

## Farmacotherapie voor angst en dwang bij mensen met psychosen

Richard Bruggeman

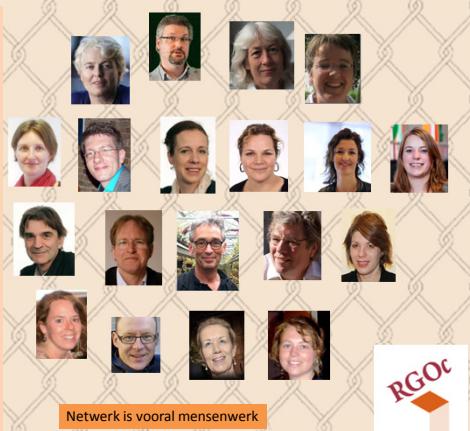


HET RGOC-PSYCHOSEN NETWERK --- 20 jaar jong !!



### RGOC Netwerk PSYCHOSEN

André Aleman  
Johan Arends  
Agna Bartels  
Richard Bruggeman  
Jooske van Busschbach  
Nykie Boonstra  
Stynke Castelein  
Charlotte de Heer  
Frederike Jörg  
Hans Klein  
Rikus Kneegtering  
Edith Liemburg  
Inez Oosterholt  
Esther Opmeer  
Marieke Pijnenborg  
Wim Veling  
Annelieke van der Waal  
Anita Wessels  
Hanneke Wigman  
Lex Wunderink



Netwerk is vooral mensenwerk

## Farmacotherapie van angst bij psychosen

Richard Bruggeman

RGOC , UCP-UMCG

- Richtlijnen Angststoornissen
- Antipsychotica
  - DA/5HT/NA/H
- Antidepressiva
  - 5HT/ DA
- Anxiolytica
  - GABA/ Glutamaat/ alfa1/5HT1a
- Overige
  - Nieuwe ontwikkelingen
- OCS tijdens behandeling

## Praten/pillen/VR/CGT/EMDR??

- |                                     |       |
|-------------------------------------|-------|
| • Sociale Angst Stoornis            | 14.9% |
| • Post Traumatische Stress Stoornis | 12.4% |
| • Obsessief Compulsieve Stoornis    | 12.1% |
| • Gen. Angst Stoornis               | 10.9% |
| • Paniek stoornis                   | 9.8%  |
| • Agorafobie                        | 7.9%  |

### Relatie met andere symptomen in PSS

- Positieve symptomen                            GAS, SAS, PS
- Negatieve symptomen                         OCS ?
- Inzicht    AS
- Depressie en angst                            AS
- Suicidaleiteit                                  PS
- Trauma in jeugd                              AS
- Toegenomen Zorg gebruik

### Richtlijn angst-stoornissen farmacotherapie

- Antidepressivum
- Antidepressivum
- Additie antipsychoticum

### Antipsychotics in the Treatment of Generalized Anxiety Disorder

- overall findings suggest that atypical antipsychotics were **effective in reducing symptoms** of anxiety among individuals with primary diagnoses of GAD.
- most research has amassed for **quetiapine**, and evidence suggests that relatively low doses of **XR 150 mg/day** consistently outperformed higher XR 300 mg/day doses,
- and initiating at 50 mg might be sufficient to produce benefit

CNS Drugs June 2014, Volume 28, Issue 6, pp 519–533  
Role of Atypical Antipsychotics in the Treatment of Generalized Anxiety Disorder  
Rachel Hershenberg Daniel F. Gros Olga Brawman-Mintzer

All antipsychotics are equal ,  
but some are more equal than others..

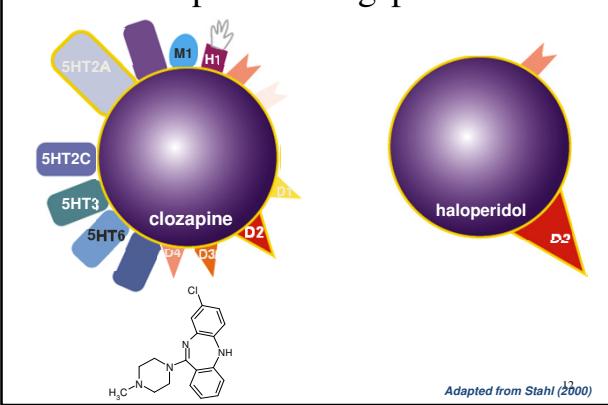


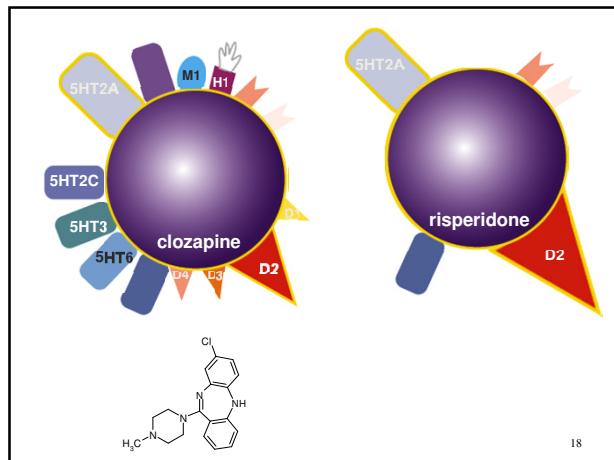
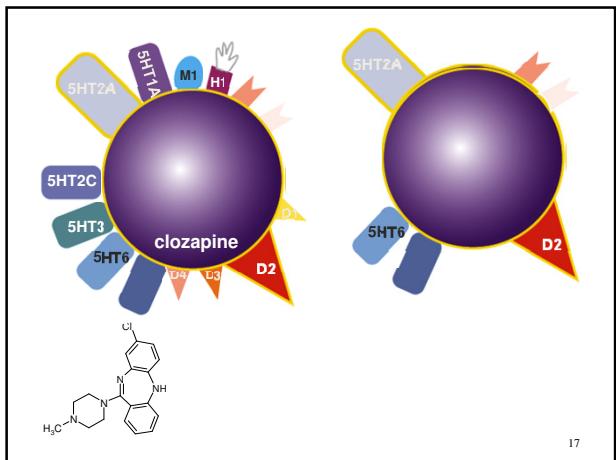
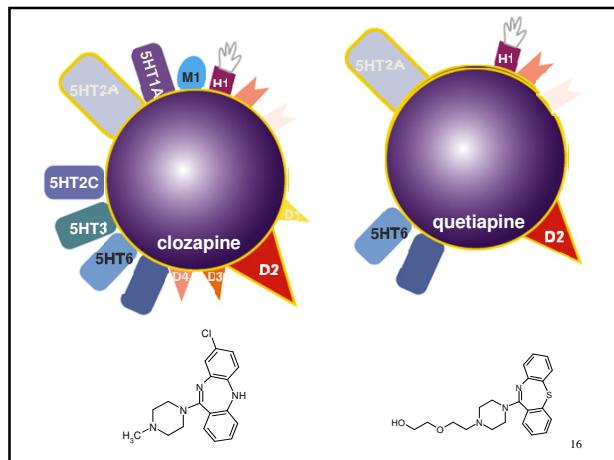
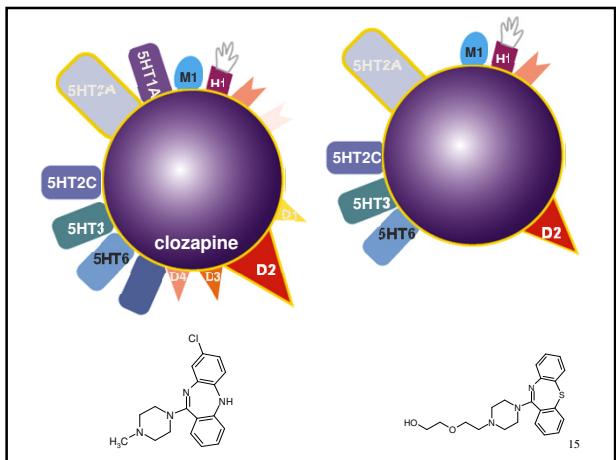
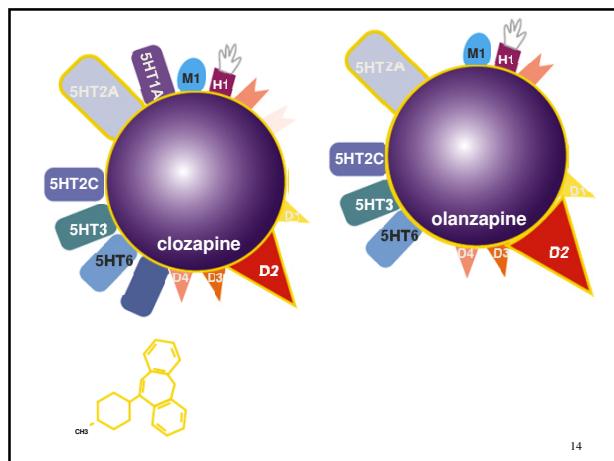
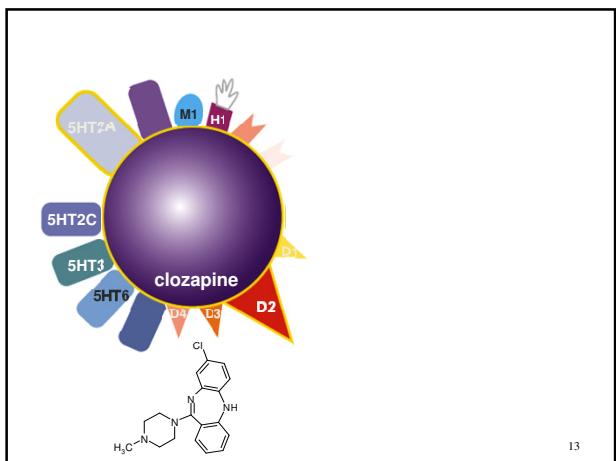
### receptor- bindingsprofiel klinische betekenis

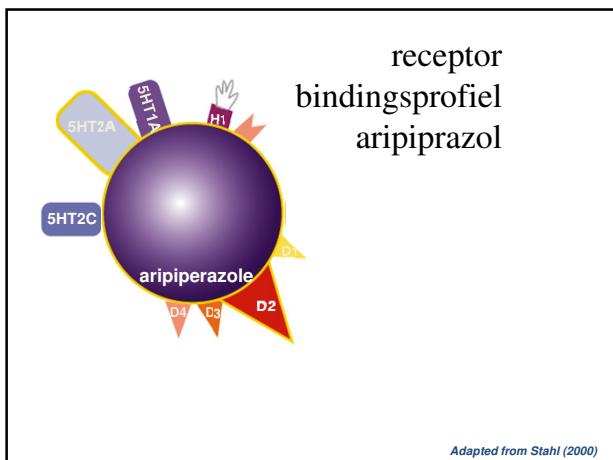
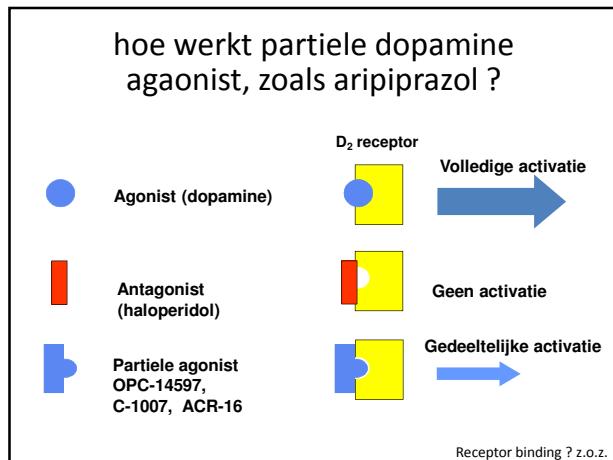
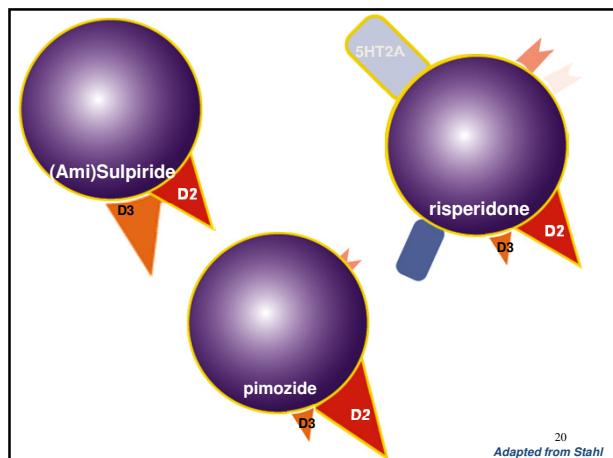
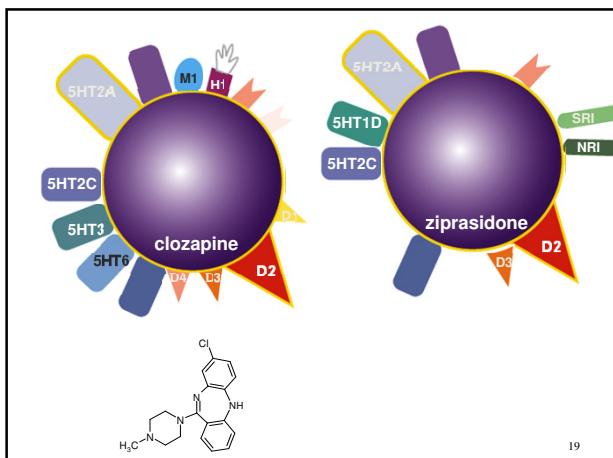
D <sub>2</sub>	antipsychotisch, EPS, PRL↑, subj. bijwerkingen
5-HT <sub>1A</sub>	angst-reducerend
5-HT <sub>2A</sub>	gedragsregulatie, negatieve sympt. ↓;
5-HT <sub>2C</sub>	gewicht
α <sub>1</sub>	sedatie, hypotensie
H <sub>1</sub>	sedatie, gewicht?
Ach	centrale en perifere bijwerkingen; EPS↓
NRI	
SRI	

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### receptor bindingsprofiel







Receptor-bindings profiel

	Aripiprazole	Olanzapine	Risperidon	Quetiapine	Ziprasidone	Clozapine	Haloperidol
D <sub>1</sub>	265*	31	75	455	9.5	85	25
D <sub>2</sub>	0.34*	11	3	160	4.8	125	1
D <sub>3</sub>	0.8*	49	14	340	7.2	280	7.8
D <sub>4</sub>	44*	27	7	1600	32	40	5
5-HT <sub>1A</sub>	1.7*	>1000		490	2450	3.4	770
5-HT <sub>2A</sub>	3.4*	4	0.6	220	0.4	12	78
5-HT <sub>2C</sub>	15*	11	26	615	1.3	8	3085
α <sub>1</sub>	57	19	2	7	10	7	46
H <sub>1</sub>	61*	7	155	11	47	6	3630
M <sub>1</sub>	>10,000	1.9	>5000	120	>10,000	1.9	1475

\*Data with cloned human receptors. Receptor-binding affinities expressed as K<sub>i</sub> [nM]. Ability [US package insert]; Amt et al. *Neuropharmacology*, 1998;18:63; Byimaster et al. *Neuropharmacology*, 1996;14:87; Data on file, Otsuka America Pharmaceutics Company Inc.; 2003; Geodon [US package insert]; Schotte et al. *Psychopharmacology*, 1996;124:57; Zyprexa [US package insert].

## antipsychotica

- Risperidon
  - Psychotische Angst ↓
- Aripiprazol
  - YBOCS ↓
- Quetiapine
  - BPRS ↓
- Olanzapine
  - BPRS anxiety-depr ↓

Reference	Design, sample	Population	Moderators	Outcomes
<b>Antipsychotics</b>				
Blin et al. [211]	Randomized trial (N = 62)	Schizophrenia	Risperidon vs. haloperidol vs. methyltrazine	Significantly greater reduction in Psychotic Anxiety Scale in risperidon vs. methyltrazine group
Glick et al. [212]	Non- randomized, prospective trial (N = 10)	Schizophrenia pts with OCS	Atypical	Significant reduction in Y-BOCS score at study endpoint (study completion; N = 9)
Kuper et al. [213]	Open-label extension of a randomized trial (N = 410)	Schizophrenia	Quetiapine	Significant reduction in BPRS anxiety/depression factor dimension over long duration
Borrelli et al. [214]	Non- randomized, prospective trial (N = 61)	Schizophrenia, schizoaffective disorder with social anxiety symptoms	Atypicals (included from existing antipsychotic to atypicals)	Significant reduction in LMAS, SDS
Tollefson et al. [215]	Randomized trial, secondary analysis (N = 323)	Schizophrenia pts	Quetiapine vs. PL; haloperidol vs. PL	Significantly greater reduction in BPRS anxiety/depression factor in olanzapine (7.5–10 mg/day) vs. PL. No significant difference for haloperidol vs. PL group

## Additie van antidepressiva bij PSS

- angst en ocd
- depressie
- negatieve symptomen
- sexuele functie stoornissen..

## Plaats van antidepressiva ?



### 1<sup>e</sup> stap antidepressiva

- Fluoxetine
  - YBOCS ↓
- Clomipramine
  - YBOCS ↓
- Sertraline
  - BPRS anx/depr ↓
- Fluvoxamine
  - YBOCS ↓
- Escitalopram
  - YBOCS 'n PANSS ↓

Reference	Design, sample	Population	Moderators	Outcomes
Agresti and Agresti [216]	Non-randomized, prospective trial (N = 9)	Schizophrenia with OCS	Fluoxetine add-on to existing antipsychotics	Significant improvement in Y- BOCS score after 12 weeks of tx
Berman et al. [217]	Randomized trial (N = 4)	Schizophrenia with OCS	Clomipramine vs. PL add-on to existing antipsychotics	Significantly greater improvement on Y-BOCS scale with clomipramine vs. PL
Mohindra et al. [218]	Randomized trial (N = 26)	Schizophrenia pts with comorbid depression	Sertraline vs. PL add-on to existing antipsychotics	Significantly greater improvement on anxiety/depression subscale of BPRS in sertraline group vs. PL
Pallanti et al. [219]	Non-randomized, prospective trial (N = 12)	Schizophrenia with tx emergent social anxiety	Clomipramine add-on to clomipramine	Significant improvement in fear and anxiety subscale of LMAS
Payenoy et al. [220]	Non-randomized, prospective trial (N = 10)	Schizophrenia with OCS	Fluoxetin add-on to existing antipsychotics	Significant improvement in dimensions of Y-BOCS
Reznik and Sleator [221]	Randomized trial (N = 30)	Schizophrenia with OCS	Fluoxetin add-on to existing antipsychotics only	Significantly greater improvement in Y-BOCS total score in combination tx group
Reznik and Sleator [222]	Non-randomized, prospective trial (N = 16)	Schizophrenia with OCS	Fluoxetin add-on to existing antipsychotics	Significantly lower scores on all Y- BOCS dimensions
Stoye et al. [223]	Non-randomized, prospective trial (N = 15)	Schizophrenia and OCD	Escitalopram add-on to existing antipsychotics	Significant improvement on all Y- BOCS scores, PANSS anxiety and anxiety items

YBOCS= Yale-Brown Obsessive Compulsive Scale, PL= placebo, PANSS= Positive and Negative Syndrome Scale, PTSD= posttraumatic stress disorder, LMAS= Life Satisfaction Inventory, OCS= obsessive-compulsive symptoms, SDS= Sheehan Disability Scale, SSRIs= selective serotonin re-uptake inhibitors, tx= treatment, Y-BOCS=Yale-Brown Obsessive Compulsive Scale.

## Tweede stap na SSRI

- SNRI- venlafaxine
  - Bij SAS, GAS
- Imipramine en clomipramine
  - Bij OCD
    - Cave QTc verlenging
- Mirtazapine
  - Overwegen bij PTSS, PS en SAS
  - Bewezen bij Negative S/
  - Minder EPS, meer gewichtstoename

## Caveat's bij antidepressiva additie

- Eerst effect AP afwachten
- Cave overactivatie leiden
  - (weinig studies met nieuwere AP)
- Let op: toename angst en agitatie bij SSRI
- Akathisie bij AD+AP: lijkt op toename klachten.

## Interacties (2)

- CYP450 interactie
  - Citalopram, escitalopram en sertraline minste interactie
- QT-tijd verlenging
  - Meeste risico bij citalopram ( $>40$  mg); escitalopram
- Synergie K-kanaal bij elke combi AP+AD
  - ECG bij start
- CLOZ met fluoxetine, fluvoxamine, paroxetine
  - Verhoging clozapine spiegels

## Anxiolytica

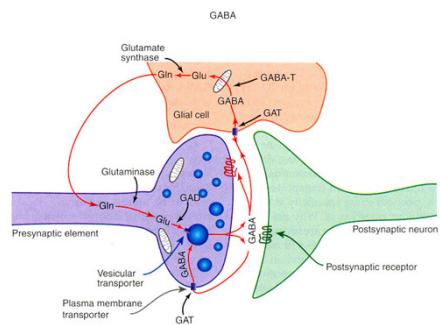


## GABA glutamaat

En de benzo's...  
En wat nog meer...

## GABA als neurotransmitter

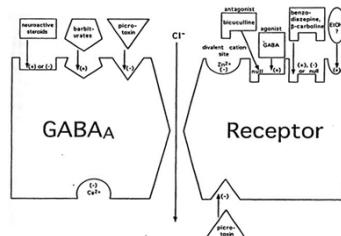
- Bij ca 30% van alle synapsen is GABA betrokken
- uit glutaminezuur gevormd door glutamaat decarboxylase (GAD)
- Actief opgenomen na afgifte in glia cellen
- gemetaboliseerd door GABA-transaminase



## Twee typen GABA receptoren

- GABA-A:
  - direct gekoppeld aan chloor ion-kanaal; inhibitie.
- GABA-B:
  - G-eiwit gekoppeld (indirect aan een K en Ca<sup>2+</sup> ion-kanaal gekoppeld); tevens een autoreceptor

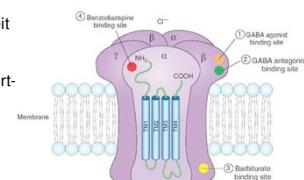
## de GABA-A receptor



Opgebouwd uit pentameren dus **5 subunits**, er zijn **5 typen subunits** (families)

## Agonisten van de GABA receptor

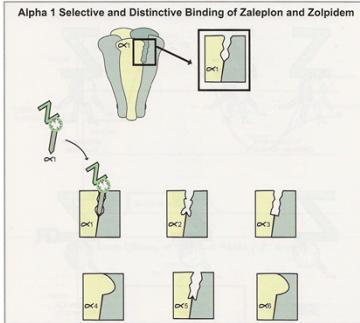
- agonisten GABA-A**
  - Benzodiazepinen en barbituraten :
  - slaapmiddelen en kalmerende middelen
- agonist GABA-B**
  - Baclofen : tegen spasticiteit
- Indirecte agonisten:**
  - GABA afbraak- en transport-anti-epileptica



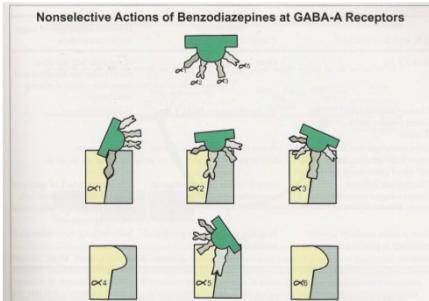
### Antagonisten:

- convulsief; induceren epilepsie
- voorbeeld: bicuculline

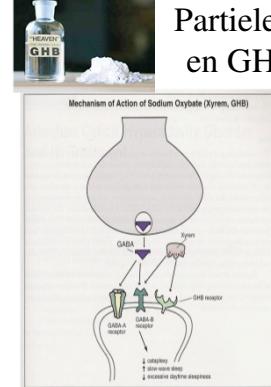
## GABA modulatie via selectieve alfa-1receptor : zolpidem



## Non selectieve werking van benzodiazepines op GABA-A receptoren

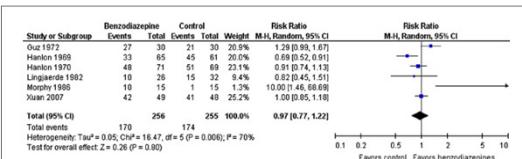


## Partiële GABA-B en GHB agonist



## De rol van benzo's

### • Uit de meta analyse...



Benzodiazepine augmentation of antipsychotic drugs in schizophrenia: A meta-analysis and cochrane review of randomized controlled trials

Markus Dold<sup>a</sup>, Chunbo Li<sup>b</sup>, Donna Gillies<sup>c</sup>, Stefan Leucht<sup>a,\*</sup>

## Toch iets te zeggen voor benzo's ?

Ma et al. (1991), China	Intervention: 4 weeks Schizophrenia with auditory hallucination control: n=60	1. Clonazepam 2 mg/d d+antipsychotics placebo-equivalent: 59.35 mg/d, 2. Antipsychotics placebo-equivalent: 58.85 mg/d,	SB-RCT (Inpatient) Adjunctive clonazepam was efficacious in treating hallucinatory symptoms; no other outcomes were assessed
Martiros et al. (1993), Germany	Intervention: 3 weeks Schizophrenia (acute episode) control: n=10	1. clonazepam 40 mg/ d+antipsychotics placebo-combination implied: 2. placebo+haloperidol 12 mg/d	DB-RCT Adjunctive clonazepam was only effective to improve affective symptoms
Morphy (1988), USA	Intervention: 4 weeks Schizophrenia control: n=15	1. Alprazolam max. 3 mg/d d+antipsychotics (constant dose), 2. Placebo+antipsychotic dose)	Adjunctive alprazolam medication was effective to improve anxiety symptoms.
Pujalte et al. (1994), France	Intervention: 2 weeks schizophrenia (n=10), schizoaffective disorder control: n=6	1. clonazepam 0.5-2.5mg/d + antipsychotics (constant dose) 2. placebo+antipsychotics (constant dose)	DB-RCT (setting not indicated) Clonazepam induced a significantly higher reduction of akathisia than placebo, but no other outcomes were assessed
Stevens et al. (1992), Germany	Intervention: 4 weeks schizophrenia control: n=29	1. lorazepam 0.05mg/kg/d + haloperidol 0.5mg/kg (mean dose) 2. placebo + haloperidol 0.5mg/kg (mean dose)	NB-RCT (Inpatient) No positive effects of adjunctive lorazepam in terms of the BPRS.
Wang et al. (2000), China	Intervention: 2 weeks schizophrenia with auditory hallucination control: n=6	1. clonazepam 2mg/d + antipsychotics 2. antipsychotics 2. placebo	NB-RCT (Inpatient) Exclusively investigation of hallucinatory symptoms
Wang et al. (2003), China	Intervention: 8 weeks schizophrenia (first episode) control: n=40	1. clonazepam 1.m. 2-4mg/d + risperidone 2.5mg/d 2. risperidone 2.5mg/d	NB-RCT (Inpatient) Usable data only 2-week treatment available without placebo, no any statistically significant difference
Xuan and Chu (2007)	Intervention: 8 weeks schizophrenia control: n=48	1. benzodiazepines (clonazepam or lorazepam or alprazolam) + risperidone 3.0mg/d (mean dose)	NB-RCT (Inpatient) No significant between-group differences in terms of the BPRS total score reduction during the

- Vrijwel alle richtlijnen geven aan:
- Geen plaats voor benzo's bij psychosen, vanwege onvoldoende effect op psychose.
- Gevaar op verslaving,
- Alleen voor acute sedatie



## Anxiolytica (2) : Pregabalin

Structuur analoog aan GABA, maar geen interactie met GABAA of GABAB

$\alpha 2\delta$  binding presynaptisch voltage dependent calcium kanaal, remt Calcium influx

Netto effect :

- Inhibitie van excitatoire neurotransmissie, glutamaat en monoamine

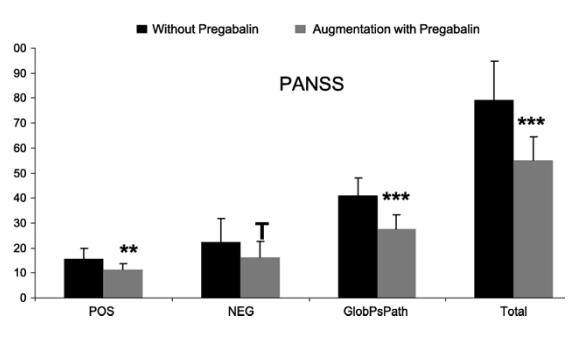
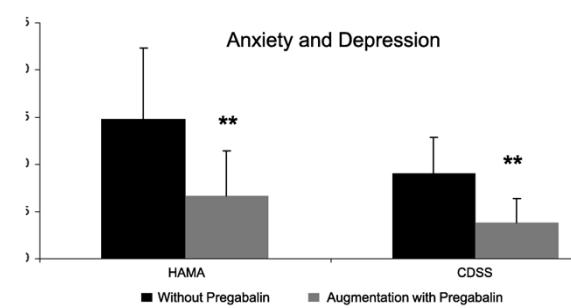


## Pregabalin

- Effectief en goed verdragen in GAS
- Snellere werking dan SSRI en SNRI's
- Effectief tegen psychische en somatische S/
- Ook bij ouderen
- Weinig interacties (let op clozapine)
- Weinig kans op afhankelijkheid/misbruik (?)
- Minimale onttrekkings S/ en rebound
- Minder sexuele functie stoornissen

Pregabline Review; Frampton: CNS Drugs 2014; 28; 835-854

## Augmentatie van Pregabalin in PSS

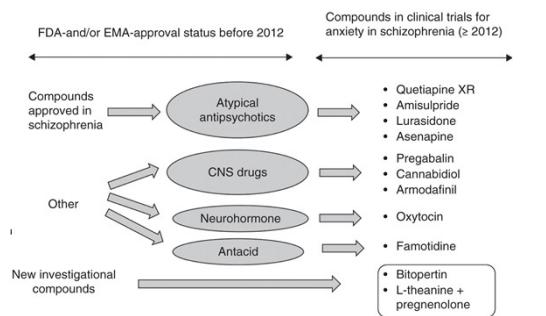


## Anxiolytica (3) buspiron

- 5HT1A partiele agonist
  - heeft mogelijk ook antidopaminerke activiteit
- Als additie bij AP:
  - positieve symptomen
  - ook effect op angst in open studie

An Open Study of Buspirone Augmentation of Neuroleptics in Patients With Schizophrenia  
Sirota, Pinkhas MD; Epstein, Bella MD; Benatov, Ruben MD, PhD;  
Sousnostzky, Michael MD; Kindler, Setti MD

## Wat zit er nog in de pijplijn ?



Published in: Ricardo P Garay, Ludovic Samalin; Ahcène Hameg; Pierre-Michel Llorca; Expert Opinion on Investigational Drugs 2015, 24, 507-517.  
DOI: 10.1517/13640994.2014.907139  
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## Combineren antipsyhotica en CGT

## OCS als gevolg van de behandeling?

### 2<sup>e</sup> gen antipsychotica (m.n. Clozapine)

- Sociale Angst en OCD
- Ook nog 6 maanden na begin
- Mannen > vrouwen
- Compulsie > obsesies

#### BELEID:

- Switch (behalve bij clozapine (?))
- Additie SSRI
- Clozapine verlagen

Poyurovski et al. CNS drugs, 2004.18 ; 989-1010

## OCS als gevolg van de medicatie?

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Poyurovski et al. CNS drugs, 2004.18 ; 989-1010

## Medicatie en OCS



<b>Obsessive-Compulsive Symptoms in Patients With Schizophrenia: A Naturalistic Cross-Sectional Study Comparing Treatment With Clozapine, Olanzapine, Risperidone, and No Antipsychotics in 543 Patients</b>																																		
Albertine A. Scheltema Beduin, MD; Marije Swets, MD; Marise Machielsen, MD; Nikie Korver, MSc; and the Genetic Risk and Outcome of Psychosis Investigators																																		
<b>Table 2. Demographic and Disease Characteristics of Patients Treated With Clozapine, Olanzapine, Risperidone, or No Antipsychotic Medication, With and Without Obsessive-Compulsive Symptoms (OCS) During the Last Week</b>																																		
<table border="1"> <thead> <tr> <th>Characteristic</th> <th>Patients With OCS During the Last Week (n = 135, 24.9%)</th> <th>Patients Without OCS During the Last Week (n = 408, 75.1%)</th> <th>Test Statistic</th> <th>P Value</th> </tr> </thead> <tbody> <tr> <td>Age, mean (SD), y</td> <td>27.2 (7.23)</td> <td>27.8 (7.70)</td> <td><math>z = -0.377</math></td> <td>.706</td> </tr> <tr> <td>Sex, male, %</td> <td>81.1</td> <td>78.4</td> <td><math>\chi^2 = 0.439</math></td> <td>.507</td> </tr> <tr> <td>Ethnicity, white, %</td> <td>74.8</td> <td>78.3</td> <td><math>\chi^2 = 1.2</math></td> <td>.179</td> </tr> <tr> <td>Age at onset of first psychosis, mean (SD), y</td> <td>21.1 (7.17)</td> <td>23.3 (6.89)</td> <td><math>z = -3.07</math></td> <td>.002</td> </tr> <tr> <td>Duration of illness, mean (SD), y</td> <td>5.59 (5.25)</td> <td>3.94 (3.94)</td> <td><math>z = -4.00</math></td> <td>&lt;.001</td> </tr> </tbody> </table>					Characteristic	Patients With OCS During the Last Week (n = 135, 24.9%)	Patients Without OCS During the Last Week (n = 408, 75.1%)	Test Statistic	P Value	Age, mean (SD), y	27.2 (7.23)	27.8 (7.70)	$z = -0.377$	.706	Sex, male, %	81.1	78.4	$\chi^2 = 0.439$	.507	Ethnicity, white, %	74.8	78.3	$\chi^2 = 1.2$	.179	Age at onset of first psychosis, mean (SD), y	21.1 (7.17)	23.3 (6.89)	$z = -3.07$	.002	Duration of illness, mean (SD), y	5.59 (5.25)	3.94 (3.94)	$z = -4.00$	<.001
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Age at onset of first psychosis, mean (SD), y	21.1 (7.17)	23.3 (6.89)	$z = -3.07$	.002																														
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## conclusies

- Angst en psychosen – a dangerous liaison
- Antipsychotica zijn effectief
  - Ook in het induceren van angst symptomen
- Antidepressiva
  - Effectief, maar let op interacties
- Anxiolytica
  - Benzos' effectieve anxiolytische werking (?)
  - Pregabalin lijkt mooi alternatief
  - Buspiron effectief op angst
- Nieuwe middelen:
  - CBD ? Oxytocin - ; overige in onderzoek
- Behandeling geïnduceerde angst
  - Clozapine 1/3, 1/3, 1/3; aripiprazol ??