




5 mei 2018

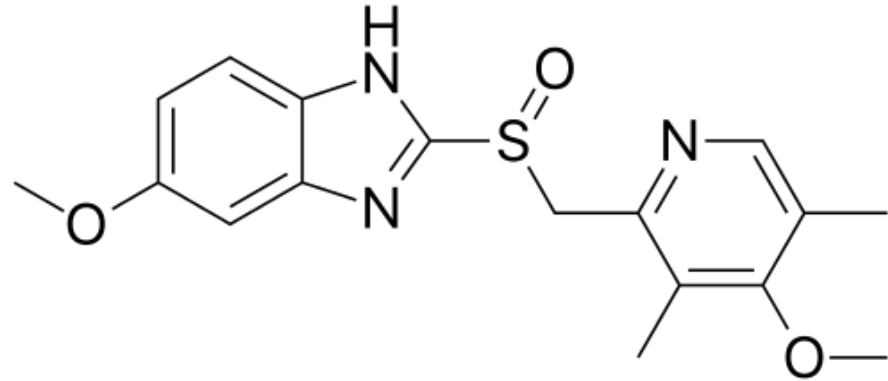
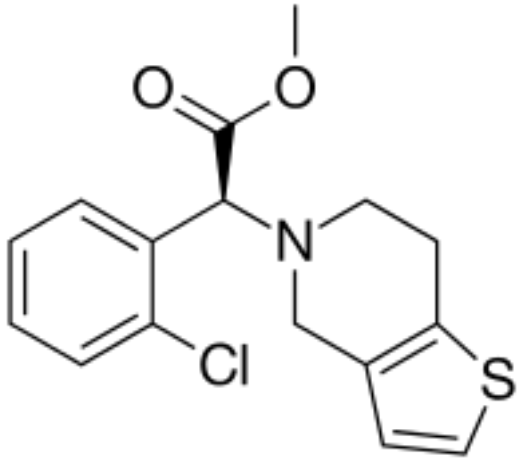


Geneesmiddelinteracties Wat mag en kan niet ?

Prof. Hans De loof en Dominique Jans

Overzicht

- Clopidogrel – PPI
- Triptanen – SSRI
- DDI Bestaat er een top-10?



Clopidogrel + PPI

gevaarlijk?

BCFI repertorium interactietabel

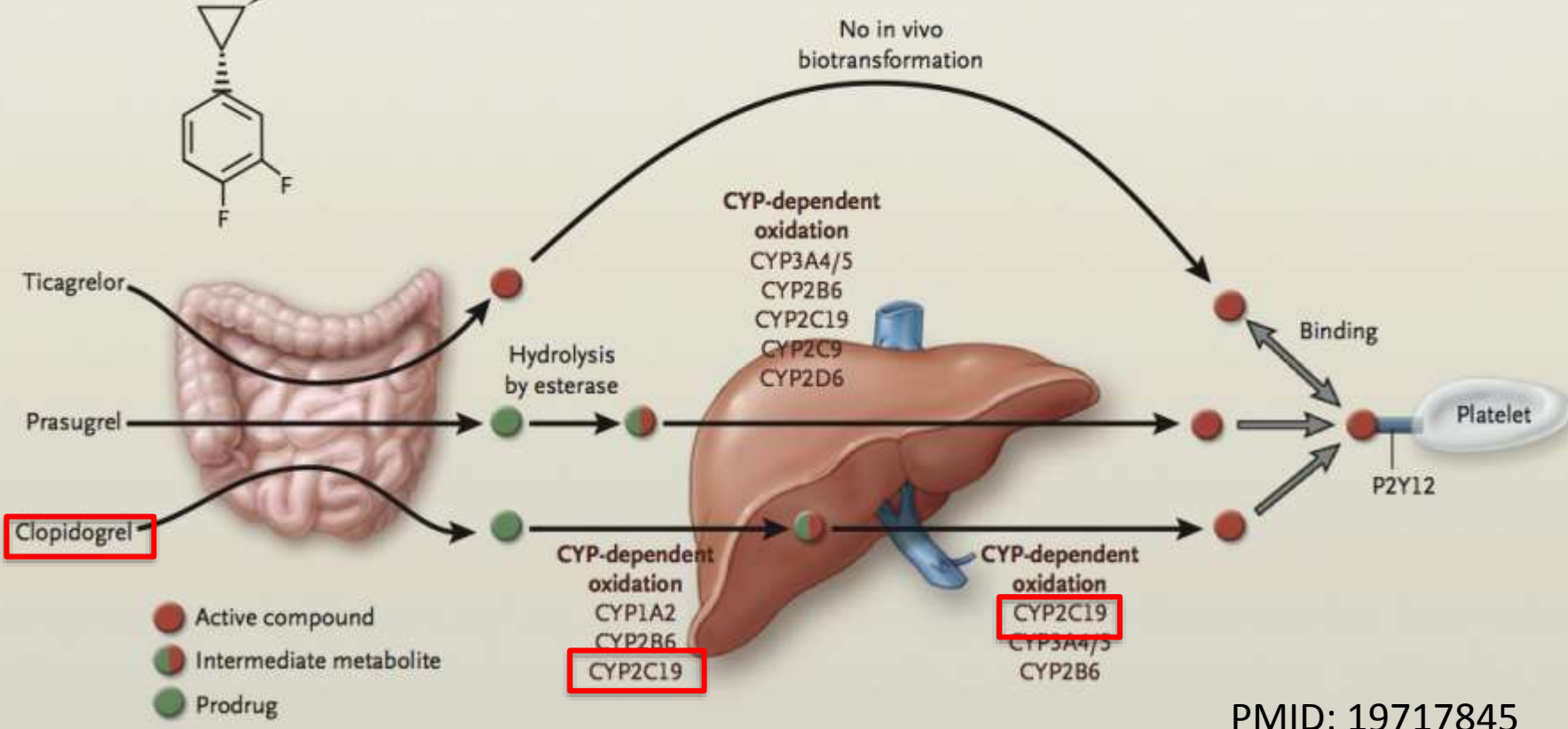
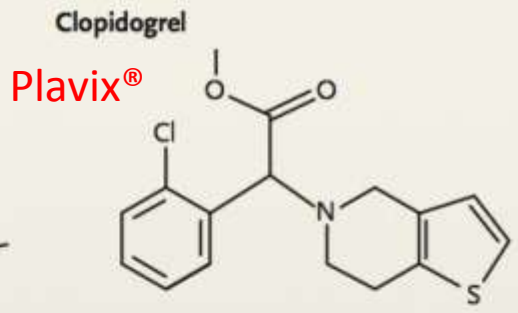
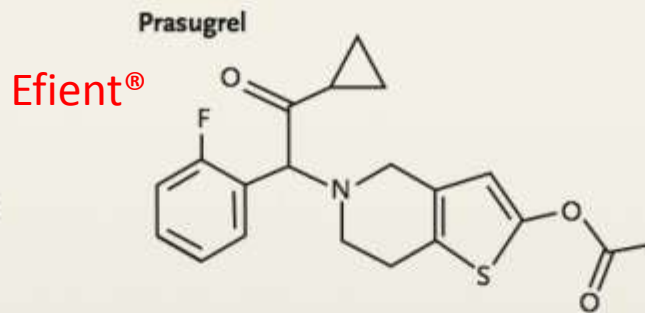
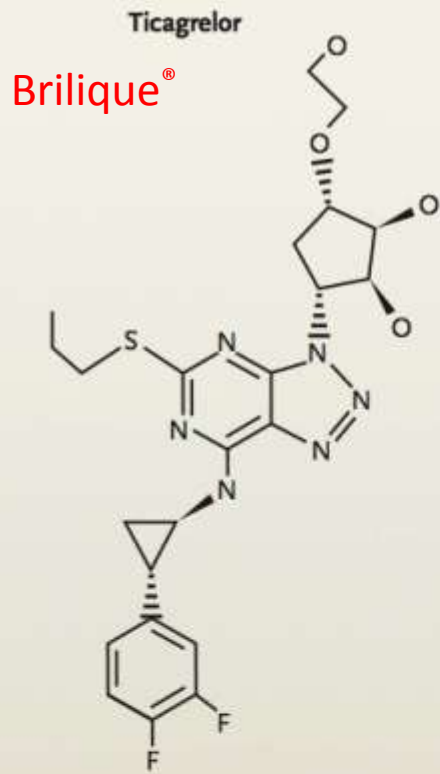
Substraten

Inhibitoren (↑ substraatplasmaconcentratie)

CYP2C19

- Citalopram, **clopidogrel**, diazepam, escitalopram, esomeprazol, **fenobarbital**, **fenytoïne**, labetalol, lansoprazol, moclobemide, omeprazol, pantoprazol, proguanil, rabeprazol

- Esomeprazol, felbamaat, **fluconazol**, fluoxetine, **fluvoxamine**, isoniazide, lansoprazol, moclobemide, modafinil, **omeprazol**, stiripentol, **ticlopidine**, topiramaat, voriconazol



PMID: 19717845



Figure 1. Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor.

EMA (mei 2009) : “Product information for all clopidogrel-containing medicines should be amended to **discourage concomitant use** of PPI and clopidogrel-containing medicines unless absolutely necessary.”

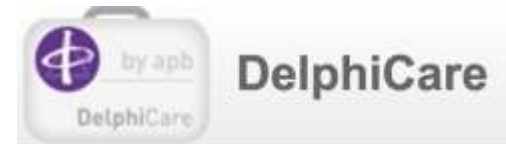
FDA (nov 2009) “The concomitant use of omeprazole and clopidogrel **should be avoided** because of the effect on clopidogrel's active metabolite levels and anti-clotting activity.”

BCFI (juni 2013) transparantiefiche: “Hoewel er geen aanwijzing is van een klinisch relevante interactie, is een **interval van ongeveer 12 uren** tussen de inname van de PPI en van clopidogrel voorzichtigheidshalve aan te raden.”

Geselecteerde items:

Specialiteit	Losec-Mups (c) 20mg tabletten, maagsapresistente	
Specialiteit	Clopidogrel EG (c) 75mg tabletten, film-	

Gevonden interacties:



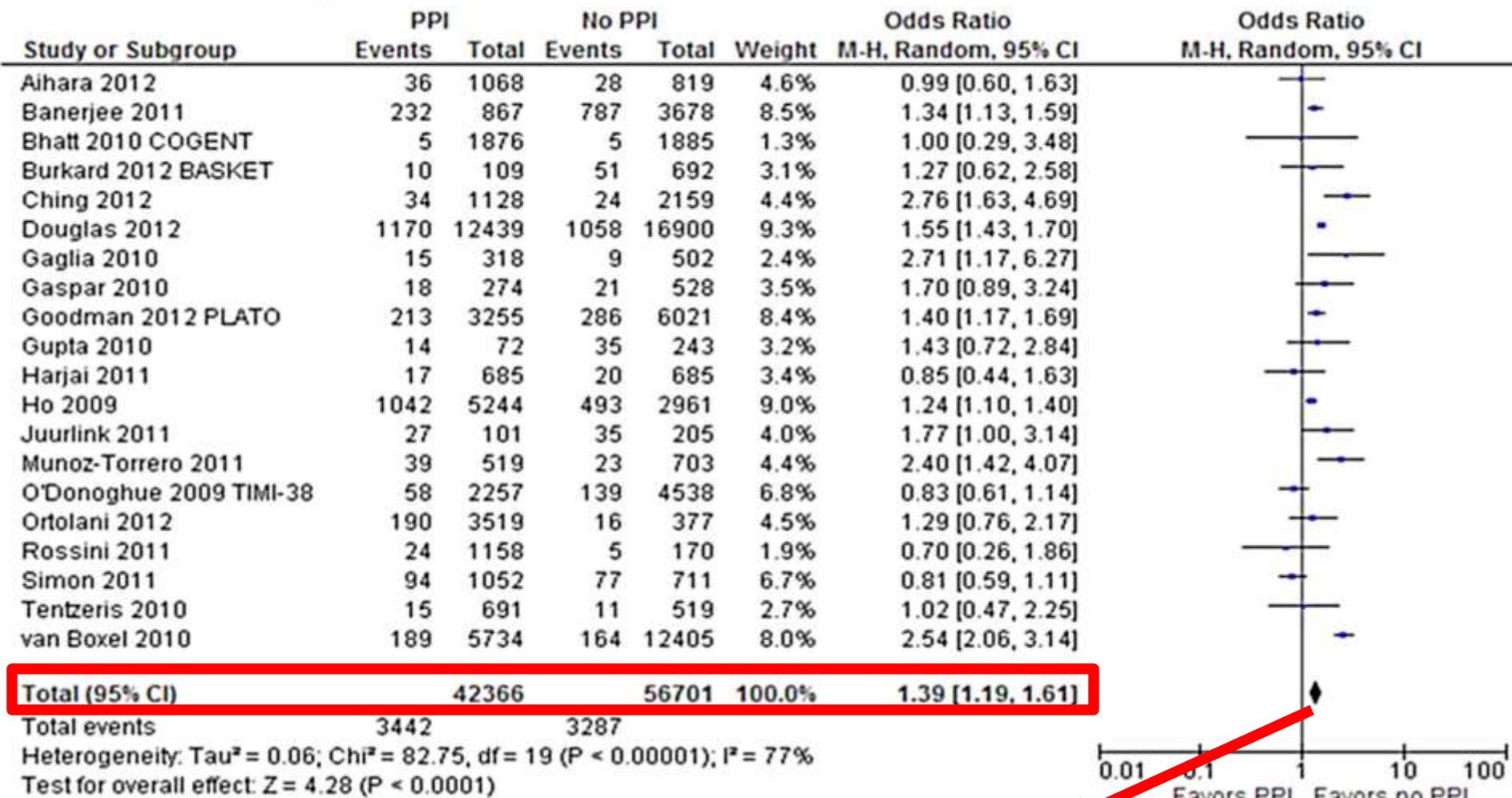
Gelijktijdig gebruik niet aanbevolen (1 interactie)



Clopidogrel EG (c) 75mg tabletten, film- - Losec-Mups (c) 20mg tabletten, maagsapresistente

Observationele Data

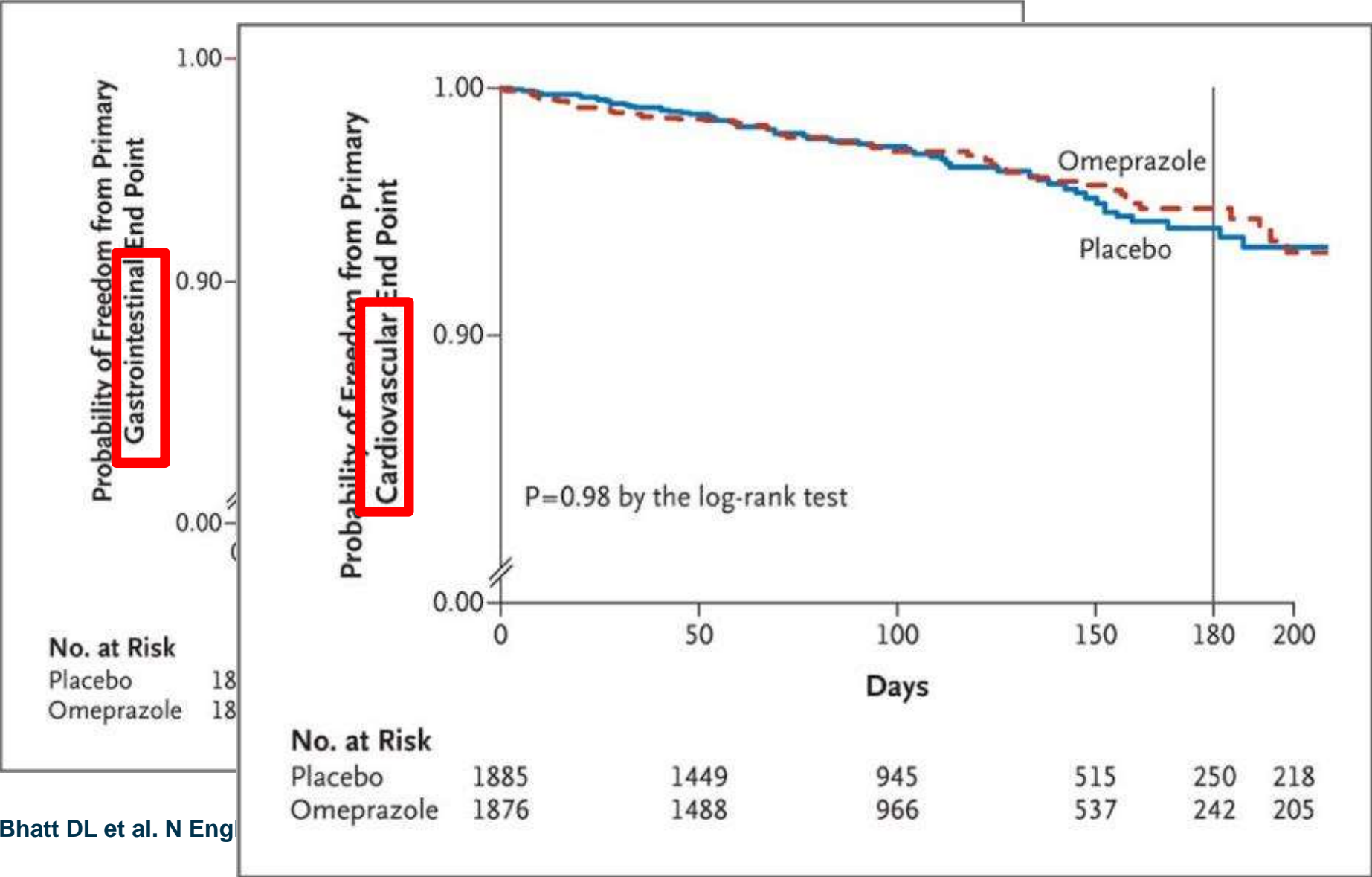
A Overall mortality



Open Heart 2015;2:e000248.

Mortality OR 1,39

Omeprazol en Clopidogrel: COGENT trial



Bhatt DL et al. N Engl



Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis

Open Heart 2015;**2**:e000248.

Rhanderson N Cardoso,¹ Alexandre M Benjo,² James J DiNicolantonio,³ Daniel C Garcia,¹ Francisco Y B Macedo,⁴ Georges El-Hayek,⁵ Girish N Nadkarni,⁶ Sebastiano Gili,⁷ Mario Iannaccone,⁷ Ioannis Konstantinidis,⁶ John P Reilly²

Conclusions: The results of our meta-analysis suggest that PPIs are a marker of increased cardiovascular risk in patients taking clopidogrel, rather than a direct cause of worse outcomes. The pharmacodynamic interaction between PPIs and clopidogrel most likely has no clinical significance. Furthermore, PPIs have the potential to decrease gastrointestinal bleeding in clopidogrel users.

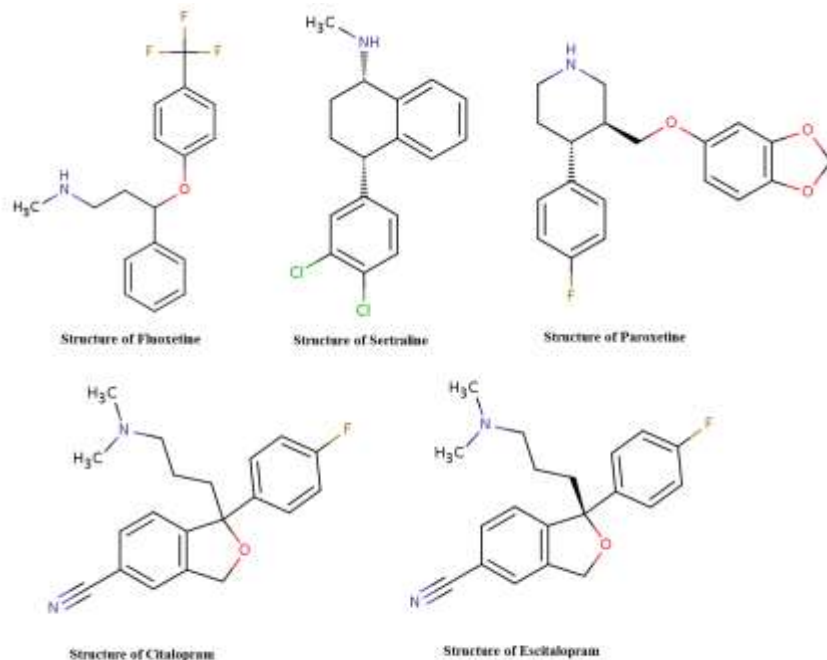
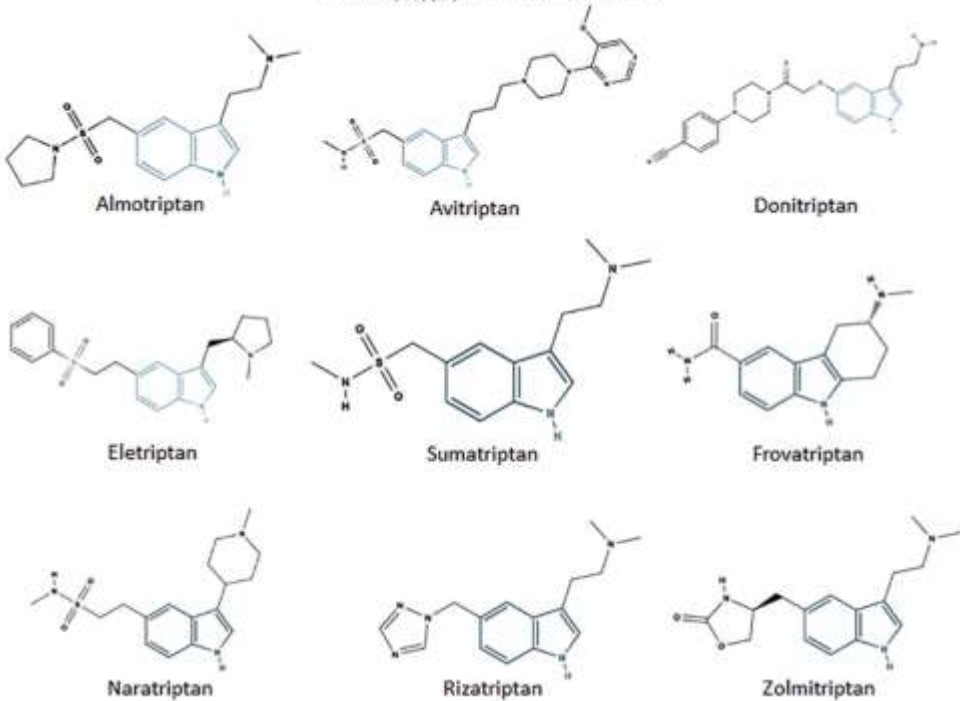
Zie ook:
PMID
29557943,
25587094,
25587089

Clopidogrel + PPI besluit

- Indien PPI geïndiceerd is **niet twifelen om te combineren** met een PPI !
- RCT's wegen veel zwaarder dan associaties uit observationele data (confounding)
- Belang van primaire bronnen vs traagheid secundaire bronnen
- Nuances moeilijk implementeerbaar in eenvoudige interactiealgoritmen/apps

Triptanen + SSRI

5-HT_{1B/1D/1F} receptor agonists



gevaarlijk?

FDA (juli 2006) “The FDA has determined that **serotonin syndrome** occurs with combined use of **triptans and a SSRI or SNRI** through reports describing serotonin syndrome in people taking these medications together.”

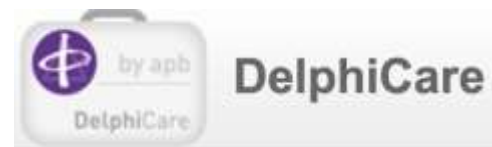
BCFI (april 2018) :” **Serotoninesyndroom bij associëren** met andere geneesmiddelen met serotoninerge werking”

SKP Imitrex® (april 2018) Na het in de handel brengen waren er zeldzame meldingen van patiënten met een serotoninesyndroom na de toediening van SSRI's en sumatriptan.

Geselecteerde items:

Specialiteit	Serlain (c) 50mg tabletten, film-	
Specialiteit	Imitrex Instant (c) 50mg tabletten, dispergeerbaar	

Gevonden interacties:



Opvolging van de patiënt of aanpassing(en) uit voorzorg (1 interactie)



Imitrex Instant (c) 50mg tabletten, dispergeerbaar - Serlain (c) 50mg tabletten, film-

Serotonin toxicity (increase in CNS 5HT efflux*)	CNS excitation	Mental state	Autonomic excitation	Typical cause
	Severe (10-100x)	Rigidity, respiratory failure	Coma Confusion	Severe hyperthermia
Moderate (5-10x)	Opsiclonus, sustained clonus, myoclonus, tremor	Agitation	Mydriasis, flushing, diaphoresis, low fever ($<38.5^{\circ}\text{C}$)	SSRI overdose
Mild (3-5x)	Inducible clonus, hyper-reflexia	Anxiety	Hypertension, tachycardia	Ecstasy use
(<3x)	Brisk reflexes	Insomnia	Nausea, diarrhoea	SSRI in therapeutic use

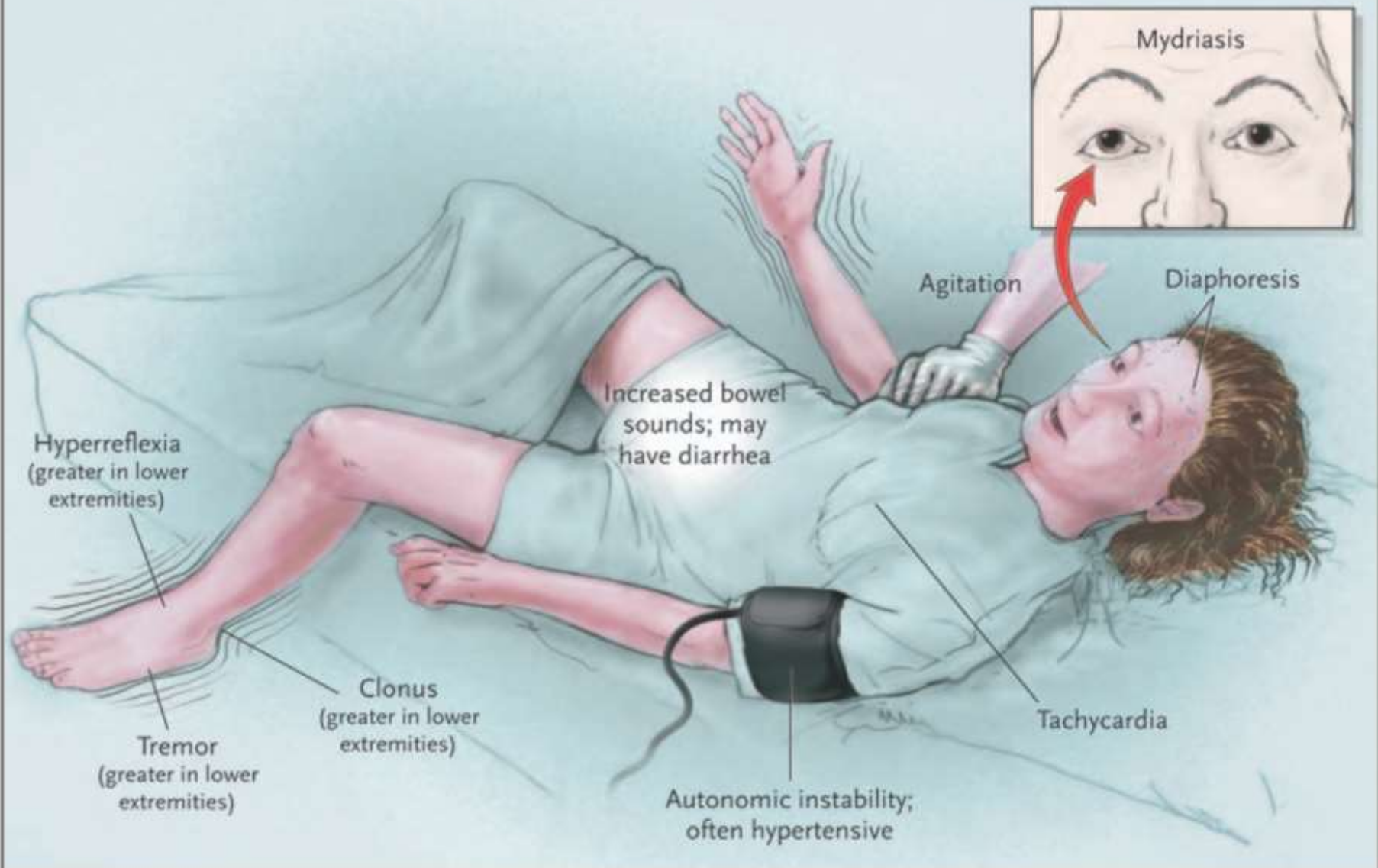
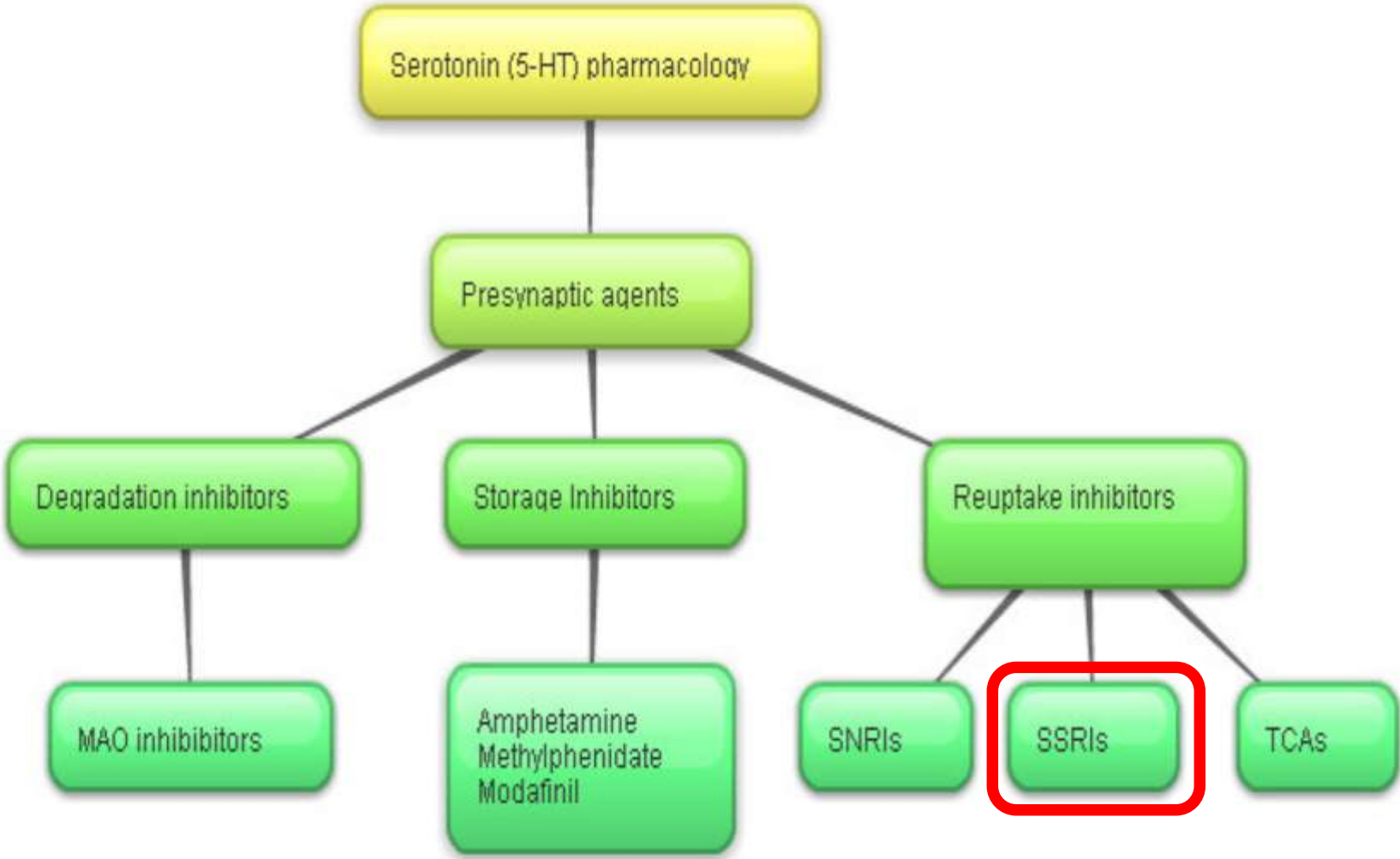


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

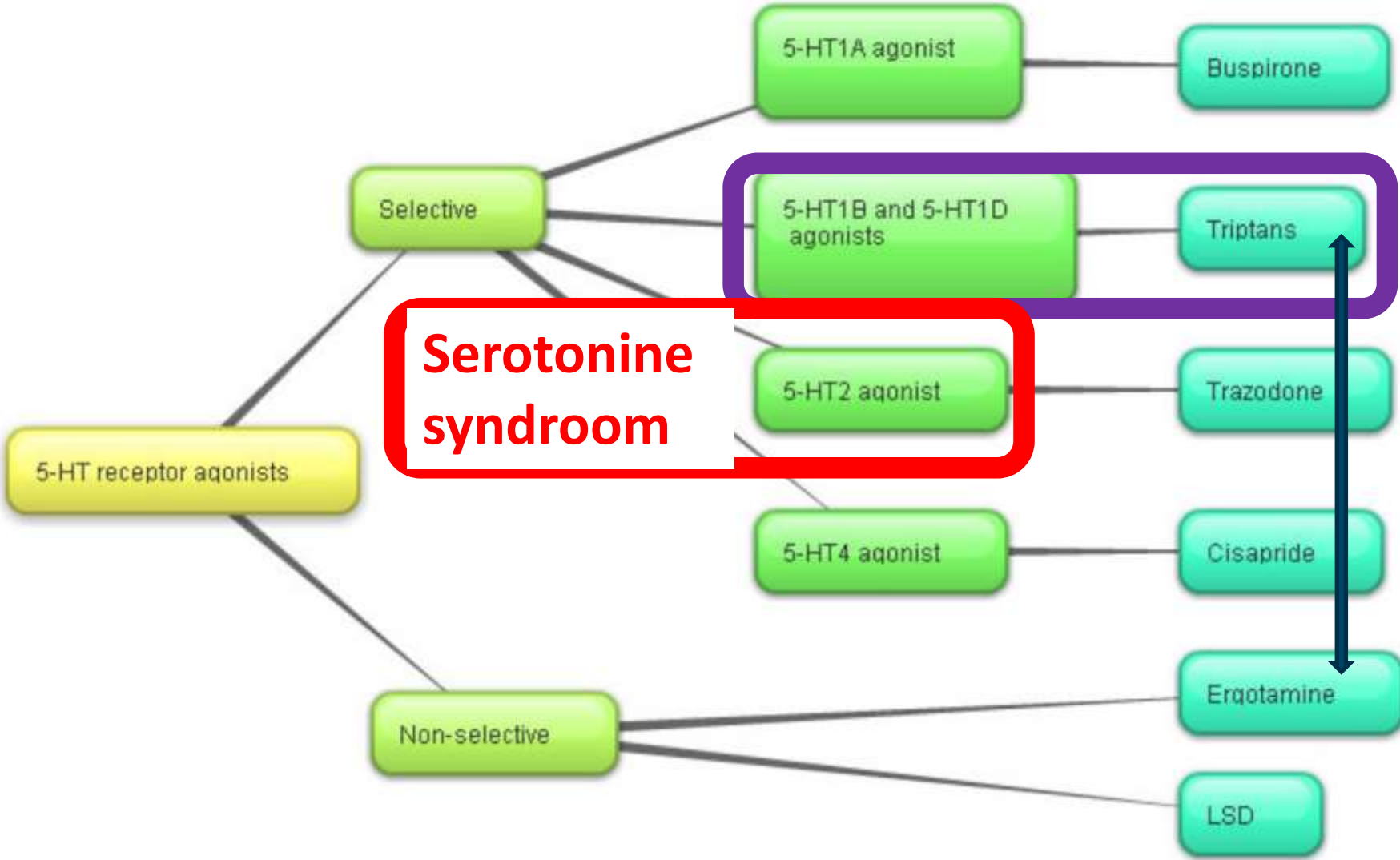
Drugs acting on serotonergic neurotransmission



<http://pharmacologycorner.com/serotonin-5ht-receptors-agonists-antagonist/>



Serotonin agonists



AHS Position Paper

The FDA Alert on Serotonin Syndrome With Use of Triptans Combined With Selective Serotonin Reuptake Inhibitors or Selective Serotonin-Norepinephrine Reuptake Inhibitors: American Headache Society Position Paper

The currently available evidence does **not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome**

Do Triptan Antimigraine Medications Interact with SSRI/SNRI Antidepressants? What Does Your Decision Support System Say?

Stephen J. Kogut, MBA, PhD

While Sclar et al. characterized the drug combination as “potentially fatal,” their finding that nearly **700,000 Americans are prescribed the combination yearly**, taken in contrast with the **very small numbers of questionable case reports** received by the FDA and/or reported in the literature, suggests that the increased risk of serotonin syndrome **is extremely low or perhaps nonexistent.**

Triptaan – SSRI → serotonine syndroom?

- Combinatie mogelijk zonder klinisch belangrijke stijging risico's serotonine toxiciteit.
- Serotonine syndroom is geen idiosyncratische onvoorspelbare reactie maar de ergere vorm van serotonine toxiciteit.
- “Te voorzichtig” zijn moet beter afgewogen worden t.o.v. het ontzeggen en aan bepaalde behandeling
- (Verhoogde toxiciteit frovatriptan bij combinatie met fluvoxamine)

TOP-10 DDI ??

Niet te missen DDI?

Checklist op vraag van

Office of the National Coordinator for Health Information Technology (ONC)

[J Am Med Inform Assoc.](#) 2012 Sep-Oct;19(5):735-43

Database checklist (1)

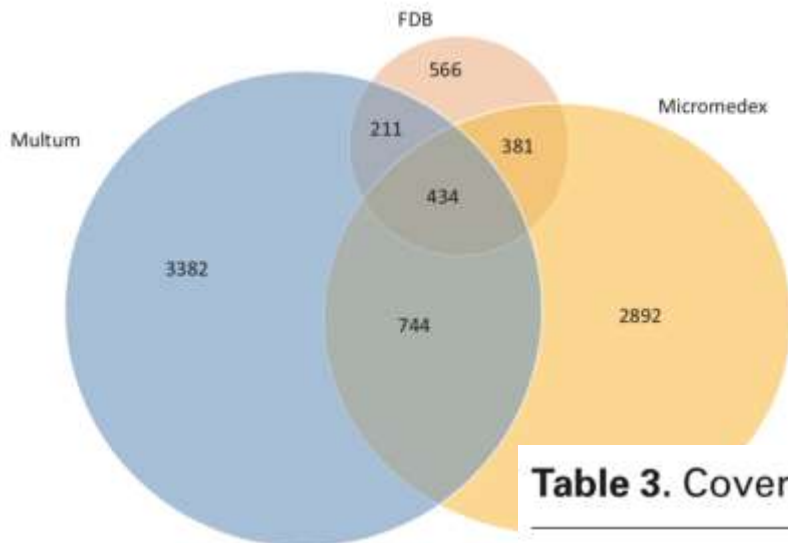
<p>MAO – inhibitors fenelzine – Nardelzine[®] moclobemide – Aurorix[®] (selegiline - Eldepryl[®])</p>	<p>SSRI</p>	<p>Serotonine-toxiciteit</p>
	<p>TCA</p>	
	<p>Opioïden fentanyl, tramadol, tapentadol, methadon, dextromethorphan</p>	
	<p>Amfetamine-derivaten Methylfenidate - Rilatine[®] - Pseudo-efedrine – Vasocedine[®] Atomoxetine – Strattera[®]</p>	<p>Hypertensieve crisis ...</p>
	<p>Bepaalde triptanen Sumatriptan – Imitrex[®] Zolmitriptan – Zomig[®] (Rizatriptan - Maxalt[®])</p>	<p>Overdosering triptan</p>

Database checklist (2)

Sterke CYP3A4 remmers proteaseremmers, azolen, macroliden,	Irinotecan – Campto®	falen antikankertherapie
	Simvastatin – Zocor®	Spier-toxiciteit- rhabdomyolyse
	Ergot-derivaten Cafergot®, Diergo®	Vasoconstrictie...
CYP3A4 – inducers sterk Rifampicine carbamazepine St-Janskruid	Protease inhibitoren Ritonavir, Atazanavir, Darunavir, Fosamprebavir, Saquinavir, Tipranavir	Falen HIV therapie

Database checklist (3)

<p>QT-verlengende-TdP</p>	<p>QT-verlengende-TdP</p>	<p>disopyramide, procainamide, quinidine, hydroxychloroquine, sotalol, azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, fluconazole, pentamidine, voriconazole, haloperidol, sulpiride, pimozide, sertindol, (es)citalopram, droperidol, granisetron, ondansetron, methadone, cocaine, donepezil</p>
<p>Tizanidine – Sirdalud®</p>	<p>CYP1A2 inhibitors Fluvoxamine – Floxyfral® Ciprofloxacin – Ciproxine® Propafenon – Rytmonorm®</p>	<p>AUC Tizanidine x 33 !</p>
<p>Atazanavir – Reyataz®</p>	<p>PPI (all)</p>	<p>BB ↓↓</p>
<p>Febuxostat – Adenuric®</p>	<p>Azathioprine – Imuran® Mercaptopurine – Puri-Nethol®</p>	<p>Azathioprine toxiciteit (ook met allopurinol)</p>



Test van de databanken

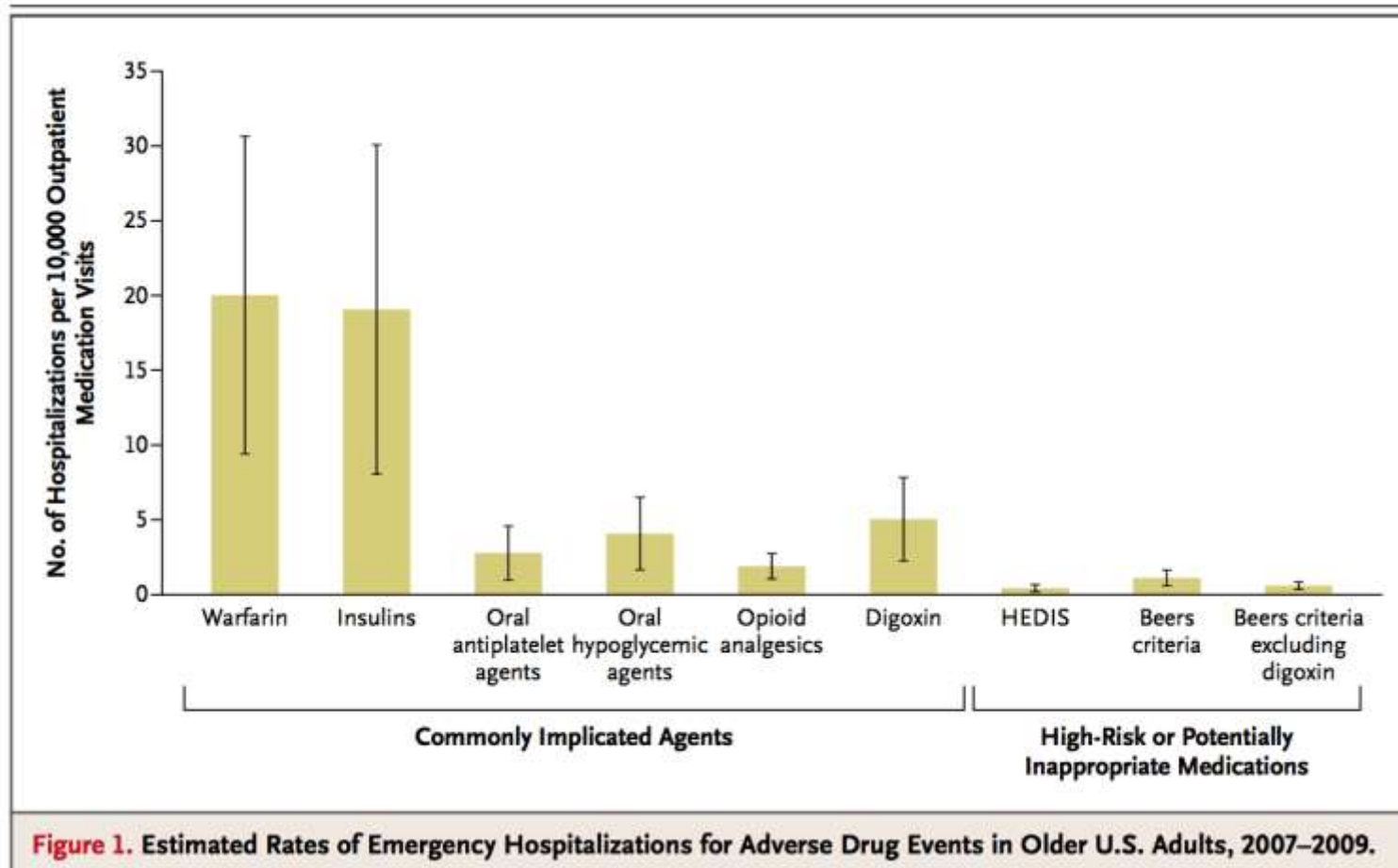
Table 3. Coverage of the ONC list ingredient pairs by KBs

Coverage	FDB (%)	Micromedex (%)	Multum (%)
Found in KB			
Contraindicated	591 (57.5)	496 (48.3)	491 (47.8)
Major/severe	189 (18.4)	398 (38.8)	324 (31.5)
Moderate	141 (13.7)	11 (1.1)	107 (10.4)
Not found	106 (10.3)	122 (11.9)	105 (10.2)
Not found in KB because:			
Versioning	38	92	20
Not on market	33	18	70
Editorial exclusion	13	12	1
Mapping problem	15	0	10
Combination therapy	5	0	4
Other	2	0	0
Total ONC ingredient pairs	1027 (100)	1027 (100)	1027 (100)

10% niet gevonden !!



Wat zijn de prioriteiten?



DR verantwoordelijk voor 1,5% spoedopnames

Our findings suggest that efforts to improve medication safety for older adults should focus on areas in which improvements are most likely to have sizable, clinically significant, and measurable effects, such as improving the management of antithrombotic and antidiabetic drugs.

Besluit

- **DE** lijst met **wat mag** en **wat mag niet** bestaat niet
- Databanken zijn *niet* perfect
- Regulator is *niet* feilloos,
heeft geen zicht op het totaalbeeld
- Er is **tijd** nodig
en **meerdere bronnen** om
DDI's **goed** op te lossen/analyseren