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ANTTI TANSKANEN

DRUG USE MODELLING METHOD PRE2DUP

From Prescriptions to Drug Use Periods

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ABSTRACT

Nationwide Prescription and Healthcare registers provide almost unlimited possibilities for pharmacoepidemiological research. If one wishes to investigate the duration of drug use or drug use at a certain time point, then Prescription register information needs to be processed in order to estimate when the drug use started and ended. The aims of this thesis were to develop a novel method to model drug purchases into drug use periods and to assess the model's validity and performance.

Prescription and Hospital Discharge register data from the Medalz-2005 (Medication use and Alzheimer's disease) cohort which includes all Finns who had special reimbursement for Alzheimer's disease and were community–dwelling at the end of 2005 were used in method development and validation. Secondly, the drug use reported in the interview in the GeMS study (the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) including persons aged 75 years or older were compared with their modelled drug use. The drug use periods were validated against expert opinion (Medalz) and compared with the interview results (GeMS). In the third study, modelling results of the developed method were compared with earlier methods with five commonly used drugs (Medalz).

This thesis presents a new method "PRE2DUP" that models continuous drug use periods from drug purchase data. The method is based on temporal sliding averages of daily dose in order to derive the duration for each drug purchase. The method takes into account hospital stays when drugs are administered in the hospital, and the regularity of drug purchases. The method joins purchases into periods in a stepwise manner, by calculating if the purchased amount of drug would be enough to last until the next purchase. According to an expert-opinion based validation, PRE2DUP correctly joined over 90% of purchases in most drug classes, and over 80% of drug use periods had the correct duration. The agreement between PRE2DUP and drug use reported in the interview was over 80% with most drug classes. In a comparison with different methods, PRE2DUP achieved 60-100% correctness whereas the other methods exhibited lower accuracies with the drugs investigated.

In conclusion, the PRE2DUP method generates accurate drug use periods from register data; this is advantageous in pharmacoepidemiological research.

National Library of Medicine Classification: QV 748, QV 771, WA 950
Medical Subject Headings: Pharmacoepidemiology; Drug Prescriptions; Drug Utilization Review; Data Interpretation, Statistical; Registries; Finland

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TIIVISTELMÄ

Sairaanhoidon ja lääkeostojen kansalliset rekisterit tarjoavat hyvät mahdollisuudet lääke-epidemiologiseen tutkimukseen. Lääkeostot eivät suoraan sovellu tutkimuskäyttöön silloin, kun tutkitaan käytön kestoa tai lääkkeen käyttöä tiettynä aikana. Näitä tutkimuskysymyksiä varten tarvitaan tietoa lääkkeen käytön aloituksesta ja lopetuksesta. Väitöstutkimuksen tavoitteena oli kehittää ja kuvata uusi menetelmä lääkkeiden käyttöjaksojen mallintamiseksi lääkeostoista sekä tutkia menetelmän validiteettia.

Tutkimusaineistona käytettiin Medalz-2005 (Medication use and Alzheimer's disease) -kohorttia, johon kuuluvat Alzheimerin taudin rajoitetun peruskorvausoikeuden saaneet suomalaiset vuoden 2005 lopussa. Mallinnuksen lähtöaineistona käytettiin henkilöiden lääkeostoja Kelan reseptitiedostosta sekä sairaalajaksoja THL:n Hoitoilmoitusrekisteristä. Menetelmää validoitiin lisäksi Hyvän Hoidon Strategia (HHS) -tutkimusaineistolla, joka seurasi 75 vuotta täyttäneiden kuopiolaisten lääkkeenkäyttöä sekä rekisteri- että haastattelutiedoin. Menetelmän tuottamien käyttöjaksojen oikeellisuutta tutkittiin asiantuntija-arvioinnein (Medalz) ja vertaamalla mallinnettua ja haastattelussa raportoitua lääkekäyttötietoa toisiinsa (HHS). Kolmannessa tutkimuksessa verrattiin uuden menetelmän sekä aiemmin käytettyjen menetelmien tuottamien käyttöjaksojen oikeellisuutta sokkoutetussa asiantuntija-arvioinnissa viiden yleisesti käytetyn lääkkeen suhteen (Medalz).

Tutkimus esittelee uuden menetelmän PRE2DUP, joka mallintaa jatkuvan lääkekäytön jaksot lääkeostoista. Menetelmä perustuu paikallisen annoksen arviointiin ajassa liukuvalla keskiarvolla. Tästä annoksesta lasketaan kullekin ostolle, kuinka pitkään lääkemäärä riittää. Menetelmä huomioi sairaalajaksot, jolloin ostettuja lääkkeitä ei käytetä. Menetelmä käyttää ajallisesti askeltavaa päätöksentekoa, jossa käyttöjaksoja luodaan tekemällä päätös riittääkö ostettu määrä seuraavaan ostoon. Asiantuntija-arvion mukaan PRE2DUP yhdisti useimmissa lääkeryhmissä lääkeostot jaksoiksi oikein yli 90 prosentissa ja oikean mittaisiksi jaksoiksi yli 80 prosentissa arvioiduista tapauksista. PRE2DUP-mallinnuksen mukainen käyttö vastasi yli 80 prosentin tarkkuudella haastattelun mukaista lääkekäyttöä useimmilla tutkituista lääkkeistä. Vertailtaessa eri menetelmiä, PRE2DUP-menetelmän tuottamista jaksoista 60 - 100 % oli asiantuntija-arvion mukaan oikein, kun puolestaan muilla menetelmillä kaikissa vertailuissa osuus oli huomattavasti pienempi.

Siten voidaan todeta, että PRE2DUP-menetelmä tuottaa oikean kestoisia lääkkeiden käyttöjaksoja rekisteriaineistoista lääke-epidemiologiseen tutkimukseen.

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to the Nordic welfare states

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The development of PRE2DUP goes back to year 2002 when Professors Sarnoff Mednick† and Matti Huttunen asked me to process prescription data into a suitable format for outcome studies. This was the start of development of methods to convert drug purchases into drug use periods. Matti Huttunen told Professor Jari Tiihonen about this method around 2004-2005. Since then I have worked with Jari, since 2011 at Karolinska Institutet, and later also in Niuvanniemi Hospital. Jari encouraged me to make this thesis and supervised me together with Professor Sirpa Hartikainen. I want to express to them my deepest thanks for this possibility.

In 2012 I started to work together with the MEDALZ group. This was a start for an extremely fruitful cooperation. Working with a bunch of talented younger PhD and other students kept me inspired, and taught me a lot about pharmacy, medical science and epidemiology. Special thanks to PhD Marjaana Koponen, who has been the guarantee of precision in many studies and contributed with huge effort to developing the drug package part of PRE2DUP. The persons supervising these students were Professor Sirpa Hartikainen, Adjunct Professor Heidi Taipale, Associate Professor Anna-Maija Tolppanen, Adjunct Professor Miia Tiihonen and Professor Riitta Ahonen. Heidi Taipale has been a vital part of improvement of PRE2DUP since 2012 and a key person in many studies in Finland and Sweden. It has been a joyful journey through the jungle of data, methods and challenges with her. PhD Pia Lavikainen has done an excellent work with statistics in many papers based on PRE2DUP processed data. PhD Sanna Torvinen-Kiiskinen gave me valuable comments to the draft of this thesis.

In projects at Karolinska Institutet we have used PRE2DUP with schizophrenia and bipolar patient data. From these projects I want to thank Professors Ellernor Mittendorfer-Rutz and Kristina Alexanderson from KI Insurance medicine for their support in this complicated task to implement such a system in a new environment. The cooperation with Jansen pharmaceuticals and Eli Lilly have led to world-class publications in Finland and Sweden. Cooperation with the Centre of Pharmacoepidemiology at KI has been fun, and especially I want to thank PhD Louise Wingård for her always positive attitude and Associate Professor Johan Reutfors for smooth cooperation. Also cooperating with Epid Research has been fruitful, and I want to name PhD Juha Mehtälä, PhD Fabian Hoti, Maila Majak and Pia Vattulainen.

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Helsinki, June 2019

Antti Tanskanen

List of the original publications

This dissertation is based on the following original publications:

I Tanskanen A, Taipale H, Koponen M, Tolppanen AM, Hartikainen S, Ahonen R and Tiihonen J. From prescription drug purchases to drug use periods – a second generation method (PRE2DUP). *BMC Medical Informatics and Decision Making, 15: 21, 2015*

II Taipale H*, Tanskanen A*, Tolppanen AM, Tiihonen J and Hartikainen S. Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. *Clinical Epidemiology, 8: 363-371, 2016.*

III Tanskanen A, Taipale H, Koponen M, Tolppanen AM, Hartikainen S, Ahonen R and Tiihonen J. Drug exposure in register-based research—An expert-opinion based evaluation of methods. *PLoS One 12(9):e0184070, 2017.*

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* Equal contributions

Contents

Abbreviations

AD	Alzheimer's disease
ADHD	Attention deficit–hyperactivity disorder
ANJA	Automated dose dispensing system
ATC	Anatomical Therapeutic Chemical
COV	Estimation of drug coverage
BZDR	Benzodiazepine and related drugs
DDD	Defined Daily Dose
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders
GeMS	The Geriatric Multidisciplinary Strategy for the Good Care of the Elderly Study
HILMO	Finnish Hospital Discharge register
ICD	International Classification of Diseases
INR	International Normalised Ratio
LAI	Long-acting injectable
NINCDS-	National Institute of Neurological and Communicative Disorders and Stroke
ADRDA	and the Alzheimer's disease and Related Disorders Association
NSAID	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PRE2DUP	Prescriptions to drug use periods
SII	Finnish Social Insurance Institution
SSRI	Selective serotonin reuptake inhibitor
VNR	The Nordic article number WHO World Health Organization
WTD	Waiting time distribution

1 Introduction

The need for a Prescription register was expressed almost 150 years ago, when chloroform, instead of iodine and water, was injected by mistake into a patient causing the patient's death; "A register of every prescription should be kept in the dispensary, and a copy of the prescription should be attached to every bottle, with name of the patient and the character of medicament clearly and legibly written." (Anon 1878). Already in those days, the need and content of prescription were formulated similar to today. The register should detail the six main aspects of a prescribed drug, 1) who prescribed it 2) to whom was it prescribed 3) when this was prescribed and dispensed 4) what is the drug (medicament) 5) how should the drug be used and 6) for which symptoms or illness has the drug been prescribed.

Although these six main dimensions of data have remained sacrosanct since the late 19th century, the way that the data content is formatted has changed over the years. Manual registers were kept by single pharmacies, in the early days, often medicines were produced in the pharmacy from raw materials. Thus, instead of products, the Prescription register contained recipes of delivered medicines. Patients and doctors were identified by names. Nowadays, the prescriber, the patient and the pharmacy which has dispensed the drug have identification codes in Nordic Prescription registers which contain records of dispensed drugs for the entire population (Figure 1) (Furu et al. 2009). In addition, each drug substance and their combinations have been categorized according to the Anatomic Therapeutic Classification (ATC) system (WHO 2016), and each drug package is coded with Nordic Article number (vnr-number) (VnrWiki 2018).

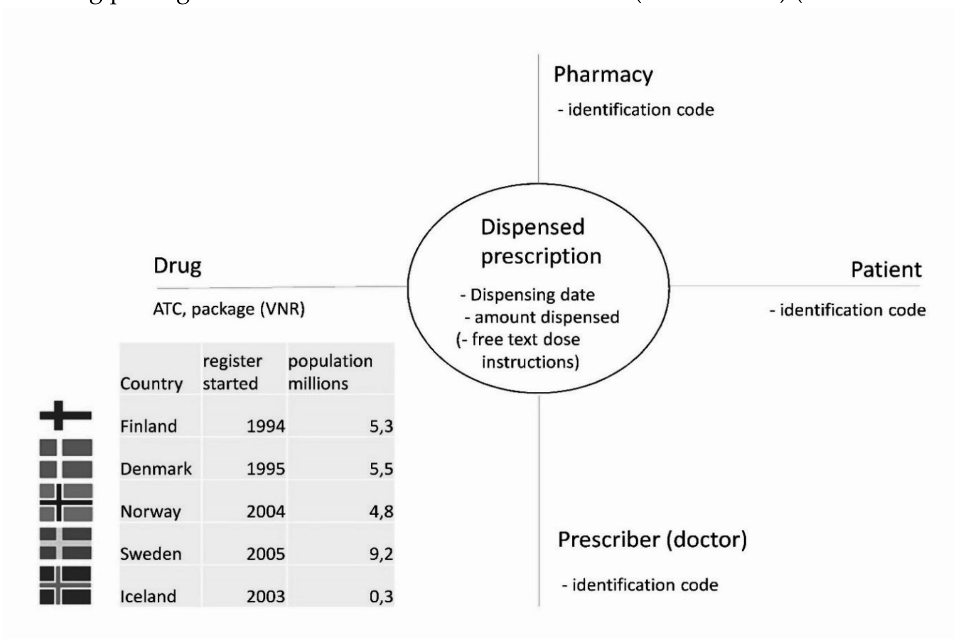

Figure 1. The contents of Nordic Prescription registers (Furu et al 2009). Free text dose instructions are not available in the Finnish and Danish registers. ATC=Anatomic Therapeutic Code, VNR= The Nordic article number.

The amount of dispensed drug is measured in Defined Daily Doses (DDDs), which are available for almost all drugs with an ATC code. One DDD refers to the average dose per day for adults when the drug is used for its main indication (WHO 2017). Instructions on how to use the drug and recording of dates of dispensing and prescribing have remained virtually unchanged over the last 100 years although many drugs are nowadays administrated in tablet form instead of as powders, liquids or creams. Free text dose instructions are stored in some of the Nordic registers. The indication of use or diagnosis is not commonly included in the Nordic Prescription registers although Norway is an exception in this respect (Furu et al. 2009).

Electronic dispensing registers have made it possible to conduct large population-based studies of drug use, real-world effectiveness, as well as identifying adverse drug effects. In clinical trials, usually one drug is compared to placebo or some other drug and persons eligible to take part in these kinds of trials are often young or middle-aged individuals with no or a restricted number of comorbidities (Kildemoes et al. 2011, Wettermark et al. 2013). In contrast, if one wishes to assess the real-world effectiveness of a drug, large register-based studies are needed without selection due to polypharmacy, comorbidities, age, and gender or socioeconomical status affecting the results. All individuals being treated with a certain drug or all persons treated in hospitals with a certain illness can be identified from registers. This is possible with Nordic registers since they encompass all residents who are identified by their unique personal identification code. This personal identification code enables reliable linkage between different data sources such as Prescription, Hospital Discharge, Mortality and Outpatient registers. The Prescription register data in Nordic countries contains purchases of drugs but it is not completely satisfactory for study designs which utilize data on drug use for a certain time period, nor to study the question of how long some drug has been used. Purchases recorded in Prescription register only show when and how much drug has been purchased; some registers also house details of dosing instructions. In the Finnish Prescription register, these instructions are not permanently stored. Prescription register data in the Nordic countries consists of details of all drugs that have been prescribed and dispensed except in Finland, where only reimbursed purchases are recorded (Kela 2014). If one wishes to assess exposure of a drug, some method is required to estimate how long each drug purchase has lasted. With this estimate, it is possible to construct drug use periods by joining subsequent time spans when they overlap or stretch to each other.

The aim of this thesis was to develop and describe a new alternative modelling method for estimating drug use periods. It was named PRE2DUP (From prescription to drug use periods). In the development and validation of the PRE2DUP method, data from the nationwide Medalz-2005 (Medication use and Alzheimer's disease) cohort were used (Tolppanen et al. 2013). The PRE2DUP method was validated against expert opinions and interviews in the GeMS study (The Geriatric Multidisciplinary Strategy for the Good Care of the Elderly). Subsequently, we compared previous published methods with expert opinion and compared their results with those obtained with PRE2DUP.

2 Review of literature

As a knowledge of drug purchases is usually unable to adequately answer most research questions, there is a need to convert purchases to duration of daily drug use with accurate and reliable methods (Stricker and Stijnen 2010). This literature review describes the methods which have been devised to resolve this problem.

In 2006, Andrade et al. reviewed the methods published between 1980 and 2004 to evaluate persistence and adherence of drug use from Prescription registers (Andrade et al. 2006). They identified 62 articles but they did not report if the methods, if any, could define time on drug. The review was United States of America weighted as 79% of studies were conducted with data from that country. Two literature reviews had originated from the Nordic countries, a mini-review evaluating 66 articles (Furu et al. 2009) and a larger review which assessed 515 articles of which 228 studies were about drug utilisation and 263 focused on effects (beneficial and adverse) of drug use (Wettermark et al. 2013).

Drug purchases are not suitable for answering research questions e.g. how long certain drugs are being used or if a person used the drug when an event with a specific outcome occurred. For this type of research, it is essential to be aware of the timing of the purchased drug use. Modelling of time on drugs or drug use periods is a complex task as many factors influence the actual drug use. Writing a prescription for a drug does not guarantee that the drug will be purchased. The failure to purchase of a prescription is referred to as primary non-adherence (Freccero et al. 2016). The incidence of primary non-adherence varies substantially between drug classes but it is also influenced by other factors (Pottegård et al. 2014). In Nordic Prescription registers only purchased prescriptions are recorded, and thus the exact rates of primary non-adherence remain largely unknown. Furthermore, one cannot be sure when the drug is actually consumed after it has been purchased and in addition, many drugs are prescribed to be taken as needed. A remarkable portion of purchased drugs are never used due low adherence, switching to other drugs, or treatment is stopped due to the disappearance of symptoms (Law et al. 2015, Freccero et al. 2016). If we assume that purchased drugs are used from the day they were purchased, how we can estimate the end of drug use of this purchase?

This literature review covers many of the studies published up to 2017. There are many studies in this field and they are rapidly increasing. Some use Prescription register data but have not defined drug use periods, and therefore these have been mainly omitted from this literature review. Nordic studies have been weighted in this selection because the novel method devised in this thesis has been implemented for Finnish and Swedish registers.

2.1 METHODS USED TO CREATE DRUG USE PERIODS

In this review, methods that calculates drug use periods have been divided into four main groups, namely fixed time, fixed dosage, prescribed dose (based on prescribed dose or days' supply) and data driven methods. The start date of drug use is commonly assumed to be the purchase date but the different methods calculate the end date of drug use for each purchase (Kreyenbuhl et al. 2011, Molero et al. 2015). When defining the end date for the entire drug use period, the estimated durations for each purchase are processed in chronological order to determine whether the purchase reaches the next prescription time, i.e. whether or not these two purchases belong to the same drug use period. If the calculated end date is at or after the next purchase, the drug use period continues with the following purchase. The start of use for the next purchase can be postponed in models that assume stockpiling of drugs at the time of purchase according to the person's purchase history of this particular drug (indicated by ATC code (WHO 2016))(Parker et al. 2015). A postponement of the next purchase may be best described with an example; let us assume that the drug should be taken as one tablet per day, and a person purchases 50 tablets at the first purchase event, and also 50 tablets also at the second purchase event occurring 40 days after the first purchase, then this person should have 10 tablets left at the time of the second purchase. In this example, the drug use is continuing without a break from the first to the second purchase. The extra 10 tablets left from the first purchase may be either disregarded or added in postponing the subsequent purchase (Arnet et al. 2014).

2.1.1 Fixed time windows

Fixed time window methods assume that drug use following each purchase last for a fixed time, for example 90 or 120 days. These methods do not take into account the purchased amount, any dosage or any other features of purchase except for the purchase date. These methods are usually based on the time interval that a single purchase can last at a maximum according to the dispensing regulations of the country or insurance system (Rikala et al. 2010). In Finland, the amount of drugs corresponding to a maximum of three months treatment can be dispensed (with some exceptions for expensive drugs), with the same rule being utilized in Sweden.

The length of time windows has varied between 28 days and 24 months in studies included in this literature review (Table 1). The purpose of the research may influence the length of time windows that are being used. Some studies aim to describe the prevalence of drug use in a population, and they often use long time windows to capture all users. A one year time window has been mostly used to describe the prevalence of drug use. Long fixed time windows should be interpreted as markers for possible drug use such as in a study of potential drug interactions where purchases during 15 months were classified as being potentially temporally overlapping drug treatments (Åstrand et al. 2006). When the aim has been to study current use of drugs, shorter and more precise time windows have been applied (Table 1).

The most commonly used fixed time window has been the "one year window" (Table 1) (Helin-Salmivaara et al. 2003, Hovstadius et al. 2010, Johnson et al. 2012, Øymar et al. 2015, Radholm et al. 2015, Frisk et al. 2016, Patel et al. 2016, Wändell et al. 2016). Six month time windows have been utilized in determining continuous use, and in some studies, there was an additional requirement that persons had to have at least two purchases during this time window (Molero et al. 2015, Khoza et al. 2012). One study defined persons having a single purchase during six months as irregular users, and those having two or more purchases as regular users (Allonen et al. 2012). The six months' fixed time window was utilized only between purchases, i.e. not after the last purchase, in a study examining potential links between attention deficit–hyperactivity disorder (ADHD) medication and criminality (Lichtenstein et al. 2012). Four months fixed windows have been common in studies conducted in countries in which a maximum of three months drug supply in one purchase is allowed. This one extra month accounts for some irregularity of purchases and allows regular use of package sizes which cover somewhat more than 90 days (Mannheimer et al. 2010, Pottegård et al. 2013, Holm et al. 2014, Wastesson et al. 2015). In the study of Pottegård and Hallas (2013) the follow-up times varied but they required that a continuous user had purchased at least 500 DDDs during the follow-up time to be considered as a continuous user, and each dispensing was assumed to last 15 weeks. When follow-up time is not fixed, this type of requirement leads to varying dose requirements between study subjects, as it may mean 500 DDDs during one year or during five years. Three months and shorter time windows have been used in countries where drugs are dispensed usually for one month at a time (Ward et al. 2006, Acri et al. 2010, Hershman et al. 2010, Le Couteur et al. 2011, Weitoft et al. 2014, Imfeld et al. 2015, Driessen et al. 2015, Zoega et al. 2015).

Table 1. Summary of studies utilizing fixed time window methods.

Study	Country	Drug group	Outcome	Number of persons	Time window, months	Year of data
Ward et al. 2006	Canada	risperidone, olanzapine, or quetiapine	compliance	45,045	1	1999-2004
Acri et al. 2010	US	highly active antiretroviral therapy	adherence	117	1-3	2004-2006
Driessen et al. 2015	UK	Glucagon-like peptide-1 receptor agonists	fracture	216,816	3	2007-2012
Mannheimer et al. 2010	Sweden	CYP2D6 drugs, SSRI	drug interactions	7 ,713,945	4	2008
Holm et al. 2014	Sweden	all	interactions	9,340,682	4	2010
Pottegård and Hallas 2013	Denmark	several	modelling	1,344,089	4	2007-2010
Wastesson et al. 2015	Sweden	antipsychotics	prevalence	9,000,000	4	2005
Allonen et al. 2012	Finland	statins	death	1,099	6	2005-2009
Khoza et al. 2012	US	antidepressants, benzodiazepines	type 2 diabetes	44,715	6	2002-2009
Lichtenstein et al. 2012	Sweden	ADHD	criminality	25,656	6	2006-2009
Molero et al. 2015	Sweden	SSRI	violent crime	856,493	6	2006-2009
Helin-Salmivaara et al. 2003	Finland	psychotropics	prevalence	500,000	12	2000
Johnson et al. 2012	US	antihypertensives	prevalence	377,838	12	2000
Øymar et al. 2015	Norway	inhaled corticosteroids	prevalence	117,008	12	2004
Patel et al. 2016	Sweden	all	cancer	9,014,975	12	2005-2010
Hovstadius et al. 2010	Sweden	all	prevalence	2,227,717	12	2006
Frisk et al. 2016	Sweden	triptans + co-medication	concomitant use	4,759	12	2014
Pottegård et al. 2013	Denmark	BZDR	cancer	1,344,089	12-60	2002-2009
Åstrand et al. 2006	Sweden	all	drug drug interaction	8,214	15	2004
Radholm et al. 2015	Sweden	antidiabetic and antidepressant	Myocardial infarction	4,083,719	24	2005-2010

SSRI: selective serotonin reuptake inhibitor, BZDR: benzodiazepine and related drugs, ADHD drugs, CYP2D6 dependent drugs.

2.1.2 Fixed dosage

Fixed dosage methods use a fixed dose assumption per fixed time, either in DDDs or units such as tablets, with the most frequent assumption being that one unit is used per day. For some drugs, the actual dose used may only occasionally be one DDD per day, in fact there is a huge variation between drug substances (Nielsen et al. 2017) and patient populations. The use of one tablet per day models reflect the fact that some drugs such as statins are most often administered with this regimen (Romppainen et al. 2014). Figure 2 presents two modelling examples with fixed dose of one tablet and one DDD per day. Dispensing A includes 100 tablets, corresponding to 100 DDDs, and dispensing B contains 40 tablets corresponding to 20 DDDs. These two modelling methods result in very different estimates of duration of use, depending on how many DDDs or fractions of one DDD each tablet contains. The fixed dosage models are often adjusted with so-called grace periods, which are time spans that are allowed between purchases as extra time from the end of the duration calculated based on the purchased amount. This grace period may or may not be added to the end of drug use periods (L H Nielsen et al. 2008). In addition, some variants of fixed time methods multiply estimated time with some factor greater than one, to allow for less than perfect adherence.

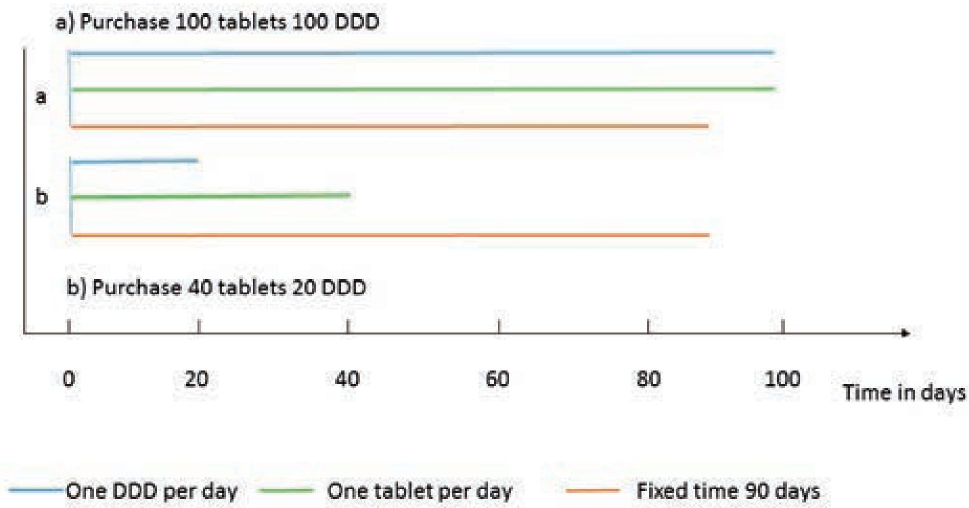

Figure 2. Example of dispensing of two different drugs and how different fixed methods will estimate the duration of their use.

2.1.3 Fixed dosage with tablets

Fixed tablet methods assume that a drug is used one tablet or some other fixed number of tablets or other units per day. This method can be used for drugs that are administered in tablet or capsule form, but not easily for drugs that are also available as injections, creams, liquids or transdermal patches. This method has frequently been used for statins (Larsen et al. 2002, Helin-Salmivaara et al. 2008, Helin-Salmivaara et al. 2009, Aarnio et al. 2014, Citarella et al. 2014, Aarnio et al. 2015, Korhonen et al. 2016) (Table 2), which are drugs that are often prescribed as one tablet per day (Romppainen et al. 2014). Cittarella et al. (2014) used a mixture of fixed tablets and fixed time windows by using one tablet per day and 90 days' minimum duration. Aarnio et al. (2014, 2015) supposed that new purchases would be started when the previous supply would be finished according to one tablet per day, i.e. stockpiling postponed the use of purchased tablets. Studies focusing on adherence calculate the deviance from perfect adherence, i.e. that one tablet is actually being taken every day. Schulz et al. (2016) used the package summary information to determine the recommended daily dose (in tablets) for each package of antihypertensive drugs. This approach did not account for personal dosage but tailored the fixed dosage assumption according to the intended use of each drug substance. Rosholm et al. (2001) compared different antidepressants and duration of drug use applying the assumption of one tablet per day with a relative grace period of one third of tablets dispensed. In persistence studies, the grace periods utilized for statins have varied between 90 and 270 days.

Table 2. Summary of example studies utilizing fixed tablet methods.

Study	Country	Drug group	Outcome	Number of persons	Tablets per day	Grace period	Follow-up
Rosholm et al. 2001	Denmark	antidepressants	duration	37,598	1	33%	1992-1997
Larsen et al. 2002	Denmark	statins	compliance	3,623	1	30	1993-1998
Citarella et al. 2014	Sweden	statins	persistence	86,002	1	0[a]	2006-2007
Helin-Salmivaara et al. 2008	Finland	statins	persistence	18,072	1	270	1995-2005
Helin-Salmivaara et al. 2009	Finland	statins	persistence	562,598	1	270	1995-2005
Aarnio et al. 2014	Finland	statins	adherence	247,051	1	0	2000-2004
Aarnio et al. 2015	Finland	statins	cost-effectiveness	247,051	1	0	2004
Korhonen et al. 2016	Finland	statins	adherence	1,924	1	0	2008-2010
Schulz et al. 2016	Germany	antihypertensives	adherence and persistence	255,500	per package	0	2004-2007

a) Minimum duration of 90 days

2.1.4 Fixed dosage with DDD

Fixed dosage methods assuming that one DDD is the daily intake, have been used fairly frequently in the Nordic studies (Table 3). One DDD per day without any grace period has been used (Bakken et al. 2013, Bakken et al. 2014, Abrahamsen et al. 2016, Rauma et al. 2016) although it often splits the drug use even after a small irregularity of use or if the dose has been lower than the nominal 1 DDD per day dose. With DDD methods, different grace periods have been applied e.g. 30 days (Haukka et al. 2009), 50 days (Sjösten et al. 2013), 90 days (Robinson et al. 2015), 180 days (Østergaard et al. 2012) or some proportional grace periods such as adding 15% to the calculated duration (Suokas et al. 2013). The use of very long grace periods in practise can lead to the preconception that the patient is receiving a lower dose and thus, violates the primary assumption of one DDD per day. In addition to simple grace periods expressed as the number of days, previous studies have also utilized more complex models, such as multiplying purchased amount of DDDs by 1.1 and adding 15 days grace period (Haukka et al. 2007), or multiplied by 1.15 and 14 days grace period (Tiihonen et al. 2012). Some studies have applied complicated definitions to ensure drug use over some time period. The drug use over one year defined by Jennum et al required at least three purchases and 60% coverage of the year, calculated by one DDD per day which results in at least 219 DDDs in one year (Jennum et al. 2015).

Table 3. Summary of studies utilizing fixed assumption in DDDs.

Study	Country	Drug group	Outcome	Number of persons	DDD per day	Grace period	Follow-up
Bakken et al. 2013	Norway	antidepressants	hip fracture	906,422	1	0	2004-2010
Abrahamsen et al. 2016	Denmark	alendronate	fractures	63,774	1	0	1996-2007
Rauma et al. 2016	Finland	antidepressant	bone mineral density	1,988	1	0	1999-2004
Haukka et al. 2009	Finland	antipsychotic	mortality	258,417	1	30	1999-2003
Sjösten et al. 2013	Finland	ATC: C02, C03, C07-C09[a]	adherence	3,211	1	50	1994-2005
Robinson et al. 2015	Sweden	finasteride and dutasteride	hip fracture	267,154	1	90	2006-2008
Østergaard et al. 2012	Denmark	antiplatelet drugs	persistence	503	1	180	1999-2001
Suokas et al. 2013	Finland	antipsychotics	polypharmacy	16,083	1	15%	1996-2007
Haukka et al. 2007	Finland	antipsychotics	validation	905	1 (0.91)[b]	15	1996-2005
Tiihonen et al. 2012	Finland	antipsychotics, antidepressants, benzodiazepines	polypharmacy	2,588	1 (0.87)[c]	14	2000-2007
Jennum et al. 2015	Denmark	psychotropics	mortality	71,107	1	40% of each year	1996-2010

a) C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin–angiotensin system)

b) the length was multiplied with 1.1

c) the length was multiplied with 1.15

A fixed duration has been defined for different long acting injectable (LAI) antipsychotics in a study investigating discontinuation (Decuypere et al. 2017). Different LAI packages contain fixed amounts of injections and they have rather fixed administration intervals in which the nominal duration of each purchase can be calculated. The base scenario adds a 28 days grace period; in the sensitivity analysis, 3 to 390 days were added to test how the grace periods affected discontinuation. This method is a combination of fixed time and product-based dosage assumption.

2.1.5 Free text dosing instructions

This group of methods utilizes prescribed dose (such as dose written in the free text field of the prescription) together with dispensed amount of drug in the calculation of the duration of use for each purchase (Shah and Martinez 2006). Days' supply resembles prescribed dose as it is a numerical expression of the duration of purchased drugs based on prescribed dose (Parker et al. 2015). In the Nordic countries, except in Finland free text dosing instructions are available in

Prescription registers (Furu et al. 2009). If one wishes to exploit these dosing instructions, then they have to be converted into some numerical format, for example into the number of tablets that are prescribed to be taken each day. However, the written dose texts are not always unambiguous as there may not be a single dose value but the text may refer to some variation (e.g. 1-2 tablets per day) and thus, converting may result in minimum, maximum and median dose. The dose text may also contain phrases like "as needed", "according symptoms" or "according to separate instructions". Instructions may also contain starting doses which may change (increase) gradually or the patient may adjust the dose according to the severity of symptoms (Shah and Martinez 2006).

Translation of dose text into prescribed dose has been frequently used in Sweden by Fastbom et al. who have developed a method to read and convert free text into numerical dose (Johnell et al. 2007). The method has no fixed assumptions of dose and is capable to handle different ways of administration. The method is bound to 'intention-to-treat', i.e. the dosage that prescriber meant at the time when prescription was written. To handle irregular purchasing behaviour and lower adherence, a grace period can be applied to the method (Qvarnström et al. 2013, Termorshuizen et al. 2016a). This method has been used for various drugs in Sweden (Johnell et al. 2007, Johnell and Fastbom 2009, Johnell and Fastbom 2011, Johnell and Fastbom 2012, Qvarnström et al. 2013, Wallerstedt et al. 2013, Haasum et al. 2016) and also in the Netherlands (Termorshuizen et al. 2016a, Termorshuizen et al. 2016b). Some insurance databases such as US Veterans Affairs Medical Center also contain dose text (Campione et al. 2005).

2.1.6 Days' supply

Some databases of certain insurance schemes include "days' supply", referring to the number of days for which drugs were dispensed from the pharmacy according to dosing instructions and as stated by the dispensing pharmacy. The coverage of his information may be incomplete (Lum et al. 2017). Burden et al. (2015) found that days' supply data needed to be corrected before it could be exploited in adherence studies**.** Cooper et al. (2009) stated that only oral drugs may have accurate days' supply values, instead for inhalations and other drug forms, the measure could be a compromise derived from complex dose regimes and thus unreliable. Burden et al. (2015) added 30 grace period to the days' supply duration and conducted a secondary analysis with 60 days and 50% grace periods.

When compared to DDD methods, on average the days' supply method gives equal or longer duration for a purchase, probably because some medications are used at a dose less than one DDD per day (Sinnott et al. 2016). The days' supply method is frequently used in the US (Reardon et al. 2010**,** Hawkins et al. 2012**,** Pfeiffer et al. 2012**,** Spence et al. 2015**,** Bushnell et al. 2016) and Canada (Kephart et al. 1995**,** Moisan and Grégoire 2010) as insurance databases record this measure.

2.1.7 Data driven methods

Data driven methods use dispensing data to determine the duration for each drug purchase and do not apply fixed assumptions (Pottegård and Hallas 2013). In addition other information such as the size of the drug package, drug class or route of administration can be exploited (Meid and Haefeli 2017). One method is to calculate average dosage of each drug and each person using the time between the first and last purchase and the dispensed amount of drugs excluding last purchase. If timing of the first purchase is denoted with t_1 and the last with t_k and purchased amounts in DDDs d_1 .. d_k, then average is $\sum_{i=1}^{k-1} d_i/(t_k - t_1)$, where the amount of last purchase is omitted (Strandberg et al. 2016). This method generates an average dose that is calculated from the whole drug use history; it does not take into account changes of dosage. The dose is then applied to calculate the duration for each purchase based on purchased amount of drug.

A retrospective method avoids the problem that future changes should not affect the current dosage estimate (Schjerning Olsen et al. 2015). In a study investigating the association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular events, cumulative purchased amount of NSAIDs and elapsed time from first purchase were utilized to produce a local dose estimate which was used for estimating the duration of the current purchase. Gislasson et al. (2006) used sliding averages with three subsequent purchases to determine local dose and thus, allowed dose changes when calculating the duration of each purchase (Gislason et al. 2006). They allowed for stockpiling by adding excess tablets left over from the previous purchase to the next purchase. The estimation of drug coverage (COV) method uses dose estimates up to the current purchase by dividing purchased amount with time (Meid et al. 2016). This method was compared with fixed tablet and DDD methods and it produced more accurate estimates of duration than fixed methods; especially with drugs that have large variations in dosage. They further developed the COV method by incorporating simulated covariates to describe the patients' state and to estimate dose and duration of single purchases (Meid and Haefeli 2017). This approach adds individual tailoring to the dose estimate and can reduce bias at population level.

The work by Meid et al. was inspired by that of Støvring et al. on the reverse waiting time distribution (WTD), i.e. the time from the last dispensing to the previous dispensing in a time window (Støvring et al. 2016, Støvring et al. 2017a, Støvring et al. 2017b). This method has been designed to determine the probability of drug use at any time point after dispensing. It does not directly generate drug use periods but instead it provides probabilities of drug use over time after each dispensing. These probabilities start to decrease after the dispensing date and thus, the results are not expressed as a duration of use but some probability for each day. Persons visiting pharmacies less frequently and those that have a lower dosage than average users are classified as restarting their drug use between every dispensing when fixed cut-offs of probability are used and have close to a zero probability when they visit the pharmacy next time. WTD is a process where the inter-arrival density from a given time point to the next drug purchase is calculated forward in time. This distribution is dependent on the selection of the starting point in time; in the modelling of the continuous time on the drug, the timing of (previous) purchase is applied (Hallas 2005, Pottegård and Hallas 2013). Then a percentile of cumulative density function is used as a cut-off value for drug purchase redemptions which are defined to belong to a continuous drug use. Longer periods than the cut off value are assumed to represent a restarting of drug use. Drug use periods can be constructed by setting a threshold value for waiting time percentiles (Laugesen et al. 2017).

2.2 VALIDATION OF REGISTER-BASED METHODS

Home inventories or interviews about current medication use are often considered as golden standards when comparing results from register-based estimates of drug use (Rikala 2012). A classic study from the Netherlands compared current drug use defined in the home inventory of 115 older persons with drug use modelled from dispensing records (Lau et al. 1997). They compared three register-based modelling methods, one based on legend duration calculated from free text dosing instructions and dispensed amount of drugs, with others were fixed time window methods of 30 and 90 days. The legend duration method produced a slight underestimation of the number of drugs used when compared to the home inventory. A fixed time window of 90 days produced overestimates, but the 30 days' time window underestimated the values as it detected only half of the drugs identified in the home inventory.

Caskie et al. (2006) compared drug use as defined in home inventory as a part of the Seattle longitudinal study with drug use based on a measure of a days' supply recorded in pharmacy records. The agreement between home inventory and dispensing data was on average 60% for those who received drugs; dispensing data underestimated drug use at the time of inventory. The study of Løkkegaard et al. (2004) from Denmark and that of Reijneveld and Stronks (2001) from the Netherlands investigated the concordance between self-reported drug use and register-based purchase histories, without actually modelling the drug use. In the study of Løkkegaard et al. (2004), hormone replacement therapy was reported accurately when this was compared with register-based dispensing data, with sensitivity of 75-80% and specifity 98% in years 1993 and 1999 (Løkkegaard et al. 2004). Reijneveld et al. examined social factors affecting self-reporting of drug use among males and compared them to drug dispensing data (Reijneveld and Stronks, 2001). They found that the average prevalence of drug use was not dependent on income, education level or occupational status. However, Dutch-born persons had slightly higher concordance between self-reported and register based drug use prevalence than those individuals born abroad (Reijneveld 2000).

A Danish study compared self-reported drug use from the Danish health and morbidity survey 2000 with register data, among 16 688 persons aged 16 or over (M W Nielsen et al. 2008). In this work, drug consumption was assessed by home interview with two methods being used to generate drug use periods from dispensing data: 1) assuming use of one DDD per day with a 10% grace period and 2) 90 days fixed time window. Good or very good (Cohen's kappa ≥ 0.60) agreement between the interview-based data was found for seven of the 17 studied drugs with the DDD method, and for eight drugs with the 90 days' time window. In this study, an additional lower dose model assuming use of 1/3 DDDs per day was tested for antipsychotic drugs. The results differed remarkably from one DDD per day model, kappa values were 0.54 for one DDD but somewhat better i.e. 0.69 for 1/3 DDDs per day. This implies that antipsychotics were often being used with at a considerably lower dose than one DDD per day among the study population.

A study from Ireland compared self-reported drug use gathered with home interviews and purchases in the past six months as a marker for current drug use among persons aged on average 69 years (Richardson et al. 2013). They observed a good agreement (kappa > 0.6) between these data sources for 15 of the studied 19 drug groups. In the study of Haukka et al. (2007) self-reported psychotropic drug use of 905 patients with schizophrenia was compared with modelled drug use from Prescription register data in Finland (Haukka et al. 2007). They used two register-based estimates for drug use, any purchases of each drug within 6 months and one DDD per day, supplemented with 10% extra time, and 15 days grace period (1.1* DDD+15). They found the highest overall concordance was for lithium (kappa 0.96) with both methods. For other psychotropic drugs, there was a better agreement when the estimates were made for at least one purchase during the last six months than for DDD model based estimates.

Romppainen et al. (2014) studied prescribed statin doses derived from free text fields in prescriptions and examined whether these has been prescribed as one tablet or DDD per day in Finland. They found that 95.8% of statin prescriptions were prescribed as one tablet per day but only 9.5% with one DDD per day. This example of statin dosing shows that some drugs may be prescribed with a fixed amount of tablets per time such that different doses are achieved by prescribing different strengths of tablets, not with different amounts of tablets.

Rikala et al. (2010) studied drug use among older Finns in Kuopio, in a study of random sample of 1000 persons aged 75 and over in 2004. This GeMS intervention study included medication assessment by conducting a comprehensive interview four times annually, 2004-2007. Psychotropic use from interview was compared with register-based drug use generated with fixed 4, 6 and 12-months windows. Psychotropics were grouped into three categories, namely antipsychotics, benzodiazepines and antidepressants. In addition to kappa values sensitivity (i.e. the proportion of register-based users of users according interview) and specificity (proportion of register-based non-users of users according to interview) values were calculated. The highest kappa values were found for the 12 months' window with agreement differing significantly between drug classes. The results showed that the trade-off between sensitivity and specificity favoured longer grace periods due to the large proportion of non-users of each of the three studied groups.

2.3 COMPARISON OF MODELLING RESULTS BETWEEN METHODS

Van Wijk et al. (2006) compared how different methods affected the proportion of persistent users of long-term cardiovascular drug treatment. These investigators used prescribed dose and purchased amount to calculate the duration of drug purchase and added grace periods of varying lengths ranging from 9 to 365 days. Secondly, they used prescribed dose and the amount of dispensed drugs (in DDDs) to calculate the duration of use. This duration was multiplied with a factor varying from 0.1 to 4 (relative grace period) to test how persistence estimates would vary according to this factor. In the third group of methods, shorter duration of the two previous methods was examined in a "combined method". They found that the proportion of persistent users varied by fourfold depending on the length of the fixed grace period (19.7-86.4%), by three-fold with a relative grace period (27.9-90.2%) and similarly (19.7–86.4%) with the combined method. These differences illustrate how the results are dependent on which method is applied to generate the drug use periods.

Meid et al. (2016) compared one DDD and one tablet per day with their own method, COV which is based on long term average of personal dose. They used German health insurance data on antithrombotics and NSAIDs and then simulated the durations of use produced with Observational Medical Dataset Simulator that exploits the Monte Carlo simulator (Murray et al. 2011). They found the average dose to be less biased and to have a smaller error with the COV method as compared to the fixed one DDD or tablet methods.

Gardarsdottir et al. (2010) investigated the effect of changing the length of fixed proportional gap (grace period) to the estimated median duration of antidepressant treatment. Each grace period was added to the end of the legend duration as calculated from dispensed units and dosing instructions. They studied new users of serotonin reuptake inhibitors (SSRI) in 2001 and showed that by increasing the grace period the estimated durations of drug use periods were increased up to 150 days, or by 300 percent. No increases occurred from 150 to 180 days, which means that all redispensings in continuous use took place within five months of the calculated end of drug use.

2.4 CURRENT STATUS OF METHODS

The development of new methods has been slow, with most methods applying a "one fixed method fits all" philosophy, i.e. models force every individual and drug to adhere to the same dose regimen or duration (Tanskanen et al. 2014). Methods based on dose text or data driven are the only major exception to this approach. The validation of different methods at an individual level has been mainly lacking and thus it is difficult to make a comparison of the validity of these methods.

3 Aims of the study

The overall aim of this thesis was to develop a novel method to generate drug use periods from prescription data and then to assess its validity and performance.

The specific aims were to:

1. Develop and describe a new modelling method - "PRE2DUP",

2. Compare the agreement between the PRE2DUP method and drug use reported in interview,

3. Compare the results of the PRE2DUP method with previously used methods by expert-opinion.

4 Materials and methods

4.1 STUDY POPULATION

4.1.1 Medalz-2005 cohort

The Medalz-2005 cohort consisted of 28 093 community-dwelling persons with clinically verified diagnoses of Alzheimer's disease (AD) on December 31, 2005 in Finland. The AD diagnosis were from the years 1999-2005 and the persons were alive on December 31th, 2005 (Tolppanen et al. 2013). Persons with AD were identified as having special reimbursement for AD, as recorded in the Special Reimbursement register.

Data for this cohort has been collected from various sources; Prescription register, Hospital Discharge register (Hilmo), Special reimbursement register and Register of care at social institutions. A special reimbursement status for AD medications is granted by the Finnish Social Insurance Institution (SII) if the predefined diagnostic criteria for AD are fulfilled (Tolppanen et al. 2013). The diagnostic criteria include clinical examination, exclusion of alternative causes, computed tomography or magnetic resonance imaging scan and confirmation of diagnoses by geriatrician or neurologist. Diagnoses of AD are made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association NINCDS-ADRDA (McKhann et al. 1984) and DSM-IV (American Psychiatric Association 1994) criteria for AD. The data was de-identified before submission to the research team and therefore no ethics committee approval was required.

4.1.2 GeMS cohort

The GeMS Study was a randomized comparative study of individuals aged ≥75 years living in city of Kuopio (Lampela et al. 2007, Rikala et al. 2010, Taipale et al. 2011). For the original cohort, 1000 persons were invited to participate. Of these, 781 participated in the study whereas 162 refused, two individuals moved away and 55 individuals died before the baseline examination in 2004. In the third interview conducted in 2006, 588 persons participated of which 19 individuals had no drug purchases and were excluded from Study II as it was designed to compare drug use between the information gathered in the interview and register-based data. The final sample for Study II was 569 persons. In the GeMS study participants were divided into two groups, intervention (n=500) and control (n=500). The intervention group participated in three comprehensive geriatric assessments, at baseline 2004, and at one and two years in 2005 and 2006, respectively.

All participants were subjected to a baseline examination in 2004 and follow-up interviews in 2005, 2006 and 2007. In the interview conducted by a study nurse, participants were asked to report what drugs they had used during last two weeks, including over-the-counter (OTC) drugs. They were encouraged to bring all their medication containers and prescriptions to the interview. The study nurse in charge had access to their medical records and specifically asked the participant about their use of drugs that were not reported by the participant but had been prescribed or recorded in their medical files. Drugs were categorized as regular and "as needed" drugs based on reported use.

In Study II, the year 2006 was selected since a fixed co-payment was removed at the beginning of the same year and thus, inexpensive drugs were also included in register data. Written informed consent was obtained from the participants to obtain and link their data to the Prescription register. This study was approved by the Research Ethics Committee of the Hospital District of Northern Savo.

In 2006, the mean age of the participants was 82.4 years; 69% (n=391) of them were women. Almost all of them, 87%, (N=492), had been diagnosed with a cardiovascular disease and every sixth person suffered from dementia (17%, N=96).

4.2 REGISTER DATA SOURCES

4.2.1 Prescription register data

The Prescription register data of the Medalz-2005 cohort used in this study covered the years 2002-2009 (3 828 292 purchases) in Study I. In Study III, the Prescription register data originated from the years 1995 to 2009 (6 115 724 purchases). The difference in the follow-up in Studies I and III is due to the fact that data covering years 1995-2001 were received and added afterwards. In Study II, prescriptions for the GeMS study cohort covered the years 2002-2007 (78 185 purchases).

Variables in the Prescription register data utilized in this study were de-identifieded id, purchase date, ATC code, amount of packages, amount of dispensed DDDs, ANJA code (whether drug was dispensed with an automated dose dispensing system) and the vnr-number. The vnr-number (VnrWiki 2018) is a code that makes it possible to identify at the package level the drug substance, strength, the number of units, dosage form and the manufacturer of the drug. In addition, data on dispensed drug product, including product name, strength, package size and drug form was utilized in defining vnr-parameters as described in section 5.1.3.

4.2.2 Hospital Discharge register data

The Hospital Discharge register includes data on all periods of hospital stays in Finnish hospitals, with discharge diagnoses recorded according to the International Classification of the Diseases (ICD) codes (Sund 2012). Variables of Hospital Discharge data included in these studies were de-identified id, start and end dates of hospital stays.

In the Medalz-2005 cohort the Hospital Discharge data was available from 1972-2009. The number of hospital care periods was high in this cohort as the rate of hospital admissions in 2002 was 0.7 hospital visits per person-year, in 2005 it was slightly elevated i.e. 1.3, and this remained the case in 2008 1.2 visits per person-year. The average length of hospital stays increased after the diagnoses of Alzheimer’s disease and with aging and thus, in 2002 there were 15 hospital days per person-year, this increased to 58 in 2005 and further to 67 hospital days in 2008. Hospital Discharge data was not available for the GeMS study.

4.3 PRE2DUP METHOD (I)

4.3.1 Overview of principles utilized in the method development

As shown in chapter 2, several methods have been used to convert drug purchases to time on drug, i.e. drug use periods. This conversion must be conducted when investigating research questions where timing and/ or duration of drug use are needed.

’From Prescription drug purchase to Drug Use Periods’ (PRE2DUP) method was developed to construct periods when a drug was being used continuously. The idea was to simulate purchasing behaviour by calculating the duration of drug supply for each purchasing event and step by step to decide whether the purchasing event was a part of 1) a continuous ongoing drug use; 2) the end of such a period; or 3) if it formed a drug use period consisting of only one purchase.

To make a decision if a drug was being used continuously between two subsequent purchases i.e. whether or not these two purchases belonged to the same drug use period, one needs to have information on how much drug was purchased (recorded in the register) and how much was being used per day, week or some other time frame. In Finland, the last of these options is only in the form of free text dosing instructions and those are not stored in the Prescription register data and would not offer a straightforward solution as dose text may allow variation in dose (or may even completely lack dosing instructions). To solve the problem caused by the lack of dosing instructions, a few observations were made. Nowadays, tablets are the most commonly used dosage form and the number of units (tablets) is recorded for each purchase. However, our goal was to develop a universal method which would be applicable for all drugs and drug forms. Furthermore, it is possible to define upper and lower limits of dosage for each drug used for therapeutic purposes with the aid of the existing literature.

In addition, a refill time distribution could be calculated for each drug package to observe the range of variation between dispensings (refills) which would also describe variations in dose. In practise, the refill distribution may reveal that a drug package has more than one common refill length. As shown in Figure 3A, a package may have two common refill lengths, representing use of 1 DDD (100 tablets/ 100 DDDs purchased every 100 days) and 2 DDDs (the same amount every 50 days) per day. However, sometimes it is difficult to estimate how a drug is being used based on the distribution of refill times (Figure 3B). In addition to the most common refill length of 30 days (corresponding to the use of one tablet per day, 0.5 DDDs per day), there are also smaller peaks at 14 and 21 days, corresponding to 2 and 1.5 tablets per day and also a long tail of longer refill lengths. In our example of the antidepressant drug, mirtazapine, longer refill lengths may represent its low dose off-label use for insomnia (Kamphuis et al. 2015). Thus, with respect to mirtazapine use in this study population, the assumption of one DDD per day would clearly not be appropriate.

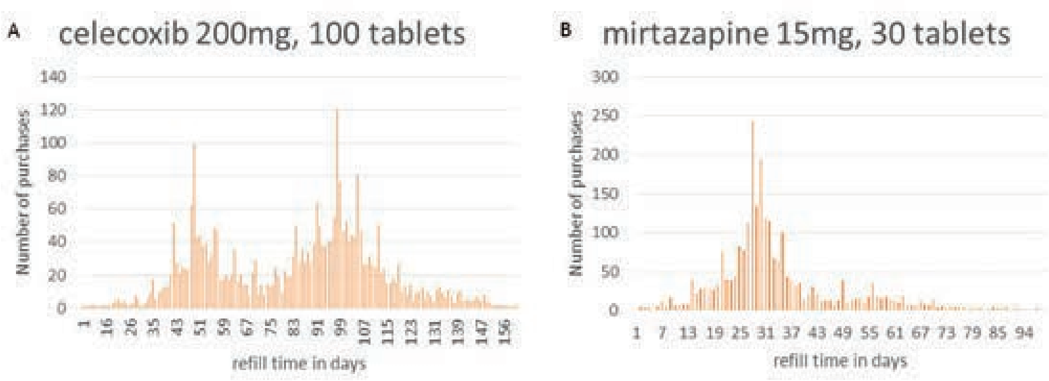

Figure 3. Refill time distribution of a package of A) celecoxib 200mg 100 tablets (representing 100 DDDs) B) mirtazapine 15 mg 30 tablets (representing 15 DDDs), in the Medalz-2005 data.

The dose used by an individual may change in time as described with examples in Tanskanen et al. (2014). For this reason, sliding average of dose was chosen as the basis of the calculation. A sliding average smoothens the random variation introduced by the random irregularity of visits to the pharmacy or the intentional difference of refill times caused by planned stockpiling of drugs. The decreased variation of calculated local dose makes the decision process less dependent on random noise. When the observation time of drug purchases lasts over several years, the spans between subsequent purchases can be extensive. These pauses in drug use can be as long as years and in such cases, it is clear that these purchases do not belong to the same uninterrupted drug use. If sliding averages were calculated over these very long time intervals, this would result in extremely low dose estimates that would be unrealistic and false.

National regulations on dispensing and reimbursement of drugs also have to be incorporated into the modelling method. In Finland, drugs can be prescribed for one year (from the beginning of 2017, for two years for most drugs) with one prescription but drugs can be dispensed with reimbursement from the pharmacy at one time not more than three months of treatment. If a one year prescription is dispensed in three month supplies, the prescription contains four dispensing. With such a prescription, after a random visit to the pharmacy the prescription contains (0+1+2+3)/4=1.5 dispensings remaining. As there are prescriptions including less than four dispensing, the expected number of remaining dispensing will be less than that, but more than zero. In addition, reimbursement regulations limit drug dispensing; for example they state that the drug can only be re-dispensed when drugs from a previous purchase will have been mostly been used according to dosing instructions. Some specific drugs have even more stringent restrictions for timing and allowed amount to be dispensed, and any good modelling method should take this into account.

The timing of visits to the pharmacy may depend on the stock of drugs that a patient has at home. This is not recorded in the registers but can be crudely estimated from previous purchases (Aarnio et al. 2014). A patient may have a large stock of one drug but the supply of some other drug is exhausted. At the visit to pharmacy, the patient may wish to collect all of his/her prescribed drugs at the same time (especially in the countryside where it may be a distance to the nearest pharmacy). Furthermore, events in the near future may affect purchasing behaviour. Holidays and traveling may bring forward pharmacy visits and administrative rules may have similar impact, for example people tend to buy more drugs (and stockpile those) than they actually need once they have exceeded the annual limit for self-co-payment (Skipper 2012). Patients may also have individual styles in their purchasing behaviour. Some people may always visit the pharmacy when there is a certain amount of drugs left at home (for example, one blister of ten tablets) whereas some persons may go to the pharmacy in a rather haphazard manner. In addition, changes in the drug user's financial situation may affect when and how much drugs are purchased from the pharmacy.

Due to these special features in drug purchasing behaviour, an algorithm was incorporated into the modelling method that investigated possible stockpiling and tested how this affected continuity decisions for drug use. In addition, a measure to calculate the personal regularity of purchases for each drug and each person was designed to allow personal drug-wise degree of irregularity for purchases.

Drugs purchased from the pharmacy are used only in outpatient settings. During stays in hospitals and public nursing homes, drugs are provided by the care unit. This means that when calculating time on the drug, the estimate of how long a drug supply will last also depends on how many days the patient spent in hospital in the near future after the drug purchase. Clearly, the length of time after the purchase during which hospital stays need to be considered will vary and it is depending on drug purchasing history. When drugs can be dispensed for three months hospital stays up to four to six months after the index dispensing and before next dispensing need to be considered. The duration of the hospital stay needs to be added to estimates of duration in calendar time. For example, if there are 200 days between two purchases, and the purchased amount is 100 DDDs and person stays at a hospital for 50 days between these purchases, the outpatient time is 150 days. Thus, the estimated dose is 100 DDDs/ 150 days = 0.67 DDDs per day. Without considering hospital stays the dose estimate would be 0.50 DDDs per day. This correction is important as lower limit of dose may guide not to join these two purchases if hospital stays would be ignored.

When devising something for the first time, previous knowledge is limited. This applies to the concept of the joining of purchases in a new situation, for example in the new dataset. When the same approach is done for the second or third time, it is possible to learn from previous attempts and to enhance the performance. A type of learning mechanism was also included in the PRE2DUP method, allowing it to learn from previous cycles when the method is rerun with the same dataset. The first round of modelling is done without previous experience about how a new study population is using the drugs. After the first run, the results can be analysed and changes made to the parameters. Drug use behaviour at the population level is, furthermore, added to the input after the initial round. This redefined set of parameters then produces new results and this recursive refining can be done as long as needed in order to achieve high quality estimates of drug use periods.

4.3.2 Validation of PRE2DUP generated drug use periods

The expert-opinion based validation of drug use periods was based on purchase histories derived from the Medalz-2005 dataset and the expertise of the reviewers. The validation was done from the view of a single purchase, is it correctly placed in the drug use period (referred to as the purchase test) and from the view of a drug use period, does it contain correct purchases and is the length from last purchase correct (referred as the drug use period test). The length of the last purchase in the drug use period was evaluated only for periods including the correct set of purchases. Validating the placement of purchase evaluated how well the method makes decisions when joining each purchase. In validating the drug use periods, it was determined how correct all joining decisions of this period were and if the duration from the last purchase was correct. This latter validation included as many placement decisions as there were purchases in the drug use period and also involved a validation of the duration from the last purchase.

The validity of drug use periods produced by the PRE2DUP method was assessed by two independent reviewers with expertise in clinical pharmacy (Heidi Taipale and Marjaana Koponen). The purchase test included 1000 randomly selected purchases and they were rated as to whether they had been correctly placed in a drug use period (i.e., single purchase period, included in a correct drug use period or being either the end or the beginning of a period). The options were correct, wrong and non-solvable. Those purchases that lacked sufficient information for making a decision (e.g., no DDD or package information) were classified as non-solvable. The drug use period test for 1000 randomly selected drug use periods was conducted to determine whether or not the periods included the correct set of purchases. This means that if the first purchase was correct, the subsequent purchases belonged to this drug use period and the last purchase correctly ended the period. In addition, possible purchases after the last one and before the first in the drug use period examined were also evaluated, to determine whether or not they should have belonged to the drug use period. In this case, the drug use periods were rated as follows; 1) the drug use period consisted of correct purchases, 2) the drug use period was incorrectly generated (i.e., the start or end of the period was incorrect, or it should have been divided into two or more periods), and 3) there was not enough information to judge correctness. In the presentation of the results for both tests, the “correct” option was defined when at least one of the reviewers stated the purchase or drug use period as correct, and “error” when both reviewers agreed that it was erroneous, with the rest classified as “non-solvable”. To assess the agreement between the two expert opinions, we used Krippendorffs alpha (K-alpha) (Krippendorff 2004) to measure how well the reviewers’ opinions matched with each other.

4.3.3 Performance test

Performance tests were done with Medalz-2005 data (2002-2009) i.e. we tested the time required for processing of one million purchases in different phases of PRE2DUP version 15.7. The test setting utilized dBase version 9.5 (dbase.com) and computer HP Elitebook laptop with Intel i7-5600U processor, 16Gt ram and 256GT SSD disk. The operating system was Windows 10 enterprise (updated to 2nd March 2018 stage). Tests were run without any other programmes running on the computer.

4.4 VALIDATION BETWEEN INTERVIEW AND PRE2DUP METHOD (II)

The drug use reported in the interview was collected as a part of the GeMS study. Drug purchases recorded in the Prescription register data (2002-2007) of the GeMS study participants were modelled with PRE2DUP to create drug use periods. Drug use modelling was conducted on all purchases during the entire six-year period. Modelling was blinded to the interview dates; the choice to use the interview year 2006 for the validation was done after the modelling. The agreement between drug use either register-based or interview-based at the individual level was assessed as concordant when at least one day of the modelled drug use fell within the two weeks' time frame before the date of the interview and the participant had reported drug use in the interview. Similarly, if there was no drug use in the preceding two weeks according to both sources, this was counted as a concordant result.

We calculated agreement in two different ways; using the modelling results based on register data as a reference and using the interview as a reference for each drug and person. The agreement was evaluated with Cohen`s kappa in both ways to test the reliability of the two references. Interpretation of kappa values were as follows: poor <0.2, fair 0.2-0.4, moderate 0.4-0.6, good 0.6-08 and very good 0.8-1.0 (Sim and Wright 2005).

4.5 COMPARING FIXED METHODS AND PRE2DUP METHOD (III)

The purchase data for expert evaluation were sampled from the Medalz-2005 cohort for the following drugs: warfarin (ATC: B01AA03), bisoprolol (C07AB07), simvastatin (C10AA01), risperidone (N05AX08) and mirtazapine (N06AX11). The drugs were selected based on which drugs were most commonly used in the study cohort and also to represent different drug groups, drug use patterns and variation in dosages. We sampled 100 purchases of each drug and derived a purchase history of the selected drug for each person. This random selection was separately done with two evaluations, one including DDD and time window methods and the other involving tablet methods. This was done as not all drug purchases contain information on the amount of tablets (for example, injections). Tablet sampling was restricted to purchase histories including only tablets.

After the sampling of two sets of 100 purchases, the drug use was modelled with PRE2DUP, three fixed length time window methods and four DDD methods (for the so-called DDD sample), and with PRE2DUP and five tablet methods for the tablet purchase sample (Table 4). The DDD methods utilized in this modelling were one DDD per day and grace periods 30, 90, 180 days (DDD_1_30 . . . DDD_1_180); one DDD per day and a 50% proportional grace period (which corresponds to 2/3 DDDs per day dose); in the latter case, the grace period was included in the last purchase (DDD_066_0).

With these methods, an example purchase of 30 DDDs would then last 60, 120, 210 and 45 days, respectively. The fixed time window methods were 90, 180 and 360 days. The time window methods assign the same duration to all purchases irrespective of the purchased amount. Thus, a purchase of 5 DDDs and 100 DDDs will last the same time, in this study 90, 180 and 360 days, respectively.

Fixed tablet methods assumed one tablet per day use with a grace period of 0, 30, 90 and 180 days being added (Table 4). Similarly to the DDD methods, a proportional grace period of 50% of purchased tablets converted into days of use (with one tablet per day dose) was applied, corresponding to a dose of 2/3 tablets per day. For a purchase of 30 tablets, the durations of drug use produced with these methods were 30, 60, 120, 210 and 45 days, respectively. Grace periods were not included in the duration of the last purchase of each drug use period with the fixed grace period methods.

Table 4. Performance of different methods for two different purchases, 30 DDDs or tablets and 100 DDDs or tablets.

Method	Abbreviation	Unit	The length of drug use (WIN) or dose value	Grace period	Duration of use for purchase of 30 DDDs/ tablets	Duration of use for purchase of 100 DDDs/ tablets
Time window of 90 days	WIN_90	(days)	90		90	90
Time window of 180 days	WIN_180	(days)	180		180	180
Time window of 360 days	WIN_360	(days)	360		360	360
1 DDD per day with 50% proportional grace period	DDD_066_0	DDD	1	50%	45	150
1 DDD per day with 30 days grace period	DDD_1_30	DDD	1	30	60	130
1 DDD per day with 90 days grace period	DDD_1_90	DDD	1	90	120	190
1 DDD per day with 180 days grace period	DDD_1_180	DDD	1	180	210	280
1 tablet per day with proportional 50% grace period	TAB_066_0	tablet	1	50%	45	150
1 tablet per day without any grace period	TAB_1_0	tablet	1	0	30	100
1 tablet per day with 30 days grace period	TAB_1_30	tablet	1	30	60	130
1 tablet per day with 90 days grace period	TAB_1_90	tablet	1	90	120	190
1 tablet per day with 180 days grace period	TAB_1_180	tablet	1	180	210	280

Hospital days during drug use were not counted as drug use days in any of the methods as the drugs administered while the patient is hospitalized are provided by the hospital. For example, a drug purchase of 30 DDDs with assumed one DDD per day use and with 30 days' grace period would last 60 days. If a person was in hospital for five days within this 60 day period, the drug supply would cover 65 days from purchase. In the review phase, hospital days were reported to the reviewers while they assessed the correctness of the judgement on the duration of drug use (Table 5).

Table 5. An example of the purchase histories utilized in the expert-opinion based evaluation of the DDD sample. The evaluated purchase is the bolded row (2006-06-27). Vnro refers to vnr number (package identifier) and time from previous purchase is in days. Hospital days are days between current and the following purchase (Data shown is not real as dates have been shifted).

Purchase date	DDD	Dose (DDDs per day)	Hospital days	Time from previous purchase	vnro	Number of packages
1998-11-08	32.66	0.32	0	NA	454165	1
1999-02-18	32.66	0.32	0	102	454165	1
1999-05-31	32.66	0.32	0	102	454165	1
1999-09-09	32.66	0.32	0	101	454165	1
1999-12-20	32.66	0.32	0	102	454165	1
2000-04-03	32.66	0.31	4	105	454165	1
2000-07-17	32.66	0.35	0	105	454165	1
2000-10-27	32.66	0.43	0	102	454165	1
2000-12-17	32.66	0.27	0	51	454165	1
2001-05-14	32.66	0.32	0	148	454165	1
2001-08-18	32.66	0.34	0	96	454165	1
2001-11-15	32.66	0.28	0	89	10940	1
2002-03-26	32.66	0.33	0	131	10940	1
2002-06-27	**32.66**	**0.34**	**0**	**93**	**10940**	**1**
2002-09-29	32.66	0.30	0	94	10940	1
2003-01-23	32.66	0.37	0	116	10940	1
2003-04-29	32.66	0.81	0	96	10940	1
2003-05-30	32.66	1.34	0	31	10940	1
2003-06-20	65.33	0.54	0	21	10966	1
2004-11-08	133.33	1.25	0	507	13423	1
2005-03-03	133.33	1.37	0	115	13423	1
2005-06-02	133.33	1.21	0	91	13423	1
2005-09-15	66.66	0.80	0	105	12469	1
2005-12-18	65.33	0.65	0	94	10966	1
2006-04-01	65.33	0.65	0	104	10966	1
2006-07-09	65.33	0.64	0	99	10966	1
2006-10-22	65.33	0.67	0	105	10966	1
2007-01-28	65.33	0.71	0	98	10966	1
2007-04-26	65.33	0.64	0	88	10966	1
2007-08-10	65.33	0.65	0	106	10966	1
2007-11-17	65.33	0.67	0	99	10966	1
2008-02-22	65.33	0.65	0	97	10966	1
2008-06-03	65.33	0.64	0	102	10966	1

In the evaluation, a list of modelling results with different models (Table 6) and purchase histories of the key purchases were generated and provided to two reviewers with a background in clinical pharmacy (Heidi Taipale and Marjaana Koponen). The reviewers were blinded to different methods and the modelling results were presented in a random order.

Table 6. The drug use periods generated with eight different methods (DDD, fixed time and PRE2DUP) shown to the reviewers. The key purchase assigns the date when the evaluated purchase took place whereas the start and end dates of use define the drug use period produced with a method to which the key purchase belongs. The order and coding of the methods were randomized (random number code in column method) for presentation of each evaluated purchase and were not known to the reviewers (Data shown is not real as dates have been shifted).

Key purchase	Start of use	End of use	Method
2002-06-27	1998-11-08	2003-12-17	21
2002-06-27	1998-11-08	2003-09-27	22
2002-06-27	2002-06-27	2002-07-29	23
2002-06-27	2002-06-27	2002-08-15	24
2002-06-27	2002-06-27	2002-09-25	25
2002-06-27	1998-11-08	2003-08-24	26
2002-06-27	2002-03-26	2003-08-24	27
2002-06-27	1998-10-25	2004-06-14	28

The reviewers used the provided information and classified the results into two main classes:

1) Does the drug use period contain correct purchases? The period can start at the selected key purchase or at an earlier purchase. The last purchase can be the key purchase or some later if the method joins the key purchase to the next. If the drug use period contained correct purchases then reviewers answered the following question: 2) Is the duration correct in its assessment from the last purchase to the end of drug use period? This was based on the purchased amount, the individual's purchase pattern of the drug and allowing for a 30% error marginal from expert defined duration.

The five classes for drug use periods were:

1. correct purchases and correct duration (abbreviated to **completely correct**, the main correctness measure),
2. correct purchases but false duration (abbreviated to **correct but false duration**, contains correct purchases but duration of the last purchase of the period is not within the margin of error),
3. correct purchases but non-solvable duration (contains correct purchases but duration of the last purchase of the period cannot be solved because of irregular drug use pattern, abbreviated to **correct, enddate not solvable**),
4. non-solvable (purchase history difficult to evaluate, abbreviated to **not solvable**),
5. wrong purchases (extra and/or missing purchases), abbreviated to **wrong**.

After the evaluation was conducted, the randomization code was opened and the results assessed. Our main goal was to compare completely correct results with different methods according to expert-opinion. The other classes were used to provide more information about how the different methods fail in their own unique ways to produce correct solutions. As we had two reviewers (Heidi Taipale and Marjaana Koponen), the inter-rater reliability was tested with Cohen's Kappa. This test measures how uniformly reviewers rate results, not the correctness of their ratings.

Secondly, the duration of drug use periods for all purchases of these drugs in the Medalz-2005 dataset (years 1995-2009) was modelled with the aforementioned methods for the following drug classes (ATC: A02, B01, C07, C08, C09, C10, G04, H02, J01, M01, N02, N03, N05, N06). The lengths of each person's drug use calculated according to these methods were compared with the lengths calculated with PRE2DUP. For example, a person who according to the PRE2DUP method used sotalol (ATC C07AA07) for 536 days and 512 days according to method one DDD per day and 90 days' grace period (DDD_1_90). The negative difference i.e. "underdays" is 24 days (536-512=24 days). These underdays and exceeding overdays were summed up separately and compared to the total time over all persons and drugs in the corresponding drug class to obtain a relative difference in drug use duration compared to PRE2DUP. A similar approach was made in terms of the number of drug use periods produced by each method as compared with PRE2DUP. The number of drug use periods was calculated to measure splitting of drug use by each method as compared to the assessment by PRE2DUP for each drug class.

Statistics were calculated with R 3.01 (www.R-project.org). Methods were implemented with dBase 9 (dBase LLC, Binghampton, NY).

5 Results

5.1 PRE2DUP (STUDY I)

The PRE2DUP consists of three major parts, i.e. the pre-processing phase, the method core, and the calculation of package refill times. The pre-processing phase modifies purchase data into a usable format and includes the calculation of sliding averages of daily dose. The method core decides which of the drug purchases belong to the same drug use period. Typical package refill lengths are calculated for all packages from purchases including a predefined minimum number of drug use histories. The pre-processing phase is run only once whereas the core and package refill lengths are usually run several times, and expert-defined parameters are improved between the consecutive runs.

PRE2DUP was implemented in the dBase language. In its current form (4/2018, version 15.7), the method has been divided into four packages: pre-processing of purchases (~ 500 lines of code), calculating statistics of purchases (~ 400 lines), the method core (~ 1,700 lines) and parameter calculation (~ 300 lines). The code has evolved over time as new features have been incorporated and data error recovery has been improved. There are two slightly different versions of PRE2DUP, one for Finnish register data (described in this thesis), and another for Swedish data. They differ only in a few aspects, for example in the version tailored for Swedish data, dose dispensing is handled differently.

5.1.1 Pre-processing

Pre-processing refers to calculations and data arrangements needed before periodising drug use. Register-data correction and harmonization of definitions (for example, ATC codes and DDD values) are conducted before the pre-processing phase. These harmonization steps before the pre-processing phase can be fairly complicated and time-consuming tasks. All purchases of the same drug during one day are joined (for example, purchases of different package sizes are calculated together). This joining could be done also for purchases within very short time intervals such as purchases on adjacent dates. However, this would require extra caution, especially for some drugs which possess an addictive potential, or drugs used for the treatment of addiction disorders, as dispensing every second or third day may represent the normal drug dispensing behaviour.

Temporal dose estimates are calculated in the pre-processing phase. PRE2DUP uses a sliding average of daily dose from three subsequent purchases. The dose estimate is based on dividing the purchased amount in DDDs by the time elapsed between two subsequent purchases, including the purchase date but not the date of the following purchase. Dose estimates are drawn from weighted average of three purchases, namely the current purchase, the previous and the next purchase are considered. Weights for these are 1:4:1, respectively, meaning that the dose estimate of the current purchase affects more the sliding estimate than the previous and the next purchase (Equation 1).

$$DDDAVG_i = \frac{DDD_{i-1} + 4DDD_i + DDD_{i+1}}{T_{i-1} + 4T_i + T_{i+1}}$$

Equation 1. Computation of temporal averages of daily dose between purchases.

In Equation 1, DDD_i is the DDD amount that is purchased at time i, and T_i is the number of days between purchase i and i+1. This formula is used for purchase i, when there are three or more purchases and there are data on the previous (t-1) and subsequent (t+1) purchases. For each person's first purchase of each ATC-code, the weights are five for i, one for i+1, and for the last purchase, one for i-1 and five for i. For the last purchase i, T_i is calculated from the previous purchase while assuming the same DDD per day value as in the previous purchase, $T_i=DDD_i/(DDD_{i-1}/T_{i-1})$, i.e. the dose does not change after the last purchase.

The calculation of the sliding average has been limited with an upper limit of days over which drug purchases are never joined. This threshold (currently 300 days) has been included in the calculus (Figure 4). If the time between two purchases of the same drug is more than a threshold value, the purchase before this pause is the last one in the sliding average calculus. Similarly, a new calculus is started after this pause.

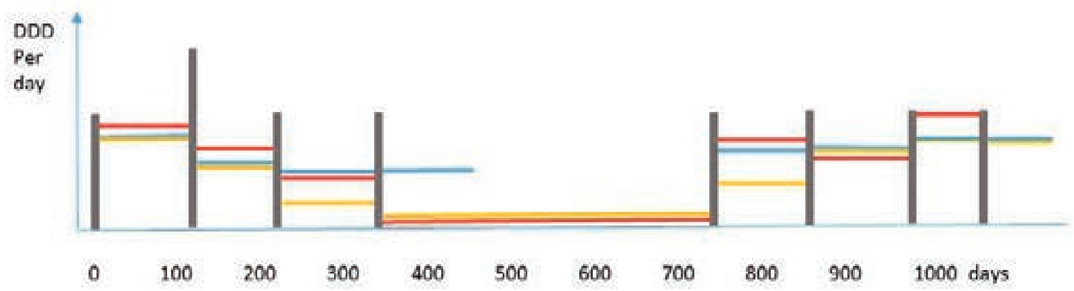

Figure 4. The impact of long breaks in drug purchases on the calculation of sliding averages of daily dose. Grey vertical lines assign timing and amount of purchases. PRE2DUP (including a restriction to avoid over 300 days breaks when joining purchases) is shown with blue vertical lines, the yellow line describes drug use periods constructed without a joining threshold and the red line describes the situation if the purchased amount is purely divided by time between purchases.

The personal variation statistic is the coefficient of variation which is measured for the sliding average of the dose in DDDs for each person and each drug. It is calculated as standard deviation divided by average of sliding averages from equation 1 and thus, it is variation scaled with the average, i.e. proportional variation. It describes variability in local dose estimates and is scaled such that the value of one corresponds to the condition where the standard deviation is equal to the average. For example, if the average local dose over all purchases is 1.5 DDDs per day and standard deviation is 1.5 DDDs, the coefficient of variation is one. This coefficient of variation is calculated only for drug purchase histories including more than two purchases.

5.1.2 Method core

The method core makes decisions on whether subsequent purchases are joined together to produce a drug use period and on the duration of drug use after the last purchase in the drug use period. Purchases are processed in chronological order and decisions are made stepwise for each purchase which is a common feature in all widely used methods to construct drug use periods.

The temporal sliding average of daily dose is the main tool to decide whether a purchase is joined to the next one and in the calculation of duration from the last purchase. Dose may change due to various reasons (such as actual dose changes or lower adherence) and the local sliding average is selected to control for the variability in the dose. Stockpiling of drugs affects the sliding average and increases deviance from actual dose. Thus, this phenomenon needs to be controlled in the method. There are three features in the PRE2DUP method to allow variability in dose estimate: i) personal variation statistic, ii) test for stockpiling event and iii) limiting stock estimate according to the number of previous purchases.

The personal variation statistic is computed for each person and the ATC code as described in pre-processing section 5.1.1. It is a multiplier of the duration and 50% of this variation is taken into account when calculating the expected length of duration of purchased drug (DVAR=0.5) (Equation 2).

$$ERFL_i = \frac{DDD_i \times (1 + DVAR \times DDDAVGcv)}{DDDAVG_i}$$

Equation 2. Calculation of the expected refill length for purchase i ($ERFL_i$). DDDi is purchased amount, DVAR is a multiplier for the personal variation statistic DDDAVGcv and DDDAVGi is the sliding average of purchase i.

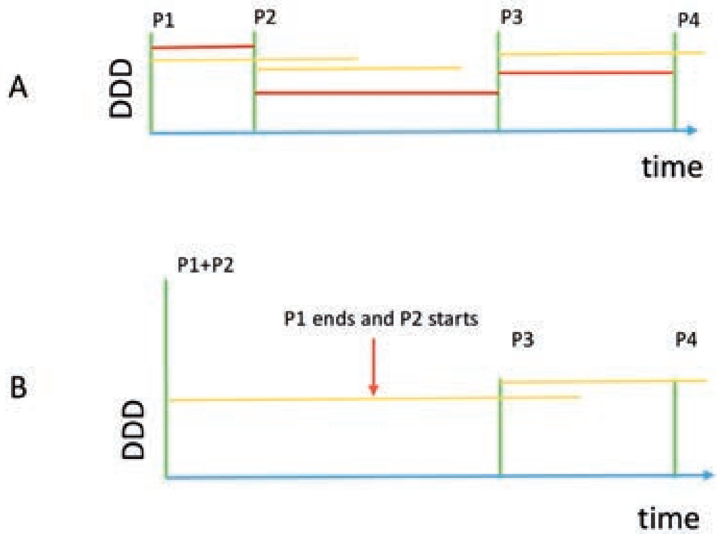

Figure 5. In figure A there are four purchases, in this case the same amount of DDDs. The time between the second and third purchases is longer than between first and second and third and fourth purchases. Thus, the local dose declines (red lines). Yellow lines describe how long a purchase would last with the estimated dose. The first purchase would last the past second purchase but the second purchase does not reach the third with estimated dose. The stockpiling test moves the current (second) purchase to the previous one (first) and calculates duration of this joined purchase (B). The stockpiling test calculates P1 and P2 together as they would have happened at the timing of P1 and calculates whether the duration of this joined purchase reaches P3.

The stockpiling test is activated when the purchased drug does not reach the next purchase according to PRE2DUP and the local dose has temporarily declined, i.e. previous and following local doses are higher than the current dose. The stockpiling test routine calculates if the current and previous purchase joined together would reach the next purchase if they were both purchased at the time of the previous purchase. Figure 5 shows how this is conducted. If the joined purchase reaches the next purchase, the drug use period continues, and the method core starts to process the next purchase. Otherwise the drug use period ends.

The duration from the last purchase is calculated when each drug use period ends. This calculation allows some stock to be left at the time of the last purchase. At the first purchase, no stock can exist and the potential size of the accumulating stock increases along with the number of purchases, the stock limiting term e^{-k} was added to the calculation of the duration of the last purchase in a period (Equation 3). This term increases the divider for the first purchases but decreases rapidly to zero when the number of purchases (k) in the period increases.

$$END = date_i + \frac{DDD_i \times (1 + DVAR \times DDDAVGcv)}{DDDAVG_i \times (1 + e^{-k})} + HD_i$$

Equation 3. Calculation of end date (END) of the last purchase in the drug use period. Purchase date is $date_i$, k is the number of purchases in this period, DDD_i is the purchased amount, HDi is the number of hospital days during the time that the drug purchase i covers, DVAR is multiplier for personal variation statistic DDDAVGcv and DDDAVGi is the sliding average of purchase i (equation 1).

The drug use period can end already at the first purchase of the new period although there may be several purchases before or after that purchase and the sliding average $DDDAVG_i$ and the personal variation statistic DDDAVGcv are available from these other purchases by the same person and drug. In these situations, measures from the person's closest previous or the following use of this drug are utilized in the modelling of a single purchase. The duration of use in this situation is calculated with this dose estimate by multiplying it with the purchased amount in DDDs. This is different from actual single purchases (a person has only one ever-purchase of the drug), and from purchases which are too far away in time from the previous and/or the following purchases or those periods contain only one or two purchases. In the latter cases, the duration is obtained from the refill time distribution of the study population as the typical refill time length for the package (described in 5.1.3).

The joining of purchases is also limited with expert-defined parameters which have been designed at various levels. Global parameters control a common restriction to all drugs such as forbidding the calculating of sliding averages of daily dose over time spans of 300 days. The concept behind the ATC- and vnr-parameters is to provide upper and lower limits for dose variation in which continuous use is possible and for which the dose is realistic. The ATC class parameters specify the dose limits for drug classes; they are hierarchical. This means that the most precise drug class parameters will be used. For example, ATC parameters have been defined for ATC codes N05 (psycholeptics, higher level), N05AD (butyrophenone derivatives, intermediate level) and N05AX08 (risperidone, drug substance level). A purchase of haloperidol (N05AD01) utilizes ATC parameters from the intermediate level (N05AD) and a purchase of risperidone from drug substance level as they are defined. However, vnr-parameters represent the most precise level of parameters and they are always used instead of ATC parameters if they are available for the particular drug purchase. Vnr-parameters are designed for separate vnr-numbers (drug package) and take into account strength, amount of drug, drug form, dosing interval (for delayed release products), and pharmaceutical properties such as whether the tablet can be divided. Vnr-parameters include minimum refill length, maximum refill length, typical refill length and corresponding DDD per day values. For example, these parameters restrict the possibility that a package of 100 tablets may not be used in less than ten days (minimum refill length) but it can last for up to 200 days (maximum refill length) when tablets are dividable.

Figure 6 shows a simplified decision process for one purchase. It considers dose estimate (sliding average), purchasing behaviour (coefficient of variation), vnr-parameters, and time to next purchase when estimating the expected refill length. The method determines if the end date produced by the expected refill length is or is not before the next purchase. If it reaches the next purchase, the method starts to process the next purchase, otherwise the method tests if there has been stockpiling from the previous purchase (stockpiling test).

If drug use period ends, then the end date to drug use period is calculated and period is written as the output (person, ATC, start and stop dates, number of purchases, days in hospital and total DDD).

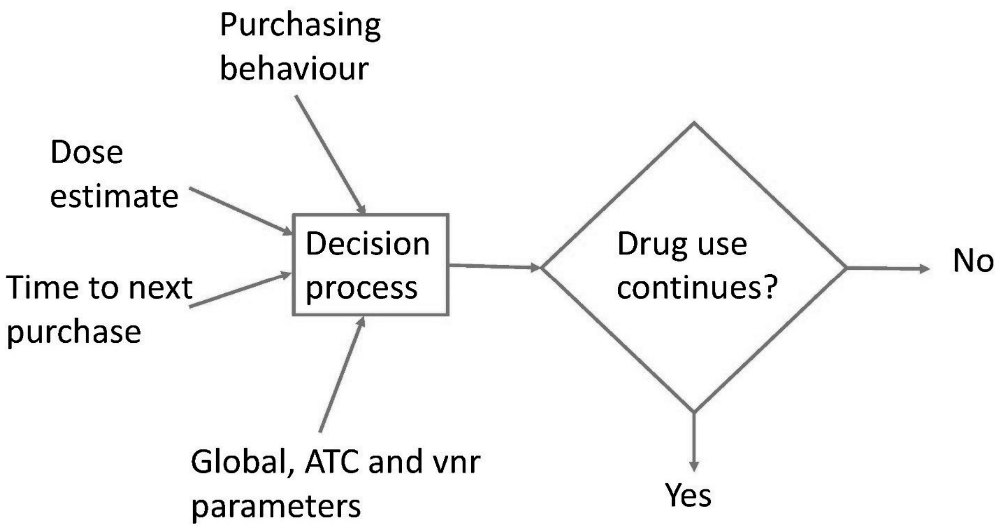

Figure 6. Simplified presentation of the decision process utilized in the PRE2DUP core. The decision algorithm is fed with information of the current and next purchase, purchased package, parameters and personal purchasing behaviour.

5.1.3 Calculation of package parameters

The estimated duration of each package (defined by the vnr-number) can be calculated only after the method core has produced drug use periods. PRE2DUP calculates the typical duration for each package as long as there are enough drug use periods that contain at least a threshold amount of purchases (limit set to 6). Only purchases with one package (vnr-number) are considered, excluding purchases in dose dispensing, and refill length, subsequently time from purchase to next purchase, is calculated without considering hospital stays. The typical length is calculated with cascading different lengths to the closest more common length. This joining is done recursively from the least common refill lengths and only refill lengths which are at most two days apart are joined. After this process, the most common refill length represents the typical duration of each package if more than ten periods have been used in this estimation.

5.1.4 Performance of PRE2DUP

The performance of PRE2DUP version 15.7 for the first part of the pre-processing phase, reading purchase data and calculating sliding averages, took 13 minutes per one million purchases. The second phase of pre-processing, calculating personal variation parameters took two minutes. Running one iteration round of the PRE2DUP core for one million purchases took 31 minutes; in this case, it produced 220,000 drug use periods in the first round, i.e. on average, it joined almost five purchases in one drug use period. The calculation of drug package parameters took two minutes. Thus, to run a typical setting of three iterations with PRE2DUP for one million purchases (one times pre-processing 13+2 min, two times package parameters 2* 2min and three times PRE2DUP core 3*31min) takes a total time of 112 minutes i.e. approximately two hours per million purchases. The time redesigning parameters between every round needs to be added; in fact, this may take much longer than running the algorithm. The number of drug use periods varies very little between runs if vnr-parameters are unchanged as the calculating parameters used in single purchase periods may alter the duration of single purchase periods but seldom join them to other periods.

Table 6 presents the number of calculated coefficient of variation parameters in the Medalz-2005 data for purchases in the time frame 1995-2009. ATC class N, nervous system was the largest group followed by C, the cardiovascular system, totalling over 270 thousands for 28,093 persons. This is almost ten parameters corresponding to ten different drugs per person. In addition, there were 236,549 drug purchase histories with less than three purchases; for those, this parameter was set to zero. The mean of coefficient varied between 0.2 and 0.3 for most ATC classes. ATC class J, anti-infectives for systemic use, shows a higher variation of almost 0.4 and ATC class L, Antineoplastic and immunomodulating agents, shows less variation. The standard deviation has a magnitude of 0.2 for all ATC classes shows fairly high personal differences in the coefficient of variation between persons.

Table 6. Coefficients of variation for sliding averages of daily doses in DDDs, described as mean with standard deviation and the number of parameters for how many person-ATC combinations these were calculated in each ATC main class.

ATC main	**Mean**	**Standard deviation**	**The number of parameters**
A Alimentary tract and metabolism	0.253	0.186	32,455
B Blood and blood forming organs	0.212	0.171	8,999
C Cardiovascular system	0.229	0.187	74,903
G Genito-urinary system and sex hormones	0.222	0.179	10,741
H Systemic hormonal preparations, excluding sex hormones and insulins	0.277	0.204	6,312
J Anti-infectives for systemic use	0.394	0.264	14,525
L Antineoplastic and immunomodulating agents	0.161	0.179	1,250
M Musculo-skeletal system	0.268	0.203	16,784
N Nervous system	0.228	0.182	94,557
P Antiparasitic products, insecticides and repellents	0.240	0.204	229
R Respiratory system	0.302	0.194	9,803
S Sensory organs	0.224	0.145	5,150
All drugs	0.248	0.192	275,708

The average number of purchases per drug use period varied between the different drug classes, the lowest mean was in anti-infectives and the highest in antineoplastics (anticancer mediations) (Table 7). The number of purchases in a drug use period was also related to the length of the drug use period as drugs are typically dispensed for three months at a time. The ratio of the number of parameters in Table 6 and the number of drug use periods in Table 7 describe on average how many periods are produced from one drug purchase history. For example in ATC class A, alimentary tract and metabolism, there are 32,455 parameters each corresponding to one drug and a person with more than three purchases. This purchase data yields 141,380 drug use periods with PRE2DUP i.e. on average 4.49 purchase per period. The ratio between parameters and drug use periods is 4.36, the average number of drug use periods with three or more purchase for all person's drugs in ATC class A.

Table 7. The number of purchases, drug use periods constructed from those and average number of purchases per drug use period by main ATC classes.

ATC main class	The number of purchases	The number of drug use periods	The mean number of purchases per period
A Alimentary tract and metabolism	634,094	141,380	4.49
B Blood and blood forming organs	187,324	27,292	6.86
C Cardiovascular system	1,874,971	196,256	9.55
G Genito-urinary system and sex hormones	255,710	45,981	5.56
H Systemic hormonal preparations, excluding sex hormones and insulins	145,813	24,453	5.96
J Anti-infectives for systemic use	276,865	23,3571	1.19
L Antineoplastic and immunomodulating agents	24,987	2,489	10.04
M Musculo-skeletal system	413,014	174,329	2.37
N Nervous system	1,688,949	246,404	6.85
P Antiparasitic products, insecticides and repellents	8,151	4,468	1.82
R Respiratory system	285,131	93,969	3.03
S Sensory organs	193,040	51,131	3.78
All drugs	5,988,049	1,241,723	4.82

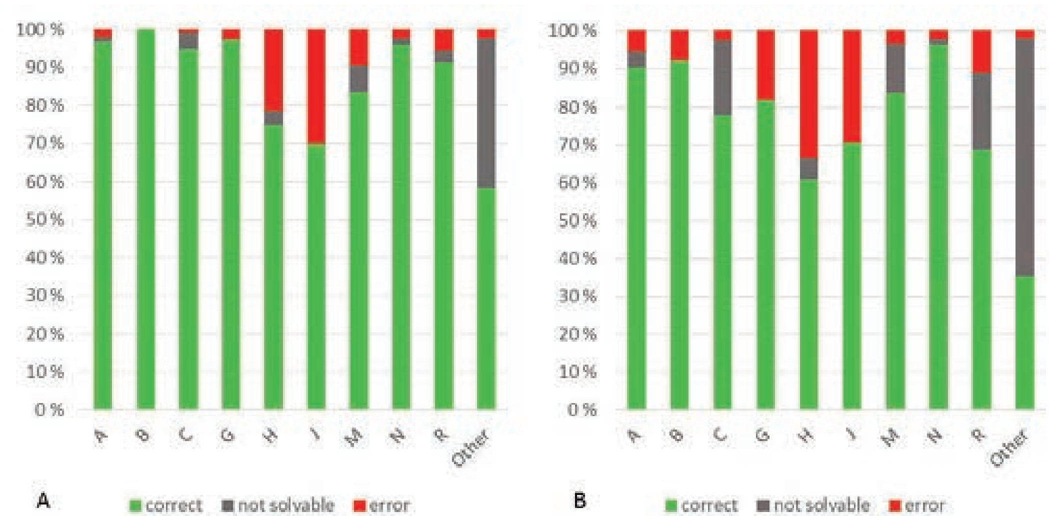

Figure 7. The results of expert-opinion based validation on A) placement of purchases into drug use periods (purchase test) and B) composition of drug use periods (drug use period test) according to ATC main classes. Drug classes are listed in preceding Table 7.

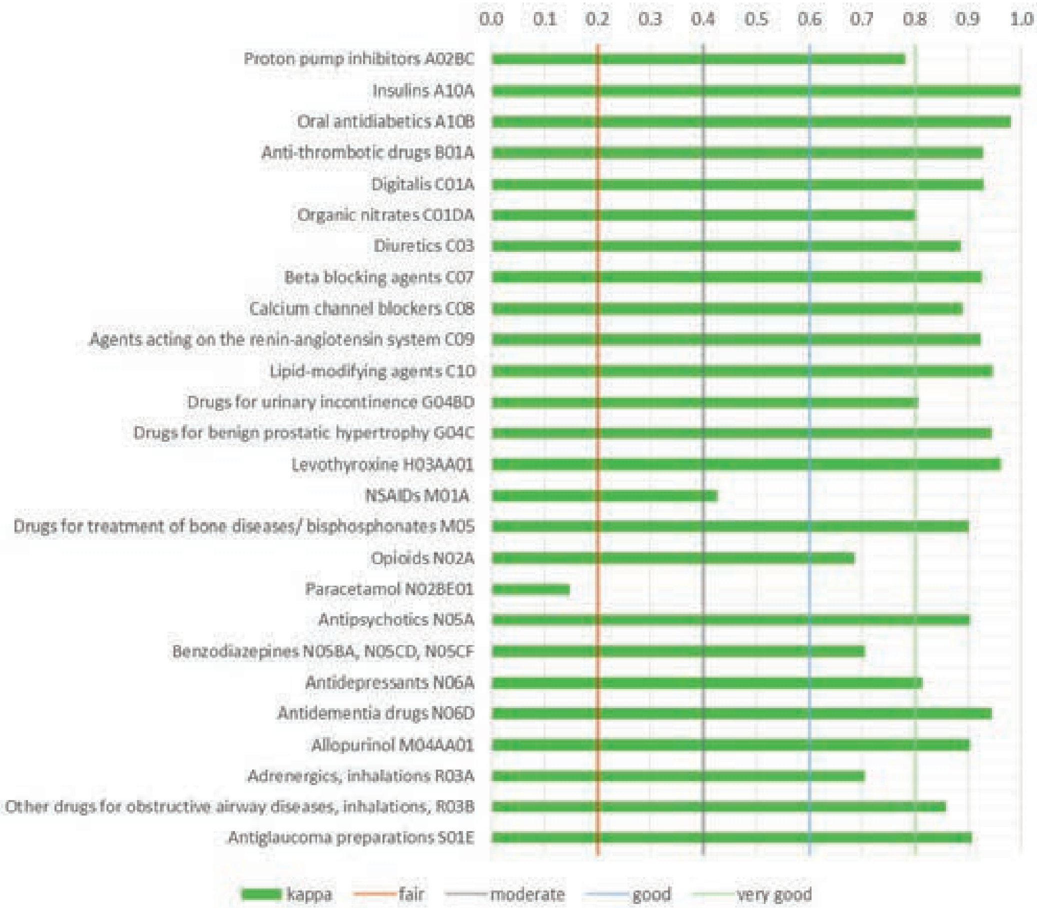

Figure 8. Kappa values of agreement between interview and PRE2DUP modelled drug use. A value of one corresponds to perfect agreement.

5.1.5 Validation of drug use periods by expert-opinion

The results on the validation of placement of purchases (purchase test) are shown in Figure 7A. The best performance was observed for drug classes A (alimentary tract and metabolism), B (blood and blood forming organs), N (nervous system), C (cardiovascular system) and R (respiratory system). In these drug classes, over 90% of purchases were correctly placed into drug use periods. The lowest performance were found in drug classes J (aAnti-infectives for systemic use) and H (systemic hormonal preparations, excluding sex hormones and insulins), for which only 70-80% of purchases were correctly placed.

The correct composition of drug use periods (Figure 7B, drug use period test) showed the best performance for drug class N (nervous system), followed by A (alimentary tract and metabolism) and B (blood and blood forming organs). Drug class M (musculo-skeletal system) had very little erroneous periods but a large number of periods that were not solvable. In this validation, the lowest performances were seen for drug classes J (anti-infectives for systemic use) and H (systemic hormonal preparations, excluding sex hormones and insulins) similarly as in purchase test as only 60-70% of drug use periods were correctly created. The group ”other” consisted of various small drug groups and many purchases had missing purchased DDD values making impossible any judgement of correctness. Thus, the number of non-solvable purchases and periods were high.

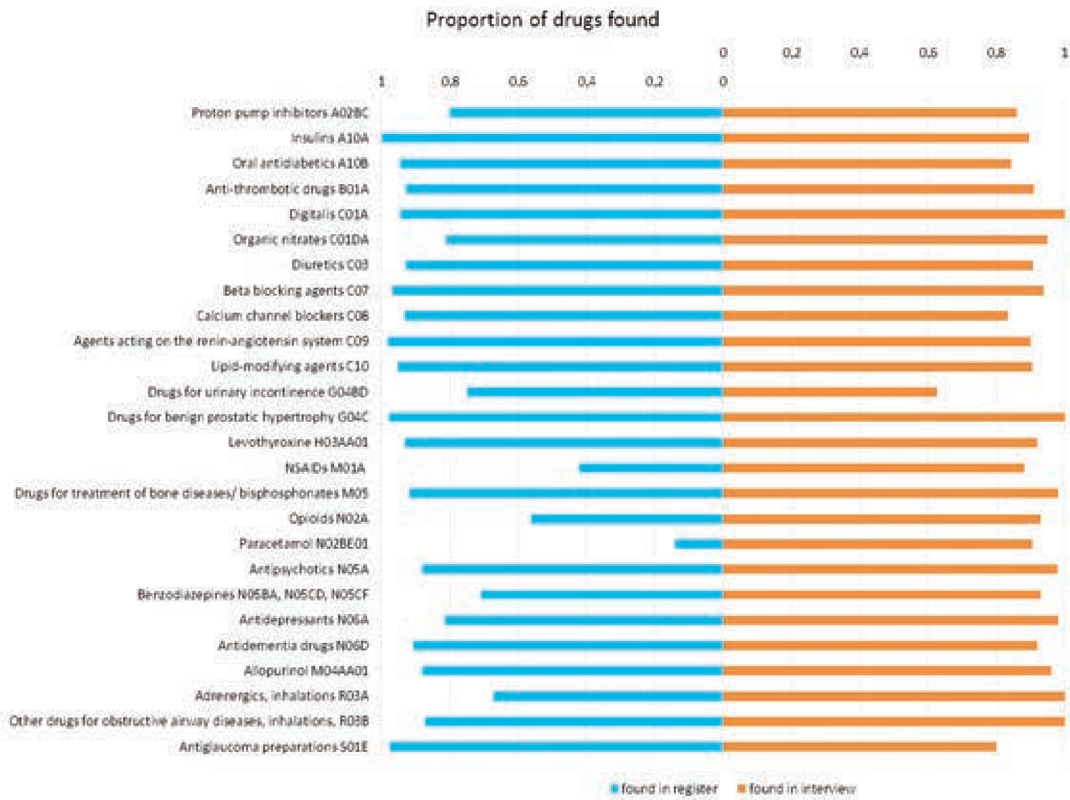

Figure 9. Proportions of drugs found from PRE2DUP-modelled data compared to the interview (blue) and the proportion found in the interview as compared to the PRE2DUP-modelled data (orange), value of 1.0 corresponds to 100% coverage.

5.2 VALIDATION BETWEEN INTERVIEW AND PRE2DUP METHOD (STUDY II)

The agreement between PRE2DUP modelled drug use and drug use assessed in interview was good or very good for most studied drugs (93%) (Figure 8). The only exceptions were NSAIDs and paracetamol, both being available OTC (without prescription).

For most drug classes, the proportion of drug use identified in the comparison between register and interview was 80% or more. The average proportion for all drug classes together was 91% identified in the interview when compared to PRE2DUP-modelled data and 83% for the opposite comparison. The proportion of paracetamol used according to PRE2DUP-modelled data and found in the interview was much lower than the corresponding comparison against modelled data (Figure 9). The same applied to NSAIDs but to a somewhat lower extent. As these both are (partly) available over the counter, not all drug use is recorded in the Prescription register data. Other drug classes showed fairly symmetric levels of coverage with the PRE2DUP-modelled data and interview as a reference.

5.3 COMPARING FIXED METHODS AND PRE2DUP METHOD (STUDY III)

The overall results of expert opinion-based evaluation on correctness of drug use periods generated with different methods for five different drugs i.e. warfarin, bisoprolol, simvastatin, risperidone and mirtazapine are shown in figure 10. On average, PRE2DUP achieved 80% of correct solutions whereas the second best method, namely the tablet method of 1 tablet per day with 180 days' grace period only managed to estimate correctly slightly over 50% of the results. The best DDD method (1 DDD per day and 180 days' grace period) achieved less than 20% correct drug use periods. Fixed time windows did not even reach 10% of correct solutions.

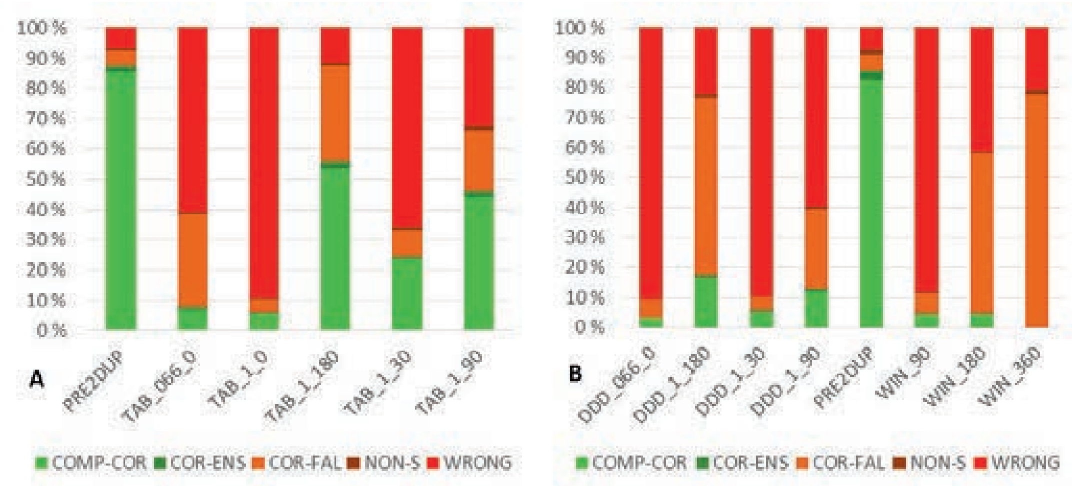

Figure 10. The results of A) different tablet methods and B) DDD and fixed time window methods and PRE2DUP included in both evaluation sets. COMP-COR: completely correct, COR-ENS: correct purchases joined but end-date not solvable, COR-FAL: correct purchases but end date wrong, NON-S: non-solvable purchase history, WRONG: contains wrong purchases. TAB(DDD)_066_0 refers to assumption of 0.66 tablets (DDD) per day, methods TAB(DDD)_1_0 to TAB(DDD)_1_90 refer to one tablet per day assumption and grace periods assigned in the end of abbreviation (from 0 to 90 days), and grace periods were not included in the last purchase. WIN_90-WIN_360 are fixed time windows of 90 to 360 days.

The correctness of drug use periods among individual drugs and methods is shown in appendix 1. PRE2DUP achieved the highest correctness – between 70-94%. The DDD methods yielded a maximum correctness of 41% whereas tablet methods managed 73% correct classifications. In contrast, the fixed time windows methods had at maximum only 11% correctness.

The drug use periods of an example drug i.e. the use of warfarin generated with different methods and with and without adding grace period in the last purchase are presented in Figure 11. Adding a grace period to the last purchase affected the DDD and tablet methods as the duration of the entire drug use period varied with this procedure. The one year fixed method (WIN_360) was the only method which joined all purchases into one continuous drug use period (as tablet method TAB_1_270 with a grace period had a break of 15 days around 3850 days from the beginning of use). The decision whether or not to add a grace period at the end has a major impact in methods having long grace periods. It is notable that adding a grace period to the end of a drug use period does not change the number of periods that a method generates but does control the length of gaps.

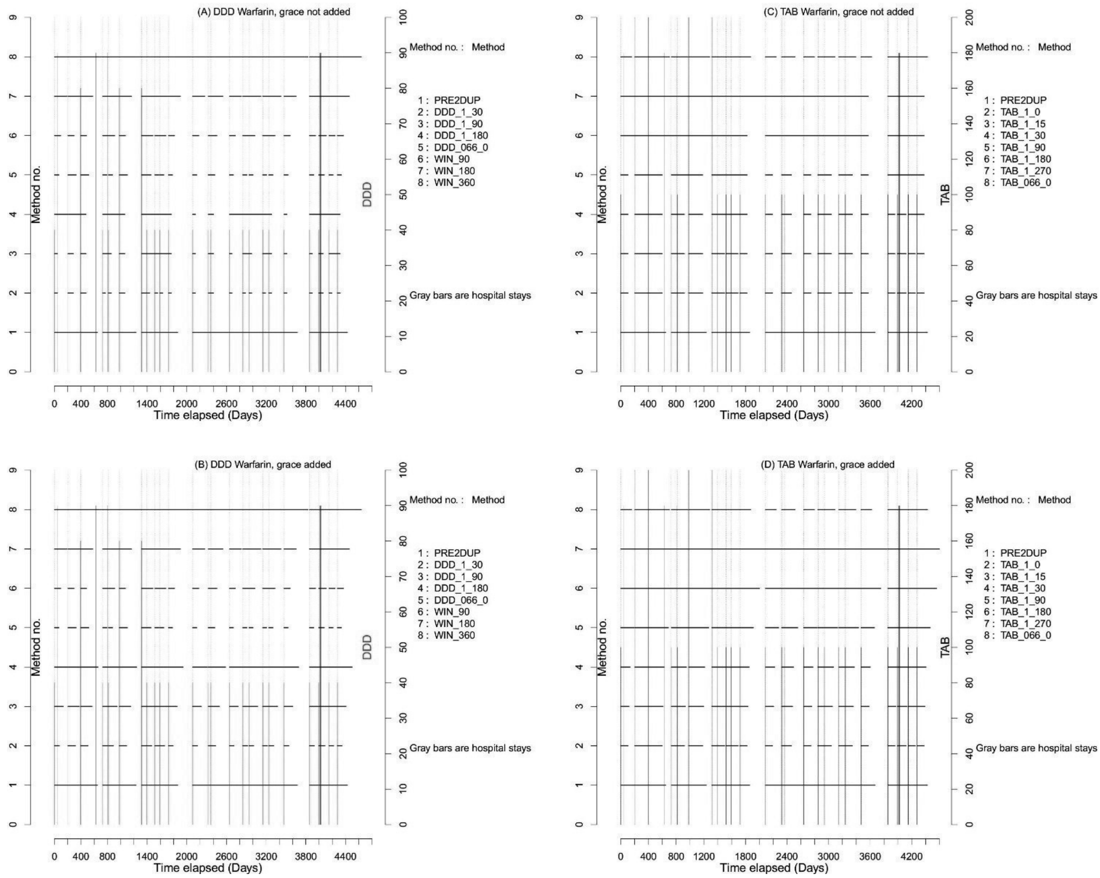

Figure 11. An example drug dispensing history of warfarin (B01AA03) over 12 years, modelled with DDD and time window methods (A and B) and tablet methods (C, D). A and C show results without adding grace period to the end of drug use and B and D with the addition of a grace period. In fixed time window methods (WIN_90 – WIN_360) and PRE2DUP no grace periods are used. Grey bars indicate hospital stays; the amount of purchase (DDD or tablets) is shown with the height of the bar at purchase (DDD 40 or 80, tablet 100 or 200).

Appendix 2 shows how much difference there was in the duration of drug use periods produced by PRE2DUP and tablet methods, and appendix 3 reveals the difference in the number of drug use periods. Time differences vary largely between drugs whereas longer grace periods shift the difference from undertime to overtime. The number of periods decrease with longer grace periods and thus, the number of overperiods decreases. This variation is larger than the difference in duration. Appendices 4 and 5 show the same comparison for DDD and fixed time methods. A fixed time window of 360 days performed very differently from the PRE2DUP and showed a very large overtime in this comparison. Fixed time windows displayed the largest difference with drugs used in a short course manner such as J01 (Antibacterials for systemic use), where durations were almost tenfold compared to PRE2DUP (WIN 360). In terms of the number of drug use periods, there were major differences when fixed time windows were compared to PRE2DUP; a time window of 90 days showed large splitting and as many as several times more periods whereas a long time window of 360 produced less periods than PRE2DUP. The performance of

DDD methods varied when drug use durations were compared, i.e. one DDD per day with a 90 days' grace period was in line with PRE2DUP for some drugs, but shorter and longer grace periods differed more extensively. The number of periods produced by the methods varied more than the duration of use and in this comparison, one DDD per day with 180 days' grace period gave the closest estimates to PRE2DUP for many drugs.

6 Discussion

6.1 PRE2DUP METHOD (STUDY I)

PRE2DUP is a data-driven method, and the focus of this theses was on its development and validation. The development of PRE2DUP started already in 2002 and earlier versions have been used in studies on psychotropics and suicide (Tiihonen et al. 2006), mortality in schizophrenia (Tiihonen et al. 2009), and market withdrawal of thioridazine (Purhonen et al. 2012). This thesis describes the development of the later versions (up to version 15.7) which began in 2012 in cooperation with Medalz study group.

6.1.1 Pre-processing

Pre-processing generates the variables needed for decision making about joining drug purchases in the PRE2DUP core. In this phase, sliding averages are calculated for local dose estimates, by using previous and following purchases, purchased amount and times between purchases. The advantage of using sliding averages is that they reduce the random variation in the dose estimate thus diminishing extreme values of doses and revealing better the possible trend of the dose (Nearing and Verrier 2002). These extreme dose values may not be realistic and are mostly attributable to very short times between purchases and unrealistic high local doses. A weakness of the way that sliding average is applied in PRE2DUP is that it uses information after the current purchase and thus, is dependent on future purchases. The calculation of the sliding average changes when there are no future purchases within the near future and the method can only apply data about the current and previous purchases. This change may affect the duration of the last purchase as in PRE2DUP, the dose estimate for the last and second last purchases are rather similar. The calculation of the sliding average could be re-formulated to use only current and prior purchases. However, then the impact of current purchase on future behaviour, for example in the case of stockpiling, could not be detected. In addition, taking into account too many previous purchases in the calculation of the sliding average would weigh the history considerably and thus, be less reactive to current dose changes. This would split drug use when the actual dose is reduced, i.e. the same amount of drug will last longer than earlier.

PRE2DUP uses symmetric weights when calculating the sliding average (i.e. weights are the same for previous and following purchases). The reason for this is that on average there is left at least one dispensing of the drug in the prescription with the same dose. Furthermore, previous purchases have almost the same probability to belong to the same prescription as the following purchase with respect to long-term drug use (more than one dispensing). This means that future dispensings are already fixed to some degree. This assumption of constant dosage is the way in which PRE2DUP estimates dose and thus the duration from the last purchase. Thus, when considering the issue of whether grace periods should or should not be added to last purchase, PRE2DUP calculates the duration of the current purchase similarly when the drug use period continues or ends, according to the recommendations of L H Nielsen et al. (2008). Although PRE2DUP does not incorporate grace periods, it allows for some stockpiling for purchases, and this is not dependent on whether the current purchase is the last purchase of the drug use period but rather is based on the number of preceding purchases.

The calculation of the coefficient of variation uses the whole drug purchase history of a person and produces an estimate of the regularity of his/her personal drug purchasing. As it is scaled to dose, it is a convenient measure of regularity. The main weakness with applying a coefficient of variation in this context is that if the dose changes permanently or there are several drug use periods over a long time, a single figure cannot capture local regularity or irregularity correctly. For example, if a person has 20 purchases altogether, and for ten of these the dose estimate is 0.5, and for other ten, it is 1.0 the average dose will be 0.75 with a standard deviation of 0.63, which results in a value of 0.35 for the coefficient of variation. This is a good estimate of variation if these dose values of 0.5 and 1.0 are mixed in order, for example 1.0, 1.0, 0.5, 1.0 etc. But if there are two separate doses, i.e. 1.0 values are in one group and 0.5 values in another, without any true variation in the dose during these two periods, then the estimate is too high. In this case, the coefficient of variation may overestimate irregularity during long follow-up times. In addition, the calculation of coefficient of variation is not local but covers the entire drug use history, which may imply that future purchases and behaviour may be many years ahead of the current purchase. The solution would be some estimation of the variation coefficient for each purchase separately, but then the individual's first purchases of the drug would not have any estimates of purchasing behaviour. Possibly by applying some limits looking backwards and forward in time would be one way achieving a more local estimate of the purchasing behaviour. No other method generating drug use period uses a measure of person-drug level irregularity.

During hospital stays in Finland, patients receive their medication from the hospital, and do not use the drugs they have purchased from the pharmacy. The general population has rather few hospital stays per year, and omitting hospital days when modelling drug use period may not change results to any major extent. When the study population is either hospitalized often or for long time periods, or both, the situation changes. Frequent and long hospital periods were common in the data examined in this thesis, involving patients with Alzheimer's disease (Tolppanen et al. 2015, Taipale et al. 2016). If the dataset includes a control population which lacks the disease, this control population will be likely to have fewer hospital days. If hospital days are ignored when modelling drug use, modelling methods may split drug use in those individuals with a higher probability for requiring hospitalization. This difference is artificial and may lead to biased estimates of persistence and adherence as hospitals stays increase the proportion of days not covered with purchased drugs. This imbalance may also lead to an erroneous conclusion that those individuals having more hospital days are less persistent and adherent with their drugs. For example, advanced age both increase the number and the length of hospital stays (Wier et al. 2009, Launay et al. 2018) and thus, it may lower the persistence estimated in the oldest persons (artefact) if hospital stays are ignored (Larsen et al. 2002). To avoid these problems and artefactual situations, PRE2DUP subtracts hospital days from calendar time on drugs when calculating sliding averages and duration of drug use from last purchase. Thus, it ensures compatible durations regardless of hospitalization (Aarnio et al. 2014).

6.1.2 Method core

The decision in joining of purchases is based on local estimate of dose, regularity of purchasing behaviour and dose limits set by experts. These expert parameters are at three hierarchical levels, from global one affecting all joining, intermediate level (ATC) and vnr-parameters for each drug package which represent the lowest (finest) level. This hierarchical structure of defining allowed doses (with upper and lower limits) supports the method to avoid unrealistic joining of two purchases. Package information has been used previously in determining intended dose for drug use (Schulz et al. 2016). However, in PRE2DUP, the package information is used to set limits for dose variation and for durations of single purchases only when population based package durations are not available. The dose limits are designed according to intended use patterns and take into account both the pharmacological and pharmacokinetic properties of the drug/ drug product so that the modelled use represents use with clinically meaningful doses. Although vnr-parameters are designed to cover the many different indications for that drug, in some cases a better knowledge of the indication for each user would improve the accuracy. As an example, folic acid is used daily in the treatment or prevention of low blood levels of folate. However, persons with rheumatoid arthritis using methotrexate therapy are recommended to take 5 milligrams of folic acid on the day after methotrexate intake (once a week). Thus, this kind of uncommon pattern of use cannot be modelled correctly with parameters which restrict a drug's use to daily intake. A better measure of once a week use would demand that there would be information on indication and/or other drugs used by the person (methotrexate) and preferably the week day of administration of methotrexate and/ or folic acid to be able to assign exposure to the correct day of the week. However, then the output should be in different format also as the effects of folic acid once a week do not last for the entire week until the next dose.

Laugesen et al. (2017) used waiting time distribution at the higher ATC level, i.e. their example was oral glucocorticoids (ATC codes H02AB01-09), not individual ATC or package level to determine the duration of a treatment episode. This ignores the possible different durations of different packages but on the other hand, drugs for continuous use are commonly prescribed for three months in Denmark. This corresponds to PRE2DUPs ability to use higher level ATC parameters, which are seldom used since the vnr-level parameters are defined for most drugs.

The stockpiling test is based on a local temporary decrease in dose which is a simple estimate of stockpiling event. Although it is a good measure, it does not recognise possible stockpiling further back in time. If the stockpiling of drugs has happened earlier, it is difficult or impossible to recognize this as stockpiling without knowledge of real temporal dose and adherence. Therefore, the stockpiling test is capable of detecting only recent stockpiling and fails to detect the consumption of previously stockpiled drug after more than one purchase. Stockpiling has been implemented also in the days' supply calculation, where at each drug purchase, the estimated stock according to intended use has been calculated and added to the duration of each purchase (Parker et al. 2015).

The estimation of the duration of drug use after the last purchase is a difficult task to solve. Drugs may be used differently after the last purchase than before or not used at all. One solution is to not take into account the drug use after the last purchase and omit time after the last purchase (Lichtenstein et al. 2012) e.g. for outcomes like death, all drug use would end before the outcome. PRE2DUP calculates estimated duration from last purchase and drug use periods contain this time from last purchase.

6.1.3 Calculation of package parameters

The preferred way to assign the duration for single purchases is to use information from the person's other drug use periods of the same drug, if it exists. This provides a good estimate of how the person uses the drug although single short periods may be at a different dose than long-term use. When the person has not used the drug during drug use periods with several purchases, it is not possible to make the dose estimate from his/her own use. In such cases, PRE2DUP uses the typical refill length of this particular package from the study population, if this has been calculated, or alternatively expert defined typical dose from vnr-parameters. The calculation of typical refill length of the population does not take into account certain personal characteristics such as age or gender. In some cases or with certain study populations, the calculation of typical refill length could be improved with either modelling typical drug use with covariates such as age and gender or by stratifying the calculation according to these variables. The latter method would produce most common refill lengths for each group but modelling could produce values in-between peaks i.e. values that are not used realistic. For example, if females typically use 3 tablets per day and males 4 tablets per day of a certain drug (package) then the modelling would result in an average dose of 3.2 tablets for females and 3.9 tablets for males. These doses would not be exact doses but merely weighted averages of dose. Waiting time distribution re-defined with covariates as a way of obtaining a better estimate of duration (Thrane et al. 2018) and COV method (Meid and Haefeli 2017) are based on such an approach.

6.2 OVERALL VALIDATION OF THE PRE2DUP METHOD (STUDY I)

The PRE2DUP method generates highly reliable drug use periods according to expert opinion validation. Many of the investigated drug classes displayed over 90% correctness with respect to the duration of drug use periods. In the placement of a single purchase, PRE2DUP achieved even higher correctness, up to 100%. Drug use periods usually contain several purchases and thus, the correctness of a drug use period required that a correct decision had to be made with every purchase in the period and possibly even the one before if there had been previous purchases. If single purchases are placed correctly in a drug use period with a probability of 99%, and the periods contain on average ten purchases, the correct placement needs to be conducted ten times. Thus, the probability to obtain correct purchases is 0.99^{10} which is approximately 0.90, i.e. 90% probability. In addition, also the duration of the last purchase needs to be modelled correctly. The proportion of correct durations over 90% means that there are almost no wrong joinings between purchases and the duration from the last purchase is extremely correct for almost all periods. Thus, the somewhat lower results for PRE2DUP in the drug use period test than in the purchase test are related to the fact that correctness of drug use period requires multiple decisions to be evaluated.

The lowest correctness was found for ATC main classes H (systemic hormonal preparations, excluding sex hormones and insulins) and J (anti-infectives for systemic use). At the time of validation, these drug classes did not have any package level parameters which would help in the control for their joining. Class H includes a variety of drugs used for relatively long-term use (such as hydrocortisone for Addison's disease) but also drugs used as short courses (such as prednisolone for acute worsening of asthma). ATC class J includes mainly antibiotics which are administered in short courses. The lower validity of PRE2DUP for modelling these two drug classes was related to the too extensive joining of short course drugs. After this validation, package wise parameters have been re-designed for these problematic drug classes.

The implementation of PRE2DUP has evolved over time and version 15.7 showed fairly good processing speed as it requires two hours computer time per million purchases with on a standard personal computer. One limitation is that the implementation of PRE2DUP is currently only available for dBase and it runs only on the Windows operating system. This limitation could be solved by implementing PRE2DUP in other environments like R or Python. With a larger variety of operating systems even more efficient servers could be used. Restrictions due to data protection may limit access to original data in the future and modelling on remote servers could be a solution.

6.3 PRE2DUP METHOD AND AGREEMENT WITH INTERVIEW (STUDY II)

The agreement between reports from interviews and PRE2DUP modelled drug use was very good for the majority of the drug classes. The proportion of drugs found in both interviews and in the PRE2DUP modelled register data, and vice versa, was over 80% for the majority of drug classes. This agreement was in line with an Irish study where agreement was good for most drug classes but poorest for M01 (anti-inflammatory and antirheumatic products) and N02 (analgesics) (Richardson et al. 2013). A Danish comparison between interview and register based data displayed a much lower agreement than found here, with the Kappa values mostly being below 0.6 (M W Nielsen et al. 2008).

Drugs that are also available OTC (NSAIDS and paracetamol) showed poor results when interviews were compared to the PRE2DUP results. OTC drugs can be purchased without prescription and are thus not recorded in the Prescription register data. Opioids were another class of drugs that showed a somewhat lower level of agreement for this direction although opioids are not available without prescription in Finland but codeine was not reimbursed and thus not recorded. A common feature for these drug classes is the use "as needed" for treating pain. If drugs are used "as needed" they may be purchased but not consumed during the two week time window examined in the interview. This also applies in a converse manner. Some drugs that have been purchased in the past may be used during the assessment period of the interview, but without there being any recent purchases. Over the counter drugs can be purchased without prescription and are thus not recorded in the register data. Other investigated drug classes showed over 60% agreement. On average, the agreement for PRE2DUP-modelled data compared with the interview was higher, i.e. drugs purchased from pharmacy were reported to be in use.

Overall, the level of agreement may be affected by either erroneous modelling or reporting in the interview. In the interview, some drugs may have been reported as being used to please the interviewer, a phenomenon often referred to as "white coat adherence", or alternatively, the respondents had forgotten that they were taking some drugs (Caskie et al. 2006). In the interview, the study nurse had access to medical records and specifically inquired about the use of non-reported drugs. However, some drugs may have been missing from the medical records, such as drugs prescribed by private practitioners. Some drugs actually used and reported in the interview may belong to a spouse or other close relative and thus, may not be recorded in the register data for the interviewee. It is also possible that some parameters were not correctly set for PRE2DUP, leading either to too short or long durations and errors in the joining of purchases. Package parameters in general allow for a lower dose use of drugs as older persons often use drugs with lower dosages than the general population. For example, continuous use of 0.5 tablets per day (corresponding to the same dose as 1 tablet every other day) is permitted for most drugs in the parameter design (for example, for benzodiazepines). However, even lower doses or longer intervals in use may be missed when decisions are made about the lower dose limits.

Hospital stays were not available in this PRE2DUP modelling study, which may explain the results in drug periods with a lower level of correctness. As the study population was 78 years or older, the number of hospital days during the months preceding the interview may be of greater significance for some patients, thus making the drug use periods shorter than they would have been if the number of days of hospitalization had been known. This would have improved the agreement level in comparisons compared with the interviews.

6.4 PRE2DUP METHOD VALIDATION AGAINST EXPERT OPINION (STUDY III)

In an expert-opinion based validation with five drugs, PRE2DUP determined completely correct solutions for up to 90-94% of drug use periods. The highest correctness was observed for mirtazapine (in the DDD evaluation set) and warfarin (in the tablet evaluation set). For both of these drugs, dose may vary at the individual level and choosing one dose assumption would be a compromise. These results show that PRE2DUP performs well in modelling of drugs with individually tailored doses. In both validation sets, the results were the lowest (70-75% of completely correct solutions) for bisoprolol. At the time of the validation, bisoprolol was the only one from these five drugs selected for validation which did not have vnr-parameters for guidance in the joining of the purchases. Although this is only one example, it still implies that the correctness of PRE2DUP may be significantly enhanced if vnr-level parameters are available. Since the validation, vnr-parameters have been designed for bisoprolol.

The expert opinion validation showed clear differences between PRE2DUP and tablet, DDD and the fixed time window methods. As drug dose varies between persons and drugs and, even within an individual and a single drug over time, it is apparent that no simple method with fixed assumptions could generate correct drug use periods for all drugs and individuals. On average, both fixed DDD and time methods had a poor performance, as even fewer than 20% of the drug use periods were correctly generated. The best performing method, one DDD per day and 180 days' grace period that was not added to the end, generated 16% of completely correct drug use periods. The best performing fixed time method generated a mere 4% correct periods. These figures describe how wrong solutions were generated with these methods for these investigated five drugs. For these methods, joining of purchases correctly was already a difficult task, and the duration of the last purchase (conducted only for periods including correct purchases) was rarely correct. In conclusion, it cannot be recommended that these methods should be used for modelling of drug use among older persons.

There may be multiple reasons for the poor performance of the DDD methods. Firstly, the definition of DDD by the World Health Organization (WHO 2016) was created as a metric that converts amounts of drugs into universal and equal dose with the value of one representing average dose of the drug when used for its main indication in adults. In register-based research, the actual indication behind the drug use is rarely known or recorded and furthermore many of drugs may be used for multiple indications, even off-label use. Secondly, the patient's age, sex, weight, comorbidities and other drugs may impact on the used dose. Older persons are more sensitive to the effects of many drugs (Mangoni and Jackson 2003), and consequently reduced dosages are usually recommended (Flammiger and Maibach 2006). An assumption of one DDD per day may therefore be particularly unsuitable for this study population. In addition, the use of several drugs to treat one disease or symptom may exert interacting effects requiring lowering of the dose of another drug, and thus, the composition of the drug regimen may impact on the dose of a drug. Thirdly, dosage may change over time due to titration of dosage, progress of illness, aging, adverse effects, or changes in body composition. Fourthly, the DDD is an average dose and it may be a dose that is seldom used. For example, one DDD of simvastatin is 30mg, but in Finland simvastatin is available in strengths of 10mg, 20mg and 40mg. In practise, either the 20mg or the 40mg dose is selected and these correspond to 0.67 DDD or 1.33 DDD, respectively. M. W. Nielsen et al. (2008) compared interview and one DDD per day modelling for antipsyhotics; it was found that there was a moderate agreement between these two approaches but it was better for 1/3 DDD per day model. This highlights that an estimate based on one DDD per day is not suitable for all drugs and populations.

Tablet methods performed better than DDD and time window methods. The best method tested was one tablet per day with a grace period of 180 days (not added to the end) which judged correctly 54% of drug use periods. Almost as good results were achieved with one tablet and a 90 days' grace period, 45% of correct solutions. These figures are still lower than the performance of the PRE2DUP method in tablet comparison which produced 86% of correct solutions. Statins are often used as one tablet per day (Romppainen et al. 2014), and the results of the best performing tablet method was good for simvastatin (73%), in contrast for warfarin, the proportion of drug use periods judged as correct was considerably lower (44%). Warfarin is an example of a drug for which there is no universal dose applied but the dose is rather constantly titrated according to International Normalised Ration (INR) values measured from blood (Flammiger and Maibach 2006). Many other factors may further impact on whether a drug is used at one tablet per day dose or not. Even pricing and the current reimbursement system may encourage the use of 0.5

tablets of higher strength instead of one tablet of lower strength. Thus, the validity of the tablet assumption should be considered from the perspective of many factors other than purely clinical considerations.

Previous studies have reported that the choice of modelling parameters for simple methods, such as altering the length of the grace period, may produce different estimates of the duration of drug use (Gardarsdottir et al. 2010, Parker et al. 2015). It is recommended that investigators should refrain from choosing different grace periods when modelling the longest exposure period (such as persistence) as compared to modelling of acute and ongoing exposure at the time of an outcome event. This selective modelling according to a particular research questions makes data incompatible when different drug use periods are generated from the same data. It remains an unanswered question how best to correct this type of "adjustment" of data according to research purposes. One of the basic ideas in the development of PRE2DUP was to conduct drug use modelling as accurately as possible, and then use the same modelled drug use periods to answer different research questions. This would ensure comparability of results within the research entity.

The difference between PRE2DUP and fixed methods varies according to which drugs are being evaluated. In the appendices, there are comparisons of different drug classes and fixed time window, DDD and tablet methods with varying grace periods. In these examples, PRE2DUP is considered as the reference method, and deviation was calculated as differences in time and the number of periods. When the length of the grace period increases, the time when the drug is being taken increases and the number of separate periods decreases. As the dose differs between individuals taking the same drug, one fixed method can produce longer and shorter drug use times, or a different number of periods as compared to PRE2DUP. For example, lipid modifying agents (ATC C10) have a 10.2% shorter times and 0.1% longer times with one tablet and 30 days' grace period method (TAB_1_30) as compared to PRE2DUP. This may not seem to be a major discrepancy, but for some patients the difference can be either notably larger or smaller. The difference in the number of drug use periods is much larger, 126% more periods and 0.1% less periods. This means that the number of periods is more than double, and in practise, never smaller than when calculated with PRE2DUP. The results of a duration or persistence study would be significantly changed with this kind of splitting of drug use periods as the average length halves when the number of periods doubles for the same total duration.

These results of study III show that only methods using personal dose estimates can reliably identify drug use periods. As the data used in this comparison consisted of the dosages used by older persons, this may in part explain the very poor performance of the DDD methods. Fixed time methods may answer the question of whether a person has used the investigated drug, but the exact timing for use cannot be correctly assessed.

7 Conclusions

Based on the results of this thesis, the following conclusions can be drawn:

1) The PRE2DUP method achieved a good agreement when compared with expert opinion based evaluation and drug use reported in interviews.

2) PRE2DUP calculates personal dose for each purchase and this estimate can vary over time. This feature makes the estimates of drug use periods more accurate than can be achieved with fixed methods for drugs used at variable doses in the same individual or by different persons.

3) Fixed time window and dosage methods were unable to estimate correctly the drug use periods for most of the investigated drugs. Thus, these methods should be avoided especially when studying duration, persistence and current use when reliable estimates of drug use periods are needed.

8 Implications

1) More research is needed to compare the various methods developed for generating drug use periods, not only determinations of how correct are the solutions that they produce, but also how much the selection of the method affects the results of pharmacoepidemiological studies.

2) The development of new methods that produce more precise estimates of drug use should be encouraged in pharmacoepidemiological research.

3) Improving the current methods is equally important as the data sources evolve and possibilities to use new sources of information become available.

4) Providing methods openly available to researchers, as easy-to-use tools could ease the transition from simple methods to more advanced alternatives.

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APPENDICES

Appendix 1. The results of A) different tablet methods and B) DDD and fixed time window methods and PRE2DUP included in both evaluation sets. COMP-COR: completely correct, COR-ENS: correct purchases joined but end-date not solvable, COR-FAL: correct purchases but end date wrong, NON-S: non-solvable purchase history, WRONG: contains wrong purchases. TAB(DDD)_066_0 refers to assumption of 0.66 tablets or DDD per day, methods TAB(DDD)_1_0 to TAB(DDD)_1_180 refer to one tablet or DDD per day assumption and grace periods assigned at the end of abbreviation (from 0 to 180 days), and grace periods not being included for the last purchase. WIN_90 to WIN_360 are fixed time windows of 90 to 360 days. Drugs were: warfarin (ATC: B01AA03), bisoprolol (C07AB07), simvastatin (C10AA01), risperidone (N05AX08) and mirtazapine (N06AX11).

A) Tablet comparison

Method	**Drug**	**WRONG**	**NON-S**	**COR-FAL**	**COR-ENS**	**COMP-COR**	**Grand Total**
PRE2DUP	B01AA03	5		5		90	100
	C07AB07	16	3	4	2	75	100
	C10AA01	5	1	4	1	89	100
	N05AX08	1	1	6	5	87	100
	N06AX11	5	0	6	1	88	100
TAB_066_0	B01AA03	69		26	2	3	100
	C07AB07	59	2	39			100
	C10AA01	62		33	1	4	100
	N05AX08	53	1	32	2	12	100
	N06AX11	60	0	24	0	16	100
TAB_1_0	B01AA03	87		8		5	100
	C07AB07	86	1	9		4	100
	C10AA01	98				2	100
	N05AX08	82	1	4	2	11	100
	N06AX11	92	0	0	0	8	100
TAB_1_180	B01AA03	3		49	4	44	100
	C07AB07	15	2	39	1	43	100
	C10AA01	8	1	17	1	73	100
	N05AX08	15	1	36	5	43	100
	N06AX11	16	0	18	1	65	100
TAB_1_30	B01AA03	74		9		17	100
	C07AB07	65	2	15	1	17	100
	C10AA01	77	1	4		18	100
	N05AX08	52	2	13	2	31	100
	N06AX11	60	0	3	1	36	100
TAB_1_90	B01AA03	51		22	1	26	100
	C07AB07	35	2	26	1	36	100
	C10AA01	34		9	1	56	100
	N05AX08	22	3	30	5	40	100
	N06AX11	20	1	13	1	65	100

Appendix 1 (Continued)
B) DDD and fixed time window comparison

Method	**Drug**	**WRONG**	**NON-S**	**COR-FAL**	**COR-ENS**	**COMP-COR**	**Grand Total**
PRE2DUP	B01AA03	8	*4*	6	4	78	100
	C07AB07	15		11	4	70	100
	C10AA01	6	*2*	4	2	86	100
	N05AX08	4	*1*	5	4	86	100
	N06AX11	3	*1*	1	1	94	100
DDD_066_0	B01AA03	96		1		3	100
	C07AB07	93		2		5	100
	C10AA01	89		8		3	100
	N05AX08	93		7			100
	N06AX11	82		13		5	100
DDD_1_180	B01AA03	34	*3*	50	1	12	100
	C07AB07	20		64	2	14	100
	C10AA01	21	*2*	62	1	14	100
	N05AX08	24		74	1	1	100
	N06AX11	11		48		41	100
DDD_1_30	B01AA03	97		1		2	100
	C10AA01	88		5	1	6	100
	N05AX08	89		9	1	1	100
	N06AX11	80		4		16	100
DDD_1_90	B01AA03	84		11		5	100
	C07AB07	70		21	2	7	100
	C10AA01	58	*2*	30	1	9	100
	N05AX08	62		36	1	1	100
	N06AX11	25	*1*	35	1	38	100
WIN_180	B01AA03	73		22	1	4	100
	C07AB07	51		47		2	100
	C10AA01	31	*2*	64	1	2	100
	N05AX08	25		68	1	6	100
	N06AX11	25		68		7	100
WIN_360	B01AA03	21	*5*	74			100
	C07AB07	19		81			100
	C10AA01	22	*1*	77			100
	N05AX08	24		76			100
	N06AX11	17	*1*	82			100
WIN_90	B01AA03	97		1		2	100
	C07AB07	92		6	1	1	100
	C10AA01	91	*1*	6		2	100
	N05AX08	73		15	1	11	100
	N06AX11	87		7		6	100

Appendix 2. Duration of drug use periods produced with tablet methods compared to PRE2DUP. ATC classes are according to the second level, i.e. therapeutic subgroup. Under time refers to the number of days where the tablet method estimates a personal drug use time shorter than that calculated with PRE2DUP, and conversely over time refers to excess time. Figures are percentages of summed under/over times of total time calculated with PRE2DUP. The last row shows total time calculated with PRE2DUP as reference time.

Method	**ATC**	**A02**	**B01**	**C07**	**C08**	**C09**	**C10**	**G04**
TAB_066_0	under time	0.0%	-2.7%	-4.9%	-1.8%	-3.8%	-2.8%	-0.1%
	over time	17.9%	8.7%	3.1%	4.8%	2.8%	1.7%	20.9%
	total difference	18.0%	11.5%	8.0%	6.6%	6.7%	4.5%	21.0%
TAB_1_0	under time	-7.4%	-12.0%	-14.0%	-8.2%	-13.0%	-14.4%	-4.7%
	over time	3.5%	3.2%	0.8%	1.5%	0.5%	0.0%	6.3%
	total difference	10.8%	15.2%	14.8%	9.7%	13.5%	14.4%	11.0%
TAB_1_15	under time	-5.4%	-11.5%	-12.8%	-7.0%	-11.6%	-12.3%	-3.8%
	over time	3.9%	3.2%	0.8%	1.6%	0.6%	0.1%	6.5%
	total difference	9.3%	14.7%	13.6%	8.5%	12.1%	12.4%	10.3%
TAB_1_30	under time	-3.7%	-10.6%	-11.5%	-5.9%	-10.1%	-10.2%	-2.9%
	over time	5.0%	3.3%	0.9%	1.6%	0.6%	0.1%	7.1%
	total difference	8.8%	13.9%	12.4%	7.5%	10.8%	10.3%	10.0%
TAB_1_60	under time	-2.1%	-8.6%	-8.6%	-4.5%	-7.5%	-7.0%	-1.9%
	over time	8.6%	3.4%	1.0%	1.7%	0.7%	0.2%	8.8%
	total difference	10.6%	12.0%	9.5%	6.2%	8.2%	7.2%	10.6%
TAB_1_90	under time	-1.4%	-6.4%	-6.0%	-3.4%	-5.5%	-4.8%	-1.4%
	over time	12.6%	3.6%	1.1%	1.8%	0.8%	0.3%	10.6%
	total difference	14.0%	9.9%	7.1%	5.2%	6.3%	5.1%	12.0%
TAB_1_180	under time	-1.2%	-2.2%	-2.5%	-1.8%	-2.7%	-1.9%	-1.1%
	over time	23.3%	4.6%	1.4%	2.1%	1.0%	1.2%	15.8%
	total difference	24.5%	6.8%	3.8%	3.9%	3.7%	3.1%	16.8%
TAB_1_270	under time	-1.1%	-1.2%	-1.6%	-1.4%	-2.1%	-1.5%	-1.0%
	over time	31.7%	6.6%	2.0%	2.5%	1.4%	2.3%	20.0%
	total difference	32.8%	7.8%	3.6%	3.9%	3.5%	3.8%	21.0%
reference time in thousand years		22.2	47.2	112.7	49.7	63.7	55.0	7.3

Appendix 2 (Continued)

Method	ATC	H02	J01	M01	N02	N03	N05	N06
TAB_066_0	under time	-16.7%	-0.3%	0.0%	-6.1%	-0.4%	-3.6%	-1.4%
	over time	6.6%	75.7%	26.3%	27.1%	21.9%	9.0%	6.7%
	total difference	23.3%	76.0%	26.3%	33.2%	22.3%	12.6%	8.1%
TAB_1_0	under time	-30.1%	-6.0%	-6.5%	-13.9%	-2.1%	-15.3%	-8.5%
	over time	1.7%	37.7%	4.1%	11.9%	9.6%	2.5%	2.0%
	total difference	31.8%	43.6%	10.6%	25.9%	11.7%	17.9%	10.5%
TAB_1_15	under time	-29.5%	-5.1%	-5.7%	-13.4%	-1.9%	-14.6%	-7.0%
	over time	1.7%	38.4%	4.3%	12.0%	9.7%	2.6%	2.1%
	total difference	31.3%	43.6%	10.0%	25.4%	11.6%	17.1%	9.1%
TAB_1_30	under time	-28.5%	-4.1%	-4.7%	-12.6%	-1.8%	-13.4%	-5.7%
	over time	1.8%	40.2%	4.9%	12.2%	9.9%	2.6%	2.2%
	total difference	30.3%	44.3%	9.7%	24.9%	11.6%	16.0%	7.9%
TAB_1_60	under time	-25.6%	-2.6%	-3.1%	-10.9%	-1.4%	-10.5%	-4.0%
	over time	2.0%	45.9%	7.5%	12.6%	10.2%	3.0%	2.4%
	total difference	27.6%	48.6%	10.6%	23.5%	11.6%	13.4%	6.4%
TAB_1_90	under time	-22.5%	-1.7%	-2.3%	-9.2%	-1.0%	-7.5%	-2.8%
	over time	2.2%	53.8%	11.4%	13.0%	10.6%	3.6%	2.7%
	total difference	24.6%	55.6%	13.8%	22.2%	11.6%	11.2%	5.5%
TAB_1_180	under time	-15.1%	-1.2%	-2.1%	-5.6%	-0.3%	-2.8%	-1.4%
	over time	2.8%	83.6%	24.2%	14.6%	12.0%	6.3%	3.6%
	total difference	17.9%	84.8%	26.3%	20.2%	12.3%	9.1%	5.0%
TAB_1_270	under time	-11.0%	-1.0%	-2.0%	-3.7%	-0.2%	-2.0%	-1.2%
	over time	4.4%	117.3%	35.6%	17.4%	13.1%	10.2%	4.5%
	total difference	15.4%	118.4%	37.6%	21.1%	13.3%	12.2%	5.7%
reference time in thousand years		9.0	17.9	36.4	5.6	9.9	111.1	171.4

Appendix 3. The number of drug use periods produced with tablet methods compared to PRE2DUP. ATC classes are according to the second level, i.e. therapeutic subgroup. Percentages represent the extent of a positive (more) or a negative (less) difference summed over all persons.

Method	**ATC**	**A02**	**B01**	**C07**	**C08**	**C09**	**C10**	**G04**
tab_066_0	more periods	5.7%	61.4%	166.5%	60.2%	117.8%	106.3%	6.2%
	less periods	-3.4%	-2.5%	-2.1%	-1.7%	-0.3%	-0.1%	-4.3%
	total difference	9.1%	63.9%	168.6%	61.9%	118.1%	106.4%	10.5%
tab_1_0	more periods	58.2%	195.6%	526.9%	409.6%	485.4%	529.1%	62.2%
	less periods	-0.3%	-0.5%	-1.1%	-0.6%	-0.1%	0.0%	-0.5%
	total difference	58.5%	196.1%	528.0%	410.2%	485.4%	529.1%	62.6%
tab_1_15	more periods	15.3%	129.1%	267.2%	145.7%	209.0%	221.6%	20.5%
	less periods	-3.1%	-0.9%	-1.5%	-0.9%	-0.2%	0.0%	-2.2%
	total difference	18.3%	130.0%	268.7%	146.6%	209.2%	221.6%	22.7%
tab_1_30	more periods	5.1%	95.2%	184.7%	81.5%	131.6%	126.1%	8.3%
	less periods	-9.6%	-1.3%	-1.8%	-1.1%	-0.3%	-0.1%	-5.8%
	total difference	14.7%	96.6%	186.5%	82.6%	131.9%	126.2%	14.0%
tab_1_60	more periods	0.8%	54.4%	92.5%	37.5%	61.5%	50.7%	1.7%
	less periods	-20.8%	-2.4%	-2.3%	-1.6%	-0.6%	-2.3%	-13.9%
	total difference	21.6%	56.8%	94.7%	39.1%	62.1%	52.9%	15.6%
tab_1_90	more periods	0.1%	28.6%	43.9%	18.4%	29.8%	21.8%	0.5%
	less periods	-28.2%	-3.4%	-2.9%	-2.2%	-1.0%	-5.9%	-20.0%
	total difference	28.2%	32.1%	46.9%	20.5%	30.8%	27.7%	20.5%
tab_1_180	more periods	0.0%	1.5%	3.1%	1.4%	2.1%	0.8%	0.0%
	less periods	-39.2%	-10.7%	-6.1%	-4.5%	-2.6%	-15.1%	-29.7%
	total difference	39.2%	12.2%	9.2%	6.0%	4.7%	15.9%	29.7%
tab_1_270	more periods	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	less periods	-44.1%	-20.7%	-11.6%	-7.8%	-5.8%	-21.2%	-34.3%
	total difference	44.1%	20.7%	11.6%	7.8%	5.8%	21.2%	34.3%
reference number of periods		62,961	20,778	30,437	14,552	20,288	20,358	11,271

Appendix 3 (Continued)

Method	ATC	H02	J01	M01	N02	N03	N05	N06
Tab_066_0	more periods	51.5%	1.0%	4.2%	19.8%	9.4%	51.1%	48.9%
	less periods	-0.7%	-4.0%	-0.4%	-1.6%	-4.6%	-0.9%	-3.1%
	total difference	52.2%	5.0%	4.6%	21.3%	14.0%	52.1%	51.9%
tab_1_0	more periods	98.61%	7.3%	28.2%	46.3%	51.4%	130.8%	271.4%
	less periods	-0.2%	-1.6%	0.0%	-0.7%	-1.0%	-0.3%	-0.1%
	total difference	98.8%	9.0%	28.2%	47.0%	52.3%	131.1%	271.6%
tab_1_15	more periods	72.5%	3.1%	12.1%	27.8%	25.8%	82.2%	92.5%
	less periods	-0.3%	-4.0%	-0.5%	-1.2%	-1.9%	-0.5%	-1.6%
	total difference	72.8%	7.1%	12.6%	29.1%	27.7%	82.7%	94.1%
tab_1_30	more periods	56.8%	1.5%	6.2%	19.7%	17.3%	58.3%	48.9%
	less periods	-0.6%	-6.2%	-3.2%	-1.7%	-3.2%	-1.1%	-2.9%
	total difference	57.3%	7.7%	9.5%	21.4%	20.5%	59.4%	51.8%
tab_1_60	more periods	35.2%	0.4%	1.4%	11.2%	9.1%	30.7%	18.7%
	less periods	-1.0%	-10.0%	-9.5%	-2.6%	-6.1%	-4.1%	-6.0%
	total difference	36.2%	10.4%	10.8%	13.7%	15.2%	34.8%	24.7%
tab_1_90	more periods	21.3%	0.1%	0.1%	6.6%	4.5%	14.9%	7.9%
	less periods	-1.6%	-13.2%	-15.5%	-3.4%	-7.9%	-8.3%	-9.1%
	total difference	22.9%	13.3%	15.6%	10.0%	12.4%	23.2%	17.0%
tab_1_180	more periods	3.8%	0.0%	0.0%	1.2%	0.2%	0.5%	0.3%
	less periods	-4.7%	-20.0%	-27.1%	-5.9%	-13.8%	-18.5%	-15.3%
	total difference	8.5%	20.0%	27.1%	7.1%	13.9%	19.0%	15.6%
tab_1_270	more periods	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	less periods	-9.2%	-24.5%	-33.1%	-8.8%	-17.0%	-27.0%	-18.5%
	total difference	9.3%	24.5%	33.1%	8.9%	17.0%	27.0%	18.6%
reference number of periods		10,229	219,738	114,620	10,623	5,831	97,666	87,813

Appendix 4. Duration of drug use periods produced with DDD and fixed time windows methods compared to PRE2DUP. ATC classes are according to the second level, i.e. therapeutic subgroup. Under time refers to the number of days where the tablet method estimates a personal drug use time shorter than that calculated with PRE2DUP and conversely over time refers to excess time. Figures are percentages of summed under/over times of total time calculated with PRE2DUP. The last row shows total time calculated with PRE2DUP as reference time.

Method	**ATC**	**A02**	**B01**	**C07**	**C08**	**C09**	**C10**	**G04**
WIN_90	over time	32.4%	1.0%	0.3%	0.5%	0.4%	0.7%	4.5%
	under time	-6.6%	-23.4%	-19.3%	-16.5%	-17.1%	-16.7%	-12.7%
	total difference	39.0%	24.4%	19.6%	17.0%	17.5%	17.4%	17.3%
WIN_180	over time	82.2%	7.7%	4.0%	5.1%	5.2%	6.7%	19.4%
	under time	-0.2%	-1.5%	-1.0%	-0.7%	-0.7%	-0.3%	-0.5%
	total difference	82.3%	9.2%	5.1%	5.7%	6.0%	7.1%	19.9%
WIN_360	over time	163.5%	29.6%	16.8%	19.2%	20.6%	22.6%	50.6%
	under time	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	total difference	163.5%	29.6%	16.8%	19.2%	20.6%	22.6%	50.6%
DDD_066_0	over time	8.9%	1.4%	0.3%	2.1%	5.9%	0.8%	2.2%
	under time	-9.9%	-23.2%	-32.5%	-11.0%	-6.6%	-27.0%	-8.3%
	total difference	18.7%	24.6%	32.8%	13.1%	12.5%	27.8%	10.5%
DDD_1_30	over time	2.0%	0.2%	0.0%	0.5%	2.3%	0.1%	0.3%
	under time	-19.4%	-38.2%	-46.4%	-20.0%	-12.9%	-41.9%	-16.2%
	total difference	21.3%	38.4%	46.5%	20.5%	15.1%	42.0%	16.5%
DDD_1_90	over time	8.0%	0.2%	0.1%	0.6%	2.5%	0.3%	0.7%
	under time	-6.7%	-20.5%	-20.2%	-7.9%	-5.5%	-13.7%	-8.6%
	total difference	14.7%	20.7%	20.2%	8.5%	8.1%	14.1%	9.3%
DDD_1_180	over time	18.3%	0.7%	0.1%	0.8%	2.8%	0.8%	2.2%
	under time	-4.1%	-8.9%	-7.4%	-3.6%	-2.6%	-5.3%	-4.7%
	total difference	22.4%	9.6%	7.5%	4.4%	5.4%	6.2%	6.9%
reference time in thousand years		25.4	48.6	121.5	52.6	68.8	60.2	29.9

Appendix 4 (Continued)

Method	ATC	H02	J01	M01	N02	N03	N05	N06
WIN_90	over time	8.0%	231.6%	29.1%	12.4%	2.5%	3.8%	1.7%
	under time	-25.7%	-7.9%	-10.7%	-16.5%	-16.7%	-19.1%	-11.4%
	total difference	33.7%	239.5%	39.8%	28.9%	19.1%	22.8%	13.1%
WIN_180	over time	31.3%	479.5%	88.6%	42.4%	13.3%	18.8%	11.4%
	under time	-2.2%	0.0%	-0.4%	-1.5%	-0.7%	-0.9%	-0.2%
	total difference	33.5%	479.5%	89.0%	44.0%	14.0%	19.7%	11.6%
WIN_360	over time	92.2%	924.0%	193.6%	108.7%	39.4%	53.9%	32.6%
	under time	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	total difference	92.2%	924.0%	193.6%	108.7%	39.4%	53.9%	32.6%
DDD_066_0	over time	3.0%	13.6%	6.8%	0.7%	0.2%	1.5%	2.7%
	under time	-31.8%	-41.0%	-15.6%	-45.6%	-39.9%	-33.4%	-8.0%
	total difference	34.8%	54.6%	22.3%	46.3%	40.1%	35.0%	10.7%
DDD_1_30	over time	0.9%	4.7%	1.2%	0.2%	0.0%	0.1%	0.4%
	under time	-47.2%	-51.4%	-29.4%	-55.1%	-51.1%	-43.5%	-14.6%
	total difference	48.1%	56.1%	30.6%	55.2%	51.1%	43.5%	14.9%
DDD_1_90	over time	1.1%	18.5%	4.3%	0.3%	0.1%	0.5%	0.8%
	under time	-32.5%	-25.8%	-17.9%	-34.7%	-24.5%	-26.1%	-6.0%
	total difference	33.6%	44.3%	22.2%	35.0%	24.6%	26.7%	6.9%
DDD_1_180	over time	2.0%	46.9%	12.8%	0.8%	0.5%	2.4%	1.7%
	under time	-20.0%	-11.9%	-9.9%	-21.7%	-11.7%	-11.8%	-3.0%
	total difference	22.0%	58.8%	22.7%	22.4%	12.2%	14.2%	4.7%
reference time in thousand years		10.1	19.0	41.0	23.0	11.1	119.7	194.0

Appendix 5. The number of drug use periods produced with DDD and fixed time window methods compared to PRE2DUP. ATC classes are according to the second level, i.e. therapeutic subgroup. Percentages represent the extent of positive (more) or a negative (less) difference summed over all persons.

Method	**ATC**	**A02**	**B01**	**C07**	**C08**	**C09**	**C10**	**G04**
WIN_90	more periods	41.4%	400.5%	871.1%	822.1%	722.5%	612.3%	213.7%
	less periods	-14.2%	-0.4%	-0.4%	-0.3%	-0.1%	-1.1%	-4.0%
	total difference	55.6%	400.9%	871.5%	822.4%	722.6%	613.5%	217.7%
WIN_180	more periods	0.7%	48.3%	57.7%	33.8%	36.3%	25.2%	9.8%
	less periods	-32.6%	-2.0%	-2.6%	-1.7%	-1.2%	-8.7%	-14.3%
	total difference	33.3%	50.2%	60.2%	35.5%	37.5%	33.9%	24.1%
WIN_360	more periods	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
	less periods	-43.8%	-17.6%	-10.8%	-6.9%	-5.7%	-21.2%	-24.1%
	total difference	43.8%	17.6%	10.8%	6.9%	5.7%	21.2%	24.1%
DDD_066_0	more periods	21.6%	207.4%	571.9%	191.4%	111.2%	428.7%	53.8%
	less periods	-1.2%	-0.1%	0.0%	-0.1%	-0.8%	-0.1%	-0.1%
	total difference	49.0%	351.3%	832.8%	330.1%	202.1%	621.1%	93.7%
DDD_1_30	more periods	63.2%	420.9%	951.4%	446.3%	246.1%	742.6%	138.0%
	less periods	-6.0%	-0.2%	0.0%	-0.2%	-0.6%	-0.1%	-1.0%
	total difference	37.6%	343.5%	814.3%	340.1%	197.9%	574.1%	79.4%
DDD_1_90	more periods	7.2%	165.3%	413.2%	137.3%	79.3%	262.5%	32.1%
	less periods	-24.5%	-0.9%	-0.7%	-1.0%	-1.5%	-4.3%	-7.8%
	total difference	26.4%	83.6%	163.2%	50.4%	33.0%	74.2%	20.7%
DDD_1_180	more periods	0.2%	10.3%	15.7%	4.5%	2.5%	5.0%	1.4%
	less periods	-36.7%	-5.5%	-3.6%	-3.1%	-3.6%	-12.9%	-16.9%
	total difference	37.0%	15.8%	19.3%	7.6%	6.1%	18.0%	18.4%
reference number of periods		69,031	22,609	32,216	15,214	21,522	22,195	23,141

Appendix 5 (Continued)

Method	ATC	H02	J01	M01	N02	N03	N05	N06
WIN_90	more periods	104.4%	10.6%	30.7%	72.4%	303.9%	171.8%	316.1%
	less periods	-1.7%	-9.4%	-7.3%	-1.3%	-1.4%	-2.8%	-2.2%
	total difference	106.0%	20.0%	37.9%	73.7%	305.3%	174.6%	318.4%
WIN_180	more periods	18.3%	0.1%	1.8%	11.1%	20.7%	20.7%	11.6%
	less periods	-4.4%	-18.0%	-18.8%	-4.4%	-6.3%	-11.4%	-10.8%
	total difference	22.6%	18.1%	20.6%	15.4%	27.0%	32.1%	22.5%
WIN_360	more periods	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	less periods	-13.0%	-27.4%	-33.5%	-11.2%	-14.9%	-27.2%	-19.0%
	total difference	13.0%	27.4%	33.5%	11.2%	14.9%	27.2%	19.0%
DDD_066_0	more periods	71.2%	15.0%	20.2%	149.6%	348.9%	163.6%	92.9%
	less periods	-0.2%	-0.1%	-0.4%	0.0%	0.0%	0.0%	-0.2%
	total difference	107.5%	16.2%	35.7%	188.4%	460.8%	201.8%	187.7%
DDD_1_30	more periods	121.7%	17.1%	47.2%	210.6%	522.4%	224.8%	266.3%
	less periods	-0.3%	-3.0%	-1.9%	-0.3%	-0.2%	-0.3%	-0.7%
	total difference	103.9%	16.5%	28.9%	126.4%	375.4%	177.9%	138.6%
DDD_1_90	more periods	55.5%	10.8%	11.5%	63.3%	186.4%	104.4%	48.3%
	less periods	-2.1%	-11.2%	-12.2%	-1.9%	-2.7%	-6.1%	-7.6%
	total difference	33.0%	13.9%	16.7%	33.1%	75.2%	58.4%	24.7%
DDD_1_180	more periods	5.3%	0.0%	0.2%	6.4%	8.9%	5.4%	1.0%
	less periods	-5.5%	-19.0%	-24.0%	-5.0%	-7.3%	-15.9%	-14.2%
	total difference	10.8%	19.0%	24.2%	11.4%	16.2%	21.3%	15.2%
reference number of periods		13,356	222,675	119,674	33,071	6,404	102,989	97,305

ANTTI TANSKANEN

Prescription register data needs to be converted to continuous drug use periods for research purposes. Thesis described a novel method "PRE2DUP" to create these periods. The method uses sliding averages to estimate local drug doses and uses stepwise decision procedure to join subsequent purchases. Method was validated against interview of older residents of Kuopio and by expert opinion within MEDALZ-cohort. Both validations showed high reliability of drug use periods produced byPRE2DUP.

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