WHO ATC/DDD methodology: Classifying and quantifying drug use

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Cochrane Webinar, 30 May 2017
Outline

• The ATC/DDD methodology
  – definitions, purpose, structure and principles
• The WHO Collaborating Centre and the Working Group
• Procedures for establishing ATC codes
• 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
History

• Developed in Norway (in collaboration with European researchers) in the early seventies

• 1976, the “Nordic Council on Medicines” decided to publish “Nordic Statistics on Medicines” using the methodology

• 1982, The WHO Regional Office for Europe established the WHO Collaborating Centre for Drug Statistics Methodology

• 1996, agreement with the World Health Organisation in Geneva concerning the global activity of the Centre
Main purpose

“International language for drug utilization monitoring and research”

- to serve as a tool for presenting drug utilization monitoring and research in order to improve quality of drug use
- to group drugs to facilitate retrieval
The WHO Collaborating Centre for Drug Statistics Methodology

- Located in the Department of Pharmacoepidemiology at the Norwegian Institute of Public Health

**Terms of reference**

- ATC coding
- Establish defined daily doses (DDDs)
- Review and revise as necessary ATC/DDD
- Stimulate use of the system
- Conduct training courses
- Technical support and capacity building
WHO International Working Group for Drug Statistics Methodology

- Nominated in December 1996
- Equal representation from the different regions in the world
- 12 members from: Australia, Croatia, Cuba, Denmark, India, Japan, Morocco, Pakistan, USA, and Zimbabwe
- Observers from: IFPMA and UMC
- Approves all new ATC codes, DDDs and alterations

IFPMA: International Federation of Pharmaceutical Manufacturers Association
UMC: The Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring)
ATC classification

Anatomical

Therapeutic

Chemical
Inclusion criteria

- New chemical entities or biologicals proposed for licensing in a range of countries
- Well defined chemical entities used in a variety of countries
- Herbal medicinal products assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data
### 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
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ALIMENTARY TRACT AND METABOLISM (1st level, anatomical main group)</td>
</tr>
<tr>
<td>A10</td>
<td>DRUGS USED IN DIABETES (2nd level, therapeutic subgroup)</td>
</tr>
<tr>
<td>A10B</td>
<td>BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS (3rd level, pharmacological subgroup)</td>
</tr>
<tr>
<td>A10BA</td>
<td>BIGUANIDES (4th level, chemical subgroup)</td>
</tr>
<tr>
<td>A10BA02</td>
<td>METFORMIN (5th level, chemical substance)</td>
</tr>
</tbody>
</table>
Structure of the ATC system

C  Cardiovascular system
   (1st level, anatomical main group)

C08 Calcium channel blockers
   (2nd level, pharmacological subgroup)

C08D Selective calcium channel blockers with direct cardiac effects
   (3rd level, pharmacological subgroup)

C08DA Phenylalkylamine derivatives
   (4th level, chemical subgroup)

C08DA01 verapamil
   (5th level, chemical substance)
“X groups”

• New 4th levels:
  – only established when at least two substances with marketing authorisations fit in the group
  – a new 4th level should be regarded a benefit for drug utilisation monitoring and research

• X groups: substances not clearly belonging to any existing ATC 4th level

A10BX Other blood glucose lowering drugs excl. Insulins
General principles for ATC classification

• Drugs are classified according to their **main** therapeutic use

• Normally only **one** ATC code for each dosage form of a medicinal product

• **Several** ATC codes:

  Clearly different therapeutic uses according to
  - 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

- Naratriptan (e.g. Naramig): Antimigraine → 5HT$_1$ agonist → N02CC02

- Formoterol (e.g. Oxis): Antiasthmatic → $\beta_2$ agonist → R03AC13
Different indications - one ATC code

Example duloxetine (strengths 20, 30, 40 and 60 mg)
  – Major depressive disorder
  – Diabetic neuropathic pain
  – Stress urinary incontinence

Overlapping dosages used for the various indications

ATC code as antidepressant (N06AX21)
<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>
### Antibiotics in the ATC system main groups

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<td></td>
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<tr>
<td></td>
<td>J02 Antimycotics</td>
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<tr>
<td></td>
<td>J04 Antimycobacterials</td>
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<tr>
<td></td>
<td>J05 Antivirals</td>
</tr>
<tr>
<td>(L)</td>
<td>Antineoplastic and immunomodulating agents</td>
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<tr>
<td>P</td>
<td>Antiparasitic products, insecticides and repellents</td>
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<td>Respiratory system</td>
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<td>S</td>
<td>Sensory organs</td>
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Several ATC codes – different pharmaceutical 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 for combinations

Main principles:

- Combinations are included in separate ATC 5\textsuperscript{th} levels in the same ATC 4\textsuperscript{th} level where the key component is classified
  - Combinations of drugs from different ATC groups
  - Combinations of drugs classified in the same ATC group

- Separate ATC 3rd or 4th levels have been established for “important” combinations
ATC alterations

Alterations of ATC codes may occur in order to reflect changes in drug therapy.

It is important to describe the version of the ATC system used in research.
ATC alterations – splitting of groups

• **Cephalosporins**
  New classification according to generations in 2005 (four new ATC 4th levels, J01DB-J01DE) - old level deleted (J01DA)

• **Immunosuppressants**
  A split of the ATC group L04AA Selective immunosuppressants from 2008 and three new ATC 4th level was established:
  - *Tumor necrosis factor alpha (TNF-α) inhibitors* (L04AB)
  - *Interleukin inhibitors* (L04AC)
  - *Calcineurin inhibitors* (L04AD)

L04AA changed – gaps in ATC 5th level codes
Procedures for new ATC codes/DDDs and alterations

• All users can apply for new ATC/DDDs and alterations

• Requests should be addressed to the WHO Centre in Oslo

• New ATC/DDDs, alterations and objections to temporary ATC codes/DDDs are discussed and decided at the two annual meetings in the WHO Working Group

• ATC Index updated once annually, valid from January
  – New ATC codes, new DDDs and alterations implemented
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
Drug exposure – expressed in DDDs

Is normally given as:

- DDDs/1000 inhabitants/day

Example: 10 DDDs/1000 inhabitants/day

May indicate that 1% of the population can receive a certain treatment continuously (i.e. daily), but this interpretation is only useful if there is good agreement with the average prescribed daily dose (PDD) and the DDD

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
Adverse drug reaction reports of warfarin (B01AA03) in Norway 2002-2011

Source: Norwegian Medicines Agency, Annual report 2011
Monitoring 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 1999-2013

ATC 2014
Sales of contraceptives in Norway (ATC gr.G03A) 1967-2013
(excl. IUDs, vaginal rings, implants and inj.)

Number of users (NorPD) 2013: 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
Practical use in drug utilization...

Challenge:

• We provide a tool where ATC and DDD are established for active ingredient(s). The users have to make the correct link between the ATC/DDD value on the medicinal product package level.
ATC/DDD is a well established tool to:

- study patterns of use and changes over time
- evaluate the impact of information efforts, regulatory changes etc
- study drug exposure in relation to risk of adverse drug reactions
- indicate over-use, under-use and misuse/abuse of drugs
- compare and exchange data internationally

Proper knowledge about the ATC/DDD system is important
ATC/DDD Toolkit
for Drug Utilization Monitoring and Research

• Online resource for anyone interested in undertaking drug utilization studies
• Guidance on how to set up and use the international ATC/DDD methodology

The Website for the Toolkit is developed and hosted by WHO Geneva

ATC/DDD publications

- ATC Index with DDDs
- Guidelines for ATC classification and DDD assignment

Annually updated, and available in English and Spanish versions
Website

www.whoocc.no