Brain Repair

ISEPP – November 2, 2012

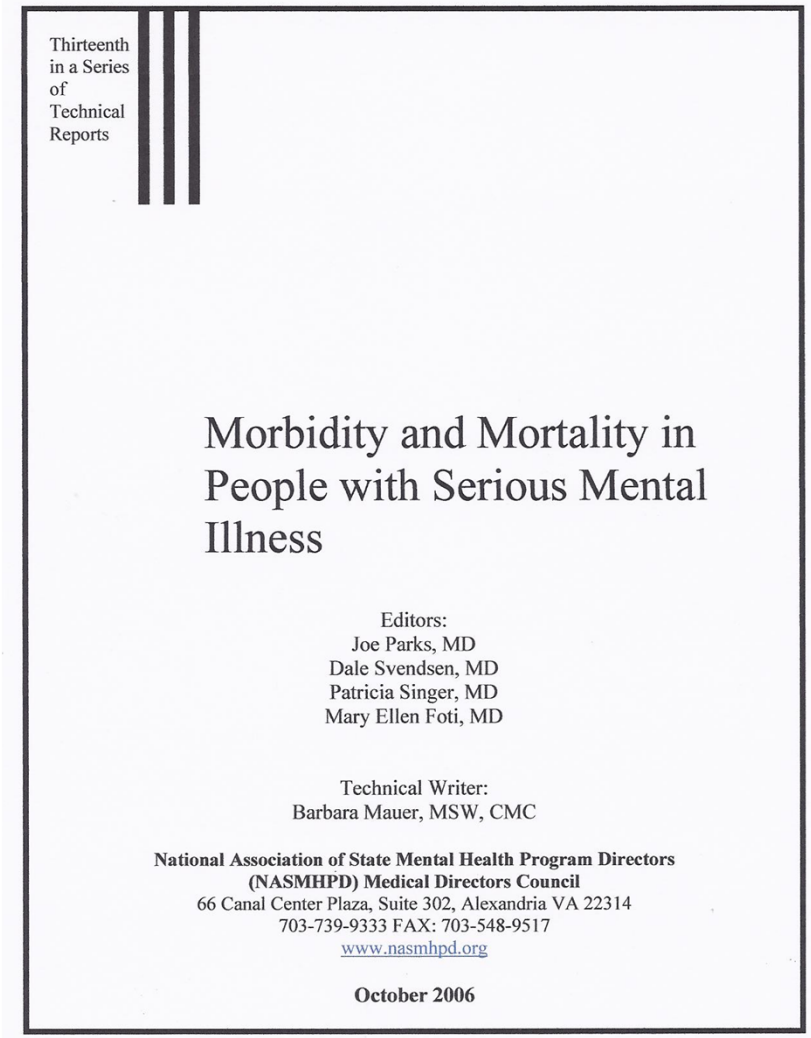
Grace E. Jackson, MD

Outline of Lecture

I. What's Happening to the Mentally Ill
II. America's Drug Problem
III. Brain Damage
IV. Brain Repair

I. What’s Happening to the Mentally Ill

National Assn of State Mental Health Program Directors



Thirteenth in a Series of Technical Reports

Morbidity and Mortality in People with Serious Mental Illness

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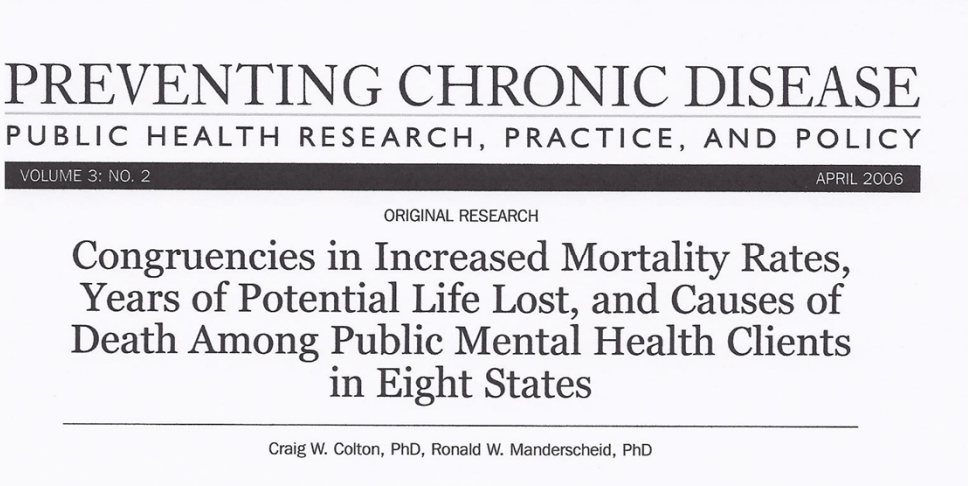
October 2006



PREVENTING CHRONIC DISEASE
PUBLIC HEALTH RESEARCH, PRACTICE, AND POLICY
VOLUME 3: NO. 2 APRIL 2006

ORIGINAL RESEARCH

Congruencies in Increased Mortality Rates, Years of Potential Life Lost, and Causes of Death Among Public Mental Health Clients in Eight States

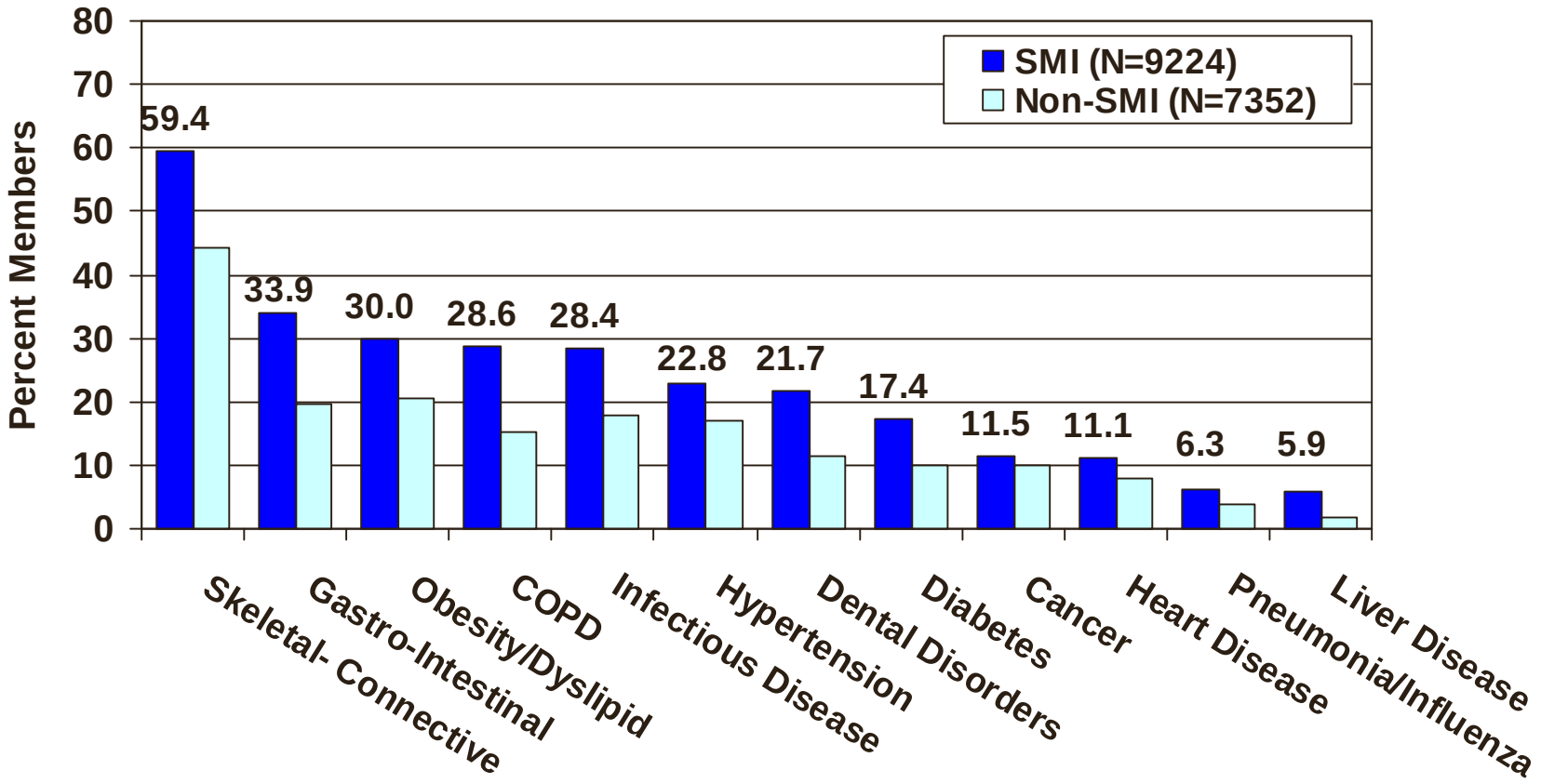
Craig W. Colton, PhD, Ronald W. Manderscheid, PhD

8 States Provided Full Data

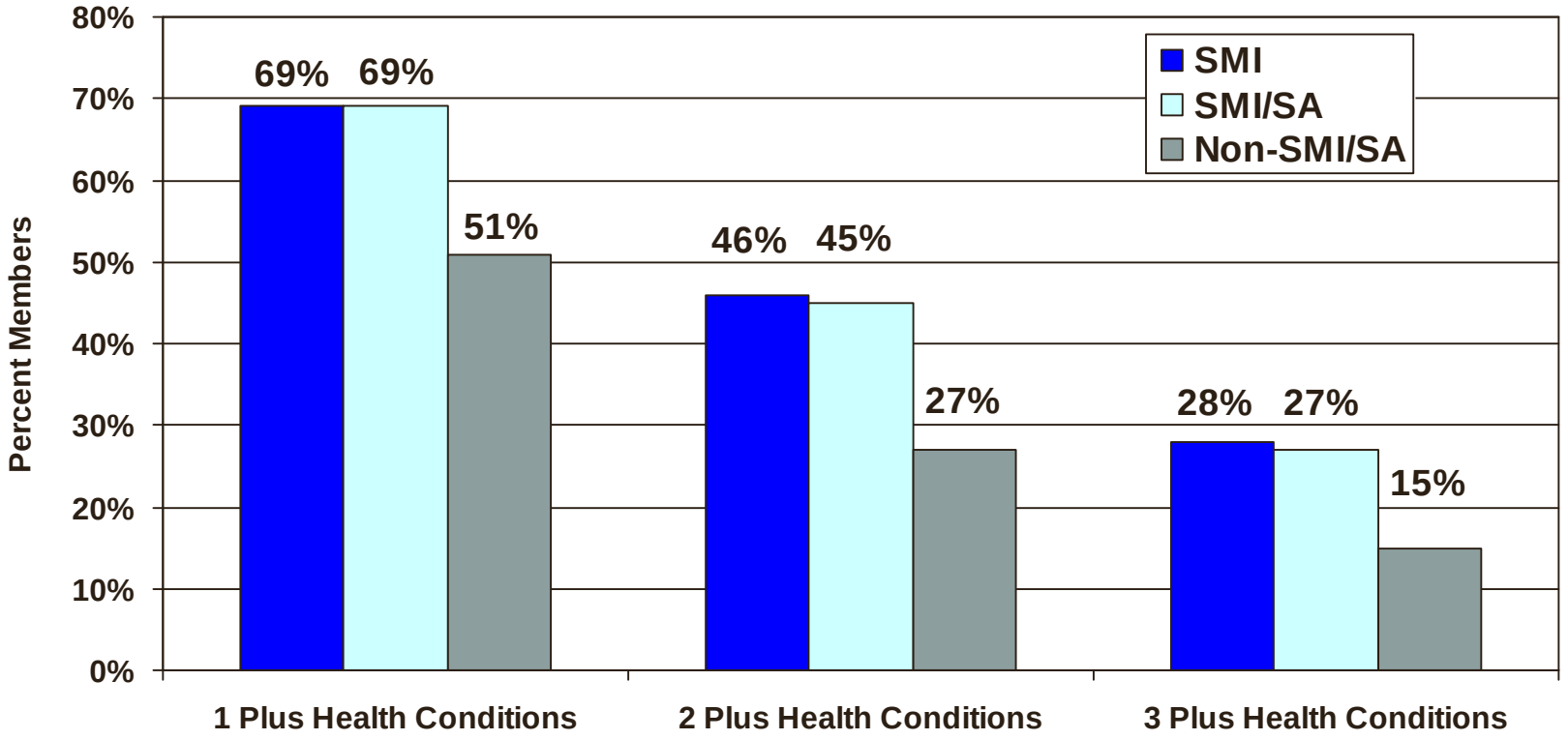
AZ, MO, OK, RI, TX, UT, VA, VT

- public mental health patients
- receiving services > 1997 to 2000
- SMI = bipolar, MDD, schizophrenia, ADHD

↑ 50-100% More Medical Problems in SMI
Maine Medicaid - 2004



Burden of Medical Illness:
Maine Medicaid 2004



Causes of Death 1997-2000…

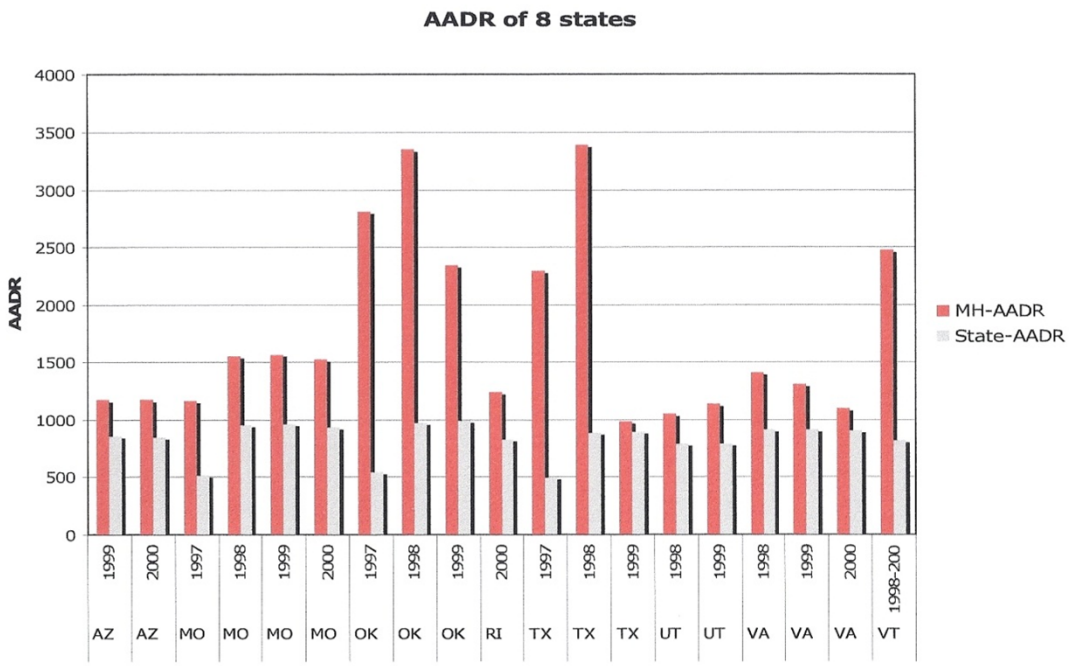
SMI deaths		non-SMI deaths	
cardiac	17-31%	cardiac	21-30%
cancer	5-10%	cancer	18-22%
suicide	5-9%	stroke	5%
chronic respiratory	4-5%	chronic respiratory	2-4%
stroke	2-5%	diabetes	2%
diabetes	1-3%	suicide	0.3-1%

Mortality Among Public MH Patients

annual death rates

SMI 1 - 3.5%

non-SMI 0.5 - 0.8%



Mortality Data for SMI

average age at death: 49 to 60

13-30 years earlier than expected

II. America’s Drug Problem

U.S.A.: Psychiatric Drugs 2009

[Source: Express Scripts 2009 Drug Trend Report]

antidepressants	10%	31,000,000
anticonvulsants	4%	12,300,000
stimulants	2%	6,754,000
*antipsychotics	2%	5,526,000

*part of Express Scripts' "mental/neurological" class:
includes lithium, dementia drugs, sub. abuse

U.S. = 4.5 % of world population

Approximately

90% of stimulant sales

60% of AP sales

50% of AD sales

40% of AED sales

National Vital Statistics preliminary data - 2011

1)	cardiac disease	596,339
2)	cancer	575,313
3)	chronic lower respiratory	143,382
4)	stroke	128,931
5)	accidents (unintentional injuries)	122,777
6)	Alzheimer’s disease	84,691
7)	diabetes mellitus	73,282
8)	influenza and pneumonia	53,667
9)	kidney disease	45,731
10)	intentional self-harm	38,285

JAMA (2000)

COMMENTARY

Is US Health Really the Best in the World?

☠ ADVERSE EFFECTS ☠

106,000 inpatient deaths

199,000 outpatient deaths

305,000 deaths from Rx

National Vital Statistics preliminary data - 2011

1)	cardiac disease	596,339
2)	cancer	575,313
3)	adverse drug reactions	305,000
4)	chronic lower respiratory	143,382
5)	stroke	128,931
6)	accidents (unintentional injuries)	122,777
7)	medical errors	98,000
8)	Alzheimer's disease	84,691
9)	diabetes mellitus	73,282
10)	influenza and pneumonia	53,667

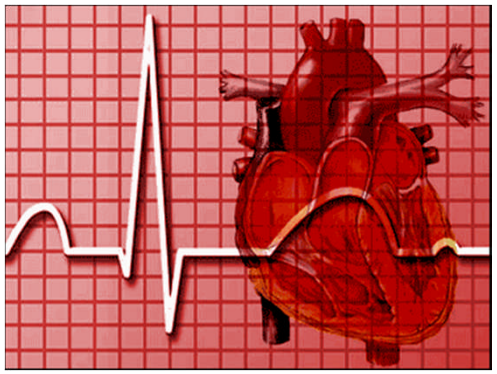
Reminder:
Compared to non-SMI, SMI patients:

- experience more illnesses than non-SMI
- die in greater numbers each year
- die earlier than expected


Drug Effects on Health of SMI

Heart Disease

#1 Cause of Death 2011



	APs	ADs
sudden death	↑2-4X	↑1.5-3.6X
heart attacks	↑5X	↑1.2-1.85X
		8-11%

Stroke

#4 Cause of Death in 2011

APs	ADs	AEDs
↑1.4-3.5X	↑1.2-2X	↑2.5-3.7X
2-4%	2 to 10%	

Diabetes Mellitus

#7 Cause of Death in 2011

APs	ADs	AEDs
↑7X	↑2X	↑2-3X

general population	9% (lifetime)
APs	≥ 20-30%
ADs	10-20%
AEDs	probably 15-25%

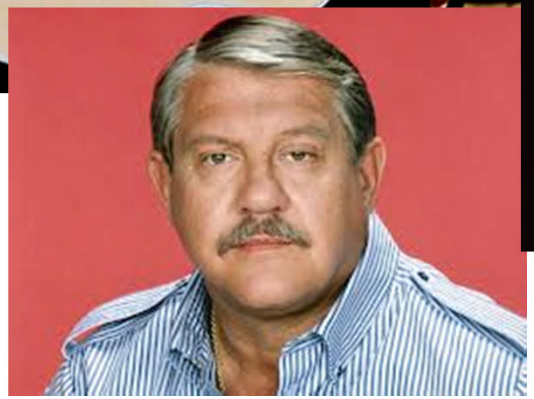
Psychiatric Drugs and Death

general population	~ 1% die per year
SMI (1997-2000)	up to 3.5% per year

lithium	15% dead in 5 to 10 yrs
ADs	20% dead in 10 yrs
APs (in general)	20-33% dead in 10 yrs

Hold on to your seat!

III. Brain Damage




THE EPIC RED SOX FAIL OF 2012
WHAT MAKES A MAN KICK?
NFL CONCUSSIONS
The Other Half Of the Story
One of many women caring for retired NFL players, Laurie Navon frequently has her picture taken with her boyfriend, Jim McMahon—in case he wakes up one day and no longer remembers her
By Melissa Segura


OHIO STATE
OHIO


IT'S TIME TO FACE ALZHEIMER'S
ESTIMATED 1 IN 8 BOOMERS AT RISK
BOOMER EXPRESS
1946
HONDA
alzheimer's association
pfizer

What is dementia ?

Dementia defined:

From Latin *de mens / de mentis*

“out of (away from) one’s mind”

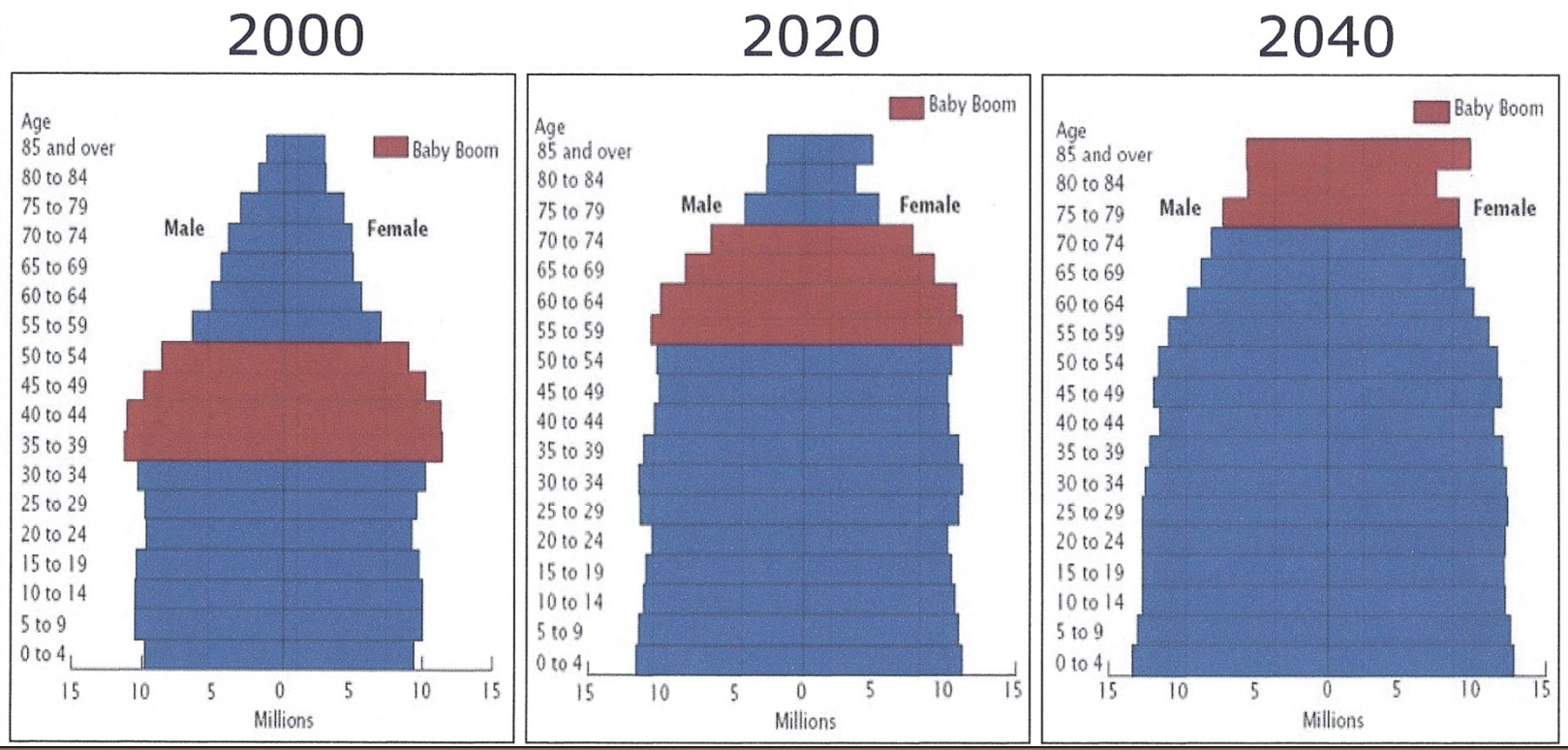
Features of Dementia

- ❖ Memory impairment
- Aphasia (impaired language)
- Apraxia (impaired ability to carry out motor activities)
- Agnosia (failure to recognize objects)
- Executive functioning deficits
  planning/organizing/abstracting
- BPSD = behavioral and/or psychiatric

≥ 65 years of age

12% to 18% to 21%

U.S. Population Pyramids



2.5% with dementia 2000 >> 4.5% with dementia in 2040

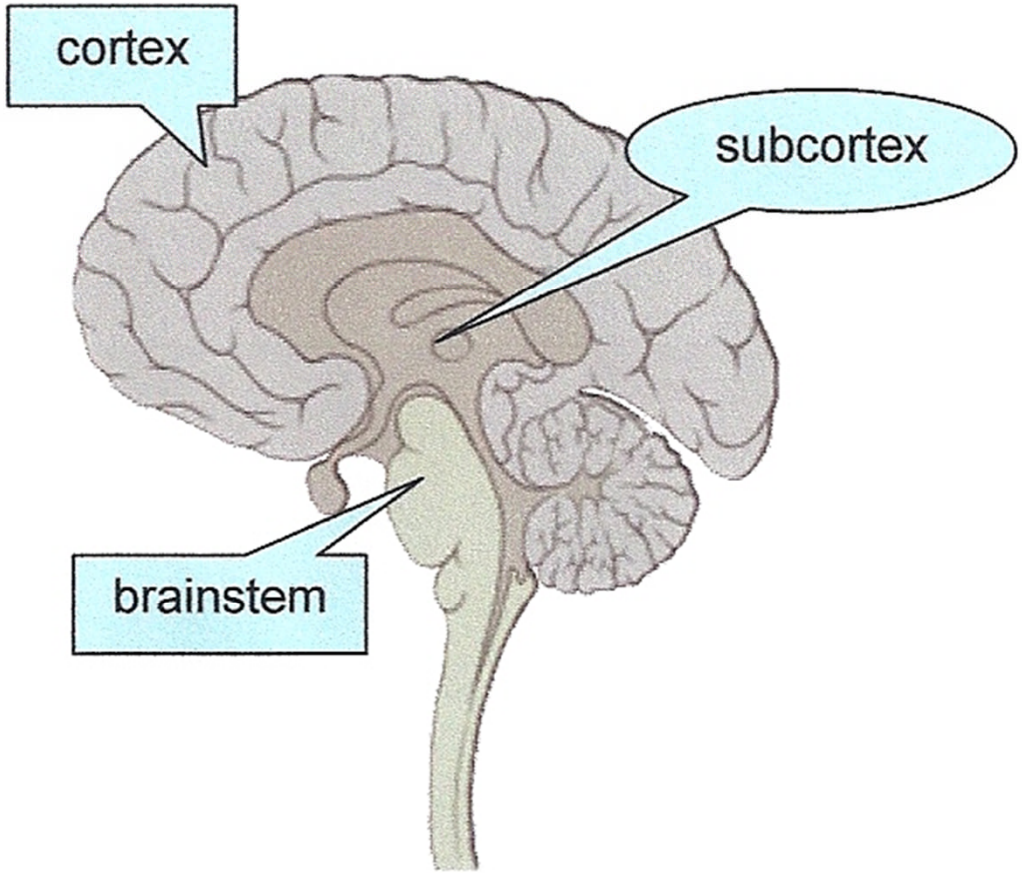
7.5 million 18 million

Prevalence of Dementia

Entire US (2000):	~ 2.5%
of 65 and older:	5-8%

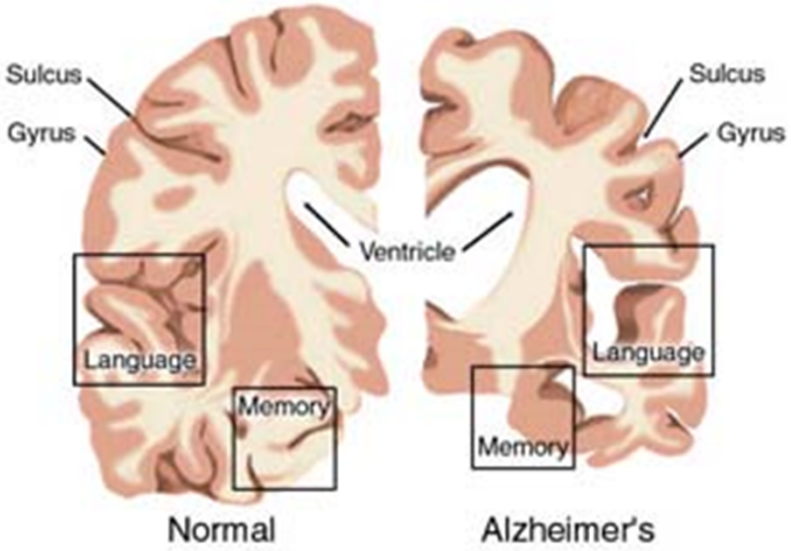
40-65	1/1000	0.1%
66-70	1/50	2%
71-80	1/20	5%
81+	1/5	20%

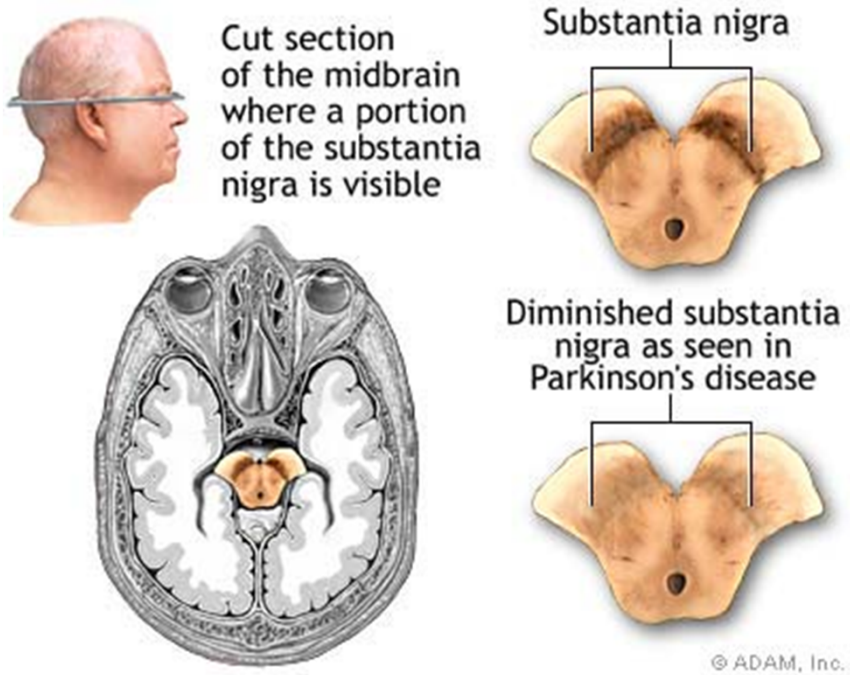
How do physicians think about dementia ?



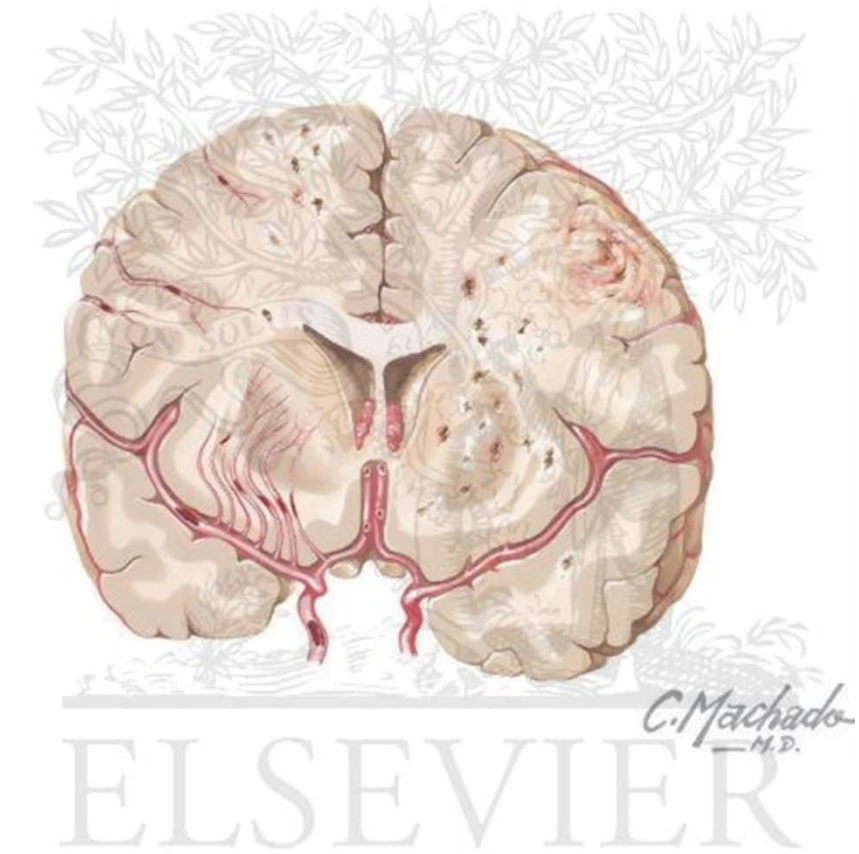
candy coating = cortex
tootsie roll center = subcortex
lollipop stick = brainstem

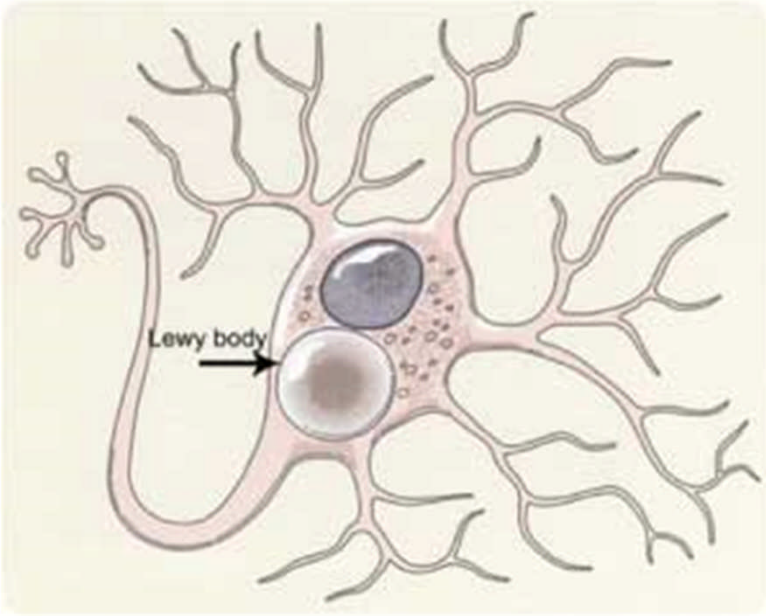
Location

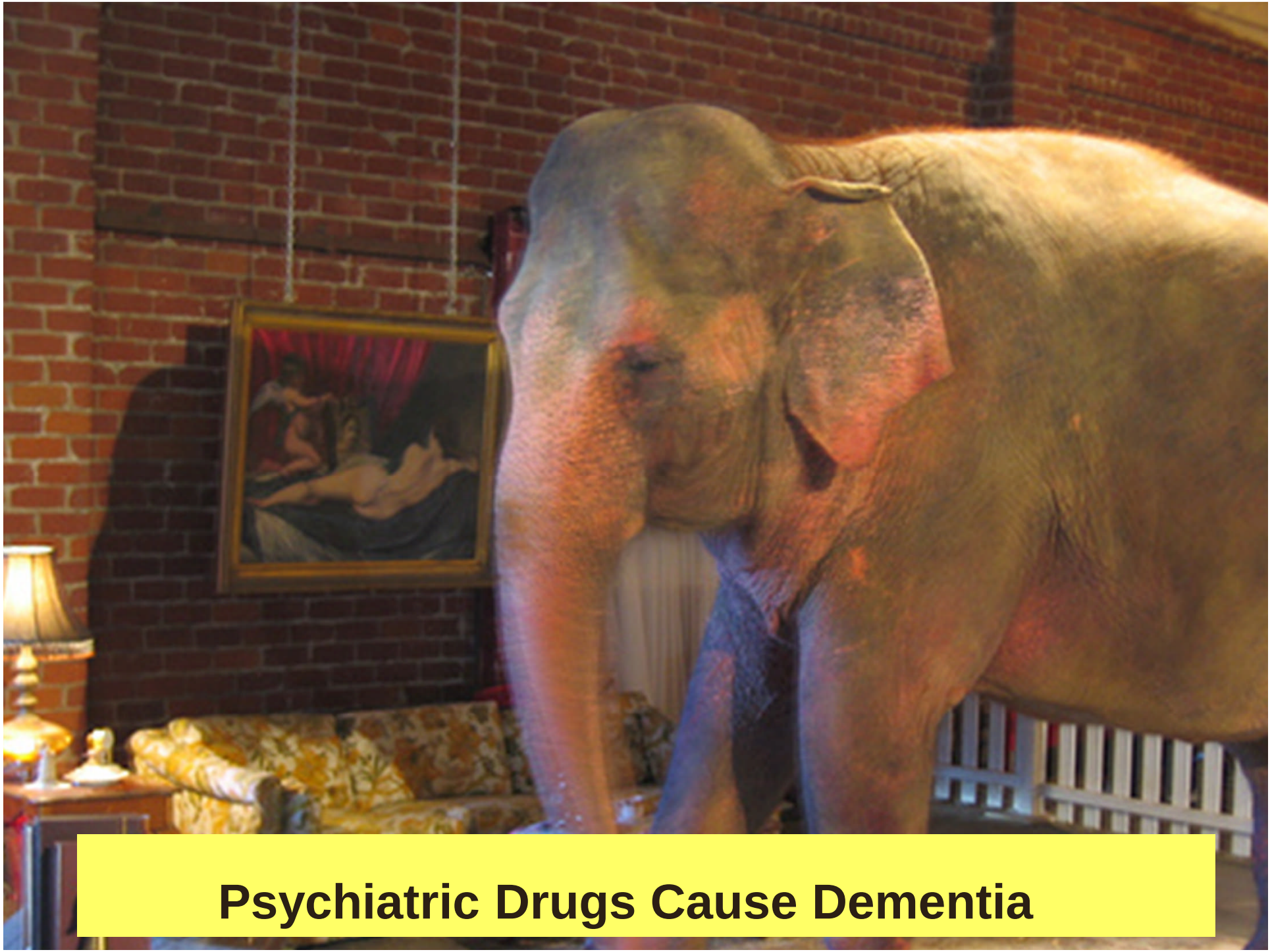

Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

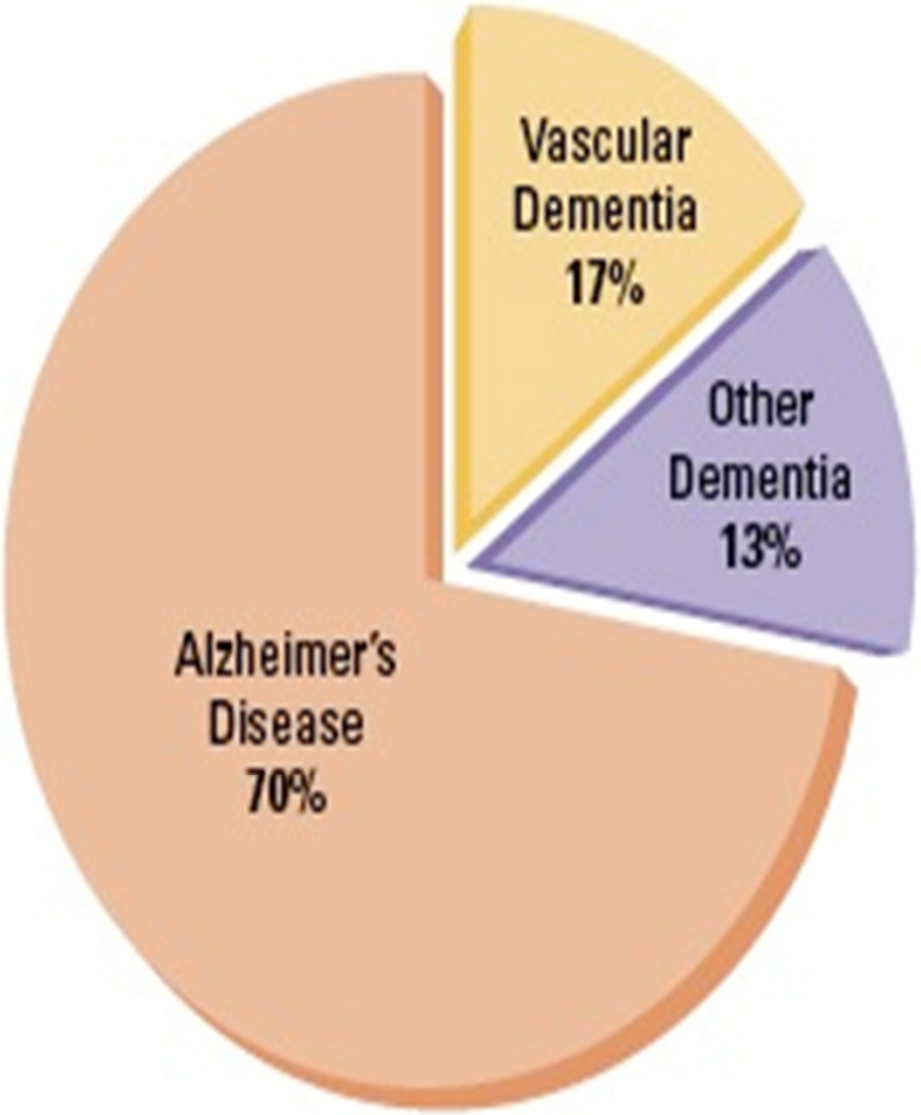

Cut section of the midbrain where a portion of the substantia nigra is visible
Substantia nigra
Diminished substantia nigra as seen in Parkinson's disease
© ADAM, Inc.

Pathology






Psychiatric Drugs Cause Dementia

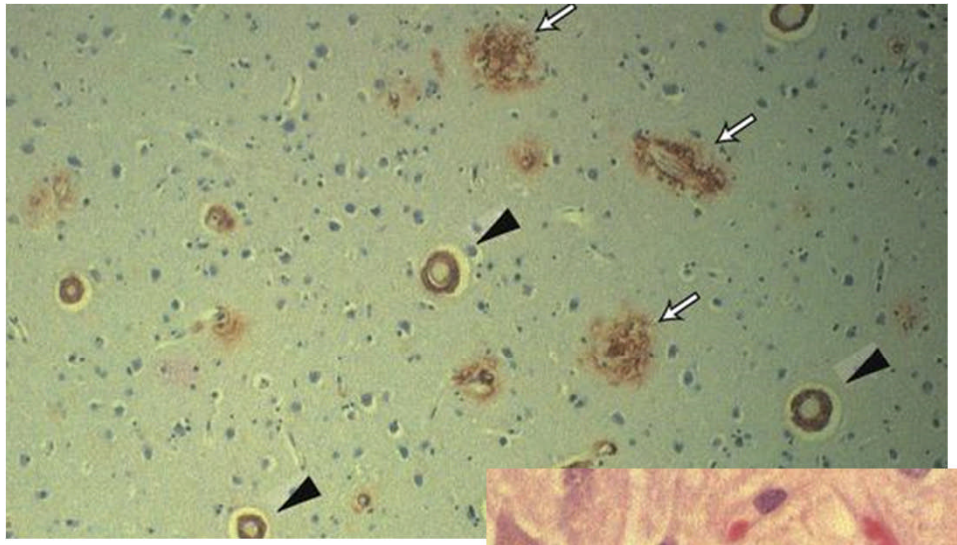


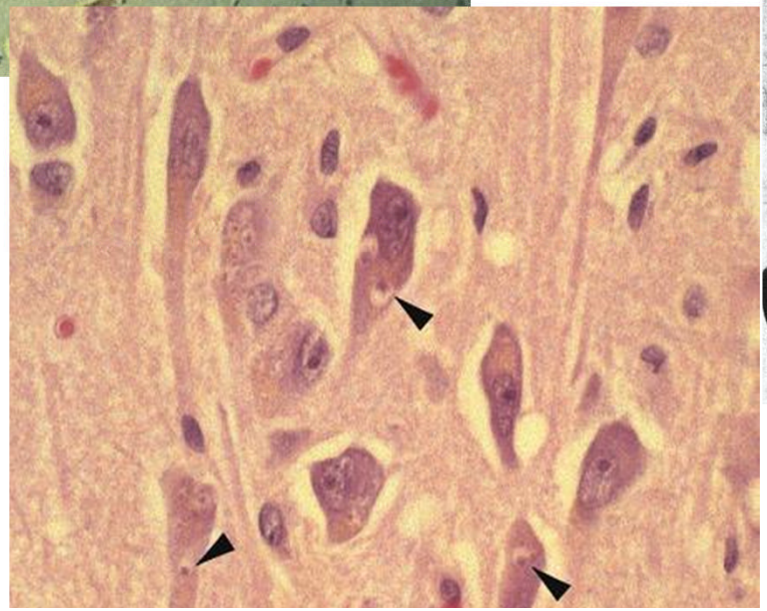
Psychiatric Drugs Cause Dementia

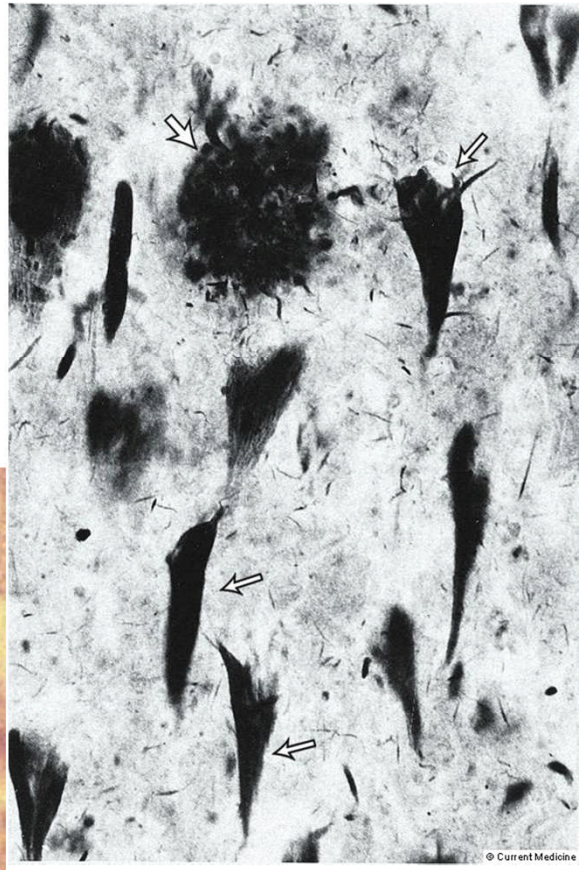
dementia: ~ 2.5% of population

APs	↑6-14X risk	≥ **50-85%**
ADs	↑2-5X risk	**4-6%**
AEDs	(bipolar)	**4-9%**
lithium	↑2X risk	**5-30%**
benzos	↑2-3X risk	**5-30%**

Alzheimer’s Pathology







Diagnosis is Not Easy…

criteria	what gets counted
Khachaturian	plaques; neocortical tangles
CERAD	neuritic plaques
Braak staging	tangles in neocortex/ERC/HC
Tierney criteria	NP in HC or NC; NFT in NC
NIA-RI	NP density/NFT by distribution

Alz Disease and AP Drugs

…despite longstanding confusion about pathological criteria for Alz. Disease,

…numerous studies have documented unexpectedly high rates of tangles and/or plaques in patients exposed to antipsychotic drugs

NY Office of Mental Health

Prohovnik et al – 1993

reviewed path diagnoses and clinical notes of patients autopsied 1/1/78 to 12/31/87

1046 cases

89% died after age 60

mean age at death: 75.2

NY Office of Mental Health

compared three groups of patients

	schiz	dementia	affective
clin AD	28%	51%	15%
path AD	56%	74%	43%

general population ≥ 65: 2 to 5.6% develop AD

AD = Alzheimer's disease

Swiss Brain Bank

Wisniewski et al – 1994

83 subjects > all with schizophrenia

all died at age 70 or older

41 died 1932-1952	36% tangles
62 died after 1953	74% tangles

AP exposed: 25% loss of neurons in HC

Pilgrim Psych Center – Part 1

Purohit et al – 1998

100 elderly patients > schizophrenia

age range: 52 to 101

mean age at death: 78.5

lifetime or retrospective assessments > Clinical Dementia Rating Scale to assess dementia (caregiver notes, records, exams)

Pilgrim – Part 1

72% were moderately to severely demented

52% had abnormal brain pathology

9% met Khachaturian criteria for Alz disease

of the schizophrenia patients with SPs (47%)

33% more SPs than other psych patients

89% more SPs than age-matched controls

37% more tangles than age-matched controls

SPs = senile plaques

Pilgrim – Part 2

Rapp et al – 2010

196 consecutive brain donations to

Mount Sinai SOM/Dept of Psych Brain Bank

Is there a link between AD pathology and dementia severity ?

[this analysis used CERAD criteria]

Pilgrim Psych Center – Part 2

Of 196 brains, removed 86 patients from this analysis due to known neurodegeneration

44% had definite neurodegeneration

57 patients with AD pathology

21 with dx of Lewy Body

4 with Parkinson's, 4 with VaD

Pilgrim Psych Center – Part 2

Of the remaining 110 brains

45% had significant brain pathology

NP density was 50% of Alz disease
tangle density was comparable to Alz.

Of these remaining 110 patients

85.5% were clinically demented

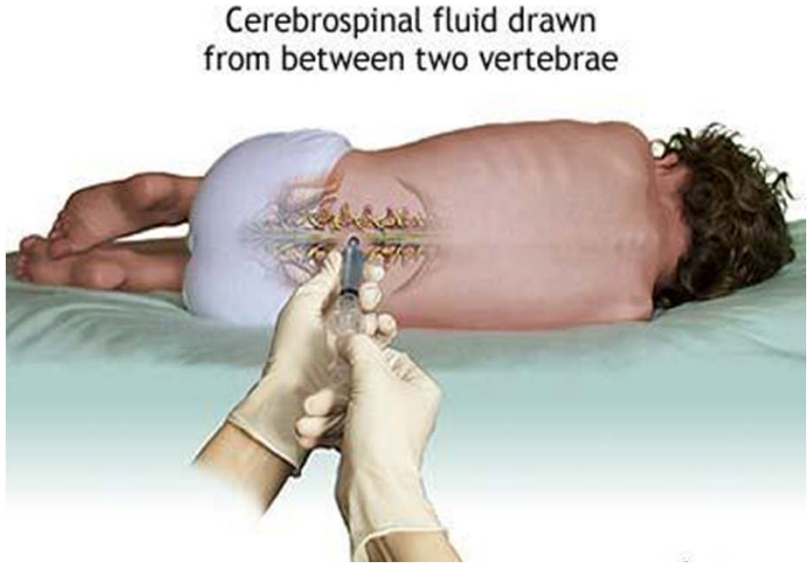
Big Picture

of 196 brains…

~70% had neurodegenerative diseases

55% developed Alzheimer's pathology

Alzheimer’s Biomarkers



Lumbar Spinal Tap

High levels of:

tau

phosphorylated tau

Low levels of:

AB-42

Brescia, Italy

Frisoni et al – 2011

compared spinal fluid

schizophrenia

Alzheimer's patients

control group

surgery requiring

spinal anesthesia

Brescia, Italy

	Schiz	Alz	controls
	n=11	n=20	n=6
mean age	69	71	61
Illness	45 yrs		
*FGA	45%		
*SGA	73%		

*current drug use
FGA = first generation antipsychotic drugs
SGA = second generation antipsychotic drugs

Brescia, Italy

lumbar CSF concentrations

	schiz	Alz	controls
AB42 (pg/mL)	465	352	638

on average > schiz 27% lower than controls

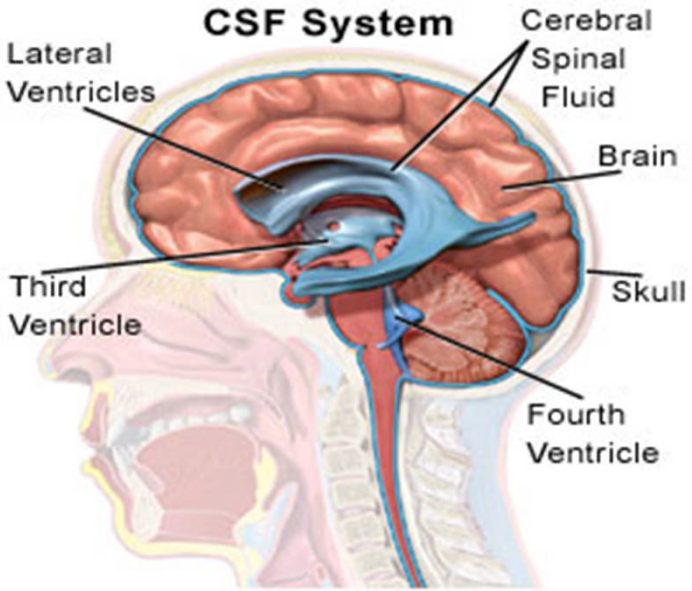
Brescia, Italy

on 6 of 8 tests of neurocognitive functioning schiz. patients were ***much more impaired than Alzheimer's disease patients***

immediate and delayed recall, letter fluency, trail making A, category fluency, visuospatial

London, UK

Clarke et al - 2011



compared 32 patients

neurosurgery for severe depression

biomarkers from ventricles (fluid-filled spaces of the brain)

London, UK

drug use within 2 weeks of surgery

	AP	no AP
	n=16	n=16
mean age	49.8	52.4
AB40	727.3	440.9
AB42	72.1	60.0
total tau	945	534.3
P-tau	98.6	88.1

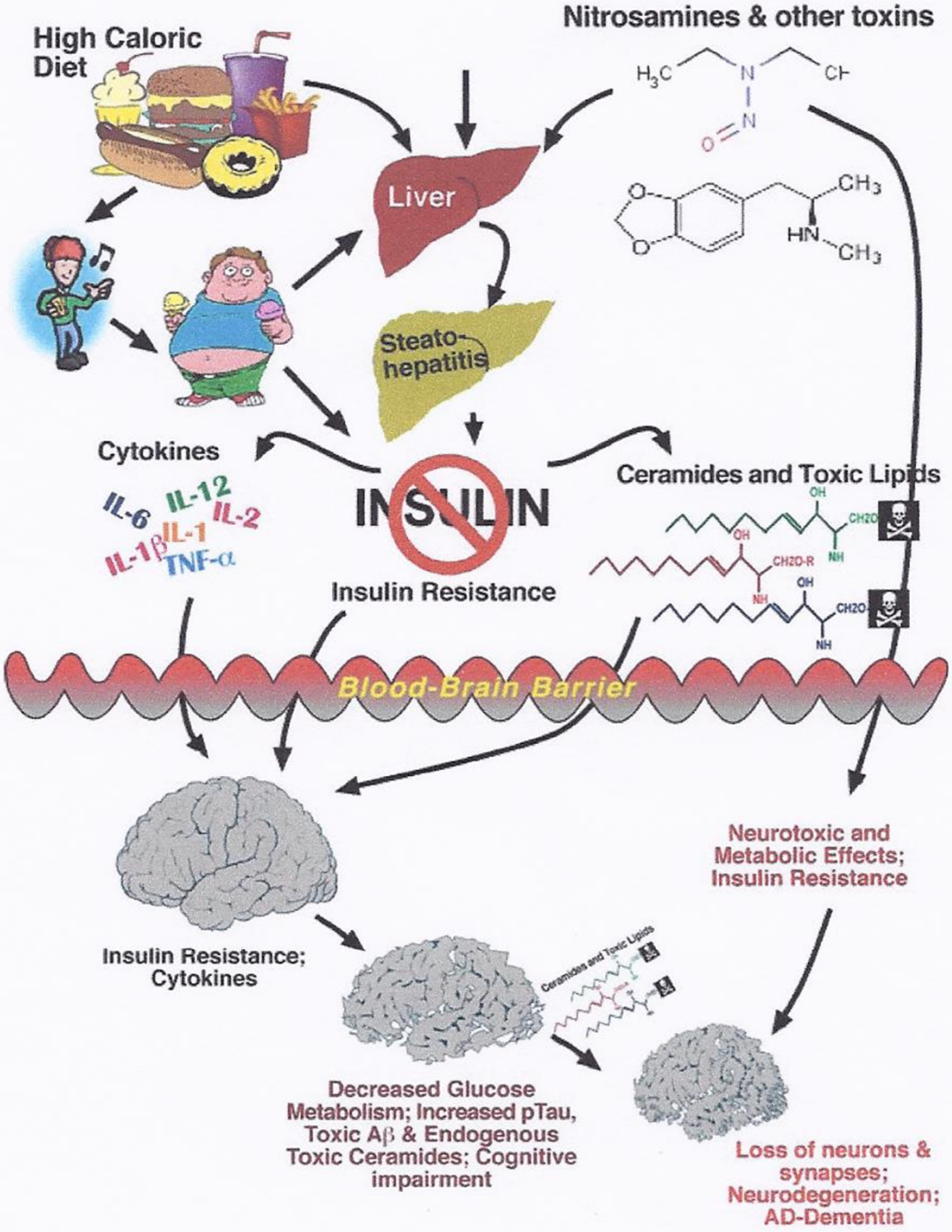
Why is this happening ?

Type I diabetes	juvenile onset insulin deficiency
Type II diabetes	insulin resistance
Type III diabetes	brain (↓ ins + IR)

Type III Diabetes

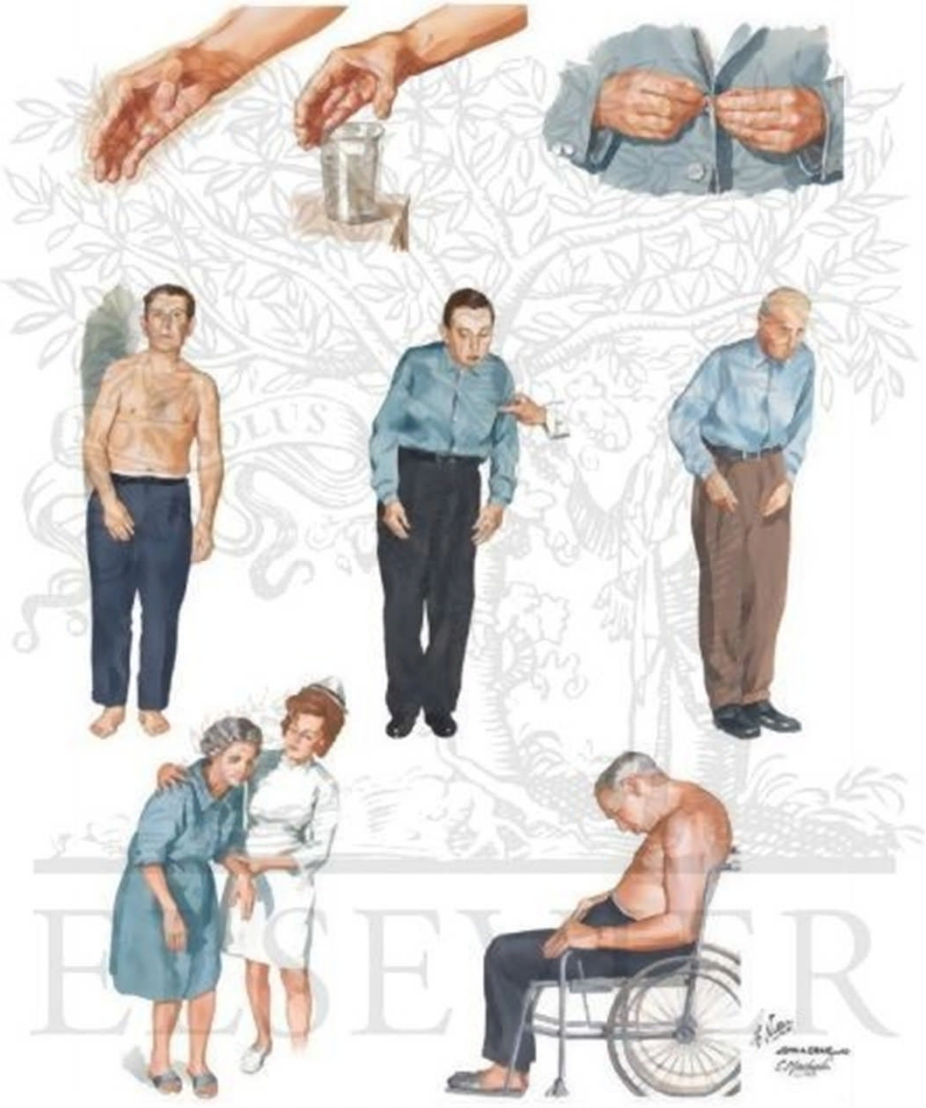
decreased insulin signaling in the brain:

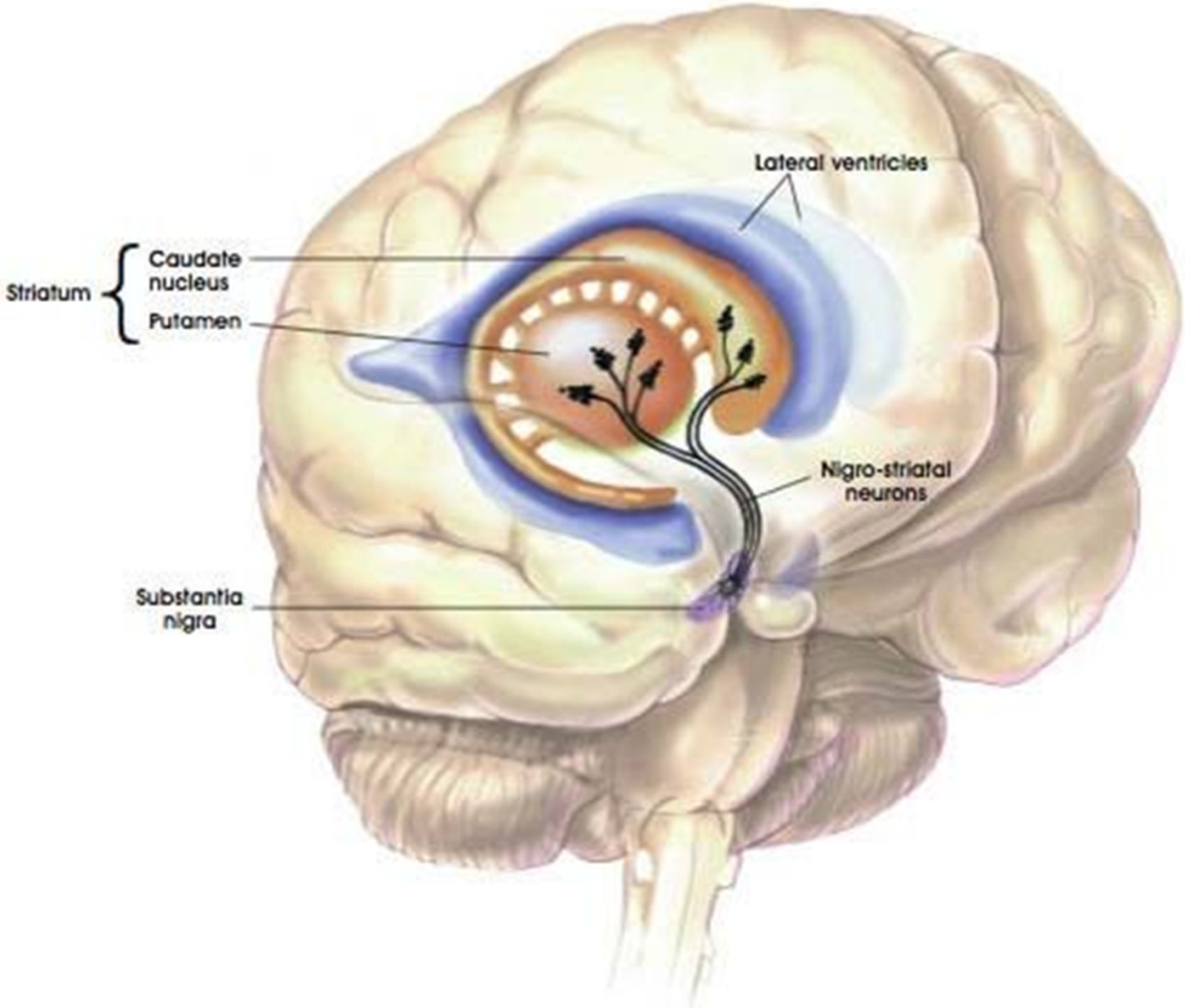
- decreased glucose > less energy
- damage to blood vessels > low blood flow
- more tau and phosphorylated tau
- more B-amyloid plaques
- more cell destruction and cell death


High Caloric Diet
Nitrosamines & other toxins
Liver
Steato-hepatitis
Cytokines
IL-6
IL-12
IL-2
IL-1β
IL-1
TNF-α
INSULIN
Insulin Resistance
Ceramides and Toxic Lipids
Blood-Brain Barrier
Neurotoxic and Metabolic Effects; Insulin Resistance
Insulin Resistance; Cytokines
Decreased Glucose Metabolism; Increased pTau, Toxic Aβ & Endogenous Toxic Ceramides; Cognitive impairment
Loss of neurons & synapses; Neurodegeneration; AD-Dementia

Parkinson’s Disease

JAMES CAVALLINI/PHOTO RESEARCHERS, INC.

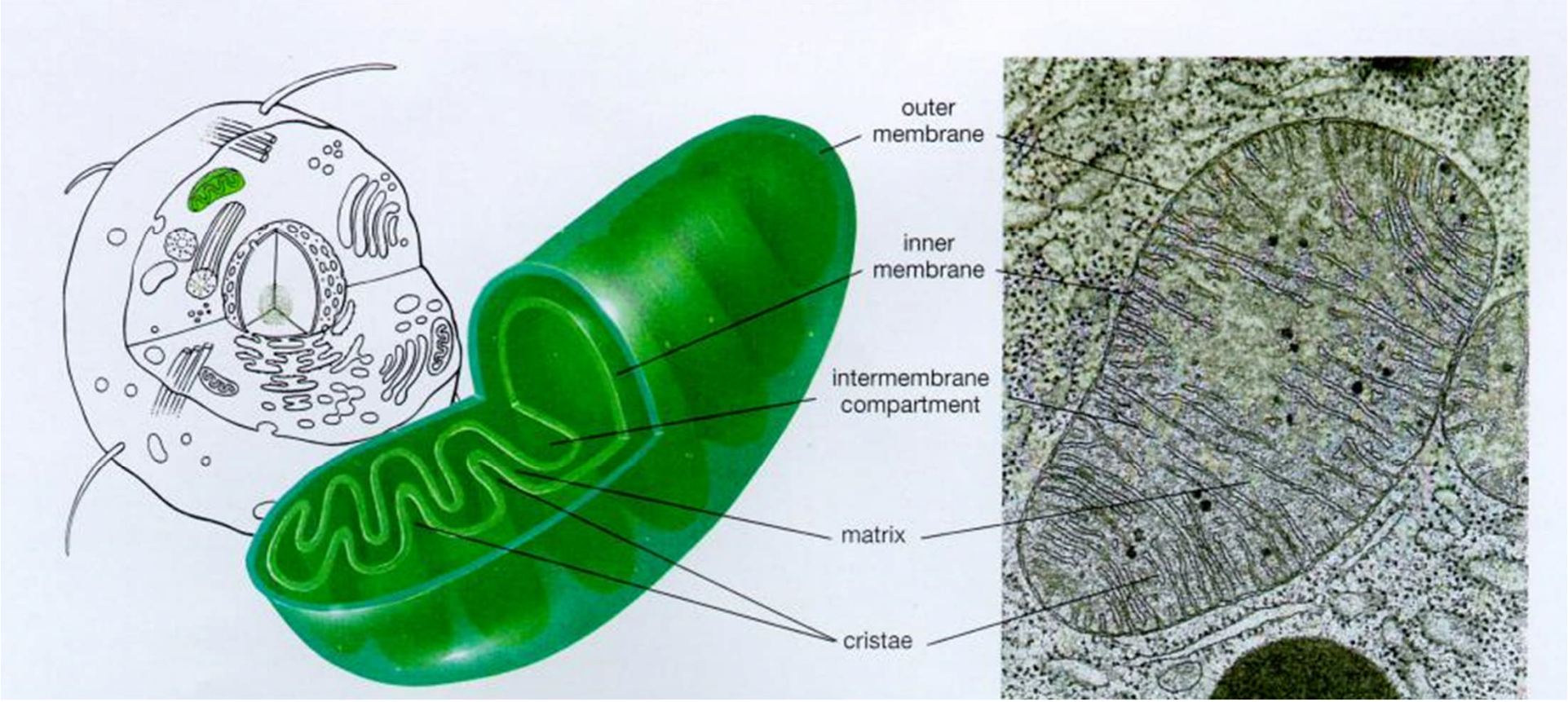



Lateral ventricles
Striatum
Caudate nucleus
Putamen
Nigro-striatal neurons
Substantia nigra

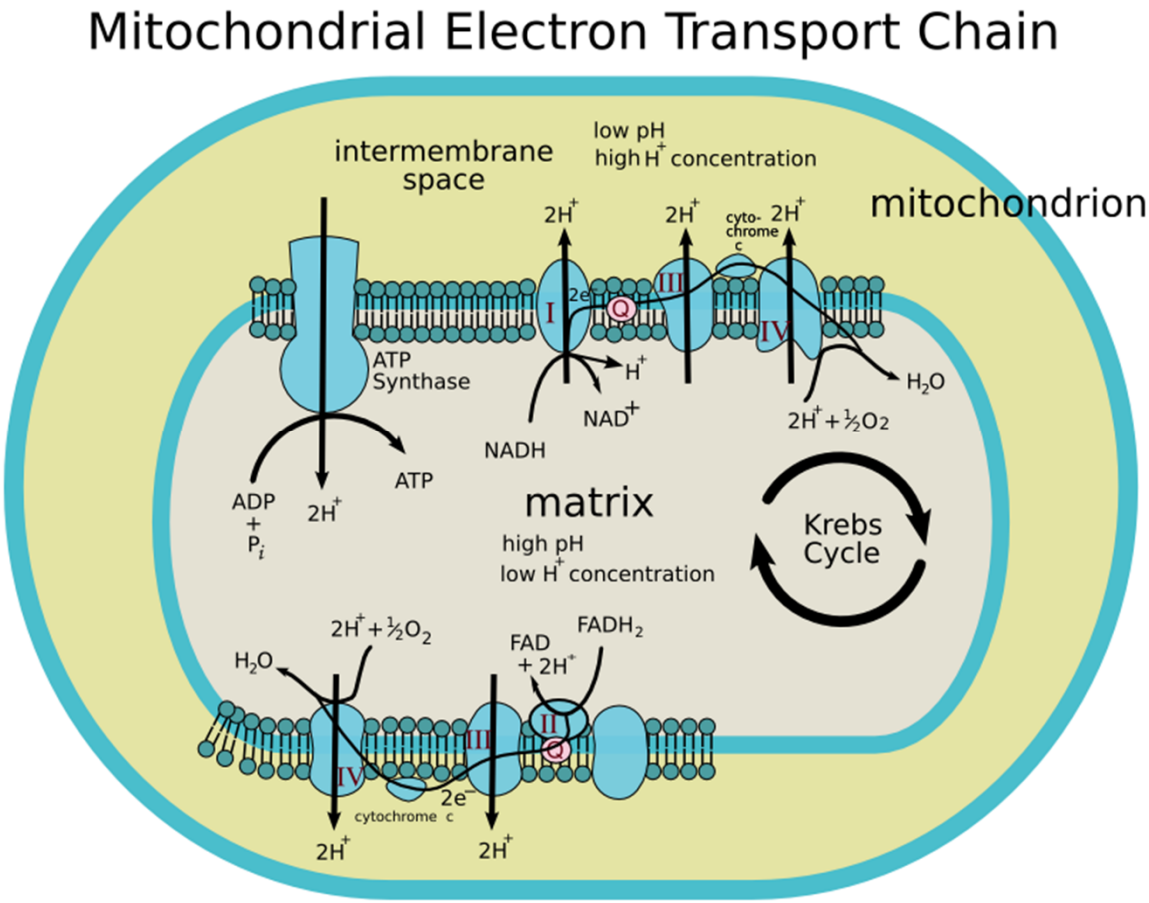
Which drugs ?

Antipsychotics	10-40%
Antidepressants	?
Stimulants	?
AEDs	?
Lithium	?

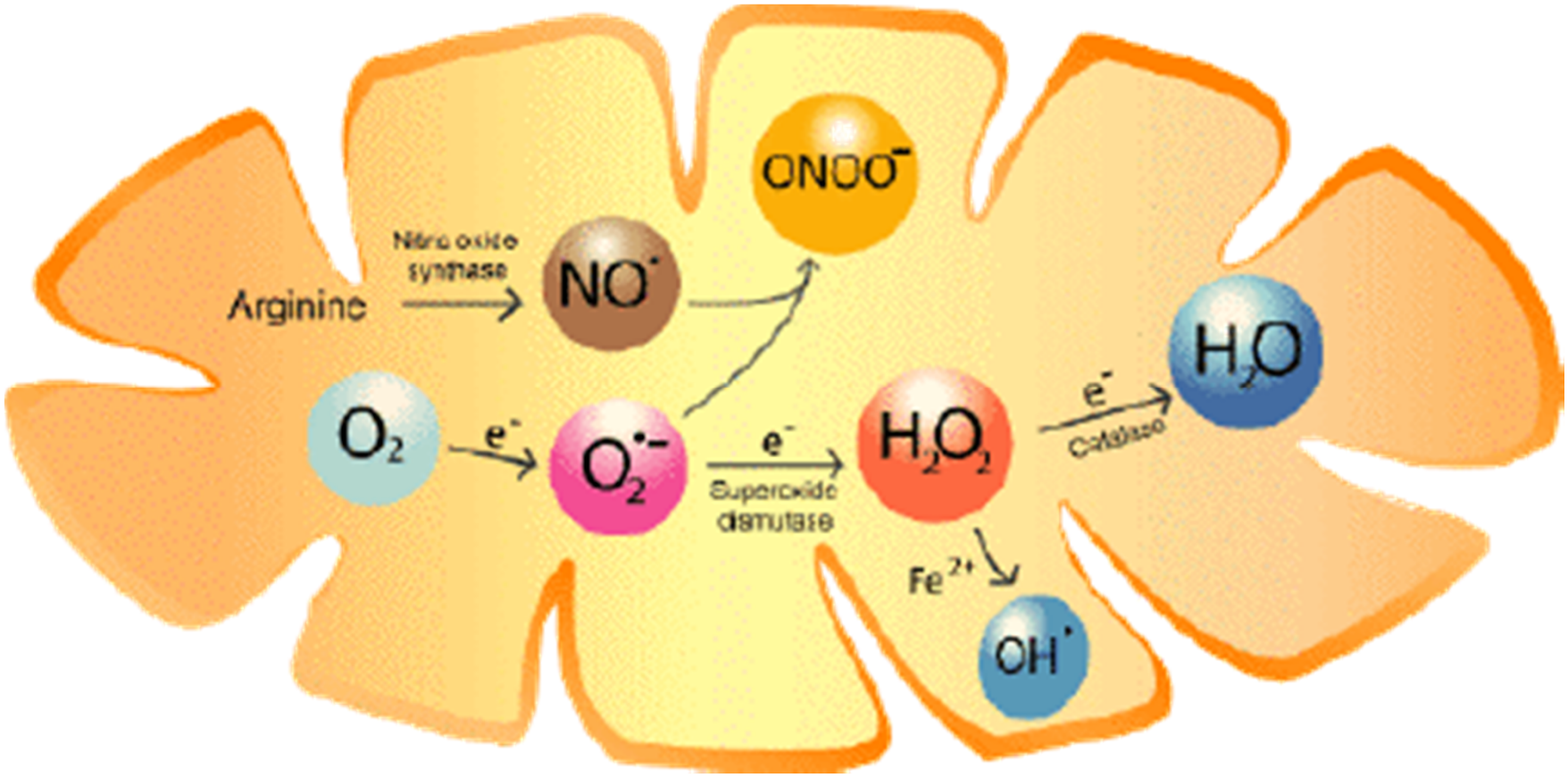
Why is this happening ?



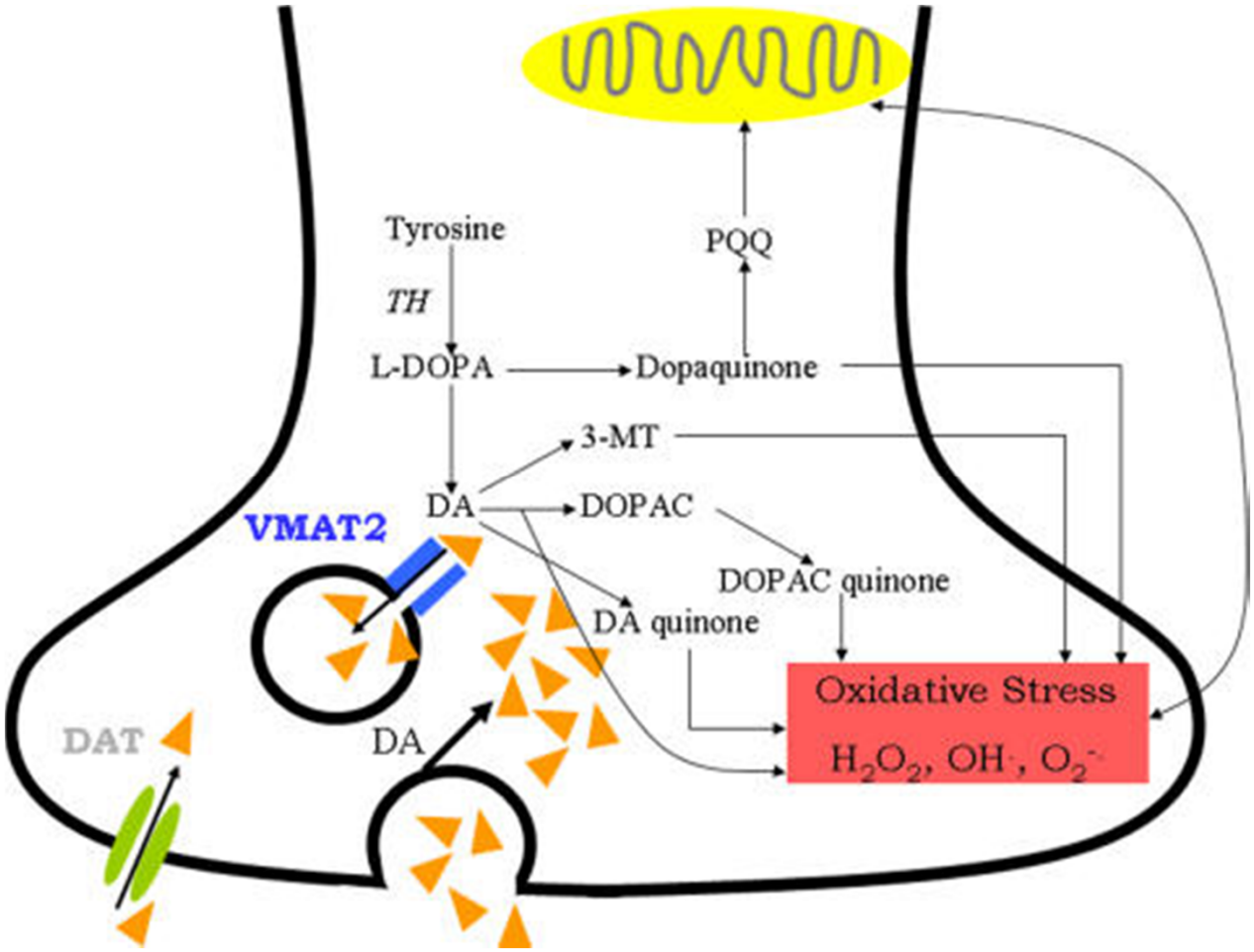
Psychiatric Drugs Impair Mitochondria



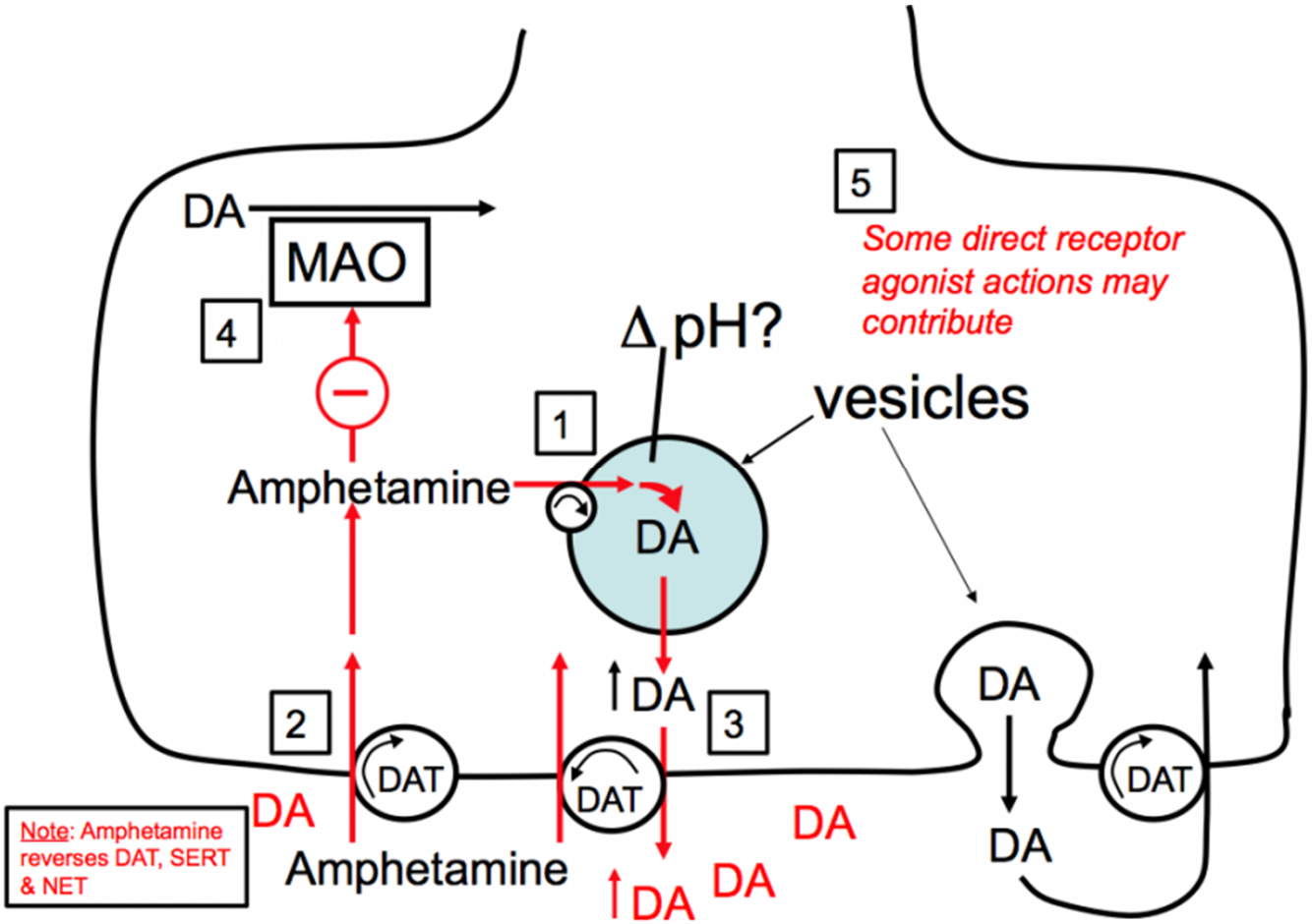
Psychiatric Drugs ↑ Oxidative Stress



oxidative stress



amphetamine



OPEN ACCESS Freely available online

PLoS one

Methylphenidate Exposure Induces Dopamine Neuron Loss and Activation of Microglia in the Basal Ganglia of Mice

Shankar Sadasivan[1], Brooks B. Pond[1,2], Amar K. Pani[1], Chunxu Qu[3], Yun Jiao[1], Richard J. Smeyne[1]*

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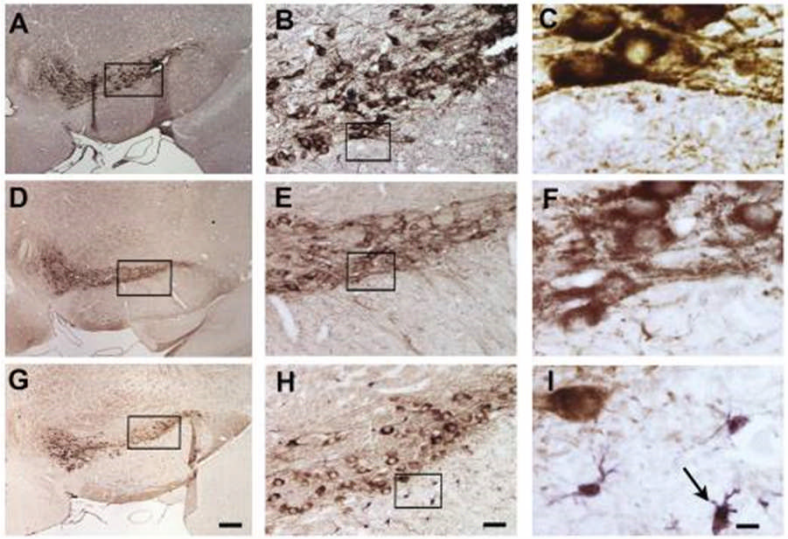
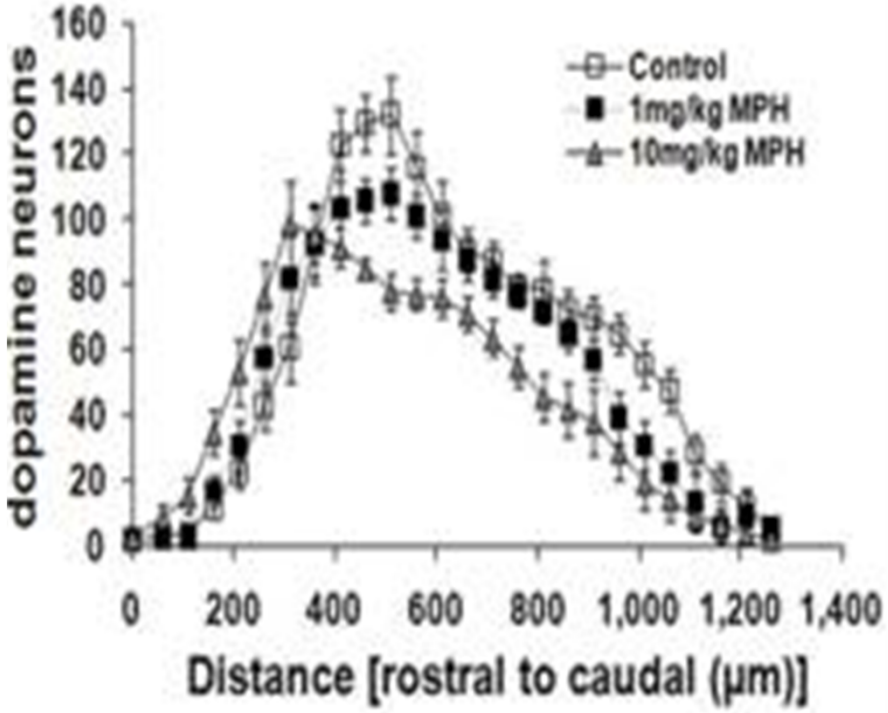
Abstract

Background: Methylphenidate (MPH) is a psychostimulant that exerts its pharmacological effects via preferential blockade of the dopamine transporter (DAT) and the norepinephrine transporter (NET), resulting in increased monoamine levels in the synapse. Clinically, methylphenidate is prescribed for the symptomatic treatment of ADHD and narcolepsy; although lately, there has been an increased incidence of its use in individuals not meeting the criteria for these disorders. MPH has also been misused as a "cognitive enhancer" and as an alternative to other psychostimulants. Here, we investigate whether chronic or acute administration of MPH in mice at either 1 mg/kg or 10 mg/kg, affects cell number and gene expression in the basal ganglia.



90 days of Ritalin > simulate childhood/teens

20% reduction in DA neurons at 10 mg/kg



“work supports studies that demonstrate that drugs which increase dopamine in the synaptic cleft can contribute to degenerative changes in the basal ganglia”

VAMC Depakote Study

Armon et al (1996)

36 Depakote patients

age range	22 to 74	(mean: 51.5)
duration of drug exposure:	1-11 years	(median: 3 yrs)

Under the influence of Depakote:

75% displayed signs/symptoms of Parkinson's disease
83% experienced hearing loss
86% were cognitively impaired

VAMC Depakote Study

After stopping Depakote:

Parkinsonian features improved in 96%

cognitive functioning improved in 72%

hearing loss improved in 48%

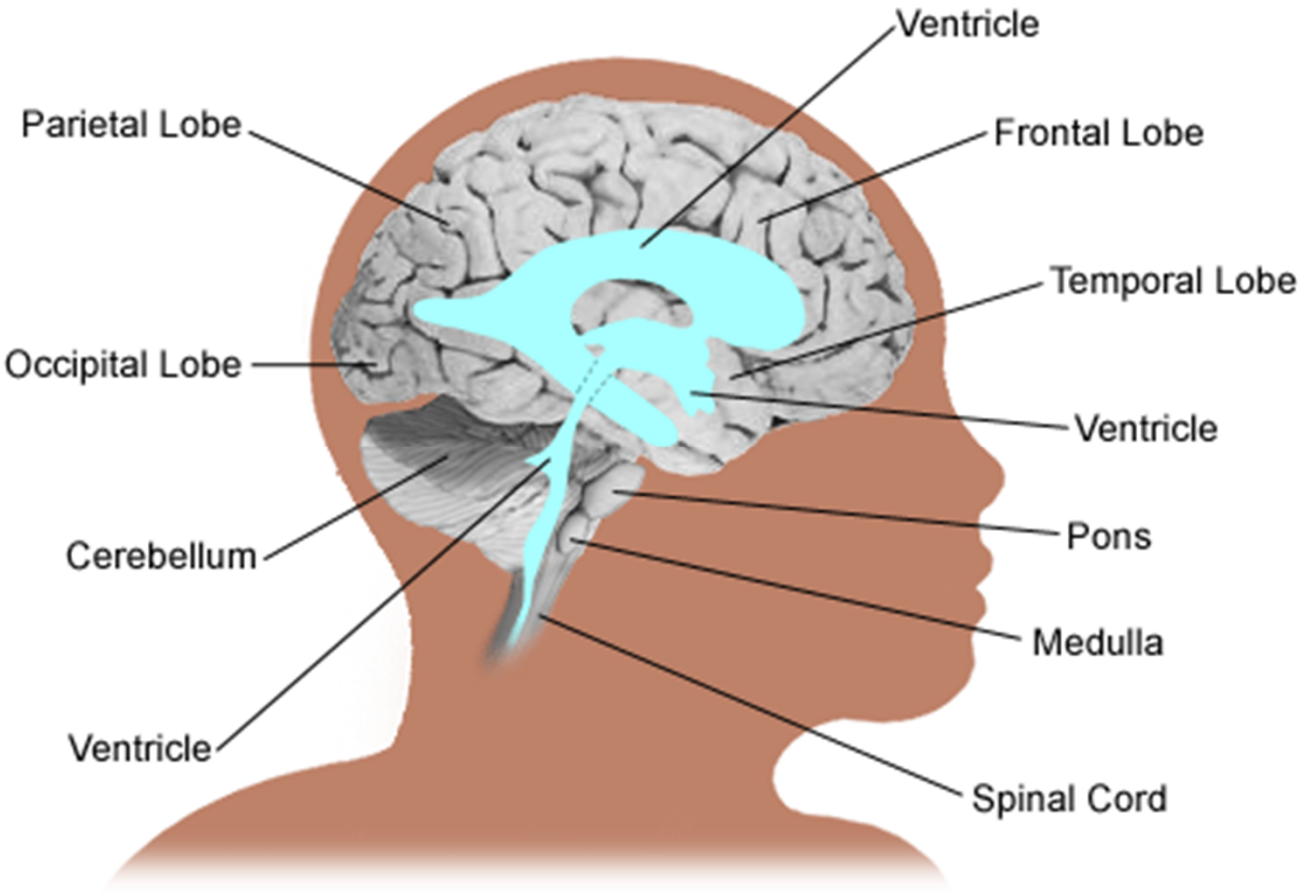
Other Causes of Drug-Induced Dementia

NPH

CJD

pseudo-tumor cerebri (PTC)

Dementia Due to Hydrocephalus



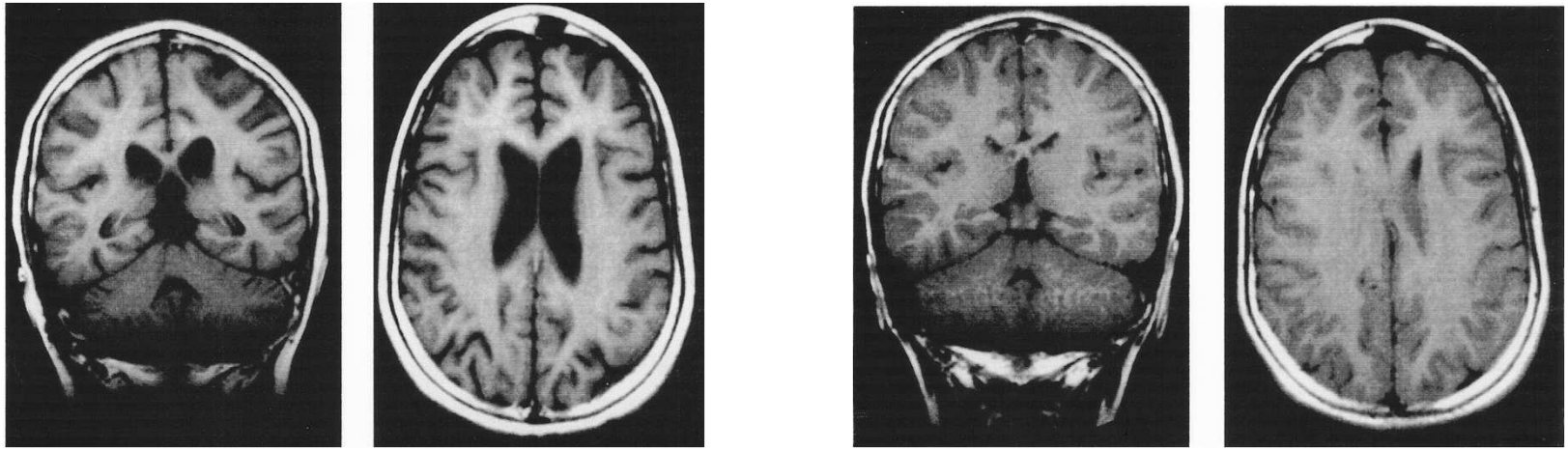
Depakote Induced Dementia

some patients develop hydrocephalus with dementia
others experience full-blown NPH

How often does this happen ?

there are many case reports in the medical literature
unknown #s of patients go undiagnosed or misdiagnosed

Depakote Dementia



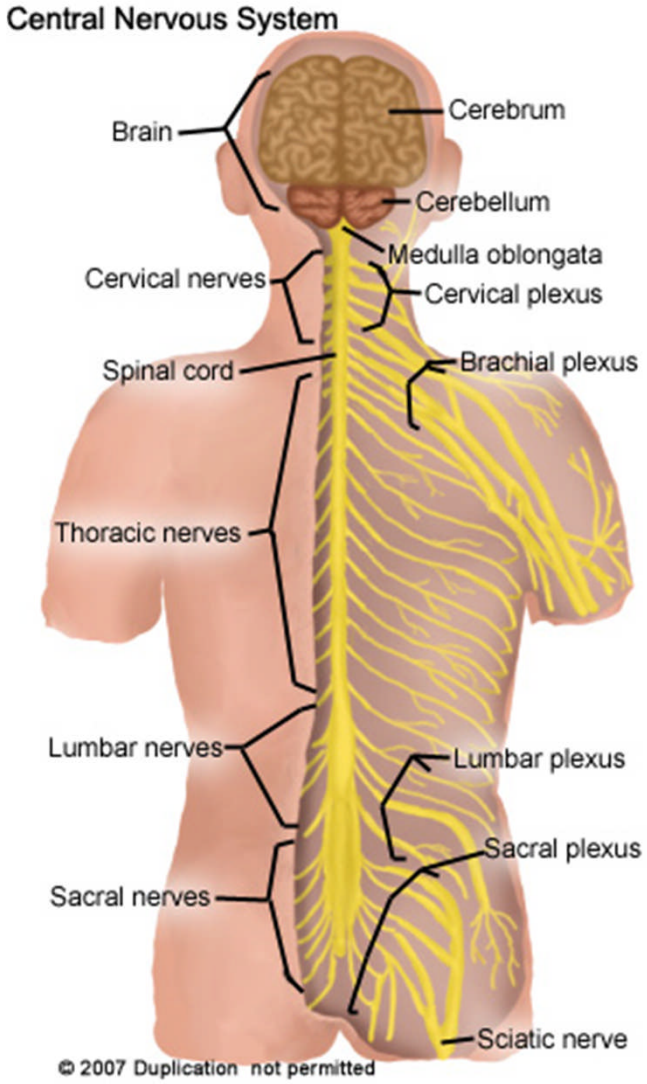
- 10 ½ yr old child on Depakote (+ AP + Cogentin)
- experienced 12 point drop in IQ over 1 year
- 1 yr after stopping drug >> brain shrinkage reversed

Nikolai Andrianov

15 medals > 7 gold, 5 silver, 3 bronze

died 3/21/11 at age 58 from MSA

MSA


Central Nervous System
Brain
Cerebrum
Cerebellum
Medulla oblongata
Cervical nerves
Cervical plexus
Spinal cord
Brachial plexus
Thoracic nerves
Lumbar nerves
Lumbar plexus
Sacral plexus
Sacral nerves
Sciatic nerve
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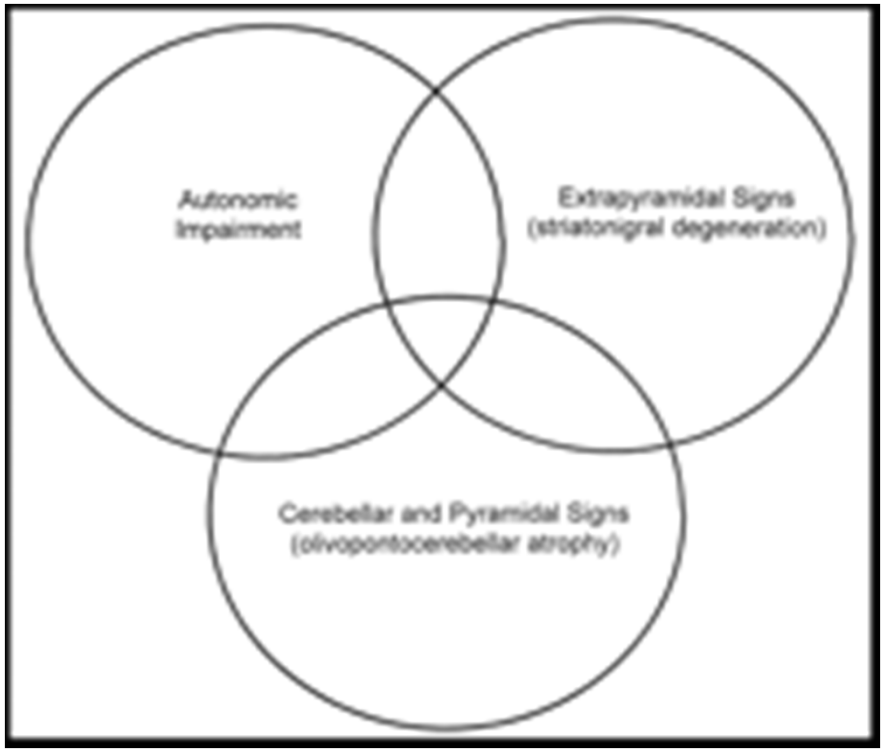
Autonomic Impairment
Extrapyramidal Signs (striatonigral degeneration)
Cerebellar and Pyramidal Signs (olivopontocerebellar atrophy)

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Multisystem Atrophy Made Worse by Lithium Treatment in a Hospice Patient: A Case Report

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Abstract

Multisystem atrophy is a neurologic condition defined as an adult-onset, progressive, neurodegenerative disease of unknown etiology. It carries a multisystem clinical course, including autonomic, urogenital, cerebellar, and parkinsonian features. Lithium toxicity, classically manifesting as increased thirst, polyuria, gastric distress, weight gain, tremor, fatigue, and mild cognitive impairment, can present in a similar manner.[1] We would like to present a patient diagnosed with progressive neurologic features typical of multisystem atrophy that also had bipolar disorder and had been taking lithium for many years. Despite normal lithium levels, it appeared as though a subclinical lithium toxicity was manifesting in the patient, and once lithium was discontinued, the patient was discharged from hospice with significant improvement in his presenting symptoms.

Keywords

multisystem atrophy, lithium, cerebellar degeneration, Shy-Drager syndrome, predominant parkinsonism, bipolar

IV. Brain Repair

Brain Repair

1) PharmARRU

2) Nutrition

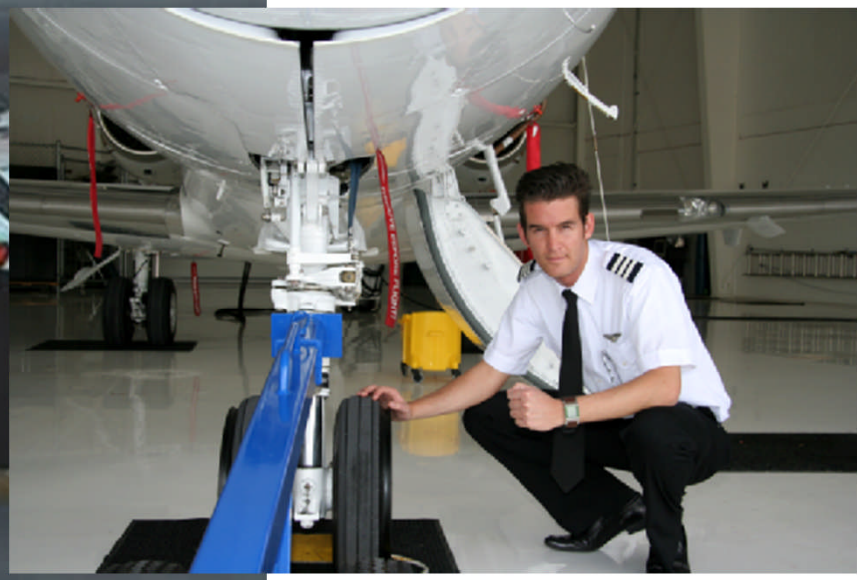
3) Lifestyle

PharmARRU

Pharmaceutical

- Avoidance
- Reduction
- Responsible Use


MALTA



Responsible Use Requires
Knowledge and Preparation

- medical history and current life situation
- active medical problems
- all of the patient's meds/supplements
- target organ toxicity
  - drug effects on medical conditions
- drug-drug interactions [DDIs]

Nutrition

1) Insulin sensitizers

2) Antioxidants

3) Fluid changers

Gingko biloba

EGb761

240 mg per day

PPAR agonist

↑ insulin sensitivity

chromium picolinate

150 to 1000 ug per day

increases IR number

lowers weight

↓ blood glc and lipids

curcumin (from turmeric)

↑ glucose uptake
GLUT4 to cell surface

boosts insulin sensitivity
PI3K/AKT paths

↑ pancreatic secretion
of insulin

decreases HbA1C levels

antioxidants

Polyphenols

resveratrol	red wine, grapeseed extract
green tea	(Epigallo-catechin-3-gallate)
Vitamin C	citrus, strawberries, tomatoes
Omega 3	DHA and EPA

(Gingko, curcumin)

vitamins

~50% of pharmaceuticals deplete vitamins

most critically > B1, B6, B9, B12, Vit D

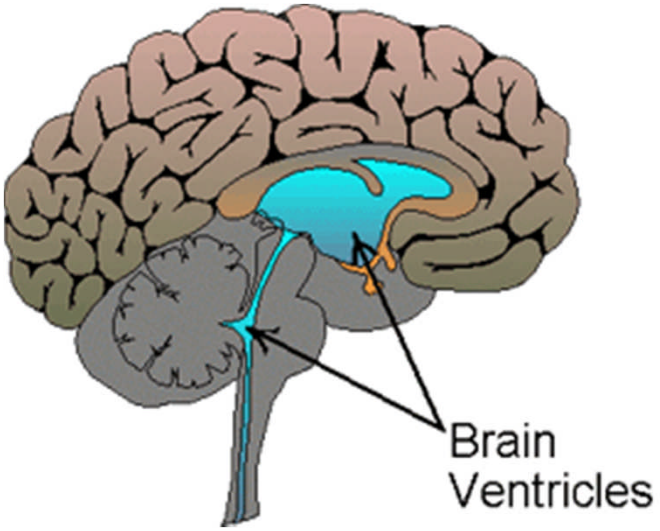
antacids

oral contraceptives

metformin

anticonvulsants

caffeine



Lifestyle

growing a healthy brain

physical exercise

time in nature

cognitive (mental) enrichment

social engagement

Recap

I. What's killing the mentally ill ?

sicker, ↓ lifespan (13 to 30 yrs)

II. America's drug problem

drugs are #3 cause of death each year

III. Brain Damage

IV. Brain Repair

PharmARRU, Nutrition, Lifestyle