

7. Muscarine of nicotine

Aangrijpingspunt voor behandelen met psychose

- Onderzoeken behandeling psychosen via
 - de muscarine weg
 - Nicotine weg (Partiele alpha zeven agonisten)
- Varenicline bij cognitieve of negatieve symptomen.
- Waarom is het zo lastig interventies te ontwerpen?

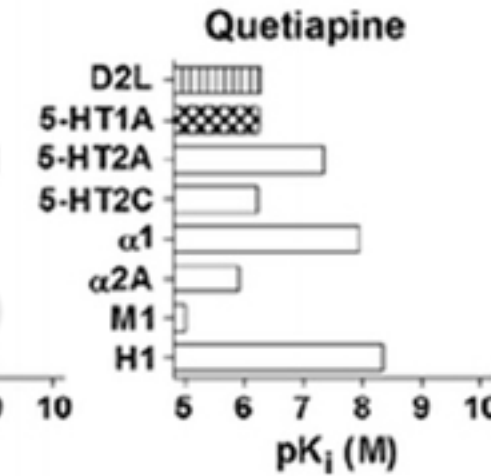
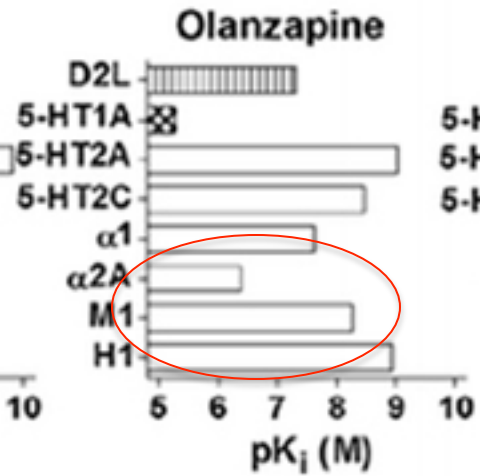
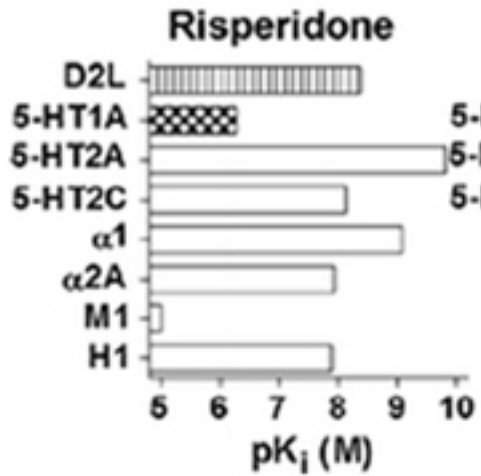
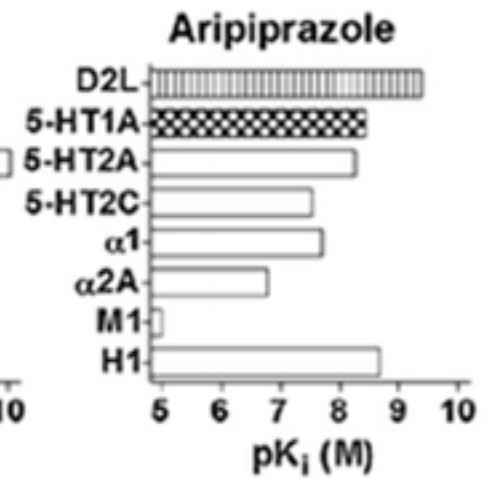
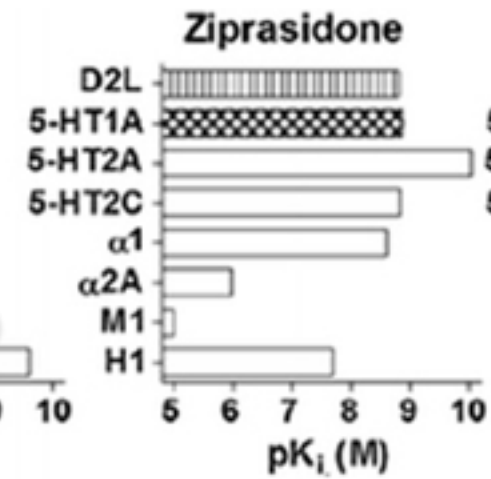
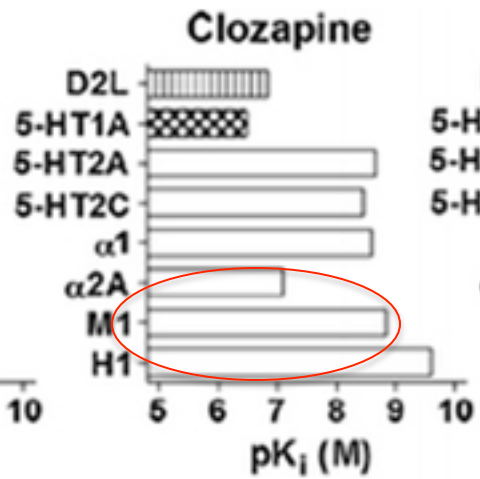
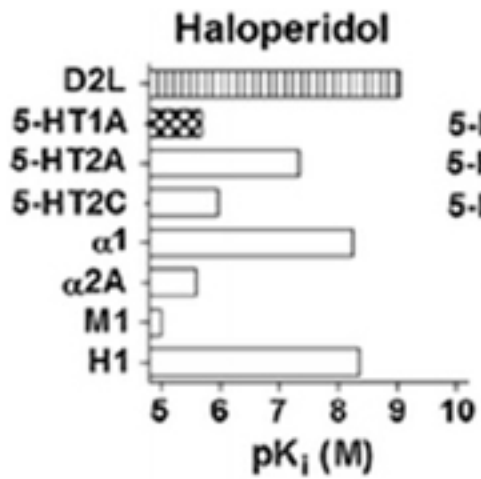


TABLE 3.
Affinity of Antipsychotics for Neurotransmitter Receptors^{*55-58}

	<i>D₂</i>	<i>D₁</i>	<i>5-HT_{2A}</i>	<i>Muscarinic</i>
Haloperidol	+++	++	+	None/questionable
Fluphenazine	+++	+	+	None
Clozapine	+	++	+++	+++
Olanzapine	++	++	+++	+++
Risperidone	+	+	+++	None
Quetiapine	+	+	+++	Antagonist <i>M₃</i> ; none at <i>M₁</i> , <i>M₅</i>
Ziprasidone	+	+	+++	None

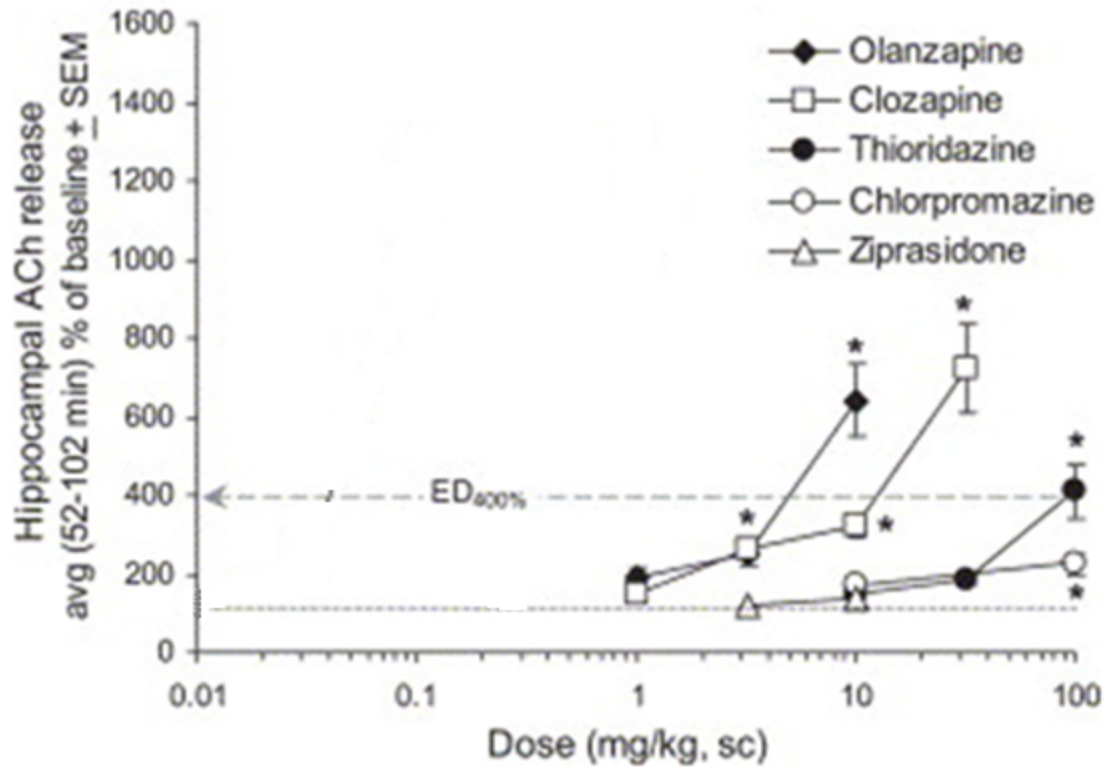
* These data are summarized from a profile of functional activity at human monoaminergic G-protein couple receptors by 462 clinical drugs. All antipsychotics shared the properties of *D₁* and *D₂* antagonism and *5-HT_{2A}* antagonism/inverse agonism; however, action at muscarinic receptors is variable.

+ = 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!

Verhoogde afgifte acetylcholine in hippocampus



Cholinerge Medicatie strategie in SCZ

- Cholinesterase remmers (AChEIs)
- Nicotine receptor agonist/modulator
- Muscarine receptor agonist/modulator

Probleem:

-(perifere) bijwerkingen

-gebrek aan selectiviteit

AChEIs

- galantamine
- rivastigmine
- donepezil

Zorgen voor langere beschikbaarheid
ACh in synaps

Geregistreerd voor AD

TABLE 1 Effects of nicotine on neurocognition among individuals with schizophrenia

Study	Significant findings	Associated neurocognitive tests
George ¹²	(+) effects on VSWM in SZ; (-) effects on VSWM in controls	VSWM, SCWT
Harris ¹⁴	(ND) IM, DM, visuospatial attention, language in SZ smokers; (+) visuospatial attention in SZ non-smokers	RBANS
Sacco ⁷	(+) VSWM, sustained attention in SZ smokers; (+) sustained attention in controls	VSWM, CPT
Zabala ¹³	(+) 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

nicotinic receptor agonist

- $\alpha 7$ nicotine receptor agonist

(SSR-180711, PNU-282987, GTS-21, DMXB-A, TC5619, EVP-6124)

- presynaptisch

- Reguleert Glutamaat & DA release

- CHRNA7 gen – chromosoom 15q13-14

- clinical trials tot 12 weken kunnen negatieve en cognitieve symptomen verbeteren

- $\alpha 4\beta 2$ nicotine receptor agonist

- varenicline

- reguleert DA release van nucleus accumbens (reward systeem),

- hoogste affiniteit voor nicotine

$\alpha 7$ agonist

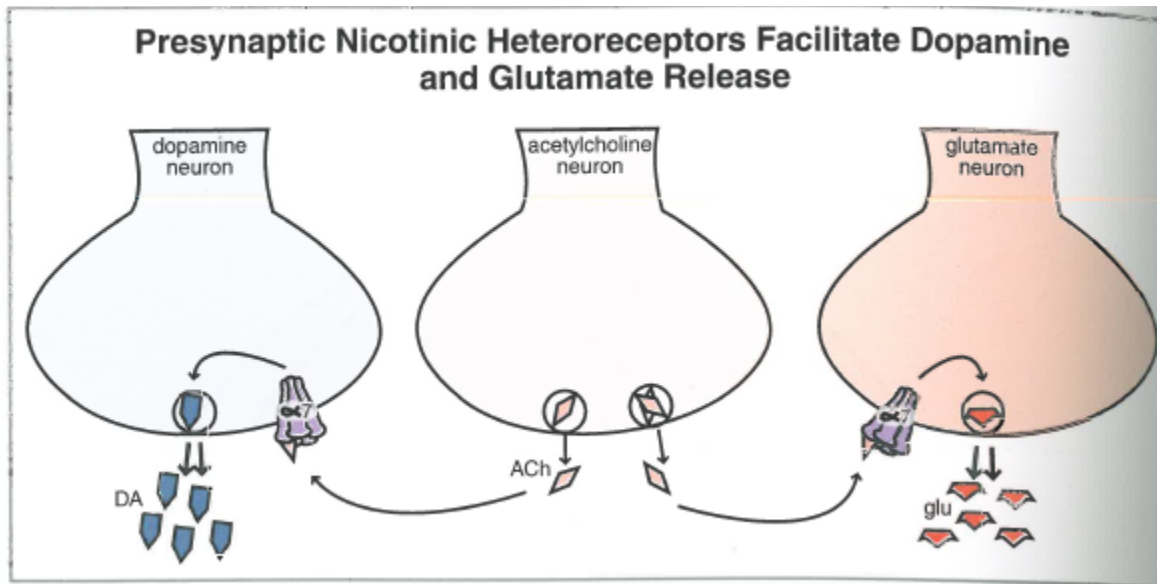


Table 2 Summarized evidence for a role of muscarinic receptors in the treatment of schizophrenia

	Domain of study	Key points
Preclinical	Neuroanatomical	Muscarinic receptors are co-localized on dopamine-containing neurons
	Neurocircuitry	Reciprocal modulatory effects of muscarinic and dopaminergic receptor activation
	Pharmacological	Muscarinic agonists produce an atypical antipsychotic-like profile in animal neurochemical, electrophysiological, and behavioral models.
	Genetics	Muscarinic M ₁ and M ₄ receptor knockout mice exhibit enhanced sensitivity to dopaminergic agonists. Antipsychotic-like effects of the muscarinic agonist xanomeline are attenuated in M ₄ knockout mice
Clinical	Genetics	Polymorphisms in the CHRM1 gene were associated with cognitive performance in schizophrenia patients; polymorphisms in CHRM4 were associated with increased schizophrenia incidence
	Post-mortem	Generally consistent findings of reduced M ₁ binding in cortex and reduced M ₄ receptor expression in hippocampus of schizophrenia patients
	Functional neuroimaging	Decreased muscarinic receptor availability in cortex and basal ganglia of schizophrenia patients
	Proof-of-concept pharmacotherapeutic treatment	The M ₁ /M ₄ -preferring muscarinic agonist xanomeline improved positive and negative symptoms, and measures of cognitive deficits, in a small double-blinded schizophrenia study

Muscarinic agonists

-M1 (xanomeline)

-M4 LY2033298

-NMDC – actieve metaboliet van clozapine
M1 agonist



Antipsychotic Drug-Like Effects of the Selective M₄ Muscarinic Acetylcholine Receptor Positive Allosteric Modulator VU0152100

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