Anatomical Therapeutic Chemical Classification (ATC) And Defined Daily Dose (DDD): Principles for classifying and quantifying drug use

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Course outline/objectives

- 1. Introduction: drug classification systems
- 2. ATC classification : definition, structure and principles
- 3. DDD: definition, concept, principles of assignment
- 4. DDD: measure of drug exposure
- 5. ATC/DDD: Applications
- 6. Resources
- 7 Group –work and discussions

INTRODUCTION

Drug classification systems

- **A drug classification system represents:**

- A common language for describing drug assortment in a country or region.

- A standard for uniformity in collection and aggregation of drug use data

- An international standard for comparison of data between countries

Why standardization

- **Standardized and validated information on drug use is essential to :**
- Allow audits of patterns of drug utilization
- Identify problems in drug use
- Initiate educational or other interventions
- Monitor the outcomes of the interventions.
- Example : International focus on:
- Comparable monitoring systems for cross-national antibacterial utilization patterns in the work against bacterial resistance.

Types of drug classification systems

- **Drugs can be classified according to:**
- Organ systems, indications, Mode of action, chemical structure, etc.
- Each classification system will have advantages and limitations
- The application will depend on the purpose, setting, knowledge of the methodology., etc

Types of drug classification systems

- **Two systems** are dominant in drug utilization research worldwide:
- **The Anatomical Therapeutic Classification (AT)** developed by the European Pharmaceutical Market Research Association (EPhMRA)
- **The Anatomical Therapeutic Chemical (ATC)** classification developed by Norwegian researchers.
- **The AT system:** drugs are classified in groups at three or four different levels.
- **The ATC classification system :** is modified and extended from the AT system by the addition of a therapeutic/pharmacological/chemical subgroup as the fourth level and the chemical substance as the fifth level.

What is ATC/DDD

- **ATC classification**
- **Anatomical:** The organ or body system on which a drug acts
- **Therapeutic:** Indication for typical use(s) of a drug
- **Chemical:** Structure and chemical properties of the active principle
- **DDD: Defined Daily Dose**
- The assumed average maintenance dose per day for a drug used for its main indication in adults

Purpose of the ATC/DDD system

- The ATC/DDD system serves as a tool for drug utilization research in order to improve quality of drug use.

- A standard for the presentation and comparison of drug consumption statistics at international, regional and local levels.

ATC/DDD: historic perspective

- **Drug utilization research**: inception in the 1960s.
- **WHO Regional Office for Europe**: 1968 consumption of drugs study (1966-1967).
- **WHO Regional Office for Europe** : 1969 Oslo symposium- DURG, ATC, DDD
- **The Nordic Council on Medicines** (NLN): 1975- published the ATC/DDD system.
- **The NLN**: 1976- published the Nordic Statistics on Medicines using the ATC/DDD methodology

ATC/DDD: historic perspective

- 1981: **ATC/DDD recommended** for international drug utilization studies.
- 1982: **Established the WHO Collaborating Centre for Drug Statistics Methodology in Oslo.**
- 1996: **Globalization** of ATC/DDD system and **centre linked directly** to WHO Headquarters in Geneva
- 2012: **Re-designation** of centre as the WHO Collaborating Centre for Drug Statistics Methodology.

Present ATC/DDD administration

- **The main activities of the Centre:**
- **Classify drugs** according to the ATC system.
- **Establish DDDs** for drugs which have been assigned an ATC code.
- **Review and revise** as necessary the ATC classification system and DDDs.
- **Stimulate and influence** the practical use of the ATC system
- **Organize and facilitate training courses** in the ATC/DDD methodology
- **Provide technical support** to countries in setting up their national medicines classification systems
- **Build capacity** in the use of medicines consumption information.

ATC/DDD: administration

- **WHO International Working Group for Drug Statistics Methodology**
- **Established in 1996**
- **Advisory** body to The WHO Collaborating Centre for Drug Statistics Methodology
- **Comprises** 12 members drawn from the WHO Expert Advisory Panels for Drug Evaluation and for Drug Policies and Management.
- **Selected** by WHO Headquarters representing a wide range of geographical and professional backgrounds
- **Experts** in clinical pharmacology, clinical medicine, international public health, drug utilization and drug regulation.
- **Represent** different users of the ATC/DDD system and different nationalities in the 6 WHO global regions.

ATC/DDD: administration

- **The terms of reference of the Working Group are:**
- **Continue** the scientific development of the ATC/DDD system.
- **Discuss and approve** all new ATC codes, DDD assignments and alterations
- **Promote use** of the ATC/DDD system as an international standard or drug utilization studies.
- **Revise guidelines** for assignment and change of ATC codes and DDDs.

ATC /DDD: administration

- **Develop** methods, manuals and guidelines for the practical application and appropriate use of the ATC/DDD system in developing countries.

- **Work with groups** involved in rational drug use initiatives

- **Integrate methods** for measurement of drug use in assessing needs and outcomes of interventions with the aim of improving drug use.

ATC /DDD: administration

- **Revise procedures** for applications for assignment of and changes to ATC codes and DDDs to ensure they are consistent and transparent.

- **Assess the sources** and availability of statistics on drug use internationally

- **Encourage** the systematic collection of comprehensive drug use statistics in all countries and regions using the ATC/DDD system as the international standard.

ATC /DDD: administration

- **The mandate of the Centre and Working Group is to:**

- **Maintain stable** ATC codes and DDDs over time to allow trends in drug consumption to be studied without the complication of frequent changes to the system.

- ***There is a strong reluctance to make changes to classifications or DDDs where such changes are requested for reasons not directly related to drug consumption studies.***

ATC: CLASSIFICATION STRUCTURE

ATC classification structure

- The **Anatomical Therapeutic Chemical (ATC) Classification System** is used for the classification of **active ingredients** of drugs according to the **organ** or **system** on which they act and their **therapeutic, pharmacological** and **chemical** properties.

ATC classification structure

- This **pharmaceutical coding system** divides drugs into different groups according to the **organ or system** on which they act and their **therapeutic indication**, **pharmacological action** and **chemical characteristics**.

- Each bottom-level **ATC code** stands for a pharmaceutically used substance, or a combination of substances, in a single indication or use.

Classification structure

- **Drugs are classified in groups at five different levels.**
- **1st level:** The drugs are divided into fourteen main groups according to the **organ system** they act on
- **2nd level:** according to the **main therapeutic** indication.
- **3rd level:** according to the **pharmacological** action or **therapeutic** sub-group
- **4th level**: according to the **chemical class**
- **5th level:** is the **chemical substance.**

ATC : 5 class levels

	ATC level	ATC code	ATC text
1	Anatomical Main Group (one letter)	A	*Alimentary tract and metabolism*
2	Therapeutic Subgroup (two digits)	A10	*Drugs used in diabetes*
3	Pharmacological subgroup (one letter)	A10B	*Oral blood glucose lowering drugs*
4	Chemical Subgroup (one letter)	A10B A	*Biguanides*
5	Chemical Substance (two digits)	A10B A02	*Metformin*

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Level 1: Anatomical groups (14)

A	ALIMENTARY TRACT AND METABOLISM
B	BLOOD AND BLOOD FORMING ORGANS
C	CARDIOVASCULAR SYSTEM
D	DERMATOLOGICALS
G	GENITO -URINARY SYSTEM AND SEX HORMONES
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL.
J	ANTI-INFECTIVES FOR SYSTEMIC USE
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
M	MUSCULO-SKELETAL SYSTEM
N	NERVOUS SYSTEM
P	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS
R	RESPIRATORY SYSTEM
S	SENSORY ORGANS
V	VARIOUS

Level 2: Therapeutic Indications

ATC2	*Selected Examples*
A10	DRUGS USED IN DIABETES
B05	BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS
C02	ANTIHYPERTENSIVES
C07	BETA BLOCKING AGENTS
H03	THYROID THERAPY
L04	IMMUNOSUPPRESSIVE AGENTS
M03	MUSCLE RELAXANTS
N01	ANESTHETICS
S01	OPHTHALMOLOGICALS
S02	OTOLOGICALS

Level 3: Pharmacological groups

ATC3	Selected examples
A02A	Antacids
A06A	Laxatives
A10A	Insulin and analogues
N05A	Antipsychotics
N06A	Antidepressants
S01A	antiinfectives
S01C	Antiinflammatory and antiinfectives in comb
S02A	Antiinfectives

Nomenclature

- **International nonproprietary names** (INN):
- are preferred.
- If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Name) names are usually chosen.

- **WHO's list of drug terms:**
- Pharmacological action and therapeutic use of drugs
- List of Terms is used when naming the different ATC levels.

ATC : Inclusion and exclusion criteria

- Inclusion criteria:
- ***Requests from the users of the system*** **-manufacturers, regulatory agencies and researchers**
- New chemical entities for licensing in a range of countries.
- Existing well defined chemical entities in a variety of countries.
- An INN established for the active ingredient or USAN or BAN
- Herbal medicinal products approved by regulatory
- Other medicinal products are considered on a case by case basis.

ATC : Inclusion and exclusion criteria

- Exclusion criteria

- A new chemical entity without an application for marketing authorisation in at least one country.

- Complementary, homeopathic and herbal traditional medicinal products are not included in the ATC system

ATC:
Principles for classification

ATC: General Principles

- **Main Principle:**
- Medicinal products are classified according to the main therapeutic use of the main active ingredient.
- **One ATC code**:
- Each route of administration
- Similar ingredients and strength
- Immediate and slow release tablets

One ATC code: “different indications”

- **Duloxetine – Indications**
- Major depressive disorder
- Stress urinary incontinence
- Diabetic neuropathic pain
- Overlapping dosages used for the various indications
- ATC code as *antidepressant (N06AX21)*

More than one ATC code

- **When a drug has:**
- Two or more strengths
- Two or more routes of administration
- Clearly different therapeutic uses.

Different ATC codes: " different strengths"

- **Sex hormones**: Dosage forms and strengths for cancer - under L02 - *Endocrine therapy*
- Other dosage forms/strengths – under G03 - *Sex hormones and modulators of the genital system*

- **Finasteride:**
- A low strength tablet for male pattern baldness - under D11AX – *Other dermatologicals*.
- A high strength tablet for benign prostatic hypertrophy (BPH) - under G04C - *Drugs used in BPH.*

Several ATC codes – “one indication”

Bone diseases/osteoporosis	**ATC group**
Vitamin D and analogues	A11CC
Calcium supplement	A12A
Estrogens/Tibolon/SERM	G03C/G03F/G03X
Parathyroid hormones	H05AA
Calcitonin	H05BA
Bisphosphonates	M05BA/M05BB

Several ATC Codes – "Administration Forms and Therapeutic Use"

- **Prednisolone**

  A07EA01 (Enemas and rectal foams)

  C05AA04 (Rectal suppositories)

  D07AA03 (Creams, ointments and lotions)

  H02AB06 (Tablets, injections)

  R01AD02 (Nasal sprays/drops)

  S01BA04 (Eye drops)

  S02BA03 (Ear drops)

ATC codes: Combination products

- Combination products with two or more active ingredients in the same 4th level are normally classified using the 5th level codes 20 or 30.
- Example:
- N01BB02 *lidocaine*
- N01BB04 *prilocaine*
- N01BB20 *combinations of lidocaine and prilocaine*

Principles for changes to ATC classification

- *Changes should be kept to a minimum.*
- **Alterations in ATC classification due to:**
- The main use of a drug has changed
- Create new groups for new substances
- Achieve better specificity in the groupings.
- **The principles of alteration:**
- - Provide space for future extension of an ATC group.
- - The ATC code for combination products to correspond to the classification of the single substances in question.

Principles for changes to ATC classification

- Deleted ATC codes are not reused for new substances.
- Obsolete drugs or drugs withdrawn are kept in the ATC system as historical data.
- On alteration of ATC code, the DDD is also reviewed.
- For example:
- classification of chloroquine was changed from ATC group M to P.

Other ATCs: ATC vet

- The ATC classification for veterinary medicinal products, ATCvet, is based on the same main principles as the ATC system for medicines for human use.

- The ATCvet classification is kept as close to the human system as possible, but with special adaptations in order to make it suitable for veterinary medicines.

- Classification can be found at website : www.whocc.no.

Other ATCs: ATC herbal

- ATC herbal is structurally similar to the official ATC system, but the herbal classification is not adopted by WHO.
- The Uppsala Monitoring Centre has published Guidelines for Herbal ATC (HATC) classification and a Herbal ATC Index.
- The Herbal ATC Index includes a list of accepted scientific names with HATC codes, while the guideline is intended to help in assigning HATC codes to herbal remedies.
- Further information : The Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring).

DEFINED DAILY DOSE (DDD)

DDD: Definition

- **The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.**

- A technical unit of measurement, represents an ”average” daily dose for the main indication

The concept of DDD

DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose (PDD)

- The DDD should reflect global dosage irrespective of the wide inter-individual and inter-ethnic variations in PK of drugs

- DDDs is a fixed unit of measurement independent of **price, currencies, package size and strength.**

- DDDs are not established for: **topical products, sera, vaccines, anti-neoplastic agents, allergen extracts, general and local anesthetics and contrast media**.

Principles for DDD assignment

- A DDD is only assigned for drugs that already have an ATC code.
- The basic principle is to assign only one DDD per route of administration within an ATC code.
- DDDs for single substances are normally based on monotherapy
- A DDD not be assigned for a substance before a product is approved and marketed in at least one country.
- The Working Group decide on inclusion/exclusion criteria for special products.

Sources used when assigning DDDs

- Approved dose recommendations for the main indication

- Submitted documentation from the applicant, peer reviewed publications and data from clinical trials

Alterations in ATC/DDD

- Alterations of ATC and DDDs may occur in order to reflect changes in drug therapy.

- It is important to describe the version of the ATC/DDD system used in research.

The prescribed daily dose (PDD)

- **Prescribed daily dose and consumed daily dose**
- The prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions.

- The PDD can be determined from studies of prescriptions or medical or pharmacy records.

- The PDD will give the average daily amount of a drug that is actually prescribed.

PDD: interpretation

- **PDD vs DDD**
- **PDD may be affected by various factors:**
- Morbidity/diagnosis
- Demographic characteristics
- Severity of illness
- Ethnic variability
- Prescribing habits
- Dispensing habits
- Patient compliance
- **Consumed daily dose –actual drug use at patient level**

DDD : measure of drug exposure

- **Outpatients: DDDs per 1000 inhabitants per day**
  Estimate of the **proportion of the population** treated daily with a particular drug or group of drugs.

For example: 10 DDDs per 1000 inhabitants per day indicates that **1% of the population** on average might receive a certain drug daily.

- **4 DDDs of amoxicillin per 1000 inhabitants per day**
  suggests that on any given day, for every 1000 persons, 4 adults received a daily dose of 1 g of amoxicillin.

The assigned DDD for amoxicillin is 1 g

DDD : measure of drug exposure

- **Inpatients: DDDs per 100 bed-days**

  For example: **70 DDDs per 100 bed days of hypnotics:**

  Estimate of the therapeutic intensity and suggests that **70% of the inpatients might receive a DDD** of a hypnotic every day.

  2 DDD of gentamicin per 100 bed-days

  Estimates that, for every 100 beds in the hospital, every day, 2 patients received 240 mg of gentamicin.

  The assigned DDD for gentamicin is 240 mg.

DDD: measure of drug exposure

- **Anti-infectives or drugs used for short period**

  DDDs per inhabitants per year

- An estimate of the average number of days for which each inhabitant is treated annually.

- Example: an estimate **of 5 DDDs per inhabitant per year** indicates that the utilization is equivalent to the treatment of every inhabitant with a five-day course during a certain year.

Pediatric DDD

- DDDs are normally assigned based on use in adults
- For pediatric medications, dose recommendations are based on age and body weight.
- Most pediatric medications are used off label and documentation regarding dose regimens is not available.
- The WHO has concluded that it is not possible to assign pediatric DDDs
- Prevalence of drug use in children to be based on PDD or indications in pediatric populations
- Use general DDD

.

Applications of the ATC/DDD

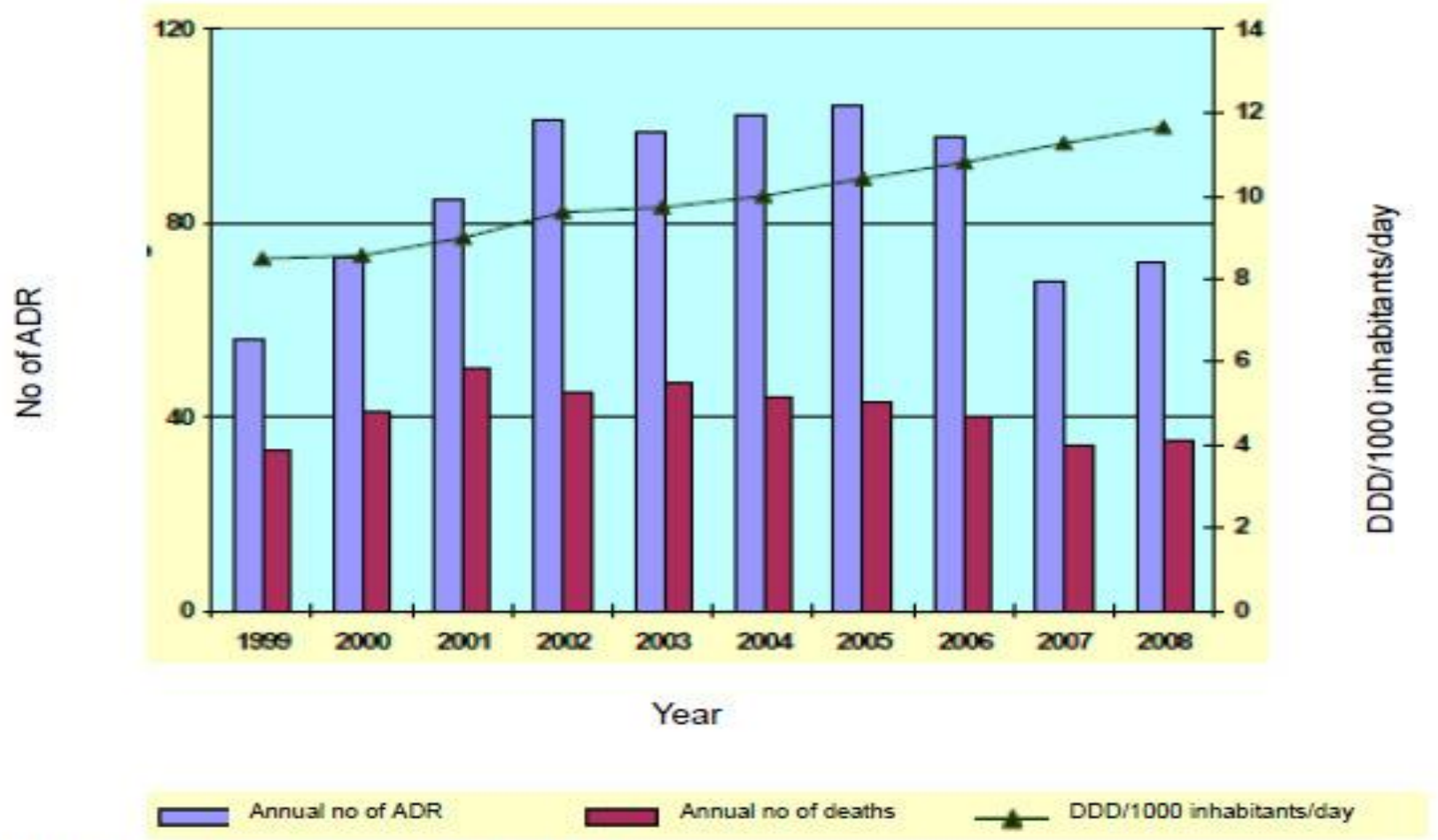
- Drug utilization and pharmacoepidemiology
- Pharmacovigilance
- Regulatory intervention
- Impact of drug use

Pharmacovigilance

- Trends in frequency of ADR reports examined against drug exposure

- Ratio: ADR/DDDs (or DDD/1000 inhab/day)

Spontaneous ADR Reports of Warfarin (B01AA03) in Norway 1999-2008



Source: Norwegian Medicines Agency, Annual report 2008

Following and Comparing Trends in Drug Expenditure

- ATC: to determine to what extent increased costs can be attributed to increased use of a drug group

- DDD: to compare costs of two formulations of the same active ingredient

- DDD: to follow the expenditure of a certain treatment

Use in Drug Utilization

- It provides a tool where ATC and DDD are
- established for generic substances.

- The users have to make the correct link between the ATC/DDD value and the medicinal product.

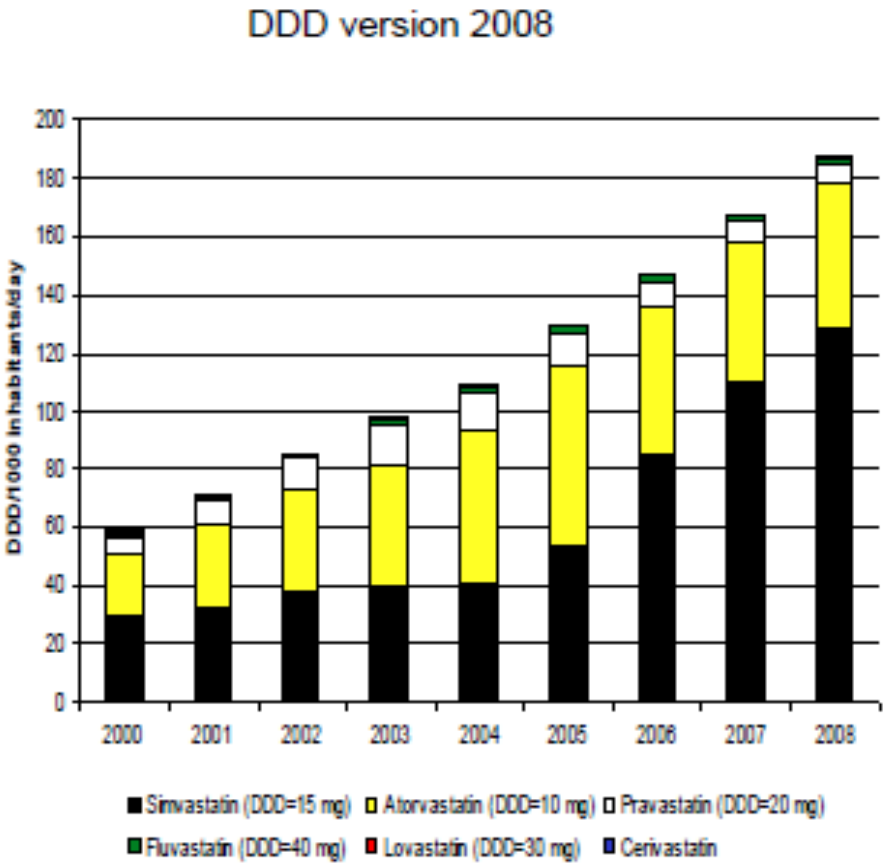
National Drug Register – Link to ATC/DDD

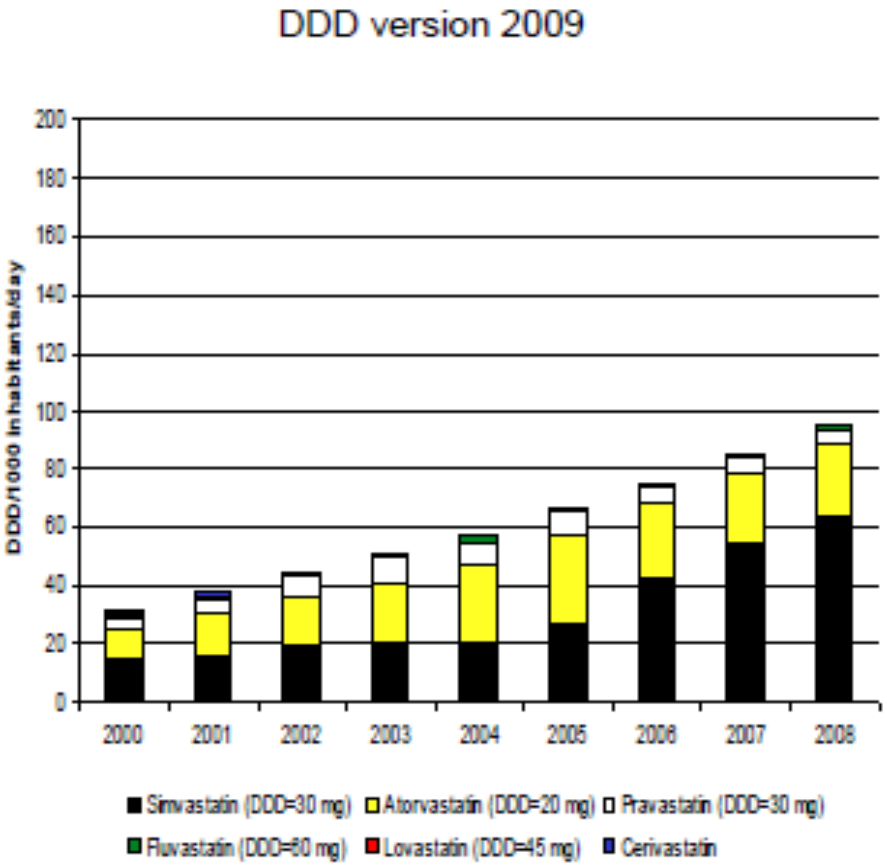
- ATC codes should be linked correctly to the product on the package level
- Number of DDDs per package should be calculated
- Procedures for updating the medicinal product register according to the latest ATC/DDD version should be introduced

Notice DDD alterations

- Be aware of:
  - Cumulative list of ATC/DDD alterations
- **www.whocc.no**
  - DDD alteration example **:**
- Statins - C10AA (changed twice, latest 2009

Sales of Statin (C10AA) in Norway 2000-2008





ATC/DDD in Drug Utilization Research

- Study patterns of drug use and changes over time
- Evaluate the impact of information efforts, regulatory changes etc.
- Study drug exposure in relation to adverse drug reactions
- Indicate over-use, under-use and misuse/abuse of drugs
- Define need for further pharmacoepidemiology studies
- Proper knowledge about the ATC/DDD system

Conclusion

- ATC/DDD system is “the gold standard” for international drug utilization research

- ATC/DDD is a tool for exchanging and comparing data on drug use at local, national or international levels

Resources

- www.whocc.no
- Annual ATC/DDD courses in Oslo, Norway
- Introduction to Drug Utilization Research (pdf)
- Guidelines for ATC classification and DDD assignment 2015 (pdf)
- Annual list of ATC index with DDDs
- A searchable version of the ATC/DDD index
- Lists of the annual ATC/DDD alterations and new ATC/DDDs
- Cumulative lists of ATC/DDD alterations performed since 1982
- List of DDDs for combined products

Group-work and discussion