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FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

VAKGROEP FMBW
ONDERZOEKSGROEP KLINISCHE FARMACOLOGIE

FARMACOTHERAPEUTISCH BIJBLIJVEN

RECENTE LITERATUUR

dr. Jan De Meulenaere - 9 februari 2022

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RECENTE LITERATUUR

1. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicenter, randomized, double-blind, placebo-controlled, phase 3 trials
2. Comparative fracture risk during osteoporosis drug holidays after long-term risedronate versus alendronate therapy
3. Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies
4. Oral antihistamine-decongestant-analgesic combinations for the common cold

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Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

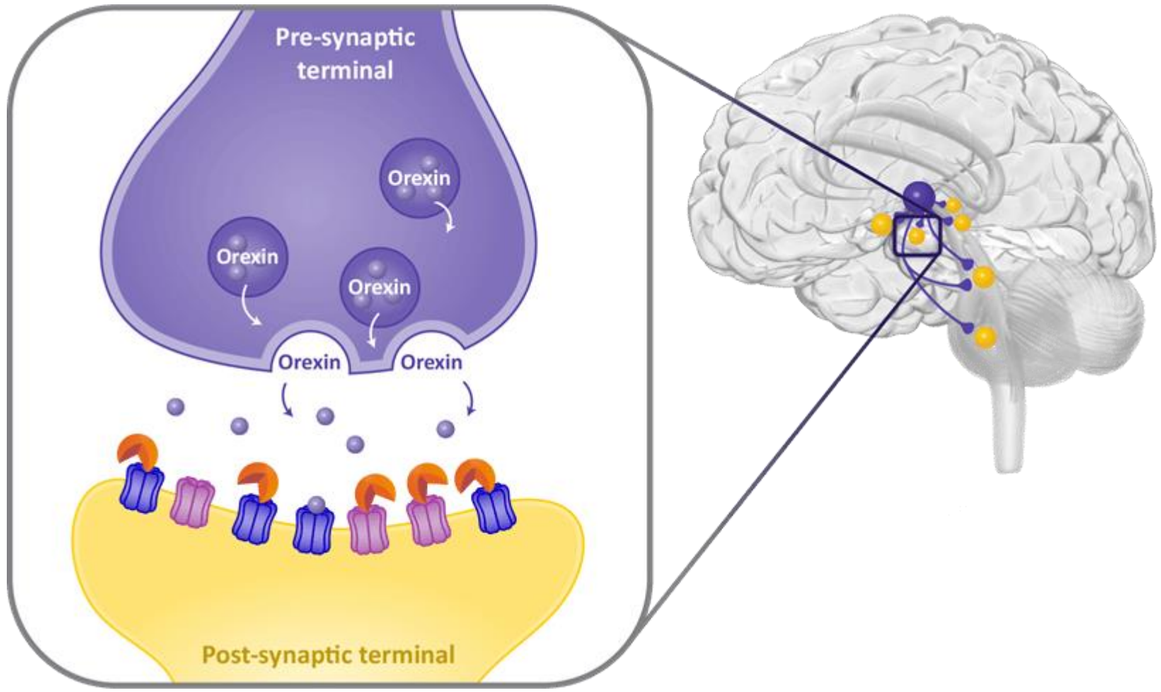
*Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators**

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Doel: doeltreffendheid en veiligheid (‘s nachts en overdag) evalueren van daridorexant, een nieuwe dubbele orexine-receptor-antagonist

Achtergrond:

- prevalentie insomnie: 5-10%
- eerstekeusbehandeling CBTi
- medicatie?



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Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Studie-opzet

- 2 multicentrische, gerandomiseerde, dubbel-blind, placebo-gecontroleerde fase-III trials
  - Studie 1: 75 ziekenhuizen in 10 landen (juni 2018 – februari 2020)
  - Studie 2: 81 ziekenhuizen in 11 landen (mei 2018 – mei 2020)
- Verloop:
  - screening periode (7-18 dg)
  - single-blind placebo inloopperiode (13-24 dg)
  - dubbel-blinde behandelperiode (3 md)
  - single-blind placebo uitloopperiode (7 dg)
- N = 930 patiënten (studie 1)
- N = 924 patiënten (studie 2)
- Interventie:
  - Studie 1: daridorexant 50mg / daridorexant 25mg / placebo
  - Studie 2: daridorexant 25mg / daridorexant 10mg / placebo

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Studie-opzet

- Uitkomstmeting
  - primair
    - verandering in WASO (wake time after sleep onset) na 1md en na 3md
    - verandering in LPS (latency to persistent sleep) na 1md en na 3md
  - secundair
    - zelfrapportage over de slaapduur
    - IDSIQ (Insomnia Daytime Symptoms and Impacts Questionnaire)

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Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

	Study 1			Study 2		
	Daridorexant 50 mg (n=310)	Daridorexant 25 mg (n=310)	Placebo (n=310)	Daridorexant 25 mg (n=309)	Daridorexant 10 mg (n=307)	Placebo (n=308)
Sex						
Female	199 (64%)	215 (69%)	210 (68%)	218 (71%)	215 (70%)	205 (67%)
Male	111 (36%)	95 (31%)	100 (32%)	91 (29%)	92 (30%)	103 (33%)
Age at screening, years	55·5 (15·3)	55·8 (15·3)	55·1 (15·4)	56·3 (14·4)	57·1 (14·0)	56·7 (14·1)
Age group, years						
<65	189 (61%)	189 (61%)	188 (61%)	188 (61%)	186 (61%)	187 (61%)
≥65	121 (39%)	121 (39%)	122 (39%)	121 (39%)	121 (39%)	121 (39%)
Race						
White	274 (88%)	287 (93%)	278 (90%)	271 (88%)	273 (89%)	267 (87%)
Black or African American	30 (10%)	19 (6%)	28 (9%)	26 (8%)	16 (5%)	29 (9%)
Asian	4 (1%)	3 (1%)	2 (1%)	11 (4%)	14 (5%)	10 (3%)
Other	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Geographical location						
USA	97 (31%)	99 (32%)	104 (34%)	108 (35%)	103 (34%)	114 (37%)
Non-USA	213 (69%)	211 (68%)	206 (66%)	201 (65%)	204 (66%)	194 (63%)

	Study 1			Study 2		
	Daridorexant 50 mg (n=310)	Daridorexant 25 mg (n=310)	Placebo (n=310)	Daridorexant 25 mg (n=309)	Daridorexant 10 mg (n=307)	Placebo (n=308)
Primary endpoints						
WASO at month 1, min						
LSM change from baseline (95% CI)	−29·0 (−32·7 to −25·3)	−18·4 (−22·1 to −14·7)	−6·2 (−9·9 to −2·5)	−24·2 (−28·5 to −19·9)	−15·3 (−19·5 to −11·1)	−12·6 (−16·8 to −8·3)
LSM difference compared with placebo (95% CI)	−22·8 (−28·0 to −17·6)	−12·2 (−17·4 to −7·0)	..	−11·6 (−17·6 to −5·6)	−2·7 (−8·7 to 3·2)	..
p value*	p<0·0001	p<0·0001	..	p=0·0001	p=0·37	..
WASO at month 3						
LSM change from baseline (95% CI)	−29·4 (−33·4 to −25·4)	−23·0 (−27·0 to −19·0)	−11·1 (−15·1 to −7·1)	−24·3 (−29·0 to −19·5)	−16·0 (−20·7 to −11·2)	−14·0 (−18·8 to −9·2)
LSM difference compared with placebo (95% CI)	−18·3 (−23·9 to −12·7)	−11·9 (−17·5 to −6·2)	..	−10·3 (−17·0 to −3·5)	−2·0 (−8·7 to 4·8)	..
p value*	p<0·0001	p<0·0001	..	p=0·0028	p=0·57	..
LPS at month 1, min						
LSM change from baseline (95% CI)	−31·2 (−34·5 to −27·9)	−28·2 (−31·5 to −24·8)	−19·9 (−23·2 to −16·5)	−26·5 (−30·6 to −22·3)	−22·6 (−26·7 to −18·5)	−20·0 (−24·1 to −15·9)
LSM difference compared with placebo (95% CI)	−11·4 (−16·0 to −6·7)	−8·3 (−13·0 to −3·6)	..	−6·5 (−12·3 to −0·6)	−2·6 (−8·4 to 3·2)	..
p value*	p<0·0001	p=0·0005	..	p=0·030	p=0·38	..
LPS at month 3						
LSM change from baseline (95% CI)	−34·8 (−38·1 to −31·5)	−30·7 (−34·0 to −27·4)	−23·1 (−26·5 to −19·8)	−28·9 (−33·4 to −24·4)	−23·1 (−27·6 to −18·6)	−19·9 (−24·4 to −15·4)
LSM difference compared with placebo (95% CI)	−11·7 (−16·3 to −7·0)	−7·6 (−12·3 to −2·9)	..	−9·0 (−15·3 to −2·7)	−3·2 (−9·5 to 3·1)	..
p value*	p<0·0001	p=0·0015	..	p=0·0053	p=0·32	..

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Secondary endpoints						
sTST at month 1, min						
LSM change from baseline (95% CI)	43·6 (38·2 to 49·1)	34·2 (28·7 to 39·6)	21·6 (16·1 to 27·0)	43·8 (38·1 to 49·4)	41·0 (35·4 to 46·6)	27·6 (22·0 to 33·3)
LSM difference compared with placebo	22·1	12·6	..	16·1	13·4	..
(95% CI)	(14·4 to 29·7)	(5·0 to 20·3)		(8·2 to 24·0)	(5·5 to 21·2)	
p value*	p<0·0001	p=0·0013	..	p<0·0001	p=0·0009	..
sTST at month 3, min						
LSM change from baseline (95% CI)	57·7 (51·2 to 64·2)	47·8 (41·3 to 54·3)	37·9 (31·4 to 44·4)	56·2 (49·8 to 62·5)	50·7 (44·4 to 57·0)	37·1 (30·8 to 43·5)
LSM difference compared with placebo	19·8	9·9	..	19·1	13·6	..
(95% CI)	(10·6 to 28·9)	(0·8 to 19·1)		(10·1 to 28·0)	(4·7 to 22·5)	
p value*	p<0·0001	p=0·033	..	p<0·0001	p=0·0028	..
IDSIQ sleepiness domain score at month 1						
LSM change from baseline (95% CI)	−3·8 (−4·3 to −3·2)	−2·8 (−3·3 to −2·2)	−2·0 (−2·6 to −1·5)	−3·5 (−4·1 to −2·9)	−3·2 (−3·8 to −2·6)	−2·8 (−3·3 to −2·2)
LSM difference compared with placebo	−1·8	−0·8	..	−0·8	−0·4	..
(95% CI)	(−2·5 to −1·0)	(−1·5 to 0·01)		(−1·6 to 0·1)	(−1·3 to 0·4)	
p value*	p<0·0001	p=0·055	..	p=0·073	p=0·30	..
IDSIQ sleepiness domain score at month 3						
LSM change from baseline (95% CI)	−5·7 (−6·4 to −5·0)	−4·8 (−5·5 to −4·1)	−3·8 (−4·5 to −3·1)	−5·3 (−6·0 to −4·6)	−4·8 (−5·4 to −4·1)	−4·0 (−4·7 to −3·3)
LSM difference compared with placebo	−1·9	−1·0	..	−1·3	−0·7	..
(95% CI)	(−2·9 to −0·9)	(−2·0 to 0·01)		(−2·2 to −0·3)	(−1·7 to 0·2)	
p value*	p=0·0002	p=0·053	..	p=0·012	p=0·14	..

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	Study 1			Study 2		
	Daridorexant 50 mg (n=308)	Daridorexant 25 mg (n=310)	Placebo (n=309)	Daridorexant 25 mg (n=308)	Daridorexant 10 mg (n=306)	Placebo (n=306)
Participants with ≥1 adverse event*	116 (38%)	117 (38%)	105 (34%)	121 (39%)	117 (38%)	100 (33%)
Adverse events* leading to treatment discontinuation	3 (1%)	7 (2%)	10 (3%)	4 (1%)	6 (2%)	7 (2%)
Participants with ≥1 serious adverse event	3 (1%)	2 (1%)	7 (2%)	3 (1%)	3 (1%)	4 (1%)
Participants with adverse event* (≥2% in any group)						
Nasopharyngitis	20 (6%)	21 (7%)	20 (6%)	13 (4%)	32 (10%)	16 (5%)
Headache	19 (6%)	16 (5%)	12 (4%)	15 (5%)	12 (4%)	11 (4%)
Accidental overdose	8 (3%)	4 (1%)	5 (2%)	4 (1%)	4 (1%)	1 (<1%)
Fatigue	7 (2%)	7 (2%)	2 (1%)	11 (4%)	7 (2%)	2 (1%)
Dizziness	7 (2%)	6 (2%)	2 (1%)	6 (2%)	4 (1%)	4 (1%)
Nausea	7 (2%)	1 (<1%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)
Somnolence	5 (2%)	11 (4%)	6 (2%)	10 (3%)	6 (2%)	4 (1%)
Fall	1 (<1%)	1 (<1%)	8 (3%)	3 (1%)	4 (1%)	3 (1%)
Upper respiratory tract infection	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	6 (2%)
Adjudicated adverse events†						
Excessive daytime sleepiness	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	1 (<1%)	1 (<1%)
Sleep paralysis	1 (<1%)	1 (<1%)	0	2 (1%)	0	0
Hallucinations	0	1 (<1%)	0	1 (<1%)	0	0
Suicidal ideation or self-injury‡	0	0	0	1 (<1%)	1 (<1%)	0

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. *Adverse events that occurred during the double-blind treatment period in the safety population are included in the table and presented with their preferred terms. †Adjudicated adverse events were reported during the double-blind treatment up to 30 days after the end of treatment or date of enrolment into the extension trial and were adjudicated blindly by an independent safety board. ‡Adjudicated adverse events belonging to the category suicidal ideation or self-injury (preferred term: suicidal ideation) were reported in two participants, one in each daridorexant group in study 2; both patients had pre-existing medical conditions (paranoid schizophrenia or depression) and the independent safety board adjudicated both adverse events as potentially related to trial treatment.

Table 3: **Adverse events in the safety analysis population (n=1847)**

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Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Veelbelovende resultaten, maar…

- kernsymptomen van insomnie (moeite met inslapen / moeite met doorslapen) werden niet bevraagd
- klinische relevantie van de IDSIQ?
- daridorexant vs. CBTi?

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Annals of Internal Medicine

ORIGINAL RESEARCH

Comparative Fracture Risk During Osteoporosis Drug Holidays After Long-Term Risedronate Versus Alendronate Therapy

A Propensity Score–Matched Cohort Study

Kaleen N. Hayes, PharmD, PhD; Kevin A. Brown, PhD; Angela M. Cheung, MD, PhD; Sandra A. Kim, MD; David N. Juurlink, MD, PhD; and Suzanne M. Cadarette, PhD

Comparative Fracture Risk During Osteoporosis Drug Holidays After Long-Term Risedronate Versus Alendronate Therapy

Doel: wat is het risico op een heupfractuur bij medicatiestop na langdurige (>3 jaar) behandeling met risedronaat vs. alendronaat

Achtergrond:

- Bisfosfonaten zijn de geneesmiddelen die het meest gebruikt worden bij osteoporose. Bij postmenopauzale hoogrisicopatiënten werd na langdurige (> 3 jaar) toediening van alendronaat, risedronaat en zoledronaat een effect op het aantal wervelfracturen en niet-wervelfracturen (waaronder heupfracturen) vastgesteld, met de andere bisfosfonaten alleen op wervelfracturen (waarvan 2/3 asymptomatisch). In absolute cijfers is deze winst klein, en men moet dit afwegen tegenover de ernst van de morbiditeit bij osteoporose, vooral van heupfracturen. De optimale behandelingsduur is nog onduidelijk, en algemeen wordt aanbevolen om de behandeling minstens 3 jaar te geven, en zeker te heroverwegen na 5 jaar. Langere therapie wordt alleen aangeraden bij hoogrisicopatiënten maar preventie van symptomatische fracturen is hier niet bewezen en het risico van zeldzame ongewenste effecten (kaakbeennecrose en atypische subtrochanterische femurfracturen) stijgt. Met sommige bisfosfonaten is een preventief effect op wervelfracturen bij chronische behandeling met corticosteroïden vastgesteld [zie Folia juni 2017]. Bisfosfonaten worden ook gebruikt bij sommige hematologische aandoeningen en bij botmetastasen.

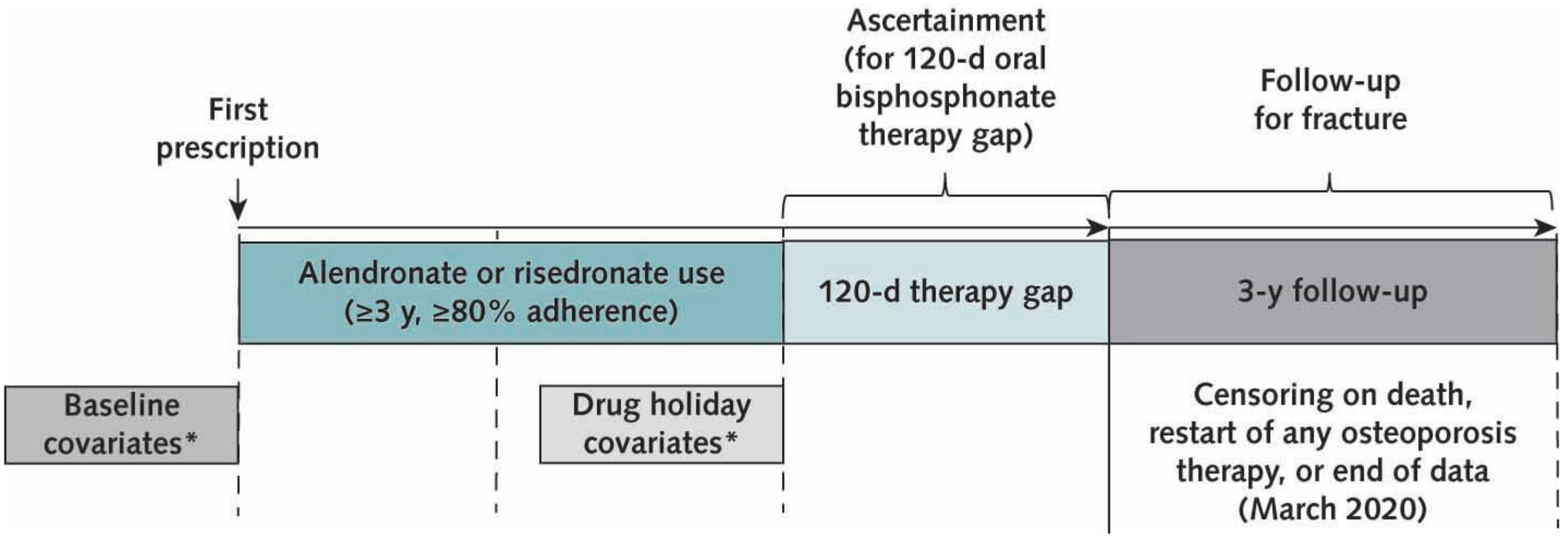
$T_{1/2}$ risedronaat <<< $T_{1/2}$ alendronaat

Comparative Fracture Risk During Osteoporosis Drug Holidays After Long-Term Risedronate Versus Alendronate Therapy

Studie-opzet

- gematchte cohortstudie op populatieniveau (Ontario, Canada)
- analyse van gegevens verkregen via administratieve data (november 2000 – maart 2020)
- studiepopulatie:
  - inclusiecriteria:
    - leeftijd: ≥ 66 jaar
    - medicatiestop na langdurige (>3j) behandeling met risedronaat of met alendronaat
  - exclusiecriteria: <120 dagen na medicatiestop
    - overlijden
    - fractuur
    - opname in verzorgingstehuis
    - opstart andere osteoporosebehandeling
  - n = 50.154 (2 x 25.077)
    - 81.8% vrouwen
    - gemiddelde leeftijd bij medicatiestop 81y
- outcome: heupfractuur

Comparative Fracture Risk During Osteoporosis Drug Holidays After Long-Term Risedronate Versus Alendronate Therapy



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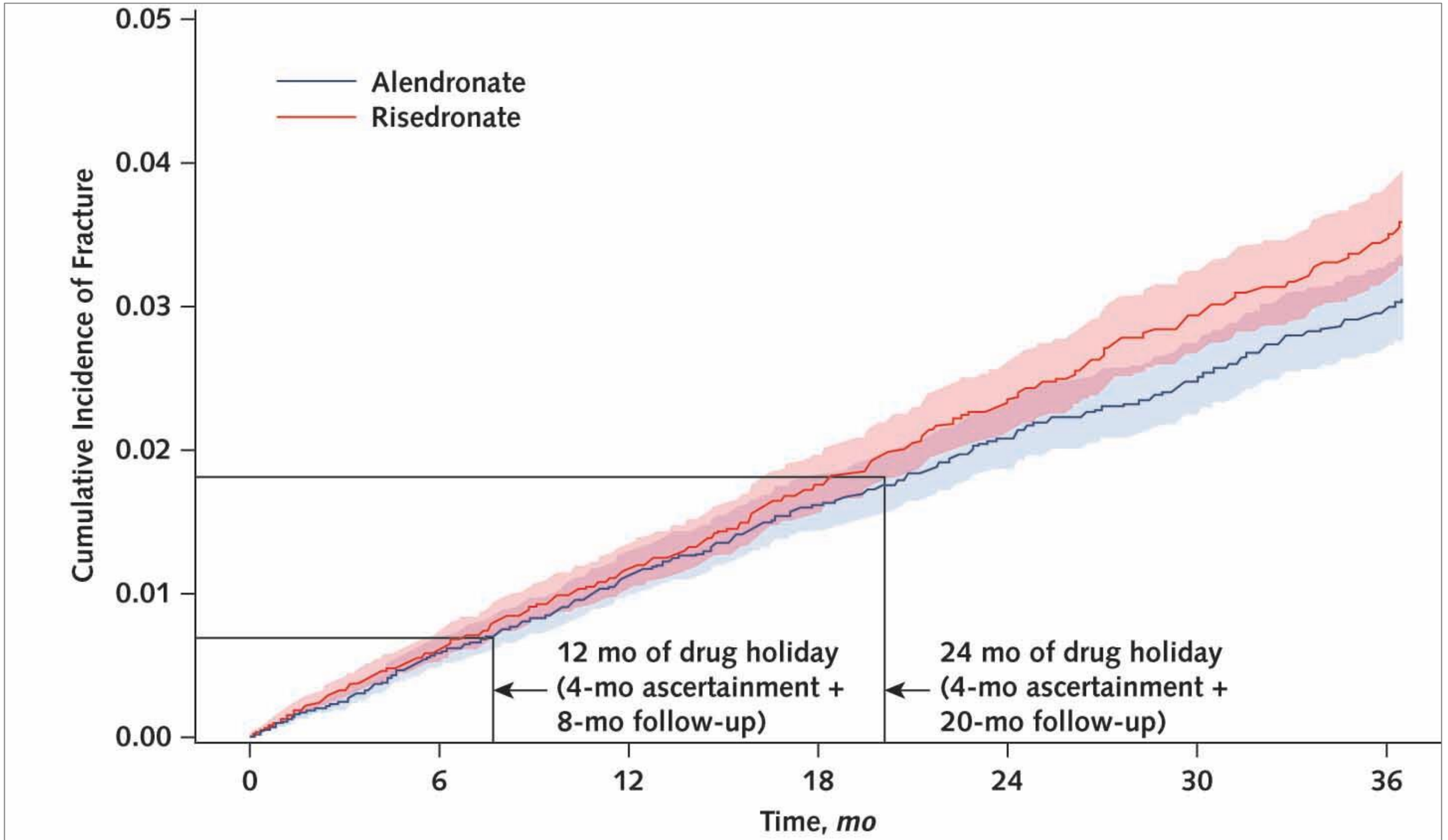

At risk, *n*							
Alendronate	25 077	17 434	14 762	12 879	11 318	10 084	8974
Risedronate	25 077	16 868	14 054	12 078	10 414	9108	7974

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Table 2. Relative Fracture Risk Associated With Therapy Gaps After Long-Term Risedronate Versus Alendronate Therapy

Analysis	Patients, *n*	Events, *n*	HR (95% CI)
Hip fracture, 3 y of follow-up	50 154	915	1.18 (1.04–1.34)
Secondary analyses			
1 y of follow-up	50 154	417	1.03 (0.85–1.24)
2 y of follow-up	50 154	704	1.14 (0.98–1.32)
2–3 y of follow-up	21 648	211	1.34 (1.02–1.75)
All available follow-up	50 154	1515	1.21 (1.09–1.33)
Men only	9152	117	1.37 (0.95–1.97)
Women only	41 002	798	1.15 (1.01–1.33)
3–5 y of therapy before drug holiday	22 698	384	1.22 (1.00–1.50)
≥5 y of therapy before drug holiday	27 456	531	1.15 (0.97–1.36)
Outcome: any fracture*	50 154	2783	1.07 (1.00–1.16)
Age ≥80 y at drug holiday	26 176	708	1.12 (0.97–1.30)
Age <80 y at drug holiday	23 978	207	1.19 (0.91–1.56)

HR = hazard ratio.
* Hip, clinical vertebral, pelvis, ribs, radius/ulna (forearm), or other osteoporotic fracture.

Comparative Fracture Risk During Osteoporosis Drug Holidays After Long-Term Risedronate Versus Alendronate Therapy

Conclusie

Hoger risico is op heupfractuur na het stoppen van risedronaat vs. alendronaat, maar…

- studie heeft beperkingen:
  - niet alle risicofactoren op fractuur zijn gekend (bv. botdichtheid, BMI, etniciteit)
  - Ontario: 70% white population
- geen pleidooi om alendronaat te verkiezen boven risedronaat!

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SYSTEMATIC REVIEW AND META-ANALYSIS

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies

Linda B. Ou[1,2,3] | Carolina Moriello[2] | Antonios Douros[2,3,4,5] |
Kristian B. Filion[2,3,5]

Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies

Doel: via een systematische review en meta-analyse het risico op plotse hartdood (SCD) en ventriculaire aritmie ten gevolge van domperidone evalueren

Achtergrond:

Domperidone is een perifere dopamine antagonist, gebruikt

- voor het verlichten van symptomen van misselijkheid en braken
- om lactatie te bevorderen (off-label)

Veiligheid? (QT-verlening)

Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies

Methodologie

- systematische review en meta-analyse
- geraadpleegde bronnen (tot december 2019): MEDLINE, PubMed, EMBASE, Scopus en CINAHL Plus
- observationele studies met >1000 subjects
- populatie
  - volwassenen (≥ 18j)
- exposuregroep: domperidone vs. referentiegroep (PPI, metoclopramide of geen gebruik)
- Kwaliteit van studies werd getoetst a.d.h.v. ROBINS-I tool en GRADE framework
- uitkomstmeting:
    - samengesteld eindpunt (SCD en ventriculaire aritmie)

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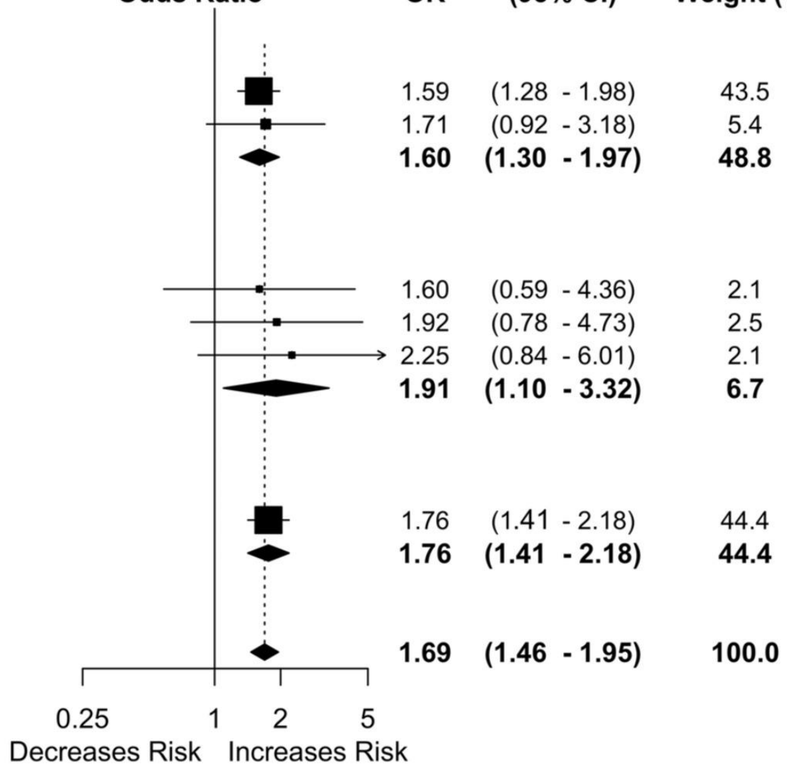
Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies

Resultaten

Study	Domperidone Cases	Domperidone Controls	Non-Use Cases	Non-Use Controls	OR	(95% CI)	Weight (%)
Moderate Risk of Bias							
Johannes 2010	169	481	740	3,498	1.59	(1.28 - 1.98)	43.5
Arana 2015	28	52	802	4,493	1.71	(0.92 - 3.18)	5.4
Random effects model					**1.60**	**(1.30 - 1.97)**	**48.8**
Heterogeneity: I^2 = 0%, τ^2 = 0							
Serious Risk of Bias							
Jolly 2009	6	12	1,004	3,018	1.60	(0.59 - 4.36)	2.1
van Noord 2010	10	30	1,258	13,384	1.92	(0.78 - 4.73)	2.5
Smolina 2016	6	NA	15	NA	2.25	(0.84 - 6.01)	2.1
Random effects model					**1.91**	**(1.10 - 3.32)**	**6.7**
Heterogeneity: I^2 = 0%, τ^2 = 0							
Critical Risk of Bias							
Chen 2015	358	242	5,794	5,910	1.76	(1.41 - 2.18)	44.4
Random effects model					**1.76**	**(1.41 - 2.18)**	**44.4**
Heterogeneity: not applicable							
Random effects model					**1.69**	**(1.46 - 1.95)**	**100.0**
Heterogeneity: I^2 = 0%, τ^2 = 0							



Domperidone and the risks of sudden cardiac death and ventricular arrhythmia: A systematic review and meta-analysis of observational studies

Conclusie

- domperidone is geassocieerd met verhoogd risico (+60%) op plotse hartdood en ventriculaire aritmie (vs. nonuse)
- het risico neemt toe met
  - de leeftijd
  - dosering (>30mg/d)

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[Intervention Review]

Oral antihistamine-decongestant-analgesic combinations for the common cold

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Oral antihistamine-decongestant-analgesic combinations for the common cold

Methodologie

- Systematische review met meta-analyse
- Geraadpleegde bronnen (tot 10 juni 2021):
  Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via (EBSCOhost), Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), LILACS (Latin American and Caribbean Health Science Information database), and Web of Science, Clarivate
  + World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov
  + farmaceutische bedrijven
  + experten

- Interventie:
  1. AH + DC
  2. AH + AN
  3. AN + DC
  4. AH + DC + AN
- Controle: elke andere behandeling (geen AB) (6 trials) of placebo (26 trials)
- Primaire uitkomstmaten:
  - Globale evaluatie v/d effectiviteit
  - Bijwerkingen

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Resultaten

- 30 gerandomiseerde gecontroleerde trials (31 vergelijkingen)
- Populatie
  - (gezonde) kinderen en volwassenen met een verkoudheid (< 1 week)
    - lopende en/of verstopte neus en niezen
    - met/zonder hoofdpijn
    - met/zonder hoesten
  - N = 6,304

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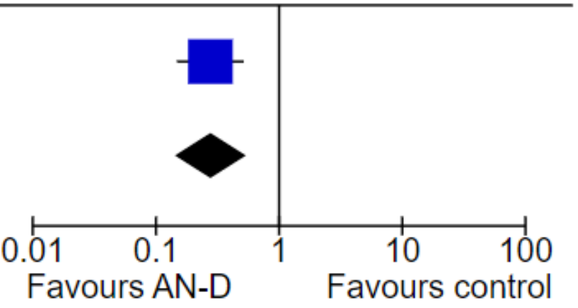
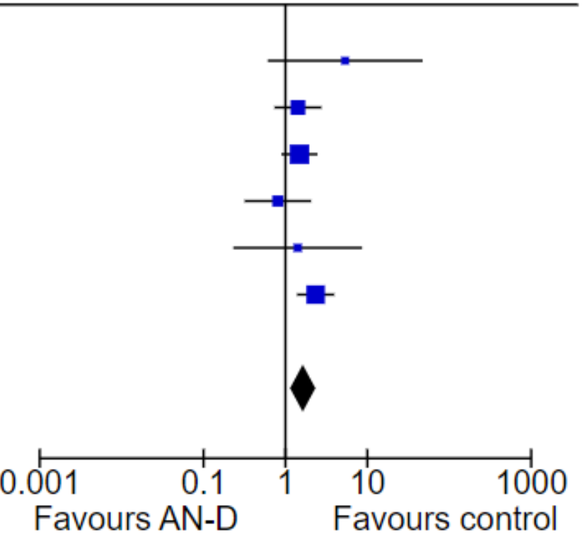
Study or Subgroup	AN-D Events	AN-D Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Middleton 1981	25	91	52	90	100.0%	0.28 [0.15 , 0.52]
Total (95% CI)		**91**		**90**	**100.0%**	**0.28 [0.15 , 0.52]**
Total events:	25		52			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.05 (P < 0.0001)



Study or Subgroup	AN-D Events	AN-D Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Eccles 2006a	5	76	1	77	2.1%	5.35 [0.61 , 46.93]
Eccles 2014	37	236	14	121	20.6%	1.42 [0.74 , 2.74]
Loose 2004	91	481	22	162	32.6%	1.48 [0.90 , 2.46]
Middleton 1981	9	90	11	91	10.9%	0.81 [0.32 , 2.06]
Sperber 1989	6	23	2	10	3.0%	1.41 [0.23 , 8.61]
Sperber 2000	51	216	25	214	30.7%	2.34 [1.39 , 3.94]
Total (95% CI)		**1122**		**675**	**100.0%**	**1.62 [1.18 , 2.23]**
Total events:	199		75			

Heterogeneity: Tau² = 0.01; Chi² = 5.47, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.99 (P = 0.003)
Test for subgroup differences: Not applicable



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Authors' conclusions **2022**

We found a lack of data on the effectiveness of antihistamine-analgesic-decongestant combinations for the common cold. Based on these scarce data, the effect on individual symptoms is probably too small to be clinically relevant. The current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children. In 2005, the US Food and Drug Administration issued a warning about adverse effects associated with the use of over-the-counter nasal preparations containing phenylpropanolamine.

Authors' conclusions **2012**

Current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.

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