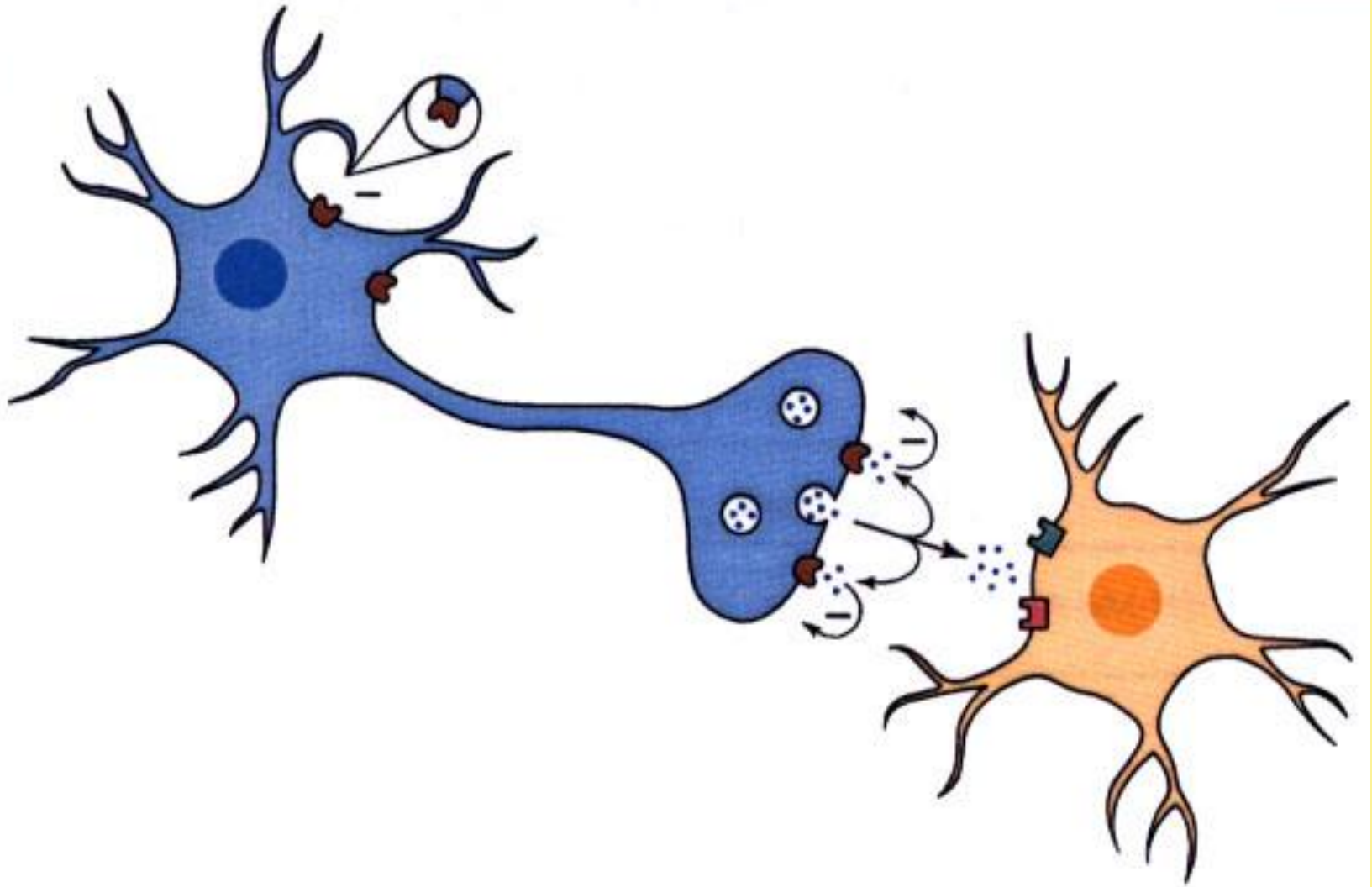


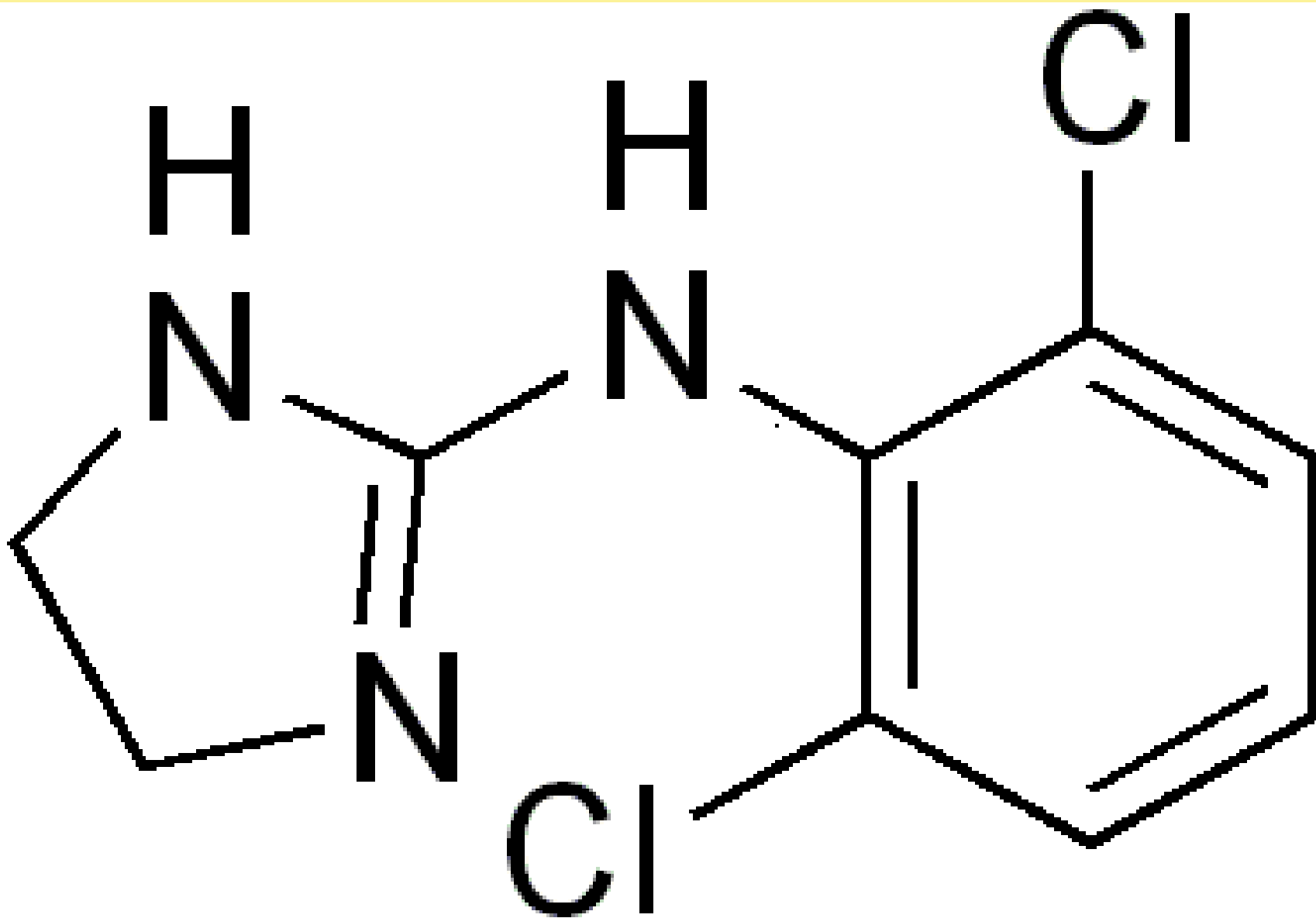
**Possible therapeutic use of
release-modifying drugs acting on
autoreceptors and neuronal
transporters**

Copenhagen , July 18th , 2010

S.Z.Langer , Tel Aviv

Somatodendritic and Terminal Autoreceptors



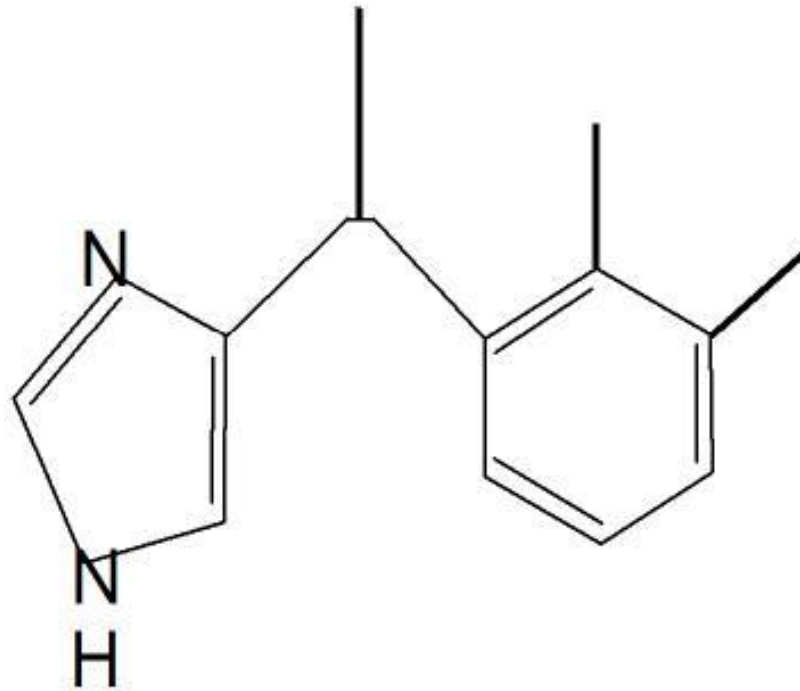


Clonidine

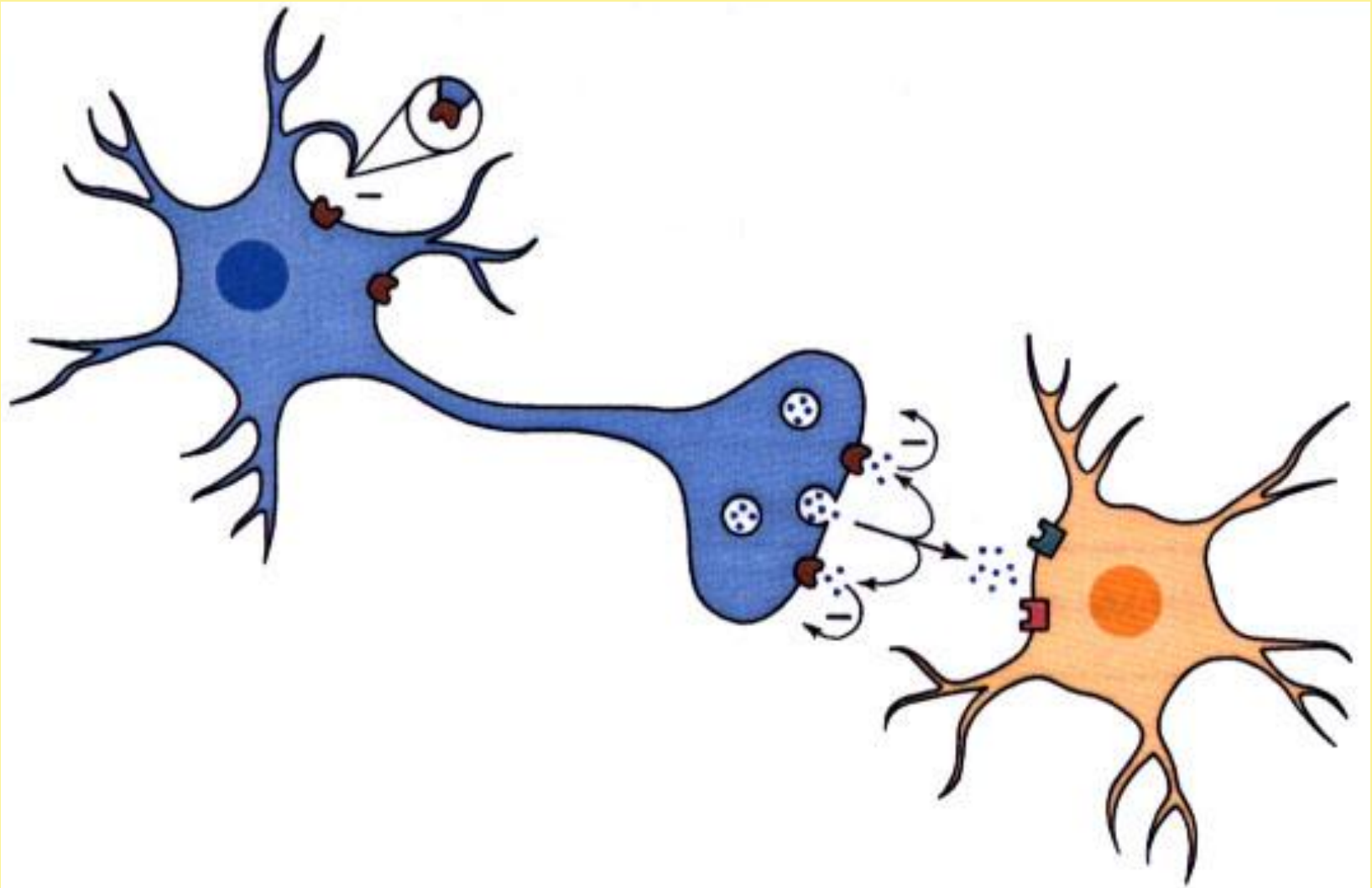
Clonidine is agonist at Alpha-2 adrenoceptors

- Alpha adrenoceptors were subclassified into Alpha-1 and Alpha-2 subtypes in 1974
- Clonidine was discovered by serendipity in 1966 (Kobinger).

DEXMEDETOMIDINE
Aproved by FDA 1999
Alpha - 2 adrenoceptor
agonist

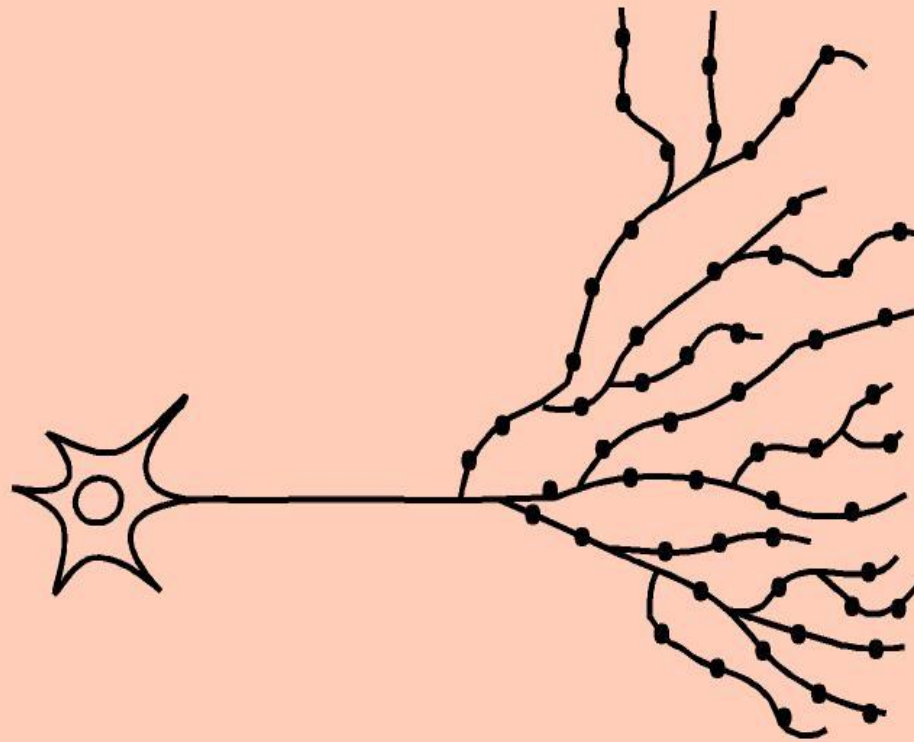


Somatodendritic and Terminal Autoreceptors



- **Only a small proportion of nerve endings are intrasynaptic.**

- * **Neurons have a very large axonal arborization and very few nerve endings make synaptic contact.**

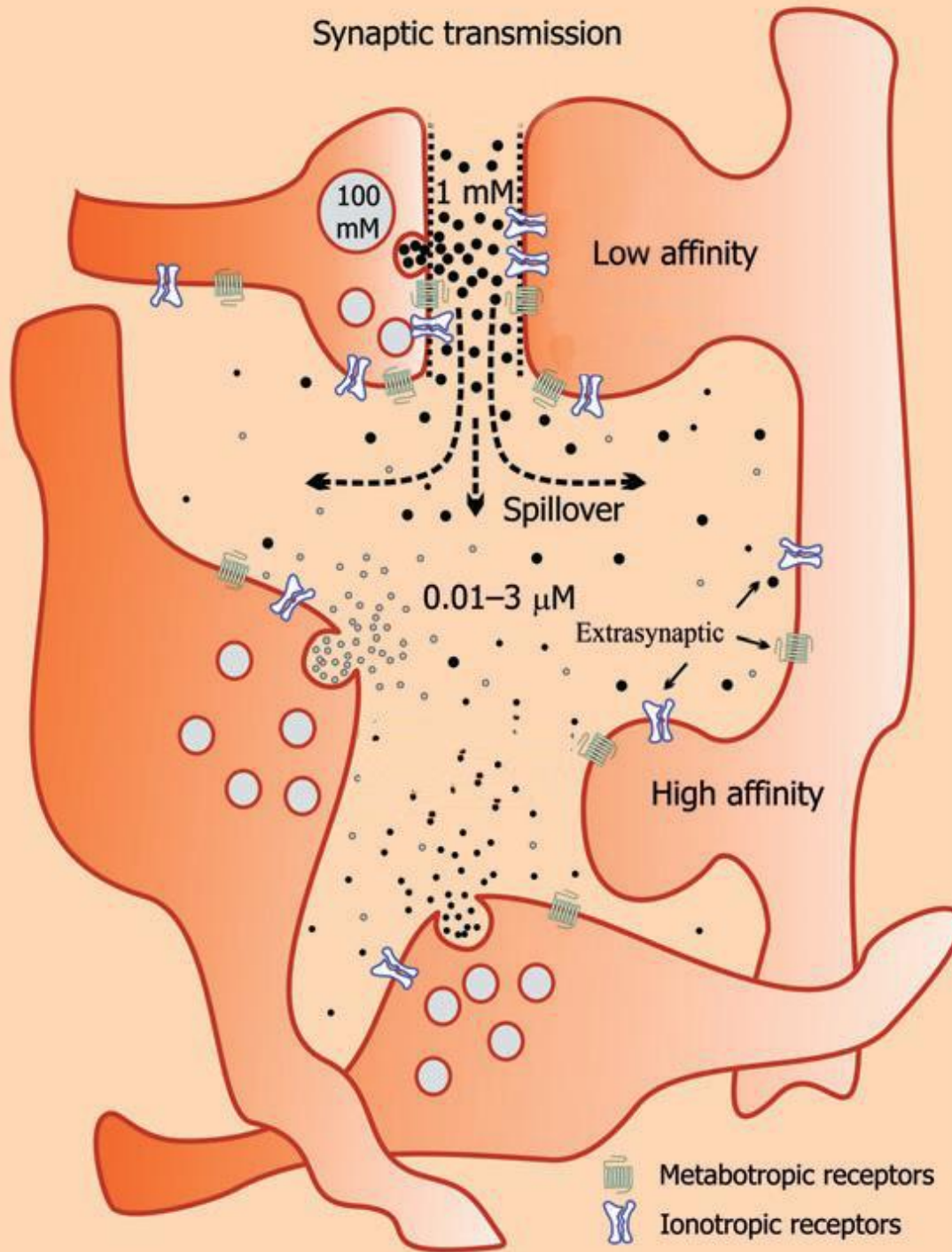


	N of boutons/cell	Non-synaptic boutons(%)
ACh	840 000	93
NA	170 000	85
5-HT	150 000	79

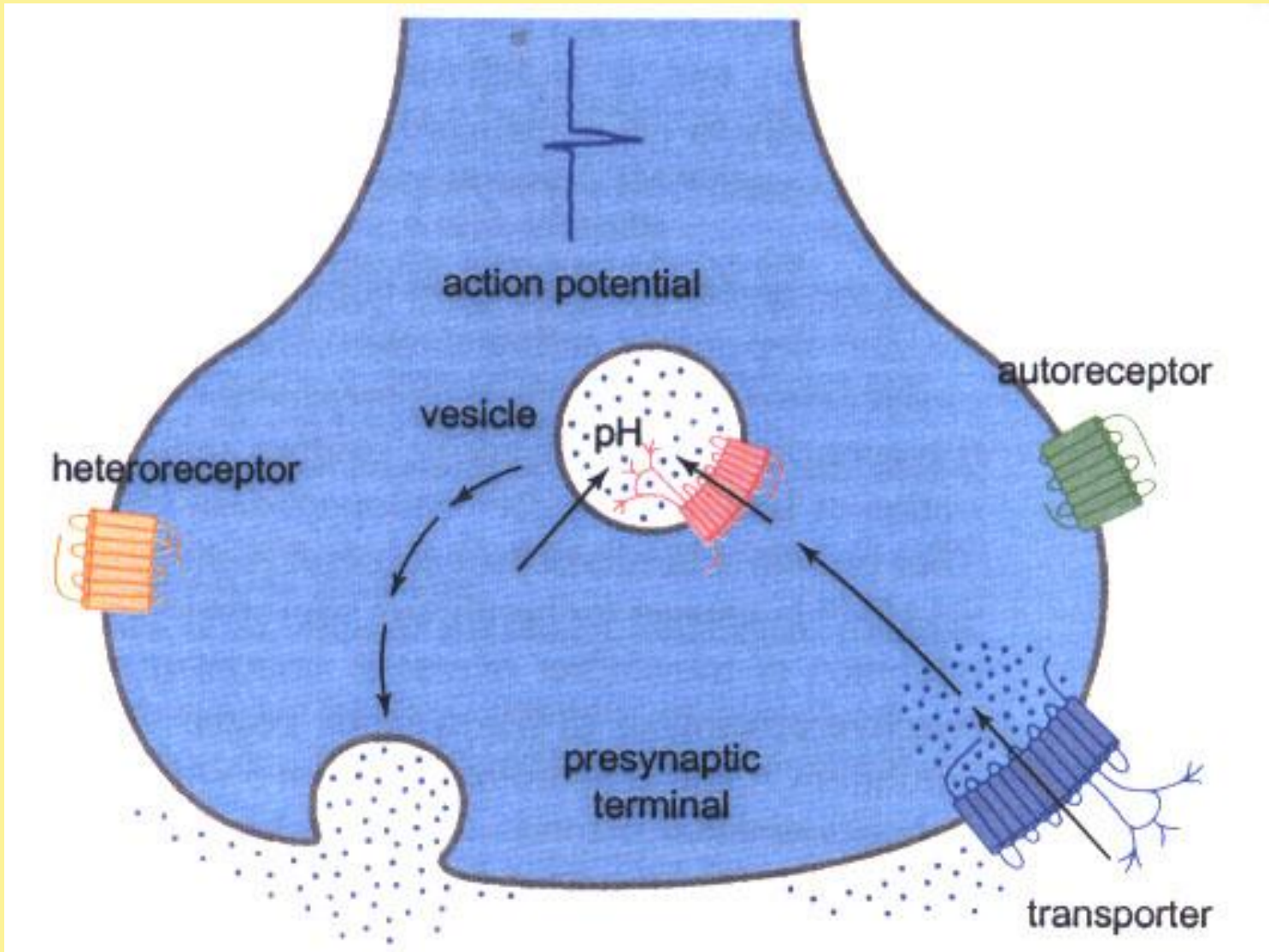
*** Inside the synapse Released transmitters reach mM concentrations.**

*** In the perisynaptic region released transmitters reach the low micromolar range.**

Synaptic transmission

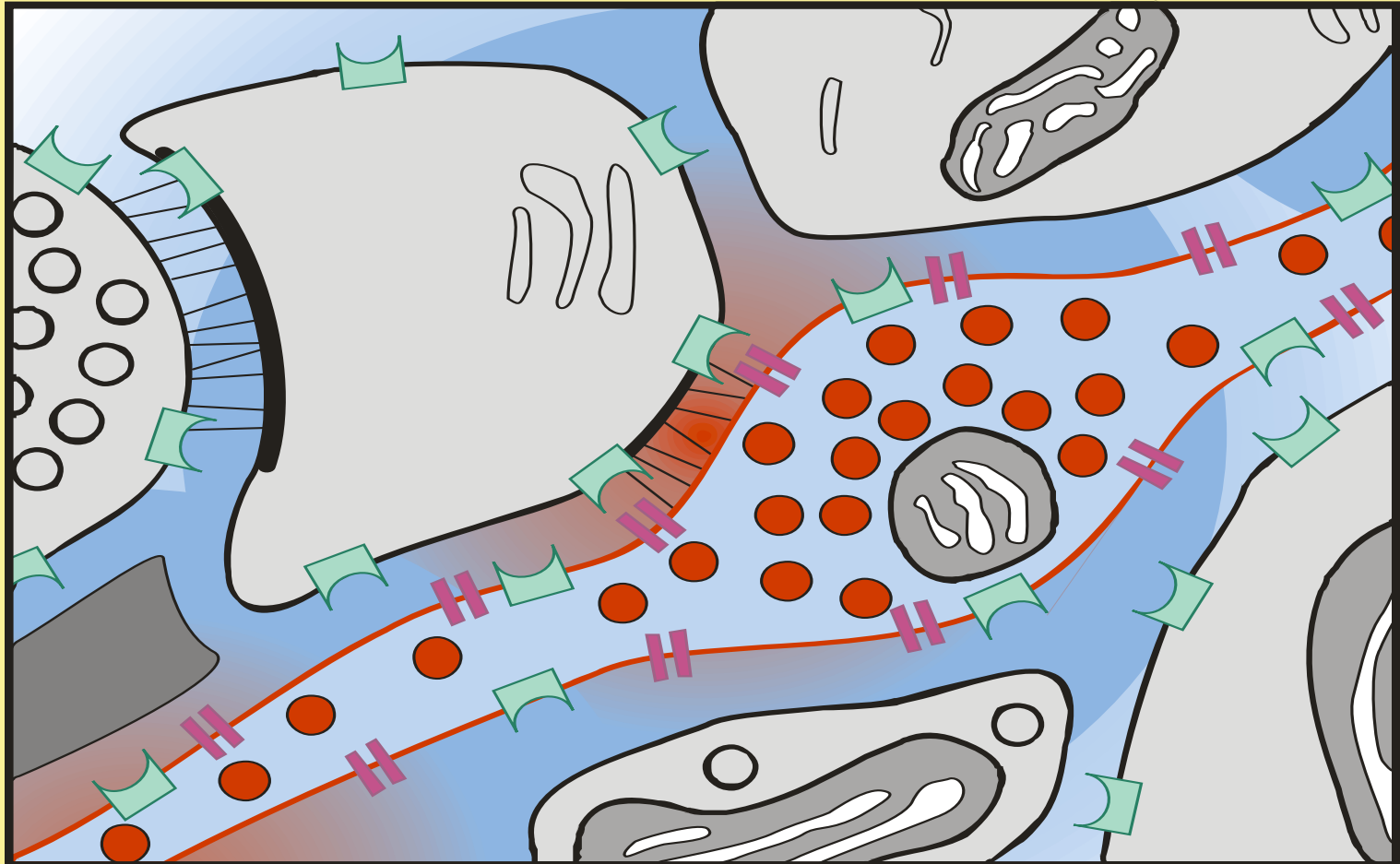


Terminal Presynaptic Receptors



DA Axon Terminals in the Striatal Complex

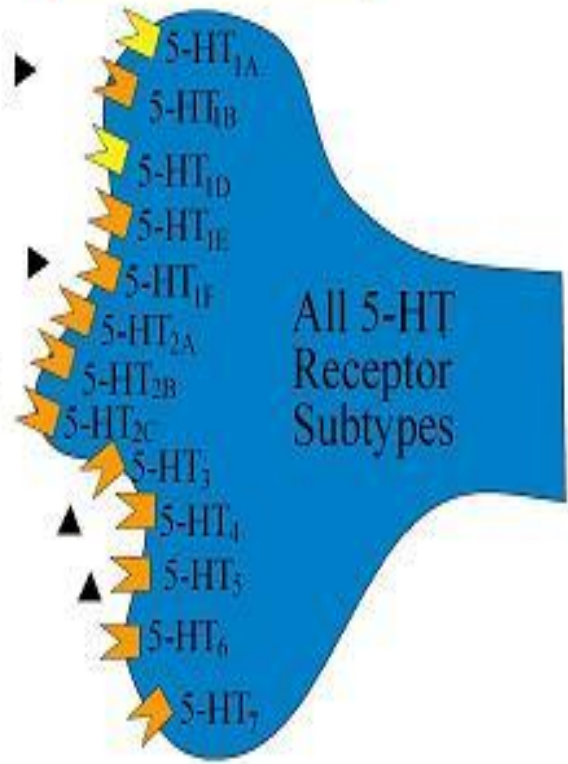
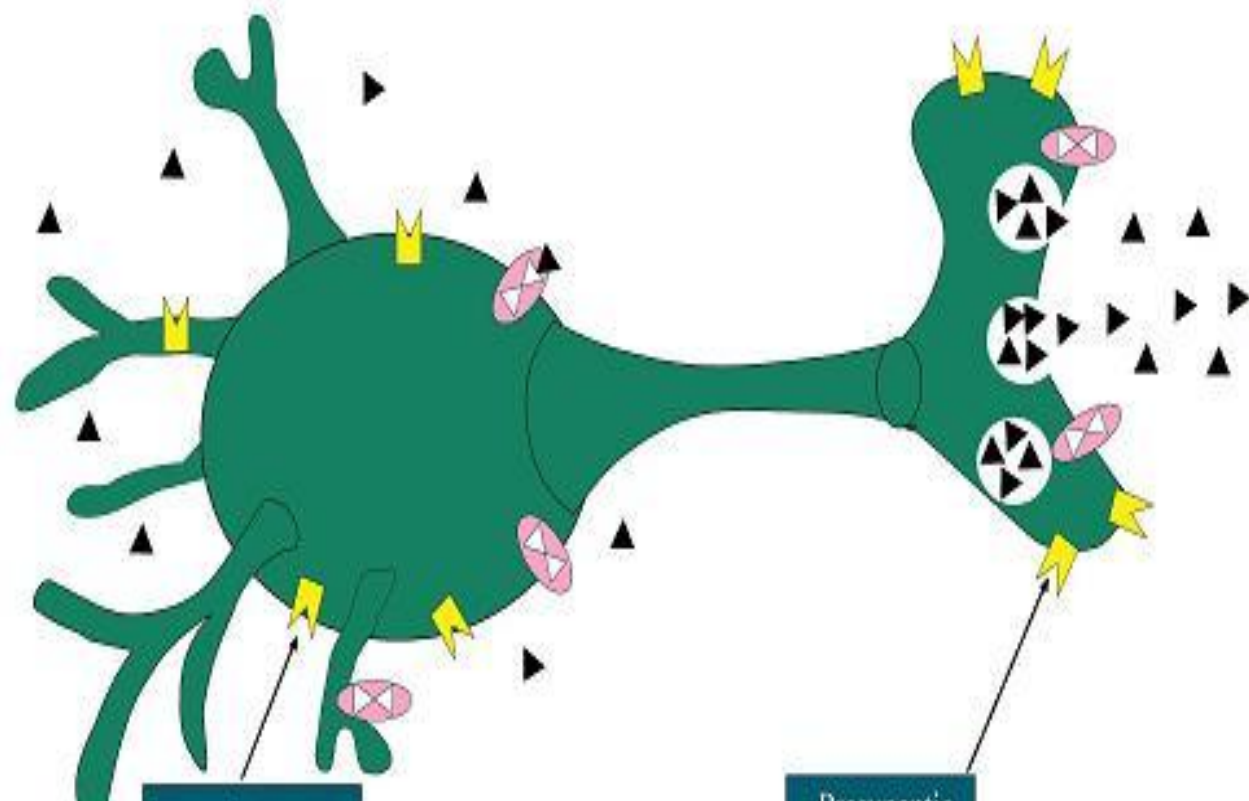
(Sesack, 2002)



MOST POSTSYNAPTIC RECEPTOR SUBTYPES ARE NOT PRESENT ON PRESYNAPTIC TERMINALS

5-HT Neuron

Postsynaptic Sites



All 5-HT Receptor Subtypes

Somatodendritic Autoreceptors
5-HT_{1A}
(inhibitory to firing rate)

Presynaptic Autoreceptors
5-HT_{1D}
(inhibitory to release)

-  5-HT Transporter
-  5-HT
-  5-HT Receptors

Presynaptic Autoreceptors

Transmitter	Inhibitory
NA	Alpha-2A
DA	D-2 / D-3
Ach	M-2 / M-4
5-HT	5-HT 1D
Histamine	H-3
GABA	<i>GABA-B</i>
Glutamate	<i>mGlu R5</i>
ATP	P2Y

***Presynaptic Heteroreceptors Modulate
Transmitter Release But Are
Sensitive to Endogenous Mediators
Different from the Neuron's Own
Transmitter***

Presynaptic Heteroreceptors

Transmitter	Inhibitory
NA	Opiate, H-3, M-2 D-2, CB-1, Adenosine
DA	M-2
Ach	Alpha-2, D-2
5-HT	Alpha-2, H-3
Glutamate	CB-1, ALPHA-2, GABA B

Pharmacological Intervention At the Level of Presynaptic Inhibitory Autoreceptors:

1) Agonists: Decreased Release

2) Partial Agonists

3) Antagonists: Increased Release

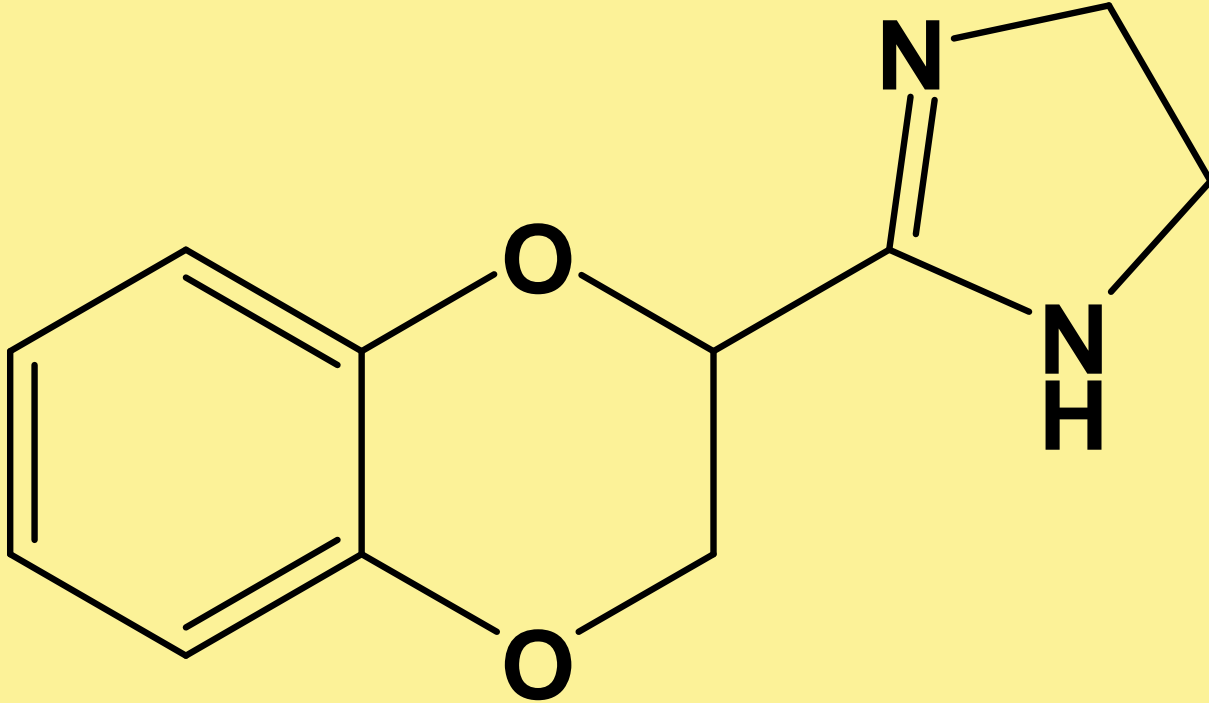
DEPRESSION

Treatment of Depression

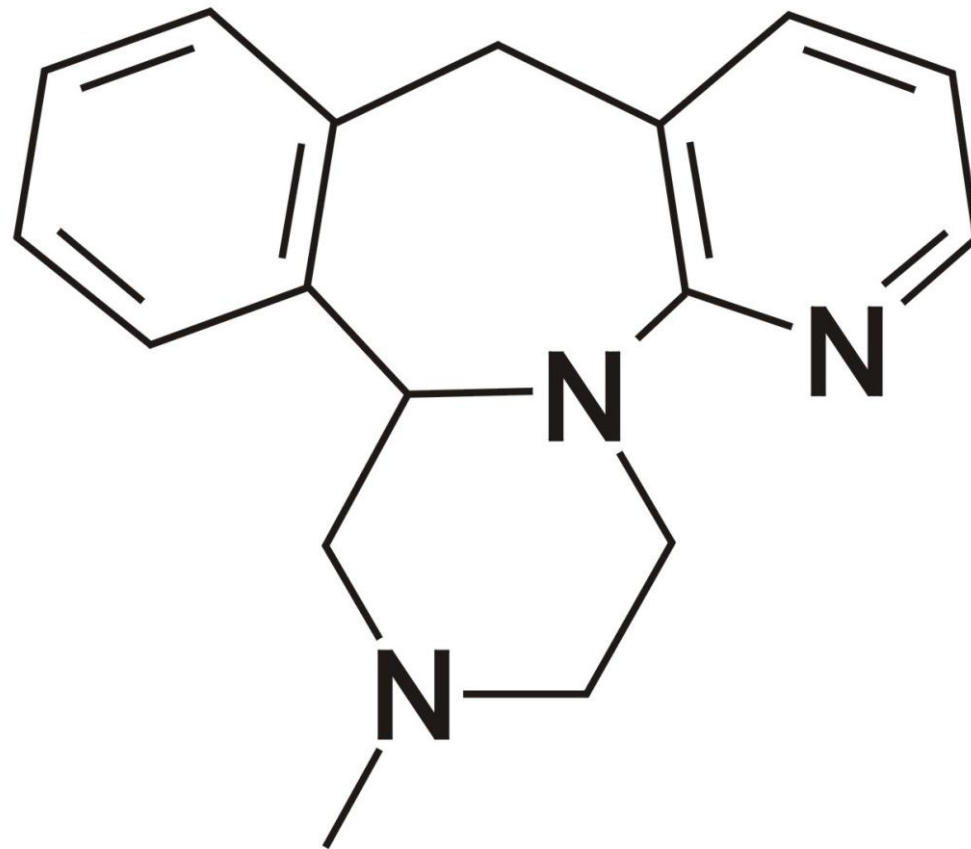
- Clinical improvement requires 3 to 4 weeks of treatment.
Side effects appear from the first day.
- Drug-resistant depression in 40% of patients.
- Frequent relapse and recurring episodes require prolonged treatment with antidepressants.

**Is a centrally acting,
selective α_2 -adrenoceptor
antagonist, such as
Idazoxan, a potential
antidepressant drug?**

**Idazoxan is a drug candidate with α_2 -
antagonistic action**



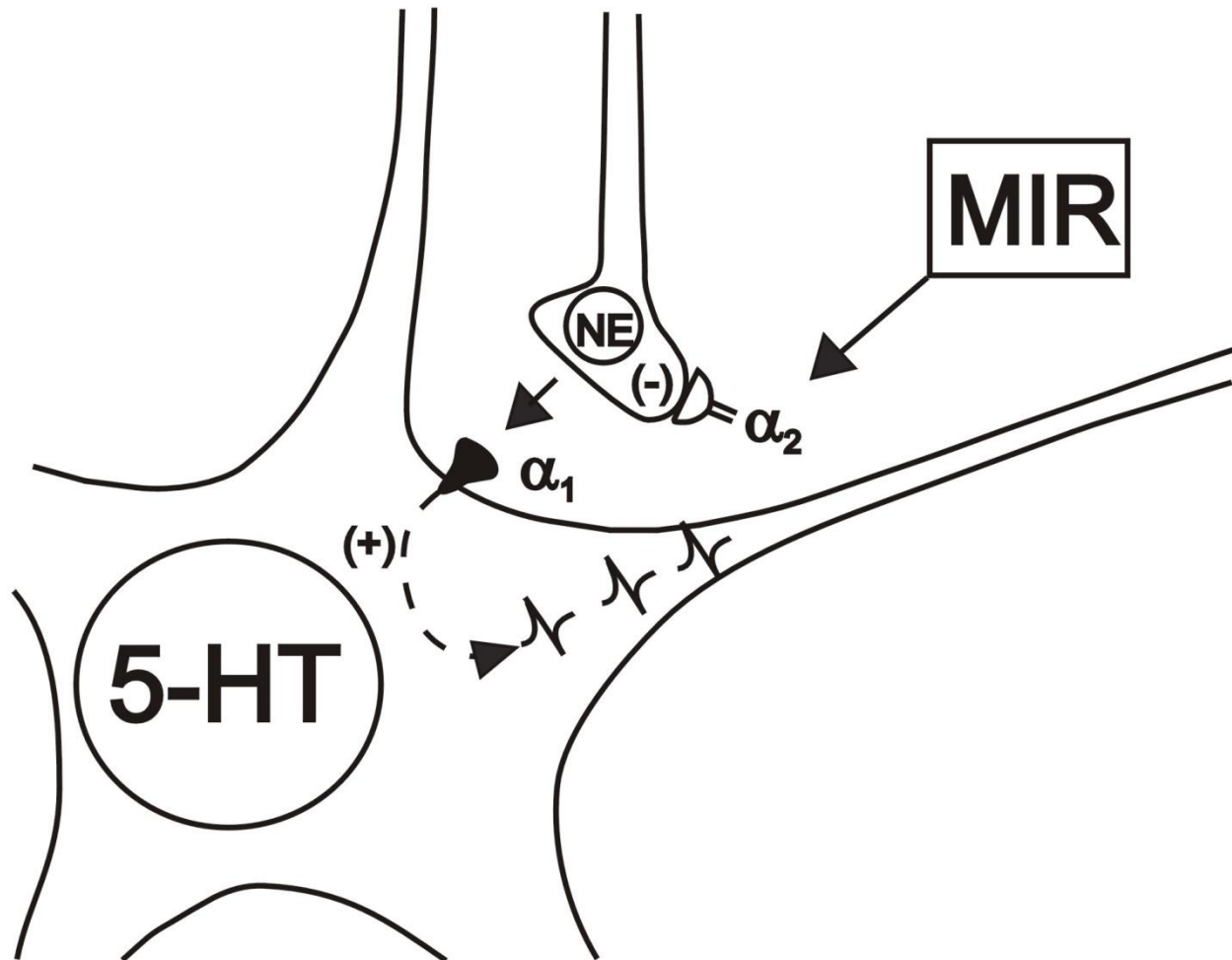
Idazoxan (IDX)

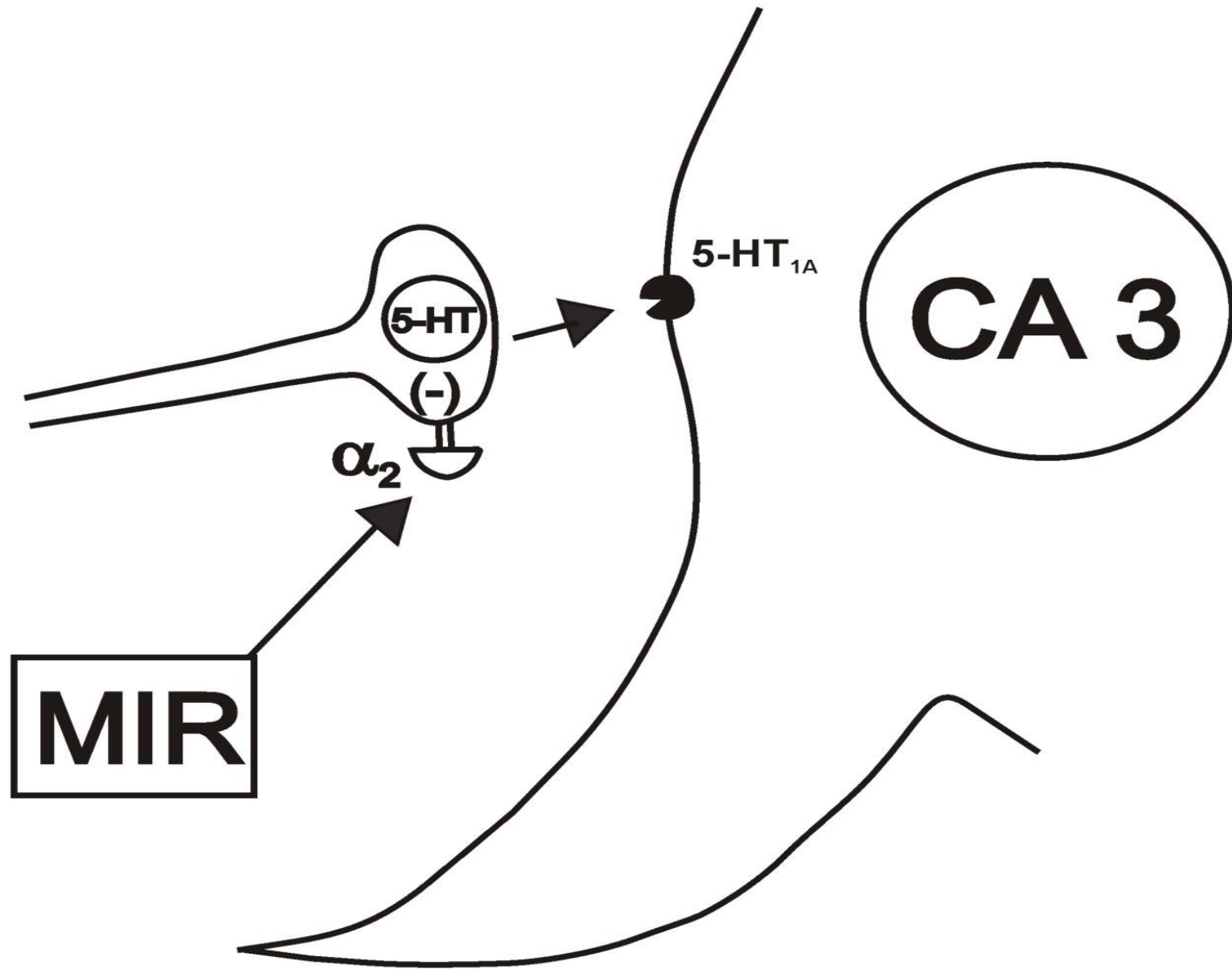


Mirtazepine (MIR)

Comparison of Idazoxan with Mirtazapine

Receptor Subtype	Antagonist Effect Mirtazapine	Antagonist Effect Idazoxan
Alpha-2	pKi 7.0	pA ₂ 8.6
Alpha-1	pKi 6.4	pA ₂ 6.1
H-1	pKi 9.3	pD' ₂ 4.8
Muscarinic	pKi 6.1	pA ₂ 4.8
5-HT-2	pKi 8.1	Inactive
5-HT-3	pKi 8.0	Inactive
Imidazoline 1	Inactive	pKi 5.9
Imidazoline 2	Inactive	pKi 7.2





Aim:

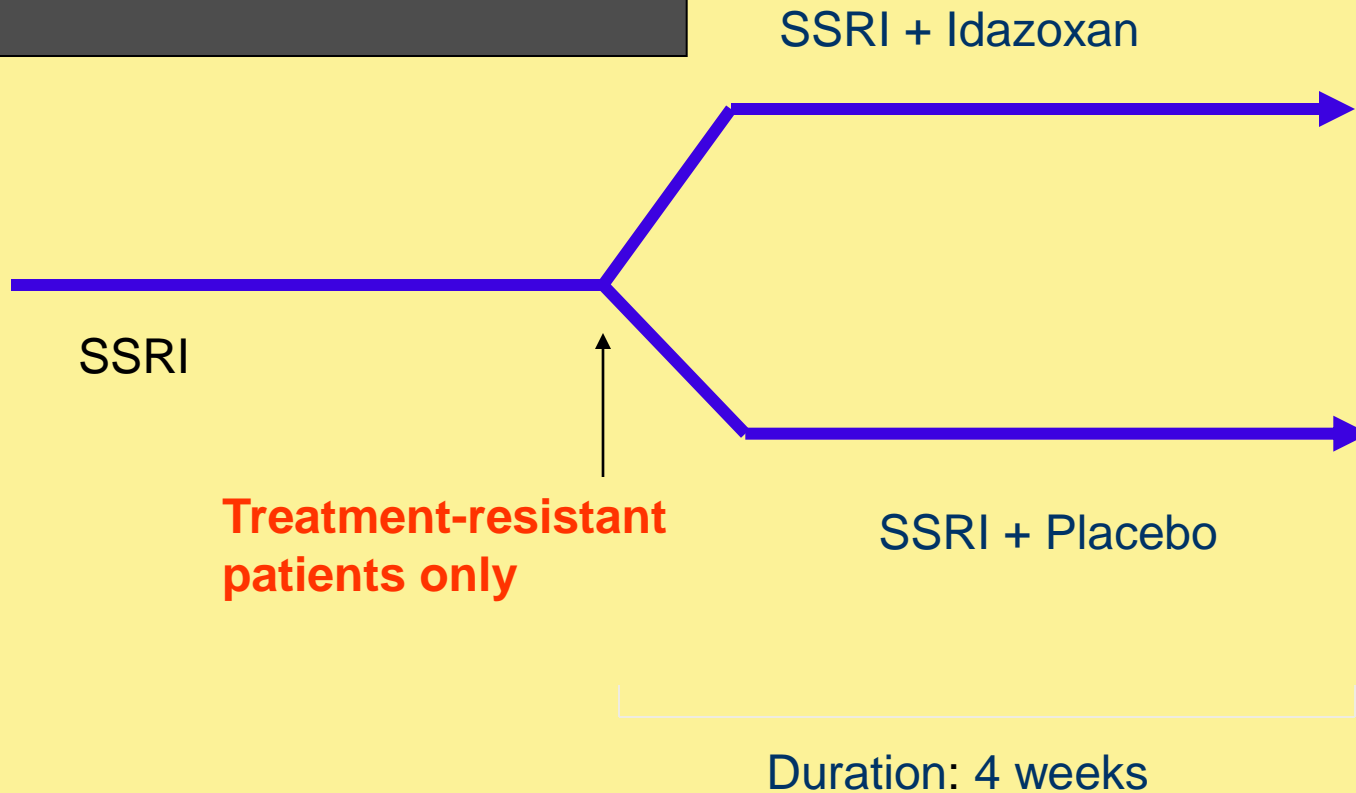
The study is designed to examine if addition of Idazoxan to SSRIs in treatment of resistant depressive patients will have a significantly improved therapeutic effect

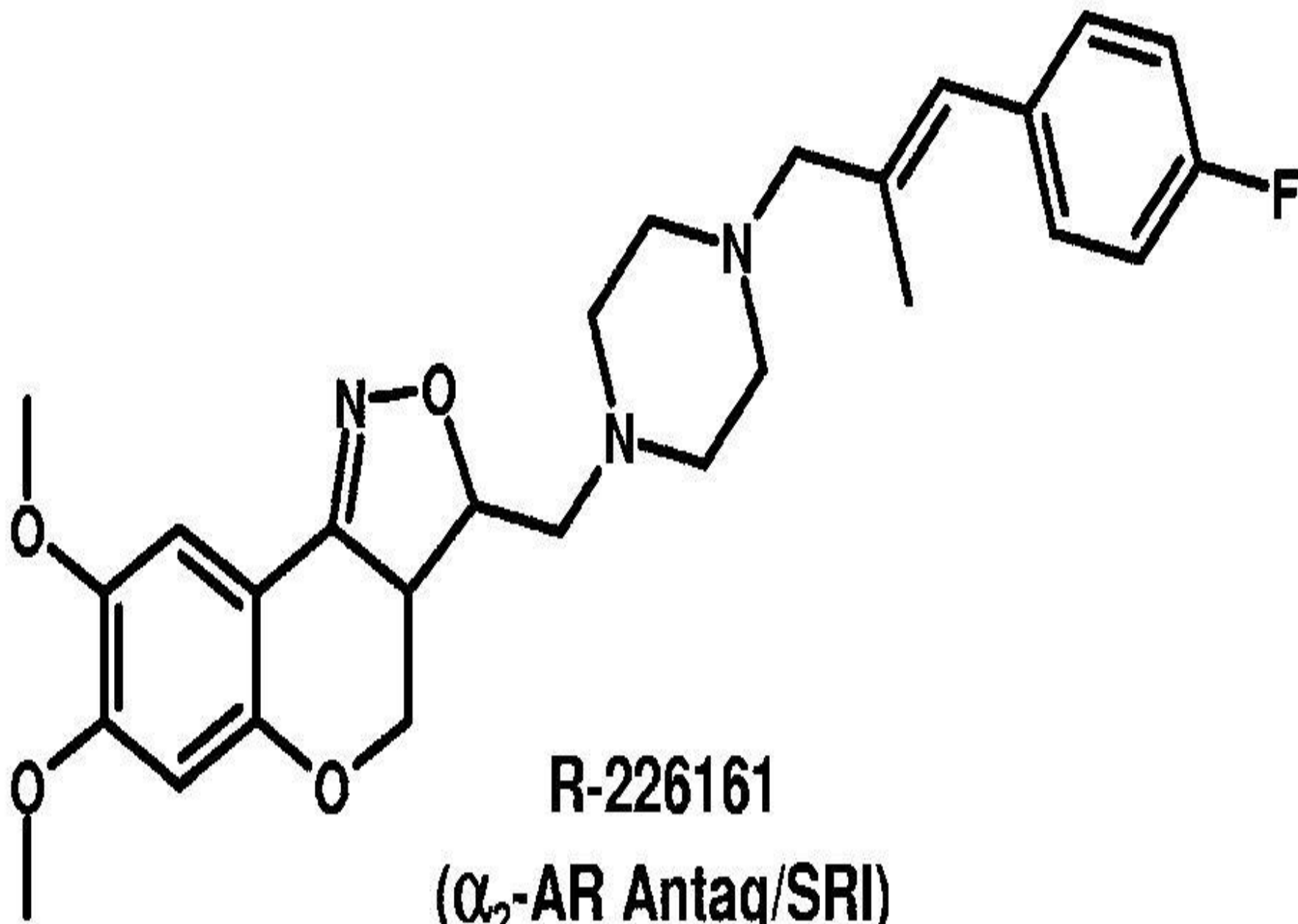
Clinical Trial Protocol

Dosage:

Idazoxan - 40 mg x 3/day

SSRI - 20 mg/day





R-226161

(α_2 -AR Antag/SRI)

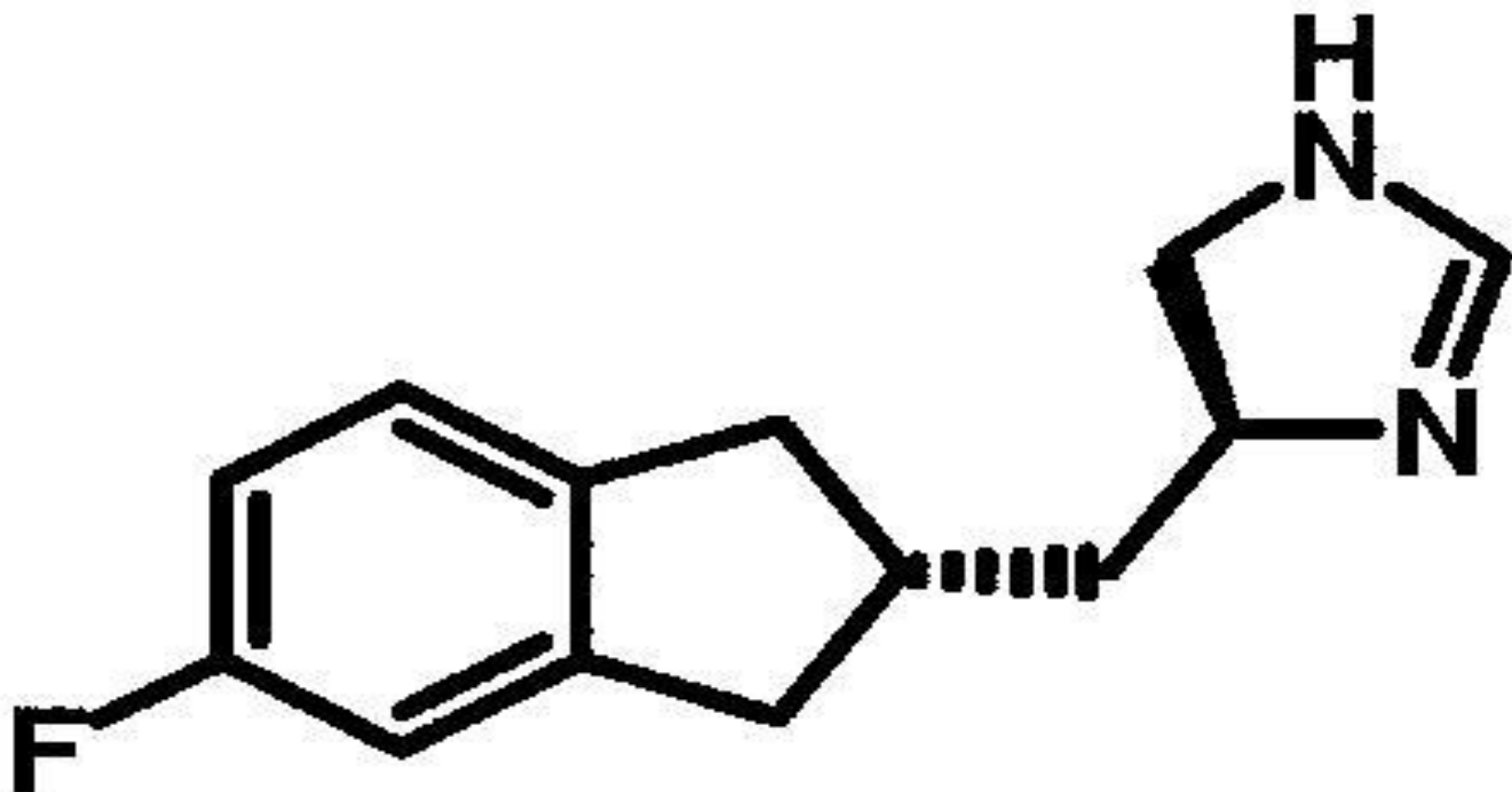
Comparison of Fipamezole with R226161

Receptor Subtype	Antagonist (nM)	
	R226161	Fipamezole
Alpha-2 A	3.1 Ki	9.2 Ki
Alpha-2 B	1.5 Ki	17.0 Ki
Alpha-2 C	0.27 Ki	55.0 Ki
Alpha-1	125.0 Ki	1,000 Ki
5-HT Transporter	1.7 Ki	300 Ki

R226161

Phase one completed

Phase two CV side effects



S 35966

(α_2 -AR Antag/SNRI)

Treatment of Depression

- Clinical improvement requires 3 to 4 weeks of treatment.
Side effects appear from the first day.
- Drug-resistant depression in 40% of patients.
- Frequent relapse and recurring episodes require prolonged treatment with antidepressants.

The Need (I)

- Depression affects 8% of adult population.
- Non responders represent up to 40% of the depressed patients.

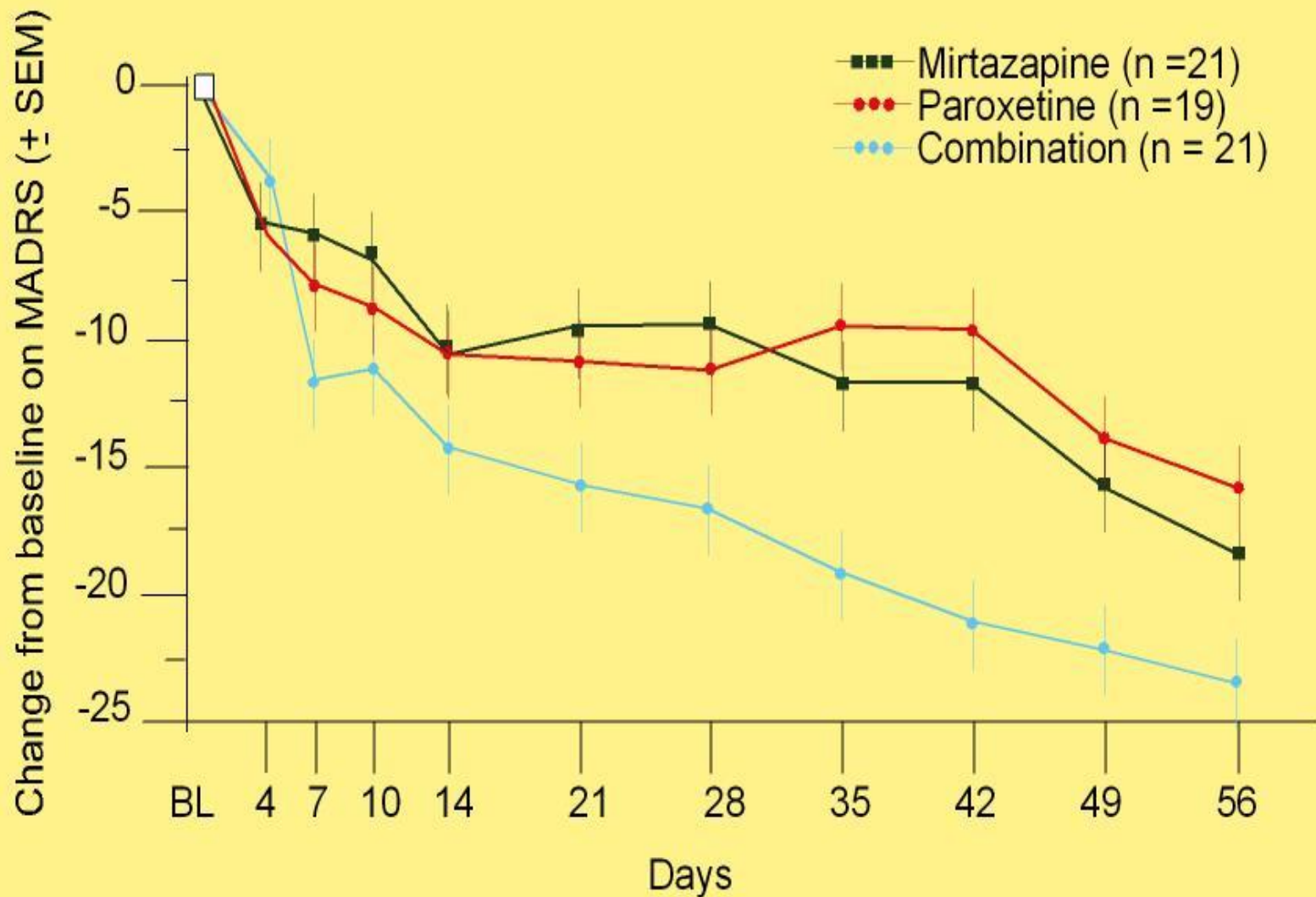
The Need (II)

- Despite the availability of a considerable number of antidepressants, two major unmet medical needs remain without solution:
 - a) The latency period in the onset of action of antidepressant effects.
 - b) Drug resistance or non responders.

The Need (III)

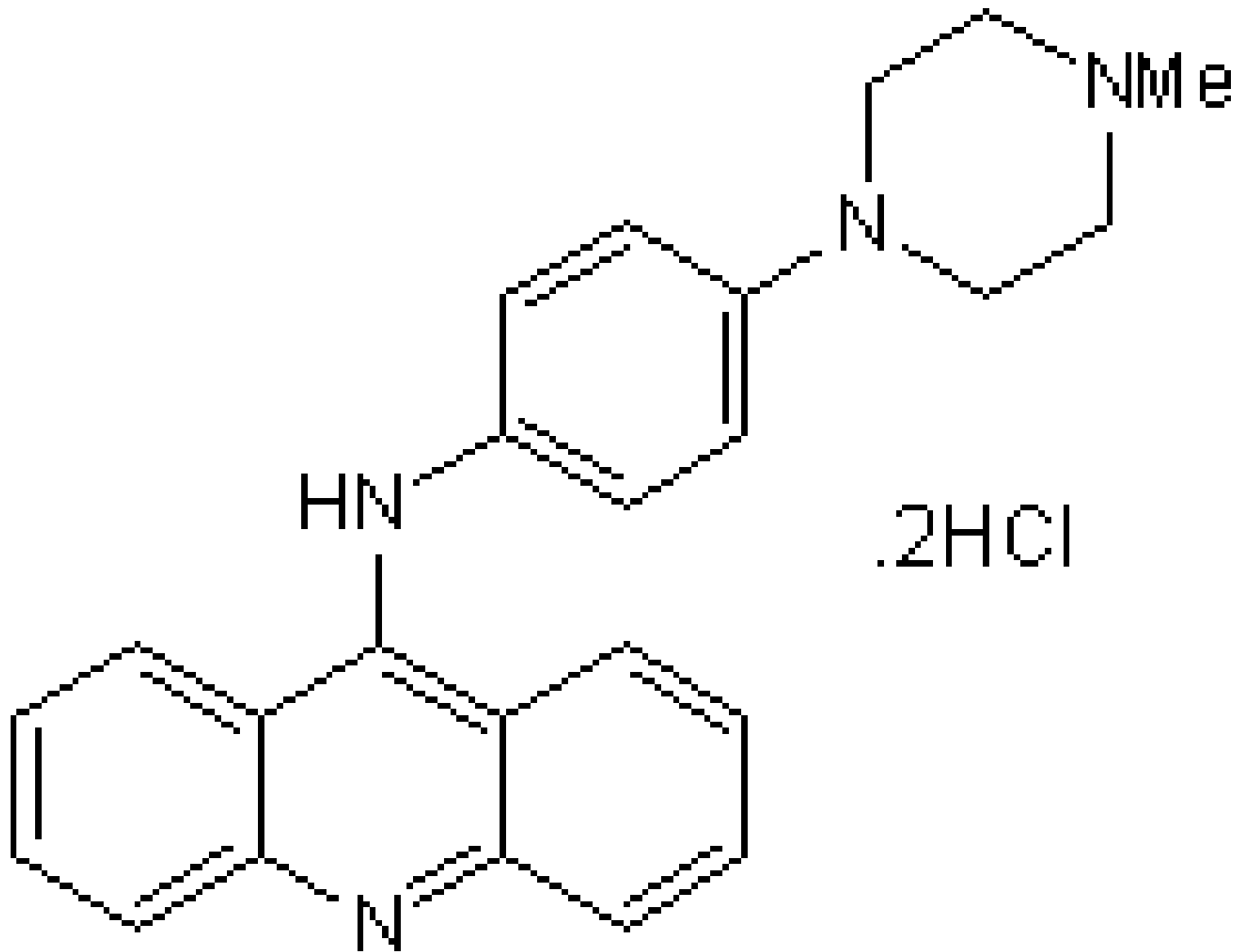
- An early onset of action of antidepressant effects is important since:
 - the first month is a period of enhanced danger for suicide attempts.
 - all side effects of administered antidepressant are present from the first day of treatment.

Analysis of total scores for the Montgomery-Asberg Depression Rating Scale (MADRS: Changes from baseline)



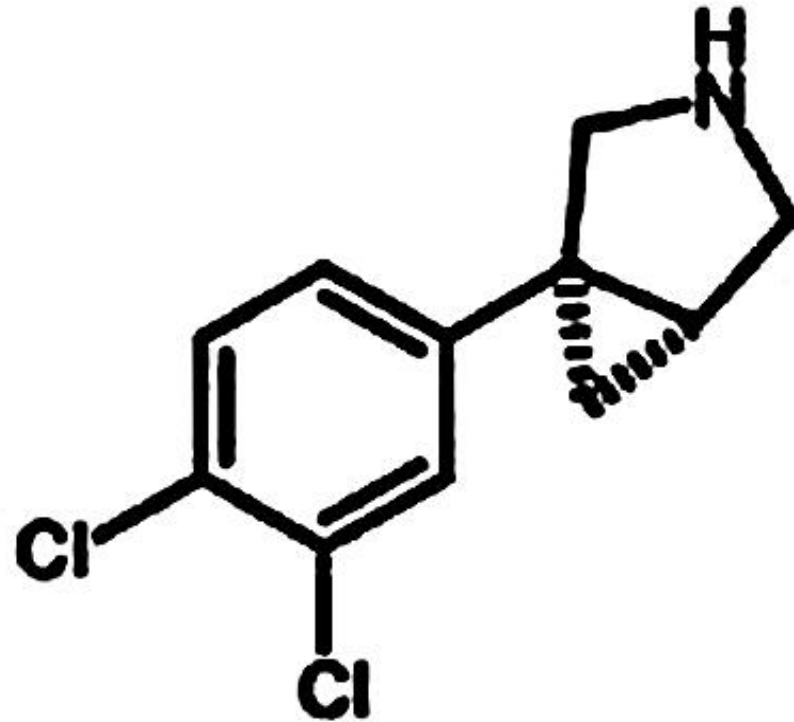
JP1302

**Selective and potent alpha-2C
adrenoceptor antagonist**



JP1302

Triple neuronal uptake inhibitors

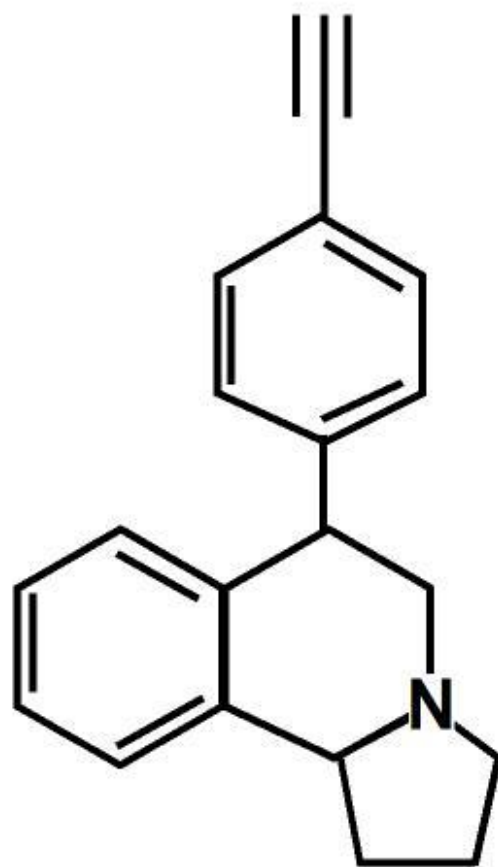


**DOV-21947((+) DOV-216303)
(SNDRI)**

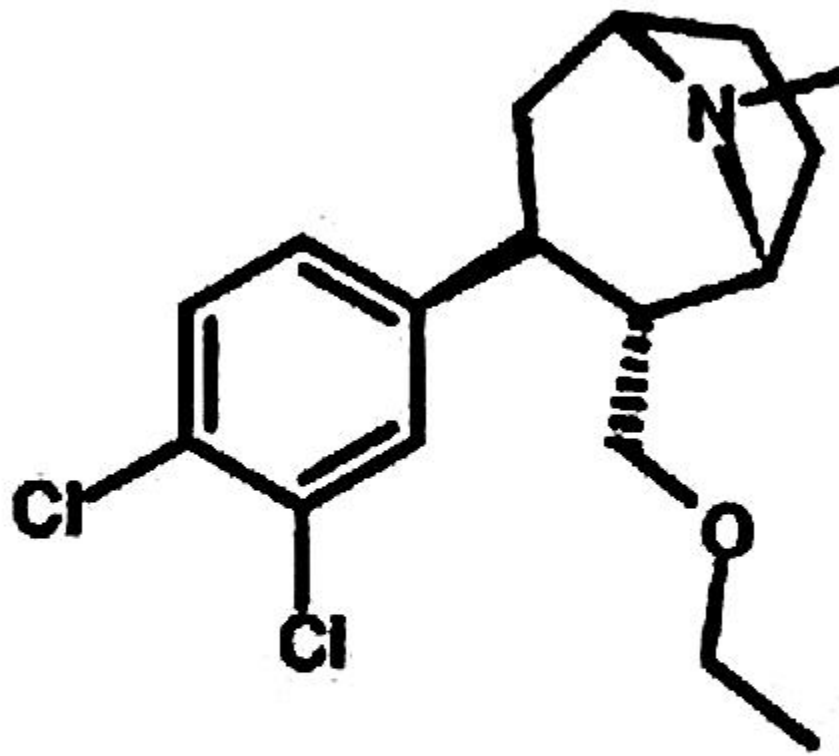
DOV 21947

Phase I completed

**Phase II double blind
versus placebo underway**



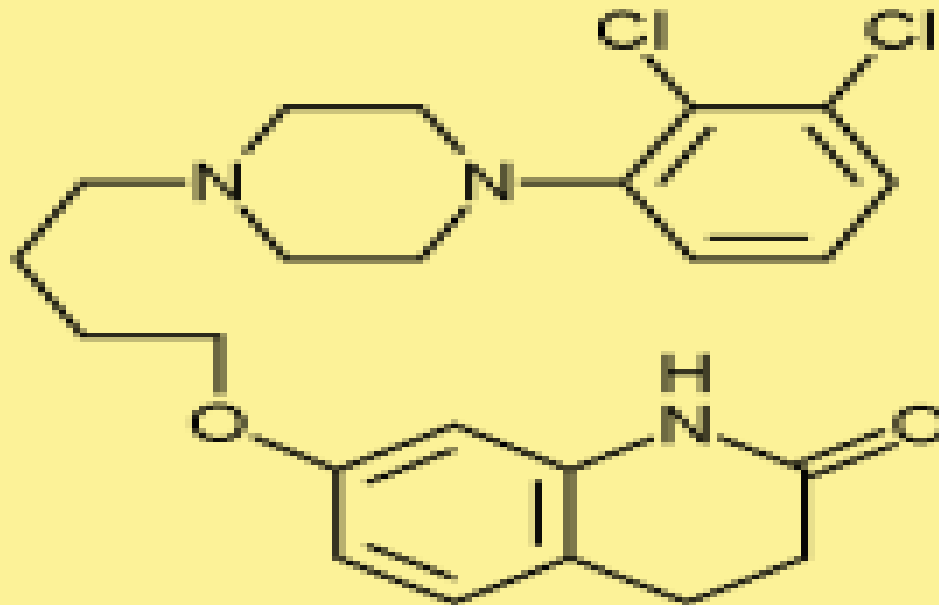
JNJ -7925476
(SNDRI)



TESOFENSINE (NS2330)
(SNDRI)

SCHIZOPHRENIA

ARIPIPRAZOLE



DA autoreceptor agonist in treatment of Schizophrenia

* **ARIPIPRAZOLE** , approved by FDA in November 2002

- Pharmacological Properties:
 - a) DA autoreceptor partial agonist
 - b) Postsynaptic D-2 receptor antagonist
 - c) Partial agonist at 5HT-1A receptors
 - d) Antagonist at 5HT-2A receptors
 - e) No elevation of prolactin levels

DA autoreceptor antagonist in treatment of Schizophrenia

Amisulpride

- * Preferential antagonist of presynaptic D2/D3 receptors.**
- * Antagonist at postsynaptic D2/D3 receptors.**
- * Selectively effective in negative symptoms of schizophrenia.**
- * Significant increases in prolactin levels.**

Idazoxan Augments Effects of Neuroleptics

- Blockade of Presynaptic Alpha-2 receptors with Idazoxan augments antipsychotic activity.
- Alpha-2 antagonists increase prefrontal Cortex DA Output ,which relief negative symptoms in Schizophrenia.
- Cognitive Enhancement.
- Glutamate release enhanced by Blockade of presynaptic Alpha-2 receptors.

**Idazoxan is indicated
in treatment-resistant
schizophrenia**

MIGRAINE

Presynaptic Receptors & Migraine

- **Inhibitory 5HT-1D receptors exist on SP Terminals.**
- **Agonists like SUMATRIPTAN, acting on presynaptic 5HT-1D receptors inhibit SP and CGRP release.**
- **Therapeutic effectiveness of SUMATRIPTAN-like drugs in Migraine is partly associated with this presynaptic effect.**

CONCLUSIONS I

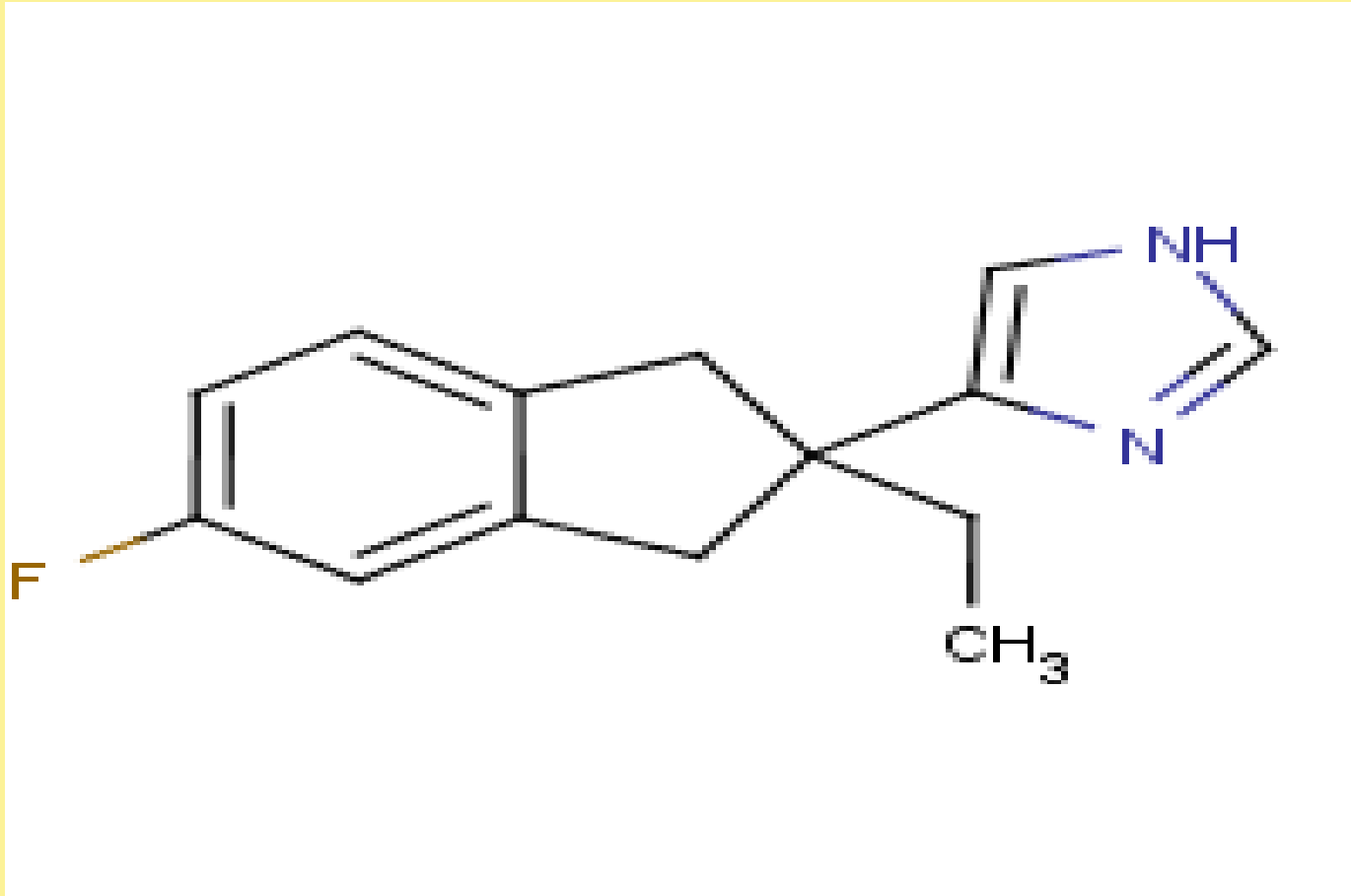
- * Presynaptic autoreceptors regulate the release of several neurotransmitters in the periphery and CNS.**
- * Presynaptic heteroreceptors may facilitate or inhibit the release of a neurotransmitter.**
- * Both presynaptic autoreceptors and heteroreceptors can be the site of action of agonist ,partial agonists or antagonist drugs.**

CONCLUSIONS II

- * Triple re-uptake inhibitors (DA/NA/5HT) represent an additional strategy in drug discovery of new antidepressants**

Presynaptic Receptors were discovered simultaneously (1971-1972) in Argentina, Germany and Sweden.

FIPAMEZOLE



4-[2-etil-5-fluoroindan-2-il]-1H-imidazol