Polypharmacy & Drug Interactions

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Badalona

1ª Jornada sobre Envejecimiento en el Paciente con Infección por el VIH
Barcelona, 15 Enero 2016
ATHENA: Older Pts Becoming More Prevalent in the HIV-Positive Population

- **ATHENA:** Observational cohort of 10,278 HIV-positive pts in the Netherlands

- **Modeling study projections:**
  - Proportion of HIV-positive pts ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive pts on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

ATHENA: Comorbidities Increase With Age and With HIV Infection

Modeling study suggests that in 2030:

• 84% of HIV+ pts will have ≥ 1 NCD
  – Increased from 29% in 2010
  – Pts with comorbidities higher in every age group in HIV+ pts vs uninfected

• 28% of HIV+ pts will have ≥ 3 NCDs

• 54% of HIV+ pts will be prescribed meds other than ART
  – Increased from 13% in 2010

• 20% will take ≥ 3 meds besides ART
  – Mostly driven by increase in CVD

Polypharmacy Among HIV+ Pts on ART: Swiss HIV Cohort and ATHENA Studies

Swiss HIV Cohort Study (N = 8444)\(^1\)
Prospective Observational study

- 115 (5.2\%) of 2233 participants 50-64 yrs of age and 64 (14.2\%) of 450 participants ≥ 65 yrs of age received ≥ 4 meds other than ART

ATHENA Modeling Study\(^2\)
Predicts that 20\% of pts will be taking ≥ 3 meds other than ART in 2030

Co-medications HUGTiP

n=331
Mean age 44.8 years

% pts on Co-med by age

<table>
<thead>
<tr>
<th>Years</th>
<th>&lt;35</th>
<th>35-50</th>
<th>51-64</th>
<th>&gt;64</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>68</td>
<td>149</td>
<td>80</td>
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N Co-med/pt by age

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Nervous system .......... 36.6%
GI / metabolism .......... 25.2%
Cardiovascular .......... 23.2%
Hematologic ............ 11.4%
Antiinfectives .......... 0.02%
Musculoskeletal .......... 0.02%
Polypharmacy. Potential consequences.

- Adherence
- Medication errors
- Safety
- Adverse effects
- Drug-drug interactions
Medication errors

- **WHO**: “more than 50% of all medicines are prescribed, dispensed or sold inappropriately”

- Medication-related errors and inappropriate medication utilization contribute to more deaths than breast cancer or HIV-related complications, accounting for anywhere between 44,000 and 98,000 fatalities per year.

WHO. Medicines: Rational use of medicine; 2010
Stawicki SP. OPUS12 Scientist 2009;3
Medication errors & the ‘six rights’

- Right patient
- Right medication
- Right documentation
- Right route
- Right time
- Right dosage

Stawicki SP. OPUS 12 Scientist 2009;3
Medication errors in older patients

• More than half (52%) of older adults in the US do not take all of their drugs as prescribed.
  – Treatment/system complexity
  – Age-related physiological changes
    • Cognition/motor function decline
    • Visual/hearing compromise
CUIDAD\O!
Causa sueño

Tome con las comidas

CUIDAD\O!
No tome con las comidas

Fecha: 23/11/190

Venc. 1 de nov. de 1920

By hand: 11/12/20

Dr. 10/12/20
Many pills, many systems

Adapted from S Khoo
Medication errors in older patients

• More than half (52%) of older adults in the US do not take all of their drugs as prescribed.
  
  – Treatment /system complexity
  
  – Age-related physiological changes
    • Cognition/motor function decline
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Polypharmacy. Potential consequences.

- Adherence
- Medication errors
- Safety
- Adverse effects
- Drug-drug interactions
Adverse effects

- The frequency of AEs leading to Rx discontinuation increases with age.

- Overlapping between AEs and aging-related symptoms
  - Drug prescription cascade
  - Geriatric syndrome
    - Cognitive impairment
    - Urinary incontinence
    - Loss of balance (falls/fractures)
Drug prescription cascade

Drug 1
- ADE interpreted as new medical condition

Drug 2
- ADE interpreted as new medical condition

Drug 3
- ADE interpreted as new medical condition

Abdulraheem IS. Aging Sci 2013;1:2
Adverse effects

• The frequency of AEs leading to Rx discontinuation increases with age.

• Overlapping between AEs and aging-related symptoms
  – Drug prescription cascade
  – Geriatric syndrome
    • Cognitive impairment
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Polypharmacy. Potential consequences.

- Adherence
- Medication errors
- Safety
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## Prevalence of potential clinically significant DDI

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>% DDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Maat</td>
<td>2004</td>
<td>220</td>
<td>25</td>
</tr>
<tr>
<td>Miller</td>
<td>2007</td>
<td>153</td>
<td>41</td>
</tr>
<tr>
<td>Shah</td>
<td>2007</td>
<td>342</td>
<td>30</td>
</tr>
<tr>
<td>Evans-Jones</td>
<td>2010</td>
<td>159</td>
<td>27</td>
</tr>
<tr>
<td>Marzolini</td>
<td>2010</td>
<td>1497</td>
<td>40</td>
</tr>
</tbody>
</table>

### Harms may result

7% prescribed at least 1 contraindicated ARV-drug combination (HOPS cohort)

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Miller et al. Pharmacother 2007;27:1379-86  
Marzolini et al. Antivir Ther 2010;15:413-23  
Shah et al. CROI 2007. Abstract 573  
Drug-drug interactions in the metropolitan area of Barcelona.

Included patients: 1259

Patients taking other drugs: 881/1259 (70.0%)

Patients with drug interactions: 563/1259 (44.7%)

Patients with severe drug interactions: 41/1259 (3.3%)
Ageing with HIV: medication use and risk for potential drug–drug interactions

Swiss HIV Cohort Study

1497 pts (1020 <50; 477 ≥ 50 years)

Potential DDIs

- 35% pts <50 years
- 51% pts >50 years

Drugs involved

- Cardiovascular drugs (lipid lowering agents, antiplatelets/anticoagulants, anti-hypertensive, antidiabetics)
- Central nervous system (anxiolytics/hypnotics, antidepressants, antipsychotics and antiepileptics)
- ART (PI, NNRTI)
Reasons for PK Drug-Drug Interactions

- **Metabolism**
  - Inhibition/induction of hepatic CYPs glucuronidation, or drug transport
  - Inhibition/induction intestinal CYP enzymes or drug transporters

- **Absorption**
  - Gastric pH
  - Food, mineral supplements

- **Excretion**
  - Inhibition of renal drug transporters

Adapted Roden DM et al. Nat Rev 2002; Marzolini CM Jan 2015
Concentration
HIV drug

Perpetrator

Co-med

AEs

Victim

Concentration co-med

Loss of efficacy

Loss of efficacy

HIV drug

Note: Understanding Exposure - Response and Exposure - Adverse Response relationship is vital to interpret PK data.

Courtesy from D. Back
What is ‘Clinically significant’ DDI?

- Drug development tends to focus on **PK changes**
  - e.g. strong (>5 fold), moderate (2-5 fold), weak (<2 fold)
  - ‘equivalence’
- Clinicians need to assess the risk of **harms**

\[
\text{Harm} = f \left( \frac{\Delta \text{PK}}{\text{T.I.}} \times \text{Consequence of breaching T.I.} \times \text{Patient factors} \times \text{Duration DDI} \right)
\]

How likely is DDI to occur?
How safe is the drug?
Therapeutic window

Wide therapeutic window

- Adverse events
- Therapeutic failure

Narrow therapeutic window

- Adverse events
- Therapeutic failure
What is ‘Clinically significant’ DDI?

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\text{Harm} = f \left( \frac{\Delta \text{PK}}{\text{T.I.}} \times \text{Consequence of breaching T.I.} \times \text{Patient factors} \times \text{Duration DDI} \right)
\]

- How likely is DDI to occur?
- Is this person at particular risk?
- How safe is the drug?
- How bad is that harm?
- How long is the period of risk?
Management of Polypharmacy in Clinical Practice

- Identify all drugs taken by the patient
  Centralized medication history

- Review the therapeutic regimen

- Identify DDIs
  Integration of DDIs in electronic prescribing systems
  Databases on DDIs
Identify all drugs taken by the patient

BHIVA Standards of Care for People Living with HIV (2013)

“A complete medication review should be undertaken at least annually by the specialist team, taking into account adherence, any difficulties with medication and drug-drug interactions.”

– Centralized medication history

– Self-preservation, CAM ....??
Management of Polypharmacy in Clinical Practice

- Identify all drugs taken by the patient
  Centralized medication history
- Review the therapeutic regimen
- Assessment of DDIs
  Integration of DDIs in electronic prescribing systems
  Databases on DDIs
Revision of the therapeutic regimen

- Remember the six rights
  Indication/Dosage/Route/Patient

- Simplify the regimen whenever it is possible
  Specific questionnaires (Hamdy)

- Promote interdisciplinar communication
  Avoid drug prescription cascade

- Avoid potentially harmful drugs in elderly patients
  Anticholinergic, benzodiacepines, antidepressant, antihistaminic...

- Use ‘less risky ARVs’
# Antiretrovirals and Interaction Potential

<table>
<thead>
<tr>
<th>Highest potential</th>
<th>Moderate Potential</th>
<th>Low Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boosted Pls</strong></td>
<td>Rilpivirine</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Perpetrators – enzyme &amp; transporter Inhibition</td>
<td>Victim - absorption (ATV); induction</td>
<td>Victim of enzyme inhibition &amp; induction. Also absorption.</td>
</tr>
<tr>
<td><strong>EVG/cobi</strong></td>
<td>Maraviroc</td>
<td>Most NRTIs</td>
</tr>
<tr>
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<td>Victim of enzyme inhibition &amp; induction.</td>
</tr>
<tr>
<td><strong>Efavirenz, nevirapine, etravirine</strong></td>
<td>Dolutegravir</td>
<td></td>
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Management of Polypharmacy in Clinical Practice

- Identify all drugs taken by the patient
  
  Centralized medication history

- Review the therapeutic regimen

- Assessment of DDIs
  
  Integration of DDIs in electronic prescribing systems

  Databases on DDIs
www.hiv-druginteractions.org

DRUG INTERACTIONS CHARTS

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CLICK HERE

Providing clinically useful, reliable, up-to-date evidence-based information

INTERACTION CHARTS FOR YOUR IPHONE

HIV iChart
A New App for iPhones and iPod Touches

The interaction charts are now available as an app which can be downloaded free of charge from the iTunes App Store.

Click here for the iTunes preview

This is an "offline" app that is downloaded to your device (~1.5 MB). An internet connection is not required to use the app, but is needed for downloading updates.
Traffic light summary of DDIs

Liverpool Website Definition:

- Green: No clinically significant interaction, or interaction unlikely
- Amber: Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration
- Red: Interaction likely, do not use or use with caution
- Yellow: No clear data, actual or theoretical

1. Are drugs necessary? [Yes/No]
   - No: Stop
   - Yes: Are there alternatives? [Yes/No]
     - Yes: Switch
     - No: Can DDI be managed? [Yes/No]
       - Yes: Accept risk, discuss with patient
       - No: Change dose
     - No: Establish monitoring plan

Adapted from S Khoo
Conclusions

• The coming norm in the HIV field
  “Elderly patient with comorbidities and polymedication”

• Potential consequences
  Adherence / medication errors
  Safety
  Drug interactions

• Risk of DDIs can be mitigated
  Complete/centralized medication history
  Avoid unnecessary treatments
  Low risk drugs
  Electronic prescribing / DDIs databases
  ➔ Proactive attitude towards DDIs
GUÍA DE INTERACCIONES MEDICAMENTOSAS DE INTERÉS EN EL PACIENTE INFECTADO POR EL VIH

José Moltó

Available at www.flsida.org