Differences between women and men in Adverse Drug Reactions

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Prevalence of Adverse Drug Reactions (ADRs)

- Clinical trials (e.g. short period of time, low number of patients, selected sample of patients)
- Post-marketing studies -> ADRs are common:
- 25% of primary care patients reported ADR in 2 weeks after the received prescription (USA)
- 12% of random sample of adult general public had ADR in a 3-month period (Sweden)
- Review studies in the EU: hospital adminissions due to ADR 3.5%; ADR during hospitalization 10.1%

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Heiat et al. Intern Med 2002
Stricker et al. BMJ 2004
Gandhi et al. NEJM 2003
Hakkarainen et al. BJCP 2013
Bouvy et al. Drug Saf 2015

Impact of ADRs

- Treatment satisfaction
  - Study among T2DM patients in the USA. Correlation between number of ADRs and satisfaction (r=-0.42)
- Quality of life (QoL)
  - Study among patients experiencing ADR of Thyrax assessing QoL before – after ADR
    - Physical QoL (-0.8), mental QoL (-1.2), daily activities (-1.4), social QoL (-1.3), overall health status (-1.3)
- Treatment adherence
  - Study among ambulatory patients on antihypertensive drugs. Experience of ADR -> reduced odds of being adherent
- Healthcare costs
  - USA: up to 30.1 billion dollars annually (increased hospitalization, prolongation of hospital stay, additional investigations etc)

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Pollack et al. Diabetes Res Clin Pract 2010
Rolfes et al. Drug Saf 2016
Berhe et al. Br J Clin Pharmacol 2017
Sultana et al. J Pharmacol Pharmacother 2013

Women versus men ♀♂

- Women included in trials but differences not investigated or reported
- Women 1.5-1.7 times more likely to develop an ADR (review study)
- Information inconsistent and incomplete at specific drug – ADR level
  - ADRs to antineoplastic drugs (men more vs women more)
  - Gastrointestinal-related ADRs (women more vs no differences)

  (study in an outpatient clinic in Canada vs study using spontaneously reported ADRs in France)
- Of 668 drugs, 307 had gender differences in drug-event combinations (Analyses of the FDA Adverse Event Reporting System)
  - No correction for differences in drug prescriptions

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Rademaker Am J Clin Dermatol 2001
Tran et al. J Clin Pharmacol 1998
Montastruc et al. Fun Clin Pharmacol 2002
Yu et al. Sci Rep. 2016

Study aims

- To assess whether reported drug-ADR combinations to a PhV centre, corrected for the number of drug users, suggest differences in the occurences between women and men
- For which 1) drugs and 2) ADRs gender differences are most outspoken

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Methods

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- ADRs spontaneously reported to Lareb
- January 1, 2003 – December 31, 2016
  - Reports from HCPs and patients
  - Data available about No. of drug users
- Drug Information System of the National Health Care Institute (ZorgInstituut Nederland)
  - Available data were summed over the years
- Included reports:
  - About drugs (excluding vaccines)
  - From patients, physicians, and pharmacists
  - Reports for patients aged 5 – 99 years

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De Langen et al. Drug Safety 2008

Outcome variable

- Specific drug-ADR combinat
- Drugs:
  - Chemical subgroup, fourth, le
    Therapeutic Chemical (ATC) c
  - Exclusion of drugs <10.000 us
- ADRs:
  - Preferred term level of the
    activities (MedDRA)
  - Exclusion of gender-specif

http://www.who.int/classifications/atcddd/en/
http://meddra.org
Gender Adverse Event Term Lists (MedDRA)

C Cardiovascular system
C10 Lipid modifying agents
C10A Lipid modifying agents, plain
C10AA Hmg CoA reductase inhibitors
C10AA01 Simvastatin
C10AA02 Lovastatin
C10AA03 Pravastatin
C10AA04 Fluvastatin
C10AA05 Atorvastatin
C10AA06 Cerivastatin

SOC Cardiac disorders
HLGT Cardiac arrhythmias
HLT Cardiac conduction disorders
HLT Rate and rhythm disorders NEC
PT Agonal rhythm
PT Anomalous atrioventricular excitation
PT Arrhythmia
LLT Arrhythmia
LLT Arrhythmia (NOS)
LLT Arrhythmia cardiac (NOS)
LLT Arrhythmia exertional

Analyses

- Bivariate logistic regression analyses
  - Gender -> reporting a specific drug-ADR combination
  - Corrected for No. of drug users
- Odds ratios with 95% CI

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Results

2,765 unique drug-ADR combinations

247 combinations: <10,000 drug users

36 combinations: Gender-specific ADR

2,482 combinations tested

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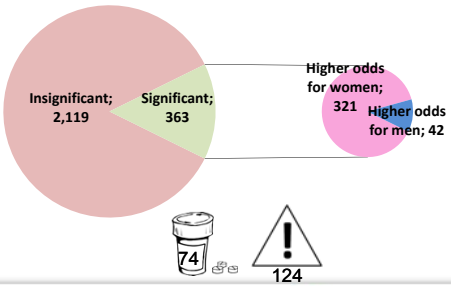
Results



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Results

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Results – Women

Thyroid hormones	Nausea
HMG CoA reductase inhibitors	Alopecia
Centrally acting sympathomimetics	Headache
Other depressants	Palpitations
Tumor necrosis factor alpha inhibitors	Dizziness

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Results – Men

Selective serotonin reuptake inhibitors
HMG CoA reductase inhibitors

Agression
Death
Pyrexia
Sexual dysfunction
Tendon rupture
Tinnitus

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Discussion and Conclusion

- Assessment of different drugs and ADRs
- Correction for No. of drug users
- No correction for multiple testing
- Power of specific combinations:
  - The number of cases in which a specific drug/ADR was included
  - The number of cases in a specific drug-ADR combination
- Based on spontaneous reporting
- Men and women differ in ADRs
- Need for further studies about underlying reasons

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