

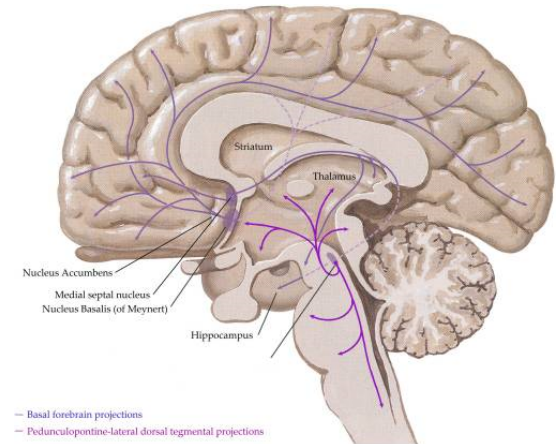
# Acetylcholine, nicotine, (muscarine) en schizofrenie

# Cognitive problemen bij psychose:

- Meest invaliderend
- Onbehandelbaar
- Aanwezig voor dat positieve symptomen er zijn
- Voorspeller slechte therapietrouw
- Voorspellen toekomstig functioneren

# Acetylcholine receptoren: Ion kanaal receptoren (ionotropic), snel

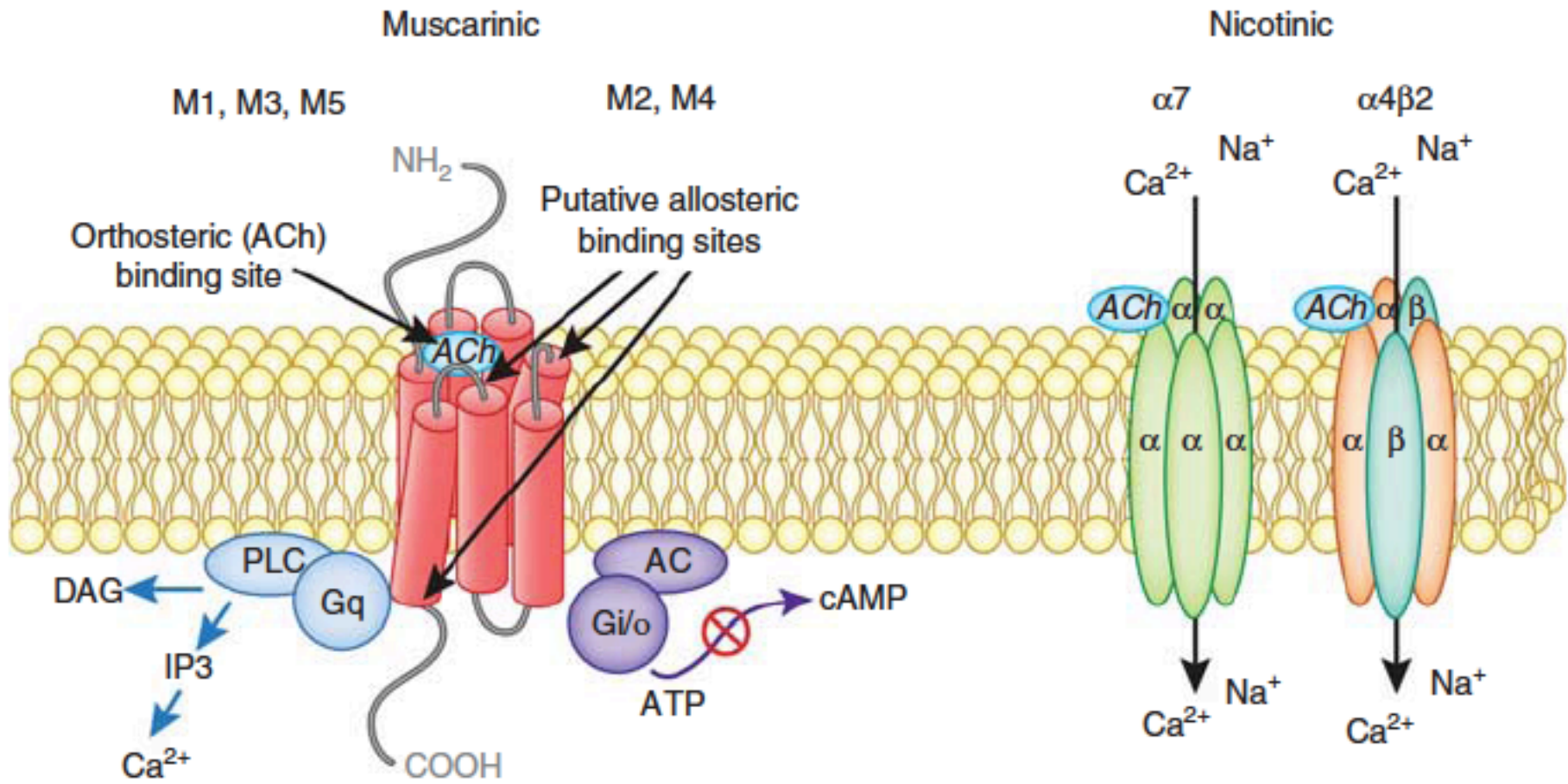
Worden met name neuronaal en in  
spieren gevonden



(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	$\alpha_{1-7}$	$\alpha 1$	$\alpha_{2-9}$	5-HT <sub>3</sub>	P <sub>2X1</sub>
	Glu R2	NR2A	Glu R6	$\beta_{1-4}$	$\alpha 2$	$\beta_{1-4}$		P <sub>2X2</sub>
	Glu R3	NR2B	Glu R7	$\gamma_{1-4}$	$\alpha 3$	$\gamma$		P <sub>2X3</sub>
	Glu R4	NR2C	KA1	$\delta$	$\alpha 4$	$\delta$		P <sub>2X4</sub>
		NR2D	KA2	$\epsilon$	$\beta$			P <sub>2X5</sub>
			$\rho_{1-3}$			P <sub>2X6</sub>		
								P <sub>2X7</sub>

Problemen vinden specifieke compounds...



- Key effectors (examples)**
- ↑ PLCβ
  - ↑ [Ca<sup>2+</sup>]<sub>i</sub>
  - ↑ MAPK

- Key effectors (examples)**
- ↑ AC
  - ↑ MAPK
  - ↑ GIRK ch.

- Key effectors (examples)**
- ↑ [Ca<sup>2+</sup>]<sub>i</sub>
  - ↑ VDCC
  - ↑ PKC



# Cholinerge hypothese psychose (1975)

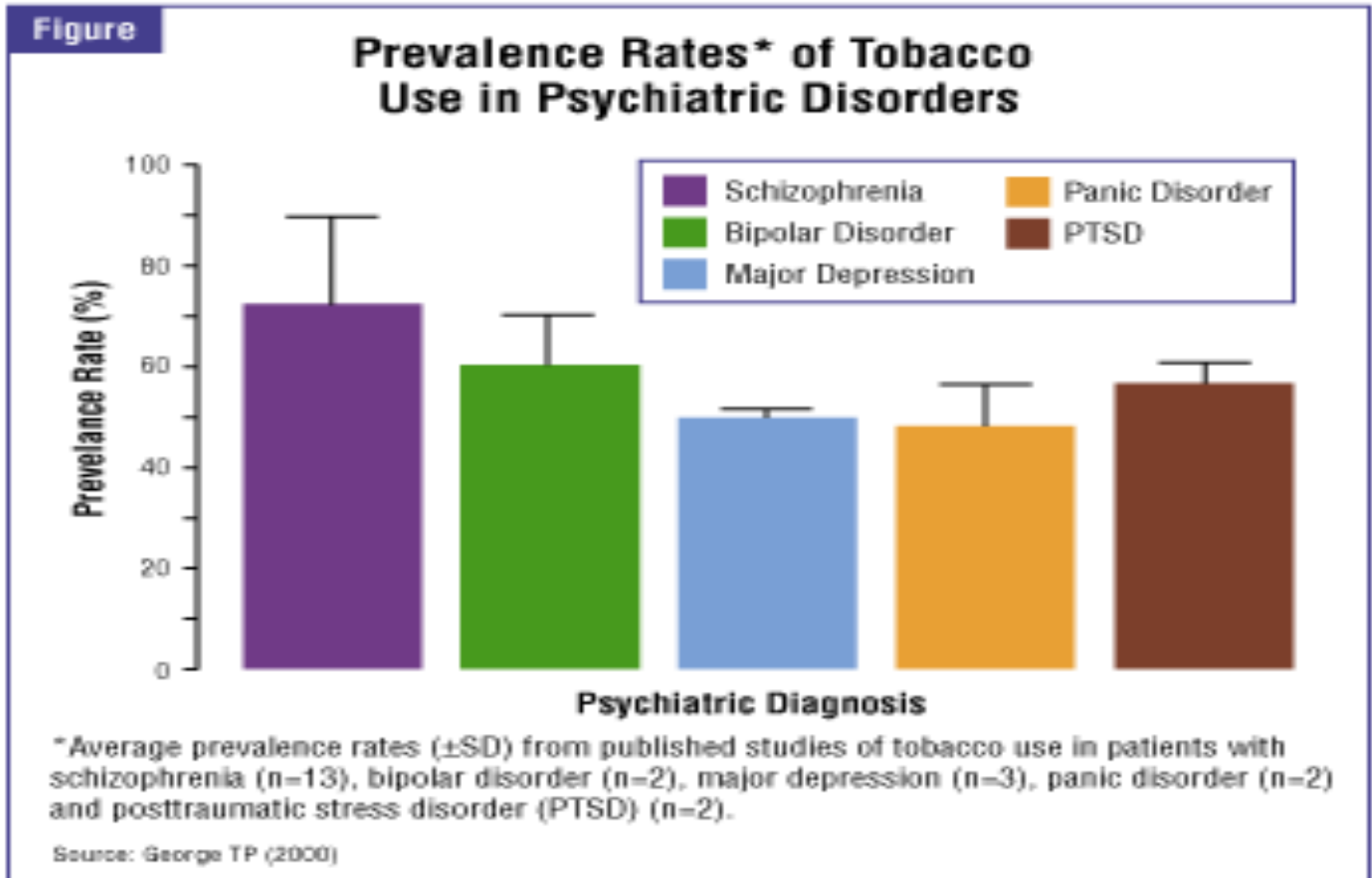
## Postmortem studies:

- verlaagde muscarine en nicotine receptoren in patienten met SCZ
- verlaagde ChAT in patienten met SCZ

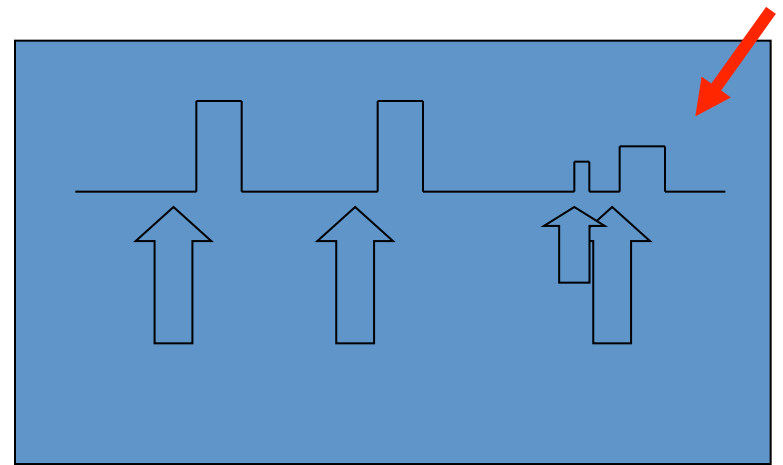
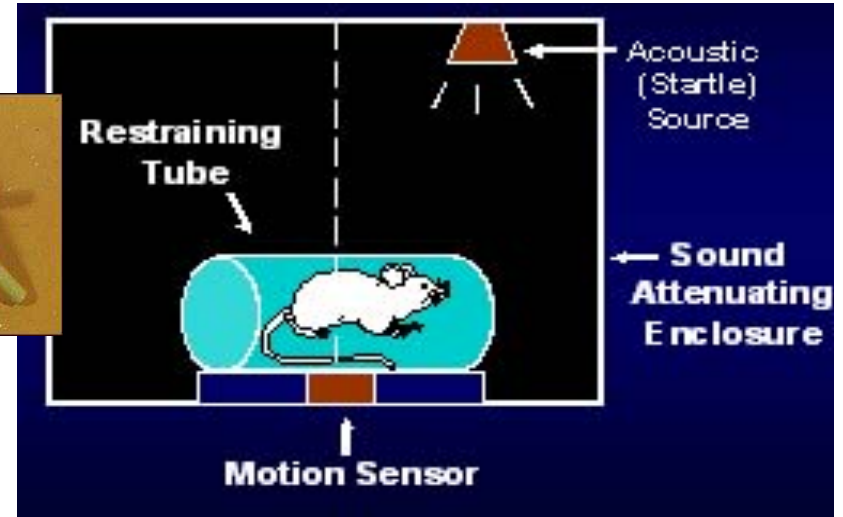
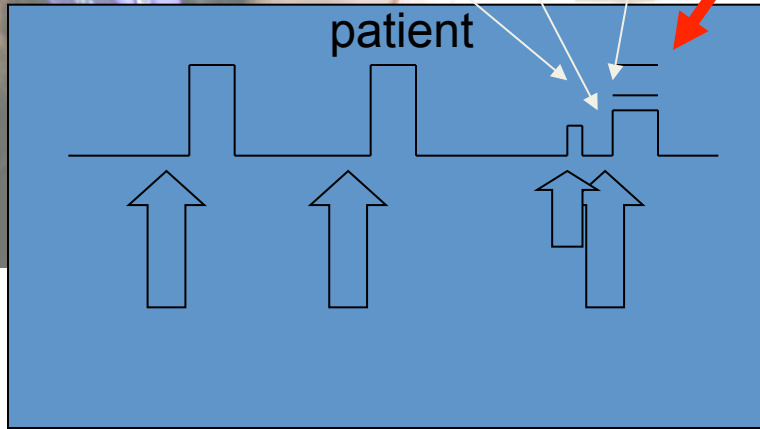
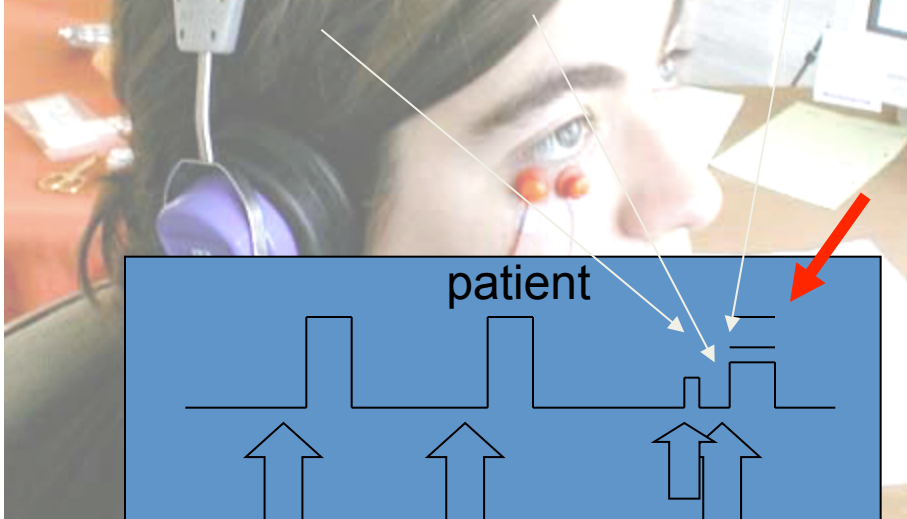
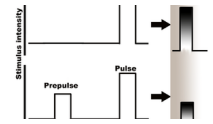
## Challenge studies:

- mACh en nACh receptor antagonist verergeren positieve/cognitieve symptomen in patienten met SCZ en induceren deze in gezonde vrijwilligers
- mACh en nACh agonist en AChEI kunnen symptoomverlichting geven

# Roken en schizofrenie



# Prepulse Inhibition (PPI)





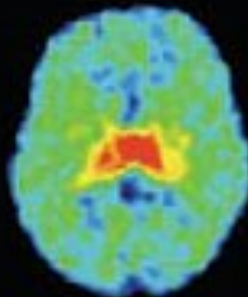
# Goed voor je geheugen?



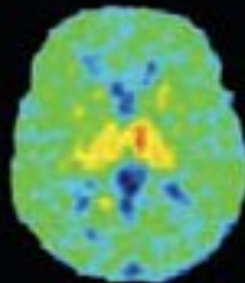


# SPECT

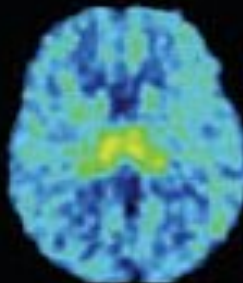
**SMOKING SATURATES RECEPTORS** As nicotine from a cigarette attaches to the  $\alpha 4\beta 2^*$ -nACh nicotinic receptors in the brain, it displaces a radiolabeled tracer (red and yellow indicate high levels of the tracer, green indicates intermediate levels, and blue indicates low levels). The nicotine from three puffs displaced 75 percent of the tracer from study participants' receptors, and the nicotine from three cigarettes, nearly all.



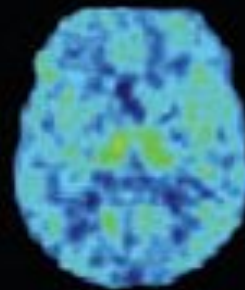
Nothing



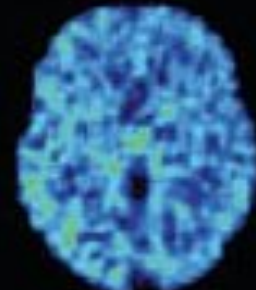
One Puff



Three Puffs



One Cigarette



Three Cigarettes

**TABLE 1****Effects of nicotine on neurocognition among individuals with schizophrenia**

<b>Study</b>	<b>Significant findings</b>	<b>Associated neurocognitive tests</b>
George <sup>12</sup>	(+) effects on VSWM in SZ; (-) effects on VSWM in controls	VSWM, SCWT
Harris <sup>14</sup>	(ND) IM, DM, visuospatial attention, language in SZ smokers; (+) visuospatial attention in SZ non-smokers	RBANS
Sacco <sup>7</sup>	(+) VSWM, sustained attention in SZ smokers; (+) sustained attention in controls	VSWM, CPT
Zabala <sup>13</sup>	(+) sustained attention, WM in SZ smokers vs SZ non-smokers; (ND) EF in SZ smokers compared with SZ non-smoker	Computerized sustained attention task, WM Stroop-I, WCST

(+), increased; (-) decreased; (ND), no difference; VSWM, visuospatial working memory; SZ, schizophrenia; SCWT, Stroop Color Word Test; IM, immediate memory; DM, delayed memory; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; CPT, Continuous Performance Task; WM, working memory; EF, executive function; Stroop-I, Stroop Color-Word Test-Interference; WCST, Wisconsin Card Sorting Test



Contents lists available at [SciVerse ScienceDirect](#)

## Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

### Targeting alpha-7 nicotinic neurotransmission in schizophrenia: A novel agonist strategy<sup>☆</sup>

Stephen I. Deusch<sup>a,b,\*</sup>, Barbara L. Schwartz<sup>c,b</sup>, Nina R. Schooler<sup>b,c</sup>, Clayton H. Brown<sup>d</sup>, Richard B. Rosse<sup>c,b</sup>, Stephanie M. Rosse<sup>b</sup>

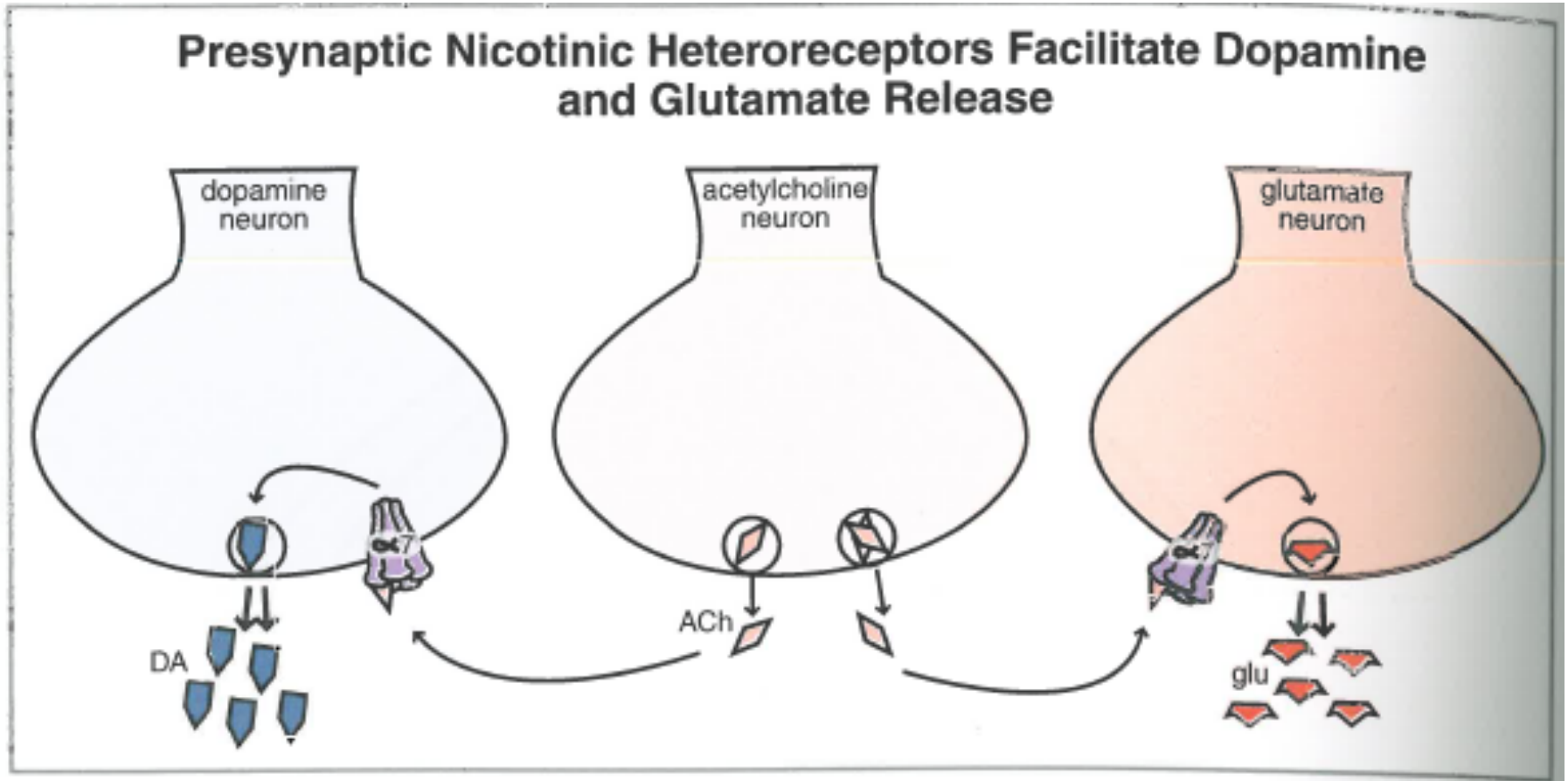
<sup>a</sup> Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, United States

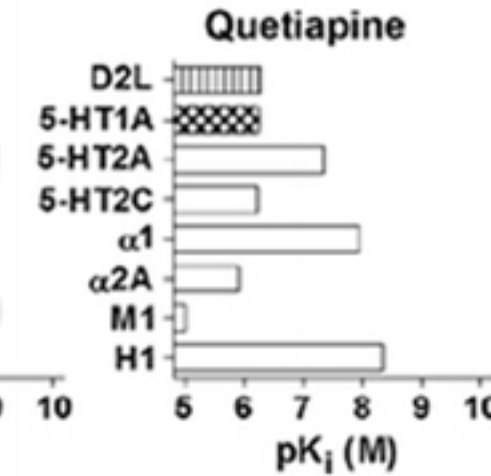
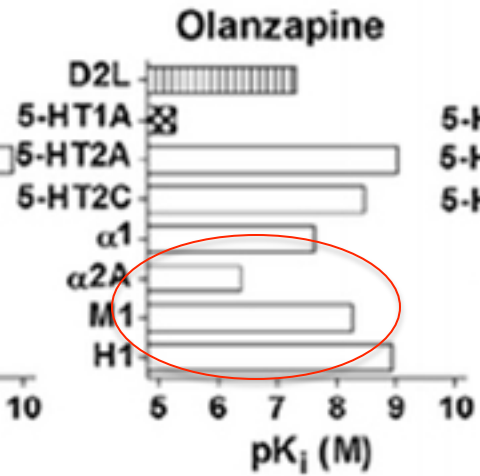
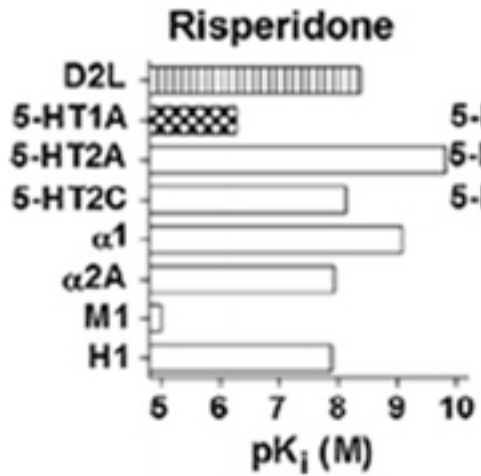
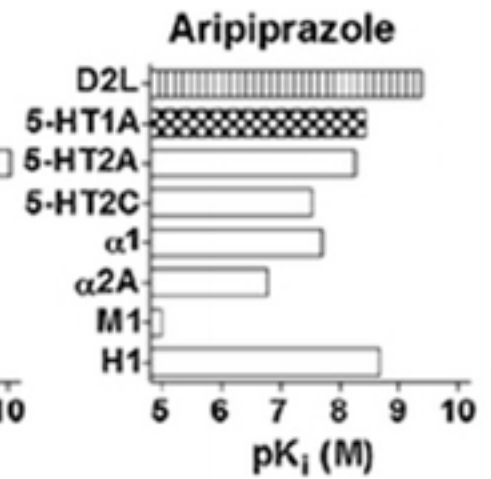
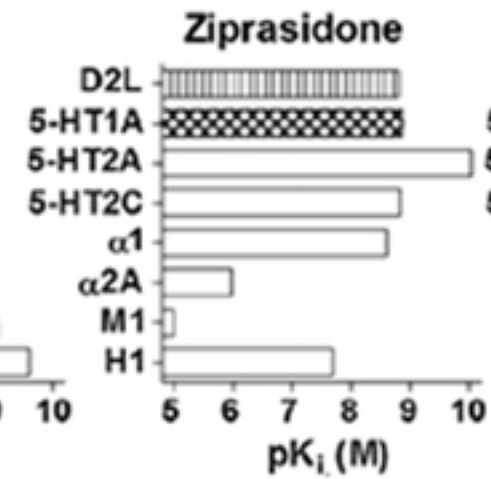
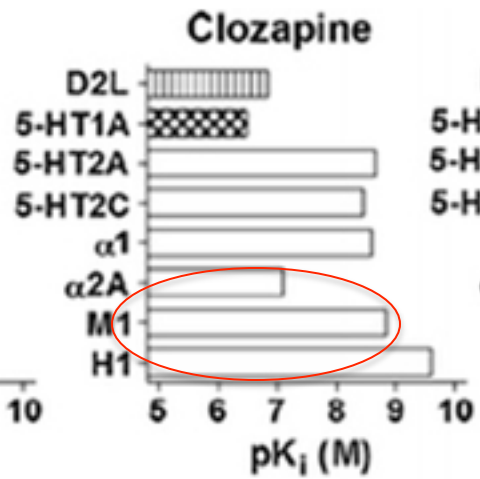
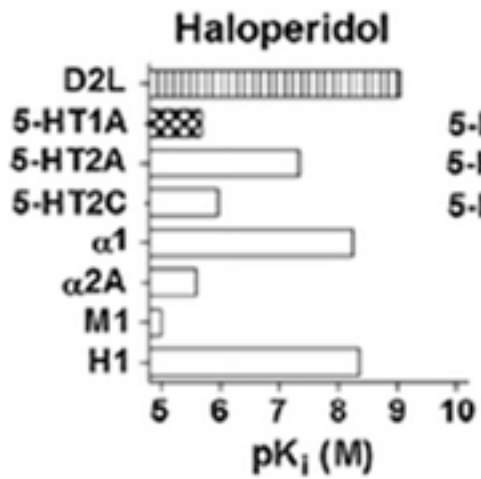
<sup>b</sup> Department of Psychiatry, Georgetown University School of Medicine, United States

<sup>c</sup> Mental Health Service, Washington DC Veterans Affairs Medical Center, United States

<sup>d</sup> Department of Epidemiology, University of Maryland School of Medicine, United States

# $\alpha 7$ agonist en effecten op dopamine en glutamaat





**TABLE 3.**  
**Affinity of Antipsychotics for Neurotransmitter Receptors<sup>\*55-58</sup>**

	<i>D</i> <sub>2</sub>	<i>D</i> <sub>1</sub>	<i>5-HT</i> <sub>2A</sub>	<i>Muscarinic</i>
Haloperidol	+++	++	+	None/questionable
Fluphenazine	+++	+	+	None
Clozapine	+	++	+++	+++
Olanzapine	++	++	+++	+++
Risperidone	+	+	+++	None
Quetiapine	+	+	+++	Antagonist <i>M</i> <sub>3</sub> ; none at <i>M</i> <sub>1</sub> , <i>M</i> <sub>5</sub>
Ziprasidone	+	+	+++	None

\* These data are summarized from a profile of functional activity at human monoaminergic G-protein couple receptors by 462 clinical drugs. All antipsychotics shared the properties of *D*<sub>1</sub> and *D*<sub>2</sub> antagonism and *5-HT*<sub>2A</sub> antagonism/inverse agonism; however, action at muscarinic receptors is variable.

+ = weak affinity; ++ = moderate affinity; +++ = strong affinity; D = dopamine; 5-HT = serotonin.

Sellin AK, Shad M, Tamminga C. *CNS Spectr.* Vol 13, No 11. 2008.

Verklaart mede lage frequentie EPS Ola/Clz!



## Conclusie

Nicotine en muscarine receptoren beide potentiële therapeutische targets voor psychose

Belangrijkste fase III onderzoeken betreffen alfa 7 (partiele) agonisten