Psychiatric Drugs

Training Lecture #1

Grace E. Jackson, MD

(last revised: 7/18/10)

Outline of Lecture

I. Major Classes of Psychiatric Drugs
II. America's Drug Problem
III. Killing the Mentally Ill
IV. Psychiatric Drug Toxicity

I. Types of Psychiatric Drugs

5 Major Classes of Psych Drugs

- Antidepressants
- Antipsychotics
- Mood Stabilizers
- Sedative Hypnotics / Anxiolytics
- Stimulants

II. America's Drug Problem

Question #1

Question #1

Most Common Disease (point prevalence)

a) asthma
b) Alzheimer's
c) diabetes
d) arthritis

Question #1
Most Common Disease

d) arthritis ☑

Somatic vs. Psychiatric

Lifetime Prevalence - USA

cancer	30-50%	depression	16%
arthritis	~ 20%	specific phobia	9%
asthma	12%	ADHD	5%
diabetes	9%	PTSD	3.5%
MI/angina	7%	bipolar	3%
stroke	3%	panic	3%
epilepsy	3%	OCD	1%
dementia	2%	schizophrenia	1%

Question #2

Question #2
Top Selling Drug Class in the U.S.A.

a) cancer medicines
b) insulin
c) asthma inhalers
d) antipsychotics

Question #2
Top Selling Drug Class in the U.S.A.

d) antipsychotics ☑

U.S. Drug Sales 2009
[IMS Health]

Total Drug Sales		300.3 billion
APs	#1	14.6 billion
lipid	#2	14.3 billion
PPI	#3	13.6 billion
ADs	#4	9.9 billion
insulin	#9	6.3 billion
stimulants	#11	5.8 billion
seizure	#13	5.3 billion

APs = antipsychotics
ADs = antidepressants

of U.S. Prescriptions - 2009

[IMS Health]

Total Prescriptions		3.9 billion
lipid	#1	210.5 million
codeine	#2	200.2 million
ADs	#3	168.7 million
ACEi	#4	162.8 million
AEDs	#7	104.5 million
benzos	#11	87.9 million
arthritis	#13	77.9 million

U.S. = 4.5 % of world population

90% of stimulant sales

63% of AP sales

51% of AD sales

41% of AED sales

U.S.A.: Psychiatric Drugs 2009

[Source: Express Scripts 2009 Drug Trend Report]

antidepressants	9.9%	31,000,000
anticonvulsants	4.0%	12,300,000
stimulants	2.2%	6,754,000
*antipsychotics	1.8%	5,526,000

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

Question #3

Question #3
Leading Cause of Death in the U.S.A.

a) heart disease
b) HIV/AIDS
c) stroke
d) cancer

National Vital Statistics Reports

CDC
SAFER · HEALTHIER · PEOPLE™

Volume 56, Number 16 June 11, 2008

Deaths: Preliminary Data for 2006

1) cardiac disease
2) cancer
3) stroke
4) chronic lower respiratory
5) accidents (unintentional injuries)
6) Alzheimer's disease
7) diabetes mellitus
8) influenza and pneumonia
9) kidney disease
10) septicemia

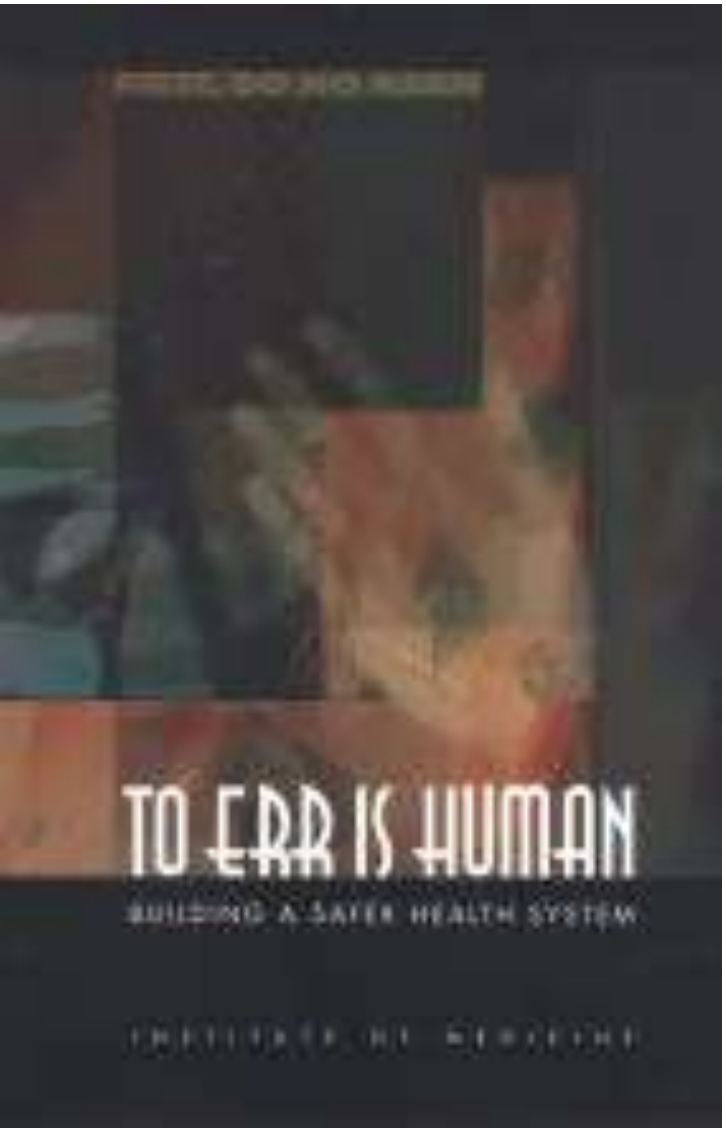
Question #3
Leading Cause of Death in the U.S.A.

a) heart disease ☑

but . . . this is only part of the story…

Institute of Medicine (1999)

44,000 to 98,000 dead from errors



Types of Errors

Diagnostic

- Error or delay in diagnosis
- Failure to employ indicated tests
- Use of outmoded tests or therapy
- Failure to act on results of monitoring or testing

Treatment

- Error in the performance of an operation, procedure, or test
- Error in administering the treatment
- Error in the dose or method of using a drug
- Avoidable delay in treatment or in responding to an abnormal test
- Inappropriate (not indicated) care

Preventive

- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

Other

- Failure of communication
- Equipment failure
- Other system failure

SOURCE: Leape, Lucian; Lawthers, Ann G.; Brennan, Troyen A., et al. Preventing Medical Injury. Qual Rev Bull. 19(5):144–149, 1993.

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

Reality Check: # of deaths (2006)

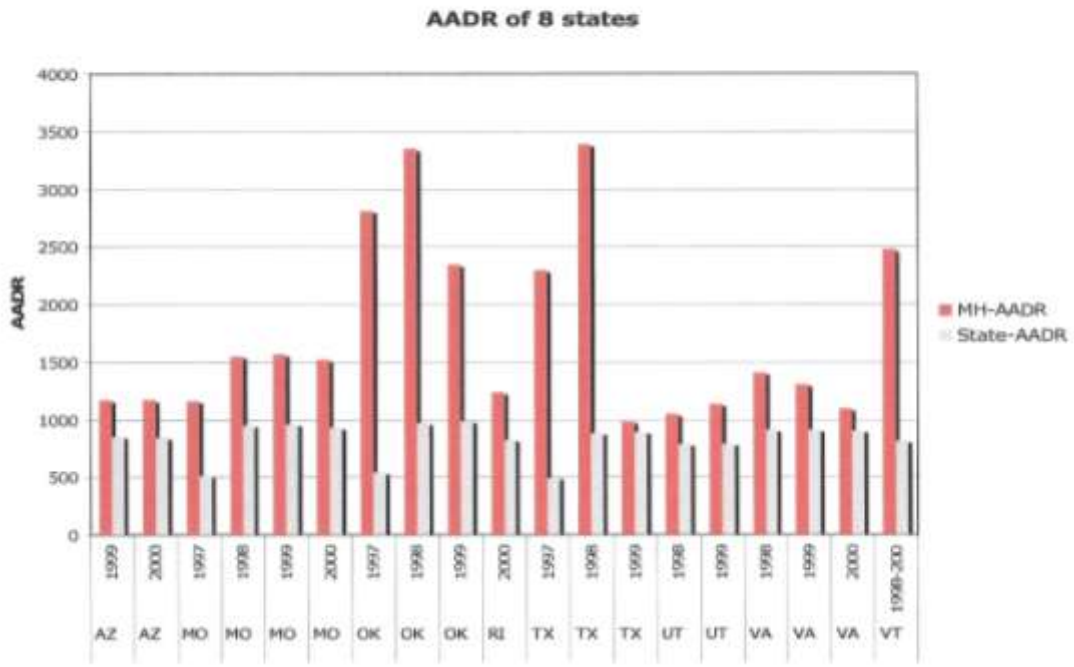
1.	cardiac disease	629,191
2.	cancer	560.102
3.	adverse drug reactions	305,000
4.	stroke	137,265
5.	accidents	124,614
6.	medical errors	98,000
7.	Alzheimer's disease	73,177
8.	diabetes mellitus	72,507
9.	flu & pneumonia	56,247
10.	septicemia	44,791

III. What's Killing the Mentally Ill

Morbidity and Mortality in Public MH Patients

[Sources: 2006 - Colton & Manderscheid & NASMHPD 13th Technical Report]

16 State Study Results: Age Adjusted Death Rate



annual death rates

SMI	1 - 3.5%
non-SMI	0.5 - 0.8%

Table 2. Mean Age at Time of Death for Public Mental Health Clients and Mean Number of Years of Potential Life Lost (YPLL) per Public Mental Health Client Who Died During a Year in Which a Service Was Received[a]

State and Year	Mean Age at Time of Death, y			Mean Number YPLL Per Deceased Mental Health Client[b]
	All Clients Who Died During Year	Male Clients Who Died During Year	Female Clients Who Died During Year	
Arizona				
1999	48.9	47.5	52.3	32.2
2000	49.6	48.5	52.7	31.8
Missouri				
1997	58.3	54.4	61.8	26.3
1998	56.9	53.6	60.6	27.3
1999	58.0	54.1	61.3	26.8
2000	56.4	53.1	59.4	27.9
Oklahoma				
1997	59.9	54.6	65.0	25.1
1998	59.9	53.2	65.3	25.1
1999	58.9	52.0	64.6	26.3
Rhode Island				
2000	60.2	53.4	65.5	24.9
Texas				
1997	55.0	52.4	58.1	28.5
1998	55.0	53.3	56.6	28.8
1999	54.0	50.8	57.3	29.3
Utah				
1998	55.1	47.2	63.8	29.3
1999	58.4	53.7	63.2	26.9
Virginia[c]				
1998	72.4	70.6	74.8	15.5
1999	74.4	72.5	76.9	14.0

Causes of death 1997-2000…

SMI	% of deaths	non-SMI	% of 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%

Missing from the discussion: dementia

Time trends in schizophrenia mortality in Stockholm County, Sweden: cohort study

Urban Ösby, Nestor Correia, Lena Brandt, Anders Ekbom, Pär Sparén

BMJ 2000

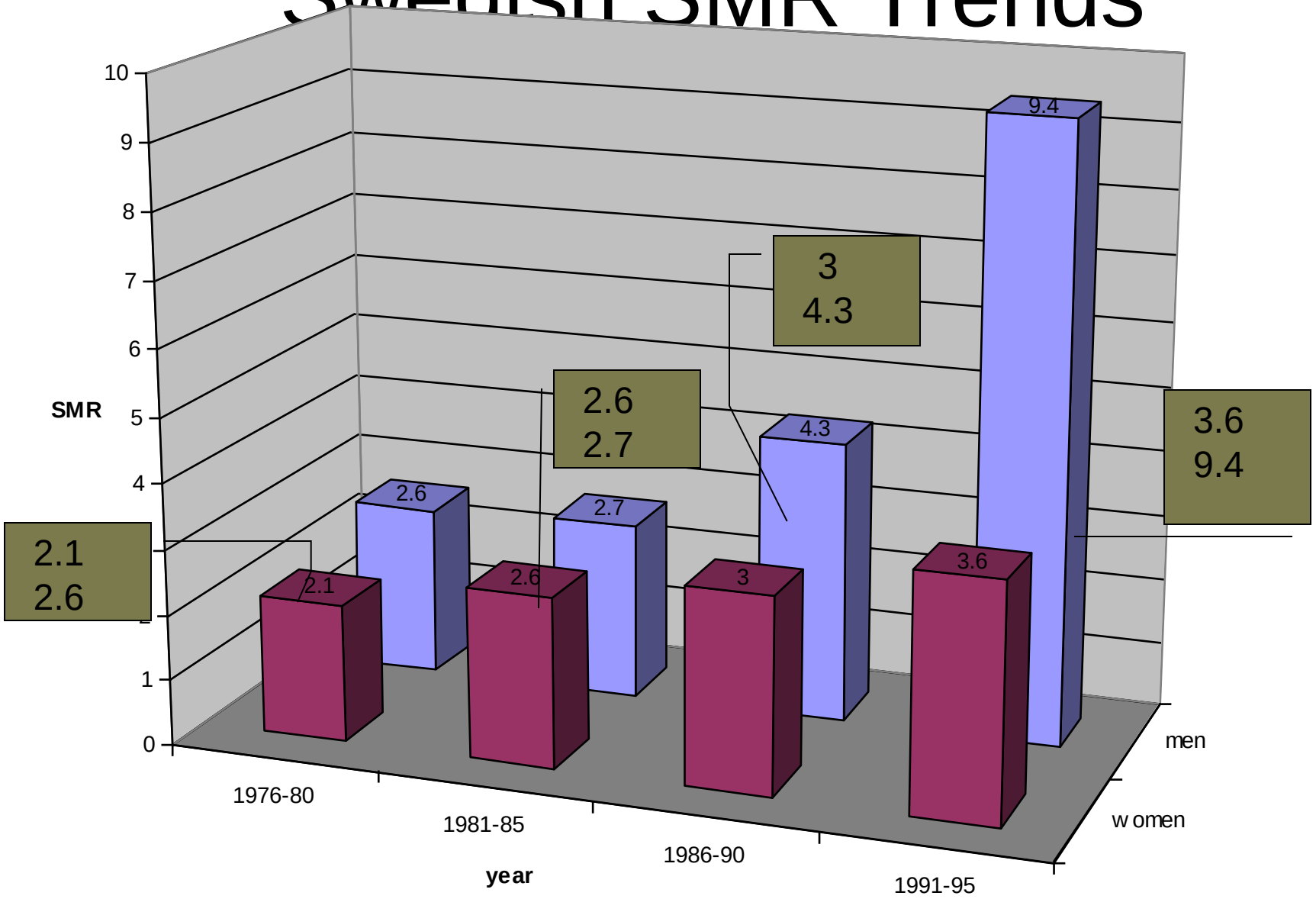
Observed over expected numbers of deaths and relative risks (95% confidence intervals) for different causes of death in patients first admitted to hospital with schizophrenia, Stockholm County, 1976-95

			All causes		Natural		Cardiovascular		Suicide		Unspecified violence	
Year	First admissions	No of deaths	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk	Observed/ expected	Multivariate relative risk
Men												
1976-80	778	196	2.6 (2.2 to 3.0)	1 (reference)*	1.7 (1.4 to 2.1)	1 (reference)†	1.7 (1.2 to 2.2)	1 (reference)†	13.2 (9.8 to 17.5)	1 (reference)*	12.1 (7.4 to 18.6)	1 (reference)
1981-5	761	162	2.7 (2.3 to 3.1)	1.1 (0.9 to 1.4)	1.8 (1.5 to 2.2)	1.1 (0.9 to 1.5)	2.0 (1.4 to 2.7)	1.5 (1.0 to 2.3)	16.9 (12.1 to 22.9)	1.1 (0.7 to 1.7)	12.6 (6.7 to 21.6)	1.1 (0.5 to 2.1)
1986-90	831	104	4.3 (3.5 to 5.2)	1.2 (0.9 to 1.6)	2.0 (1.4 to 2.7)	1.2 (0.9 to 1.8)	4.2 (2.9 to 6.0)	2.9 (1.8 to 4.7)	27.7 (19.9 to 37.6)	1.4 (0.9 to 2.1)	21.1 (11.2 to 36.1)	1.8 (0.9 to 3.5)
1991-5	631	36	9.4 (6.6 to 13.1)	1.7 (1.2 to 2.5)	4.4 (2.3 to 7.4)	2.4 (1.3 to 4.3)	8.3 (3.3 to 17.1)	4.7 (2.1 to 10.4)	47.8 (27.3 to 77.6)	1.6 (0.9 to 2.9)	45.2 (16.6 to 98.4)	3.8 (1.5 to 9.3)
Test for trend				P=0.01		P=0.02		P<0.001		P=0.07		P=0.01
Women												
1976-80	815	259	2.1 (1.9 to 2.4)	1 (reference)*	1.7 (1.5 to 2.0)	1 (reference)†	1.7 (1.4 to 2.1)	1 (reference)*	17.1 (12.2 to 23.3)	1 (reference)*	7.4 (2.7 to 16.0)	1 (reference)*
1981-5	667	176	2.6 (2.2 to 3.0)	1.2 (1.0 to 1.5)	2.0 (1.7 to 2.4)	1.3 (1.0 to 1.6)	2.1 (1.6 to 2.7)	1.3 (0.9 to 1.8)	28.5 (20.0 to 39.5)	1.5 (1.0 to 2.4)	9.9 (2.7 to 16.0)	1.4 (0.4 to 5.0)
1986-90	768	102	3.0 (2.5 to 3.7)	1.2 (1.0 to 1.6)	2.0 (1.5 to 2.6)	1.3 (0.9 to 1.7)	3.1 (2.1 to 4.3)	1.7 (1.1 to 2.6)	35.3 (23.6 to 50.6)	1.5 (0.9 to 2.5)	15.8 (4.3 to 40.4)	2.3 (0.7 to 8.3)
1991-5	551	26	3.6 (2.5 to 5.4)	1.3 (0.8 to 2.0)	2.1 (1.2 to 3.5)	1.3 (0.8 to 2.3)	5.0 (2.1 to 4.3)	2.7 (1.4 to 5.4)	58.6 (29.2 to 104.8)	1.9 (0.9 to 3.9)	20.1 (0.5 to 111.7)	3.4 (0.4 to 28.6)
Test for trend				P=0.05		P=0.04		P=0.002		P=0.04		P=0.13

*Controlling for age at diagnosis and follow up.
†Controlling for age at diagnosis.

Changes in SMR - all cause mortality

Swedish SMR Trends

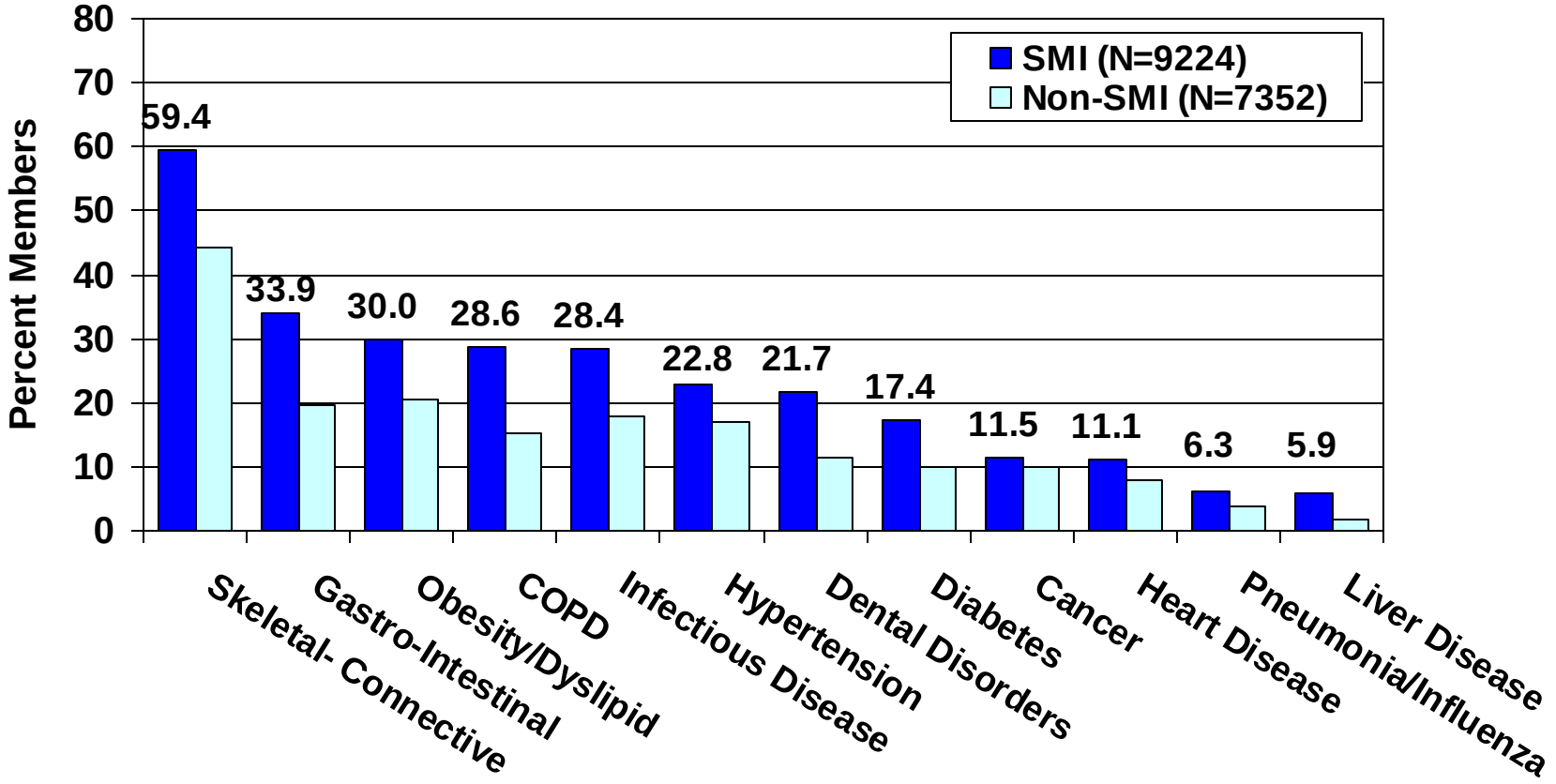


Public MH patients = 5.9 million per year

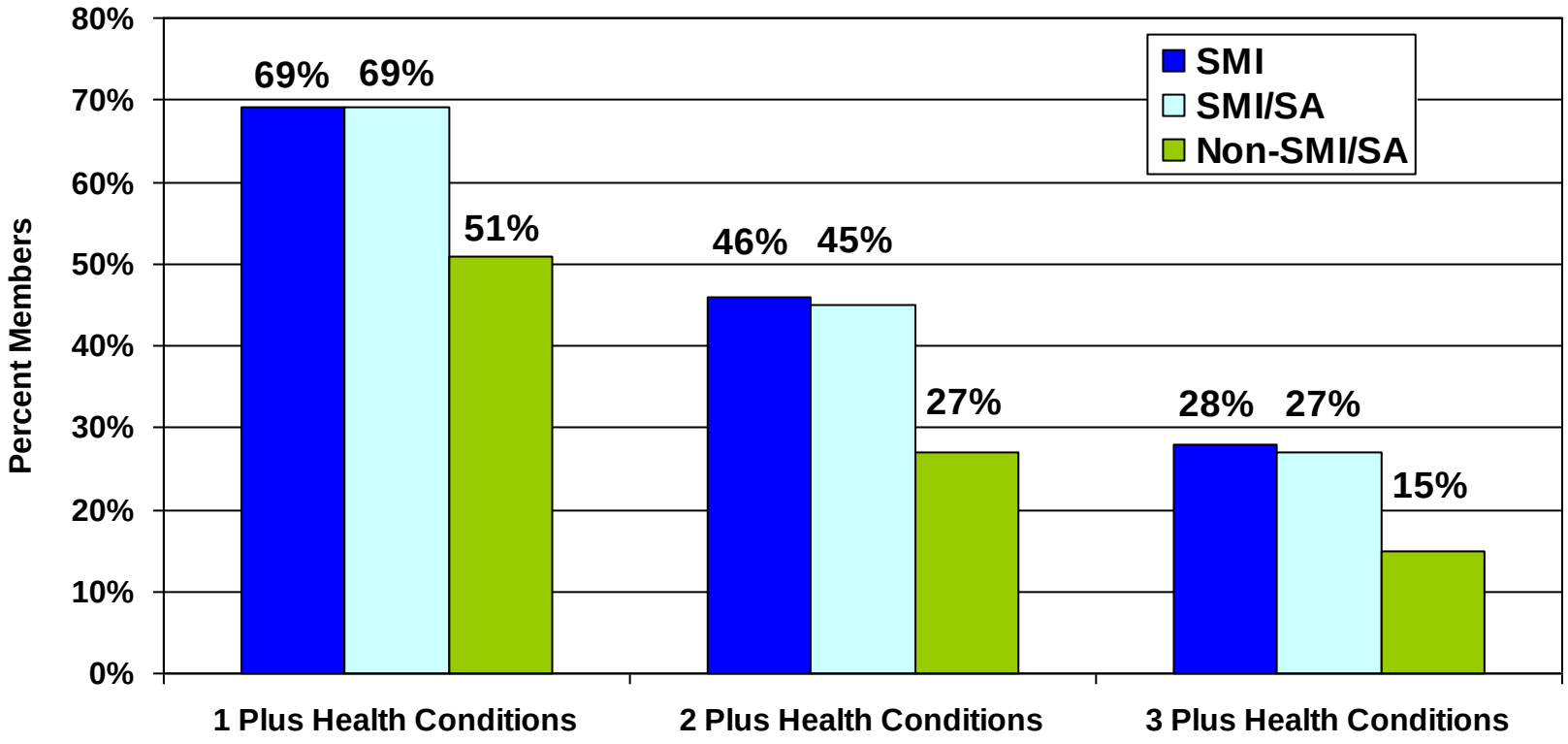
Compared to non-SMI, those with SMI:

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

High Rate of Health Disorders
SMI Compared to Non-SMI Groups
Maine Medicaid – 2004



Burden of Medical Illness: Maine Medicaid 2004



IV. Psychiatric Drug Toxicity

Psychiatric Drugs ↑ the Odds of Disease

	AD	AP
• Risk of heart disease	↑ 1.4-2x	↑ 2-3x
• Risk of diabetes	unclear	↑ 1.2-7x
• Risk of pneumonia	↑ 1.6x	↑ 1.9x
• Risk of suicidality	↑ 2-15x	unclear
• Risk of stroke	↑ 1.3-1.6x	↑ 1.4-6x
• Risk of dementia	↑ 2-5x	↑ 2-14x

Dementia defined:

- From Latin *de mens / de mentis*

out of (away from) one's mind

Features of Dementia

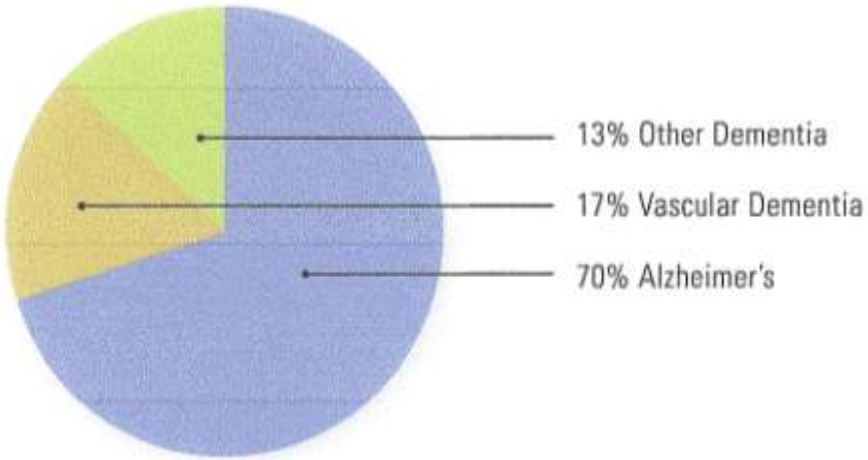
- ❖ Memory impairment
- Aphasia (impaired language)
- Apraxia (impaired ability to carry out motor activities)
- Agnosia (failure to recognize objects)
- Executive functioning deficits

  planning, organizing, sequencing, abstracting

Prevalence of Dementia in USA

- Ages 40-65 1 in 1000
- Ages 65-70 1 in 50
- Ages 70-80 1 in 20
- Age 80+ 1 in 5

Causes of Dementia in People Aged 71+, ADAMS, 2002

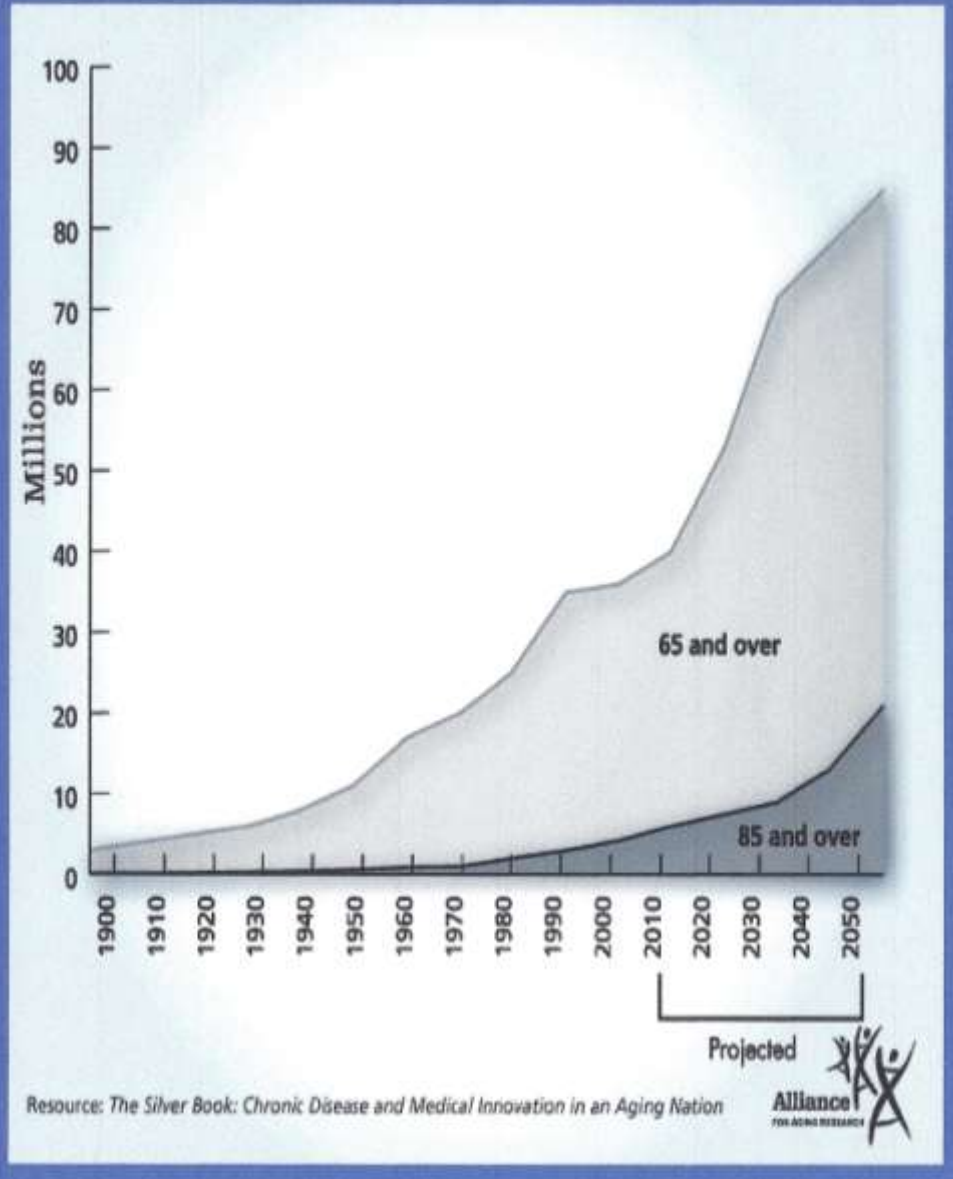


≥ 65 with dementia

2.3% in 2000 ➔ 4.5% in 2040

7.6 million 18.3 million

Number of People Age 65 and Over, by Age Group, Selected Years 1990-2000 and Projected 2010-2050

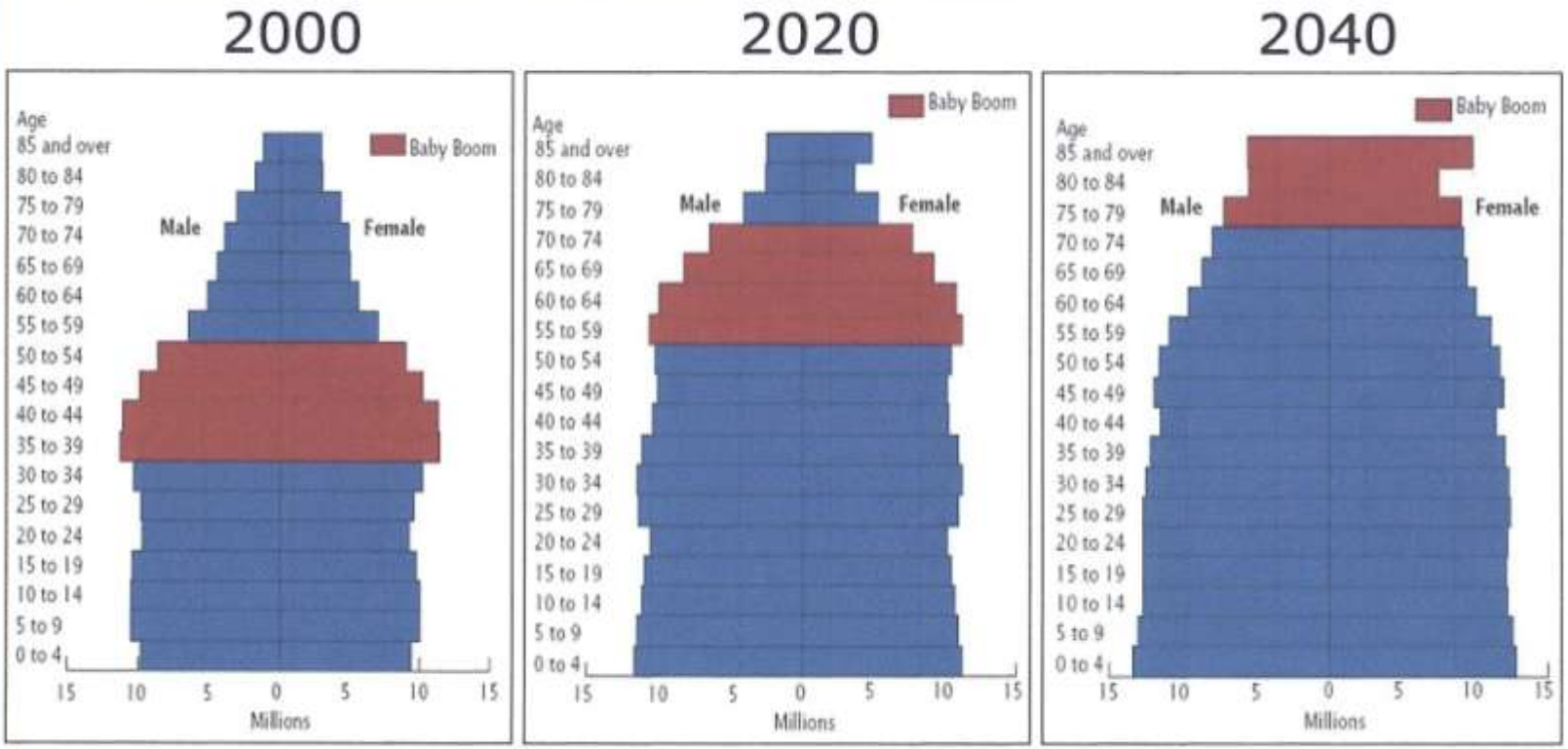


Federal Interagency Forum on Aging-Related Statistics 2004, *Older Americans*

≥ 65 years of age

12% to 18% to 21%

U.S. Population Pyramids



Source of charts: U.S. Census Bureau, "65+ in the United States: 2005," December 2005.
Prepared by the UNC Institute on Aging

UNC IOA Institute on Aging

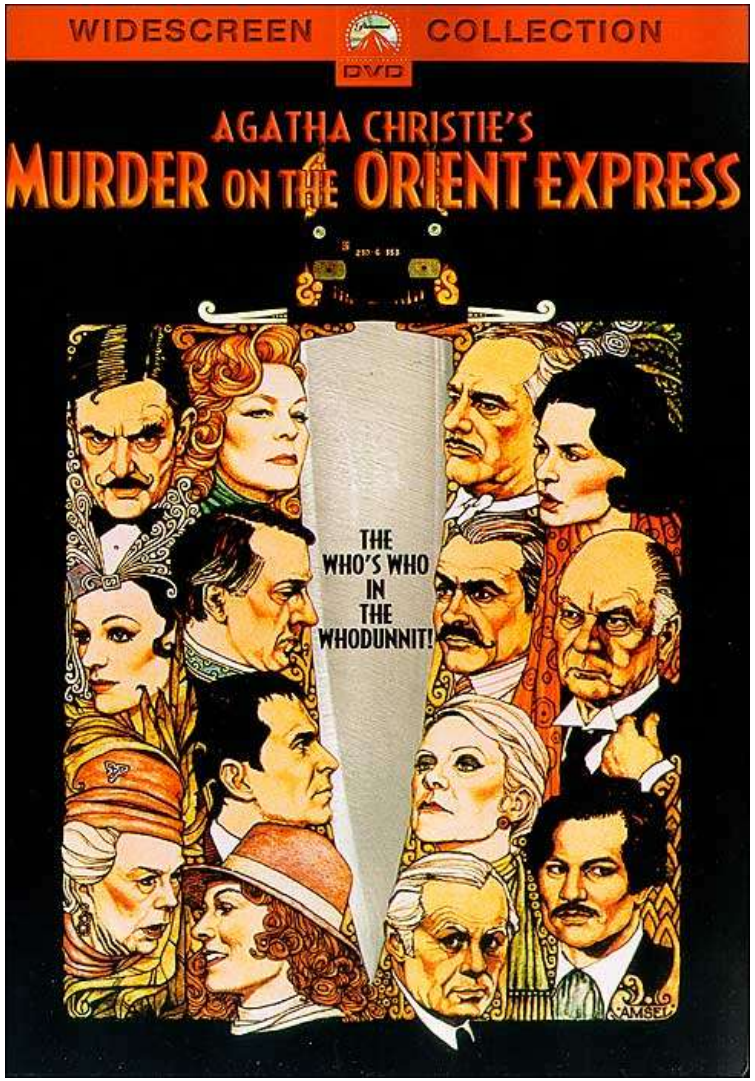
Drug-Induced Dementia

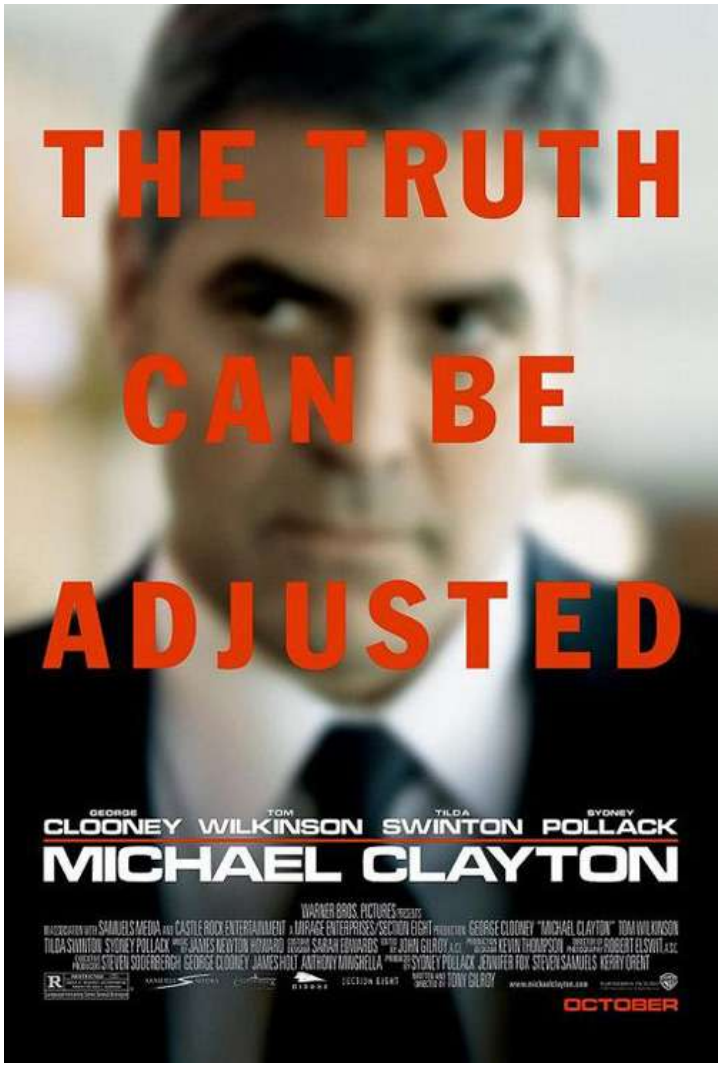
DSM-IV, Text Revision (2000)

Substance-Induced Persisting Dementia

"*Features are those associated with dementias generally…can occur in association with…alcohol, sedatives, hypnotics and anxiolytics, or other or unknown substances*…"

A perfect crime…





Antipsychotic Timeline

*timeline = year that the drug was invented or first used

1st generation drugs 1950 to 1960s

Thorazine, Haldol, *Clozaril

2nd generation drugs 1970 to 1990s

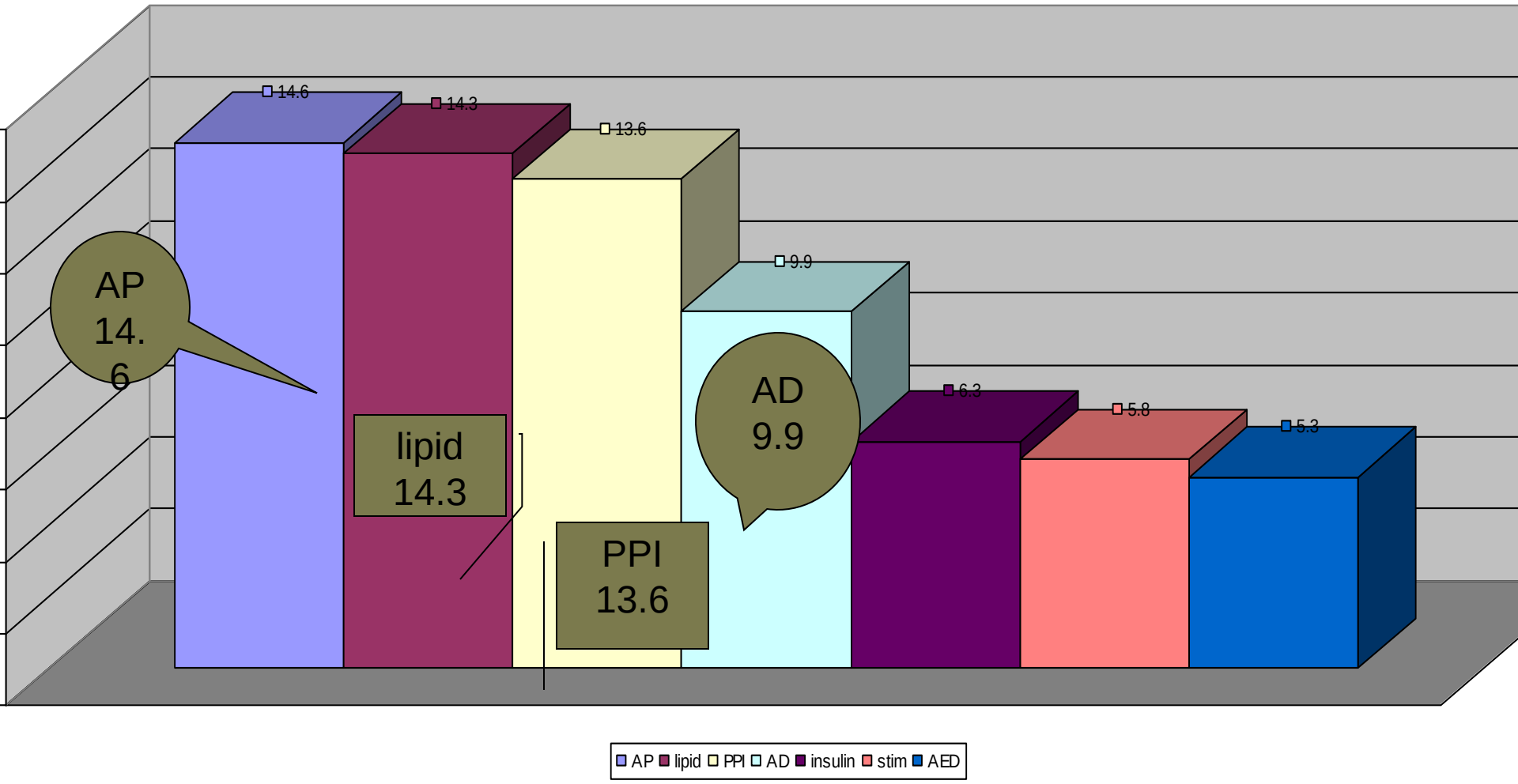
Risperdal, Zyprexa, Seroquel, Geodon

3rd generation drugs 2000 to 2010

Abilify

*Invented in 1958, clozapine was introduced in Europe in the early 1960s. It did not gain FDA approval in the U.S.A. until 1989. Partly for this reason, American physicians refer to it as a “second generation” drug.

U.S. Drug Sales – 2009 ($ billions)



Dept. of Veterans Affairs

Kales et al (2007)

23,436 patients (national database)

≥ 65 years of age

diagnosis of dementia in 2002 or 2003

12-month mortality risk after starting a psychiatric drug

12,821 avoided psychiatric drugs

18% died within one year

10,615 started psychiatric drugs

23% using newer APs died

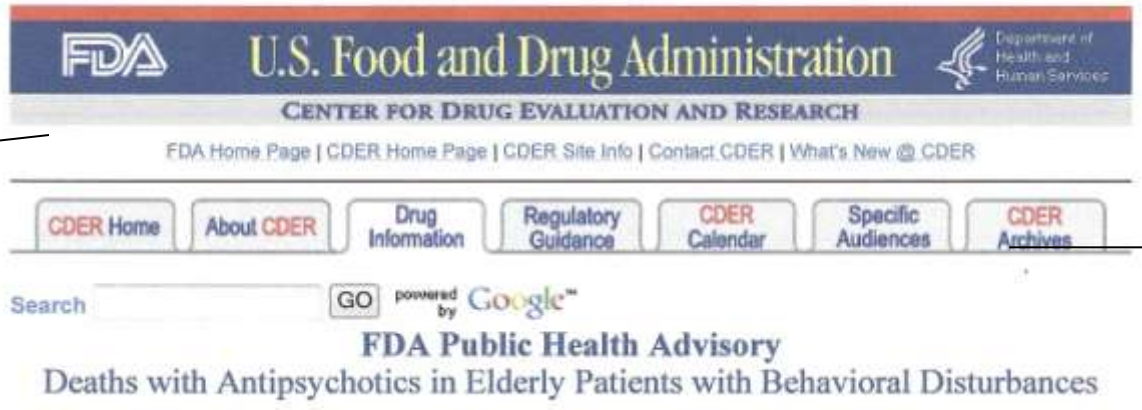
25% using old (“conventional”) APs died

29% using both kinds of APs died

Other folks started to notice the same trend in different patients…

Black Box Warnings
"not for dementia-related psychosis"

4/11/05


U.S. Food and Drug Administration

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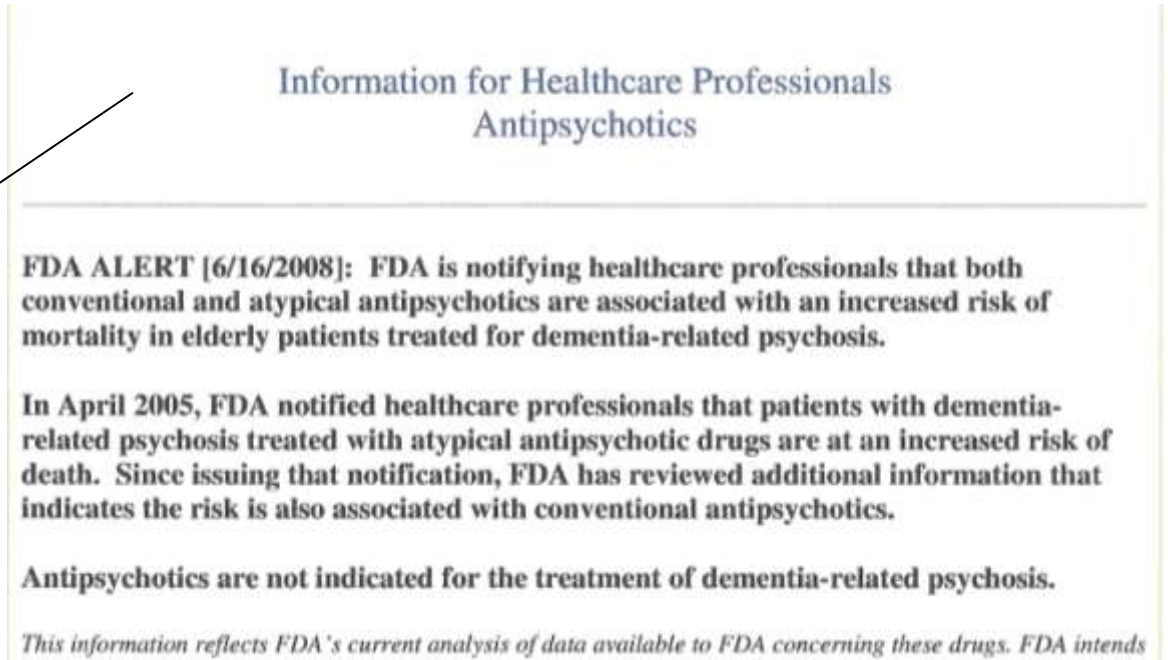
FDA Public Health Advisory

Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances

2nd generation

6/16/08
1st and 2nd


Information for Healthcare Professionals
Antipsychotics

FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

In April 2005, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends

In England, some physicians began to wonder ---

what would happen to dementia patients if they stopped taking antipsychotic drugs ?

U.K. - DART-AD

Dementia AP Reduction Trial

Enrolled residents of nursing or residential homes in four areas (2001-2004); followed patients to April 2006

All patients had been diagnosed with possible or probable Alzheimer's and all had taken APs for ≥ 3 months (APs = risperidone, thioridazine, haloperidol, trifluoperazine, or chlorpromazine)

Mean duration of drug use: 25 months

DART-AD
Ballard et al (2009)

- 165 patients were randomly assigned to antipsychotic (83) or placebo (82)

- Assessed patients according to treatment fidelity (compliance) and outcome…

- Primary outcome: 12-month mortality

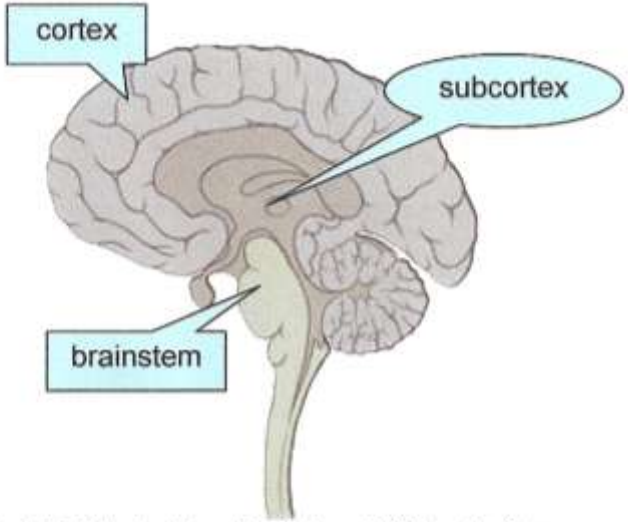
Outcomes Based Upon Continuing Use of Drugs vs. Placebo

	APs	PBO
% surviving		
1 year	75%	79%
2 year	46%	71%
3 year	30%	59%
3 ½ years	26%	53%

APs = antipsychotic drugs
PBO = placebo

Antipsychotic drugs are deadly for dementia patients…

- what about giving them to the non-demented ?



Tootsie Pops reproduced with permission of Tootsie Roll Industries. Brain from Wikimedia Commons.

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

name		location	functions
the cortex	=	outer (or top) layer	"human" functions planning, intending, meaning
the subcortex	=	middle layer	"animal" functions appetite, sex, emotions
the brainstem	=	base layer	"vegetative" functions sleep/wake, breathing, heart beat

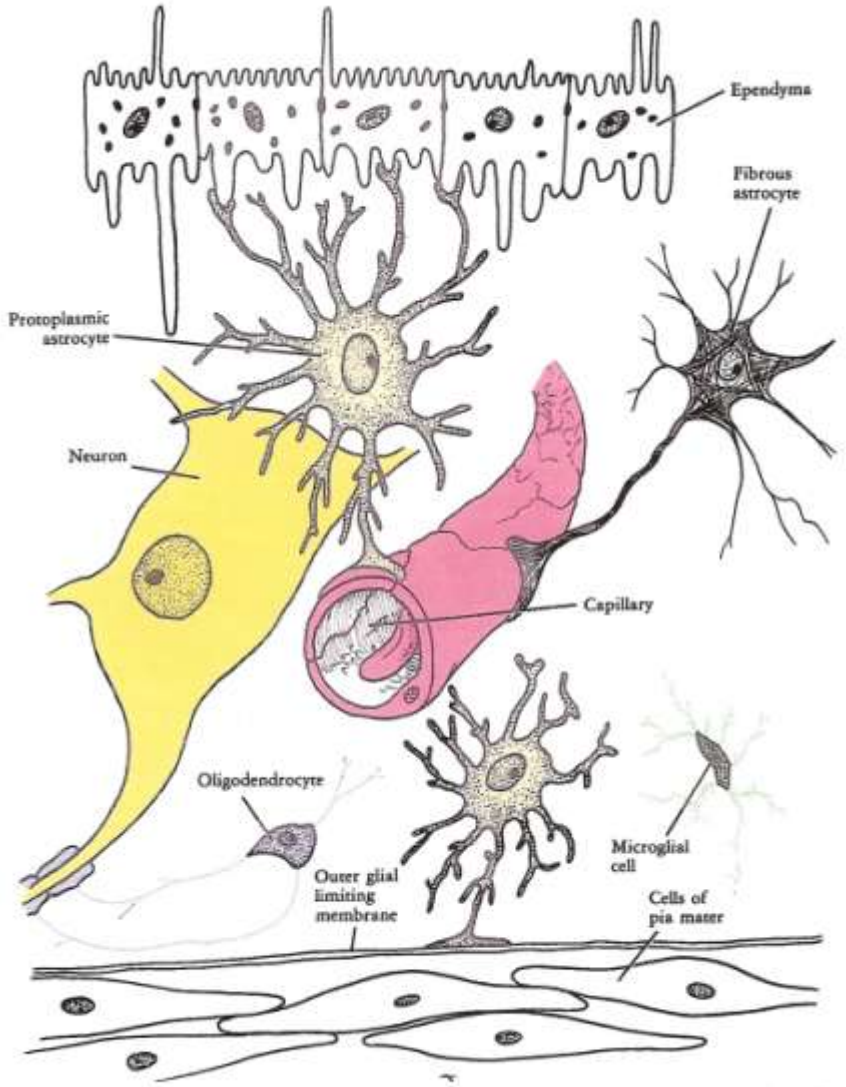
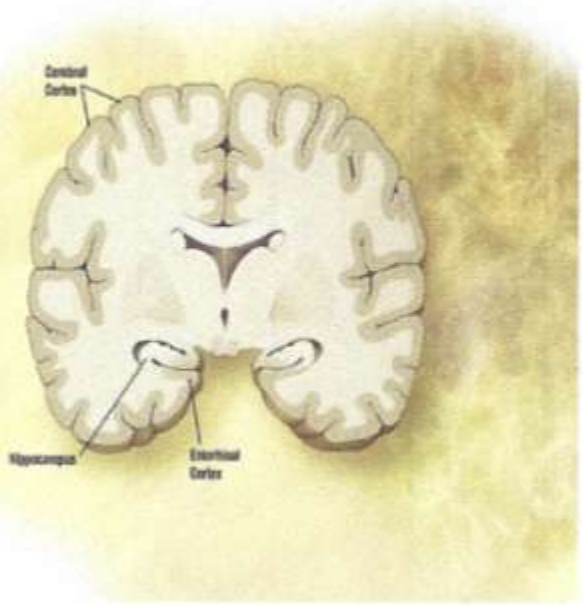
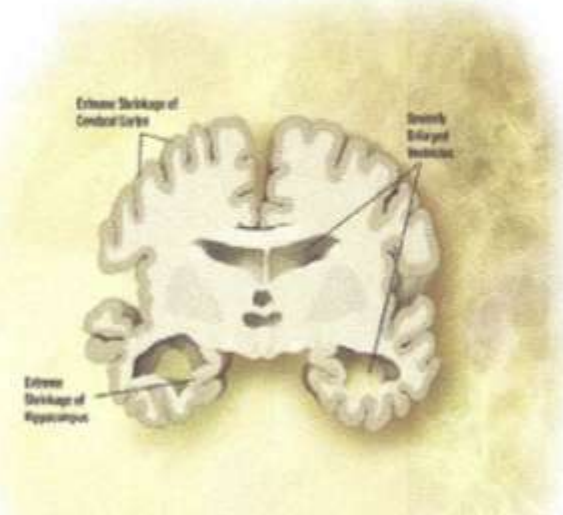


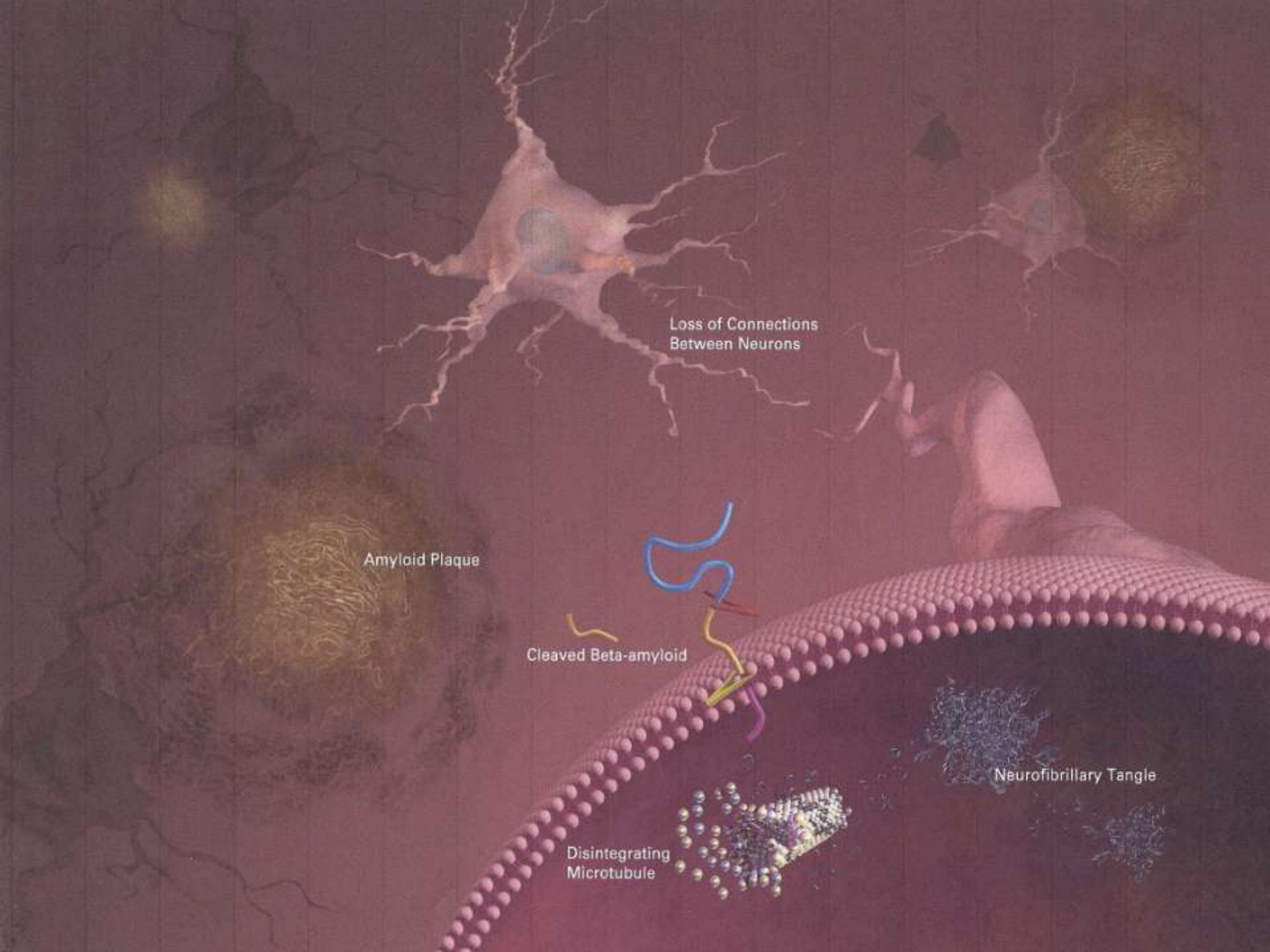
FIGURE 3-1 A diagrammatic representation of the arrangement of different types of neuroglial cells.



Preclinical AD



Severe AD


Loss of Connections
Between Neurons
Amyloid Plaque
Cleaved Beta-amyloid
Neurofibrillary Tangle
Disintegrating
Microtubule

How Do Doctors Diagnose Alzheimer's Disease?

No way to know for sure while a patient is still living…

1) look at symptoms and how they evolve
2) "biomarkers" are in development
3) gold standard = autopsy pathology

Postmortem Pathology

Do Antipsychotic Drugs Cause Alzheimer's Disease ?

If they do, we should expect to see evidence of Alzheimer's pathology (abnormal anatomy) among patients who have received antipsychotic drugs…

Postmortem Studies of Humans

1988 Buhl and Bojsen-Moller – 100 patients (consecutive autopsies)

schizophrenia	35% Alz. pathology
non-psych controls	0% Alz. pathology

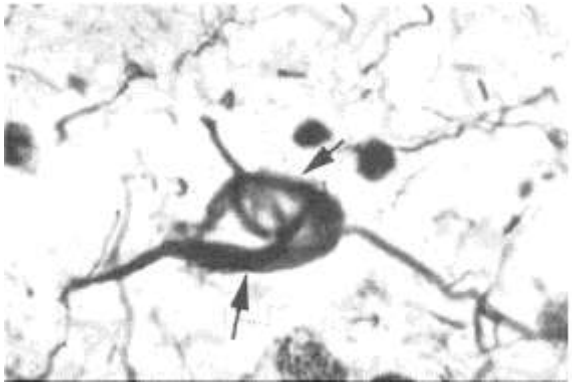
1989 Soustek – 225 pts with chronic schizophrenia (dying in 1975-85)

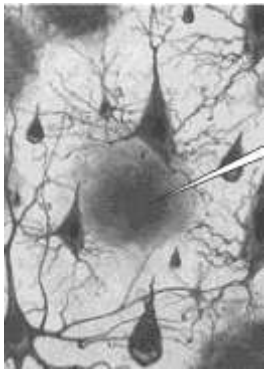
41% showed Alz. pathology

6x higher rate than general population

1994 Wisniewski – 102 patients with history of schizophrenia

41 died prior to antipsychotic era	46% had tangles
62 died after antipsychotic era	74% had tangles





2002 Bozikas – 18 schizophrenia patients vs. 14 age-matched controls

patients had 400% ↑ tangle density in cortex (layer II of EC)

patients had ↑ plaque density (throughout the brain)

2005 Ballard et al – studied 40 patients with Lewy body dementia

23 patients avoided antipsychotic drugs

17 patients received antipsychotics

when compared to the other patients, the 17 drug-consumers exhibited:

30% higher density of cortical plaques

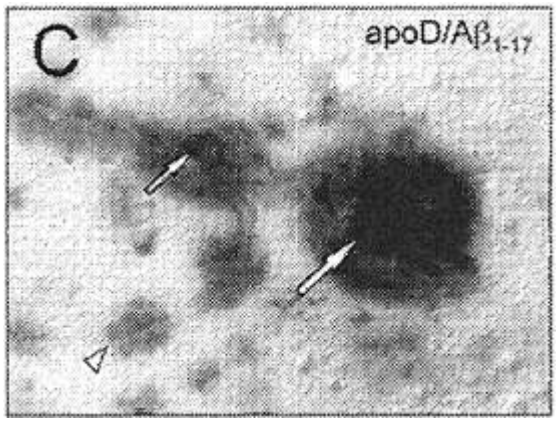
65-367% higher density of tangles

apoD is marker of neuropathology

University of Pittsburgh (Desai et al, 2005)

apoD is key a feature of Alzheimer's disease

63% of the beta-amyloid plaques contained apoD



Thomas et al (2001)
autopsy study of brain levels of apoD (ug/mg)

	schiz n=20	bipolar n=8	controls n=19
% using APs	90% (18)	75% (6)	0
DLPFC	0.244	0.233	0.115
caudate	0.132	0.112	0.059

apoD levels were 2X higher in users of APs

APs = antipsychotic drugs (1st generation and clozapine)

apoD in Animals

mice and rats (multiple investigations) >>

14 to 45 days of OLZ, RISP, or CLZ

all three drugs resulted in higher mRNA and higher protein levels of apoD in cortical and subcortical regions of brain

mRNA = messenger RNA (a molecular precursor for protein synthesis)

Other Postmortem Studies
rabbits, rats, monkeys, guinea pigs

1958 – 1975

all showed damage to cortex, subcortex, and brainstem following brief (2 wks) or chronic exposure (up to 1 yr)

University of Pittsburgh
(2005, 2007, 2008)

Do lab techniques (specimen processing) affect the structure of the brain?

As an aside:

What about drugs?

Experiment

18 adult male macaques (4.5 to 5.3 yrs old)

oral doses of haloperidol or placebo (27 months)
oral doses of olanzapine (17 months)

relevant doses of drugs vis-à-vis human therapy

1-1.5 ng/mL for HAL

10-25 ng/mL for OLZ

Changes in Behavior and Brain

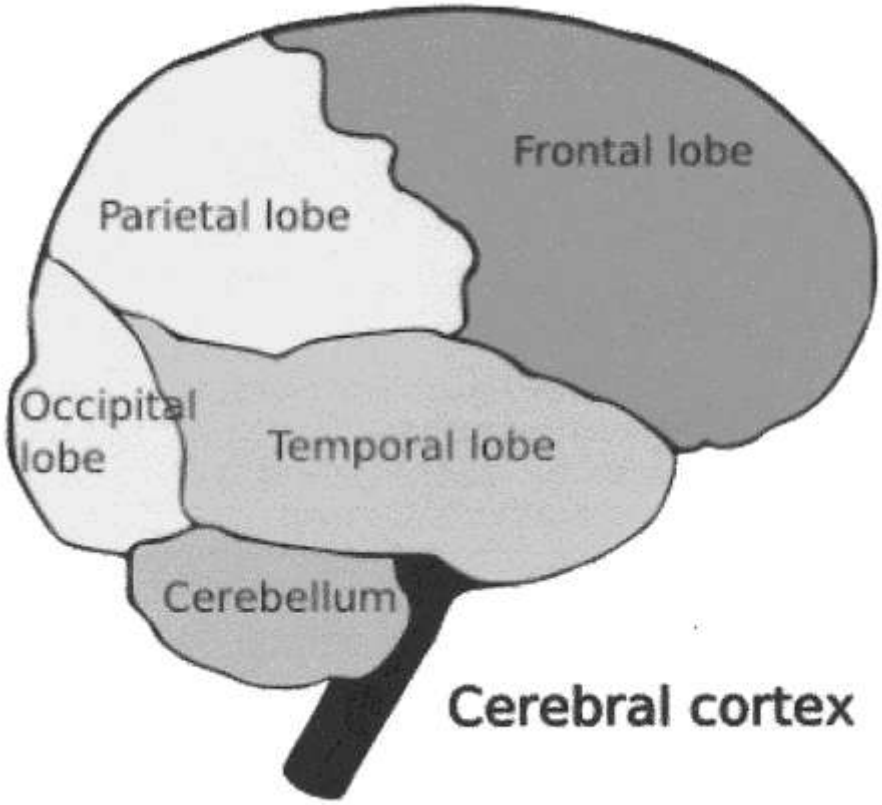
4 of 6 monkeys on OLZ >> aggressive
2 of 6 monkeys on HAL >> aggressive

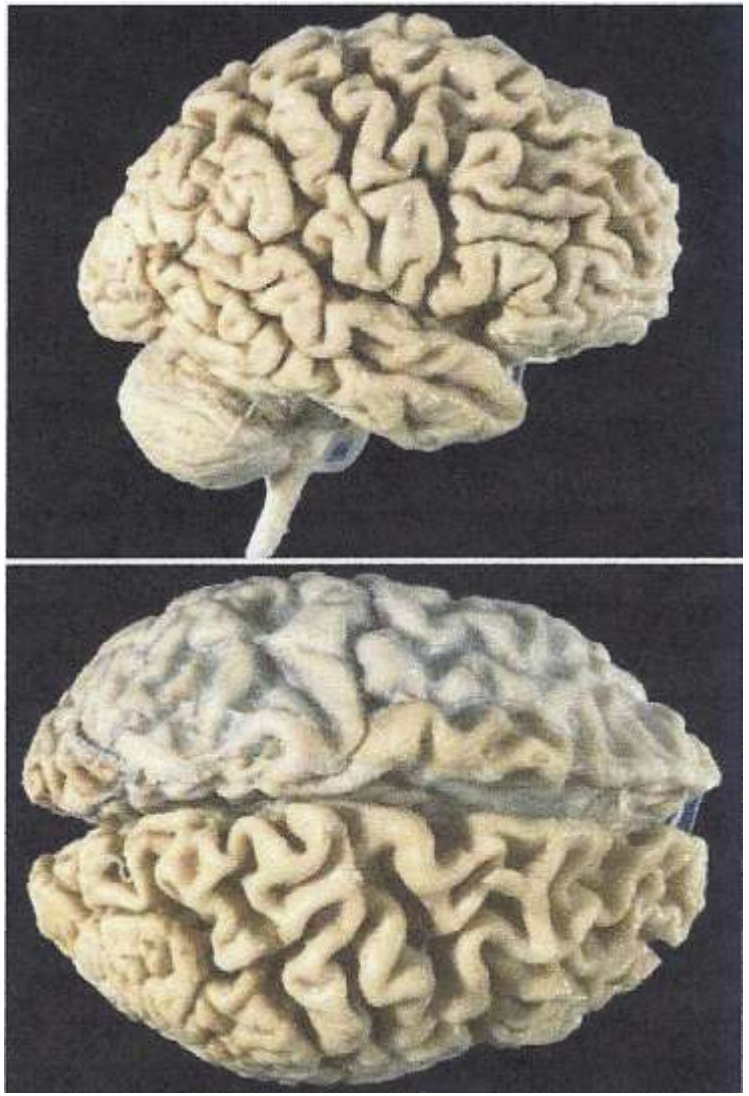
atrophy of cortex/cerebellum/brainstem

HAL 9% lower volume of brain
9% decreased brain weight

OLZ 10.5% lower volume of brain
11% decreased brain weight

f/u Studies of Parietal Lobe



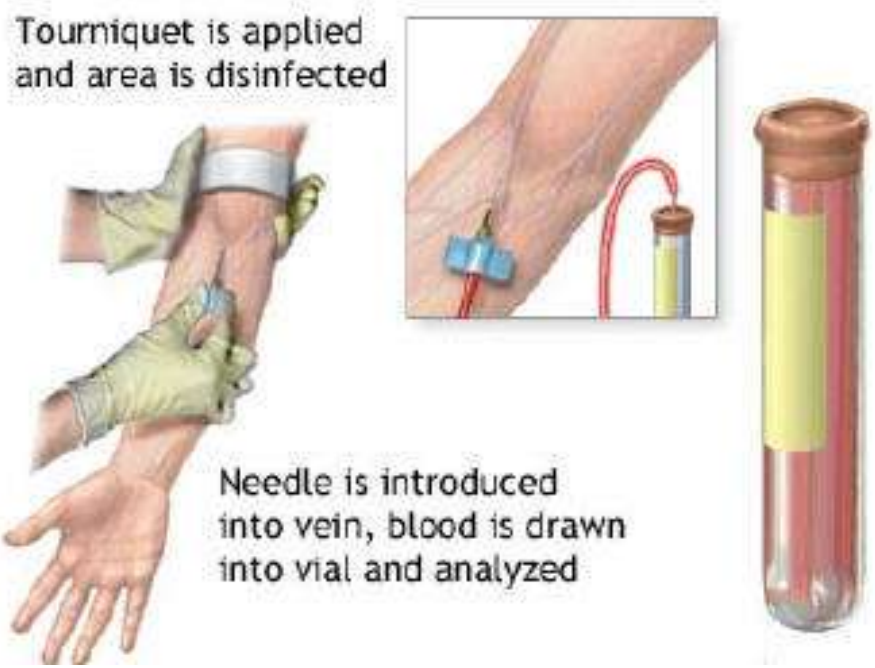


Parietal Lobe Cell Loss

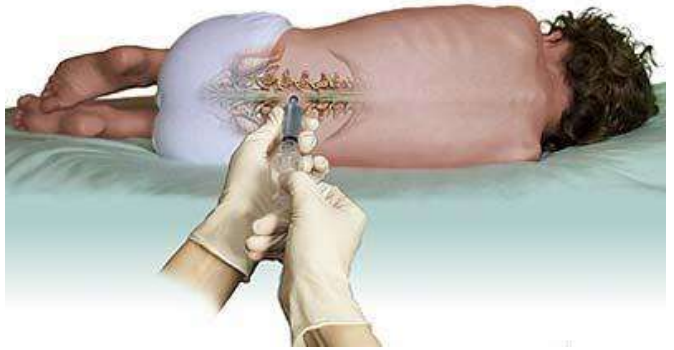
Reductions in Cell Number After Drug Treatment

	haloperidol	olanzapine
total cells	10.6%	7.4%
neurons	6.3%	5.5%
oligodendrocytes	13.9%	11.8%
astrocytes	20.4%	20.5%

Biomarkers in Humans



Cerebrospinal fluid drawn
from between two vertebrae



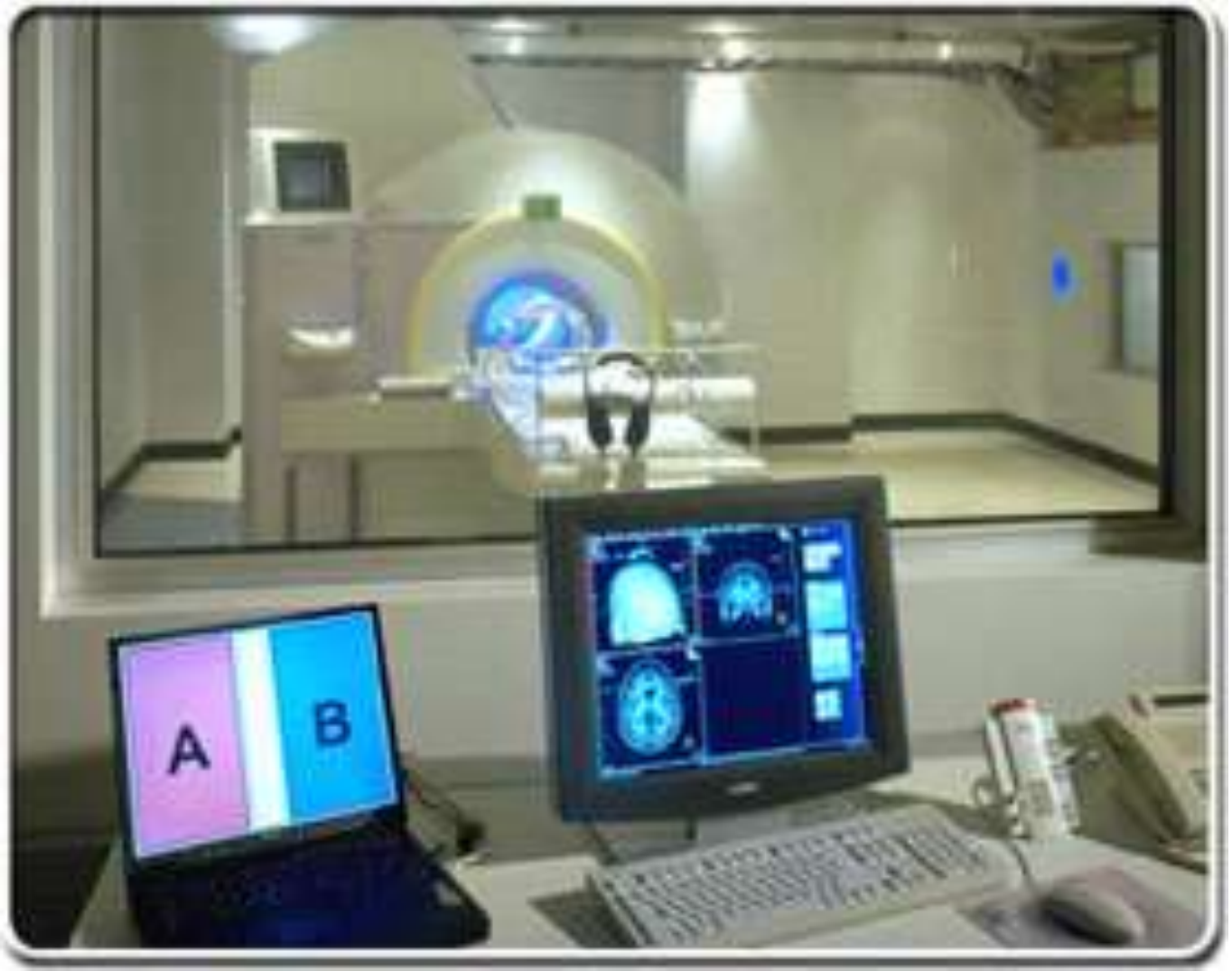
Old and new antipsychotics *all* increase Alzheimer's proteins…

Protein changes in antipsychotic recipients, relative to drug-free controls:

		source	biomarker	change
Austria	2005	(CSF)	tTG	↑ 200-400%
Italy	2005	(CSF)	tau	↑ 24%
USA	2002	(blood)	apoD	↑ 58%

CSF = cerebrospinal fluid

Neuroimaging
(brain scans)



Numerous studies…

Without exception, “before and after” brain scans have revealed shrinkage (atrophy) of the brain under the influence of *old or new* antipsychotic drugs

In some cases, patients have experienced a 4-9% reduction in volume in < 3 years

What about children ?

NIMH / UCLA study
child onset schizophrenia

- Using sophisticated neuroimaging methods (3D “cortical mapping”), longitudinal studies were performed on three groups of adolescents

- Goal: check changes in brain anatomy
  over time (baseline, 2.3 years, 4.6 years)

Multiple brain scans > age 13.5 to 18

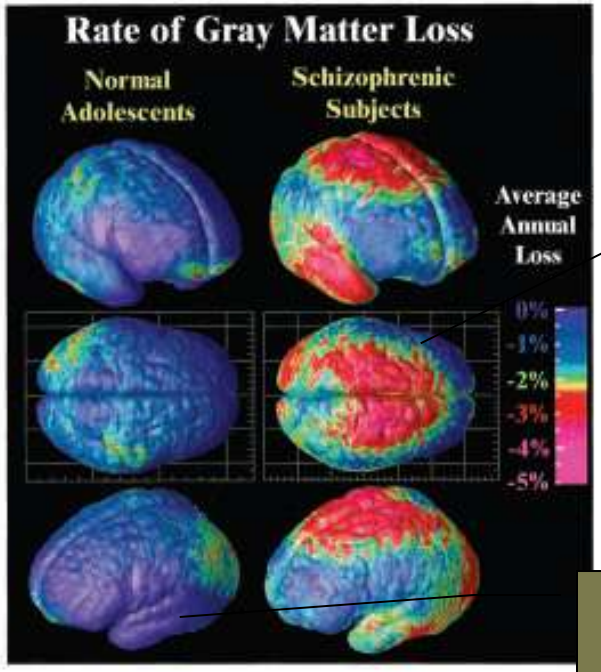
Study Design:
12 children with Childhood Onset Schizophrenia
(onset of symptoms before age 12)
all had histories of poor response to / intolerance
of at least two typical antipsychotic

10 children with transient psychosis
mood and behavioral problems

12 age & gender matched "normal" controls

Psychiatric patients received treatment with the following antipsychotic drugs: risperidone, olanzapine, or clozapine.

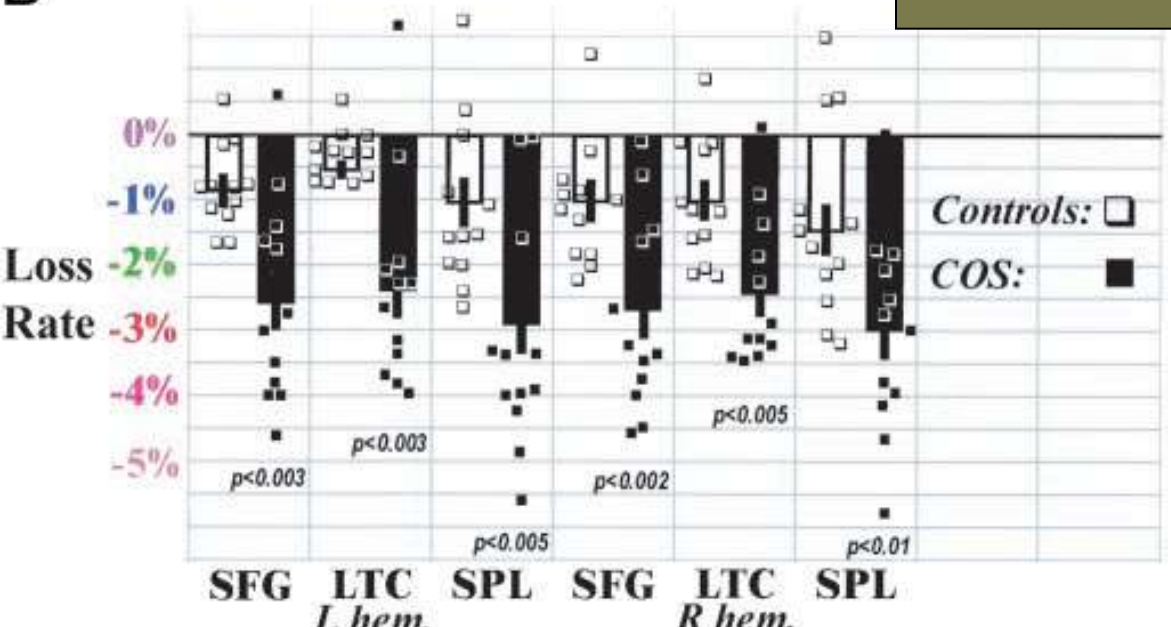
A



Schiz on AP drugs
2 to 3.5% per yr

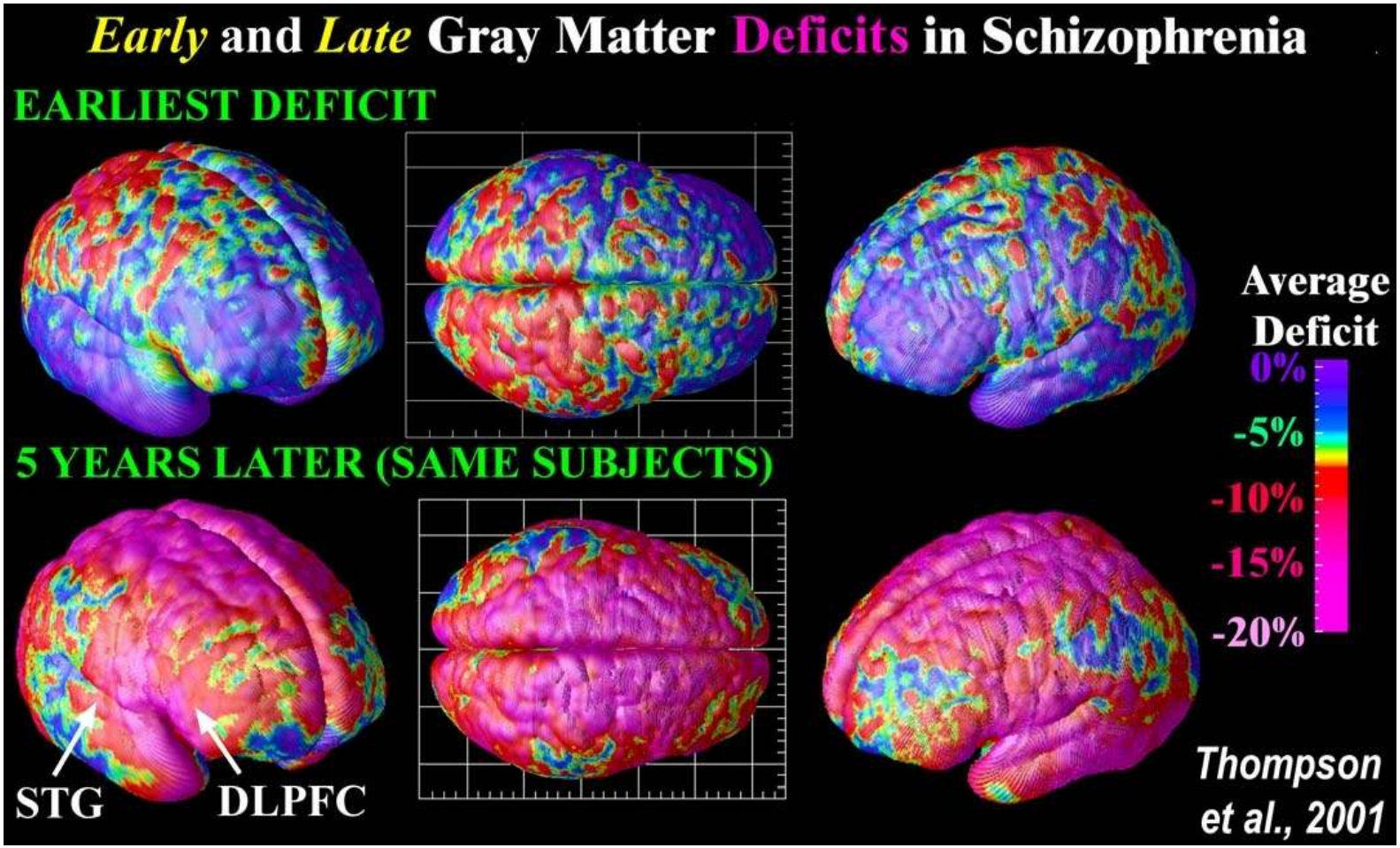
Normal teens
0.9 to 1.4% per yr

B



Gray Matter Loss Due to “Disease”

Thompson et al (2001) – multiple scans of teens (aged 13.9 to 18.6)
UCLA & NIMH



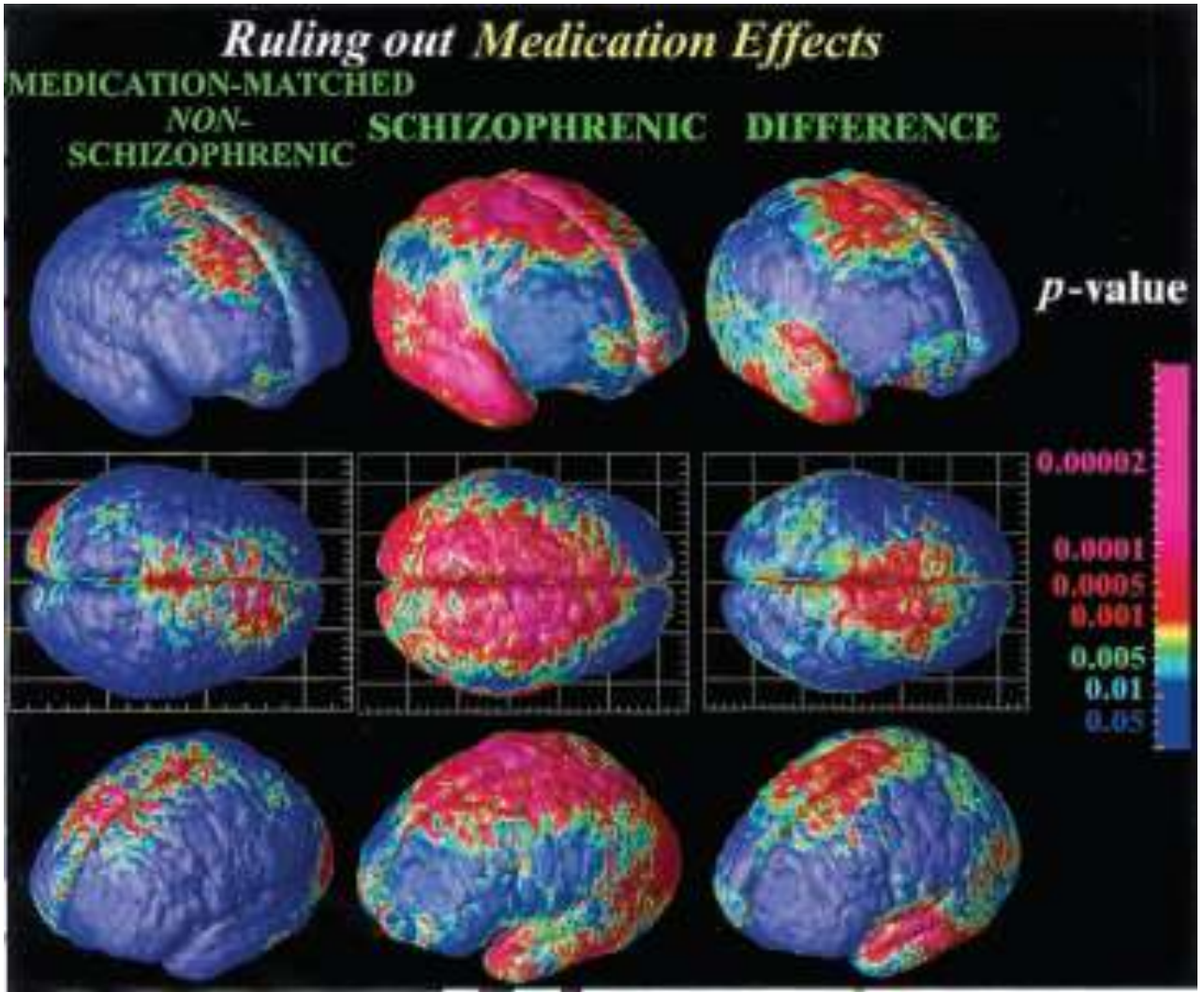
Reduced Exposure to APs

no gray matter deficit in temporal lobe

(Med Matched ?)

Psychosis NOS
n=10
2 were drug-free
at baseline and f/u
7.5% ↓

Schizophrenia
n=12
4.6 yrs + of NLs
13.0% ↓



Recap of Lecture

I. Major Classes of Psychiatric Drugs
II. America's Drug Problem
III. Killing the Mentally Ill
IV. Psychiatric Drug Toxicity