) dosage of pain medication are also prescribed higher dosages of psychiatric medication.

Design and study population: The study will be a nationwide register-based cohort study. The study population consists of patients with BPD that received pharmacological treatment for BPD. In the secondary analysis the study population consists of patients with BPD and a psychiatric comorbidity, who received pharmacological treatment for BPD.

Procedure: BPD patients will be identified via the DNPR. Pharmacological treatment of BPD will be defined as any treatment with the following drugs: NSAID (ATC: N01A*), Acitomenophen (ATC: N02BE01), Opiods (N02A*)[13]. Pharmacological treatment for psychiatric comorbidity will be defined as any treatment with the following drugs: Antipsychotics (ATC:N05A), Antidepressants (ATC: N06A), Selective Serotonin Reuptake Inhibitors (SSRI) (ATC: N06AB), and anxiolytica (ATC: N5B*)[41] Pharmacological treatment that can be used in the treatment of both BPD and psychiatric disorders will be defined as any treatment with the following drugs: Antiepileptica (ATC: N03A) and Tricyclic antidepressants (ATC: N06AA)**.** All data on pharmacological treatment will be identified using the Register of Medicinal Products Statistics[7]. From time of BPD diagnosis and the following three years, pharmacological treatment for both somatic illness and psychiatric comorbidity in Daily Defined Dosage (DDD) per year will be calculated[42].
Information on somatic comorbidity for calculation of Charlson Comorbidity index[39] (CCI) at time of BPD diagnosis, will be retrieved from the DNPR. Data on psychiatric comorbidity will be identified using NPD-Psych. Information on marital status, vital status, and immigration status will be retrieved from the Civil Registration System (CPR)[35]. Patients that are not alive or have emigrated within three years after BPD diagnosis are considered lost to follow-up and excluded from the cohort. Descriptive data on the socioeconomic status, education level and equivalent available income will be retrieved from Statistics Denmark[38]. All data comprising each variable will be retrieved from 1th of January 2007 to 31th of December 2017 (three years before and after study period).

Measures of outcome: Primary outcome is pharmacological treatment in DDDs defined as high (above the 50th percentile and low (below the 50th percentile) of pain medication. Secondary outcome is psychiatric medication in BPD patients with psychiatric comorbidity in DDD's defined according to high (above the 50th percentile) and low (below the 50th percentile) dosages of pain medication.

Statistics: We will use Fisher's exact test and t-test to compare patients' baseline characteristics with 95% confidence intervals (CI) and p-values. Time dependent Cox regression will be performed separately for patients with specific and unspecific BPD to examine dosage of pharmacological treatment over time comparing patients with and without psychiatric comorbidity. The analysis will be performed with 95% CI and adjusted for the following confounders: age, sex, CCI, level of education, equivalent available income, marital status and the presence of psychopharmacological treatment.
To examine dosage of psychopharmacological treatment over time comparing patients with psychiatric comorbidity and low vs high dose of pharmacological treatment of BPD, time dependent Cox regression will be performed reporting 95% CI and adjusting for the following confounders: age, sex, CCI, level of education, equivalent available income, marital status.

Ethics

All studies will be based on national clinical registries and approval is obtained by The Danish Health Data Board and the Danish Data Protection Agency (18/3337). According to Danish law, further ethical approval is not required for purely registry-based studies. All data will be stored on Statistics Denmark's servers and will be anonymized ensuring no patients can be identified.

PhD Outline

The PhD will be conducted within a timeframe of three years (six semesters).

	1st semester	2nd semester	3rd semester	4th semester	5th semester	6th semester
Data collection	**X**					
PhD Courses	**X**	**X**	**X**			
Data analysis		**X**	**X**	**X**	**X**	
Writing articles			**X**	**X**	**X**	**X**

References

1. Hawker GA. The assessment of musculoskeletal pain. *Clinical and experimental rheumatology* 2017;35 Suppl 107(5):8-12.
2. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Current medical research and opinion* 2012;28(7):1221-9.
3. Annagur BB, Uguz F, Apiliogullari S, Kara I, Gunduz S. Psychiatric disorders and association with quality of sleep and quality of life in patients with chronic pain: a SCID-based study. *Pain medicine (Malden, Mass.)* 2014;15(5):772-81.
4. Purabdollah M, Lakdizaji S, Rahmani A. Relationship between Sleep, Pain and Inflammatory Markers in Patients with Rheumatoid Arthritis. *Journal of caring sciences* 2017;6(3):249-55.
5. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet (London, England)* 1999;354(9186):1248-52.
6. Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. *Mayo Clinic proceedings* 2015;90(1):139-47.
7. Macfarlane GJ, Barnish MS, Jones GT. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. *Annals of the rheumatic diseases* 2017;76(11):1815-22.
8. Smith D, Wilkie R, Uthman O, Jordan JL, McBeth J. Chronic pain and mortality: a systematic review. *PloS one* 2014;9(6):e99048.
9. de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, et al. The association of depression and anxiety with pain: a study from NESDA. *PloS one* 2014;9(10):e106907.
10. Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2017.
11. Fairbank J, Gwilym SE, France JC, Daffner SD, Dettori J, Hermsmeyer J, et al. The role of classification of chronic low back pain. *Spine* 2011;36(21 Suppl):S19-42.
12. Williams N.S BCJK, O'connell P. R. *Bailey & Love's Short Practice of Surgery, 25th edn*. London: Hodder Arnold (London), 2008 2008.
13. Stochkendahl MJ, Kjaer P, Hartvigsen J, Kongsted A, Aaboe J, Andersen M, et al. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2018;27(1):60-75.
14. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2010;19(12):2075-94.
15. The National Institute of Clinical Care and Excellence . Low back pain and sciatica in over 16s: assessment and management. Full guideline: Assessment and noninvasive treatments. 2016.
16. The National Institute of Clinical Care and Excellence. Low back pain and sciatica in over 16s: assessment and management. Full guideline: Invasive treatments. 2016.
17. Chou R, Deyo R, Friedly J, Skelly A, Weimer M, Fu R, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92.
18. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ* 2015;350:g6380.
19. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007;146(2):116-27.

20. Wasan AD, Michna E, Edwards RR, Katz JN, Nedeljkovic SS, Dolman AJ, et al. Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. *Anesthesiology* 2015;123(4):861-72.
21. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *The Clinical journal of pain* 2010;26(1):1-8.
22. Breckenridge J, Clark JD. Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *The journal of pain : official journal of the American Pain Society* 2003;4(6):344-50.
23. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med* 2006;166(19):2087-93.
24. Ciaramella A, Poli P. Chronic Low Back Pain: Perception and Coping With Pain in the Presence of Psychiatric Comorbidity. *The Journal of nervous and mental disease* 2015;203(8):632-40.
25. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *Jama* 1998;280(2):147-51.
26. Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer MC, et al. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. *Pain* 2007;129(3):332-42.
27. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain* 2005;113(3):331-9.
28. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *International journal of epidemiology* 2014;43(2):476-93.
29. Chaturvedi SK. Prevalence of chronic pain in psychiatric patients. *Pain* 1987;29(2):231-7.
30. World Health Organization W. International statistical classification of diseases and health related problems (The) ICD-10. *Diss. World Health Organization* 2004.
31. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain* 2004;111(1-2):77-83.
32. Tegethoff M, Belardi A, Stalujanis E, Meinlschmidt G. Comorbidity of Mental Disorders and Chronic Pain: Chronology of Onset in Adolescents of a National Representative Cohort. *The journal of pain : official journal of the American Pain Society* 2015;16(10):1054-64.
33. Reme SE, Tangen T, Moe T, Eriksen HR. Prevalence of psychiatric disorders in sick listed chronic low back pain patients. *European journal of pain (London, England)* 2011;15(10):1075-80.
34. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scandinavian Journal of Public Health* 2011;39(7 suppl):30-33.
35. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *European Journal of Epidemiology* 2014;29(8):541-49.
36. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38-41.
37. Andersen JS, Olivarius Nde F, Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011;39(7 Suppl):34-7.
38. Statistics Denmark D. Statistics Denmark - http://dst.dk/en/OmDS, 2016.
39. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases* 1987;40(5):373-83.
40. Nordic Medico-Statistical Committee. Classification of Surgical Procedures (NCSP), version 1.16, 2009.
41. Taylor D. The Maudsley Prescribing Guidelines in Psychiatry. 2012.

42. World Health Organization W. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). *World Health Organisation* 2014.