Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD): principles for classifying and quantifying drug use

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Disclosure

• Author is an employee of Merck

• A lot of slides are adopted from a prior ICPE English short course on drug utilization by Hege Salvesen Blix
Outline

• The ATC/DDD methodology
  – definitions, purpose, structure and principles

• Real world applications of ATC/DDD
What is ATC/DDD?

• ATC (Anatomical Therapeutic Chemical) classification
  – Don’t confuse it with Anatomical Therapeutic (AT) classification developed by European Pharmaceutical Market Research Association (EPhMRA)

• DDD (Defined Daily Dose) *The assumed average maintenance dose per day for a drug used for its main indication in adults*

Introduction to Drug Utilization Research, WHO 2003
Main Purpose

• “International language for drug utilization research”
  – to serve as a tool for presenting drug utilization research in order to improve quality of drug use
  – to compare data within a country and between countries
The WHO Collaborating Centre for Drug Statistics Methodology

- Established in 1982 as a European WHO Centre
- Since 1996 a global WHO Centre
- Located in the Department of Pharmacoepidemiology at the Norwegian Institute of Public Health
- The staff of the Centre is responsible for drug consumption statistics in Norway
The WHO Centre

• To classify drugs according to the ATC system and assign DDDs

• To review and revise as necessary the ATC classification system and DDDs

• To stimulate and influence the practical use of the ATC system

• To organize training courses in the ATC/DDD methodology
ATC Main Group

- 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. sex hormones and insulins
- J Antiinfectives 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
Structure of ATC Code

- **A** ALIMENTARY TRACT AND METABOLISM (1st level, anatomical main group)
- **A10** DRUGS USED IN DIABETES (2nd level, therapeutic subgroup)
- **A10B** BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS (3rd level, pharmacological subgroup)
- **A10BA** BIGUANIDES (4th level, chemical subgroup)
- **A10BA02** METFORMIN (5th level, chemical substance)
General Principles for ATC Classification

• Drugs are classified according to their main therapeutic use
• Only one ATC code for each administration form
• Several ATC codes:
  • Clearly different therapeutic uses reflected in different
    – Routes of administration (e.g. topical, systemic)
    – Strengths
“Simple” Codes

- Linagliptin (e.g. Trajenta): Antidiabetic → DPP-4 inhibitor → A10BH05
- Lamivudine (e.g. Epivir): HIV → Antiviral → J05AF05
- Sumatriptan (e.g. Imigran): Antimigraine → 5HT1 agonist → N02CC01
- Formoterol (e.g. Oxis): Antiasthmatic → β2 agonist → R03AC13
Different Indication – One ATC Code

• Example duloxetine:
  • –Major Depressive Disorder (Cymbalta: 30mg, 60mg)
  • –Stress Urinary Incontinence (Yentreve: 20mg, 40mg)
  • –Diabetic neuropathic pain (Cymbalta)
• Overlapping dosages used for the various indications

• ATC code as antidepressant (N06AX21)
### Several ATC codes – “one indication”

<table>
<thead>
<tr>
<th>Bone diseases/osteoporosis</th>
<th>ATC group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D and analogues</td>
<td>A11CC</td>
</tr>
<tr>
<td>Calcium supplement</td>
<td>A12A</td>
</tr>
<tr>
<td>Estrogens/Tibolon/SERM</td>
<td>G03C/G03F/G03X</td>
</tr>
<tr>
<td>Parathyroid hormones</td>
<td>H05AA</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>H05BA</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>M05BA/M05BB</td>
</tr>
</tbody>
</table>
Several ATC Codes – Different 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)
Defined Daily Dose (DDD)

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

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

- Useful for measuring and comparing volume of drug use.

- Should not be interpreted as the recommended or prescribed dose but as an international compromise based on review of available documentation.

- DDD may even be a dose that is seldom prescribed, because it is an average of two or more commonly used doses size.
Sources Used When Assigning DDDs

• Approved dose recommendations for the main indication

• Submitted documentation from the applicant, textbooks, and data from clinical trials
Commonly Used Measures

- DDDs per 1000 inhabitants per day
- DDDs per 100 bed-days
- DDDs per inhabitants per year
ATC/DDD Alterations

• 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.
Drug Exposure – Expressed in DDDs

• Is normally given as:
  • DDDs/1000 inhabitants/day  *Example: 10 DDDs/1000 inhabitants/day*
  • Indicates that 1% of the population can receive a certain treatment continuously (i.e. daily)
  • Note: Only true if the DDD is equal to the actual dose used
  • Used as surrogate for point prevalence (therapeutic intensity)
Applications of the ATC/DDD

• Drug utilization and pharmacoepidemiology
  – Pharmacovigilance
  – Regulatory intervention and 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
Sales of Contraceptives in Norway (ATC gr.G03A) 1967-2013 (excl. IUDs, vaginal rings, implants and inj.)
Practical Use in Drug Utilization…

• Challenge:
  – 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
- It is recommended that this task is administered by persons with detailed knowledge of the methodology
- Note:
  - Unofficial ATC codes and DDDs
  - Lack of update according to annual ATC/DDD alterations
Drug Register – Example

<table>
<thead>
<tr>
<th>Unique identifier</th>
<th>Brand name and formulation</th>
<th>Strength</th>
<th>Package size</th>
<th>ATC code</th>
<th>Generic name</th>
<th>DDD value</th>
<th>DDD/package</th>
</tr>
</thead>
<tbody>
<tr>
<td>454173</td>
<td>Zocor tablets</td>
<td>20mg</td>
<td>100</td>
<td>C10AA01</td>
<td>simvastatin</td>
<td>30mg</td>
<td>66.67</td>
</tr>
<tr>
<td>438454</td>
<td>Efexor depot capsules</td>
<td>150mg</td>
<td>98</td>
<td>N06AX16</td>
<td>venlafaxine</td>
<td>100mg</td>
<td>147</td>
</tr>
</tbody>
</table>

Are Published Data Comparable?

- ESSENTIAL INFORMATION:
  - Which ATC codes and DDDs are used
Notice DDD alterations

• Important to 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

[Graph showing sales trends for different statins (C10AA) from 2000 to 2008 for DDD version 2008 and DDD version 2009.]
ATC/DDD in Drug Utilization Research

- Study patterns of 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
“Success Factors”

- Correct link of ATC code and DDD value (i.e. number of DDDs/package) at the medicinal product package level
- Request new ATC codes and DDDs if they are not available
- Describe the ATC/DDD version used, i.e. give proper references in all publications and statistics
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
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.... or annual ATC/DDD courses in Oslo, Norway