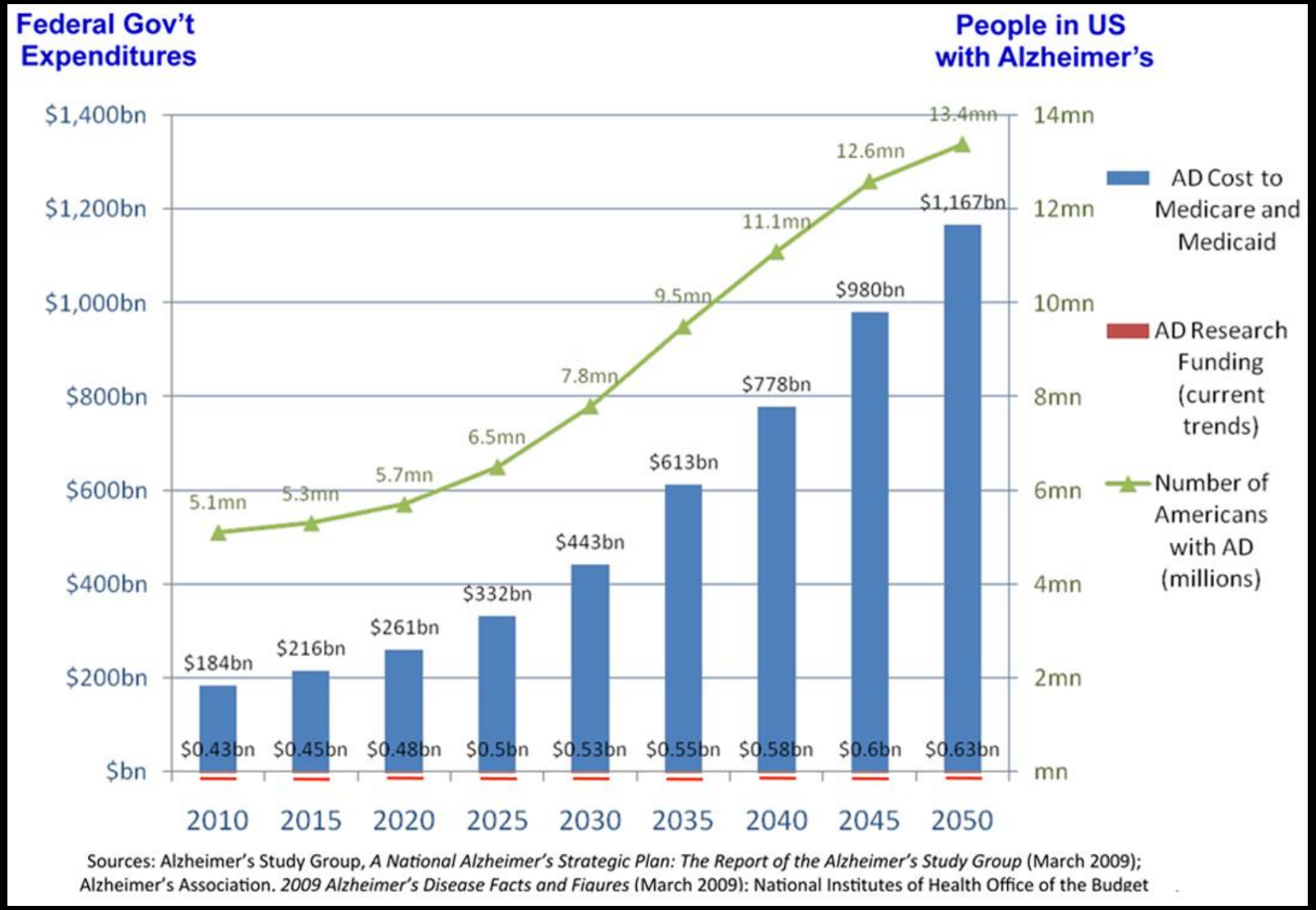
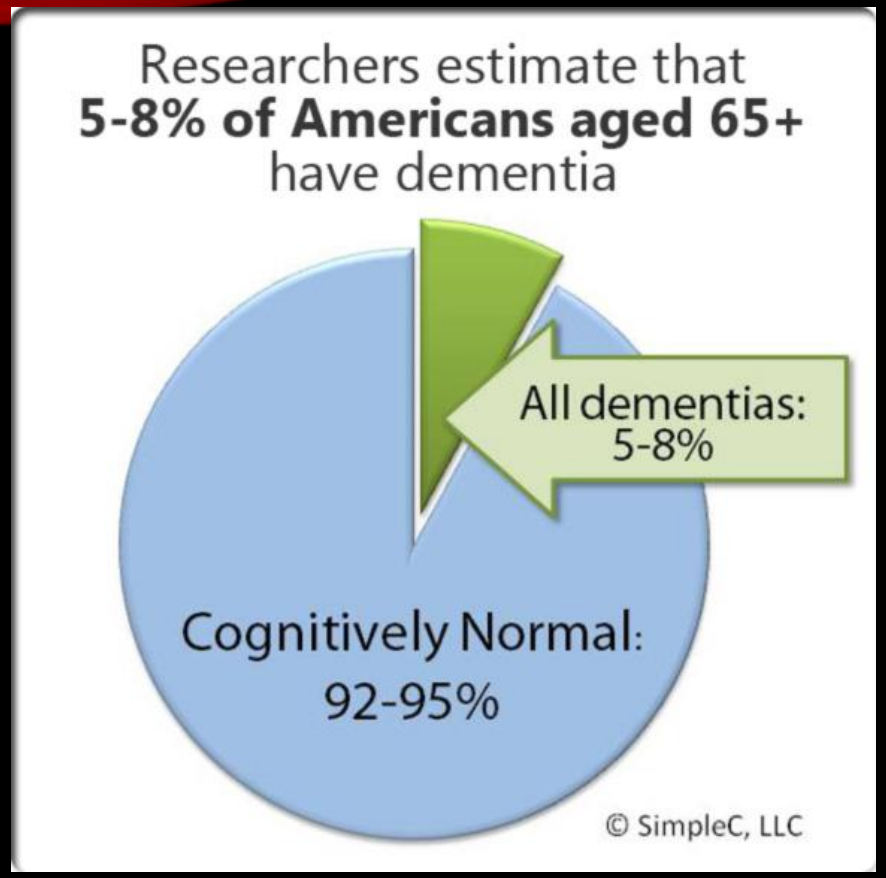
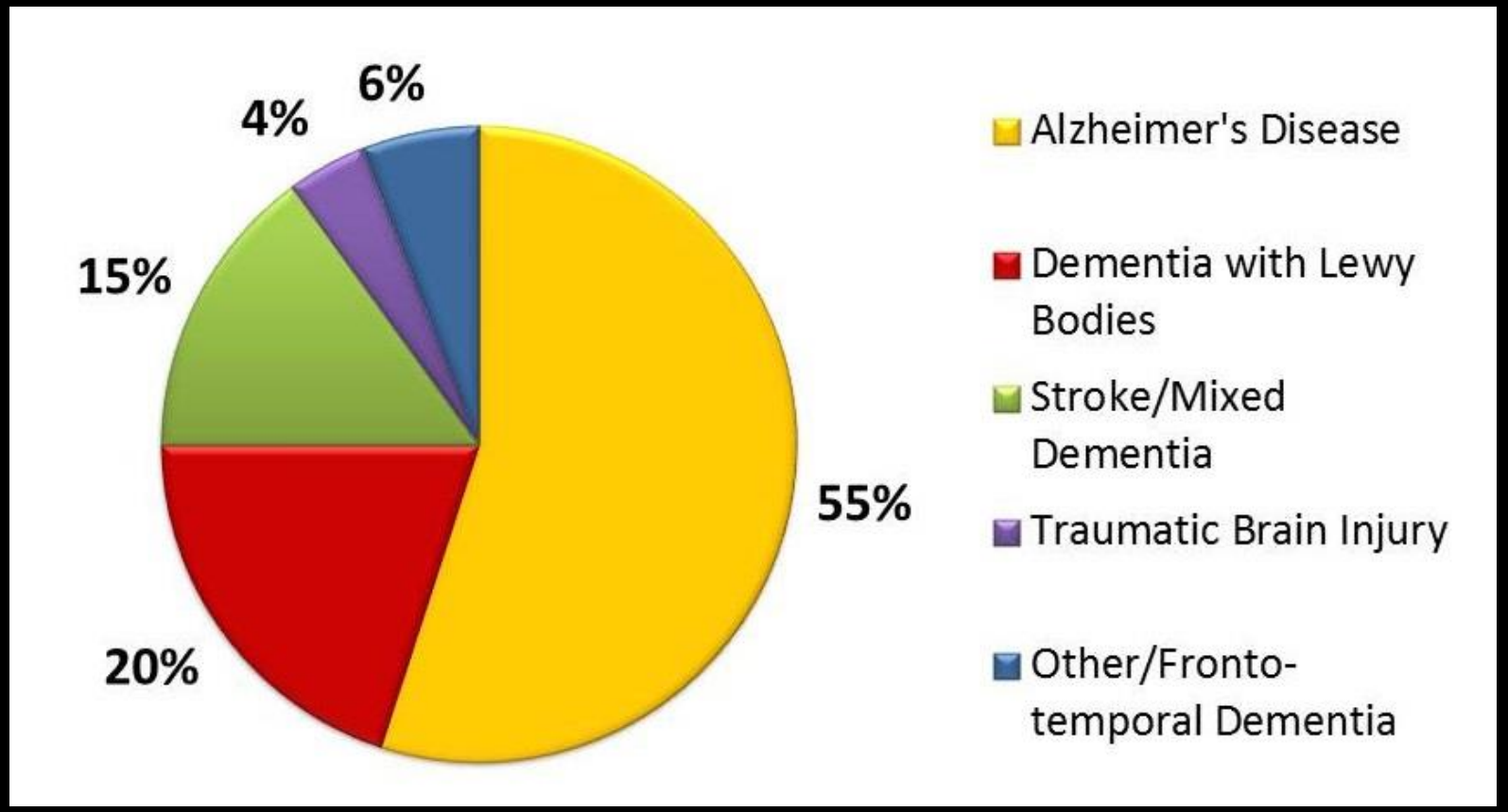
UPDATE ON NEURO/PSYCH MEDICATIONS

Steve Williams, Pharm.D. - clinical pharmacist, clinical professor

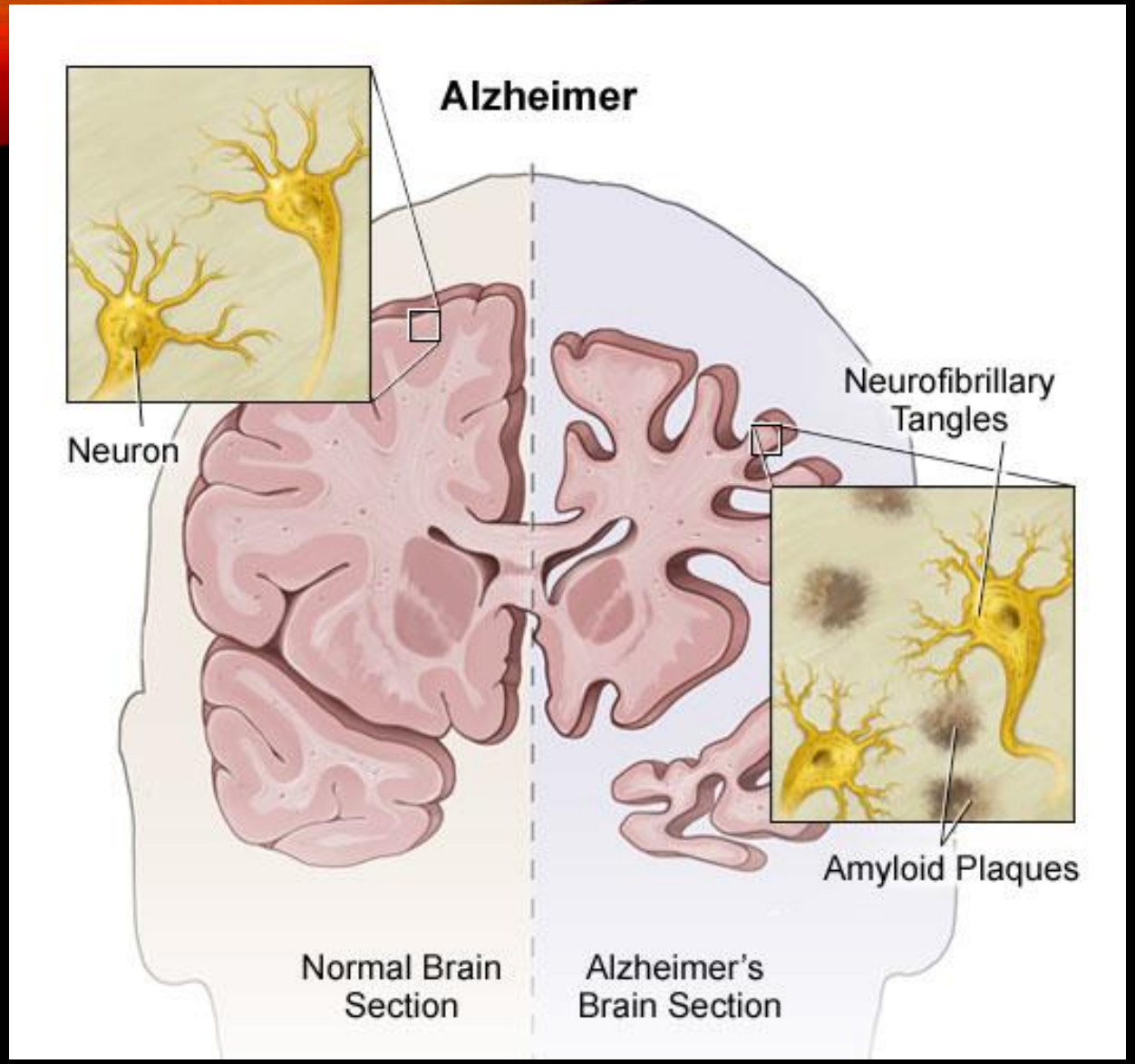
DEMENTIA

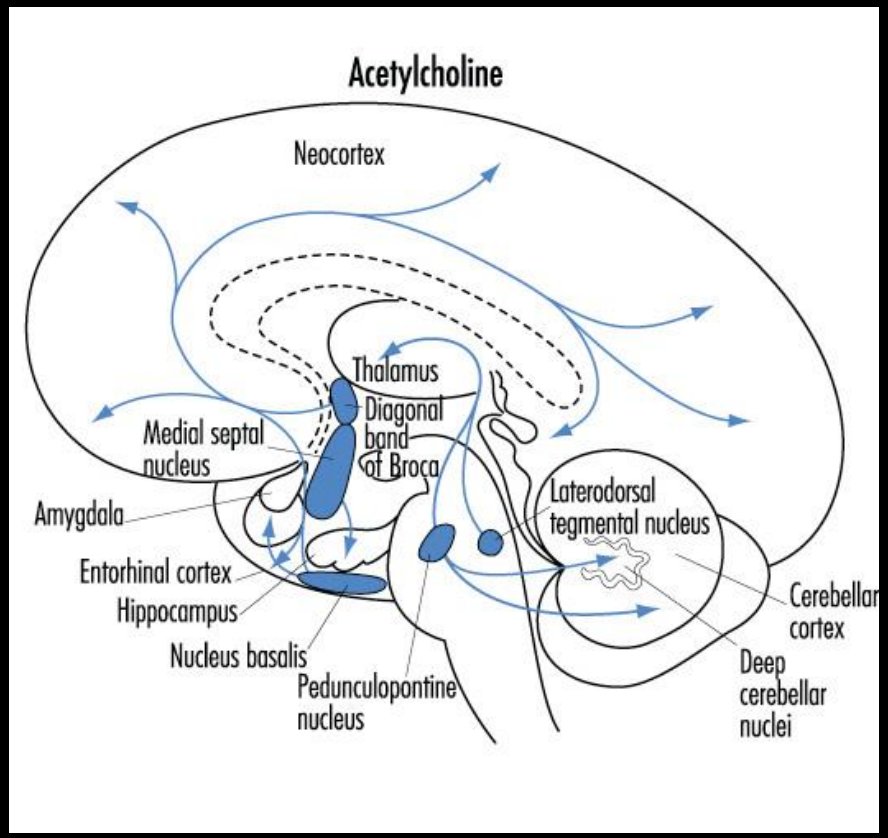

Federal Gov't Expenditures
People in US with Alzheimer's
$1,400bn
$1,200bn
$1,000bn
$800bn
$600bn
$400bn
$200bn
$bn
14mn
12mn
10mn
8mn
6mn
4mn
2mn
mn
5.1mn
5.3mn
5.7mn
6.5mn
7.8mn
9.5mn
11.1mn
12.6mn
13.4mn
$184bn
$216bn
$261bn
$332bn
$443bn
$613bn
$778bn
$980bn
$1,167bn
$0.43bn
$0.45bn
$0.48bn
$0.5bn
$0.53bn
$0.55bn
$0.58bn
$0.6bn
$0.63bn
2010
2015
2020
2025
2030
2035
2040
2045
2050
AD Cost to Medicare and Medicaid
AD Research Funding (current trends)
Number of Americans with AD (millions)
Sources: Alzheimer's Study Group, A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group (March 2009);
Alzheimer's Association. 2009 Alzheimer's Disease Facts and Figures (March 2009): National Institutes of Health Office of the Budget

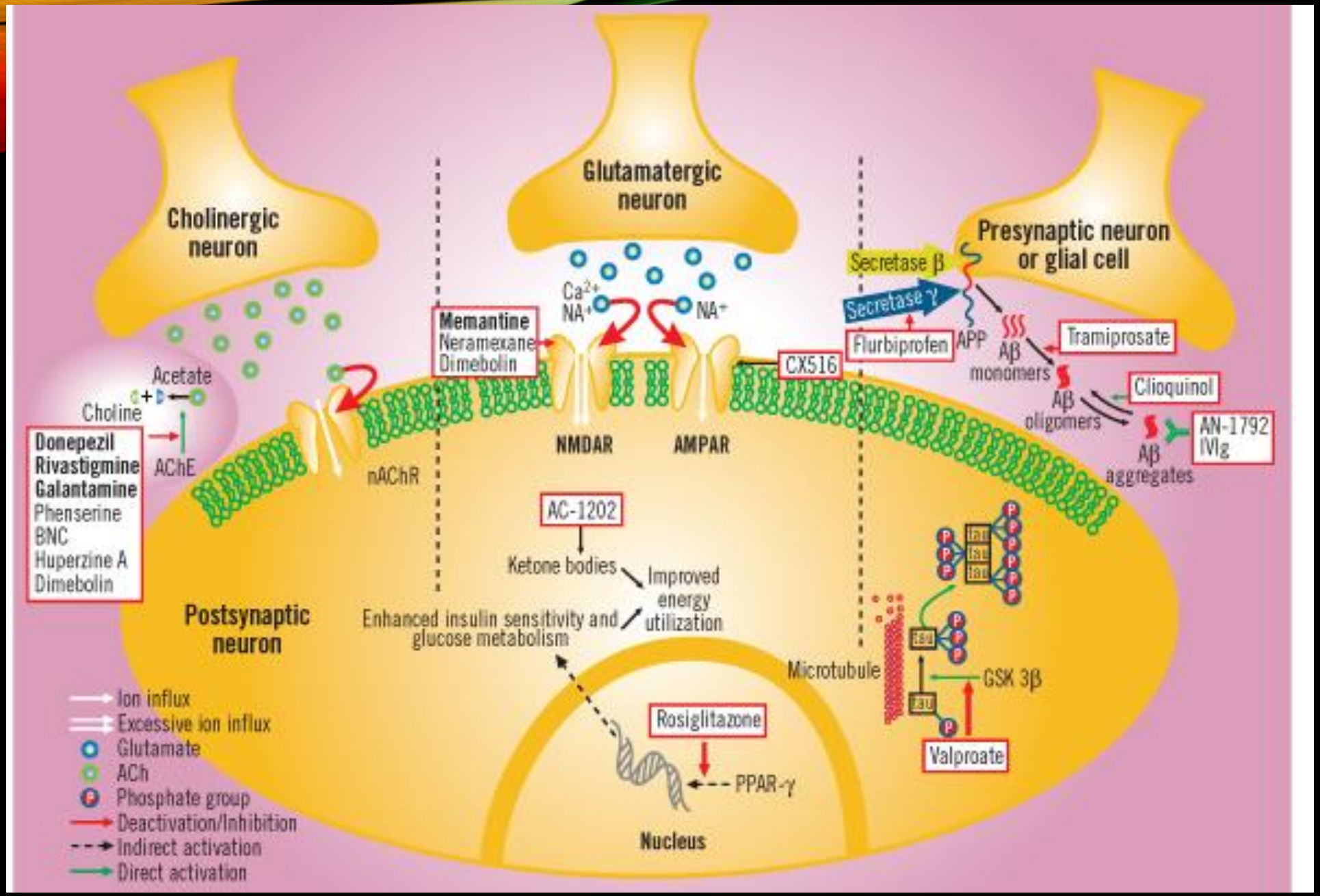

Researchers estimate that
5-8% of Americans aged 65+
have dementia
All dementias:
5-8%
Cognitively Normal:
92-95%
© SimpleC, LLC


6%
4%
15%
55%
20%
Alzheimer's Disease
Dementia with Lewy Bodies
Stroke/Mixed Dementia
Traumatic Brain Injury
Other/Fronto-temporal Dementia

Type of Dementia	% of Dementias	Symptoms	Pathology
Alzheimer's	55	Memory: names, recent events, language deficits (aphasia, apraxia), Late: mood/aggression	Atrophy generalized, esp. temporal, pit.
Lewy Body	20	Visual hallucinations, cognition fluctuation Parkinsonian: gait, tremor, rigid tone, falls – sensitive to antipsychotics, PD meds	Atrophy, Lewy bodies cortex
Vascular	15	Focal signs, stepwise decline	Stroke, diabetes
Pseudo	*	Mimics dementia	Depression, bipolar,
Other	10	Nutritional, trauma, AIDS, thyroid, drugs/alcohol	Fe, B12, folate,


Alzheimer
Neuron
Neurofibrillary Tangles
Amyloid Plaques
Normal Brain Section
Alzheimer's Brain Section


Acetylcholine
Neocortex
Thalamus
Diagonal band of Broca
Medial septal nucleus
Amygdala
Entorhinal cortex
Hippocampus
Nucleus basalis
Pedunculopontine nucleus
Laterodorsal tegmental nucleus
Cerebellar cortex
Deep cerebellar nuclei


Cholinergic neuron
Glutamatergic neuron
Presynaptic neuron or glial cell
Postsynaptic neuron
Acetate
Choline
AChE
Donepezil
Rivastigmine
Galantamine
Phenserine
BNC
Huperzine A
Dimebolin
nAChR
Memantine
Neramexane
Dimebolin
Ca2+
NA+
NA+
NMDAR
AMPAR
CX516
Secretase β
Secretase γ
Flurbiprofen
APP
Aβ monomers
Tramiprosate
Aβ oligomers
Clioquinol
Aβ aggregates
AN-1792
IVIg
AC-1202
Ketone bodies
Improved energy utilization
Enhanced insulin sensitivity and glucose metabolism
Microtubule
tau
GSK 3β
Valproate
Rosiglitazone
PPAR-γ
Nucleus
Ion influx
Excessive ion influx
Glutamate
ACh
Phosphate group
Deactivation/Inhibition
Indirect activation
Direct activation

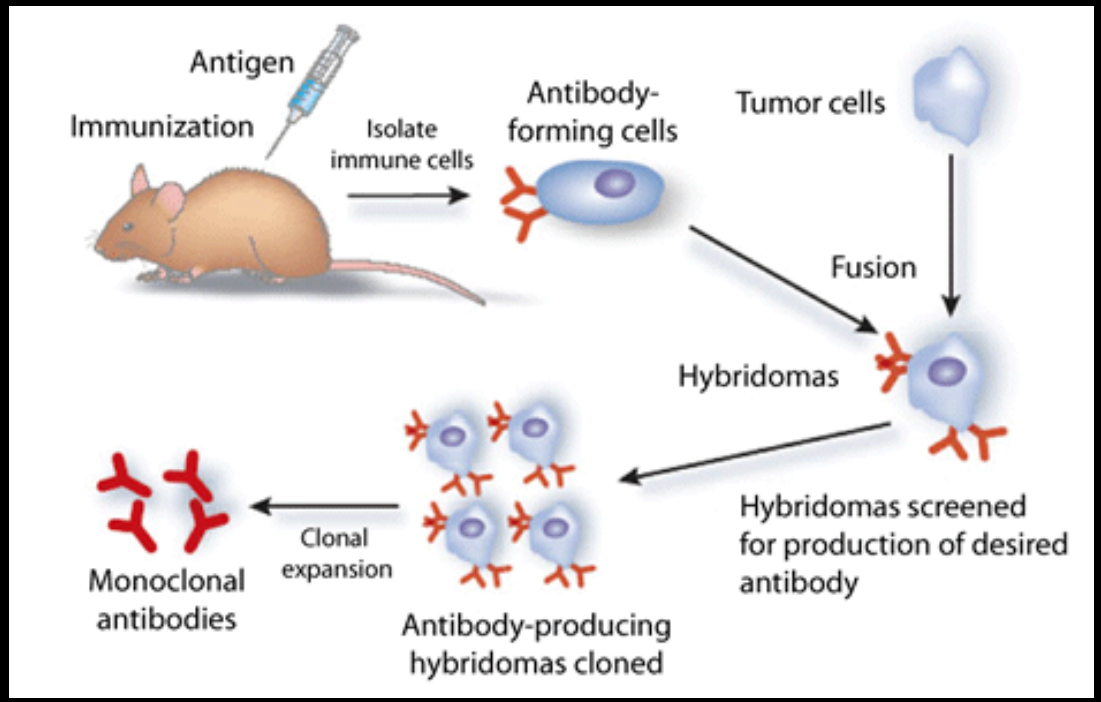
FDA-approved drugs

The U.S. Food and Drug Administration (FDA) has approved five medications (listed below) to treat the symptoms of Alzheimer's disease.

Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	All stages	2000
5. donepezil and memantine	Namzaric	Moderate to severe	2014

ADUCANUMAB

- Sept 1 2016 Nature
- MAB targeting amyloid plaque
- **Scientists may have 'game changer' drug to treat Alzheimer's**



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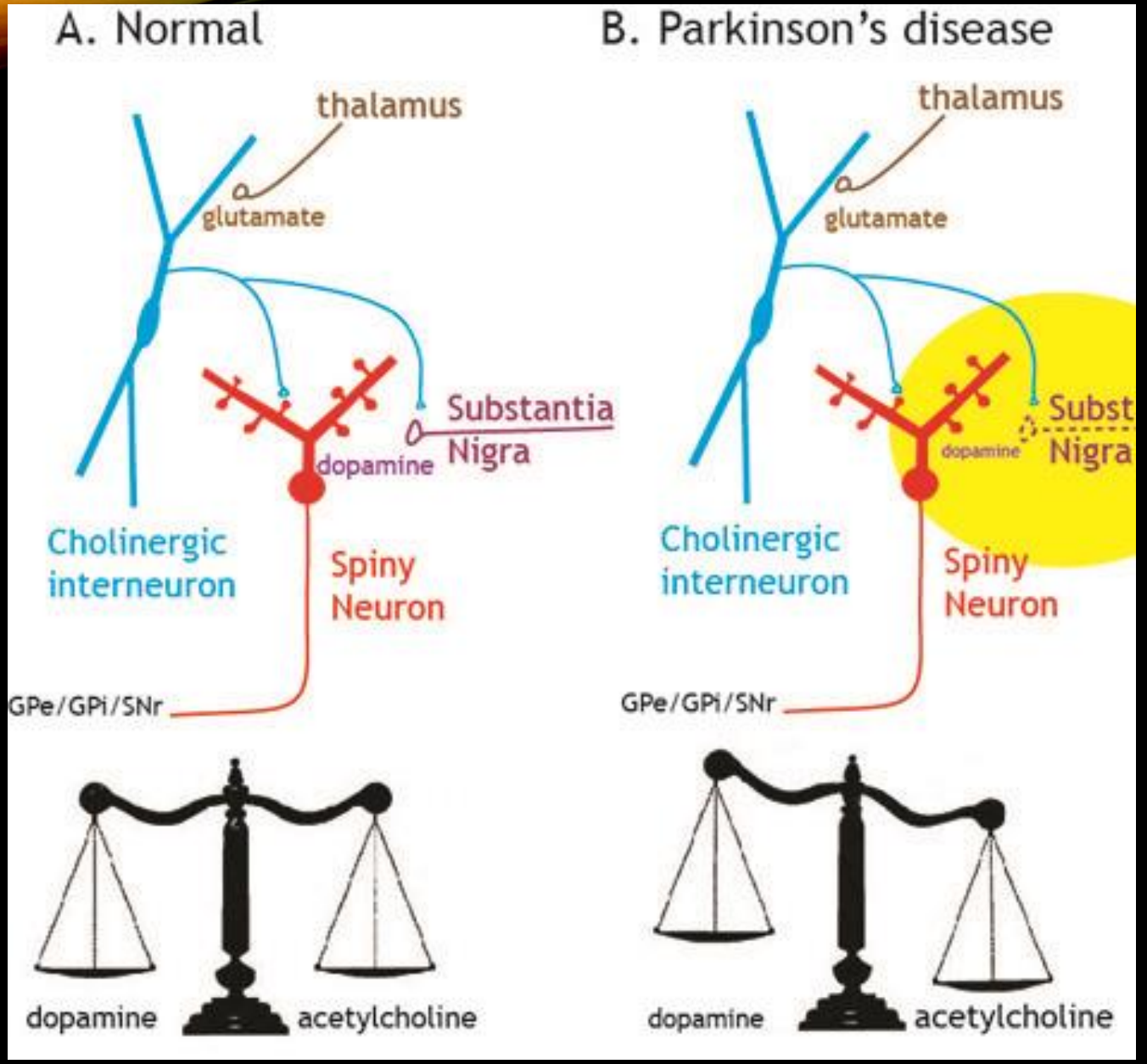

A. Normal
thalamus
glutamate
Substantia
Nigra
dopamine
Cholinergic
interneuron
Spiny
Neuron
GPe/GPi/SNr
dopamine
acetylcholine
B. Parkinson's disease
thalamus
glutamate
Subst
Nigra
dopamine
Cholinergic
interneuron
Spiny
Neuron
GPe/GPi/SNr
dopamine
acetylcholine

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. ***[See Warnings and Precautions (5.1)]***

NUPLAZID (PIMAVANSERIN)

- Parkinson's Disease - Psychosis
  - Caused by low dopamine
  - Medications increasing dopamine can cause hallucinations
  - Clozapine and Quetiapine used – mechanism is serotonin (5-HT_{2A}) receptor blockade
  - Pimavanserin $5HT_{2A}$ inverse agonist
  - 2016

	5-HT_{2A}	D_2	H_1	α
NUPLAZID™	✓	—	—	—
Seroquel®	✓	✓	✓	✓
Zyprexa®	✓	✓	✓	✓
Risperidone	✓	✓	—	✓
Clozapine	✓	✓	✓	✓

Atypical Antipsychotics second generation

Clozapine (Clozaril)

Olanzapine (Zyprexa)

Quetiapine (Seroquel)

Aripiprazole (Abilify)

Brexpiprazole (Rexulti)

Cariprazine (Vraylar)

Asenapine (Saphris)

Risperidone (Risperdal)

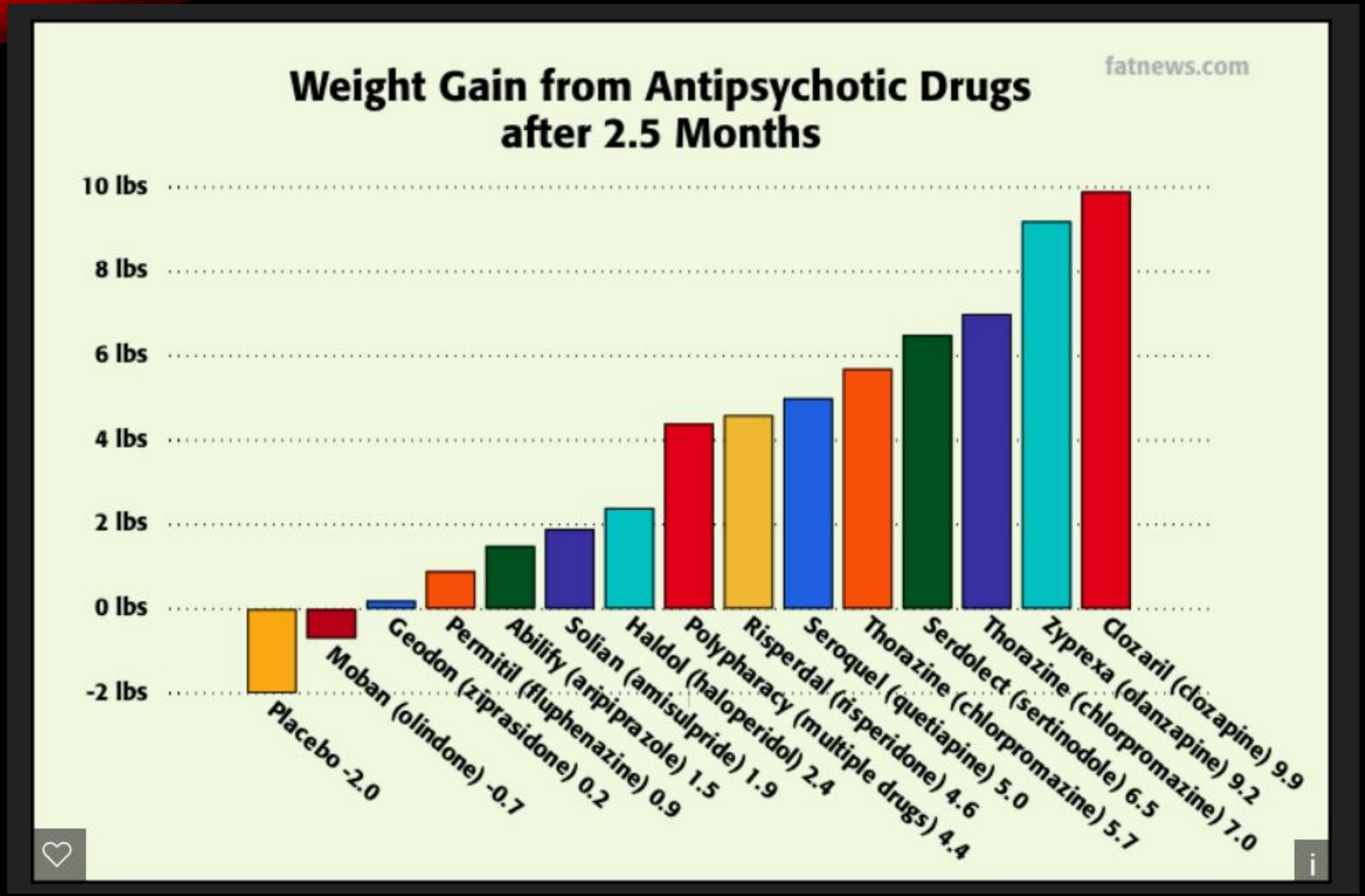
Ziprasidone (Geodon)

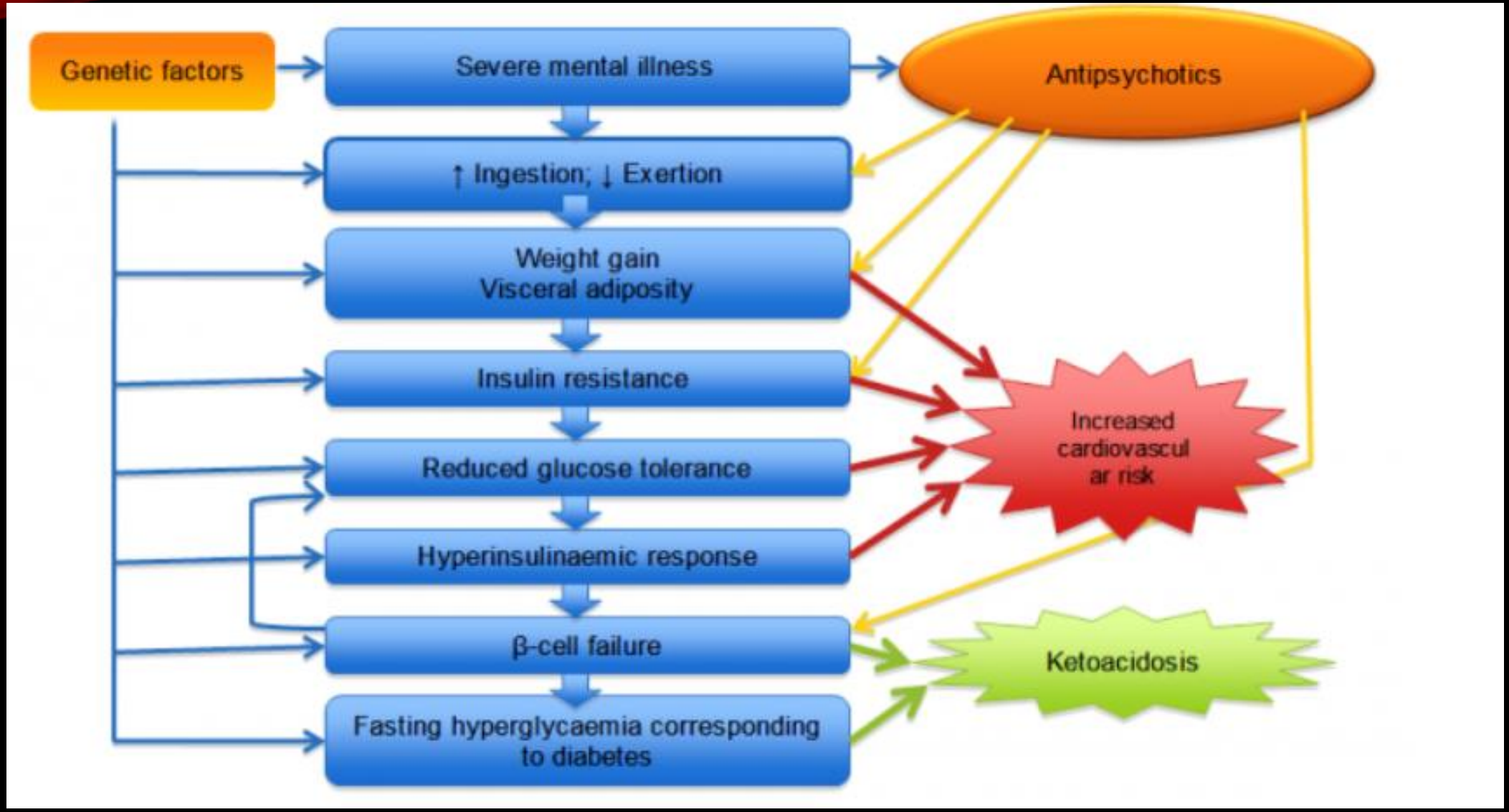
Lurasidone (Latuda)

Paliperidone (Invega)

Iloperidone (Fanapt)

	SEDATION	WEIGHT GAIN	EPS
Best choice	Aripiprazole	Aripiprazole	Clozapine
	Iloperidone	Lurasidone	Iloperidone
	Lurasidone	Ziprasidone	Quetiapine
	Paliperidone	Asenapine	Aripiprazole
	Risperidone	Iloperidone	Asenapine
	Ziprasidone	Paliperidone	Lurasidone
	Asenapine	Risperidone	Olanzapine
	Olanzapine	Quetiapine	Ziprasidone
	Clozapine	Clozapine	Paliperidone
Worst choice	Quetiapine	Olanzapine	Risperidone

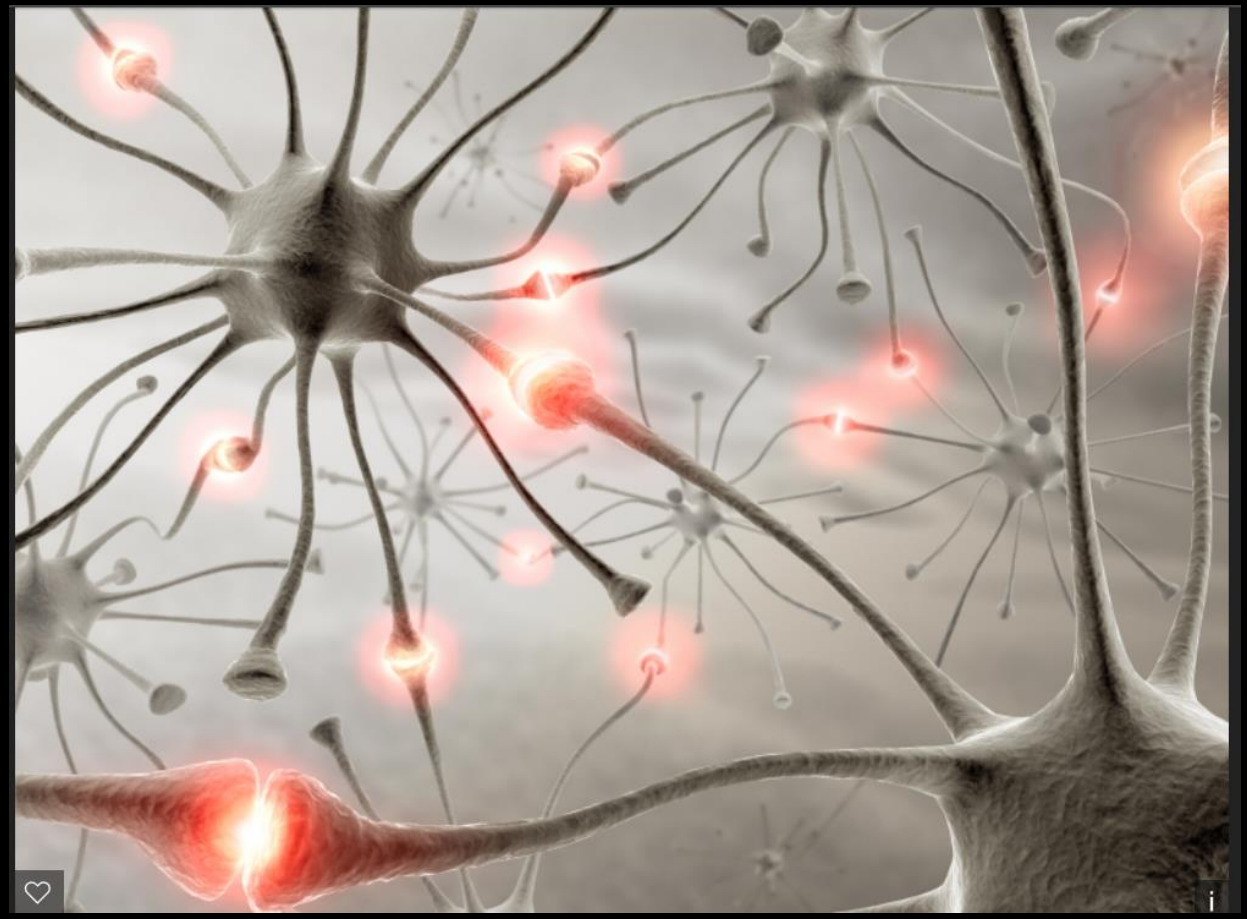

Weight Gain from Antipsychotic Drugs
after 2.5 Months
fatnews.com
10 lbs
8 lbs
6 lbs
4 lbs
2 lbs
0 lbs
-2 lbs
Placebo -2.0
Moban (olindone) -0.7
Geodon (ziprasidone) 0.2
Permitil (fluphenazine) 0.9
Abilify (aripiprazole) 1.5
Solian (amisulpride) 1.9
Haldol (haloperidol) 2.4
Polypharacy (multiple drugs) 4.4
Risperdal (risperidone) 4.6
Seroquel (quetiapine) 5.0
Thorazine (chlorpromazine) 5.7
Serdolect (sertinodole) 6.5
Thorazine (chlorpromazine) 7.0
Zyprexa (olanzapine) 9.2
Clozaril (clozapine) 9.9

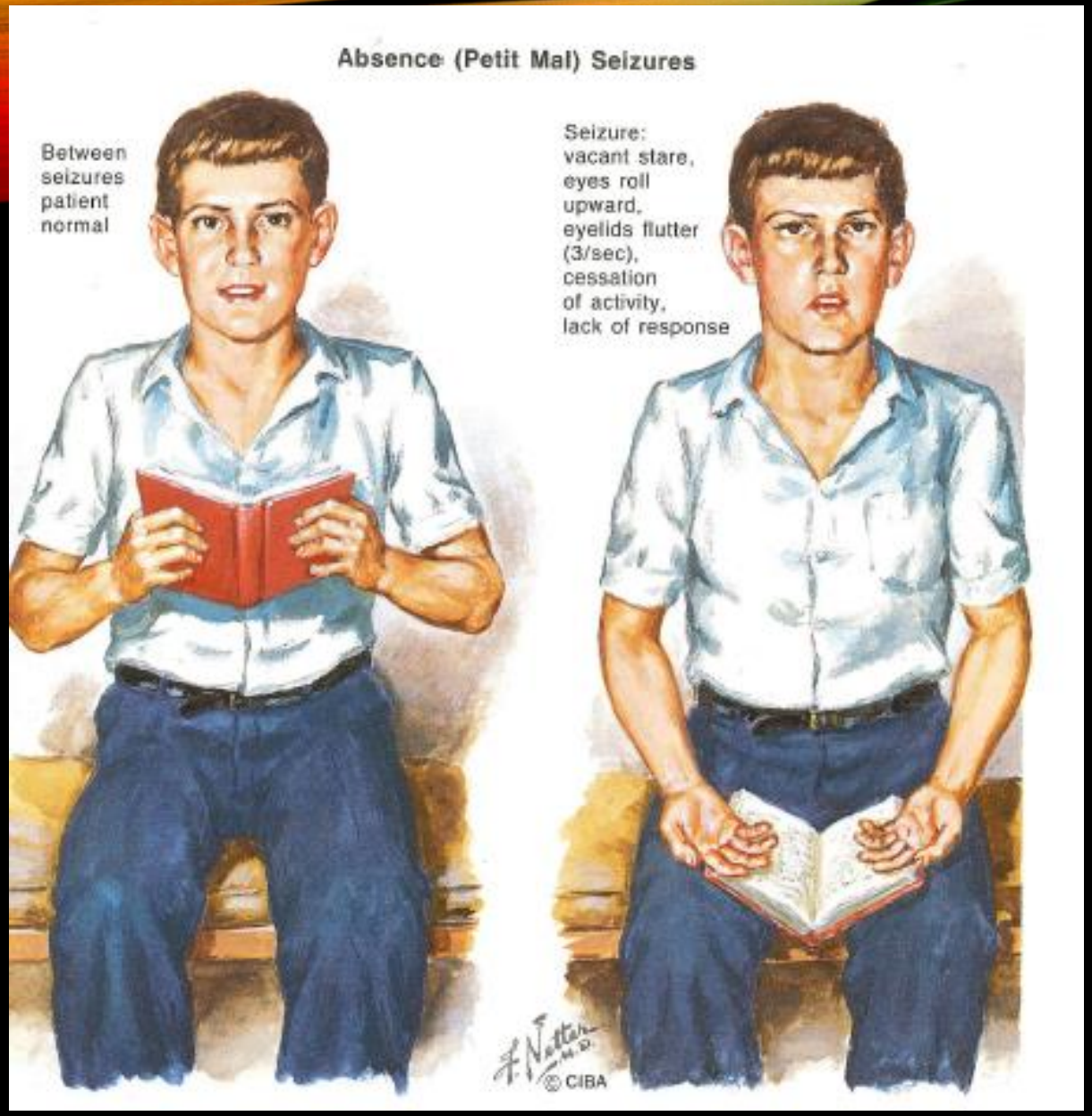

Genetic factors
Severe mental illness
Antipsychotics
↑ Ingestion; ↓ Exertion
Weight gain
Visceral adiposity
Insulin resistance
Reduced glucose tolerance
Hyperinsulinaemic response
β-cell failure
Fasting hyperglycaemia corresponding to diabetes
Increased cardiovascular risk
Ketoacidosis

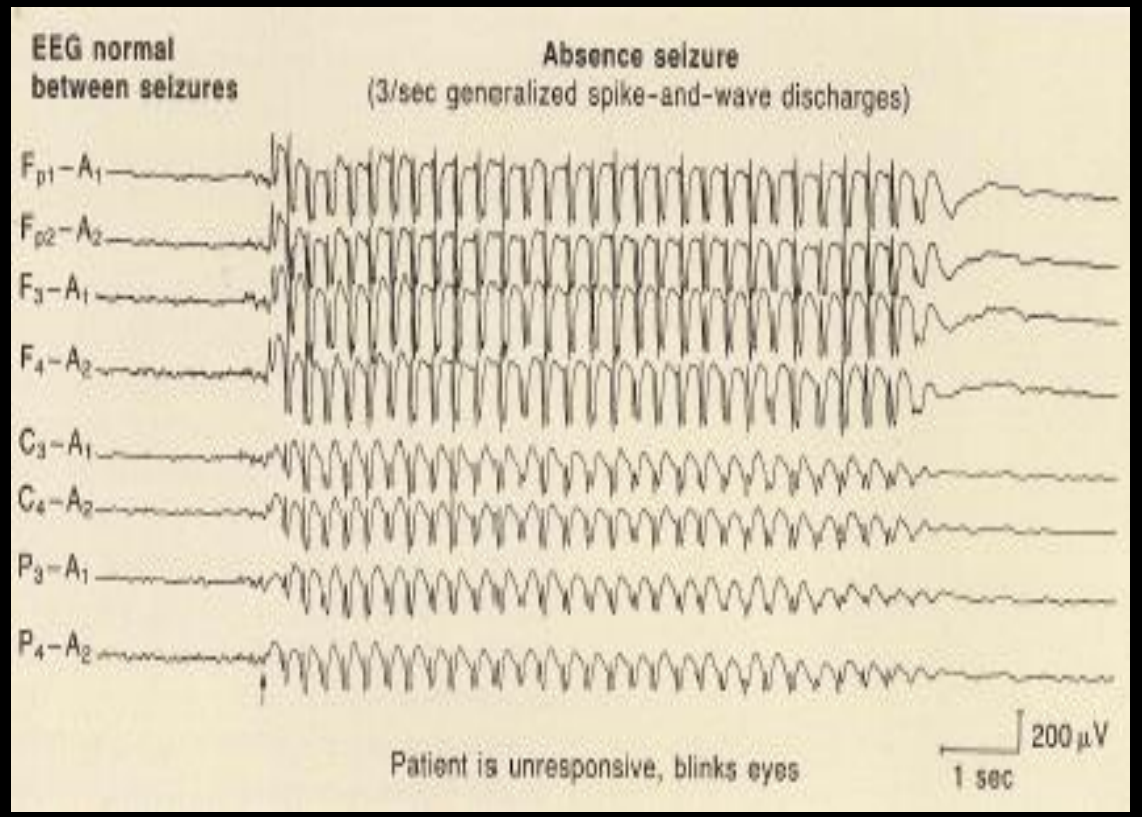
Extrapyramidal Symptoms

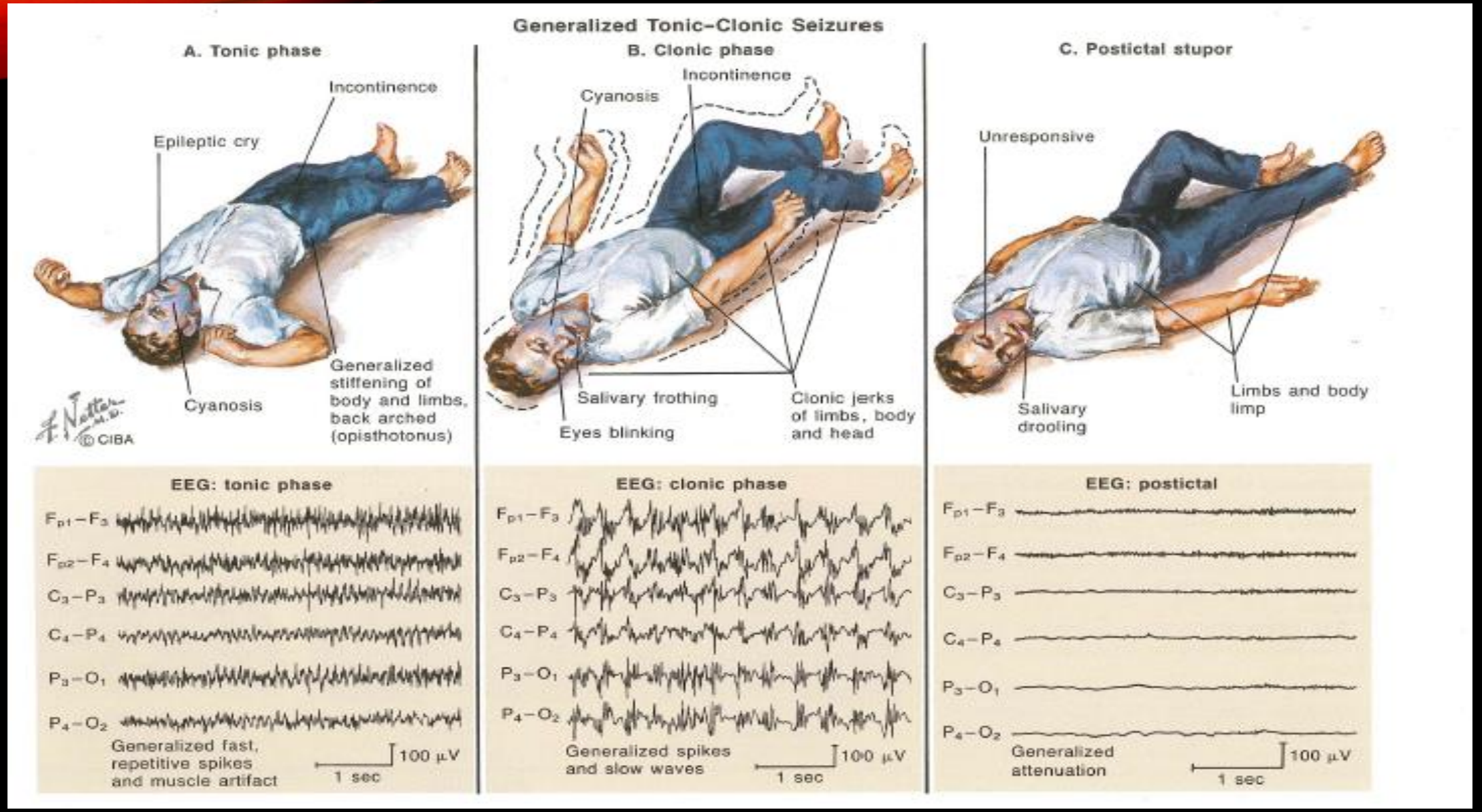
Reaction	Onset	Features
Acute dystonia	Hours to 5 days	Spasm of tongue, neck, face & back
Parkinsonism	5 – 30 days	Tremor, shuffling gait, drooling, stooped posture, instability
Akathesia	5 – 60 days	Compulsive, repetitive motions; agitation
Tarditive dyskinesia	Months to years	Lip-smacking, worm-like tongue movement, 'fly-catching'

Epilepsy




Absence (Petit Mal) Seizures
Between seizures patient normal
Seizure: vacant stare, eyes roll upward, eyelids flutter (3/sec), cessation of activity, lack of response
F. Netter M.D.
© CIBA

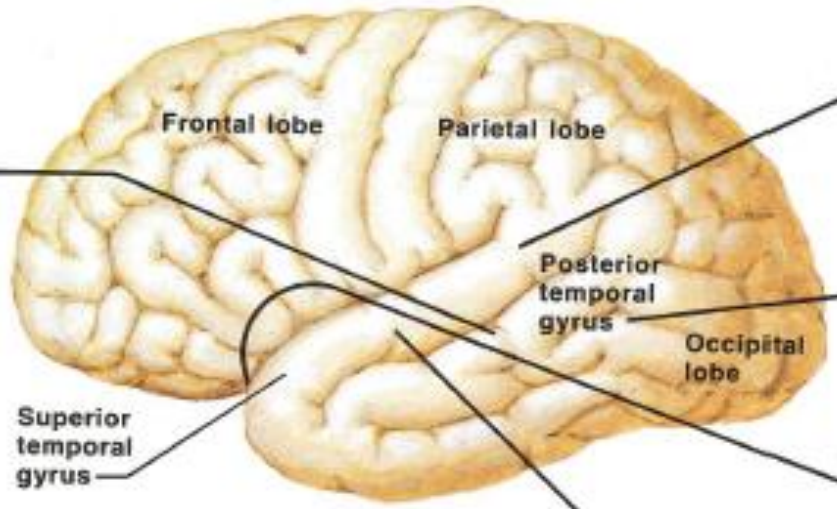

EEG normal between seizures
Absence seizure
(3/sec generalized spike-and-wave discharges)
$F_{p1}-A_1$
$F_{p2}-A_2$
F_3-A_1
F_4-A_2
C_3-A_1
C_4-A_2
P_3-A_1
P_4-A_2
Patient is unresponsive, blinks eyes
200 μV
1 sec


Generalized Tonic–Clonic Seizures
A. Tonic phase
Incontinence
Epileptic cry
Cyanosis
Generalized stiffening of body and limbs, back arched (opisthotonus)
© CIBA
B. Clonic phase
Incontinence
Cyanosis
Salivary frothing
Eyes blinking
Clonic jerks of limbs, body and head
C. Postictal stupor
Unresponsive
Salivary drooling
Limbs and body limp
EEG: tonic phase
Fp1–F3
Fp2–F4
C3–P3
C4–P4
P3–O1
P4–O2
Generalized fast, repetitive spikes and muscle artifact
100 μV
1 sec
EEG: clonic phase
Fp1–F3
Fp2–F4
C3–P3
C4–P4
P3–O1
P4–O2
Generalized spikes and slow waves
100 μV
1 sec
EEG: postictal
Fp1–F3
Fp2–F4
C3–P3
C4–P4
P3–O1
P4–O2
Generalized attenuation
100 μV
1 sec

Complex Partial Seizures

Impairment of consciousness: cognitive, affective symptoms

Dreamy state; blank, vacant expression; déjà vu; jamais vu; or fear



Formed auditory hallucinations. Hears music, etc

Formed visual hallucinations. Sees house, trees that are not there

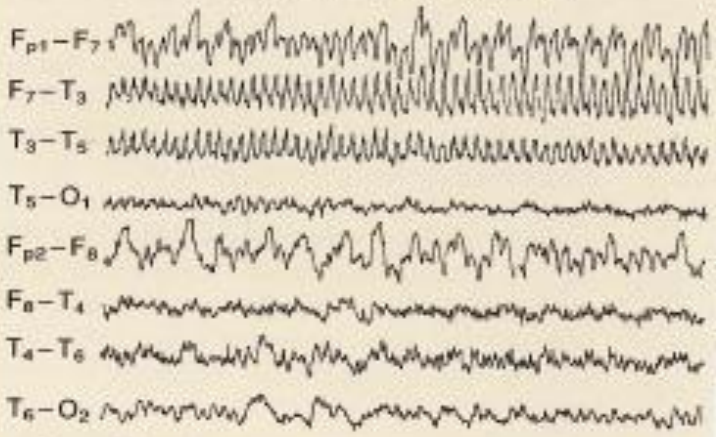
Bad or unusual smell

Olfactory hallucinations

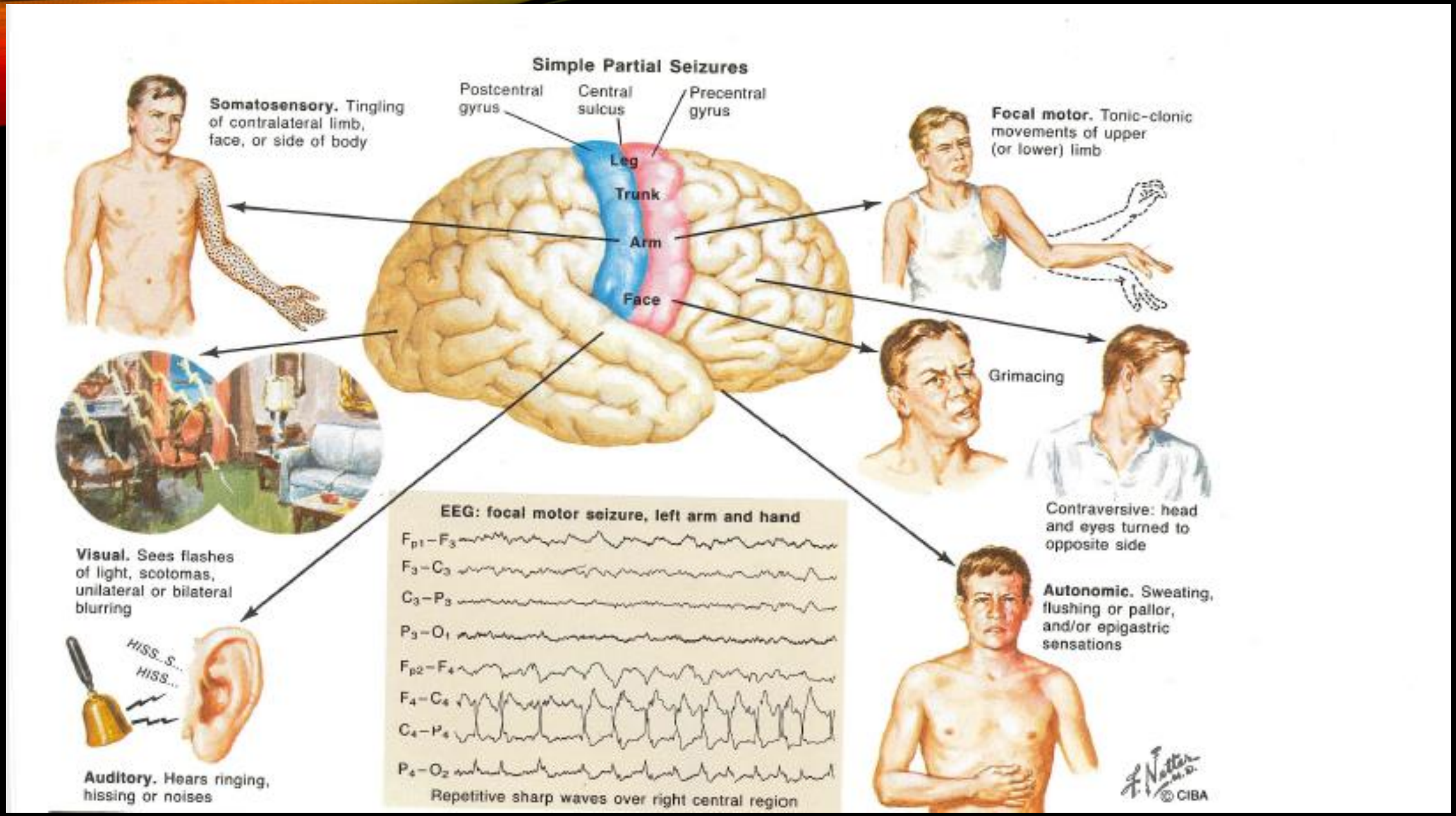
Psychomotor phenomena. Chewing movements, wetting lips, automatisms (picking at clothing)

Dysphasia

EEG: left temporal lobe seizure



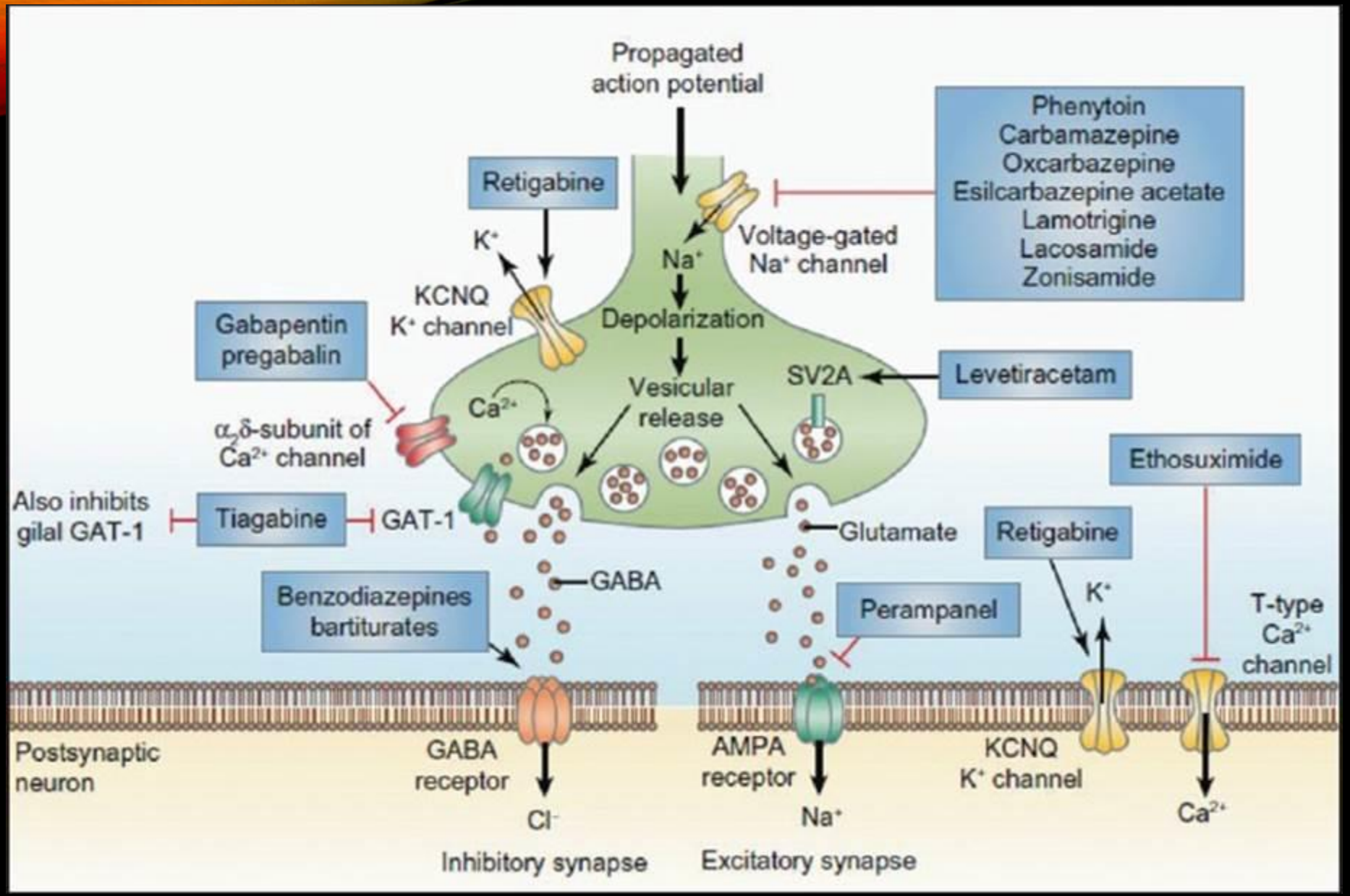
Repetitive sharp waves over left temporal region


Simple Partial Seizures
Postcentral gyrus
Central sulcus
Precentral gyrus
Leg
Trunk
Arm
Face
Somatosensory. Tingling of contralateral limb, face, or side of body
Focal motor. Tonic-clonic movements of upper (or lower) limb
Grimacing
Contraversive: head and eyes turned to opposite side
Visual. Sees flashes of light, scotomas, unilateral or bilateral blurring
HISS...S...
HISS...
Auditory. Hears ringing, hissing or noises
EEG: focal motor seizure, left arm and hand
Fp1–F3
F3–C3
C3–P3
P3–O1
Fp2–F4
F4–C4
C4–P4
P4–O2
Repetitive sharp waves over right central region
Autonomic. Sweating, flushing or pallor, and/or epigastric sensations
F. Netter M.D.
© CIBA

- 1857- Bromides
- 1912-Phenobarbital
- 1938-Phenytoin (Dilantin)
- 1954- Primidone
- 1960- Ethosuximide (Zarontin)
- 1974-Carbamazepine (Tegretol)
- 1975 Clonazepam (Klonopin)
- 1978- Valproate (Depakote)

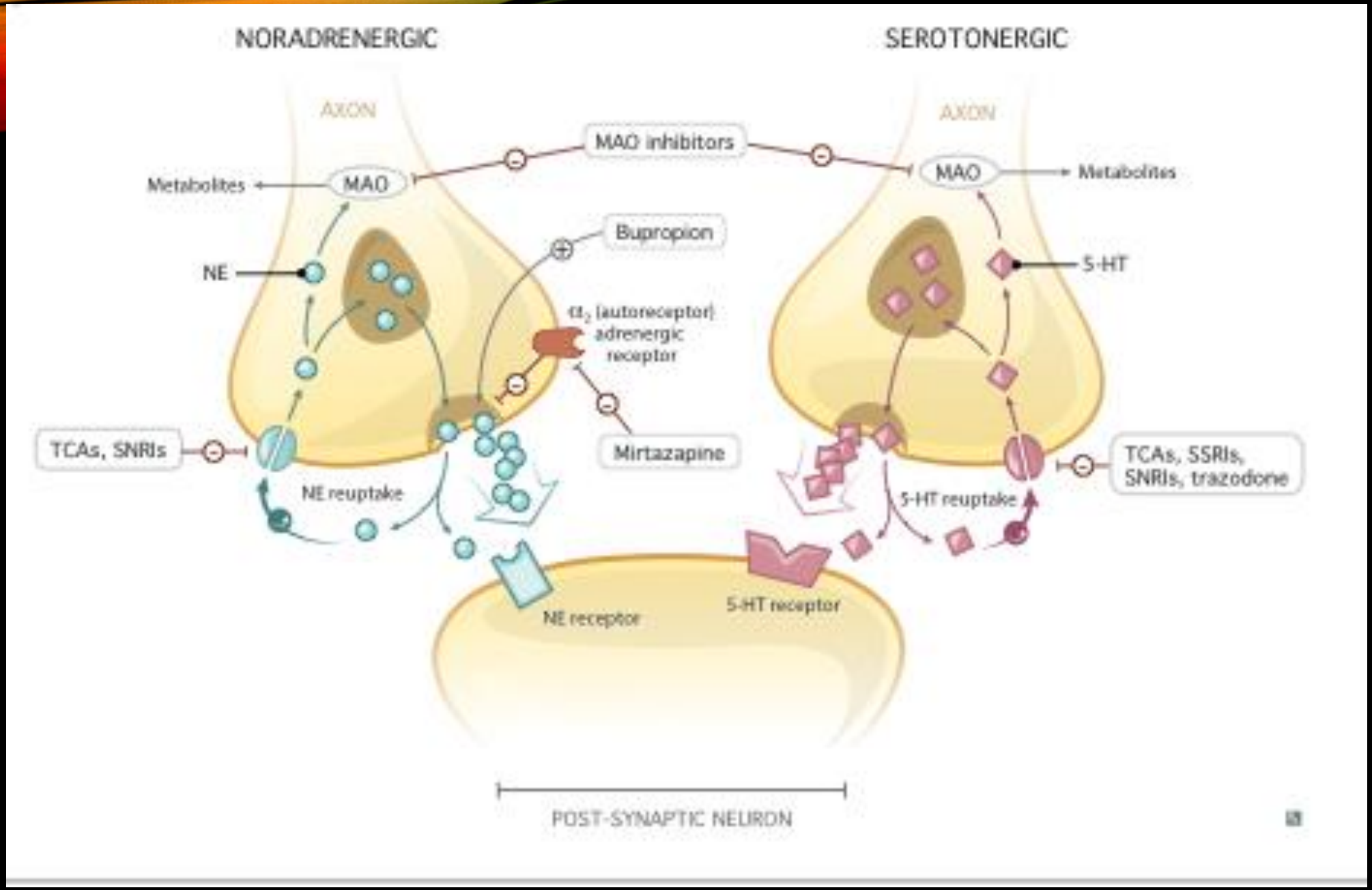
- 1993- Felbamate (Felbatol)
- 1993- Gabapentin (Neurontin)
- 1995-Lamotrigine (Lamictal)
- 1997-Topiramate (Topamax)
  Tiagabine (Gabitril)
- 1999- Levetiracetam (Keppra)
- 2000- Oxcarbazepine (Trileptal
- 2000-Zonisamide (Zonegran)
- 2005- Pregabalin (Lyrica)
- 2009- Lacosamide (Vimpat)
- 2009- Rufinamide (Banzel)
- 2010-ACTH (Acthar)
- 2011- Clobazam (Onfi)
- 2012 – Ezogabine (Potiga)
- 2012-Perampanel (Fycompa)
- 2013-Oxcarbazepine (Oxtellar XR)

- Vigabatrin (Sabril) 2009
- Topiramate (Topamax XR) 2013
- Eslicarbazepine (Aptiom) 2014
- Brivaracetam (Briviact) 2016


Propagated action potential
Phenytoin
Carbamazepine
Oxcarbazepine
Esilcarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Retigabine
K+
KCNQ K+ channel
Na+
Voltage-gated Na+ channel
Depolarization
Gabapentin pregabalin
α2δ-subunit of Ca2+ channel
Ca2+
Vesicular release
SV2A
Levetiracetam
Ethosuximide
Also inhibits glial GAT-1
Tiagabine
GAT-1
Glutamate
Retigabine
GABA
Benzodiazepines barbiturates
Perampanel
K+
T-type Ca2+ channel
Postsynaptic neuron
GABA receptor
Cl−
AMPA receptor
Na+
KCNQ K+ channel
Ca2+
Inhibitory synapse
Excitatory synapse

ANTIDEPRESSANTS

Mechanisms, differences, uses,


NORADRENERGIC
SEROTONERGIC
AXON
AXON
MAO inhibitors
Metabolites
MAO
MAO
Metabolites
Bupropion
NE
5-HT
α_2 (autoreceptor) adrenergic receptor
TCAs, SNRIs
Mirtazapine
TCAs, SSRIs, SNRIs, trazodone
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
POST-SYNAPTIC NEURON

Selective serotonin reuptake inhibitors (SSRIs)

- Citalopram (Celexa)
- Escitalopram (Lexapro, Cipralex)
- Paroxetine (Paxil, Seroxat)
- Fluoxetine (Prozac)
- Fluvoxamine (Luvox)
- Sertraline (Zoloft, Lustral)

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)
- Milnacipran (Ixel, Savella)
- Tofenacin (Elamol, Tofacine)
- Venlafaxine (Effexor)

Serotonin modulators and stimulators (SMSs)

- Vilazodone (Viibryd)
- Vortioxetine (Trintellix)

).[15]

VORTIOXETINE

- serotonin modulator and stimulator
- September 30, 2013, the Food and Drug Administration approved (Brintillex)
- to avoid confusion with the blood-thinning medication **Brilinta** in the United States, but on May 2, 2016, the US FDA approved a name change to **Trintellix**

Serotonin antagonists and reuptake inhibitors (SARIs)

- Reboxetine (Edronax)
- Viloxazine (Vivalan)

Atomoxetine (Strattera)

Tetracyclic antidepressants (TeCAs)

- Amoxapine (Asendin)
- Maprotiline (Ludiomil)
- Mianserin (Bolvidon, Norval, Tolvon)
- Mirtazapine (Remeron)
- Setiptiline (Tecipul)

Tricyclic antidepressants (TCAs)

- Amitriptyline (Elavil, Endep)
- Amitriptylinoxide (Amioxid, Ambivalon, Equilibrin)
- Clomipramine (Anafranil)
- Desipramine (Norpramin, Pertofrane)
- Dibenzepin (Noveril, Victoril)
- Dimetacrine (Istonil)
- Dosulepin (Prothiaden)
- Doxepin (Adapin, Sinequan)
- Imipramine (Tofranil)
- Lofepramine (Lomont, Gamanil)
- Melitracen (Dixeran, Melixeran, Trausabun)
- Nitroxazepine (Sintamil)
- Nortriptyline (Pamelor, Aventyl)
- Noxiptiline (Agedal, Elronon, Nogedal)
- Pipofezine (Azafen/Azaphen)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)

Atypical antipsychotics

- Aripiprazole (Abilify) – specifically approved as an **adjunct** for major depressive disorder
- Brexpiprazole (Rexulti) – specifically approved as an adjunct for major depressive disorder
- Lurasidone (Latuda) – specifically approved as an adjunct for depressive episodes in bipolar disorder
- Olanzapine (Zyprexa) – specifically approved as an adjunct for major depressive disorder
- Quetiapine (Seroquel) – approved as an adjunct for both major depressive disorder and depressive episodes in bipolar disorder

MAJOR DEPRESSIVE DISORDER

- Which is the best?
- Individualizing effects and side effects

Selecting Medication

Many safe, efficacious, inexpensive medications are available

- SSRIs and SNRIs are first line; SSRIs are most commonly used; some SSRIs are approved for anxiety disorders
- Many generic formulations available; no absolute class advantage
- Little data to guide selection of medication for individual patients
- Medications differ mainly in adverse effect profiles

Additional Considerations

Considerations

- Prior successful use or family history of use
- Patient concerns discussed during the clinical interview (eg, sexual adverse effects)
- Breast-feeding: consult LactMed®

Specific recommendations

- Insomnia: mirtazapine
- Fatigue, amotivation: SNRI or bupropion
- Pain: duloxetine
- Cognitive impairment: vortioxetine

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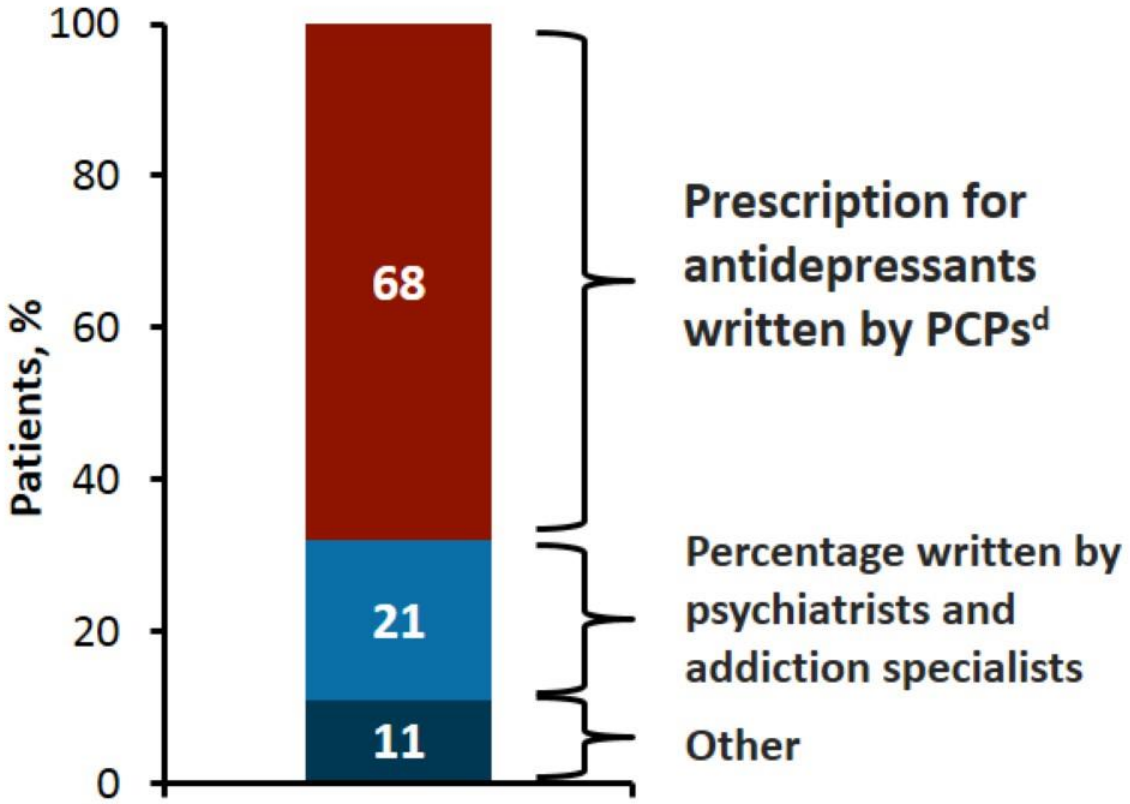
- Pain: duloxetine
- Cognitive impairment: vortioxetine

MDD Treatment in Primary Care

PCPs manage approximately one-third to one-half of nonelderly adults[a,b] and nearly two-thirds of older adults[c] who receive treatment for MDD.

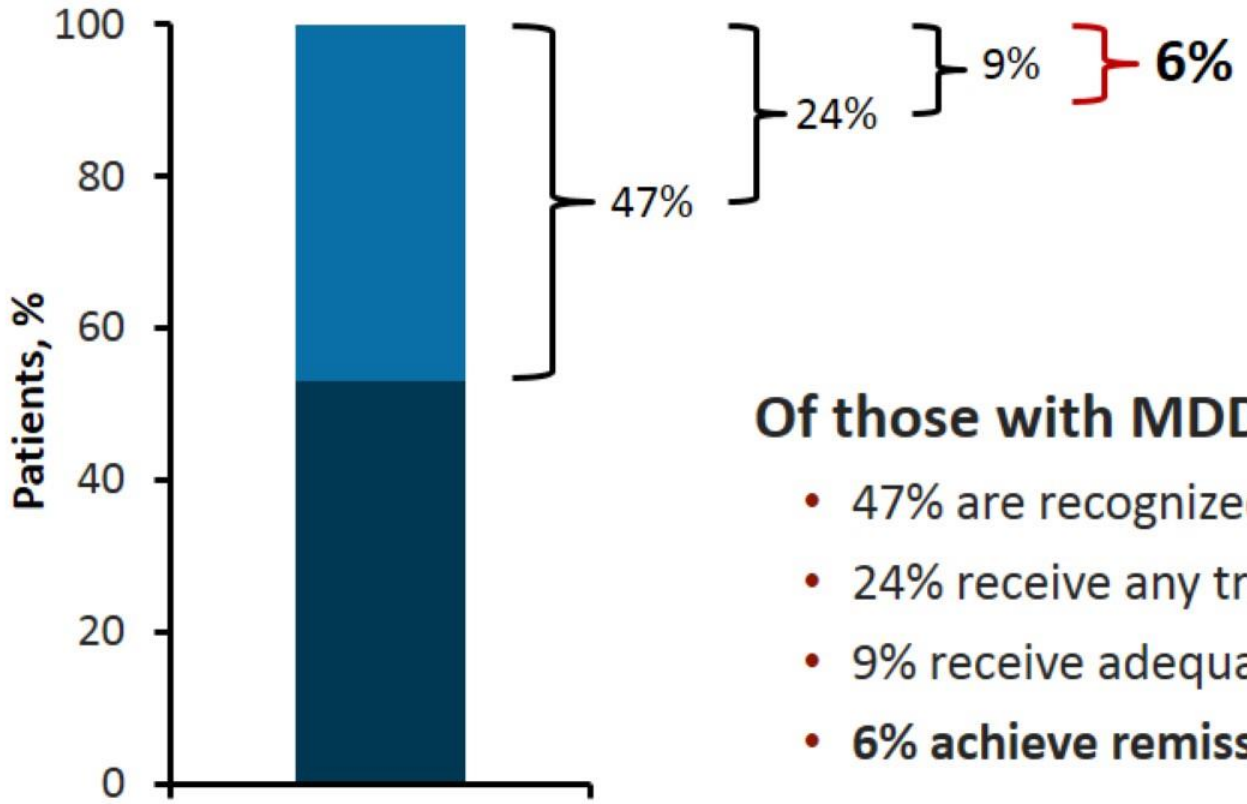


PCPs include pediatricians, obstetrician/gynecologists, physician assistants, and nurse practitioners.

a. Kessler RC, et al. *JAMA*. 2003;289:3095-3105[2]; b. Pincus HA, et al. *JAMA*. 1998;279:526-531[3]; c. Harman JS, et al. *J Gen Intern Med*. 2006;21:926-930[4]; d. Mark TL, et al. *Psychiatr Serv*. 2009;60:1167.[5]

Undertreatment of Patients With MDD

12.5% of primary care patients have had MDD in the past year



Of those with MDD

- 47% are recognized clinically
- 24% receive any treatment
- 9% receive adequate treatment
- **6% achieve remission of symptoms**

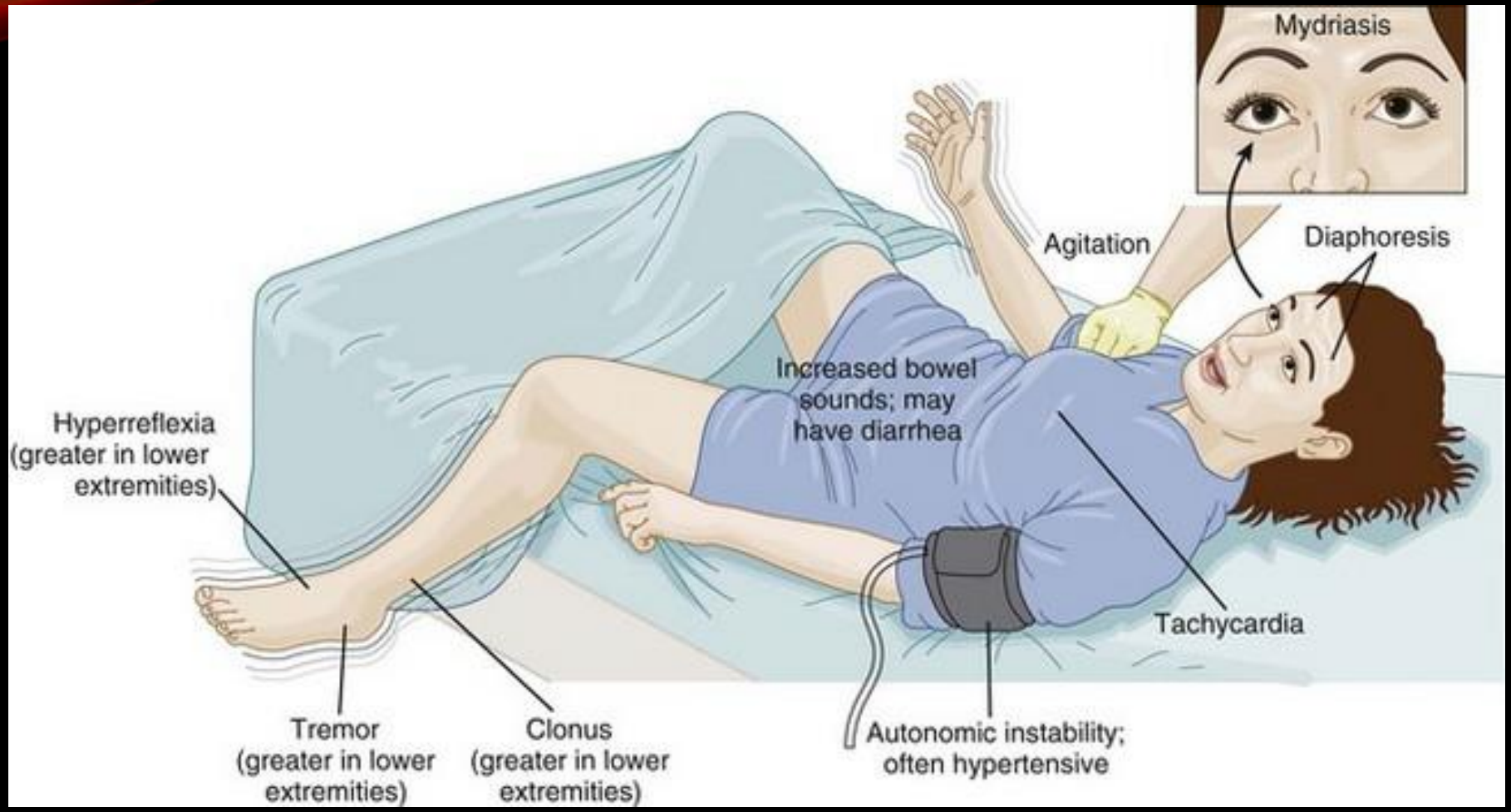
Pence BW, et al. *Curr Psychiatry Rep*. 2012;14:328-335.[6]


SYMPTOMS OF ANXIETY DISORDERS
Simple phobia
Fear of snakes
Fear of blood
Fear of flying on a plane
Fear of elevator
Panic disorder
Fear of dying
Panic attack
Fear of going
Shortness of breath
Chest pain
Obsessive-compulsive disorder
Fear to use public toilets
Obsession
Thoughts of sex
Hallucinations
Thoughts of murder
Mixed anxiety and depressive disorder
Anxiety
Inner tension
Depression
Increased aggressive
Social phobia
Fear of excessive humiliation
Fear of public speaking
Fear to use public toilets
Post-traumatic stress
Reliving trauma
Mental s tupor
Nightmares
Irritability

ALTERED MENTAL STATUS + ELEVATED TEMPERATURE

IN ADDITION TO SEPSIS, CONSIDER THE FOLLOWING (CULPRIT IS OFTEN POLYPHARMACY)

	EXPOSURE	MUSCLE TONE	MUCOSA & SKIN	PUPILS	BOWEL SOUNDS	REFLEXES
NEUROLEPTIC MALIGNANT SYNDROME	ANTIPSYCHOTICS	RIGID	WET	NORMAL	↔	BRADYREFLEXIA
SEROTONIN SYNDROME	SEROTONERGICS (antidepressants, fentanyl, linezolid, sumatriptan, ondansetron)	RIGID	WET	↑	↑	↑
ANTICHOLINERGIC TOXIDROME	ANTICHOLINERGICS	NORMAL	DRY	↑	↓	NORMAL
MALIGNANT HYPERTHERMIA	INHLALED ANESTHETICS SUCCINYLCHOLINE	RIGID	WET	NORMAL	↓	↓

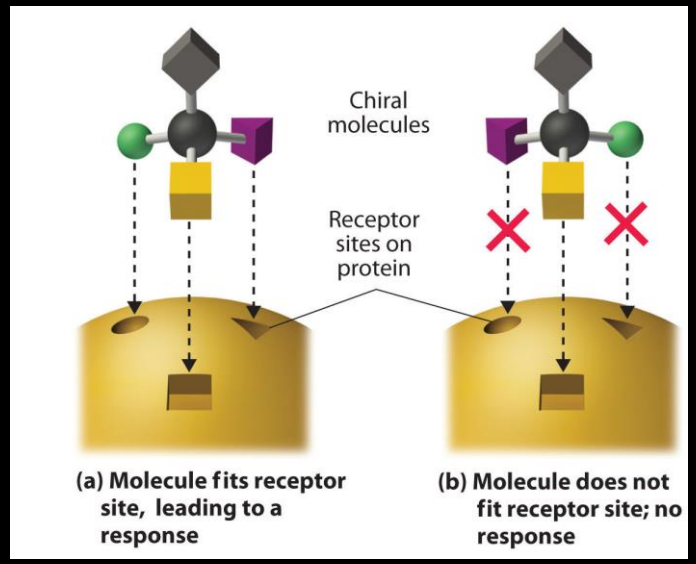

Mydriasis
Agitation
Diaphoresis
Increased bowel sounds; may have diarrhea
Hyperreflexia (greater in lower extremities)
Tachycardia
Tremor (greater in lower extremities)
Clonus (greater in lower extremities)
Autonomic instability; often hypertensive

Are they really new?

PATENT EXTENSION

- Long acting
- Chiral change
- New route (nasal)
- New indication (age, disease)
- Combinations

- Slightly change chemical




QUESTIONS?
COMMENTS?
CONCERNS?