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SYMPOSIUM

Actualités pharmacothérapeutiques 2023

Bienvenue !

Le symposium va bientôt commencer

Infos pratiques

✓ **Accréditation**

- Vous êtes en présentiel → n'oubliez pas de signer la feuille de présence avant de partir

- Vous êtes à distance → cliquez sur les pop-ups qui apparaîtront sur votre écran de manière aléatoire, quelques fois par heure. Cela nous permettra de confirmer votre présence

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Infos pratiques

✓ **Questions**

- Vous êtes <u>en présentiel</u>
  - questions **à la fin** de chaque présentation
  - pendant la pause

- Vous êtes <u>à distance</u>
  - questions **dans le “chat“**

Infos pratiques

- ✓ **Interactivité via sondages**
  - les participants en ligne :
    les sondages apparaîtront sur votre écran
  - les participants dans la salle :
    nous vous communiquerons les résultats

Programme scientifique

13h45 Introduction
13h50 Faut-il conseiller les formes effervescentes?
14h20 Etudes randomisées vs observationnelles: points forts, points faibles

14h50 **Pause**
15h20 Nouveautés dans le traitement médicamenteux de l'insuffisance rénale chronique
15h50 Le rôle de la glycoprotéine P (P-gp) dans les interactions médicamenteuses

Orateurs

- ✓ Camille Bertrand MPharmSc
- ✓ Marie-Laurence Lambert MD, PhD
- ✓ Catherine Veys MD
- ✓ Jean-Marie Maloteaux MD, PhD

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Actualités pharmacothérapeutiques 2023

Faut-il conseiller les formes effervescentes?

Camille Bertrand MPharmSc

Quiz 1

Q1 : What is the main class of medicine (i.e. registered as a medicine) in effervescent form in Belgium?

a) Laxatives
b) Mucolytics and expectorants
c) Painkillers and anti-inflammatories
d) Vitamins

Feedback quiz 1

Q1 : What is the main class of medicine (i.e. registered as a medicine) in effervescent form in Belgium?

a) Laxatives
b) Mucolytics and expectorants
c) Painkillers and anti-inflammatories
d) Vitamins

Quiz 2

Q2 : What are the risks of effervescent forms?

a) Higher mortality from all causes
b) Higher risk of cardiovascular disease
c) An increase in blood pressure
d) All answers are correct

Feedback quiz 2

Q2 : What are the risks of effervescent forms?

a) Higher mortality from all causes
b) Higher risk of cardiovascular disease
c) An increase in blood pressure
d) All answers are correct

Quiz 3

Q3 : In which patients should particular attention be paid to the amount of sodium in medicines?

a) Patients on a strict low-salt diet
b) Adults on antibiotics
c) Children
d) Diabetics

Feedback quiz 3

Q3 : In which patients should particular attention be paid to the amount of sodium in medicines?

a) Patients on a strict low-salt diet
b) Adults on antibiotics
c) Children
d) Diabetics

Summary

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1. Introduction

1.1. Specialities in effervescent form in Belgium

Group	Proportion	Name (examples)	Sodium content	Amount of NaCl
Painkillers and anti-inflammatories	51%	*Dafalgan® eff. 1g*	565 mg	1 400 mg
		Sedergine 1g ®	460 mg	1 200 mg
		Aspirine 500®	250 mg	638 mg
		Brufen®	197 mg	491 mg
Vitamins and minerals	41%	*D-Vital Forte®*	10 mg	26 mg
		Steovit Forte®	96 mg	245 mg
		Upsa-C®	284 mg	724 mg
Mucolytics and expectorants	5%	*Acetylcystéine EG®*	145 mg	370 mg
		Lysomucil®	157 mg	401 mg
Laxative	3%	*Spagulax*	120 mg	306 mg

Folia mai 2023, Sodium dans les médicaments: risques cardiovasculaires, https://www.cbip.be/fr/articles/4084?folia=4079

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1. Introduction

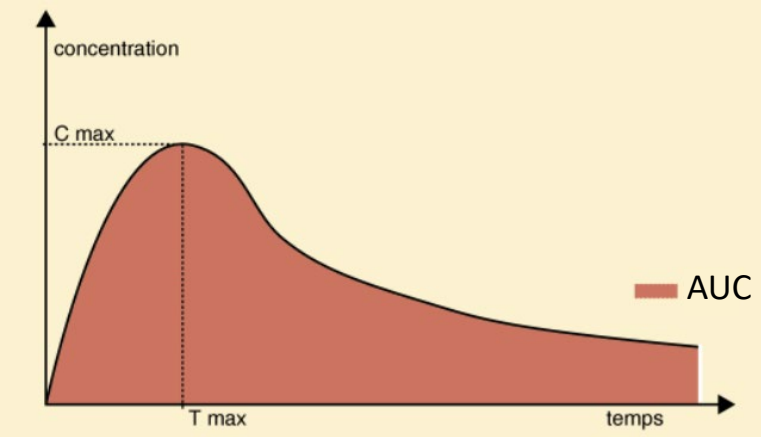
1.2. How does it work?

$$Na^+ + HCO_3^- + R\text{-}COOH \longrightarrow CO_2 + H_2O + RCOO^- + Na^+$$

In water, the carbonate or bicarbonate reacts with the acid to release carbon dioxide, which acts as a disintegrating agent for the tablet.

2. Advantages of effervescent forms

2.1. Pharmacokinetics



Bioavailability refers to the fraction of an administered dose that reaches the general circulation and the rate at which it does so.

It is characterised by three parameters :

- The **maximum concentration of the substance** (C_{max}) reached in the plasma;
- The **time** taken to reach it (T_{max});
- The **area under the curve** (AUC), which gives an idea of the total quantity reaching the general circulation.

Prescrire, C'est-à-dire ? Biodisponibilité, mai 2018, tome 38 (415) : page 349.

2. Advantages of effervescent forms

2.1. Pharmacokinetics

Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers (2000)

Table 1 The time to maximum serum concentration (t_{max}), the maximum serum concentration (C_{max}) and the area under the curve 0–3 h ($AUC_{0-3\ h}$) after a 1000-mg dose of paracetamol effervescent tablets (Pinex Brusetablett, Alpharma AS) compared with ordinary paracetamol tablets (Panodil, SmithKline Beecham). Values are given as mean with the 95% confidence interval

Parameter	Effervescent paracetamol	Ordinary paracetamol	*P* value
t_{max} (min)	27 (20–34)	45 (34–56)	0.004
C_{max} (μmol/l)	143 (104–158)	131 (118–168)	0.203
$AUC_{0-3\ h}$ ($\mu mol \cdot h \cdot l^{-1}$)	224 (195–253)	198 (171–225)	0.003

- ***Objective***: to compare the rate of absorption between ordinary paracetamol tablets and effervescent paracetamol tablets.
- ***Methods***: open randomised crossover study with 20 healthy volunteers. Given 1000 mg of either ordinary paracetamol or effervescent paracetamol with 3 weeks wash-out period.
- ***Limitations***:
  - Area under the curve only form 0 to 3h
  - Open study
  - Only 20 healthy volunteers, baseline characteristics not presented
  - Sponsorised

Rygnestad, T., Zahlsen, K., & Samdal, F. A. (2000). Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. European journal of clinical pharmacology, 56, 141-143

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2. Advantages of effervescent forms

2.1. Pharmacodynamic

Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study (2000)

Table II Calculated Time to Onset of Analgesia and Time to Remedication

	Effervescent Acetaminophen, 1000 mg	Tablet Acetaminophen, 1000 mg	Effervescent Placebo	Tablet Placebo
Number of patients	60	60	62	60
Patients with onset, *n* (%)	42 (70.0)*	42 (70.0)+	12 (19.4)	9 (15.0)
Time to onset of analgesia (h)				
Median	0.34^A§ (20 minutes)	0.75° (45 minutes)	NE	NE
95% CI	[0.33-0.58]	[0.50-0.75]		
Time to meaningful pain relief (h)				
Median	0.75^Δ¶ (45 minutes)	1.00° (60 minutes)	NE	NE
95% CI	[0.50-1.00]	[1.00-1.13]		
Time to remedication (h)				
Median	2.11* (2 h: 07 min)	2.69+ (2 h: 41 min)	1.00	1.00
95% CI	[1.6-3.0]	[2.0-3.12]	[—]	[—]
Remedicated patients, *n* (%)	[illegible]*	44 (73.[illegible])*	62 (100)	56 (93.3)

Values are presented as mean ± standard deviation. NE, not estimable. Median time was not estimable since less than 50% of patients achieved an onset of analgesia and a meaningful pain relief.
*$p \leq 0.001$ versus effervescent placebo.
#$p \leq 0.01$ and +$p \leq 0.001$ versus tablet placebo.
Δ$p \leq 0.001$ versus effervescent placebo. Comparison based on survival distributions.
°$p \leq 0.001$ versus tablet placebo. Comparison based on survival distributions.
§$p = 0.0081$ and ¶$p = 0.0064$ versus tablet acetaminophen.

- ***Objectives***: to determine and compare, using the post-dental pain model and a stop-watch method, the time to onset of analgesia of two formulations of acetaminophen 1000 mg
- ***Methods***: randomized, double-blind and double dummy, placebo-controlled study.
- ***Limitations***:
  - Sponsorised

Møller, P. L., Nørholt, S. E., Ganry, H. E., Insuasty, J. H., Vincent, F. G., Skoglund, L. A., & Sindet-Pedersen, S. (2000). Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study. The Journal of Clinical Pharmacology, 40(4), 370-378.

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2. Advantages of effervescent forms

2.2. Other advantages

- ✓ Taste ?
  - Citric acid
- ✓ Reduced risk of acute overdose
  - Needs a lot of water to dissolve 6-8 tablets
  - Nausea
- ✓ Easy to use in case of swallowing disorders

3. Risks associated with effervescent forms

3.1. Cardiovascular risks and mortality (2013)

Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study

Table 3 Odds ratios and 95% confidence intervals for composite cardiovascular outcome* and individual outcomes for sodium-containing formulations group compared with standard formulations group (OR=1)

	OR (95% CI)	
	Unadjusted	Adjusted†
Composite cardiovascular outcome*	1.13 (1.09 to 1.18)	1.16 (1.12 to 1.21)
Individual outcomes		
Incident non-fatal myocardial infarction	0.90 (0.85 to 0.96)	0.94 (0.88 to 1.00)
Incident non-fatal stroke	1.21 (1.15 to 1.28)	1.22 (1.16 to 1.29)
Vascular death	0.62 (0.31 to 1.24)	0.70 (0.31 to 1.59)
Hypertension	6.80 (6.41 to 7.21)	7.18 (6.74 to 7.65)
Heart failure	0.95 (0.91 to 1.00)	0.98 (0.93 to 1.04)
All cause mortality	1.30 (1.25 to 1.35)	1.28 (1.23 to 1.33)

*Incident non-fatal myocardial infarction, incident non-fatal stroke, and vascular death.

- ***Objective***: To determine whether patients taking formulations of drugs that contain sodium have a higher incidence of cardiovascular events compared with patients on non-sodium formulations of the same drugs.
- ***Methods***: case control study
- ***Limitations***:
  - Observational study ➔ confounding variables (sodium intake…)
  - No OTC drugs included

*George, J., Majeed, W., Mackenzie, I. S., MacDonald, T. M., & Wei, L. (**2013**). Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. Bmj, 347.*

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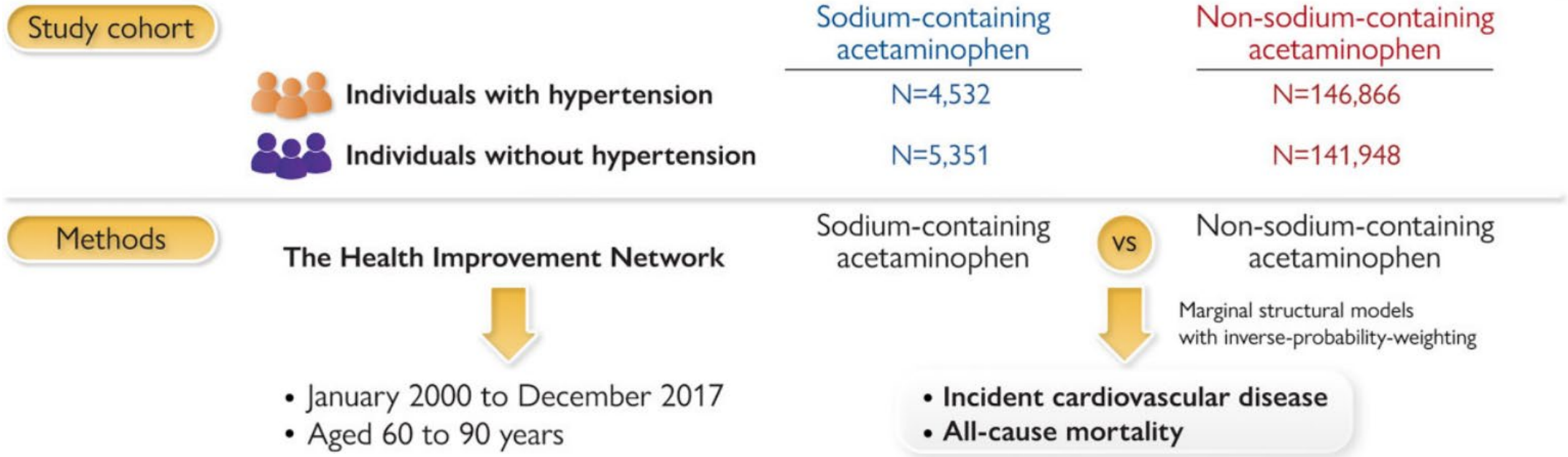
3. Risks associated with effervescent forms

3.1. Cardiovascular risks and mortality (2022)

Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension

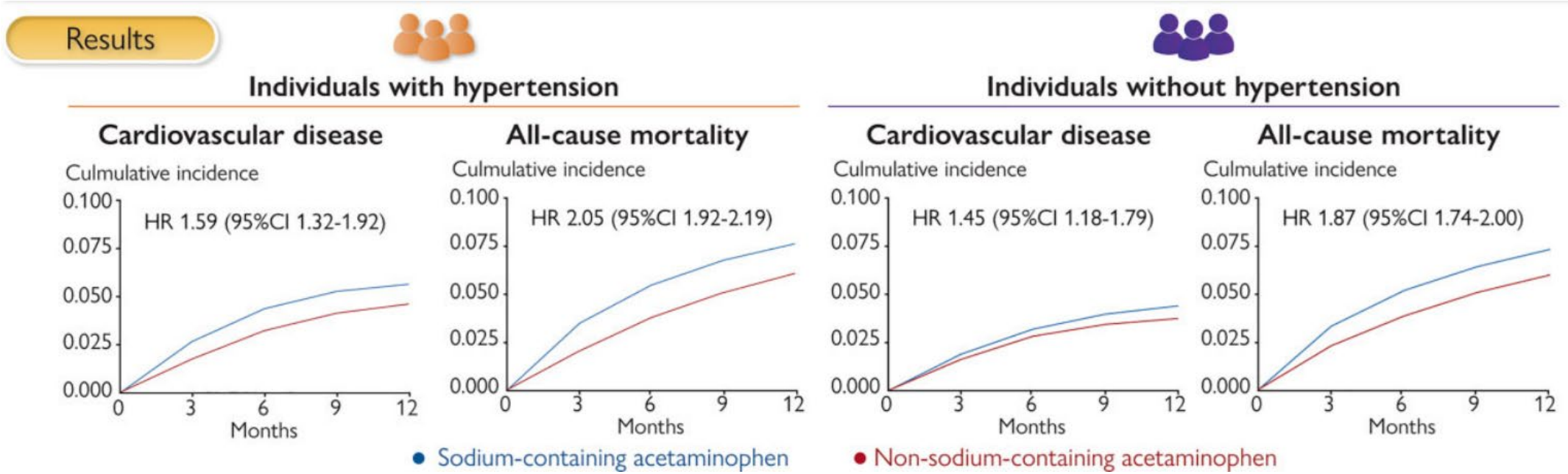


*Zeng, C., Rosenberg, L., Li, X., Djousse, L., Wei, J., Lei, G., & Zhang, Y. (**2022**). Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. European Heart Journal, 43(18), 1743-1755.*

3. Risks associated with effervescent forms

3.1. Cardiovascular risks and mortality (2022)

Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension



*Zeng, C., Rosenberg, L., Li, X., Djousse, L., Wei, J., Lei, G., & Zhang, Y. (**2022**). Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. European Heart Journal, 43(18), 1743-1755.*

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4. Clinical case

Jean-Pierre, aged 75, secondary cardiovascular prevention and rheumatological condition

- CV prevention : Asaflow ® 1x/day
- Cholesterol : Totalip® 10mg 1x/day
- Recent rheumatological condition : Medrol 4 mg®
- Calcium + vitamin D : Steovit® compr. efferv. Forte Orange
- Pain : Dafalgan® efferv. 1g 3x/day
- Cough : Lysomucil® efferv. 1x/day in the morning

4. Clinical case

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Médicaments	Teneur en sodium par comprimé	Teneur en NaCl par comprimé	Teneur en sel par jour
Asaflow®	/	/	/
Totalip®	10 mg	25,5 mg	25,5 mg
Medrol®	/	/	/
Steovit®	96.1 mg	245 mg	245 mg
Dafalgan®	565 mg	1400 mg	4200 mg
Lysomucil®	157 mg	401 mg	401 mg
			4,87g de sel par jour

5. Take home message

- ✓**In all patients**, and **particularly those suffering from hypertension**, it is certainly preferable to avoid medicines with a high sodium content, especially when several tablets are taken daily or when they must be taken for a long time.

- ✓In patients on a **strict low-salt diet**, effervescent forms must be avoided

Thank you for your attention!

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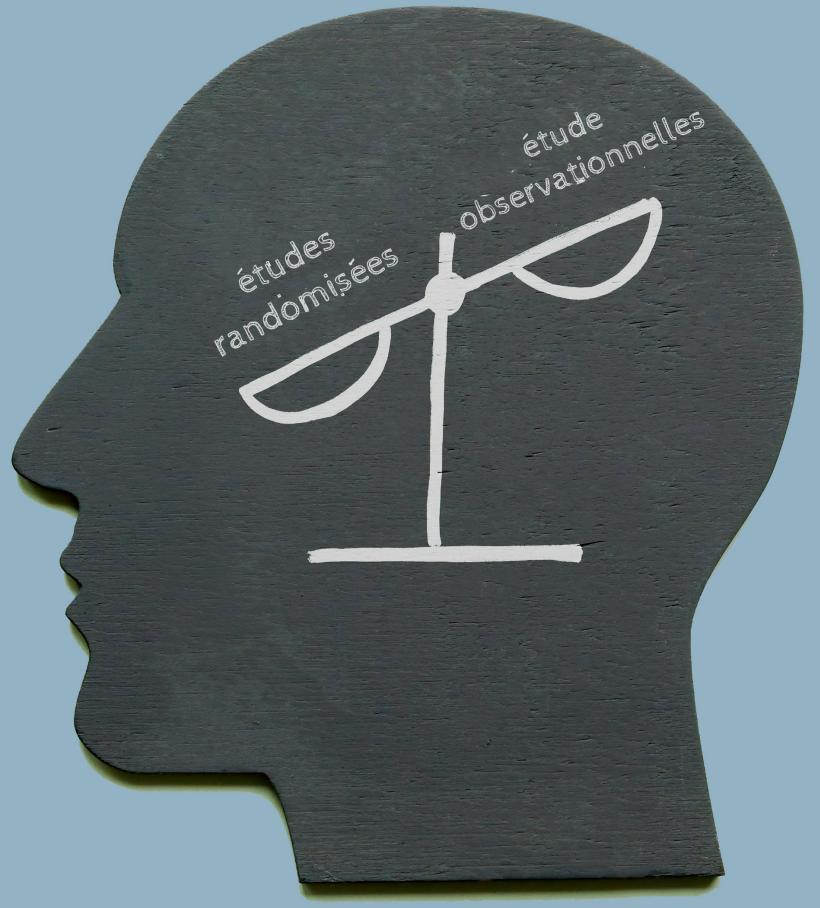
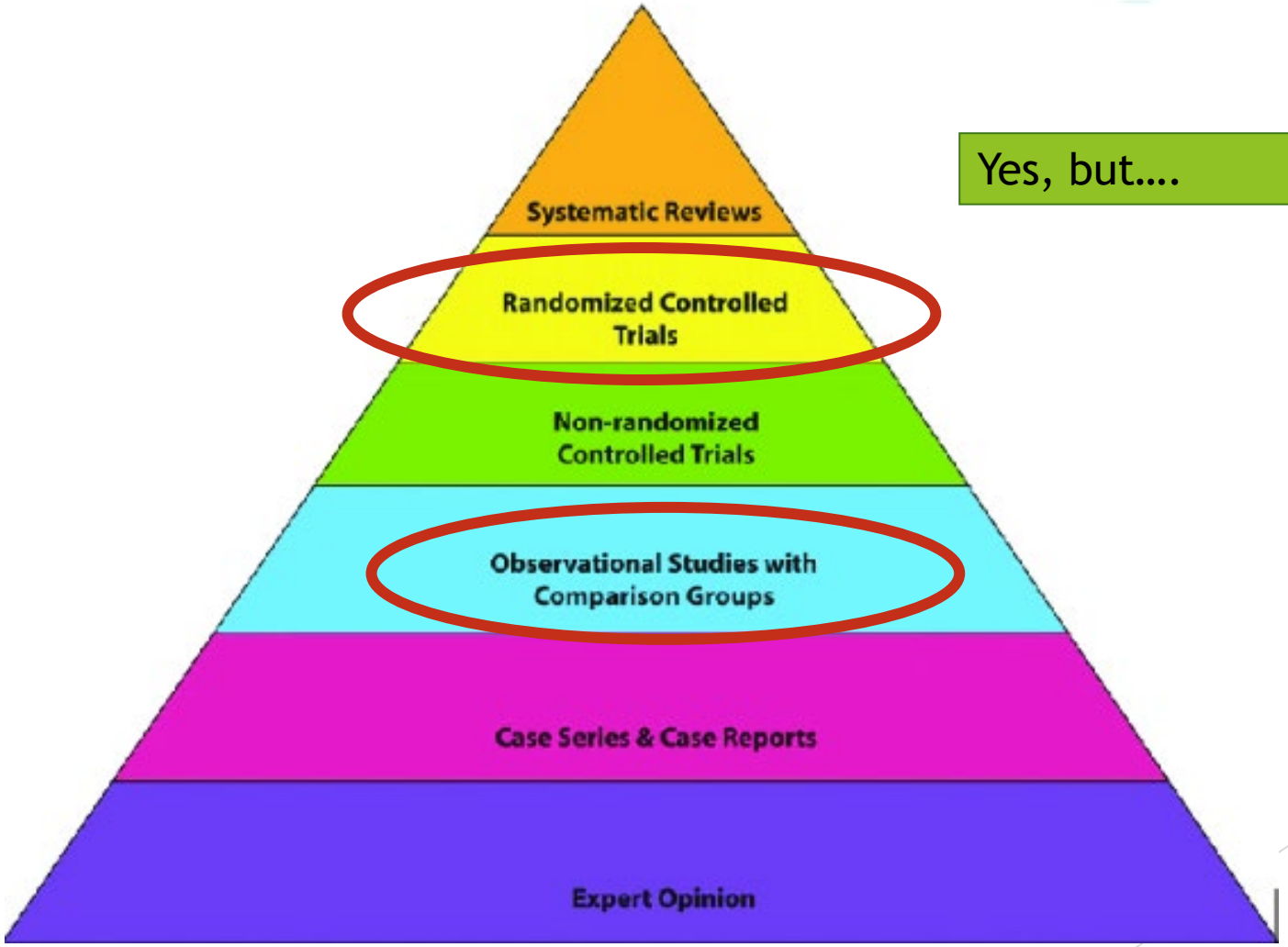


Etudes randomisées vs observationnelles: points forts, points faibles

Marie-Laurence Lambert MD, PhD

RCT vs études observationnelles: une hiérarchie…



Yes, but….

RCT vs études observationnelles

- RCT: études expérimentales / interventionnelles - manipulation de l'exposition
  ('situation idéale': patients sélectionnés, suivi intensif, réévaluations fréquentes…)

Vs

- Etudes observationnelles: pas de manipulation de l'exposition

Plan

- Pourquoi les RCT sont le « gold standard » de la recherche clinique…
- … et pourquoi les RCT ne nous disent pas tout que nous avons besoin savoir

- Pourquoi il est si difficile de déterminer une association causale à partir d'une étude observationnelle
- … et pourquoi les études observationnelles sont parfois indispensables …

- … et pourquoi nous voulons plus de RCT!

Pourquoi les RCT sont le gold standard de la recherche clinique…

Comment tester un (nouveau) médicament?

- Les patients guérissent aussi sans pilule, effet placebo
  - ➔ il faut **comparer** des patients qui prennent un médicament avec des patients qui ne le prennent pas
  - **Essai clinique contrôlé**

- ➔ Il faut que les groupes comparés soient comparables et ne diffèrent QUE par la prise du médicament
  - ➔ randomisation
  - **Essai clinique contrôlé, randomisé**

- ➔ Il faut que les investigateurs ne soient pas biaisés quand ils évaluent les résultats
  - ➔ double (triple) aveugle
  - **Essai clinique contrôlé, randomisé , en double aveugle**

Les RCT : « gold standard » de la recherche clinique parce que

- Si les groupes comparés sont comparables en tous points SAUF en ce qui concerne le médicament …
- … les différences observées au niveau des résultats sont attribuables au médicament
- ▫ **relation de causalité** entre exposition (médicament) et effet
  (dans la population étudiée)

… et pourquoi les RCT ne nous disent pas tout ce que nous avons besoin de savoir..

Les RCT…

- Etudes difficiles et très couteuses
  - Durée limitée
  - Nombre limité de participants
  - Participants très sélectionnés…

Nous avons besoin de savoir…

Comment ce médicament fonctionne-t-il dans la « vraie vie »?

- RCTs : patients sélectionnés, conditions de suivi idéales, temps limité
  - Où sont…
    - Les femmes?
    - Les personnes âgées?
    - Les co-morbidités?
    - Les femmes enceintes, allaitantes?
    - Les patients de milieu défavorisé?
  - Observance?
  - Efficacité sur le long terme?

Nous avons besoin de savoir…

Quels sont les effets de ce médicament pour ce qui importe vraiment aux patients?

- Critères de jugement « de substitution » (*surrogate endpoints)*
  - permettent des études <u>plus courtes</u> …
    - densité osseuse vs risque de fracture?
    - cholestérol vs risque cardio-vasculaire?
    - oncologie: retarder l'évolution vs survie globale? QoL?
    - Alzheimer: diminution des plaques amyloïdes vs amélioration cognitive

Nous avons besoin de savoir…

Quels sont les effets de ce médicament pour ce qui importe vraiment aux patients?

- Critères de jugement « de substitution » (*surrogate endpoints)*
  - permettent des études plus courtes …
  - … Mais risque important de surestimation des bénéfices (> 40%)
    Ciani, BMJ 2022
  - … ou même de grossières erreurs *(ex:* fluorides et ostéoporose…)

Nous avons besoin de savoir…

Quelle est la sécurité de ce médicament?

- ➔ Les RCT ne peuvent mettre en évidence des effets secondaires rares ou/et survenant sur le long terme

Nous avons besoin de savoir…

… si un médicament donné est meilleur que ce qui existe déjà …

- … pas s'il est meilleur qu'un placebo…
- (! nécessité d'études comparatives)

Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial

Ferrante, Lancet 2022

Pourquoi il est si difficile de déterminer une association causale à partir d'une étude observationnelle…

Comment tester un (nouveau) médicament?

- Les patients guérissent aussi sans pilule, effet placebo
  - ➔ il faut **comparer** des patients qui prennent un médicament avec des patients qui ne le prennent pas
  - **Possible dans une étude observationnelle**

- Il faut que les groupes comparés soient comparables et ne diffèrent QUE par la prise du médicament
  - **Jamais le cas dans une étude observationnelle!**
  - **Facteurs de confusion connus … inconnus?**

- Il faut que les investigateurs ne soient pas biaisés quand ils évaluent les résultats
  - Possible dans une étude observationnelle

Etudes observationnelles

- Différents designs…
  - Etudes de cohorte rétrospectives, prospectives
  - Etudes cas-témoins

- Plus faciles, moins chères que RCT

- A l'ère de Big Data, exploitation possible de grosses bases de données informatisées
  - Electronic Health Records
  - Bases de données administratives
  - Registres …

Etudes observationnelles…

- Comparabilité des groupes comparés difficile à garantir
  - ➔ facteurs de confusion (inconnus)
  - ➔ association apparemment causale entre exposition (médicament) et résultat expliquée par un facteur tiers

Etablir une relation de causalité avec une étude observationnelle est un exercice périlleux...

Paracetamol lors de la première année de vie → Asthme vers 6-7 ans

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme

Facteur de confusion

Paracetamol lors de la première année de vie

Asthme vers 6-7 ans

Fièvre lors de la première année de vie

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme

Etudes observationnelles…

- Comparabilité des groupes comparés difficile à garantir
- Plus sujettes aux biais (sélection, information)

Biais d'information

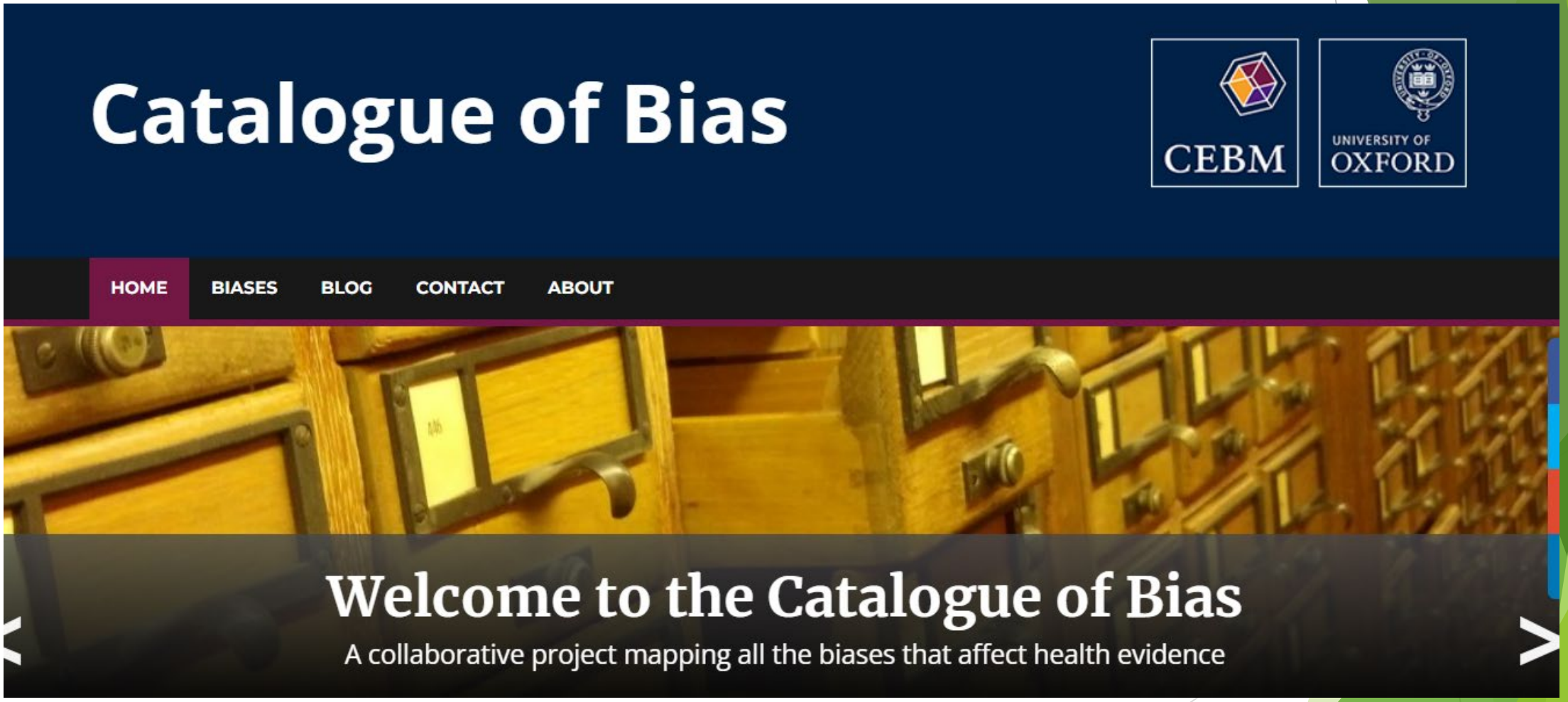
Paracetamol lors de la première année de vie

Evalué par questionnaire (rétrospectif) aux parents

Asthme vers 6-7 ans

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme



+/- 50 types de biais… (pas uniquement études observationnelles…)

Etudes observationnelles…

- Comparabilité des groupes comparés difficile à garantir
- Plus sujettes aux biais (sélection, information)

- ➔ Etablir un lien de causalité est un exercice périlleux…

- Développement de méthodes épidémiologiques / statistiques pour améliorer la comparabilité / ajustement pour facteurs de confusion – ex *propensity score matching*

- Résultats d'études observationnelles = SIGNAL (≠ causalité)
  - Plusieurs signaux similaires dans différentes populations ➔ plus probable!

… et pourquoi les études observationnelles sont parfois irremplacables …

Nous avons besoin de savoir…

Quelle est la sécurité de ce médicament?

- Pharmacovigilance
- Pharmacoepidemiologie
- Etudes cas-témoins

- Permettent l'étude d'effets secondaires rares, et/ou tardifs, à partir d'études observationnelles

- Nécessaires quand une RCT est impossible/ inacceptable: ex grossesse et lactation

Etude cas-témoin pour étude d'effets secondaires rares

- Benfluorex (Mediator®) et insuffisance mitrale en France (et dexfenfluramine en Belgique)
- Acide valproïque (Depakine®) pendant la grossesse et autisme de l'enfant
- Quinolones et anévrysme de l'aorte
- Glitazones et cancer vésical

Nous avons besoin de savoir…

… Comment ce médicament fonctionne-t-il dans la « vraie vie »?

(>< situation idéale RCT)

› Eur J Cancer. 2021 Sep;155:136-144. doi: 10.1016/j.ejca.2021.07.001. Epub 2021 Aug 6.

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

« Real world evidence »… ?

Eur J Cancer. 2021 Sep;155:136-144. doi: 10.1016/j.ejca.2021.07.001. Epub 2021 Aug 6.

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

- Comparaison des résultats des RCT avec les résultats d'études observationnelles (N=263) par indication
- 63% des études observationelles ont rapporté une survie inférieure à celle des RCT correspondants
- 78% des études : qualité méthodologique très faible…
- Les études de qualité la plus faible, étaient celles qui montraient une survie supérieure aux RCT correspondants.

Nous avons besoin de savoir…

… Comment ce médicament fonctionne-t-il dans la « vraie vie »?

- Big data: exemple des bases de données administratives

Eligibilité à un traitement de seconde ligne chez les patients asthmatiques

- Omalizumab (Xolair®) : traitement de seconde ligne chez les patients asthmatiques non contrôlés par un traitement bien conduit ICS-LABA

- Etude des traitements (ICS+LABA) dans l'année précédant l'initiation d'un traitement par omalizumab chez les patients asthmatiques

- Sur base des données de remboursement *(étude descriptive)*

Bases de données administratives

Omalizumab (Xolair®) : indiqué comme traitement de seconde ligne chez les patients asthmatiques non contrôlés

› ERJ Open Res. 2019 Nov 25;5(4):00253-2018. doi: 10.1183/23120541.00253-2018. eCollection 2019 Oct.

Real-life effectiveness of omalizumab in difficult-to-treat *versus* severe asthma: a national cohort study in Belgium

Results: Between 2010 and 2016, omalizumab treatment was initiated in 2068 patients with asthma; only 24% fulfilled the eligibility criteria, mainly due to nonadherence to high-dose ICSs + LABAs. The

A l'ere de big data…
Exemple: bases de données administratives (remboursement…)

Les plus

- Exploitation de données existantes
- Très grande taille, population d'intérêt exhaustive , pas de biais de sélection, suivi dans le temps
- Analyses descriptives
  - Observance, durée de traitement
  - Profil patients, age sexe
  - Positionnement d'un médicament dans la stratégie thérapeutique, co-médications…
  - …

Les moins

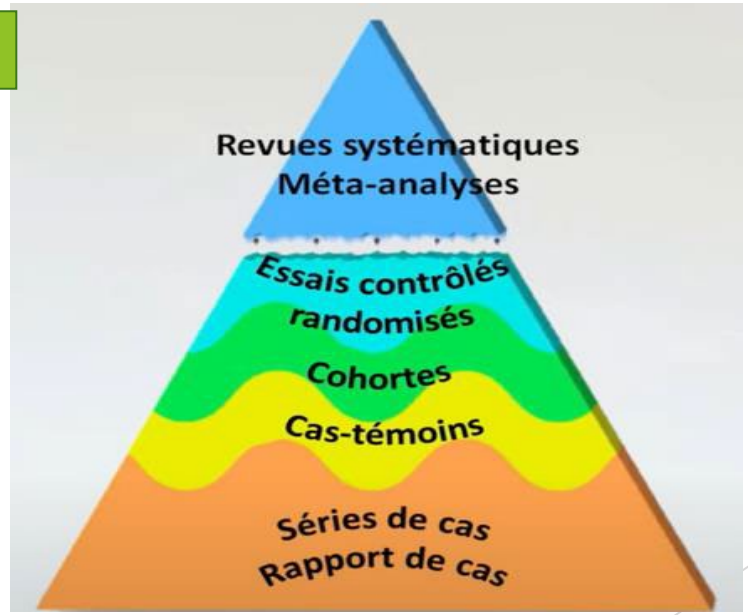
- Pas de données cliniques
- Informations limitées
- Nécessité de « proxys »
- Etudes **analytiques** difficiles

RCT vs études observationnelles: une hiérarchie?

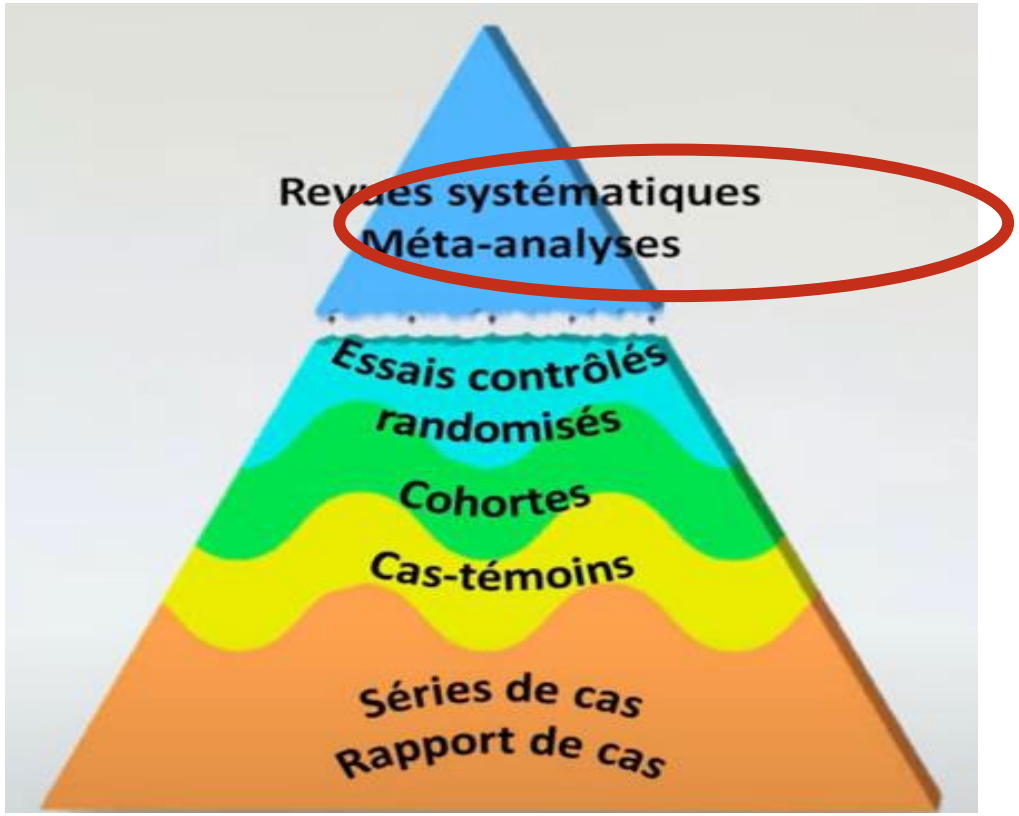
RCT: un design *a priori* superieur

Yes, but….

Une bonne étude observationnelle vaut mieux qu'un mauvais RCT



RCT vs études observationnelles: une hiérarchie?



Par exemple
Cochrane Reviews
MAIS M-A n'est pas supérieure s'il s'agit d'une méta-analyse d'études de mauvaise qualité!

… pourquoi nous avons besoin de plus (et de meilleurs) RCT…

Faut-il accélérer l'accès des patients aux médicaments « innovants »?

- "Early access" Argument utilisé (par l'industrie) pour obtenir une mise sur le marché plus rapide
  - … au détriment de la qualité de l'evidence

- "Shift" de la génération de l'evidence vers des études post-marketing, rhétorique de "real world evidence"

Boyle & al, Eur J Cancer, 2021

Illusion de l'evidence générée après mise sur le marché d'un nouveau médicament …

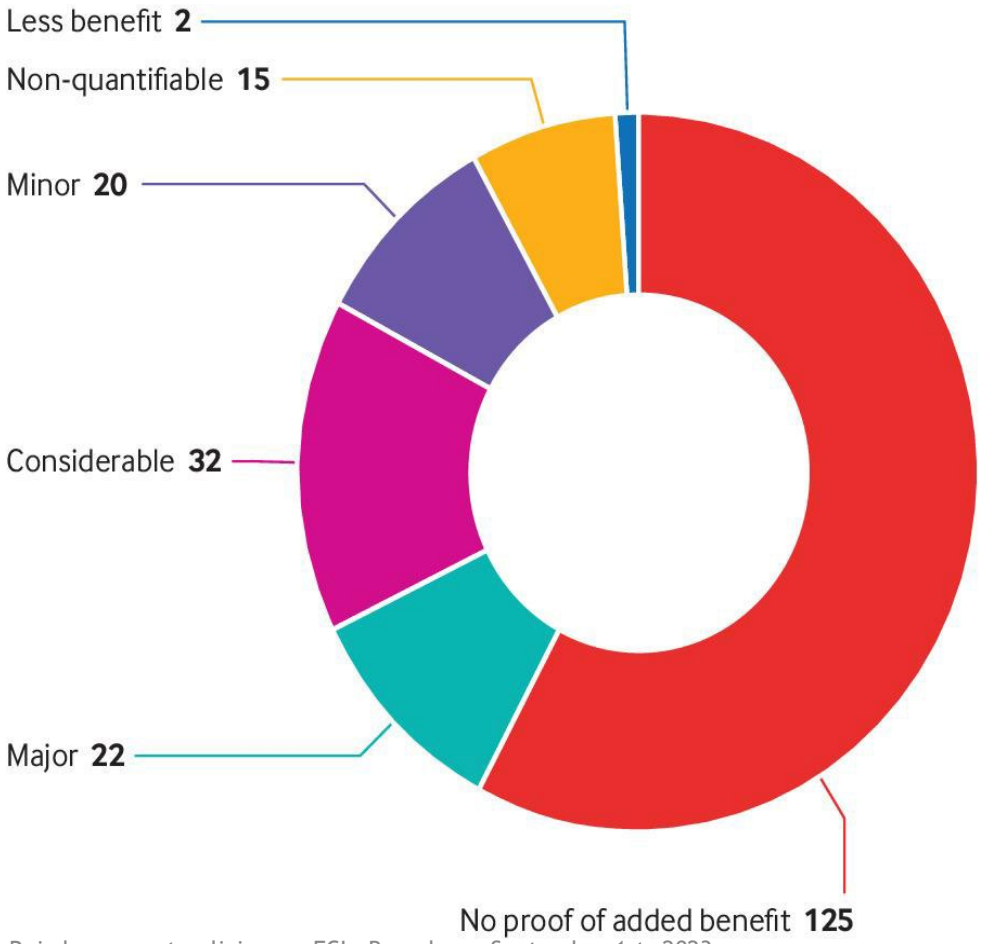
- Certains argumentent qu'une information limitée au moment de la mise sur le marché, est le prix pour un accès plus rapide à l'innovation …

- cet argument sous-entend que la recherche effectuée après mise sur le marché permettra de confirmer le benefice pour les patients…

- … mais un problème bien connu des études réalisées post-marketing est que souvent … *elles ne sont jamais réalisées*.

Wieseler & al, BMJ 2019

Nouveaux medicaments: “innovation” vs “avancée thérapeutique avérée”



Evaluation indépendante de la valeur ajoutée des nouveaux medicaments en Allemagne, 2011-2017

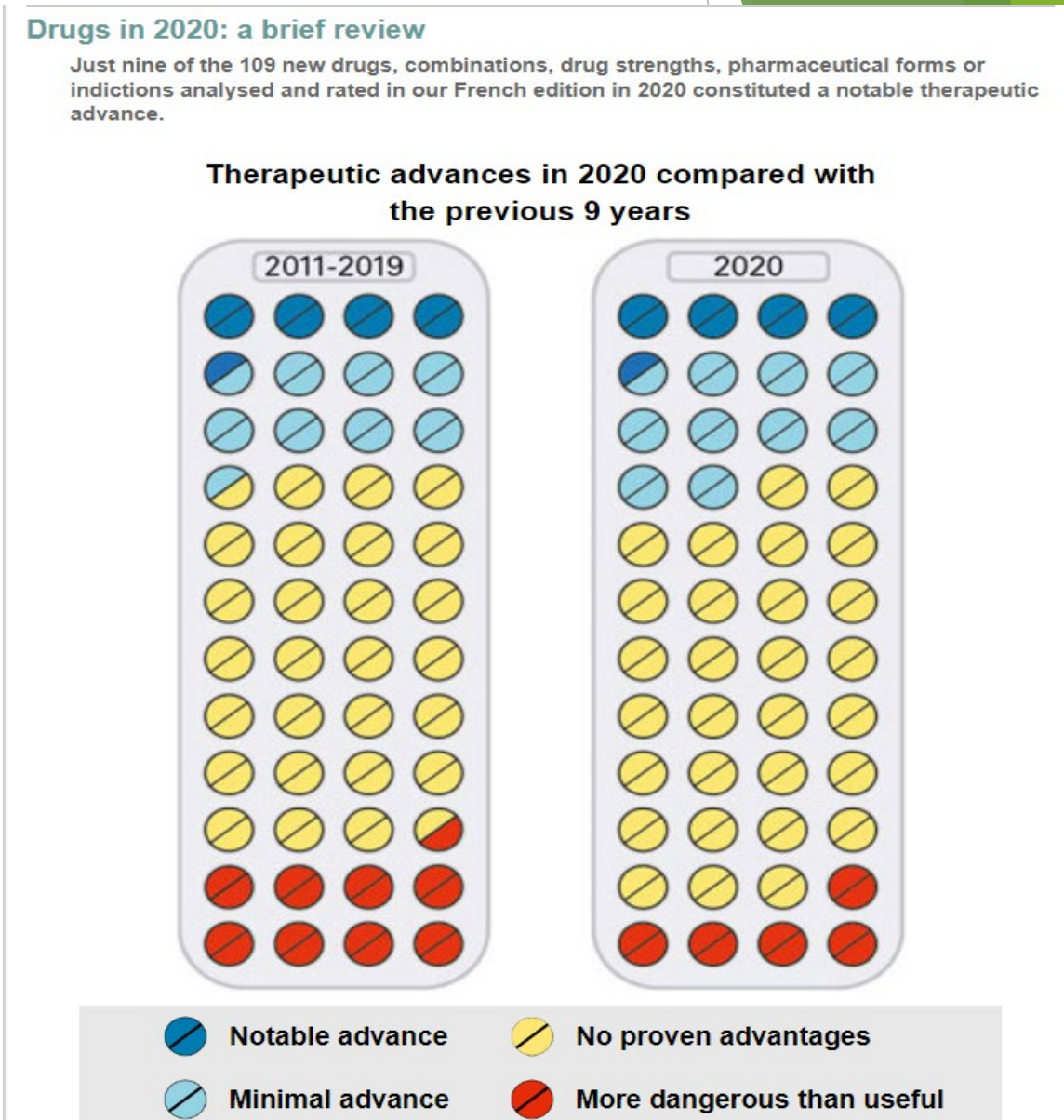
“Preuve” : bénéfice statistiquement significatif sur des critères de jugement pertinents pour le patient , RCT ou très large effet dans un essai non randomisé

Wieseler & al, BMJ 2019

Nouveaux medicaments: “innovation” vs “avancée thérapeutique avérée” ?

Prescrire INTERNATIONAL
A critical eye on new drugs authorised in Europe

Prescrire ratings 2020



A retenir (1/3)…

- Les RCT sont et restent le gold standard de la recherche clinique
  - … mais ils ne peuvent répondre à toutes les questions que l'on se pose
- Nous avons besoin de plus – et de meilleurs - RCT
  - Plus représentatifs de la population cible (femmes, personnes âgées, première ligne…)
  - Critères de jugement importants pour les patients
  - Comparative effectiveness… »
  - Financés sur fonds publics…

Cochrane Database of Systematic Reviews February 2017
Industry sponsorship and research outcome
A. Lundh, J. Lexchin, B. Mintzes, J.Schroll, L.Bero.
https://doi.org/10.1002/14651858.MR000033.pub3
34% more favourable conclusions in sponsored trials

A retenir (2/3)…

- Les études observationnelles fournissent un complément utile (pas un substitut) - et parfois indispensable..
  - En particulier pour étudier la sécurité du médicaments (effets secondaires ou tardifs) + grossesse & lactation
  - Pour étudier l'efficacité en vie réelle (« effectiveness »)
  - Plusieurs signaux = plus probable
- Chaque type d'étude comporte des difficultés méthodologiques: une bonne étude observationnelle vaut mieux d'un mauvais RCT.
- « real world data » : un complément, pas un substitut

ANALYSIS

Check for updates

1 Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany

2 Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium

Correspondence to: B Wieseler
beate.wieseler@iqwig.de

Cite this as: *BMJ* 2023;380:e073100
http://dx.doi.org/10.1136/bmj-2022-073100
Published: 2 March 2023

Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy?

Real world data are advocated as an alternative approach to RCTs for closing knowledge gaps on drugs, but **Beate Wieseler and colleagues** argue that this approach is the wrong remedy for current challenges in drug development

Beate Wieseler, [1] Mattias Neyt, [2] Thomas Kaiser, [1] Frank Hulstaert, [2] Jürgen Windeler[1]

BMJ: first published as 10.1136/bmj-20

A retenir(3/3)…

- La rhétorique d'accès précoce à l'innovation, et l'importance données aux « real world data » dans la génération de l'évidence
  - se font actuellement au détriment de l'évidence… et donc des patients
  - Beaucoup d'incertitudes persistent quant au rapport bénéfice/risque des nouveaux médicaments
- Il est important d'exiger le maintien de standards de preuve lors de la mise sur le marché des nouveaux médicaments + des études comparatives


The End

En attendant, continuez à apprendre grâce à l'Auditorium du CBIP :

- plus de 30 e-learning **gratuits**
- **accréditation** prévue
- **interactifs** & sur base de **cas pratiques**
- fondés sur les **preuves**

PAUSE

Nous vous retrouvons à 15h20

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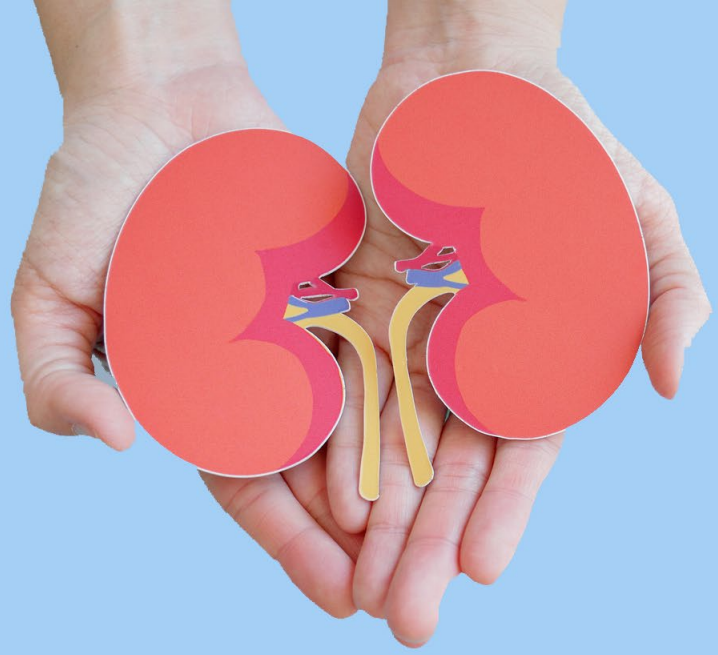
SYMPOSIUM

Actualités
pharmacothérapeutiques
2023



Nouveautés dans le traitement médicamenteux de maladie rénale chronique

Catherine Veys MD

Recent developments in drug therapy for chronic kidney disease (CKD)

- ✓Joachim Vandenhoven, MD, BCFI employee
  - ✓No conflicts of interest
- ✓Catherine Veys, MD, CBIP employee
  - ✓No conflicts of interest

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Recent developments in drug therapy for chronic kidney disease (CKD)

- ✓Focus on pharmacotherapy, and more specific on new drug options

- ✓Medicines for chronic kidney disease: a practical guide (NPS Medicinewise (https://www.nps.org.au/news/medicines-for-chronic-kidney-disease-a-practical-guide)

- ✓Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (https://kdigo.org/guidelines)

Definition and staging of CKD

- ✓Case: Albert
  - ✓64 years old, in good health
  - ✓Hypertension (145/90 mmHg)
  - ✓Dyslipidaemia
  - ✓No other cardiovascular diseases, no diabetes

  - ✓eGFR: 71 ml/min/1,73m², UACR 26 mg/g

  - ✓Drugs:
    - ✓Chloortalidon 50 mg ½ /d
    - ✓Simvastatine 40 mg 1/d

Poll: Definition and staging of CKD

- ✓Case: Albert
  - ✓eGFR: 71 ml/min/1,73m², UACR 26 mg/g

- ✓Poll: Does this patient have CKD?
  A. Yes, he has decreased GFR (< 90 ml/min/1,73m²).
  B. No, his GFR is still above 60 ml/min/1,73m².
  C. No, he has mildly decreased GFR, but his UACR is still below 30 mg/g and he has no other signs of kidney damage.
  D. Yes, he has microalbuminuria.

Definition and staging of CKD

- ✓KDIGO definition of CKD:
  - ✓abnormalities in kidney structure or function
    - ✓kidney structure:
      - ✓ Albuminuria > 30 mg/24u or > 30 mg/g creatinine
      - ✓ Other abnormalities in urine sediment, in kidney biopsy or on imaging
      - ✓ History of kidney transplant
    - ✓kidney function:
      - ✓ GFR < 60 ml/min/1,73m²
  - ✓present for more than 3 months
  - ✓with implications for health
      - ✓ Drug toxicity, adverse events of interventions for prevention or treatment
      - ✓ Elevated cardiovascular risk, metabolic and endocrine complications

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Definition and staging of CKD

- ✓KDIGO proposes to stage CKD on the base of:
  - ✓**C**ause
  - ✓**G**FR
  - ✓**A**lbuminuria

GFR categories (GFR in ml/min/1,73m²)		
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

Albuminuria categories (UACR in mg/g creat)		
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Severely increased

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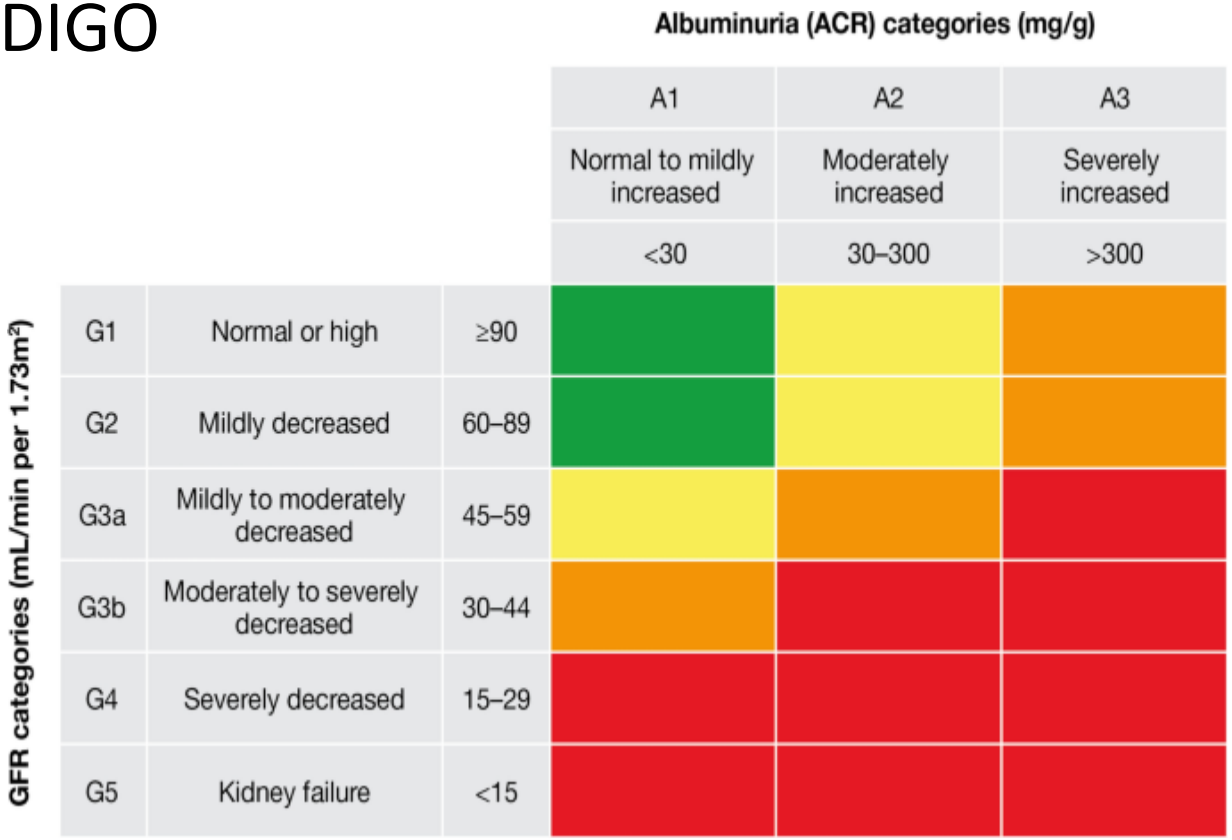
Definition and staging of CKD

KDIGO



GFR categories (mL/min per 1.73m²)				Albuminuria (ACR) categories (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30–300	>300
G1	Normal or high	≥90				
G2	Mildly decreased	60–89				
G3a	Mildly to moderately decreased	45–59				
G3b	Moderately to severely decreased	30–44				
G4	Severely decreased	15–29				
G5	Kidney failure	<15				

Risk of CKD progression, kidney failure, acute kidney injury and CV and all cause mortality:

- Green: low (no CKD if no other markers of kidney disease)
- Yellow: moderately incrased
- Orange: high
- Red: very high

Feedback poll: Definition and staging of CKD

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  D. Yes, he has microalbuminuria.

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Management of CKD

- ✓Goals
  - ✓Treat underlying kidney disease and comorbid conditions
  - ✓Delay progression of CKD
  - ✓Avoid acute kidney injury

- ✓Rationale:
  - ✓High cost of therapy in end stage renal disease
  - ✓Risk factor for cardiovascular disease (also for decreased physical condition and cognitive functioning)
  - ✓Higher risk for drug adverse events and complications during interventions and procedures

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Pharmacotherapy for CKD

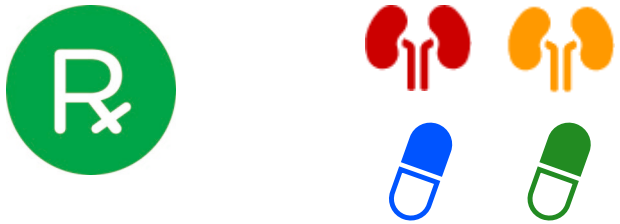
- ✓Treating underlying and comorbid conditions
- ✓Adapt drug posologies and avoid nephrotoxic drugs
- ✓Sick day rules to avoid acute kidney injury
- ✓**Specific drugs to delay progression of CKD**

- ✓Whole patient approach
- ✓Not everything at once, focus on the long term

Pharmacotherapy for CKD

- ✓Treating underlying and comorbid conditions
  - ✓Hypertension
  - ✓Diabetes
  - ✓Dyslipidaemia/high cardiovascular risk
  - ✓Glomerulonephritis, systemic disease with effects on kidneys

- ✓Adapt drug posologies to decreased kidney function and avoid nephrotoxic medication



Pharmacotherapy for CKD

- ✓Sick day rules to prevent acute kidney injury:
  - ✓Decrease dose or stop temporarily specific drugs during episodes (<24h) with high risk for dehydration (heat, fever, vomiting, diarrhea):
    - **S** sulfonylurea
    - **A** ACE-I
    - **D** diuretics (including MRA)
    - **M** metformin
    - **A** ARB
    - **N** NSAID
    - **S** SGLT2-I

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Specific drugs to delay progression of CKD

- ✓ACE-inhibitors and angiotensine receptor blockers (ARB, sartans)

- ✓Sodiumglucose cotransporter 2 inhibitors (SGLT2-I, gliflozins)
- ✓Finerenone (a novel mineralocorticoid receptor antagonist (MRA))

Poll: ACE-I and ARB in CKD

- ✓Remember Albert?
- ✓1 year later:
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 143/85mmHg
  - ✓eGFR: 56 ml/min/1,73m²
  - ✓UACR: 42 mg/g creatinine

- ✓Poll: Should this patient receive an ACE-I or ARB?
  A. Yes, this is clearly recommended.
  B. Yes, this could be considered.
  C. No, not yet.

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ACE-I and ARB in CKD

- ✓Large meta-analysis by Xie et al. (2016)
  - ✓Clear benefits on renal and cardiovascular end points
  - ✓No effect on cardiovascular or all cause mortality
  - ✓Results difficult to interpret
- ✓Smaller meta-analyses by Cochrane and KDIGO in “pure” renal trials
  - ✓Confirm benefits on renal end points
  - ✓No effect on cardiovascular morbidity or mortality or all cause mortality
- ✓Almost all data comes from 3 large trials in patients with diabetes and 2 small trials in patients without diabetes

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ACE-I and ARB in CKD

- ✓Conclusion:
  - ✓Mostly studied in patients with CKD and diabetes
  - ✓Mainly evidence for a renoprotective effect
  - ✓Effect on cardiovascular events less clear
  - ✓Greatest evidence for beneficial effects in patients with severe albuminuria
  - ✓Less (in patients with diabetes) or insufficient (in patients without diabetes) evidence for beneficial effects in patients with moderate albuminuria

ACE-I and ARB in CKD

- ✓KDIGO recommendation
  - ✓Patients with diabetes:
    - ✓Recommended for all patients with high blood pressure, CKD and moderately to severe albuminuria (G1-4, A2-3)
  - ✓Patients without diabetes:
    - ✓Recommended for all patients with high blood pressure, CKD and severe albuminuria (G1-4, A3)
    - ✓Suggested for all patients with high blood pressure, CKD and moderate albuminuria (G1-4, A2)

- ✓Titrate to maximum tolerated dose

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Feedback poll: ACE-I and ARB in CKD

- ✓Albert
  - ✓65 years, good health, no diabetes, dyslipidaemia
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- ✓Poll: Should this patient receive an ACE-I or ARB?
  A. Yes, this is clearly recommended.
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  C. No, not yet.

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Poll: Recent developments in drug therapy for CKD

- ✓Remember Albert?
- ✓You started him on an ACE-inhibitor titrated to maximal tolerated dose but after 2 months his values remain more or less the same:
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of an SGLT2-I?
  - A. No, because he has no diabetes.
  - B. Yes, he qualifies for the use of an SGLT2-I, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of an SGLT2-I. I would certainly prescribe it.

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Poll: Recent developments in drug therapy for CKD

- ✓Remember Albert?
- ✓You started him on an ACE-inhibitor titrated to maximal tolerated dose but after 2 months his values remain more or less the same:
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of finerenone?
  - A. No, because he has no diabetes.
  - B. Yes, he qualifies for the use of finerenone, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of finerenone. I would certainly prescribe it.
  - D. FinereHOW? Never heard of it before.

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SGLT2-I in CKD

- ✓Sodium-glucose cotransporter 2-inhibitors (gliflozins)
  - ✓Initially developed to reduce blood glucose in people with diabetes
  - ✓In early development: evidence for lowering proteinuria and improving renal hemodynamics
  - ✓In cardiovascular outcomes trials: evidence for a significant benefit on renal outcomes, but < 25% of included patients had CKD
  - ✓Primary kidney trials with canagliflozin (CREDENCE), dapagliflozin (DAPA-CKD) and empagliflozin (EMPA-KIDNEY)

SGLT2-I in CKD

- ✓CREDENCE 2019 (Folia oktober 2019)
  - ✓Canagliflozine (Invokana®) 100 mg vs placebo
  - ✓4401 patients with type 2-diabetes, eGFR 30-90 ml/min/1,73m² and severe albuminuria (G2-3, A3)
  - ✓All patients on stable, maximum tolerated dose ACE-I or ARB
  - ✓Primary endpoint: composite of ESRD, doubling of serumcreatinine or death from renal or cardiovascular causes: HR 0,70 (95%CI 0,59 to 0,82); NNT: 22 over 2,6 jaar
  - ✓Also statistically significant reductions for composite endpoints of CV death, AMI and stroke, with or without heart failure hospitalisations, but not for cardiovascular and all cause mortality

SGLT2-I in CKD

- ✓DAPA-CKD 2020 (Folia februari 2021)
  - ✓Dapagliflozine (Forxiga®) 10 mg vs placebo
  - ✓4504 patients, e-GFR 25-75 ml/min/1,73 m² and moderate to severe albuminuria (UACR > 200 mg/g) (G2-3(4), A(2-)3)
  - ✓2/3 with type 2-diabetes; 1/3 without
  - ✓All patients on stable, maximum tolerated dose ACE-I or ARB

  - ✓Primary endpoint: composite of ESRD, >50% decrease in GFR or death from renal or cardiovascular causes: HR 0,61 (95%CI 0,51 to 0,72); NNT 19 over 2,4 years
  - ✓Also significant reduction of all cause mortality (unexplained), but not of cardiovascular mortality, no data on cardiovascular morbidity
  - ✓Subgroupanalysis: results independent of diabetes status, GFR or UACR

SGLT2-I in CKD

- ✓EMPA-KIDNEY 2022 (Nieuwigheden Geneesmiddelen september 2023)
  - ✓Empagliflozin 10 mg (Jardiance®)
  - ✓ 6609 patients with
    - ✓ or GFR 20-45 ml/min/1,73m² (G3b-4, A1-3)
    - ✓ or GFR 45-90 ml/min/1,73m² and UACR > 200 mg/g (G2-G3a, A(2-)3)
  - ✓1/2 with diabetes, 1/2 without
  - ✓85% of patients on clinically appropriate dose ACE-I or ARB

  - ✓Primary endpoint: composite of ESRD, > 40% decrease in GFR or death from renal or cardiovascular causes: HR 0,72 (95%CI 0,64 tot 0,82); NNT: 26 over 2 years
  - ✓No significant reduction of cardiovascular or all cause mortality, no data on cardiovascular morbidity
  - ✓Subgroupanalysis: results independent of diabetes status or GFR, only significant benefit in patients with severe albuminuria (A3), not in patients with mild tot moderate albuminuria (A1-2)

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SGLT2-I in CKD

- ✓Comments
  - ✓All trials were terminated early, which tends to overestimate effects in the intervention group
  - ✓Almost all patients received a stable, maximum tolerated dose ACE-I or ARB
  - ✓Investigated population enlarged from CREDENCE over DAPA-CKD to EMPA-KIDNEY:
    - ✓Inclusion of patients without diabetes, with roughly same efficacy
    - ✓GFR-range from 20-90 ml/min/1,73m², without clear differences in efficacy, no patients with GFR < 20/ml/min/1,73m² included
    - ✓Inclusion of patients with less severe albuminuria, but only evidence for beneficial effect in patients with severe albuminuria

SGLT2-I in CKD

- ✓Contra-indications
  - ✓Type 1-diabetes
  - ✓Antecedents of ketoacidosis under treatment with SGLT2-I

- ✓Adverse events
  - ✓Hypoglycaemia (in patients with diabetes, in association with other hypoglycaemic agents)
  - ✓Genital and urinary tract infections
  - ✓Rare but severe: ketoacidose, gangrene of Fournier, lower limb amputations

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SGLT2-I in CKD

- ✓Renal indications in SPC:
  - ✓Canagliflozine: no specific renal indication, only type 2-diabetes in general
  - ✓Dapagliflozine and empagliflozine: treatment of chronic kidney disease (without further specifications)
- ✓Recommendations
  - ✓KDIGO recommends SGLT2-I as first line treatment in patients with CKD and diabetes and GFR > 20 ml/min/1,73m², alongside metformin
  - ✓Not incoporated yet in guidelines for patients with CKD without diabetes
- ✓Reimbursement in B
  - ✓All gliflozines: reimbursed (A, a prioiri) on certain conditions in type 2-diabetes
  - ✓Dapagliflozine: additionally reimbursed (B, a priori) in patients with chronic kidney disease with or without diabetes and GFR < 60 ml/min/1,73m² and UACR > 200 mg/g
  - ✓Empagliflozine: not yet reimbursed for CKD without diabetes

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Feedback poll:
Recent developments in drug therapy for CKD

- ✓Albert
  - ✓started on an ACE-inhibitor titrated to maximal tolerated dose 2 months ago
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of an SGLT2-I?
  - A. No, because he has no diabetes.
  - **B. Yes, he qualifies for the use of an SGLT2-I, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.**
  - C. Yes, he qualifies for the use of an SGLT2-I. I would certainly prescribe it.

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Finerenone in CKD

- ✓Finerenone (Kerendia®) is a novel mineralocorticoid receptor antagonist (MRA, other molecules in this class: spironolactone, eplerenone)
- ✓Finerenone is a nonsteroidal MRA, highly selective for the mineralocorticoid receptor
- ✓Other (side-)effects profile than spironolacton and eplerenone
- ✓In small studies of short duration: decrease of albuminuria with spironolactone and eplerenone; not investigated on a large scale (AE)

Finerenone in CKD

FIDELIO-DKD 2020 (Folia maart 2023)	FIGARO-DKD 2021 (Folia maart 2023)
5674 patients with type 2 diabetes and CKD with - or GFR 25-60 ml/min/1,73m² and UACR 30-300 mg/g (G3(-4) A2) - or GFR 25-75 ml/min/1,73m² and UACR > 300 mg/g (G(2-)3(-4) A3)	7352 patients with type 2 diabetes and CKD with - or GFR 25-90 ml/min/1,73m² and UACR 30-300 mg/g (G2(-4) A2 - or GFR > 60 ml/min/1,73m² and UACR > 300 mg/g (G1-2 A3)
Finerenone 20 mg vs placebo Reduced initial dose (10 mg) if GFR < 60 ml/min/1,73m², augmented after 1 month if stable GFR and K < 4,8 mmol/l	
All patients on a stable, maximum tolerated dose ACE-I or ARB	
All patients had a serum K concentration below 4,8 mmol/l	
Patients with heart failure excluded	

Finerenone in CKD

FIDELIO-DKD (2020)	FIGARO-DKD (2021)
Renal end point (composite of ESRD, > 40% decrease in GFR, renal mortality)	
HR 0,82 (95%CI 0,73 to 0,93); NNT 29 over 3 years	HR 0,87 (95%CI 0,76 to 1,01)
Cardiovascular end point (composite of cardiovascular mortality, nonfatal AMI, nonfatal CVA, heart failure hospitalisations)	
HR 0,86 (95%CI 0,75 to 0,99); NNT 42 over 3 years	HR 0,87 (95%CI 0,76 to 0,98); NNT 47 over 3,5 years
No significant effect on cardiovascular or all cause mortality	
Effect consistent across GFR- and UACR- subgroups	

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Finerenone in CKD

- ✓Comments
  - ✓Almost all patients received a stable, maximum tolerated dose ACE-I or ARB
  - ✓No data in heart failure patients yet
  - ✓Clear evidence for patients with GFR 25-60 ml/min/1,73m² and UACR > 30 mg/g from FIDELIO-DKD
  - ✓Results from FIGARO-DKD more difficult to interpret: more heterogenous population and negative result on renal end point
  - ✓Patients with GFR < 25 ml/min/1,73m² not included
  - ✓Could the other, older (and cheaper) MRA have the same effects in this population?

Finerenone in CKD

- ✓Contra-indications
  - ✓Hyperkaliaemia
  - ✓Note that severe renal insufficiency still is a contra-indication for the use of spironolactone and eplerenone
- ✓Adverse events
  - ✓Hyperkaliaemia remains a concern
  - ✓No endocrine adverse events with finerenone (gynaecomastia, amenorrhoe, impotence)
- ✓Interactions
  - ✓Increased risk of hyperkaliaemia in association with other kalium-sparing drugs (NSAID, trimethoprim, heparins, ACE-I and ARB) or kalium supplements
  - ✓Finerenone is a substrate of CYP3A4

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Finerenone in CKD

- ✓Indication in SPC
  - ✓Only in patients with CKD and diabetes
  - ✓All stages of CKD, in the presence of albuminuria
- ✓Recommendations
  - ✓KDIGO suggests use of finerenone in patients with CKD and diabetes and GFR > 25 ml/min/1,73m², normal serum kalium concentration and albuminuria (UACR > 30 mg/g)
  - ✓Finerenone can be added to ACE-I/ARB and SGLT2-I.
- ✓Reimbursement in B
  - Reimbursed (B, a priori), largely within the limits of FIDELIO-DKD inclusion and exclusion criteria

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Poll: Recent developments in drug therapy for CKD

- ✓Albert
  - ✓started on an ACE-inhibitor titrated to maximal tolerated dose 2 months ago
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of finerenone?
  - **A. No, because he has no diabetes.**
  - B. Yes, he qualifies for the use of finerenone, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of finerenone. I would certainly prescribe it.
  - D. FinereHOW? Never heard of it before.

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Which drug to chose?

- ✓ACE-I or ARB remains first choice
  - ✓SGLT2-I and finerenone not investigated as first line-therapy
  - ✓Years of experience, well known safety profile
  - ✓Cheap (5-7,5 €/month)
  - ✓Also used to treat frequent comorbidities (hypertension, heart failure)
  - ✓Best evidence in patients with CKD with severe albuminuria

- ✓SGLT2-I and/or finerenone can be added
  - ✓No direct comparisons
  - ✓Very few data on triple association
  - ✓New drugs, no long term experience, no long term data on efficacy and safety
  - ✓More expensive (50-70€/month)
  - ✓Principally evaluated in diabetes, not yet incorporated in guidelines for people without diabetes
  - ✓Only reimbursed under certain conditions

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Which drug to chose?

	SGLT2-I	Finerenone
Indication	Canagliflozin: only in diabetes Dapagliflozin and empagliflozin: also without diabetes All CKD classes (without further specification)	Only in type 2-diabetes Only in CKD with albuminuria
Trial evidence	Less clear evidence in mild to moderate albuminuria	Best evidence in CKD G3 A2-3, no evidence in GFR < 25/ml/min/1,73m² Exclusion of patients with heart failure
KDIGO recommendation	Recommended as first-line hypoglycaemic agent alongside metformin No receommendation yet outside diabetes	Suggested in patients with CKD and diabetes with albuminuria
Adverse events	Rare but severe: keto-acidosis, gangrene of Fournier, amputations	Hyperkaliaemia greatest concern
Reimbursement in B	Canagliflozin only in type 2-diabetes on certain conditions Dapagliflozin also outisde diabetes (G3-4 A(2-)3) on certain onditions Empagliflozin not yet outside diabetes	Only in type 2-diabetes (G3(-4) A2-3) on certain conditions

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Take home

- ✓CKD classification (C-)G-A
- ✓Whole patient approach
- ✓Not everything at once, focus on the long term
- ✓Don’t forget
  - ✓Non-pharmalogical interventions
  - ✓Underlying and comorbid conditions
  - ✓Adapt posologies and avoid nephrotoxic drugs
  - ✓Sick day rules
- ✓Specific drugs to delay CKD progression
  - ✓ACE-I or ARB remains first choice
  - ✓SGLT2-I and/or finerenone can be added, in some patients, in accordance with evidence base, approved indication and reimbursement conditions

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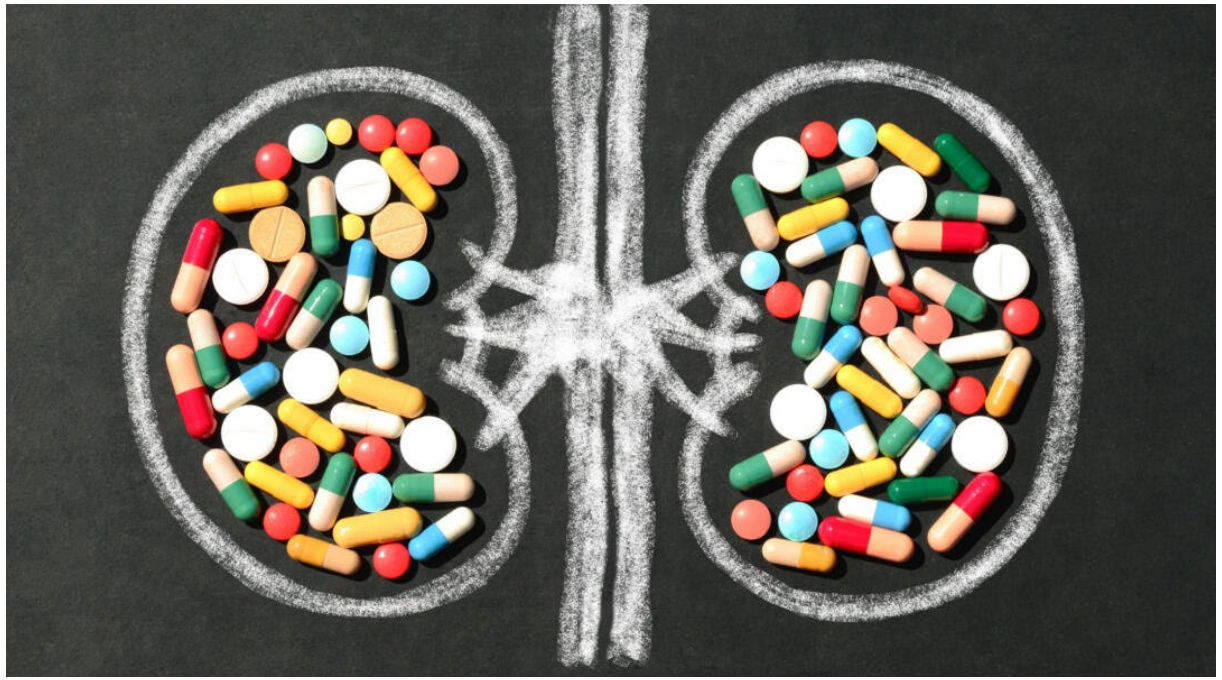
Recent developments in drug therapy for chronic kidney disease (CKD)

Thank you for your attention.



Questions?

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Actualités
pharmacothérapeutiques
2023

Le rôle de la glycoprotéine P (P-gp) dans les interactions médicamenteuses

Jean-Marie Maloteaux MD, PhD

✓I do not have conflicts of interest

Why this topic?

A patient on chronic treatment with the **DOAC dabigatran** reports that she suffers from nose bleeding and bruises. She started a few days before **clarithromycin**.

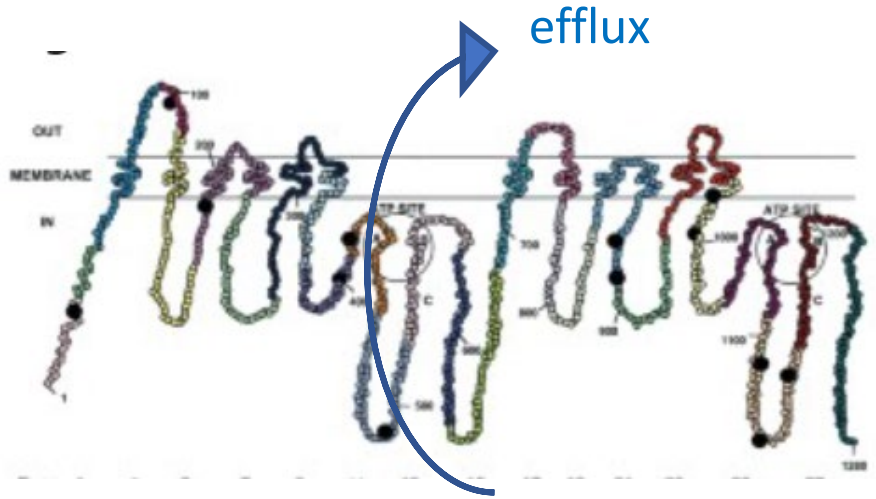
An interaction is suspected : clarithromycin can have increased the plasmalevels of dabigatran, leading to bleeding.

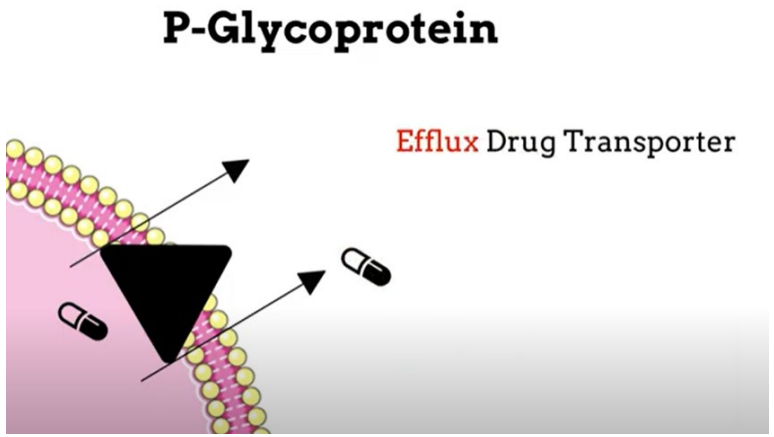
Curious to know more about this interaction?

Scope of the presentation

- What is P-gp?
- How can P-gp impact drug response and cause drug-drug interactions?
- P-gp-substrates, -inhibitors and –inducers in our BCFI/CBIP publications
- Some clinically relevant drug interactions via P-gp
- P-gp in the blood-brain barrier
- Future prospects

What is P-gp? (P-Glycoprotein)





✓ P-glycoprotein (P-gp) is an efflux transporter, present in the membranes of certain cells.
✓ It actively pushes endogenous substances and drugs out of the cells (>< passive diffusion).
✓ “Protective” cellular/tissular function.

PS : First identified in cancer cells resistant to chimiotherapy : P-gp = MDR (Multi-Drug-Resistance)-protein.

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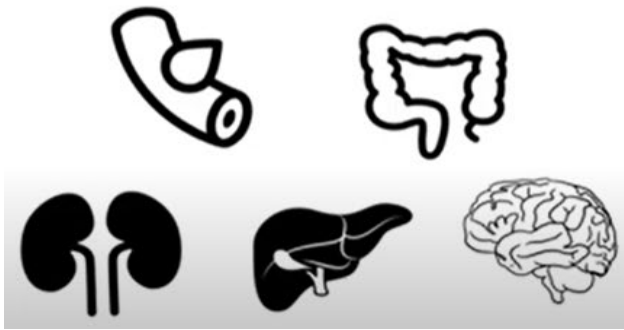
How can P-gp impact drug response?

P-Glycoprotein

Found in ...



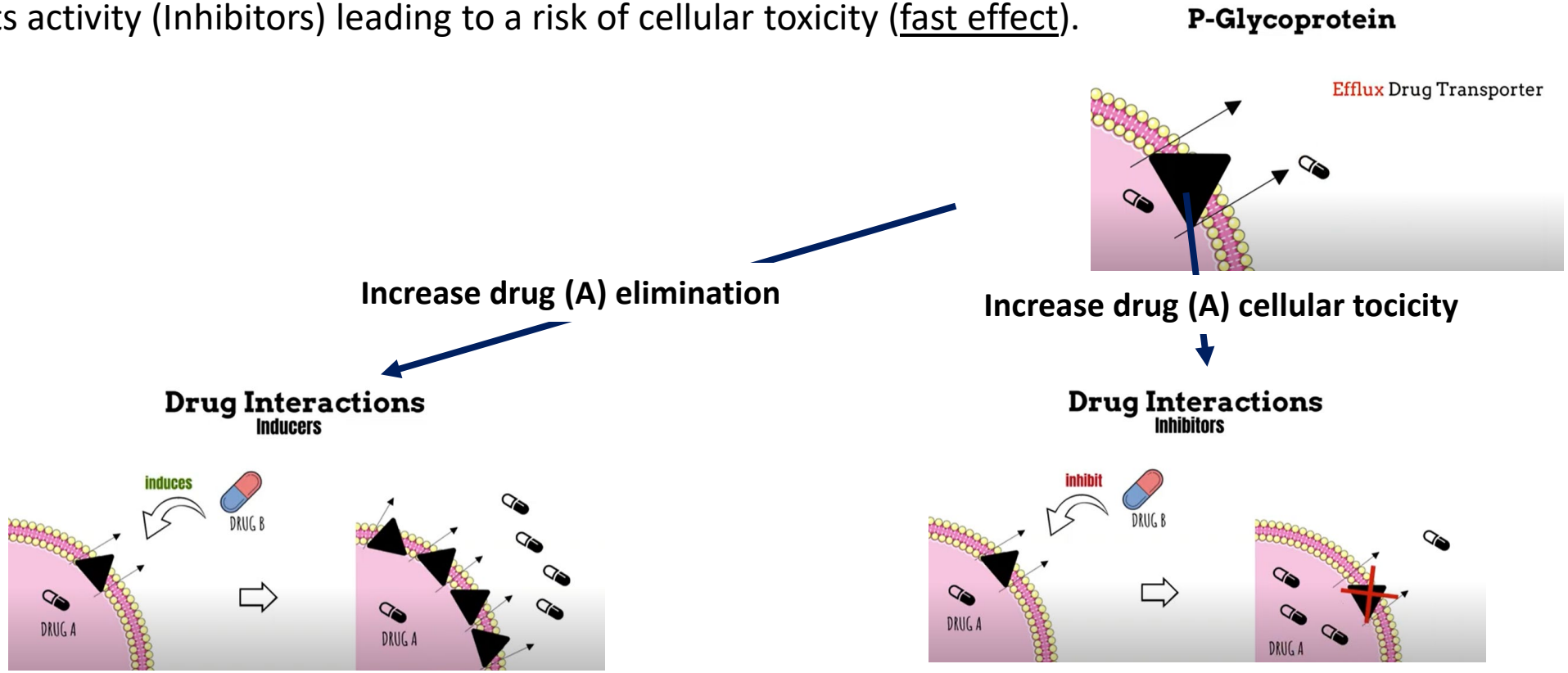
Affects ...

- absorption (in the intestine),
- distribution (to the brain, lymphocytes, testes, or placenta)
- elimination (in the urine and bile).

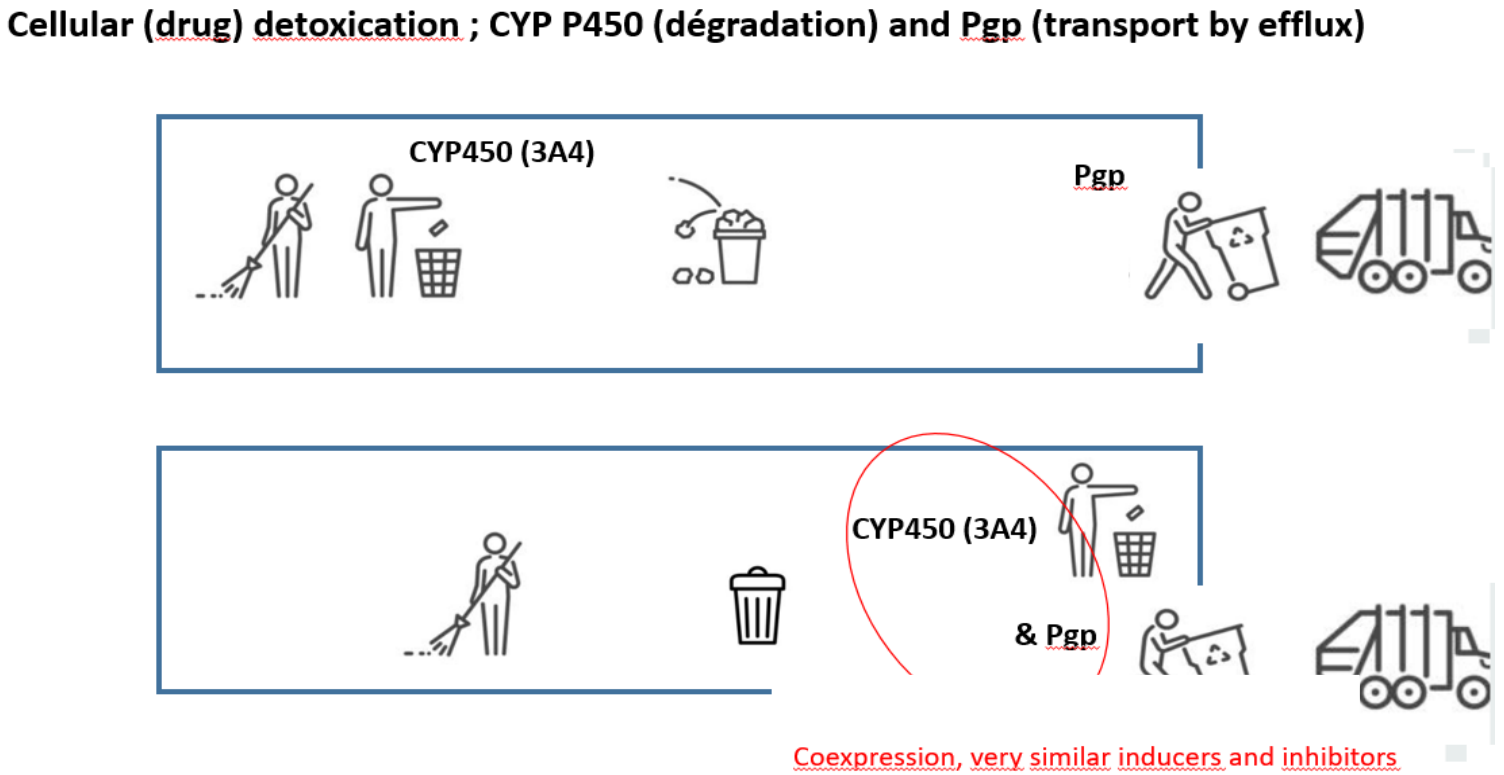
How can P-gp cause drug-drug interactions?

✓ Drug interactions occur because some drugs can

- induce the expression of P-gp (Inducers, ↑amount of P-gp) (slow effect)
- inhibit its activity (Inhibitors) leading to a risk of cellular toxicity (fast effect).



The interplay between P-gp and CYP3A4



✓ The tissue distribution of CYP3A4 (metabolism) and P-gp (transport) is similar

✓ There is considerable overlap between CYP3A4 and P-gp inhibitors, inducers, and substrates.

P-gp-substrates, -inhibitors and –inducers in our BCFI/CBIP drug formulary

9.3.1. Colchicine

La colchicine diminue l'inflammation provoquée par les cristaux d'acide urique formés au niveau des articulations; elle n'exerce pas d'effet analgésique en soi.

Interactions

- Risque accru de myopathie en cas d'association à des statines ou des fibrates.
- La colchicine est un substrat du CYP3A4 et de la P-gp (voir Tableau Ic. dans Intro.6.3. *et* Tableau Id. dans Intro.6.3.) avec risque d'intoxication à la colchicine (avec entre autres rhabdomyolyse, neuropathie, dépression médullaire, atteinte rénale et hépatique) en cas d'association à des inhibiteurs du CYP3A4 ou des inhibiteurs de la P-gp [voir Folia novembre 2009].

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Répertoire > Introduction > Intro.6.3. Interactions

Tableau Id. Substrats, inhibiteurs et inducteurs de la glycoprotéine P (P-gp)

Les substrats, les inhibiteurs et les inducteurs avec lesquels on s'attend à des interactions cliniques particulièrement importantes sont indiqués en gras. Bien évidemment, cela ne signifie pas que les interactions avec les médicaments qui ne sont pas mis en gras soient dénuées de risques. Pour plus d'informations, voir Intro.6.3. Interactions des médicaments

Ctrl F

Substrats	Inhibiteurs (↑ concentration plasmatique du substrat)	Inducteurs (↓ concentration plasmatique du substrat)
Acalabrutinib, **afatinib**, **alfentanil**, ambrisentan, amisulpride, amitriptyline, **apixaban**, **atazanavir**, atorvastatine, **azithromycine**, **binimétinib**, **brentuximab védotine**, budésonide, canagliflozine, carvédilol, **céritinib**, cétirizine, **ciclosporine**, **citalopram**, clopidogrel, **cobimétinib**, **colchicine**, **dabigatran**, **dabrafénib**, darolutamide, **dasatinib**, **daunorubicine**, desloratidine, dexaméthasone, **digoxine**, diltiazem, **docétaxel**, **dompéridone**, **doxorubicine**, **dropéridol**, **édoxaban**, elbasvir, élétriptan, eliglustat, emtricitabine, **erlotinib**, **érythromycine**, éthinylestradiol, **étoposide**	Abémaciclib, **amiodarone**, azithromycine, brigatinib, **ciclosporine**, **clarithromycine**, diltiazem, érythromycine, glécaprévir, idébénone, isavuconazole, **itraconazole**	Apalutamide, carbamazépine, lorlatinib, **millepertuis**, **rifampicine**

Methodology described in Intro.2.1.6.

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Some important substrates (Table Id)

- ✓ Anti-HIV-drugs: e.g. **atazanavir***, **fostemsavir**, maraviroc*, ritonavir*, **saquinavir***…
- ✓ DOAC's: **apixaban*, dabigatran, edoxaban, rivaroxaban***
- ✓ Opioids: **alfentanil*, fentanyl***, **morphine**
- ✓ **Ciclosporin***
- ✓ **Colchicine***
- ✓ **Digoxin**
- ✓ **Domperidone***
- ✓ Loperamide*
- ✓ …

In our interactions e-learnings : the "usual suspects" !

* also substrate of CYP3A4

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Some important inhibitors (Table Id)

- ✓ Anti-HIV-drugs: **ritonavir***, **saquinavir***
- ✓ Macrolide-antibiotics: azithromycin, **clarithromycin***, erythromycin*
- ✓ Antimycotics (azole-derivates): isavuconazol, **itraconazol***, **ketoconazol***
- ✓ Immunosuppressive drug: **ciclosporin**
- ✓ Anti-aritmicum: **amiodaron**
- ✓ Calcium-channel blockers: diltiazem, **verapamil***

- ✓ Grapefruit*

* also (potent) CYP3A4-inhibitor

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Some important inducers (Table Id)

- ✓ Carbamazepine*
- ✓ **Rifampicin***
- ✓ **St John's Wort***

* also (potent) CYP3A4-inducer

Some clinically relevant drug interactions via P-gp

- ✓colchicine + P-gp-inhibitors
- ✓DOAC’s + P-gp-inhibitors / P-gp-inducers
- ✓ciclosporin + P-gp-inhibitors / P-gp-inducers

colchicine + P-gp-inhibitors

Folia
Pharmacotherapeutica

S'abonner

Folia Pharmacotherapeutica novembre 2009

version PDF

Pharmacovigilance: intoxication par la colchicine par interaction avec des inhibiteurs du CYP3A4 ou de la glycoprotéine P

La colchicine (Colchicine Opocalcium®) est utilisée dans la crise de goutte. Alors que ce médicament est disponible chez nous depuis longtemps, il vient seulement d'être enregistré comme " médicament " et commercialisé aux Etats-Unis. Lors de l'évaluation du dossier d'enregistrement, la

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colchicine + P-gp-inhibitors

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence:
  - ↑ risk of (severe) intoxication (e.g. severe diarrhoea, myopathy, neuropathy, bonemarrow depression, renal- and hepatic complications)
  - Cases of life-threatening and fatal intoxications

- ✓ Do not use colchicine + (potent) inhibitor of CYP3A4 or P-gp (certainly in patients with hepatic or renal impairment)
- ✓ If not possible to avoid combination with P-gp-inhibitor: use lowest dose of colchicine and be alert for symptoms of intoxication (e.g. diarrhea)

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DOAC’s + P-gp-inhibitors / P-gp-inducers

DOAC’s: apixaban, edoxaban, dabigatran, rivaroxaban

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence: ↑ risk of bleeding
- ✓ If possible, avoid combination. Monitor for signs and symptoms of bleeding. (+ instructions in SPC)

- ✓ **Inducers**: carbamazepine, rifampicin, St John’s wort
- ✓ Consequence: ↑ risk of thromboembolic effects (↓ therapeutic effect)
- ✓ If possible, avoid combination (replace inducer or DOAC) + instructions in SPC (depending on indication)

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ciclosporin + P-gp-inhibitors / P-gp-inducers

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence: ↑ risk of nephrotoxicity
- ✓ Avoid (potent) inhibitors of P-gp. If not possible, monitor ciclosporin plasma concentrations and renal function

- ✓ **Inducers**: rifampicin, carbamazepine, St John's wort
- ✓ Consequence: ↑ risk of transplant rejection (kidney/liver/heart)! (↓ therapeutic effect)
- ✓ Avoid (potent) inducers of P-gp (combination with St John's wort is a contra-indication). If not possible to avoid combination: monitor ciclosporin plasma concentrations

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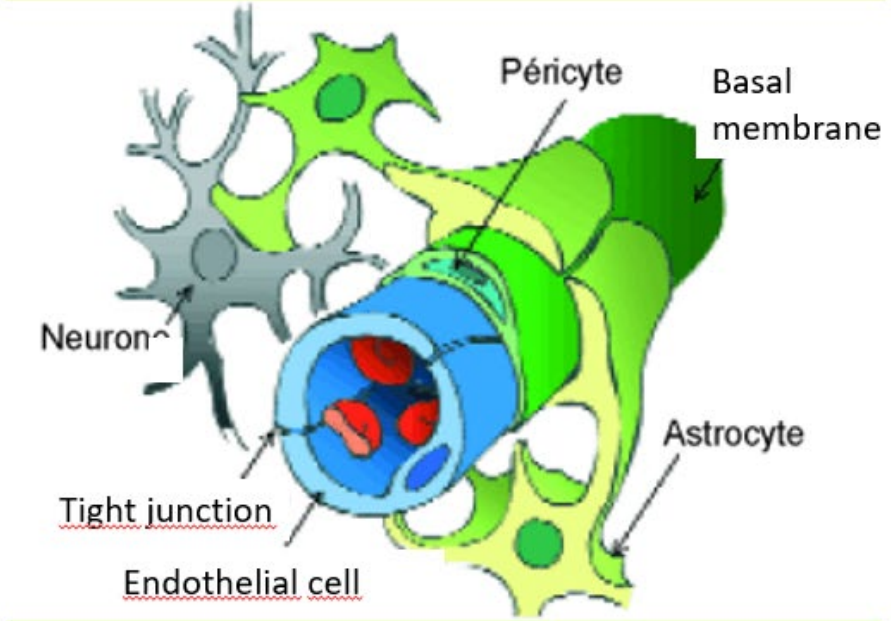
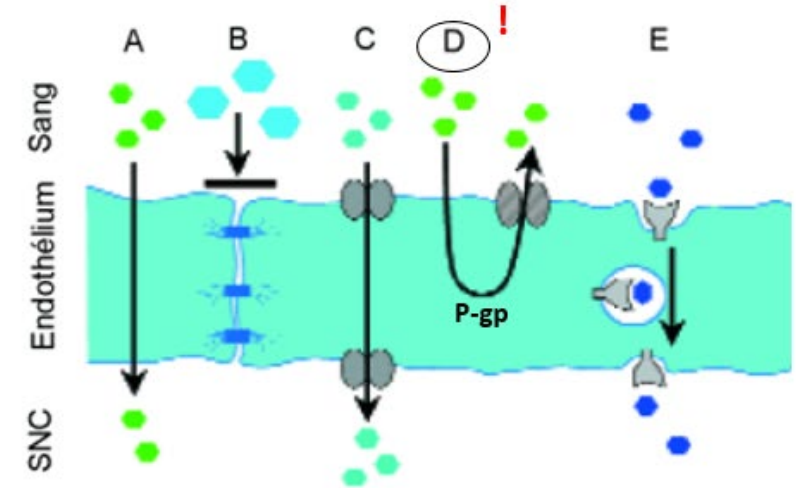
P-gp in the blood-brain barrier

✓ P-gp reduces the entry of drugs into the central nervous system.

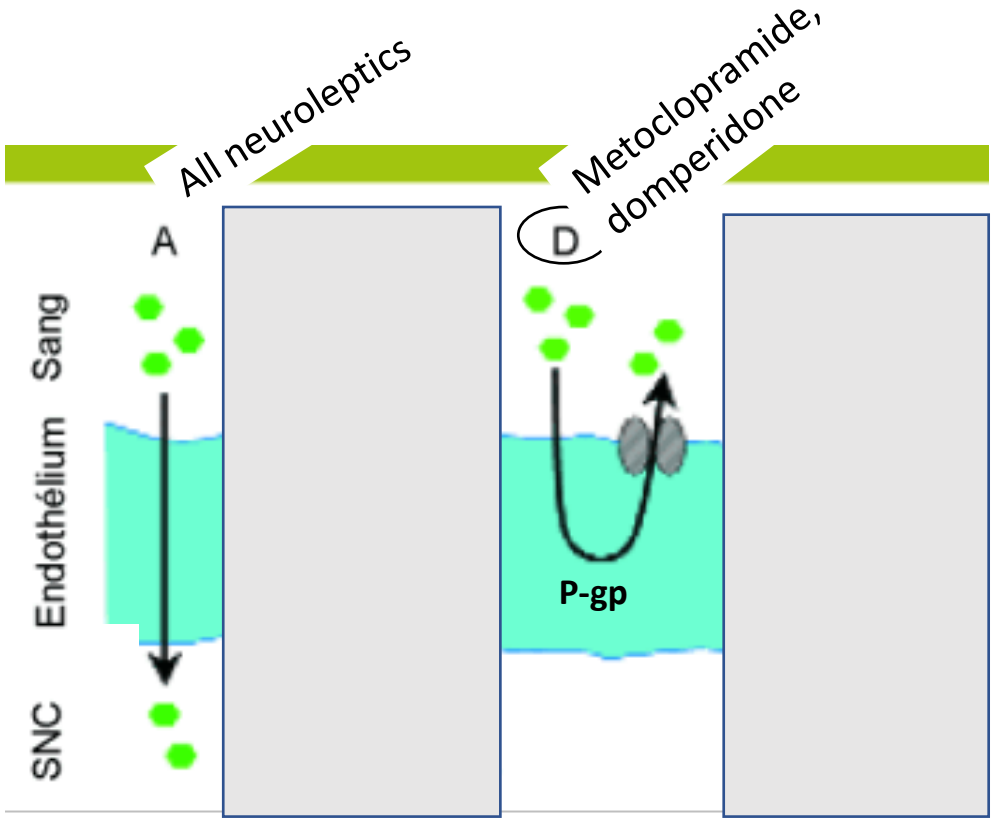


Histological components of the Blood-Brain Barrier

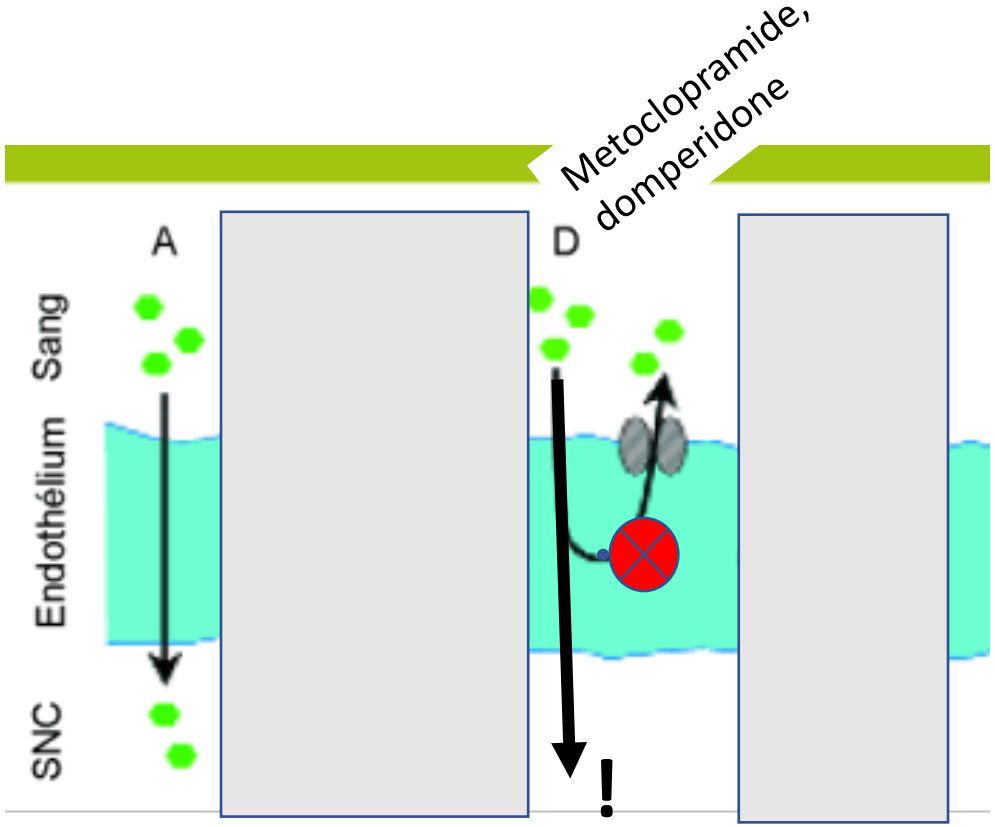


Different exchanges through the BBB.
A. Small lipophilic molecules, B no passage of large or hydrophilic molecules, C active transport, D active efflux (P-gp), E receptor or uptake sites mediated endocytosis

Drugs and the blood-brain barrier (BBB)
Metoclopramide, domperidone,… (dopamine antagonists)

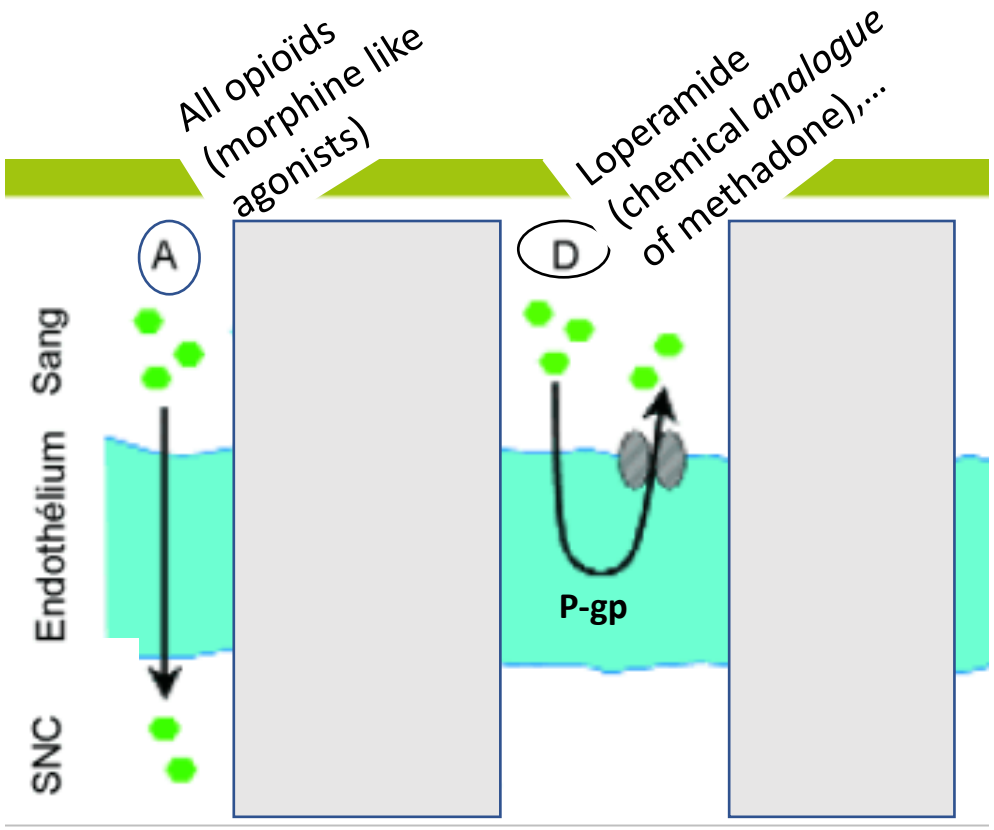


No central effects of these dopaminergic antagonists metoclopramide and domperidone.
Fast efflux by P-gp.

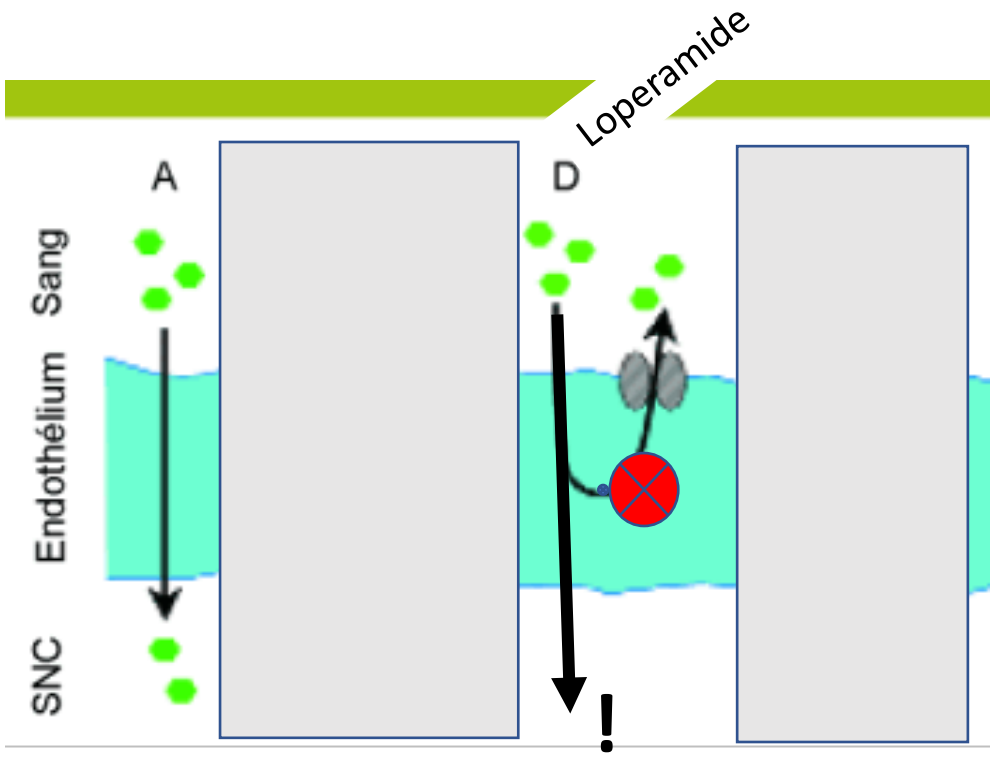


Interaction **<u>with Pgp inhibitor</u>**:
CNS effects, Dyskinesia, Dystonia, Parkinson like syndrome, Sedation.
Neuroleptic-like effects.

Drugs and the blood-brain barrier (BBB)
Loperamide (peripheral opiate agonist, antidiarrheic)

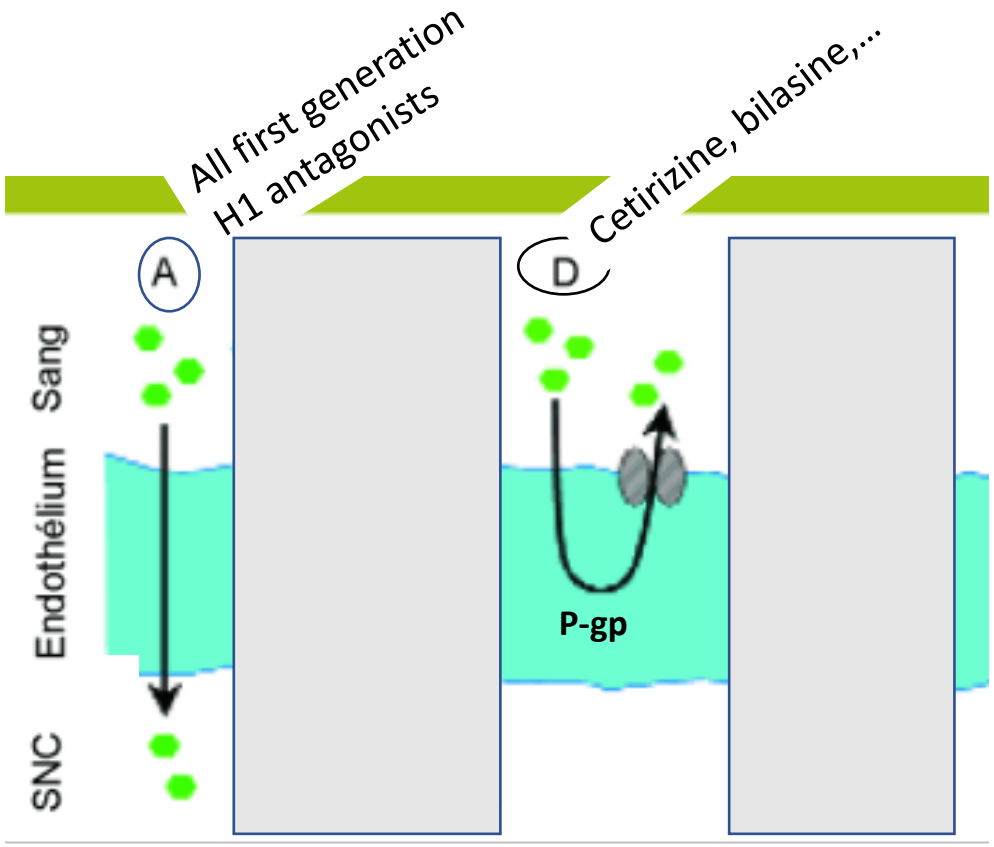


No central effects (morphine like analgesic) of loperamide. Fast efflux by P-gp.
Peripheral effects on digestive symptoms.

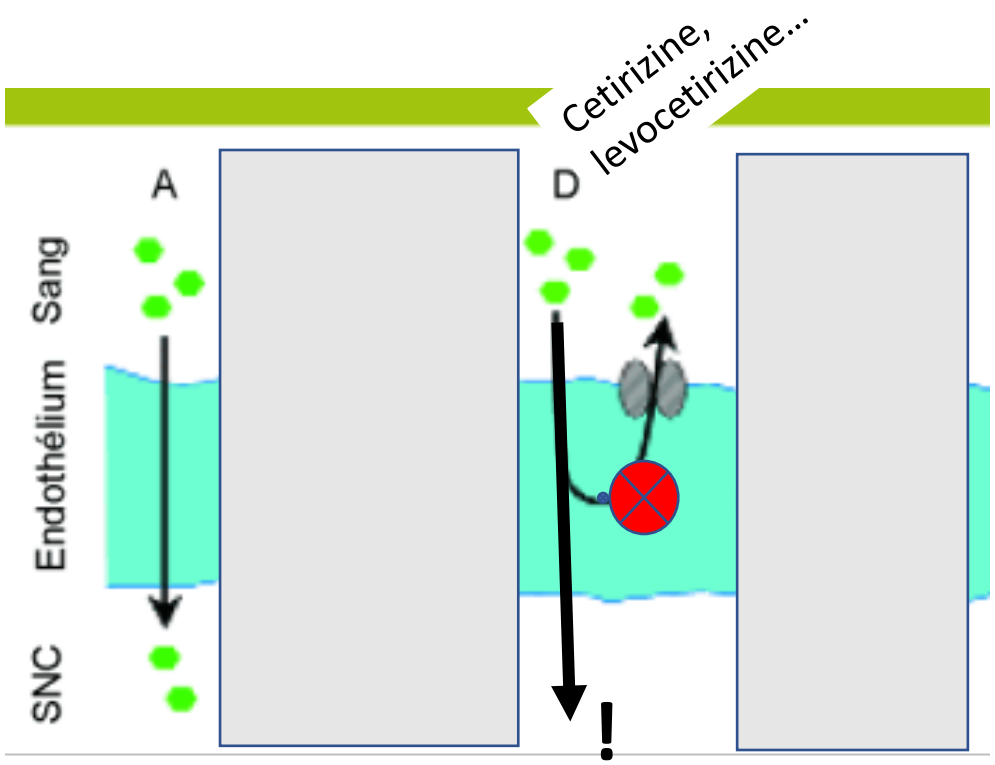


Interaction **with Pgp inhibitor**:
CNS effects, Sedation, respiratory depression, death.
Central opiate effects.

Drugs and the blood-brain barrier (BBB)
Cetirizine, Levocetirizine (non sedative H1 histamine antagonists)



No central effects of these more recent histamine antagonists. Fast efflux by P-gp.
Peripheral effects only on allergic symptoms.

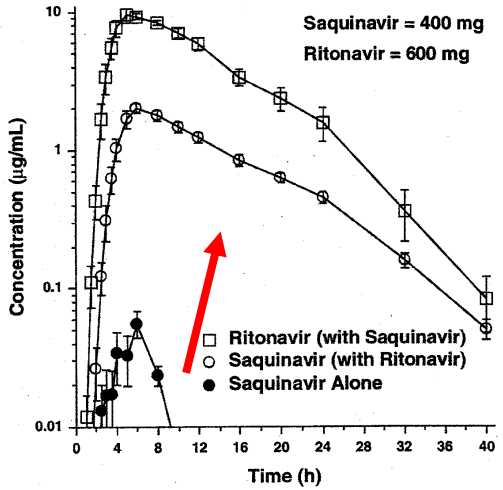


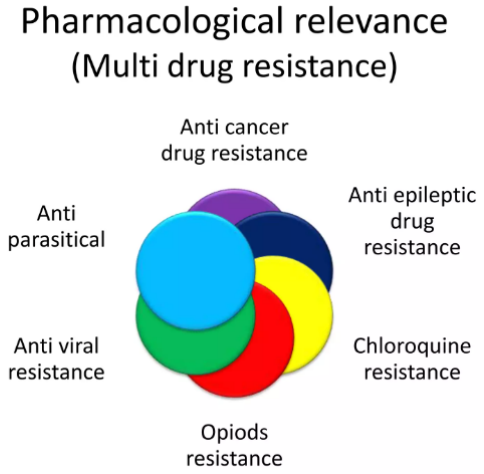
Interaction **with Pgp inhibitor**:
CNS effects, Sedation, vertigo, concentrations problems, sleep inducers.
Central antihistamiic effects.

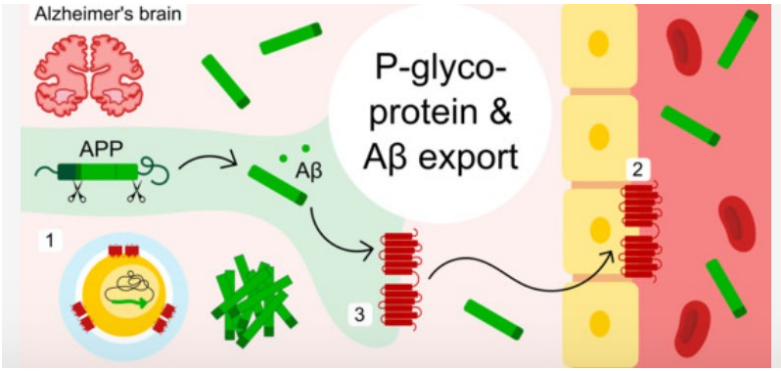
Future prospects

✓Several effects of P-gp-inhibition or -induction are being investigated

- The example of co-medication of interest : saquinavir + ritonavir or lopinavir + ritonavir (anti-HIV) : ritonavir is a Pgp-inhibitor, increasing saquinavir or lopinavir concentrations and efficacy
- Mechanisms of tolerance to opioids ; anti-HIV and antibacterial resistance
- The role of P-gp in the export of ß-amyloid in Alzheimer's disease and the possible interest of a P-gp inducer …







Thank you for your attention!

Quiz 8

Question 1

✓Do all drugs of a same therapeutic class (e.g. all calcium channel blockers) behave similarly face to P-gp (are they all substrates or inhibitors, or inducers)?

1. Yes, I agree
2. No, I do not agree

Feedback quiz 8

Question 1

✓Do all drugs of a same therapeutic class (e.g. all calcium channel blockers) behave similarly face to P-gp (are they for example all inhibitors)?

1. Yes, I agree
2. No, I do not agree

Quiz 9

Question 2

✓The effect of a P-gp-inducer appears very fast (within a few hours).

1. Yes, I agree
2. No, I do not agree

Feedback quiz 9

Question 2

✓The effect of a P-gp-inducer appears very fast (within a few hours).

1. Yes, I agree
2. No, I do not agree

Quiz 10

Question 3

✓A patient on chronic treatment with dabigatran asks if he can use a supplement with St John's wort. What do you answer?

1. I strongly advise against, but I discuss the necessity of another antidepressant.
2. No problem, I agree with the patients suggestion.

Feedback quiz 10

Question 3

✓A patient on chronic treatment with dabigatran asks if he can use a supplement with St John's wort. What do you answer?

1. I strongly advise against, but I discuss the possibility of another antidepressant.
2. No problem, I agree with the patients suggestion.

Évaluation: Quiz 11 - 14

✓ Êtes-vous satisfait de ce symposium? Comment jugez-vous les critères suivants, sur une échelle de 1 à 5 :

- Contenu
- Aspects techniques
- Organisation en général

✓ Avez-vous une préférence de date ou de période pour l'édition 2024 du symposium ?

- Septembre - octobre
- Novembre - décembre
- Autre

✓Préférez-vous suivre cette formation le matin ou l'après-midi ?

- Matin
- Après-midi
- Autre

✓ Avez-vous des commentaires ou des suggestions à nous donner ?

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Merci pour votre attention!