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

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Introduction to Drug Utilisation Research
Disclosures

• No conflicts of interest

• The following personal or financial relationships relevant to this presentation existed during the past 12 months/during the conduct of the study:
  – Employment by commercial entity - No
  – Consultancies or advisory Board memberships - No
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  – Royalties from a commercial entity - No
  – Stock ownership or options - No
  – Other - No
Outline

• The ATC/DDD methodology
  – definitions, purpose, structure and principles
• The WHO Collaborating Centre and the Working Group
• Applications of ATC/DDD
Definitions

- **ATC**
  Anatomical Therapeutic Chemical classification

- **DDD (Defined Daily Dose)**
  The assumed average maintenance dose per day for a drug used for its main indication in adults
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 group drugs to facilitate retrieval
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

Terms of reference:

- 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
The WHO International Working Group for Drug Statistics Methodology

• 12 members from: Australia, Denmark, Ecuador, Ghana, India, Japan, Morocco, Pakistan, Sri Lanka, The Netherlands, and Zimbabwe

• Two meetings annually:
  – Approves all new ATC codes, DDDs and alterations
  – Responsible for scientific development
p.33:
“….. Each classification system will have its advantages and limitations and its usefulness will depend on the purpose, the setting used and the user’s knowledge of the methodology ….”

Also available from the WHO website:
http://www.who.int/medicines/areas/quality_safety/safety_efficacy/utilization/en
ATC – main groups

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 the ATC code

<table>
<thead>
<tr>
<th>Level</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>A</td>
<td>ALIMENTARY TRACT AND METABOLISM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1st level, anatomical main group)</td>
</tr>
<tr>
<td>2nd</td>
<td>A10</td>
<td>DRUGS USED IN DIABETES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2nd level, therapeutic subgroup)</td>
</tr>
<tr>
<td>3rd</td>
<td>A10B</td>
<td>BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3rd level, pharmacological subgroup)</td>
</tr>
<tr>
<td>4th</td>
<td>A10BA</td>
<td>BIGUANIDES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4th level, chemical subgroup)</td>
</tr>
<tr>
<td>5th</td>
<td>A10BA02</td>
<td>METFORMIN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5th level, chemical substance)</td>
</tr>
</tbody>
</table>
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 indications – 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)

The 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
Sources used when assigning DDDs

- Approved dose recommendations for the main indication
- Submitted documentation from the applicant, textbooks, and data from clinical trials
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 proton pump inhibitor (A02BC) in Norway in DIDs and cost per DDD 1999-2013
Sales of contraceptives in Norway (ATC gr.G03A) 1967-2013
(excl. IUDs, vaginal rings, implants and inj.)

NorPD 2013: about 320 000 women
Sales of agents used in e.g. hypertension in the Nordic countries in 2012

Source: Health statistics in the Nordic countries 2013, Nomesco*

* Nordisk Medicinalstatistisk Komité 97:2012
Sales of two antibacterials 1998-2006
in DDD/1000 inhabitants/day
(theoretical example)

A: courses of 4 days
B: courses of 8 days

19% reduction
Sales of two antibacterials 1998-2006
in number of courses
(theoretical example)

10% increase
Practical use in drug utilization…

Challenge:

• We provide 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 statins (C10AA) in Norway 2000 - 2008

DDD version 2008

DDD version 2009

- Simvastatin (DDD=15 mg)
- Atorvastatin (DDD=10 mg)
- Pravastatin (DDD=20 mg)
- Fluvastatin (DDD=40 mg)
- Lovastatin (DDD=30 mg)
- Cerivastatin

- Simvastatin (DDD=30 mg)
- Atorvastatin (DDD=20 mg)
- Pravastatin (DDD=30 mg)
- Fluvastatin (DDD=60 mg)
- Lovastatin (DDD=45 mg)
- Cerivastatin
“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
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
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
More information

www.whocc.no

.... or annual ATC/DDD courses in Oslo, Norway
Multiple choice questions
Multiple choice questions

1) Which of the statements is not correct?

a. Drugs are classified according to their main therapeutic use
b. Only one ATC code for each administration form
c. Only one ATC code for each substance
d. ATC can be used for drug utilisation research
e. DDD is linked to an ATC code
Multiple choice questions

2) Which of the statements is not correct?

The ATC/DDD methodology is applied to
a) assess drug use in the adult population
b) assess drug use in humans
c) assess use of drugs in hospitals
d) assess use of drugs in nursing homes
e) assess use of drugs in animals
3) Brekkbein® is a new bisphosphonate. It is indicated for primary hyperparathyroidism, osteogenesis imperfecta, and osteoporosis. Which ATC code would you choose?

a) H05BX Other anti-parathyroids agents
b) M05BA Bisphosphonates
c) M05BB Bisphosphonate combinations
d) M05BC Bone morphogenic proteins
e) M05BX Other drugs affecting bone structure and mineralisation
4) Defined daily dose (DDD) is defined as

a) The DDD is the maintenance dose per day for a drug used for its main indication in adults above 18 years
b) The DDD is the mean dose per day for a drug used for its main indication in a country
c) The DDD is the dose per day for a drug used for its main indication
d) The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults
e) The DDD is the assumed average dose per day for a drug used for its main indication
Multiple choice questions

5) Akerselva® is a new antitrombotic agent (dosage 50 mg x 1 in adults and 40 mg in the elderly 65+). It is also indicated for fish allergy (20 mg x 1). The ATC code is B01AX11.

The DDD is

a) 20 mg
b) 25 mg
c) 40 mg
d) 50 mg
e) 70 mg