


ABC

ARIPIRAZOL, BREXPIRAZOL, CARIPIRAZINE

EEN NIEUWE KLASSE ANTIPSYCHOTICA, OF VEEL MEER?
VAN THEORIE NAAR PRAKTIJK

RIKUS KNEGTERING, VOORJAAR 2019

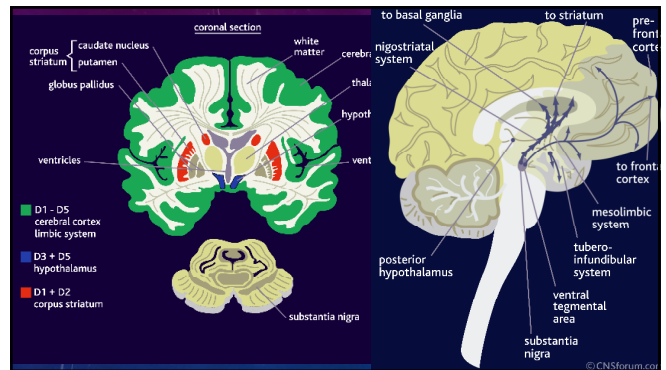
SOME BASIC NEUROSCIENCE OF THE DOPAMINE SYSTEM



DISCLOSURES – DR. RIKUS KNEGTERING

Bedrijf	Sponsoring / onderzoeksgeld	Honorarium of andere (financiële vergoeding)	Aandeelhouder	Andere relatie, namelijk spreker
AstraZeneca	x	Geen: opbrengsten lezingen en boeken naar stichtingen (St. Lentis, RGOe/UMCG voor reserach en educatie Stichting Julia		x
BMS	x			x
Janssen	x			x
Lilly	x			x
Lundbeck	x			x
Stichting Roos	x			
Pensioen: Zorg en Welzijn en ABP			x	

NEDERLANDSE VERENIGING VAN PSYCHIATRIE



ARIPIRAZOLE, BREXPIRAZOLE, CARIPRAZINE

Aripiprazole FDA approved 2002

Brexipiprazole FDA approved april 2015. Europa 2019

Cariprazine FDA approved september 2015 Europa 2018

Cc1ccc(cc1)N2CCN(C2)CCOC3=CC=C(NC(=O)N3)c4ccccc4Cl

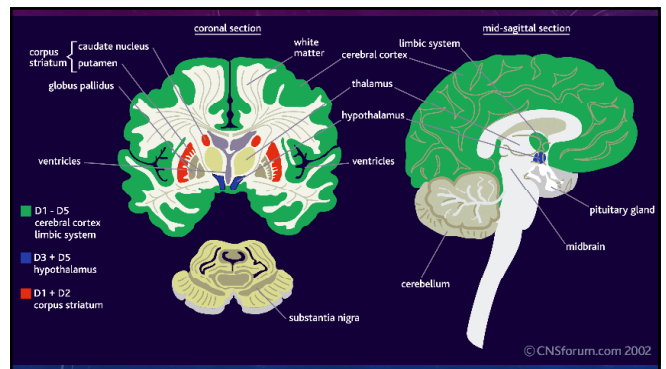
aripiprazole

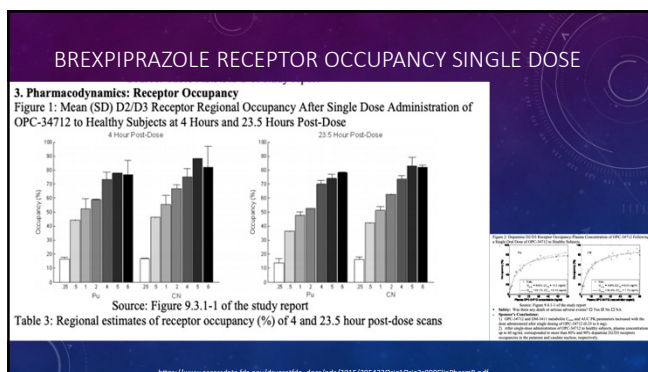
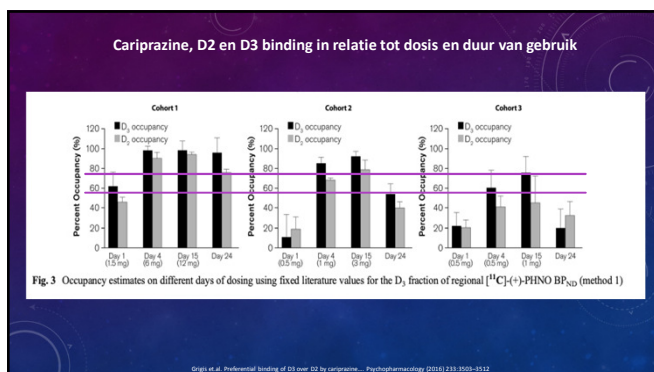
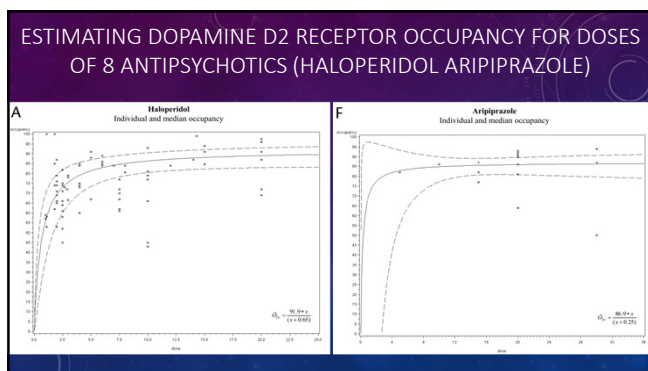
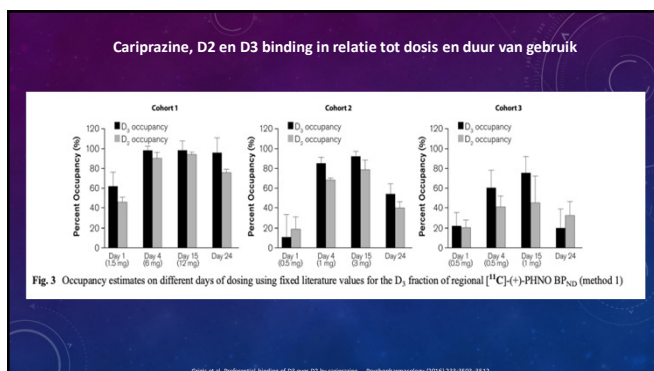
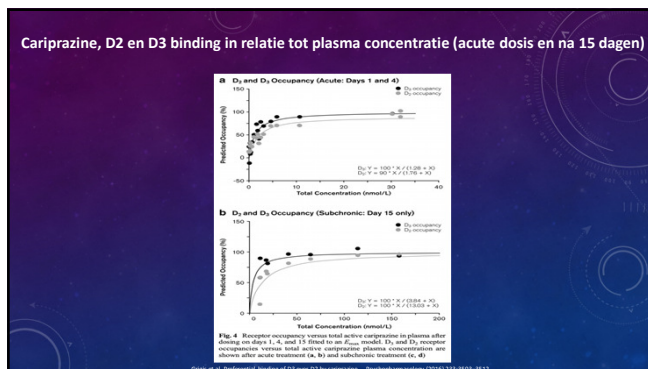
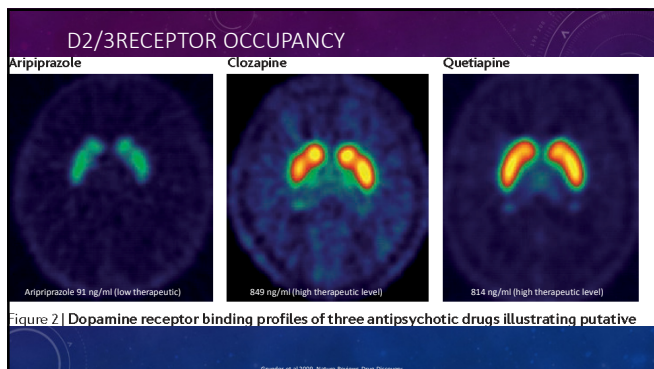
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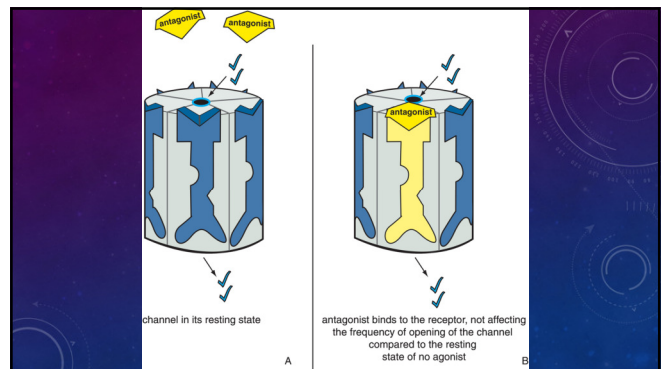
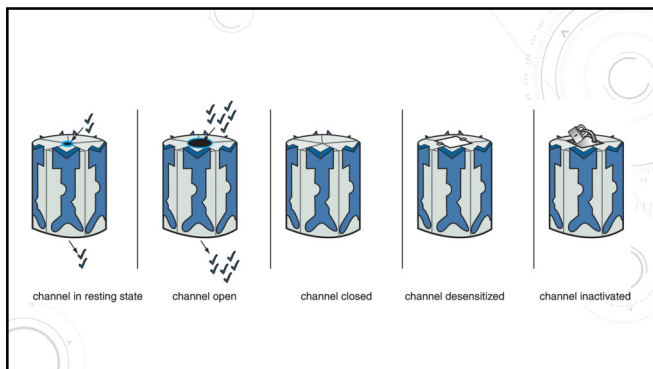
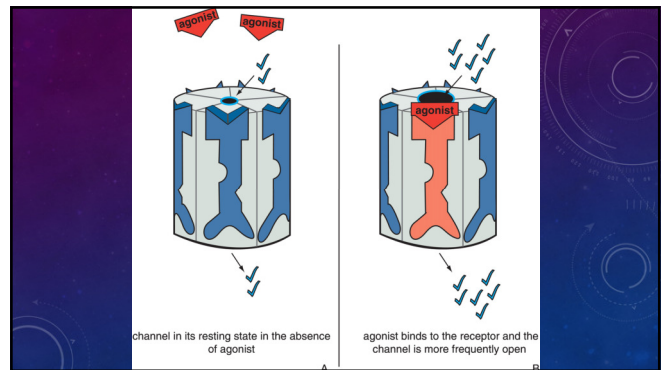
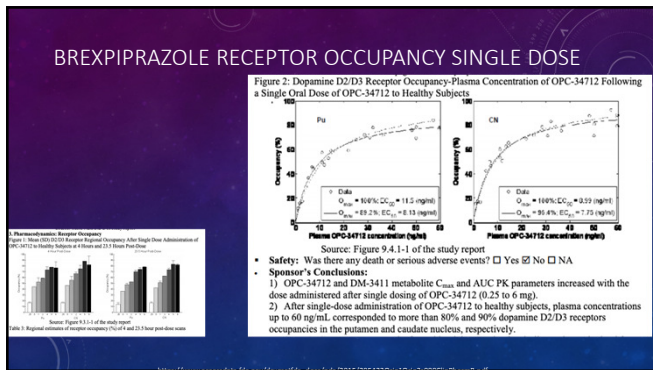
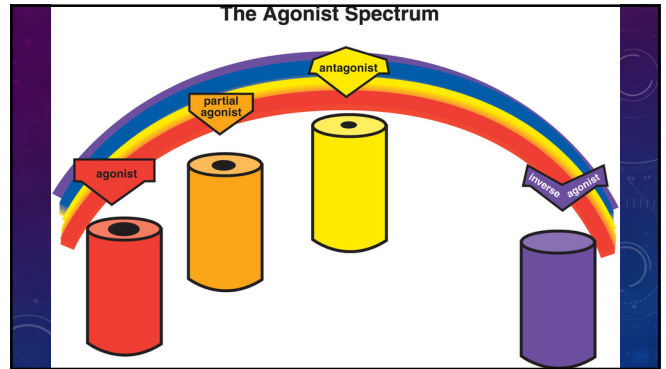
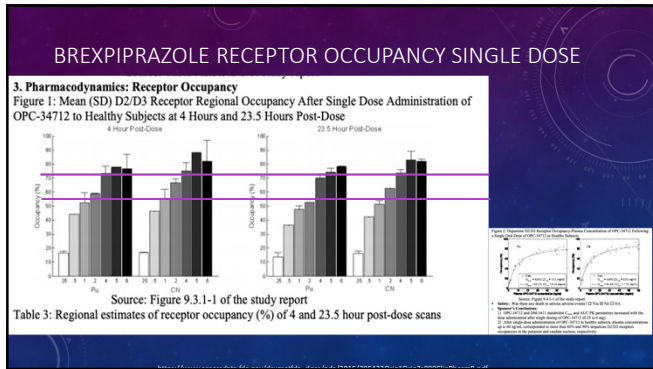
brexipiprazole

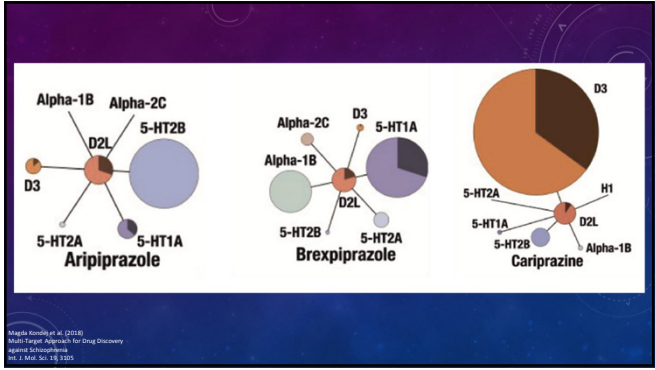
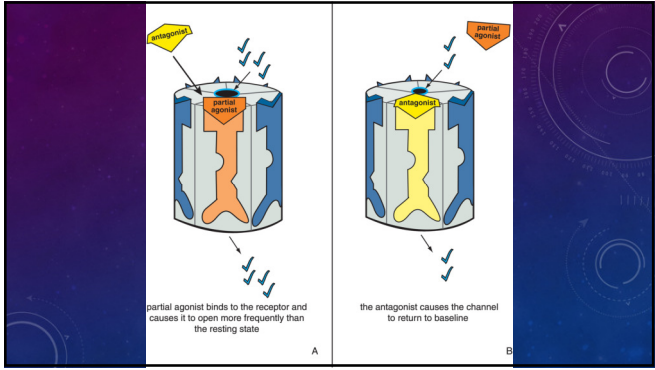
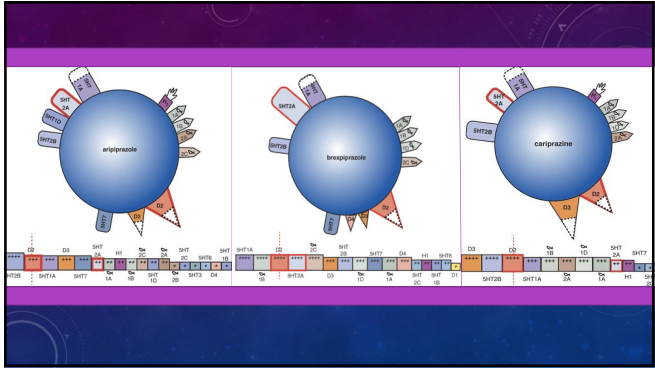
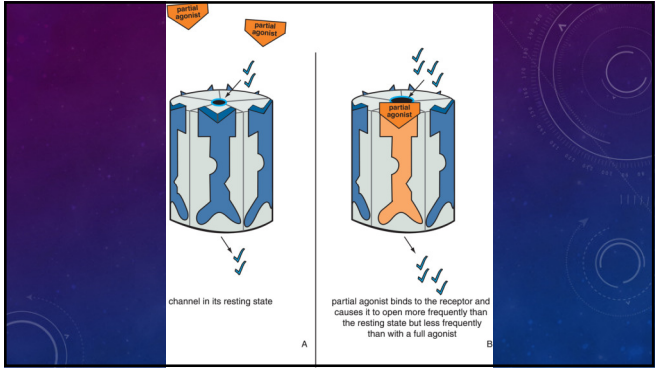
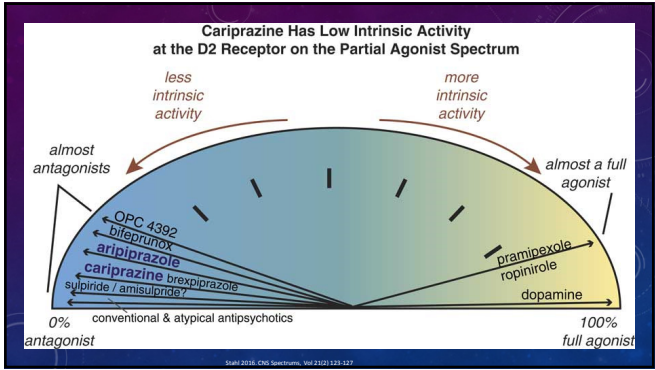
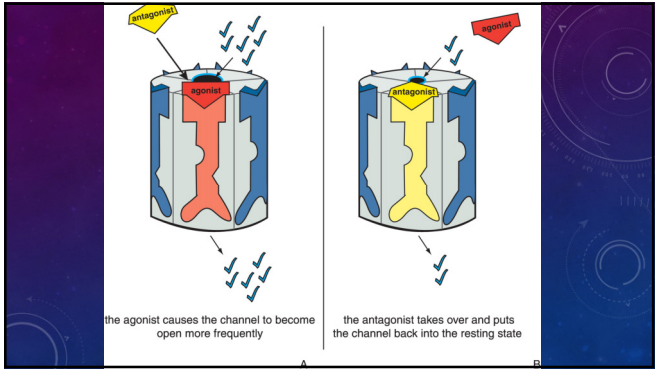
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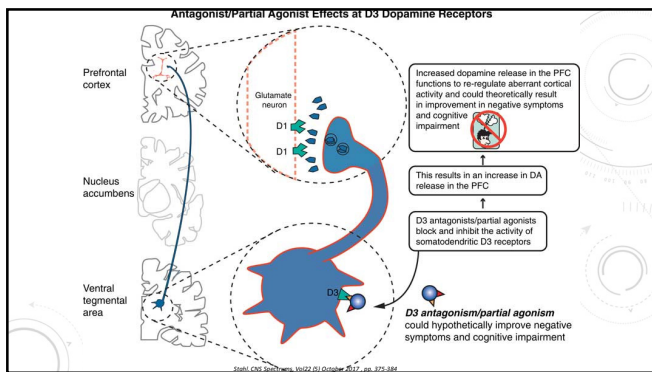
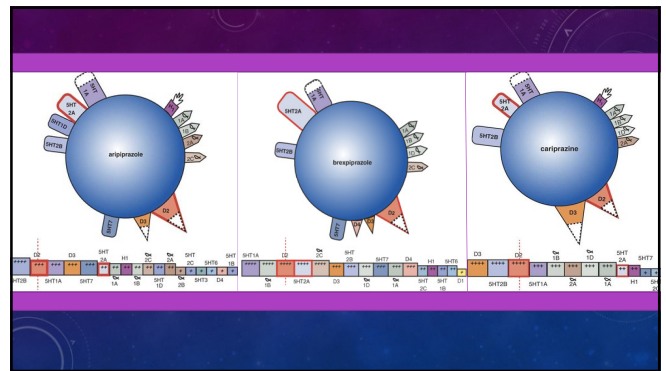
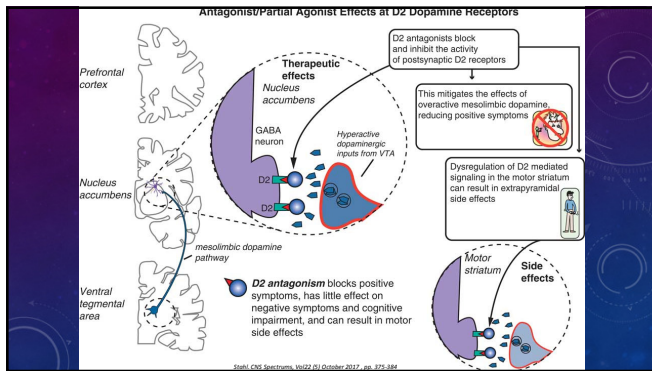
cariprazine











WAT IS ER MET ACATHISIE EN NIEUWE MIDDELEN

Akathisie: Onmogelijkheid stil te zitten.

- Objectief waarneembaar gedeelte (onrust in ledematen)
- Klachten: inwendige onrust, onmogelijkheid stil te zitten, aandrang tot bewegen

- Nieuwere antipsychotica: vooral 2.

Receptor bindingsprofielen en mogelijk effecten van aripiprazol, bupropion en caripiprazol		
Receptor antagonisme	Receptor Partieel agonisme	Theoretische effecten
D2	D2 A B C	Positieve symptomen ↓, bewegingsstoornissen (EPS), prolactine ↑
D3	D3 C	Positieve symptomen ↓, prolactine ↓?
SHT2a >> D2	SHT1a B	Positieve symptomen ↓, negatieve symptomen ↓, antidepressief, verbetering cognitief?
SHT2a	B	Antipsychotisch?
SHT2b	AC	Antidepressief? Prognostief?
SHT2c		Antipsychotisch? Antidepressief? Gewicht ↑
SHT7	(B)	Antidepressief, verbetering cognitief
Histamine 1		Sedatie
Alfa 1		Bloedruk verlagend, mictie verbetering bij prostaat hypertrofie, vermindering nachtmerries bij trauma.

Rondag et al. Multi-Target Approach for Drug Discovery against Schizophrenia. Int. J. Mol. Sci. 2018, 19, 3105; bewerking Knegering 2019

WAT IS ER MET ACATHISIE EN NIEUWE MIDDELEN

POTENTIELE EFFECTEN VAN NIEUWE MIDDELEN

- Antipsychotisch (relatieve effectiviteit?)
- Antidepressief effecten ?
- Anxiolytische effecten ?
- Procognitieve effecten?
- Weinig EPS ?
- Relatief weinig kans op metabool syndroom
- Vermindering negatieve symptomen?
- Acatisie??





Aripiprazole, brexpiprazole, and cariprazine: Not all the same
Understanding the key differences among these agents can help inform treatment decisions

Citrone 2018, Current Psychiatry, Vol 16 (4) 25-34, c



the proof is in the pudding...

Efficacy among antipsychotics is similar – there is overlap for most choices

Overall change in symptoms

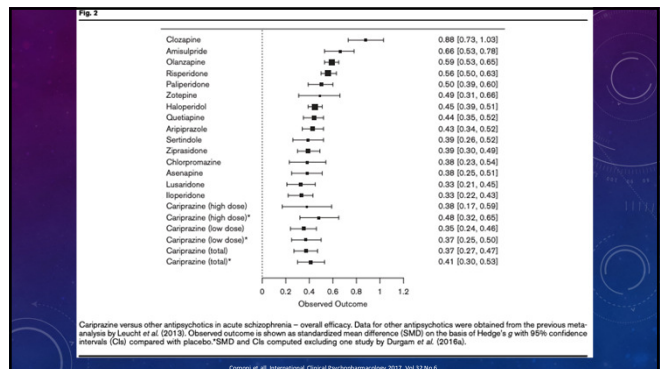
Drug	Standardized mean difference [95% CrI]	Effect size of antipsychotic compared with placebo
Clozapine	-0.88 (-1.03 to -0.73)	
Amisulpride	-0.66 (-0.78 to -0.53)	
Olanzapine	-0.59 (-0.65 to -0.53)	
Risperidone	-0.56 (-0.63 to -0.50)	
Paliperidone	-0.50 (-0.60 to -0.39)	
Zotepine	-0.49 (-0.64 to -0.31)	
Haloperidol	-0.45 (-0.51 to -0.39)	
Quetiapine	-0.44 (-0.52 to -0.35)	
Aripiprazole	-0.43 (-0.53 to -0.34)	
Sertindole	-0.39 (-0.52 to -0.26)	
Ziprasidone	-0.39 (-0.49 to -0.30)	
Chlorpromazine	-0.38 (-0.54 to -0.23)	
Asenapine	-0.36 (-0.51 to -0.20)	
Lurasidone	-0.33 (-0.45 to -0.21)	
Risperidone	-0.33 (-0.43 to -0.22)	

Leucht et al. Lancet 2013;382(9896):951-962.

Table 1. US Food and Drug Administration approved indications for aripiprazole, brexpiprazole, and cariprazine [Actavis, 2015; Alkermes, 2015; Otsuka, 2014, 2015a, 2015b].

	Aripiprazole	Brexpiprazole	Cariprazine
Schizophrenia (adults)	✓	✓	✓
Schizophrenia (adolescents)	✓		
Schizophrenia or bipolar mania associated agitation (adults) via intramuscular route	✓		
Schizophrenia depot injection	✓		
Bipolar disorder (adults and pediatric patients), acute monotherapy for mania	✓		
Bipolar disorder (adults and pediatric patients), acute adjunctive treatment to lithium or valproate for mania	✓		
Bipolar disorder (adults only), acute treatment of manic or mixed episodes	✓		✓
Bipolar disorder (adults only), maintenance treatment	✓		
Adjunctive treatment of major depressive disorder (adults)	✓	✓	
Tourette's disorder (pediatric patients)	✓		
Irritability associated with autistic spectrum disorder (pediatric patients)	✓		

Frankel and Schwartz. 2017 Ther Adv Psychopharmacol Vol. 7(1) 29-41




Side effects of treatments for schizophrenia can impose a significant overall burden on patients

In a study of 1,825 participants with psychosis:

- 77%** reported medication side effects
- 61%** reported impairment in their daily life as a result of medication side effects
- 30%** reported moderate or severe impairment in their daily life as a result of medication side effects

Morgan et al., Aust N Z J Psychiatry 2013;48(8):752-752. (C) AstraZeneca, NIP 2019

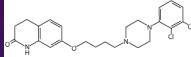
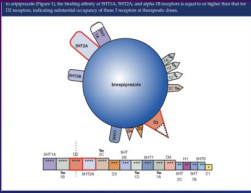
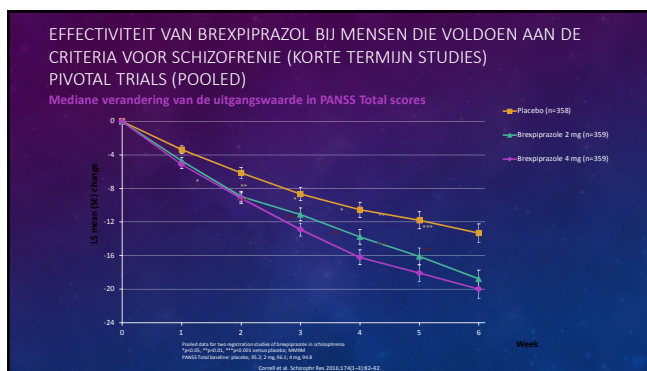
BREXIPRAZOL PHARMACOKINETIEK



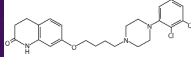
- 1 keer per dag, tijdens of buiten de maaltijd
- Advies startdosis 1 mg/dag (dag-4), 2 mg/dag (dag 5-7). Vanaf dag 8 tot maximal 4mg/dag
- Tmax: 4 uur
- T-el halfwaardetijd: 91 hours
- Eiwit binding: >99%
- Lever metabolisme: CYP2D6 en CYP3A4; (dosis verlaging geadviseerd bij trage metabolisering CYP2D6 of bij gebruik van CYP3A4/CYP3A4 remmers of sterke CYP3A4 inducers)
- Bij een matige tot sterke leverfunctie stoornissen of ernstig nierfalen: max dosis 3 mg/dag.
- Geen belangrijke metabolieten bekend

Chen et al., Int J Clin Pract. 2015;35(5):535-40; Brexpiprazole PI (February 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/201430Orig1s010/Brexpiprazole_PI_201802.pdf

BREXIPRAZOL

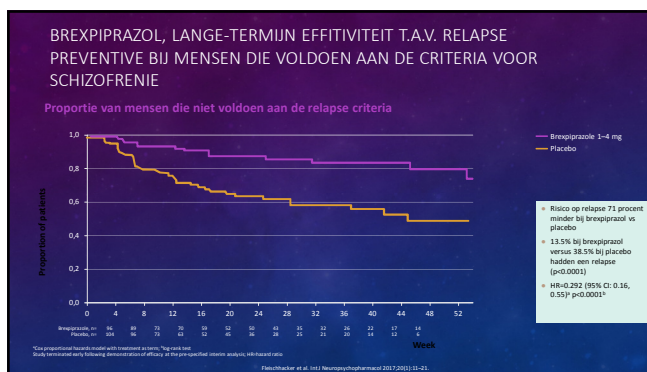




BREXIPRAZOL SAMENVATTING



- FDA toegelaten: July 10, 2015, Europa 2019
- Dosis bij psychosen (schizofrenie): 2-4 mg/dag
- Voordelen: 1 keer per dag, minder akathisie dan aripiprazol en cariprazine, weinig EPS, geen QT tijd verlenging, nauwelijks invloed op prolactine.
- Nadeel: beperkt dosis titratie nodig

Chen et al., Int J Clin Pract. 2015;35(5):535-40; Brexpiprazole Drug Approval Package, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/201430Orig1s010/Brexpiprazole_PI_201802.pdf



CARIPRAZINE

The diagram illustrates the metabolic pathway of cariprazine. Cariprazine is converted to desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). A graph below shows the concentration of these metabolites over time, with labels for SH720, SH726, SH728, SH730, SH732, SH734, SH736, SH738, SH740, SH742, SH744, SH746, SH748, SH750, SH752, SH754, SH756, SH758, SH760, SH762, SH764, SH766, SH768, SH770, SH772, SH774, SH776, SH778, SH780, SH782, SH784, SH786, SH788, SH790, SH792, SH794, SH796, SH798, SH800.

Cariprazine (CAR)
 T_{max} 3-6 uur
 $T_{1/2}$ el 2-4 dagen

Desmethyl cariprazine (DCAR)
 $T_{1/2}$ el 3-7 dagen

Didesmethyl cariprazine (DDCAR)
 $T_{1/3}$ el 1-3 weken

Steady state 1-2 weken

Steady state 4-8 (-12) weken

Na 12 weken zijn de gemiddelde DDCAR 400% en DCAR 30 % in relatie tot de cariprazine concentratie

CARIPRAZINE SAMENVATTING

- Toegelaten door FDA: September 17, 2015, Europa 2018
- Dosering: 1.5-6 mg/dag bij mensen die voldoen aan de criteria voor schizofrenie.
- Voordelen: 1 maal daags, weinig of geen sedatie, geen waarschuwing voor QT tijd verlenging, weinig invloed op prolactine (negatieve symptomen?)
- Nadelen: vrij veel akathisia en bewegingsstoornissen (EPS), dosis titratie.
- Voor of nadeel: metabolieten, totaal lange halfwaardetijd

Cariprazine (CAR)
 T_{max} 3-6 uur
 $T_{1/2}$ el 2-4 dagen

Desmethyl cariprazine (DCAR)
 $T_{1/2}$ el 3-7 dagen

Didesmethyl cariprazine (DDCAR)
 $T_{1/3}$ el 1-3 weken

Steady state 1-2 weken

Steady state 4-8 (-12) weken

Na 12 weken zijn de gemiddelde DDCAR 400% en DCAR 30 % in relatie tot de cariprazine concentratie

CARIPRAZINE FARMACOKINETIEK

- Oraal, een maal daags, met of zonder maaltijd
- Geadviseerde start dosis bij schizofrenie 1.5 mg/dag, in stappen van 1,5 per dag verhogen tot als einddosis 1,5 tot 6 mg per dag (hoger meer bijwerkingen niet meer effectiviteit)
- T_{max} : 3-6 hours
- $T_{el1/2}$: 2-4 days (1-3 week didesmethyl cariprazine)(zie verder)
- Eiwit binding: 91-97%
- Lever metabolisering via: CYP3A4, en (minder) via CYP2D6. Bij gebruik van sterke CYP3A4 inhibitors halveer de dosis; cariprazine wordt afgeraden bij patiënten CYP3A4 Inducerende middelen gebruiken
- Niet aangeraden bij ernstig lever of nier problemen. Important metabolites:
- Twee belangrijke metabolieten die farmacologisch net zo goed werken als de moederstof

Cariprazine (CAR)
 T_{max} 3-6 uur
 $T_{1/2}$ el 2-4 dagen

Desmethyl cariprazine (DCAR)
 $T_{1/2}$ el 3-7 dagen

Didesmethyl cariprazine (DDCAR)
 $T_{1/3}$ el 1-3 weken

Farmacotherapeutisch Kompas > Geneesmiddelen >	
Volwassenen:	Beginndosering: 1,5 mg 1x/dag. Geleidelijk ophogen met 1,5 mg per keer tot max. 6 mg/dag. Na starten en bij iedere dosisverandering meerdere weken controleren op bijwerkingen en respons, vanwege de lange halfwaardetijd van cariprazine en werkzame metabolieten.
$T_{1/2}$	de effectieve (functionele) halfwaardetijd voor cariprazine en desmethylcariprazine: ca. 2 dagen, voor didesmethylcariprazine: 8 dagen en voor cariprazine (totaal): ca. 1 week.

EFFECTIVITEIT CARIPRAZINE IN DE KORTE TERMIJN BEHANDELING VAN SCHIZOFRENIE

LANGE-TERMIJN EFFITIVITEIT (RELAPSE PREVENTIE) BIJ MENSEN MET DSM CLASSIFICATIE SCHIZOPHRENIE – CARIPRAZINE

Cumulatief aantal mensen met een relapse

- Relapse bij 24.8% van met cariprazine-behandelden versus 47.5% bij placebo
- HR=0.45 (95% CI: 0.28, 0.73)
- p<0.001 voor tijd tot terugval cariprazine versus placebo

Durgam et al., Schizophrenia 2016; 17(2):164-171

EFFECTIVITEIT CARIPRAZINE IN DE KORTE TERMIJN BEHANDELING VAN SCHIZOFRENIE

Mediane verandering in PANSS Totaal scores

Durgam et al. 2014

Durgam et al. 2015

Kane et al. 2015

FIGURE 3. Change from baseline in PANSS total score (SUMMED, ITT Population) ITT, intent-to-treat; SUMMED, summed effects pooled with repeated measures; PANSS, Positive and Negative Syndrome Scale; *P < 0.05; **P < 0.01; ***P < 0.001 vs placebo.

WHAT ABOUT CARIPAZINE AND NEGATIVE SYMPTOMS?

LANGE-TERMIJN EFFITIVITEIT (RELAPSE PREVENTIE) BIJ MENSEN MET DSM CLASSIFICATIE SCHIZOPHRENIE – CARIPRAZINE

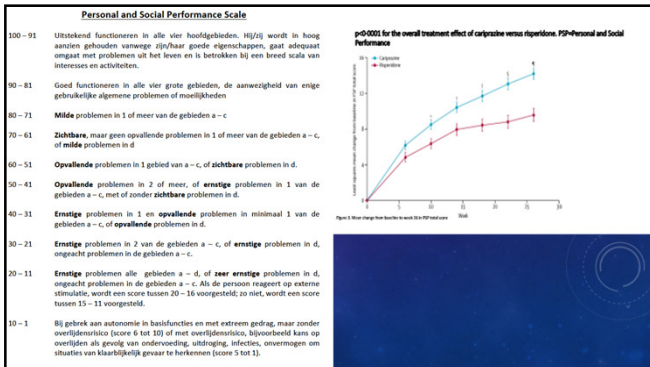
WHAT ABOUT CARIPAZINE AND NEGATIVE SYMPTOMS?

Gedrukt van cariprazine leidde tot een grotere gemiddelde verandering in de totale behoeften in PWS-P30G vanaf de baslijn tot week 20 dan bij risperidon (4.59 punten voor cariprazine versus -7.44 punten voor risperidon; totale behoeften gemiddelde verschil -1.46, 95% CI: -1.38 tot -1.53; p=0.002; effectiviteit 0.31)

p<0.0001 for the overall treatment effect of cariprazine versus risperidone, P30-Personal and Social Performance

Figure 2. Mean change from baseline to week 20 in PWS total score for negative symptoms

Figure 3. Mean change from baseline to week 20 in P30 total score



TOLERABILITEIT: NUMBERS NEEDED TOT HARM (NNH)

	Acatheisie		
	Schizofrenie	Bipolair manisch	Additie depressie
Aripiprazol	25	12	5
Brexpiprazol	112		15
Cariprazine	15	7	

Medication	Gewichtstoename ≥7%	Slaaperigheid AEs	Acatheisie AEs
Aripiprazole	21	20*	25
Brexpiprazole	17	50	112
Cariprazine (to 6 mg/day)	34	100	15

BIJWERKINGEN (ONGEWENSTE EFFECTEN)

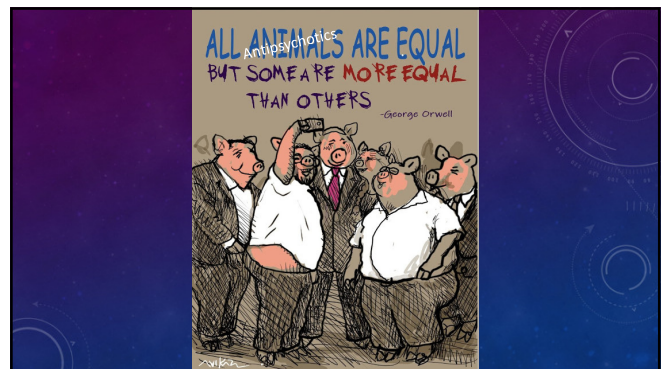
- ### SAMENVATTING ARIPIPRAZOL, BREXPIPRAZOL EN CARIPRAZINE
- Effectieve antipsychotica (vergelijking met depot, amisulpride of clozapine?)
 - Mogelijk antidepressieve effecten, in ieder geval van aripiprazol en brexpiprazol bij de additie aan antidepressiva
 - Relatief weinig sedatie, weinig invloed prolactine (en seksueel functioneren)
 - Acatheisie kan een probleem zijn, vooral bij cariprazine and in mindere mate aripiprazol
 - EPS kan een probleem zijn bij cariprazine
 - Relatief gunstig t.a.v. gewicht (vooral cariprazine)
 - Zijn de gevonden effecten van cariprazine op negatieve symptomen klinisch relevant?
 - Farmacokinetiek van cariprazine is complex, met voor en nadelen.

Safety and tolerability of aripiprazole, brexpiprazole, and cariprazine

	% of patients discontinuing because of an adverse event			% of patients with the most commonly encountered adverse event			
	Active medication	Placebo	NNH	Adverse event	Active medication	Placebo	NNH
Aripiprazole							
Schizophrenia	7%	9%	NA	Akathisia	8%	4%	25
Bipolar mania	11%	10%	100	Akathisia	13%	4%	12
Bipolar mania (adjunct)	12%	6%	17	Akathisia	19%	5%	8
Major depressive disorder (adjunct)	6%	2%	25	Akathisia	25%	4%	5
Brexpiprazole							
Schizophrenia	8%	15%	NA	Weight increased	4%	2%	50
Major depressive disorder (adjunct)	3%	1%	50	Akathisia	9%	2%	15
Cariprazine							
Schizophrenia (pooled 1.5 to 6 mg/d)	9%	12%	NA	Extrapyramidal	17%	8%	12
Bipolar mania (3 to 6 mg/d)	12%	7%	20	Extrapyramidal	26%	12%	8

Reproduced with permission from Citrome L. The ABC's of dopamine receptor partial agonists - aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. Int J Clin Pract. 2015;69(11):1211-1220.
 NA, not applicable as the rate observed with medication is lower than that observed with placebo; NNH, number needed to harm.

Citrome 2018. Current Psychiatry. Vol 16 (4) 25-34. c





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