Brain Repair

ISEPP – November 2, 2012
Grace E. Jackson, MD

Outline of Lecture

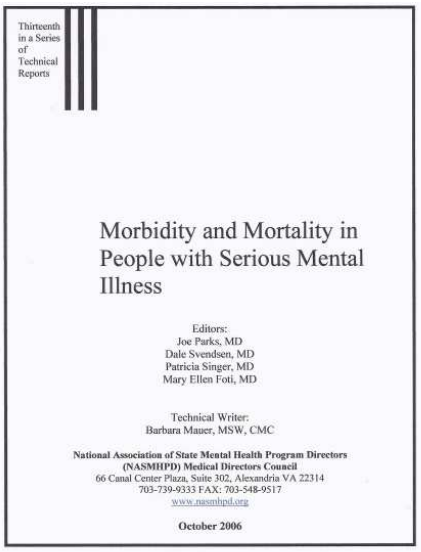
I. What's Happening to the Mentally Ill
II. America's Drug Problem
III. Brain Damage
IV. Brain Repair

This presentation has four goals:

1) to describe the health problems of the mentally ill
2) to explain problems associated with pharmaceutical use in the USA
3) to provide a brief overview of brain damage due to psychiatric drugs
4) to introduce possible methods for 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

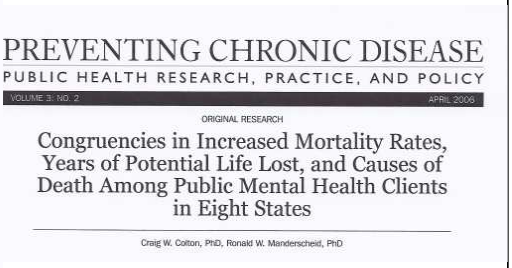
Morbidity and Mortality in People with Serious Mental Illness

Editors:
Joe Parks, MD
Dale Svendsen, MD
Patricia Singer, MD
Mary Ellen Foti, MD

Technical Writer:
Barbara Mauer, MSW, CMC

National Association of State Mental Health Program Directors
(NASMHPD) Medical Directors Council
66 Canal Center Plaza, Suite 302, Alexandria VA 22314
703-739-9333 FAX: 703-548-9517
www.nasmhpd.org

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

Approximately ten years ago, the Center for Mental Health Services, in collaboration with the National Association of State Mental Health Program Directors commissioned a study of "mental health performance measures."

Between 1999 and 2001, **sixteen participating states** were awarded grants to review a variety of outcomes affecting public mental health clients. Eight states provided full data for mortality rates among individuals diagnosed with serious mental illness or SMI (defined as: schizophrenia, bipolar disorder, major depressive disorder, and/or ADHD).

Results were published in two important papers in 2006:

Colton, C.W. and Manderscheid (2006). "Congruencies in Increased Mortality Rate, Years of Potential Life Lost, and Causes of Death Among Public Mental Health Clients in Eight States," *Preventing Chronic Disease: Public Health Research, Practice, and Policy* 3 (2): 1-14.

Parks, J., Svendsen, D., Singer, P., and Foti, M.E. *Morbidity and Mortality in People with Serious Mental Illness*. Thirteenth in a Series of Technical Reports (Alexandria, VA: National Association of State Mental Health Program Directors, October 2006).

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

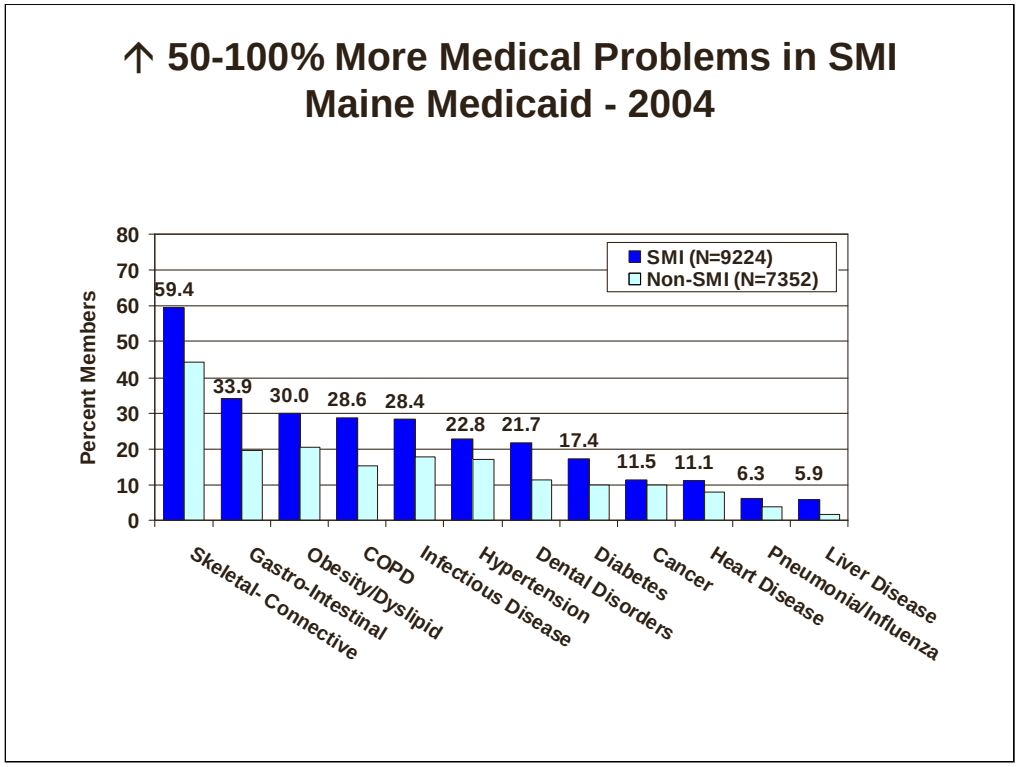
To place the findings of this study in perspective:

- approximately six million individuals receive treatment in the public mental health system each year

- these data were limited to patients who received services between 1997 and 2000

SMI = serious mental illness

defined in this study as schizophrenia, bipolar disorder, MDD (major depressive disorder), or ADHD

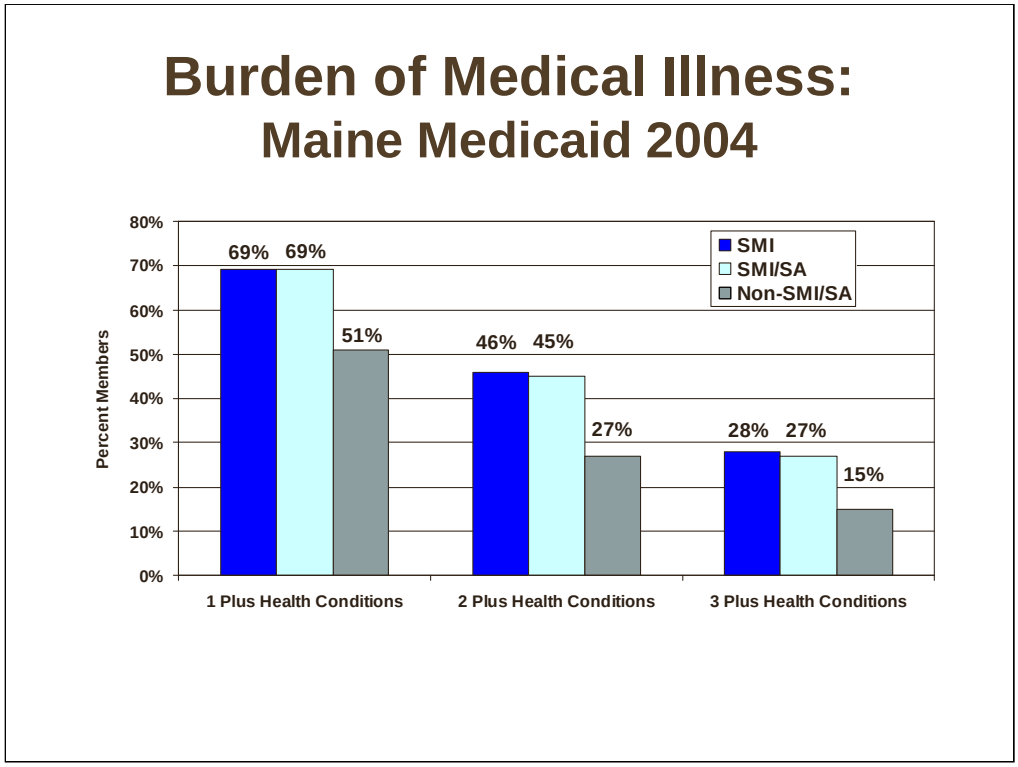


Participating states in the sixteen state study documented an excess burden of medical conditions in public health clients. Although Maine did not participate in the Sixteen State Study, researchers in Maine eventually examined the health outcomes for their public mental health clients. When compared to patients without SMI, Maine Medicaid beneficiaries (fiscal year 2004) experienced significantly higher rates of medical illnesses:

	SMI	non-SMI
skeletal	59%	~43%
gastrointestinal	33.9%	~20%
obesity/high lipids	30%	20%
COPD	28.6%	~18%
hypertension	22.8%	~18%
diabetes	17.4%	10%

Sources of data:

Freeman, E. and Yoe, J.T. *The Poor Health Status of Consumers of Mental Healthcare: Behavioral Disorders and Chronic Disease*, Presentation to NASMHPD Medical Directors Work Group, May 2006;Yoe, JT and Freeman, E. (June 19, 2009). The Interdependence of Mental Health and Physical Health. Presented at the SAMHSA National Grantee Conference – Washington, DC; and NRI (summer 2008), "Using Data, Changing Practice."



The Maine Medicaid Study also found that patients diagnosed with SMI not only experienced higher rates of specific illnesses, but also experienced higher rates of combined (multiple) and serious diseases.

This slide compares the 2004 prevalence of medical conditions among the Seriously Mentally Ill (SMI with and without substance abuse) vs. non-SMI [Medicaid recipients without mental health conditions or substance abuse]:

	SMI	non-SMI
1 plus conditions	69%	51%
2 plus conditions	46%	27%
3 or more conditions	28%	15%

[Source of data: Freeman, E. and Yoe, J.T., as referenced above.]

Key Point:
Among recipients of Medicaid, SMI was associated with higher rates of physical medical disease.

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%

Data collected from half of the participants in the **Sixteen State Study** revealed that patients with SMI died primarily of the same "natural" causes which affected the non-mentally ill: cardiac disease, cancer, stroke (cerebrovascular disease), chronic respiratory conditions, and diabetes.

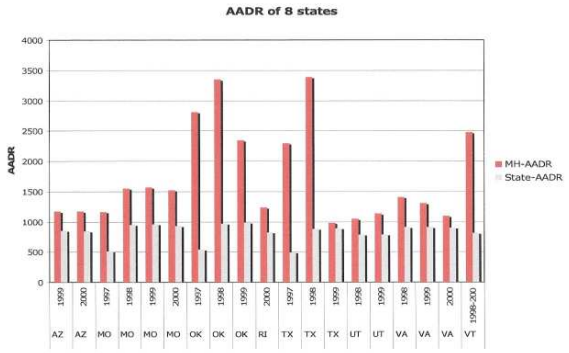
*Interestingly, cancer-related deaths were less common among people with SMI. One of the reasons for this finding may have been the chemotherapy properties of certain psychopharmaceuticals taken by individuals with SMI.

Mortality Among Public MH Patients

annual death rates

SMI 1 - 3.5%

non-SMI 0.5 - 0.8%



This slide depicts annual age-adjusted death rates for SMI vs. the non-mentally ill. [data from subset of the Sixteen State Study]

1) in all 8 states which supplied mortality data (AZ, MO, OK, RI, TX, UT, VA, and VT), the seriously mentally ill had higher rates of death than the general population

1 to 3.5% of SMI died each year

2) when matched by age to non-mentally ill individuals, patients with SMI died at an earlier age -- **on average, the SMI patients died 13 to 30 years earlier than expected**

mean age at time of death: 49-60

3) most mental health patients died of natural causes, such as heart disease and respiratory conditions

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

Express Scripts, a pharmaceutical benefits management company, produces annual drug trend reports. The information in this slide was obtained from the April 2010 Drug Trend Report. Approximately 10% of U.S. residents used an antidepressant at some time in 2009; 4% used anticonvulsants; 2% used stimulants; and approximately 2% used an antipsychotic.

These numbers exclude drug use by non-commercially insured patients, such as veterans and active duty military personnel; institutionalized patients (e.g., residents of nursing homes, prisons, jails, and state hospitals); and patients who rely upon publicly funded programs, such as Medicaid and Medicare.

How Did They Do It:

Prescription drug use was evaluated by examining pharmacy claims from two independent, random samples of approximately 3 million commercially insured individuals. The prevalence of use was calculated by dividing the # of insured members taking medications in a certain drug class by the total number of insured.

To place the aforementioned figures in context, the Express Scripts database revealed the following patterns of non-psychiatric drug use in 2009:

pain killers	17.8%
heart disease, hypertension	15.7%
high cholesterol drugs	12.1%
asthma medications	8.7%
ulcer disease (antacids)	8.2%
diabetes	5.0%
anti-virals	4.5%

U.S. = 4.5 % of world population

Approximately

90% of stimulant sales
60% of AP sales
50% of AD sales
40% of AED sales

Although the U.S. population comprises only 4.5% of the planet's human inhabitants, Americans account for a disproportionate share of the world's pharmaceutical *sales*:

90% of the world's stimulants
63% of the world's antipsychotics
51% of the world's antidepressants
41% of the world's anti-epileptics

[Source of sales data: IMS Health]

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

The federal government (via The Centers for Disease Control and Prevention) collects and analyzes vital statistics and publishes the results in annual summaries. Each year, approximately 0.8% of the entire U.S. population succumbs to illnesses or accidents (roughly 2.5 million deaths per year).

According to the government, the leading causes of death in the USA in 2011 were cardiac disease, cancer, chronic lower respiratory conditions, stroke, and accidents.

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

In 2000, the prestigious *Journal of the American Medical Association* (aka, JAMA) featured an article by Johns Hopkins University professor, Dr. Barbara Starfield. Using data culled from a variety of inpatient and outpatient investigations, Starfield's analysis estimated that adverse effects of medication (i.e., ***"therapeutic" doses of prescription drugs taken exactly as prescribed***) account for approximately 305,000 deaths per year.

106,000 inpatient deaths due to pharmaceuticals
199,000 outpatient deaths due to pharmaceuticals

[Note: Given the fact that "adverse drug reactions" are rarely reported, and given the fact that drug-related heart attacks, strokes, pneumonias, and cancers are seldom attributed by physicians or governmental agencies to pharmaceuticals, these estimates were absurdly conservative.]

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

If one integrates Dr. Starfield's data into the federal government's annual report on vital statistics, pharmaceuticals become the #3 leading cause of death in the USA.

Furthermore:

*if one incorporates findings from the Institute of Medicine's 1999 publication, *To Err Is Human*, medical errors belong on the list as the #7 cause of death. (Medical errors include missed diagnoses, wrong diagnoses, the administration of inappropriate drugs, and errors in drug dosing.

Reminder:
Compared to non-SMI, SMI patients:

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

To recap:

compared to people without Serious Mental Illness, public mental health care recipients with SMI:

experience higher rates of medical disease

die in greater numbers each year (1-3.5% vs. 0.5-0.8%)

die 13 to 30 years earlier than expected

There's an elephant in the room …

the impact of psychiatric drugs upon morbidity (illness rates) and mortality (death rates) of patients with SMI is usually ignored or minimized

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%

Numerous epidemiological studies (population based studies of human patients) have documented increased risks of cardiac disease among the users of psychiatric drugs. These risks have not been explained by the presence of other variables, such as lifestyle or pre-existing health conditions.

In other words, even after "controlling for" mental illness severity and medical co-morbidity, and even after adjusting statistical equations for lifestyle factors (such as smoking, poverty, and/or lack of exercise), the use of psychiatric drugs has been a significant risk factor for sudden death and heart disease.

Antipsychotic drugs (APs) have been associated with a 100-300% increase in the risk of sudden cardiac death; and a 400% increase in the risk of heart attacks (myocardial infarction).

Antidepressant drugs (ADs) have been associated with a 50% to 260% increase in the risk of sudden cardiac death; and a 20-85% increase in the risk of heart attacks. (In some studies, as many as 8-11% of antidepressant drug users have experienced a heart attack during treatment.)

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%	

Just as psychiatric drugs contribute to elevated rates of heart disease, these pharmaceuticals also elevate the risk of stroke (acute “brain attacks” > caused by impaired blood flow, bleeding, and/or changes in cell metabolism).

Antipsychotic drugs elevate the risk of stroke by 40-250%.

Antidepressant drugs elevate the risk of stroke by 20-100%.

Antiepileptic drugs (aka, anticonvulsants) which are commonly used for “bipolar disorder” elevate the risk of stroke by 150-270%.

Diabetes Mellitus

#7 Cause of Death in 2011

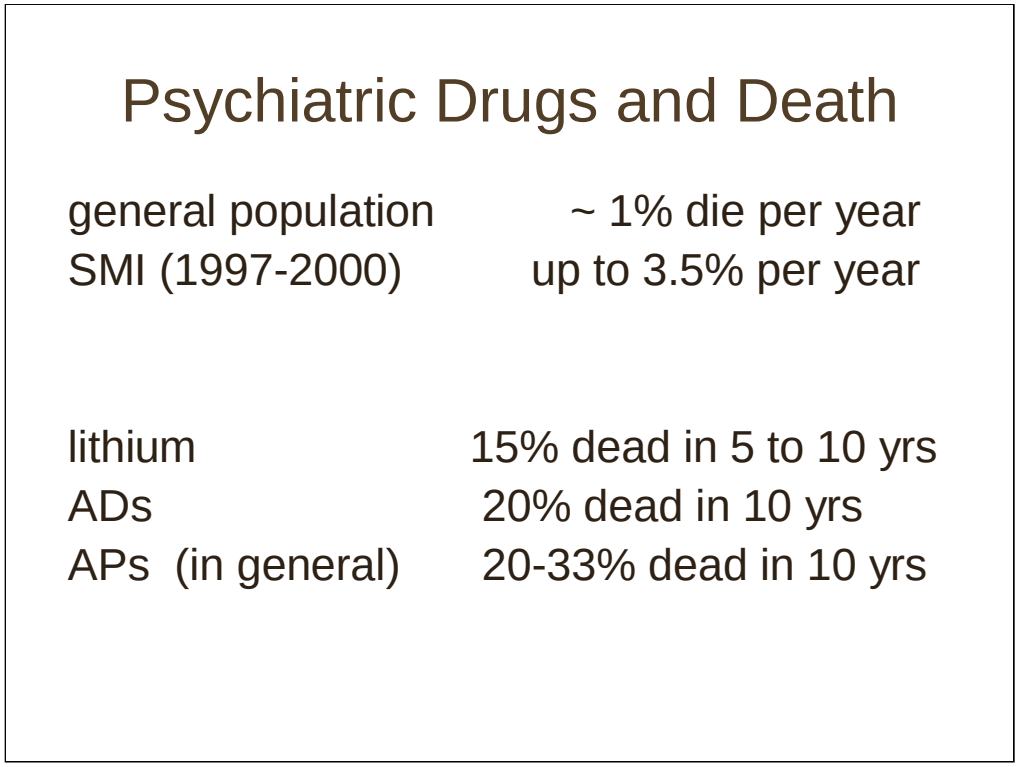
APs	ADs	AEDs
↑7X	↑2X	↑2-3X

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

The term “diabetes” is taken from the Greek word, “diabainein” meaning siphon. The implication is a gushing or overflow of fluid > specifically, of urine. Historically, physicians have identified and treated two major kinds of diabetes: ***diabetes mellitus*** characterized by sugar in the urine (mellitus = honey sweet); and ***diabetes insipidus***, characterized by excessive urination (insipidus = without taste).

The slide above refers to the #7 leading cause of death in the USA: **diabetes mellitus (Type I and Type II)**. Childhood onset or Type I diabetes mellitus, is caused by an autoimmune deficiency which impairs the body’s ability to make insulin. Type II diabetes mellitus refers to an *acquired disease* involving decreased insulin production and decreased insulin response (e.g., insulin resistance).

This slide compares the rates of **Type II Diabetes Mellitus** in the general population of the USA (lifetime prevalence: 9%) versus psychiatric drug users: **At least 20-30% of antipsychotic drug users** are developing Type II DM; ~**10-20% of chronic antidepressant drug users** are developing Type II DM; ~**30-50% of some anti-epileptic drug users** are developing insulin resistance (pre-diabetes) >> of these, 1/2 are expected to progress to diabetes



Approximately 1% of the US population dies each year.

Several studies of patients exposed to different classes of psychiatric drugs have shown high mortality rates: 15-33% of the patients have died within ten years.

Hold on to your seat!

III. Brain Damage

What do all of these people have in common ?

Answer: dementia

Glen Campbell >	Alzheimer's disease
Alex Karras >	kidney failure > dementia due to multiple causes
Jim McMahon >	post-traumatic dementia
Pat Summitt >	early-onset Alzheimer's disease

This is the Rose Bowl in Pasadena, CA …

On January 1, 2011, even the Rose Bowl football game took up the cause of Alzheimer's disease and dementia …

On January 1, 2011, the winner of the Presidential Trophy in the Annual Tournament of Roses parade was a float entitled:

The Boomer Express >> “It’s Time to Face Alzheimer’s”

Why was this float entered in the 2011 parade ?

Answer: to commemorate the arrival of the Baby Boom generation into retirement (and with this change in US demographics, to recognize the arrival of more and more Americans with dementia)

What is dementia ?

Dementia defined:

From Latin *de mens / de mentis*

"out of (away from) one's mind"

The word "dementia" is derived from the Latin terms

de mens / de mentis

meaning "**out of (or 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

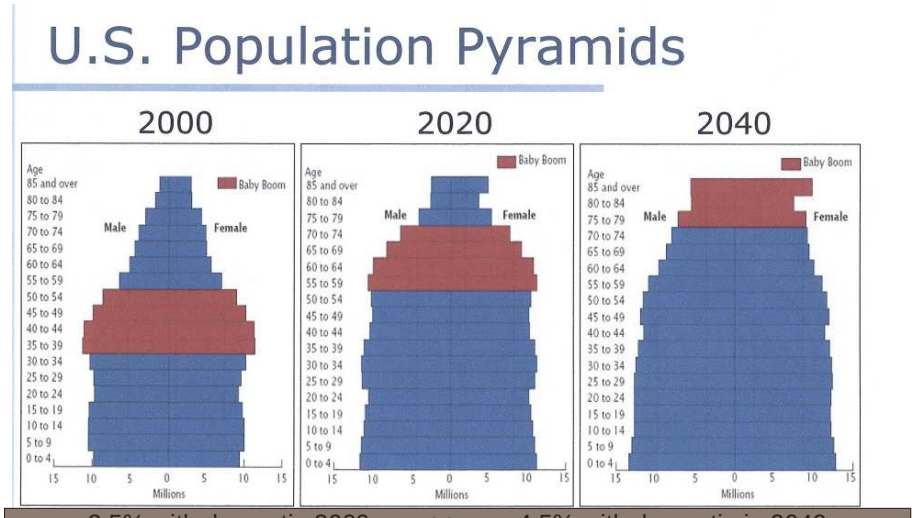
In performing their clinical duties, American psychiatrists are trained to use a specific classification system known as the *Diagnostic and Statistical Manual of Mental Disorders* (aka, the *DSM*). According to past and current editions of the DSM, the defining feature of dementia (as a diagnosis) is the impairment of memory. This is a short-sighted and frequently erroneous view, as some forms of dementia begin with problems other than memory difficulties.

The term dementia refers to a syndrome of signs and symptoms – such as deficits in thinking, perceiving, feeling, moving, speaking, writing, planning, or behaving – which are caused either by toxins, by disease processes outside the brain (e.g., diabetes, hypothyroidism, cancer), or by degenerative conditions which originate inside the central nervous system (e.g., Parkinson's disease, Pick's disease, Creutzfeld-Jakob disease, multiple sclerosis).

Key Points:
Dementia is arguably under-recognized by psychiatrists in the United States for at least three reasons: 1) due to the inordinate emphasis which the *DSM* has placed upon the loss of memory; 2) due to a socio-cultural expectation that dementia should appear only in old age; and 3) due to the tendency of physicians to attribute dementia-symptoms in psychiatric patients to mental illness, rather than to toxins or somatic (bodily) disease.

≥ 65 years of age

12% to 18% to 21%



2.5% with dementia 2000 >> 4.5% with dementia in 2040
7.5 million 18 million

With the end of World War II came the return of soldiers to the U.S. mainland, and with their return came an explosion in the birth of babies. The so-called "Baby Boom Generation" refers to this population subgroup whose members were born between 1946 and 1964.

As the "Baby Boomers" move into their retirement years (red bars in the slides above), the overall structure of the U.S. population changes from a pyramid shape (2000) to a rectangle shape (2040) – a phenomenon which some researchers have called "The Squaring of the Population Pyramid."

These demographic shifts have important implications for economic and healthcare policy, because the number of retirees (aged 65 and older) will reach an historical high point by 2040:

12% of the population in 2000

18% of the population in 2020

21% of the population in 2040

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%

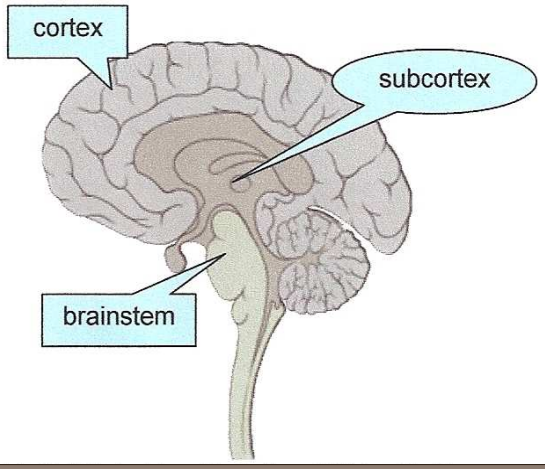
In 2000, approximately 2.5% of the US population was suffering from dementia. The prevalence of dementia rises with age (e.g., 20% of those older than 80).

Currently, 5-8% of Americans aged 65 or older are said to experience full-blown, clinical dementia.

*This “5-8%” figure excludes individuals with milder forms of forgetfulness or cognitive slowing, otherwise known as MCI {mild cognitive impairment}. This 5-8% estimate also excludes the cognitive problems which are increasingly prevalent among young people in the USA.

How do physicians think about dementia ?

In general, physicians do *not* think about dementia >> but when they do [see next slide] …



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

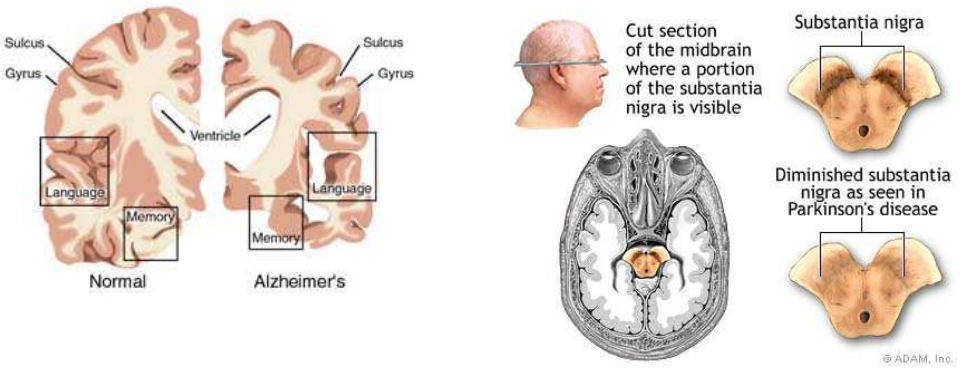
…they think about the brain **location** and **pathology**

(pathology = what does the brain look like physically or structurally, in terms of abnormal anatomy).

One way to think about the brain is by comparing its structure to the parts of a tootsie roll lollipop:

candy coating (outside)	=	brain cortex
tootsie roll center	=	brain subcortex
lollipop stick	=	brainstem

Location

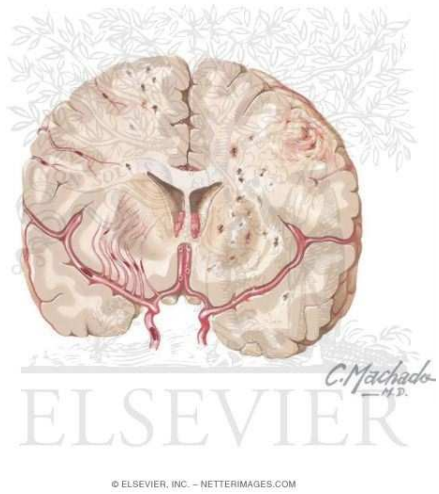


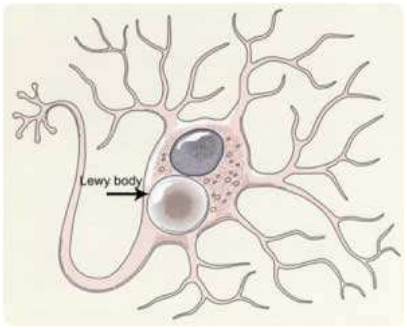
Examples of Location

The image on the left shows some of the structures (temporal lobe) which are affected in Alzheimer's disease. This is an example of a dementia that is believed to originate in the **cortex** (lollipop "candy coating").

The image on the right shows pictures of the **brainstem** (lollipop stick) as it is affected in early Parkinson's disease. Parkinson's disease is a neurodegenerative condition which frequently culminates in dementia.

Pathology

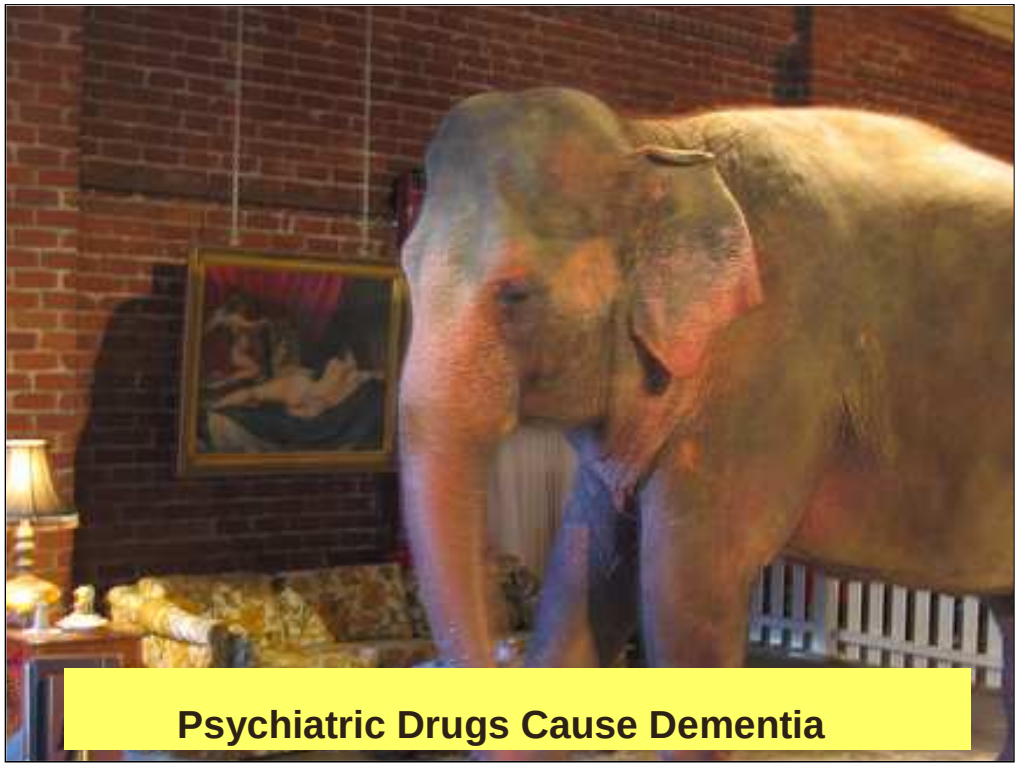




Examples of Pathology

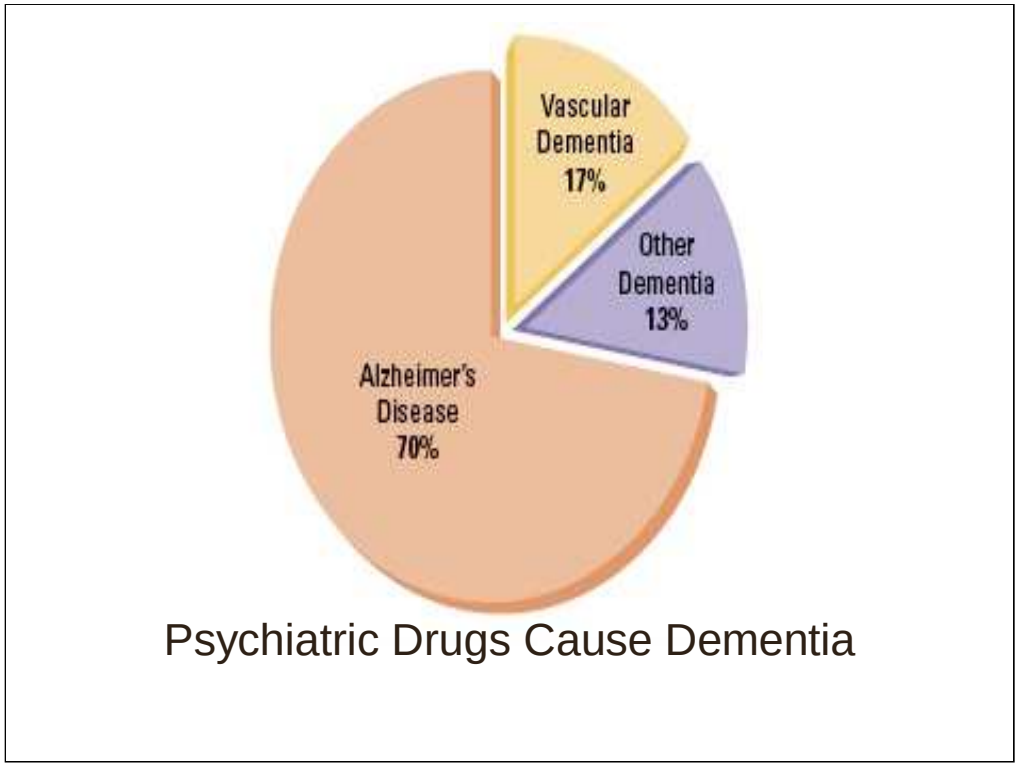
The image on the left shows the brain as it would appear at autopsy following the death of a patient with vascular dementia. The picture highlights vascular changes (interrupted blood flow) to the cortex of the brain.

The image on the right shows a cartoon of brain tissue as it would appear under a microscope. This specific picture features a neuron (brain cell) with an abnormal protein component known as a Lewy body. Lewy bodies are a feature of several neurodegenerative conditions, including Lewy body dementia and Parkinson's disease.



There is, of course, another elephant in the room …

most discussions of dementia ignore the role of pharmaceuticals – specifically, psychiatric drugs – in causing or enhancing brain damage.



To reiterate:

Dementia, per se, is not a disease but refers to a cluster of symptoms.

Dementia can be caused by many different kinds of brain diseases.

At this time, the leading cause of dementia in the USA is *purportedly **Alzheimer's disease** (70% of all dementias).

The second most common cause of dementia is **vascular disease**. Vascular dementia reflects the brain damaging effects of ischemic stroke (plugged or narrowed blood vessels); hemorrhage (bleeds); inflammation (vasculitis/ cerebritis); and/or mitochondrial disorder (such as MELAS).

***purported** = more than 50% of all dementias are actually "mixed" >> autopsy analyses of dementia patients frequently reveal the presence of one or more neurodegenerative pathologies (such as vascular disease + Lewy bodies).

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%**

Although few in number, epidemiological studies which have specifically investigated the rates of dementia among the users of psychiatric drugs display a startling pattern. ***Every major class of psychotropic medication has been linked to an elevated risk (and elevated rate) of dementia.***

APs = antipsychotic drugs

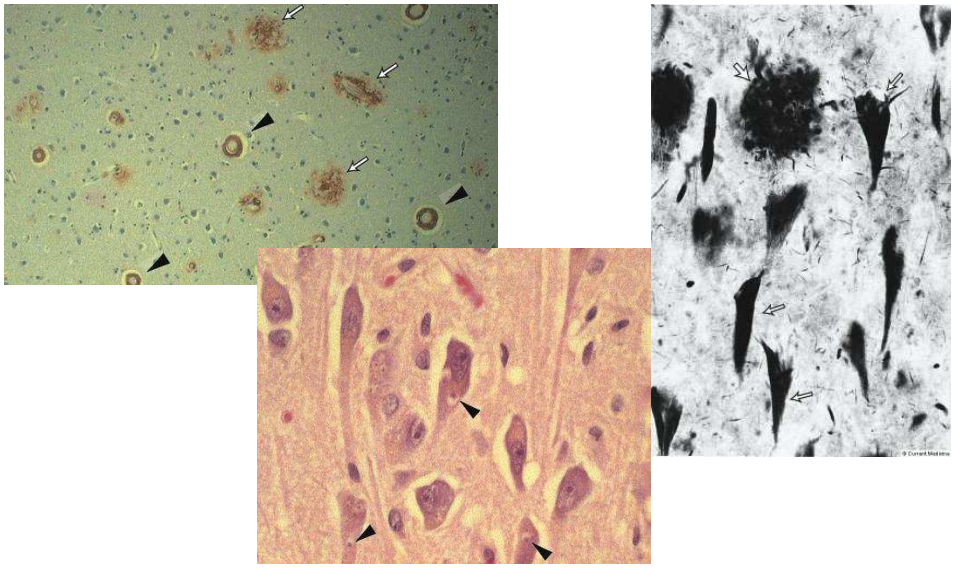
ADs = antidepressant drugs

AEDs = antiepileptic drugs [aka, anticonvulsants – used for bipolar disorder]

lithium = lithium salts used to treat bipolar disorder

benzos = benzodiazepines [aka, minor tranquilizers]

Alzheimer's Pathology



The structural abnormalities which accompany Alzheimer's disease include:

Upper left: **beta-amyloid plaques**

Arrowheads point to accumulations of beta-amyloid protein in clusters known as "plaques" >> These beta-amyloid plaques accumulate both inside and outside of neurons. (Neurons, along with glia, are the major cell types that constitute the brain.)

Far right: **tau tangles**

Dark, spike-shaped objects in this slide are neurofibrillary "tangles." Composed of a protein known as tau, these chemically modified strands build up inside of neurons and impair brain function.

Center: **granulovacuolar degeneration (GVD)**

Arrowheads point to dark granules surrounded by clear zones (vacuoles) in neurons of the temporal lobe (cortex). While GVD occurs in normal ageing, this process is more extensive in Alzheimer's disease and other neurodegenerative conditions.

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

The clinical diagnosis of Alzheimer's disease is based upon a patient's symptoms (usually, after a clinician has ruled out other causes of dementia). However, the **definitive diagnosis of Alzheimer's disease can only be made after death**, based upon a pathologist's examination of brain tissue.

Historically, the determination of Alzheimer's disease has depended upon sophisticated laboratory methods which permit the identification of plaques and tangles using a microscope. Various diagnostic criteria – involving inspection of the location and density of plaques and/or tangles – have evolved over time. Due to the lack of standardized lab techniques for processing brain material; and due to changes in the interpretation of tangles and plaques, the autopsy determination of Alzheimer's disease remains a subject of confusion and controversy.

This slide shows a few of the schemes that have been used to diagnose Alzheimer's disease:

NPs = neuritic plaques (aka, "senile plaques" or "amyloid plaques")
Khachaturian criteria = plaque counts consisted of *neuritic plaques* plus *diffuse plaques* > diffuse plaques are considered to be a part of "normal" ageing
CERAD = Consortium to Establish a Registry for Alzheimer's disease
HC = hippocampus
NC = neocortex
ERC = entorhinal cortex
NFT = neurofibrillary tangles [tau tangles]
NIA-RI = National Institute on Ageing – Reagan Institute

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

Over the years, research teams have offered various opinions about the presence or absence of Alzheimer's disease in the brains of people diagnosed with schizophrenia. These differences of opinion have been strongly influenced by variations in lab techniques, by shifting thresholds for diagnosing Alzheimer's disease, and by changes in the patterns of treatment.

Importantly, when the medical literature is carefully reviewed, many lines of evidence converge upon a dramatic finding.

Whether the changes are called "full blown Alzheimer's disease", "atypical variant" of Alzheimer's disease, or "pre-Alzheimer's" disease, ***the brains of patients exposed to antipsychotic drugs have repeatedly revealed high levels of plaques and/or tangles, in excess of the changes associated with normal ageing*.**

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

In their review of more than 1000 patients who died within New York state mental institutions, Prohovnik et al investigated the density of tangles (tangles in the neocortex or hippocampus) and senile plaques (abnormal accumulations of plaques beyond the inferior temporal lobe).

By reviewing clinical notes and pathology results, the researchers compared the prevalence of clinical (antemortem) vs. anatomic (postmortem) Alzheimer's disease in three groups of patients:

544 patients diagnosed with schizophrenia

258 patients diagnosed with dementia

47 patients diagnosed with affective disorder (depression, bipolar)

NY Office of Mental Health

compared three groups of patients

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

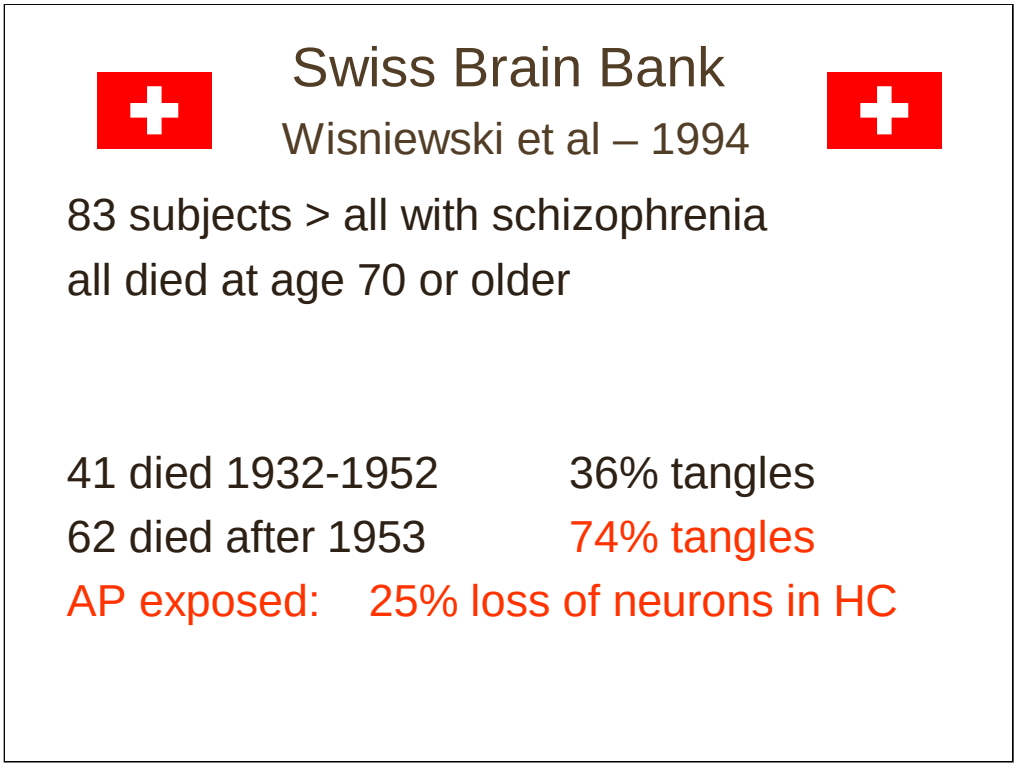
general population ≥ 65: 2 to 5.6% develop AD

AD = Alzheimer's disease

Recall that in the U.S. general population, an estimated 3-8% of individuals aged 65 or older will develop dementia. Of these, 70% will be diagnosed with Alzheimer's disease.

Findings of the New York State study confirmed a high rate of clinical Alzheimer's disease (28%) and Alzheimer's pathology (56%) among patients who had been institutionalized for the treatment of schizophrenia.

Although Prohovnik et al did not discuss these patients' treatment histories, their diagnoses of schizophrenia and their treatment settings (state institutions) strongly imply a pattern of chronic exposure to antipsychotic drugs.



Drawing upon a set of brains maintained at Geneva University in Switzerland, Wisniewski et al (Staten Island, NY) compared plaques and tangles in 102 patients who had received treatment for schizophrenia.

Among the 41 patients who died prior to the era of antipsychotic drugs: 36% developed neurofibrillary tangles (always with plaques)

Among the 62 patients who died after the arrival of antipsychotic drugs:

74% exhibited neurofibrillary tangles (always with plaques). A separate analysis of cell number in the hippocampus revealed a ***25% reduction in neurons after the introduction of antipsychotic drugs.***

In their published study, the authors commented:

"…We conclude on the basis of previous and present…studies that it is not schizophrenia per se but instead the chronic treatment of schizophrenics with neuroleptics that produces earlier, more frequent, and accelerated development of neurofibrillary pathology…"

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)

In 1998, researchers at Mount Sinai Medical Center reported the autopsy results of 100 elderly patients who had received treatment for schizophrenia at Pilgrim Psychiatric Center (Long Island, NY).

The investigators evaluated the prevalence of clinical dementia (based upon lifetime interviews with the patients, or based upon a methodical review of clinical progress notes) and the prevalence of Alzheimer's brain pathology.

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

Based upon assessments of cognitive functioning, 72% of the schizophrenia patients met criteria for moderate to severe dementia.

Based upon assessments of plaque and tangle density, 52% of the schizophrenia patients demonstrated abnormal brain pathology.

Using the Khachaturian criteria, 9% satisfied the strict definition of Alzheimer's disease anatomically.

The research team compared brain pathology in the 100 schizophrenia patients with 47 patients who had been treated for other psychiatric conditions. Then, they analyzed the brains of 50 (non-institutionalized) control cases who lacked diagnoses of dementia or mental illness. Of the patients who had received treatment for schizophrenia, 47% demonstrated senile plaques. Their plaque density was 33% higher than other psychiatric patients; and 89% higher than age-matched controls. In addition, patients who had received treatment for schizophrenia also displayed 37% more tangles than age-matched controls.

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]

A follow-up study was undertaken by researchers at the Mount Sinai Medical Center.

This time, the goal was to explore the association between Alzheimer's disease pathology and dementia symptoms in almost 200 patients who had been treated for schizophrenia.

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

The research team started with an analysis of 196 consecutive brain donations. Strangely enough, the investigators excluded 86 patients with clear evidence of neurodegeneration:

57 patients met criteria for Alzheimer's disease
21 patients met criteria for Lewy body dementia
4 patients demonstrated Parkinson's disease
4 patients demonstrated vascular disease

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

In the remaining 110 patients, the research team compared Alzheimer's disease pathology with the presence and severity of dementia symptoms.

Of these 110 patients, 45% exhibited significant neurodegenerative changes. Plaque density was 50% lower than full-blown Alzheimer's disease. However, ***tangle density was equivalent to full-blown Alzheimer's***.

Hospital progress notes revealed that 85% of these patients had met criteria for clinical dementia.

Big Picture

of 196 brains…

~70% had neurodegenerative diseases
55% developed Alzheimer's pathology

Of the 196 patients who had received treatment for schizophrenia:

~ 70% developed neurodegenerative conditions
55% exhibited Alzheimer's disease pathology

Alzheimer's Biomarkers

Lumbar Spinal Tap

High levels of:
tau
phosphorylated tau

Low levels of:
AB-42

As the current method for confirming Alzheimer's disease requires an autopsy analysis of brain tissue, neurologists and psychiatrists are working diligently to establish objective evidence (biomarkers) that can be measured in living patients.

Although standardized "reference ranges" have not yet been determined, medical researchers have focused upon the levels of various abnormal proteins that can be measured in the cerebrospinal fluid which bathes the brain.

Theoretically, an Alzheimer's diseased-brain produces and secretes excessive levels of tau protein (and phosphorylated tau) and beta-amyloid. High levels of tau can be traced both within, and beyond, the brain in the spinal fluid.

Meanwhile, AB-42 -- the specific form of amyloid protein in Alzheimer's disease plaques -- accumulates inside the brain tissue and inside the fluid-filled spaces of the brain, known as ventricles. These AB-42 proteins get stuck in the cranium. Hence, ventricular levels of AB-42 are *higher* than normal, but spinal fluid levels outside the brain (as shown in this slide) are *lower* than normal.

Brescia, Italy
Frisoni et al – 2011

compared spinal fluid

schizophrenia
Alzheimer's patients
control group
surgery requiring
spinal anesthesia

Researchers in northern Italy analyzed biomarkers of Alzheimer's disease in three groups of patients:

11 patients with the diagnosis of schizophrenia

20 patients receiving treatment for Alzheimer's disease

6 patients (controls) receiving spinal anesthesia for hip or pelvic surgery

Brescia, Italy

	Schiz n=11	Alz n=20	controls 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

All of the patients receiving treatment for schizophrenia had been diagnosed prior to age 40. The investigators excluded patients with a history of substance dependence, neurological disease, or unstable medical conditions.

Of the 11 patients labeled with schizophrenia:

45% were taking first-generation antipsychotic drugs at the time of testing

73% were taking second-generation antipsychotic drugs at the time of testing

Brescia, Italy

lumbar CSF concentrations

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

on average > schiz 27% lower than controls

Both the patients diagnosed with schizophrenia and Alzheimer's disease had lower levels of AB-42 in their spinal fluid samples, when compared to non-demented, surgical controls. These differences were statistically significant.

Brescia, Italy

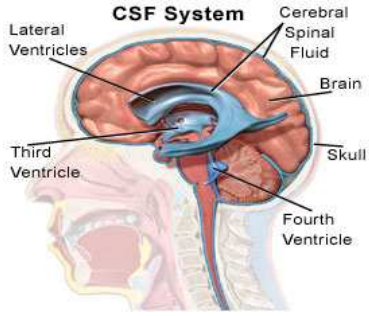
on 6 of 8 tests of neurocognitive functioning schiz. patients were ***much more impaired than Alzheimer's disease patients***

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

Equally astounding, the Italian research team performed neuropsychological testing on all three groups of patients.

On six out of eight tests of cognitive functioning, the patients who were receiving treatment for schizophrenia were significantly more impaired than the Alzheimer's disease patients.

London, UK
Clarke et al - 2011



compared 32 patients

neurosurgery for severe depression

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

Researchers in the UK (London) compared the levels of Alzheimer's disease biomarkers drawn from the ventricles of each patient's brain.

Recall that the levels of tau, phosphorylated tau, and AB-42 are all expected to be elevated in the ventricular fluid of patients affected by Alzheimer's disease.

In this study, 32 patients – all of whom were suffering from severe depression – had elected to undergo neurosurgery as a treatment for their condition.

The investigators compared biomarkers in 16 patients who had been taking antipsychotic drugs for at least 2 weeks prior to surgery (vs. 16 patients who had avoided treatment with antipsychotic drugs).

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

When compared to depressed patients who had avoided antipsychotic drugs, patients exposed to antipsychotic medications experienced higher levels of Alzheimer's disease biomarkers.

Why is this happening ?

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

As previously discussed (see slide #21), two major forms of diabetes mellitus have been described in the history of medicine. **Type I diabetes mellitus** refers to an early onset disease, caused by a failure of the pancreas to produce sufficient amounts of insulin. This results in high levels of glucose and inflammation. Eventually, the sugar-insulin imbalance results in damage to multiple organs of the body (nerves, retina, kidney, heart). **Type II diabetes mellitus** is an acquired failure of the pancreas, liver, and muscles to use or to respond to insulin appropriately. Over time, the body may also lose the capacity to produce adequate amounts of insulin. The same organ breakdowns can occur (kidney, retina, nervous system, heart damage).

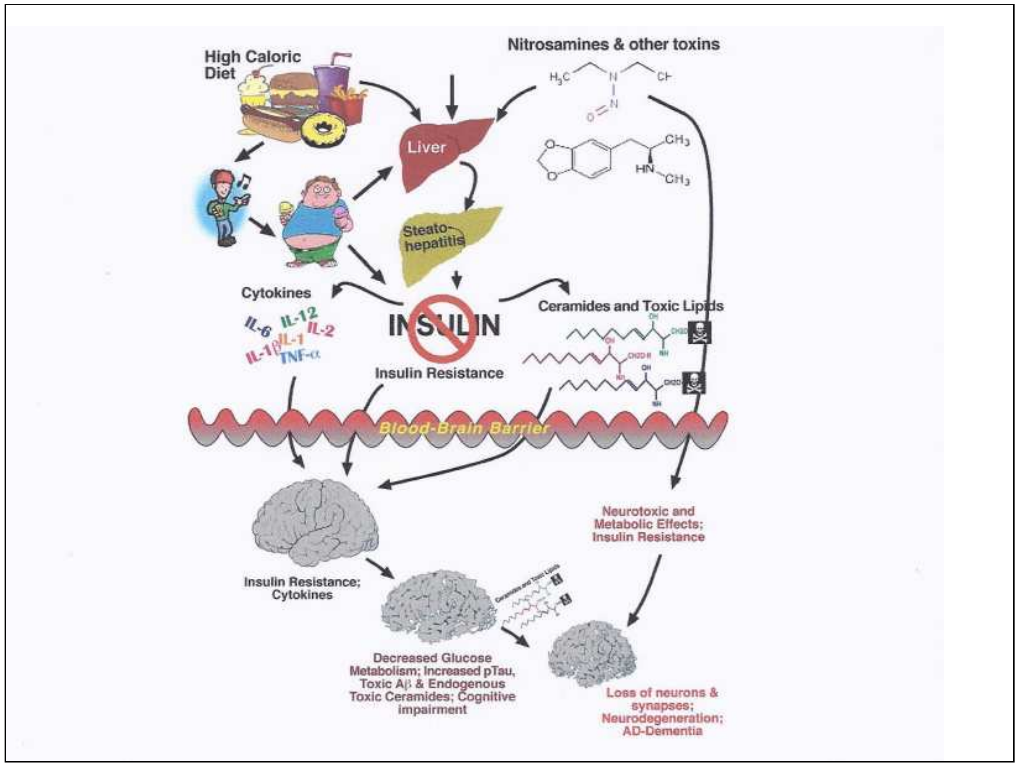
Only in the past 10 years, however, researchers have discovered that the brain itself makes and responds to insulin. Drawing upon sophisticated experiments in animals, and postmortem discoveries in humans, Dr. Susan de la Monte and others have proposed the existence of a **Type III diabetes mellitus**. This type of sugar-insulin imbalance, within the brain, appears to result in the pathological changes and dementia symptoms of Alzheimer's disease.

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

Numerous teams of scientists have studied the consequences of decreased insulin synthesis and decreased insulin signaling in the brain. When the brain loses the ability to make and respond to insulin, a cascade of changes (described above) lead to cell damage and death.



This picture – created by Dr. Susan de la Monte of Brown University – depicts the various pathways that have been proposed and tested in explaining the cause of Type III diabetes mellitus and Alzheimer's disease.

*Of special interest for psychiatrists should be the connection between diet, lifestyle factors, and toxins which can cause a fatty liver (aka, non-alcoholic steatohepatitis or NASH). With the impairment of liver function, including hepatic insulin resistance, comes the breakdown of fats. This results in the production of toxic lipid products known as ceradmides. Neuroscientists have documented the harmful effects of ceramides in genetic and acquired conditions, noting that these substances travel through the bloodstream, cross the blood-brain barrier, and ultimately damage cells of the brain.

Multiple classes of psychiatric drugs have been implicated as a cause of fatty liver disease (antipsychotic drugs, antidepressants, and anticonvulsants). Even more clearly, the causal relationship between multiple classes of psychiatric drugs and insulin resistance -- even in the absence of weight gain or obesity -- has been repeatedly demonstrated in animals and humans. Together, both of these processes contribute to the neurodegenerative potential of widely used, psychiatric drugs.

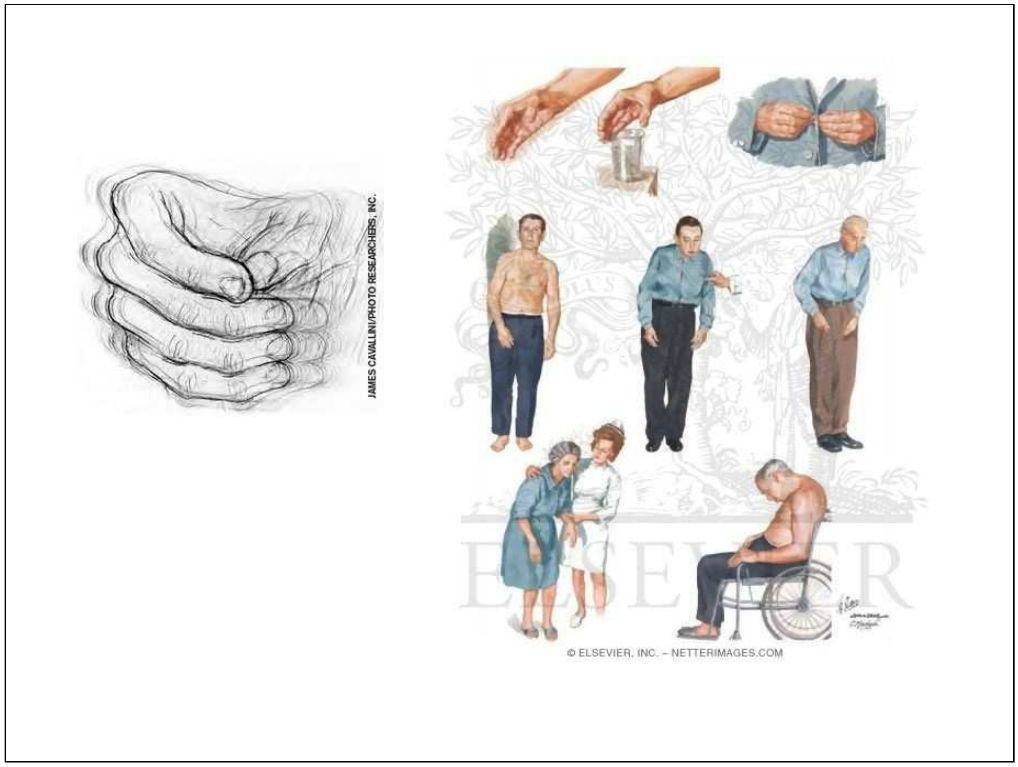
Parkinson's Disease

Parkinson's disease – like Alzheimer's disease – is a common form of neurodegeneration.

This photo shows two famous individuals who are known for their public battles against Parkinson's disease:

former world heavyweight boxing champion: Muhammad Ali

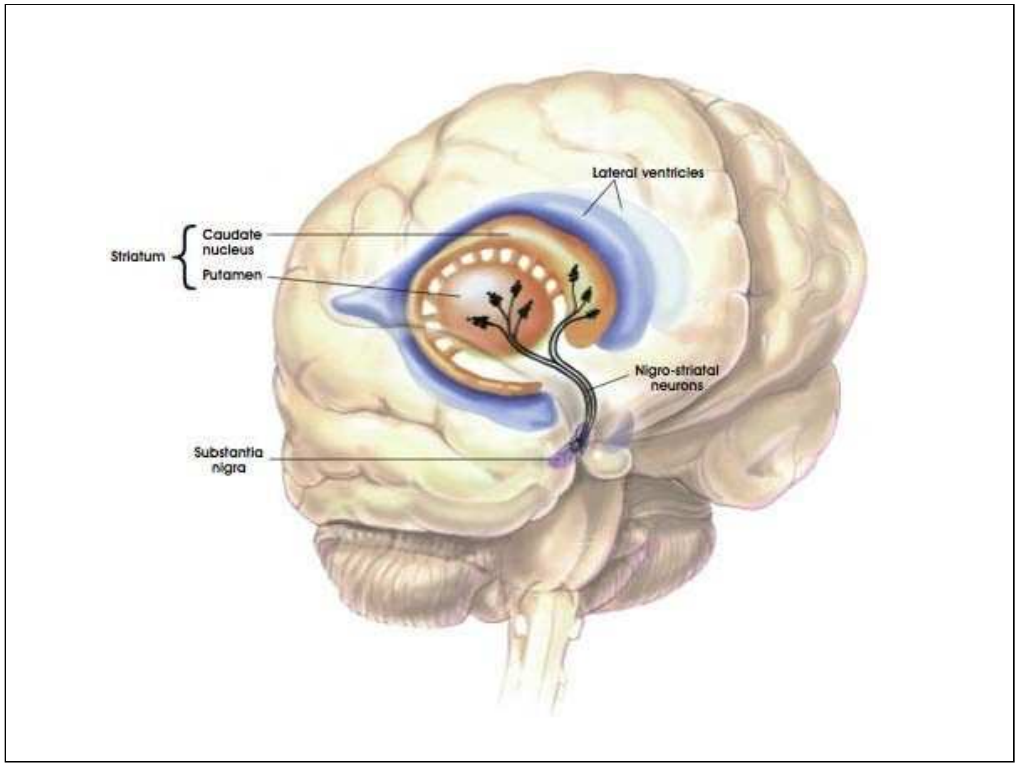
actor/author/producer/philanthropist: Michael J. Fox



The features of Parkinson's disease include motor and non-motor symptoms.

Motor symptoms include tremor (typically, an involuntary "pill rolling" movement of index finger and thumb), difficulty initiating movement (e.g., rising from a chair), abnormal gait (small, shuffling steps and difficulty lifting the feet), postural instability (imbalance and falls), and cogwheel rigidity (a "racheting" stiffness of the limbs).

Non-motor symptoms include sleep problems (restless legs, insomnia), pain, urinary or digestive difficulties (e.g., urgency, constipation, weight loss), fatigue, autonomic instability, anxiety, depression, psychosis, and/or cognitive impairment (problems with attention, concentration, and planning). In late or advanced stages of Parkinson's disease, clinical dementia affects at least 20% of patients.



This slide depicts the major areas of the brain which exhibit damage in Parkinson's disease.

Historically, Parkinson's disease has been attributed to the loss of cells from the **midbrain** – **an anatomical region located within the brainstem**. [Recall the structure of the brain in comparison to a tootsie roll lollipop: the brainstem is analogous to the lollipop stick.]

Neuroscientists have proposed that the motor symptoms of Parkinson's disease originate in the loss of 60% or more of the dopamine neurons in a specific region of the midbrain (the "substantia nigra"). The death of these nigral cells creates a ripple effect which extends to subcortical regions of the brain (recall the analogy tootsie roll lollipop: subcortex = "tootsie roll center").

Drawing upon advances in modern research techniques and instrumentation, newer studies have documented diverse and extensive pathology in Parkinson's disease. Thus, the structural determinants now include degenerative changes within multiple pathways (serotonin, acetylcholine, dopamine) throughout the brain -- brainstem, subcortex, and cortex.

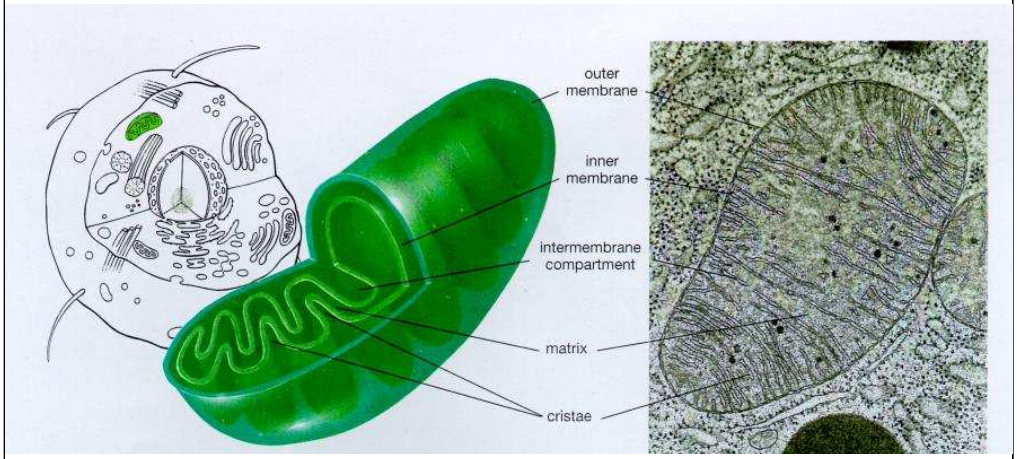
Which drugs ?

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

All of the major classes of psychiatric drugs have been known to cause or enhance symptoms of Parkinson's disease. Although textbooks of pharmacology and psychiatry have commonly referred to these drug-induced syndromes as "**Pseudo-Parkinsonism**" -- based upon the belief that the drugs fail to inflict permanent structural damage to the brain – the "pseudo" designation has often been erroneous.

***The exact prevalence of drug-induced Parkinson's disease is unclear*.** Of the major classes of psychiatric medication where this problem has been intensively explored, antipsychotic medications have been linked to Parkinsonian *symptoms* in at least 10 to 40% of drug consumers. In fact, from the 1950s through early 1960s, doctors were encouraged to prescribe high doses to ensure the emergence of Parkinsonian symptoms, based upon the misguided belief that psychosis would be eradicated in this process. Animal experiments performed around that time period confirmed drug-induced cell damage in the brain regions associated with Parkinson's disease.

Why is this happening ?



While the precise etiology of Parkinson's disease remains the subject of speculation and research, years of investigation have confirmed essential roles for ***mitochondrial impairment*** and ***oxidative stress***.

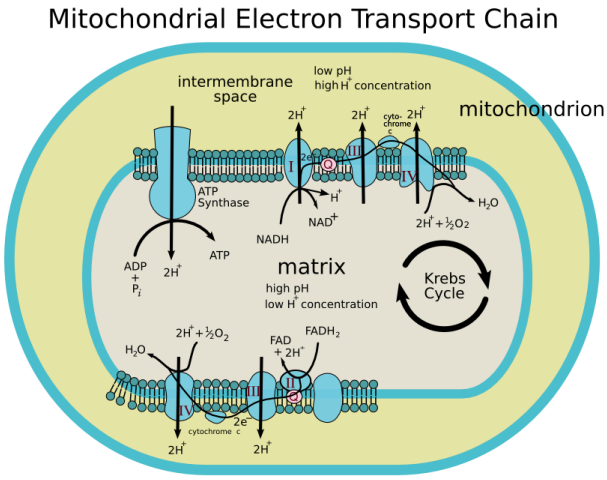
Shown in this slide:

above left: cartoon image of a mitochondrion

above right: mitochondrion seen through the lens of an electron microscope

Mitochondria (plural for "mitochondrion") are the power-generating units inside the body. Located in almost every cell (except mature red blood cells), they provide energy in the form of adenosine triphosphate or ATP, regulate programmed cell death, store calcium, and participate in the synthesis and detoxification of certain chemicals.

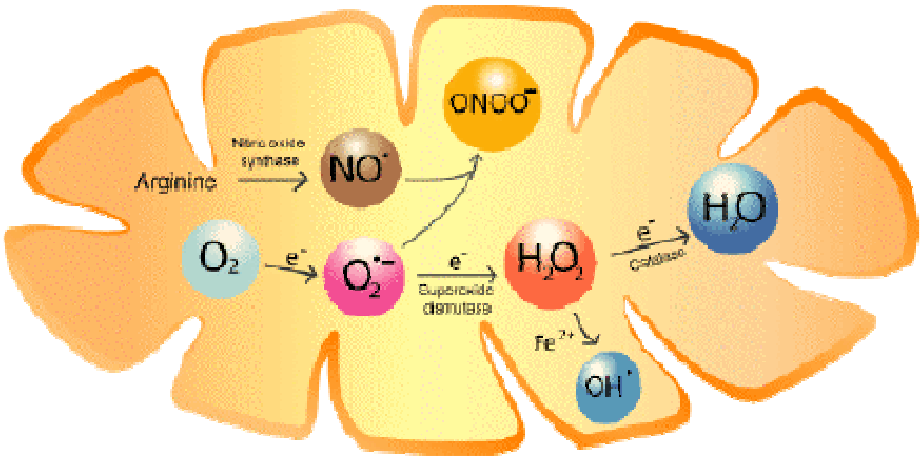
Psychiatric Drugs Impair Mitochondria



Like other mitochondrial toxins (e.g., nerve agents, insecticides), many psychiatric medications have been found to inhibit energy production by interfering with metabolic processes in the cell.

This picture depicts energy-producing pathways inside a mitochondrion. Many psychiatric drugs interfere with enzymes in the **Krebs cycle** (aka, TCA cycle) or impair specific “complexes” that form the **electron transport chain**. Depending upon the extent of damage which occurs as these processes fail, psychiatric drugs can and do contribute to various forms of cell death (apoptosis, necrosis, and autophagy).

Psychiatric Drugs ↑ Oxidative Stress



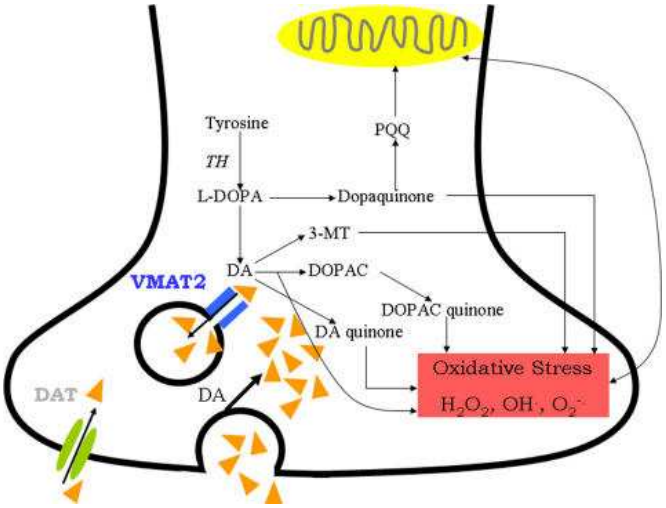
In order to maintain proper energy and health, cells produce ATP by burning fuels in the presence of oxygen. During the process of energy production, mitochondria give off chemical species known as free radicals. Mitochondria also produce free radicals when they are injured by radiation or exogenous chemicals. When the body produces *too many free radicals*, or *when the body's natural defense systems against these substances become overwhelmed*, the end result is a phenomenon known as **oxidative stress.**

Many psychiatric drugs induce or enhance oxidative stress.

This slide depicts some of the **free radicals** which form inside mitochondria during the processes of energy production and oxidative stress:

$O2^-$	**superoxide radical**
H202	**hydrogen peroxide**
OH^-	**hydroxyl radical**
$ONOO^-$	**peroxynitrite**

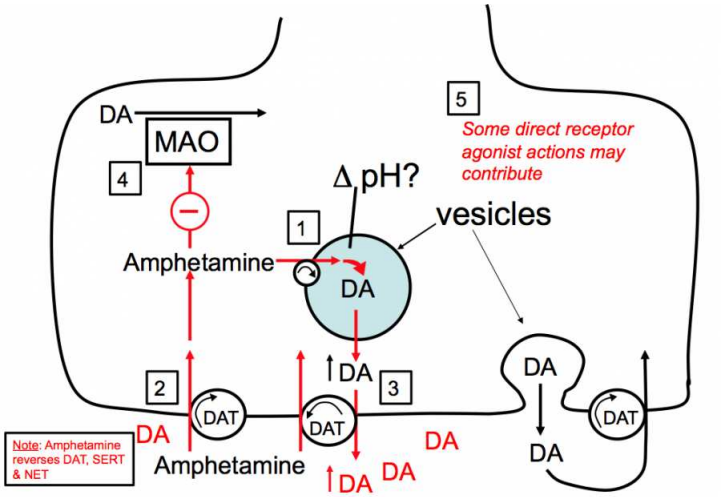
oxidative stress



Within the nerve endings of dopamine-producing cells, dopamine (DA) is released into the cytoplasm from storage vesicles via a special transporter (VMAT2). DA also collects inside the cell when it re-enters the neuron from the external environment (via the Dopamine Transporter, aka DAT). Inside the cell (and, according to some research, outside the nerve terminals as well) pools of free dopamine undergo chemical breakdown. Some of these metabolic processes are harmless, but some dopamine spontaneously "oxidizes" to form free radicals and toxic metabolites (aminochrome and quinones). When the body's natural defenses are overwhelmed, the net result is mitochondrial impairment and oxidative stress.

Research involving several "recreational" stimulants, such as MDMA (Ecstasy) and methamphetamine, has proven that oxidative stress is a cause of damage to axons and nerve endings in the brain regions associated with Parkinson's disease. Similar processes occur with pharmaceuticals. ***A robust body of evidence links prescription stimulants and antidepressants to an increased risk of Parkinson's disease***. Treatment-induced modifications of serotonin and dopamine levels, followed by the spontaneous oxidation of these chemicals, may explain how this happens. In other words, prescription drugs – just like street drugs – induce oxidative stress and mitochondrial damage in the brain. Depending upon the location and intensity of this damage, various neurodegenerative conditions can and do emerge.

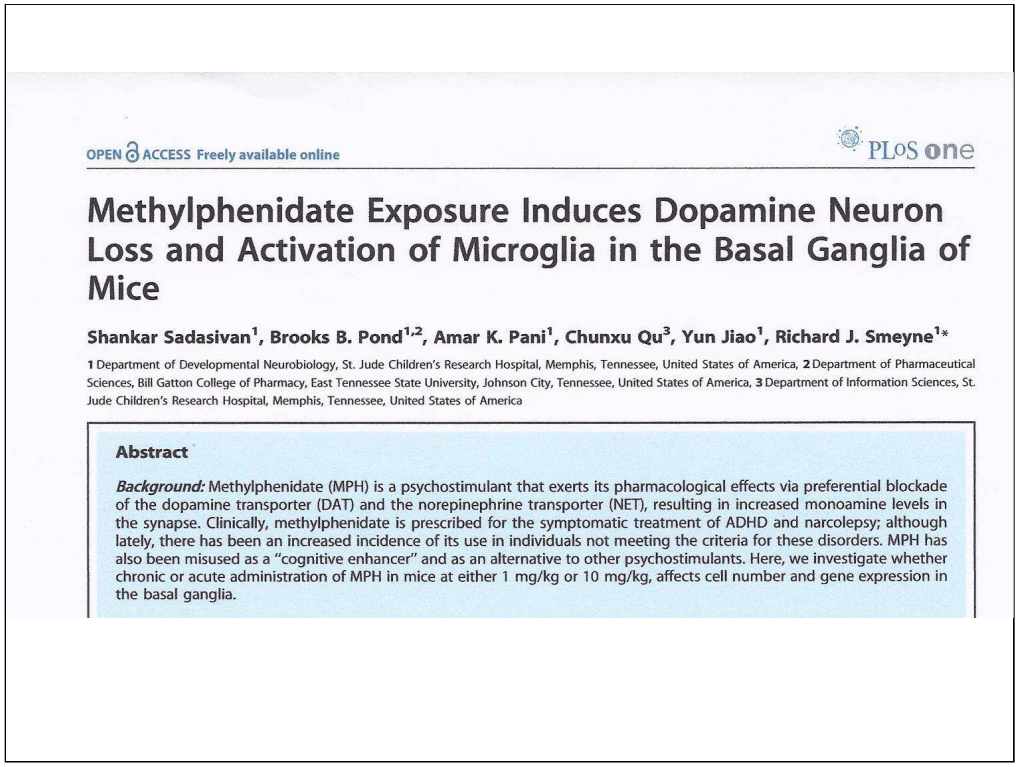
amphetamine



This slide shows how **amphetamine** – a prescription drug which is commonly prescribed to children and adults to alter behavior, energy, and cognition – is believed to increase dopamine (DA) levels inside and outside a neuron.

Although it is presumed to work via a slightly different mechanism of action, another prescription stimulant known as **methylphenidate (Ritalin)** also boosts dopamine levels in the brain.

The point of this slide is to reiterate the fact that prescription drugs enhance intracellular and/or extracellular levels of dopamine. Some of this dopamine auto-oxidizes, forming dangerous breakdown products. These substances can harm brain cells in the same regions which are affected in Parkinson's disease.



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]*

1 Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America, **2** Department of Pharmaceutical Sciences, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, Tennessee, United States of America, **3** Department of Information Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, United States of America

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.

In the first-of-its-kind investigation, researchers in Tennessee intentionally explored the effects of methylphenidate (Ritalin) upon cell loss and inflammation in brain regions affected by Parkinson's disease. Their experiment involved the 90-day administration of methylphenidate to 4-week old Swiss Webster mice, in an attempt to mimic the effects of chronic drug treatment (from pre-adolescence to early adulthood).

Protocol:

researchers compared the effects of two doses of methylphenidate:

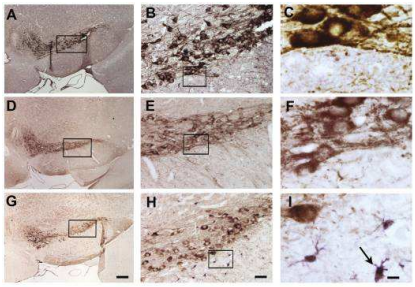
1 mg/kg injected intraperitoneally, once each day

10 mg/kg injected intraperitoneally, once each day

animals were injected daily for 5 days per week

brains were examined at the end of this treatment period

*Note: In terms of interspecies comparisons of stimulant doses, the 1 mg/kg per day injection in this experiment was arguably too conservative. In other research protocols, twice-a-day injections of methylphenidate (2 mg/kg or more) have been used in rodents to simulate the brain effects of therapeutic doses in humans.

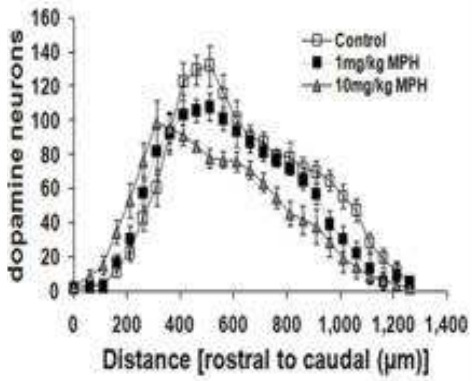


90 days of Ritalin > simulate childhood/teens

Notwithstanding the conservative doses used in this study, the research team observed several important results. Following the chronic exposure to methylphenidate, animals exhibited a dose-related increase in brain inflammation and a dose-related decrease in the number of dopamine neurons within several brain regions associated with Parkinson's disease.

When compared to unmedicated controls (mice injected with saline water), the stimulant-exposed mice (10 mg/kg) experienced a 20% reduction in dopamine cells in the substantia nigra. Even mice exposed to the very low dose of medication (1 mg/kg) displayed regional losses of dopamine neurons, relative to the unmedicated controls.

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"

The research team concluded the following about methylphenidate (MPH):

"We found that the chronic exposure to both 1 mg/kg and 10/mg/kg MPH increased the sensitivity of substantia nigra pars compacta (SNpc) dopamine neurons to oxidative stress based on a significantly increased …dopamine neuron loss…

"Methylphenidate's mechanism of action…results in an increase in extracellular dopamine, which has been shown to quickly form free radical adducts. Since increased free radical production has been shown to increase the sensitivity of SNpc neurons to environmental or administered [chemicals], it is possible that long-term MPH could be a contributing etiological factor in a multi-hit hypothesis for induction of Parkinson's disease.

''…we hypothesize that an increase in free radical formation along with a concomitant neuroinflammatory response increases the sensitivity of the SNpc dopamine neurons to a later oxidative challenge. This conclusion is supported by a recent epidemiological study that showed that long-term amphetamine usage…results in a significantly higher risk for developing Parkinson's disease"

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

Stimulants and antidepressants are not the only drugs linked to Parkinson's disease. In a 1996 publication, researchers from a neurology clinic at the Durham (NC) Veterans Administration Medical Center performed a study of 36 epilepsy patients.

After noticing significant hearing loss in two seizure patients who had been taking valproic acid (Depakote) chronically, the clinicians reviewed the medical records of 36 epilepsy patients who had been similarly treated.

After observing a high rate of neurological problems in this group of drug consumers, the physicians performed a "trial taper" of the Depakote in 35 of the 36 patients.

VAMC Depakote Study

After stopping Depakote:

Parkinsonian features improved in 96%
cognitive functioning improved in 72%
hearing loss improved in 48%

The mechanisms through which Depakote damages the brain and other organs are multifactorial: by depleting B vitamin levels and carnitine; by elevating brain levels of ammonia and homocysteine; by causing fatty liver disease and the release of ceramides; by inducing insulin resistance; and by triggering apoptosis (programmed cell death).

One essential property of Depakote which has been repeatedly confirmed is its **mitochondrial toxicity** (e.g., this medication impairs energy production and intensifies oxidative stress).

For patients who suffer from genetic conditions known as mitochondrial diseases, the added burden imposed by Depakote is especially dangerous. In these individuals, it is not uncommon for the drug to provoke or enhance seizures, deafness, diabetes, visual disturbances, muscle breakdown, and severe dementia. For other individuals, these same problems occur in the form of a ***drug-induced mitochondriopathy***. However, provided that the anticonvulsant is withdrawn early enough, many harmful effects can be reversed or reduced.

Other Causes of Drug-Induced Dementia

NPH

CJD

pseudo-tumor cerebri (PTC)

Concurrent with the epidemic rise of so-called “bipolar” disorders in the USA has been the expanded use of medications known as mood stabilizers. The intended biological effect of these drugs is a *slowing of brain activity*. Not infrequently, however, the alleged mood *stabilizers* (lithium and anticonvulsants) become brain *de-stabilizers*.

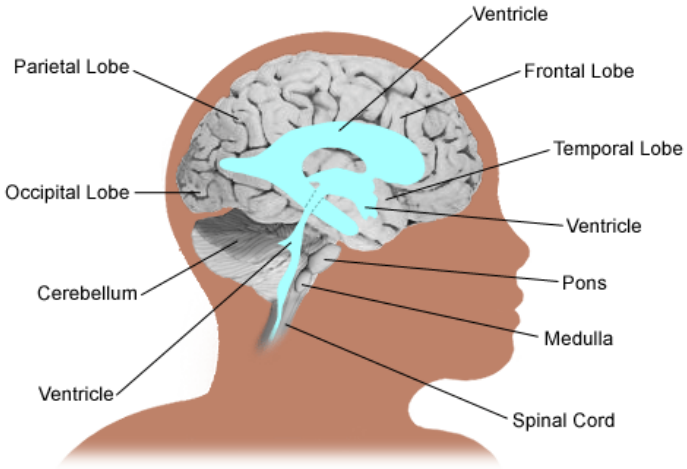
Many physicians and patients are unaware of the fact that these bipolar treatments cause a range of neurological conditions, each associated with dementia:

NPH = normal pressure hydrocephalus (see next slide)

CJD = acquired Creutzfeldt-Jakob disease >>
when caused by drugs, this mimics an infectious disease which results in punched out spaces in the brain tissue -- aka, spongiform degeneration [e.g., seen with lithium]

PTC = “false” tumor of the brain >> associated with elevated pressure inside the skull due to alterations in fluid balance; symptoms include visual disturbances, headache, dizziness, and/or cognitive impairment [e.g., seen with lithium]

Dementia Due to Hydrocephalus



The human brain contains cavities known as ventricles. Inside these spaces, specialized cells produce and reabsorb “cerebrospinal fluid.” The appropriate turnover of this liquid each day is necessary for optimal brain functioning, as it permits the removal of waste products and toxins.

Dementia is sometimes caused by a genetic or acquired condition – hydrocephalus -- which involves an imbalance between the production, flow, and removal of cerebrospinal fluid. As the overloaded ventricles expand, damage to surrounding brain tissue produces a classic triad of symptoms:

cognitive disturbances	wacky
urinary incontinence	wet
abnormal gait (ataxia)	wobbly

When these abnormalities occur (but without a concurrent rise in intracranial pressure), the resulting a disorder known as **normal pressure hydrocephalus or NPH**.

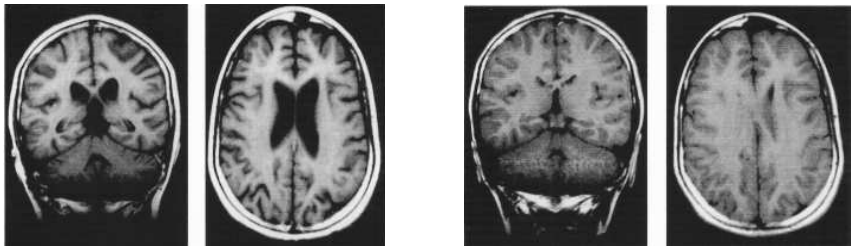
Depakote Induced Dementia

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

This picture shows the before and after brain scans (magnetic resonance imaging) of a child who experienced significant cognitive deterioration while taking Depakote.

Left image: dilated fluid spaces (ventricles), prominent cortical shrinkage under the influence of Depakote

.

Right image: resolution of fluid expansion and brain shrinkage after stopping Depakote

AP = antipsychotic drug (in this case, thioridazine)
Cogentin = an anticholinergic drug given to prevent or reduce movement abnormalities caused by other pharmaceuticals

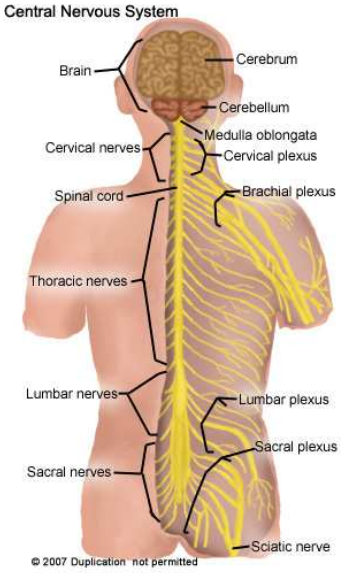
Nikolai Andrianov
15 medals > 7 gold, 5 silver, 3 bronze
died 3/21/11 at age 58 from MSA

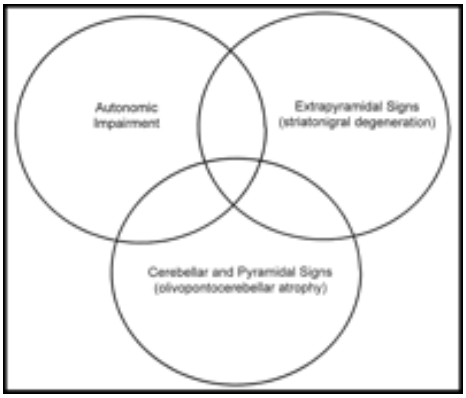
Before Michael Phelps emerged on the Olympics scene, the greatest champion of all time was Soviet gymnast Nikolai Andrianov.

Competing for more than 20 years, he achieved 15 Olympic medal victories, and he is still regarded as the greatest athlete to grace his sport.

Sadly, Andrianov died in March 2011 at the age of 58, the victim of a tragic neurologic condition known as Multiple System Atrophy or MSA. This disease left him unable to speak and unable to move his arms or legs.

MSA





Multiple system atrophy affects many regions of the brain and spinal cord. The resulting symptoms arise from damage to cells in diverse pathways which lead to and from the brain:

autonomic dysfunction >> resulting in unstable blood pressure and heart rate, dizziness, alterations in sweating, changes in urinary and bowel control, etc

extrapyramidal dysfunction >> resulting in the deterioration of involuntary movements > as seen in Parkinson's disease

cerebellar and pyramidal signs >> resulting in the deterioration of voluntary movements and the impairment of muscular coordination

Case Report

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

American Journal of Hospice & Palliative Medicine®
29(7) 570-573

DOI: 10.1177/1049909111434633
http://ajhpm.sagepub.com
SAGE

Ellen Babinsky, DO[1], and Richard S. Levene, DO, FAAFP, FAAHPM[1,2]

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

Physicians in Florida recently published a case report in the *American Journal of Hospice and Palliative Care*.

The case involved a 65 yo Caucasian male who had been treated for bipolar disorder for years -- most recently, with two antidepressants and lithium. The patient developed problems with unsteady gait, resting tremor, and vomiting. Over several months, his vomiting and tremor worsened. He developed difficulties speaking (dysphasia), lost the ability to walk independently, and experienced deteriorating memory. He was referred for home hospice care with the diagnosis of MSA (multiple system atrophy).

The new doctors who evaluated this patient in hospice noted his medications, then weaned and stopped his lithium. ***The patient experienced dramatic improvement in many symptoms and was able to be discharged from hospice care***.

* The case is an important illustration of iatrogenic dementia and disability. These problems were mismanaged by many different clinicians for several years, due to their failure to appreciate the neurodegenerative potential of psychiatric drugs.

IV. Brain Repair

Brain Repair

1) PharmARRU

2) Nutrition

3) Lifestyle

Given the fact that increasing numbers of people around the world are being exposed to psychiatric medications (and are increasingly maintained on these substances indefinitely), the problem of drug-induced brain damage is on the rise.

For this reason, a public health priority for all medical specialists and policy makers should be attached to the topic of brain repair.

While no one knows the extent to which drug-induced dementia can be reversed, once it has emerged, three possible measures offer hope in terms of preventing or reducing the scope of this tragedy.

PharmARRU

Pharmaceutical
- Avoidance
- Reduction
- Responsible Use

Pharmaceutical Avoidance = the most prudent form of treatment for psychiatric patients *avoids the use of neurotoxic drugs

Pharmaceutical Reduction = for active users of medication, the most prudent treatment involves harm reduction – a strategy of carefully modifying existing regimens by stopping drugs immediately when indicated; and by reducing doses as quickly as patients can safely tolerate

Responsible Use = whenever psychiatric drugs are prescribed, their use requires extensive preparation and medical knowledge

* avoiding neurotoxic drugs -- while this statement may seem like common sense, the current American health care system encourages (if not coerces) the use of brain-damaging treatments. This situation will not change until policy makers, administrators, hospitals, clinics, and others protect clinicians and patients who value safer, more effective treatments.

What are these pilots doing outside their planes ?

>> every flight begins with a pre-flight inspection

The Responsible Use of Psychiatric Drugs must begin with a similar process of preparation for the safety of each patient.

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]

The Responsible Use of Psychiatric Drugs requires knowledge of information gleaned by methodical reviews of past medical records, and gleaned from unhurried, comprehensive interviews of the patient and/or patient's caregivers.

Unfortunately, in the era of "fifteen minute med checks" and declining reimbursement schemes, most prescribers of psychiatric drugs are not given the time or the tools which are needed to perform these tasks.

Nutrition

1) Insulin sensitizers

2) Antioxidants

3) Fluid changers

Based upon the scientific research which has demonstrated causal mechanisms of brain damage and associated dementia, several nutritional approaches are emerging as potential methods for mitigating drug-induced harm.

Gingko biloba

EGb761

240 mg per day

PPAR agonist

↑ insulin sensitivity

Many neuroscientists and clinical researchers have proposed that the insulin-sensitizing effects of Gingko may be of benefit to dementia patients. Although clinical trials in humans have yielded variable results, some patients have experienced significant improvements in cognition and/or reductions in the rate of mental deterioration.

Note:

*As Gingko biloba is an inhibitor of platelets, a dilator of blood vessels, and a reducer of blood sugar levels, it must be used with caution in patients who are already taking medications for high blood pressure, diabetes, and/or the prevention of blood clots and stroke.

chromium picolinate

150 to 1000 ug per day

increases IR number
lowers weight
↓ blood glc and lipids

Chromium picolinate is another insulin sensitizer that reduces body weight and lowers glucose and fats in the bloodstream. Via these mechanisms, it has been proposed as a potential supplement in the treatment of diabetes-related dementias.

Often used by body builders to assist with fat loss, chromium has been found to enhance several cognitive tasks in at least one study of older adults.

curcumin (from turmeric)

↑ glucose uptake
GLUT4 to cell surface

boosts insulin sensitivity
PI3K/AKT paths

↑ pancreatic secretion
of insulin

decreases HbA1C levels

Curcumin – the major constituent of the yellow spice (turmeric) used in curries – has been extensively studied in the treatment of many medical conditions.

Based upon laboratory experiments of non-human animals and cell cultures. scientists have established anti-diabetic, anti-inflammatory, and cancer fighting properties of this food.

Research involving the use of curcumin as a treatment for dementia is still in an early phase of development. Limited investigations in human patients have yielded equivocal results, but many scientists remain hopeful about the potential of curcumin to reverse or prevent “type III” diabetes through its effects upon insulin and other properties (e.g., metal ion chelation).

Note:

*Curcumin must be used with caution in patients who are already taking medications for high blood pressure, diabetes, and/or the prevention of blood clots and stroke. Due to its effects on the biliary system, curcumin is not recommended for patients with gallbladder disease.

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)

Numerous antioxidants have been found to prevent or improve the cognitive deficits which accompany neurodegenerative conditions. The beneficial effects of these nutrients is based upon the importance of reducing oxidative stress and preserving mitochondrial function.

DHA = docosahexaenoic acid

EPA = eicosapentaenoic acid

vitamins

~50% of pharmaceuticals deplete vitamins

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

- antacids
- oral contraceptives
- metformin
- anticonvulsants

At least 50% of pharmaceuticals interfere with the absorption and excretion of essential nutrients.

Among the various classes of psychiatric medications, the most renowned "depleters" of vitamins are the anticonvulsants (such as Dilantin, Depakote, Tegretol).

Particularly for patients maintained on combinations of prescription drugs, clinical providers should consider the possibility of cognitive, emotional, and/or behavioral changes which may reflect inadequate tissue levels of B vitamins, vitamin D3 (e.g., 1,25-dihydroxycholecalciferol), and Co-enzyme Q10 (ubiquinone).

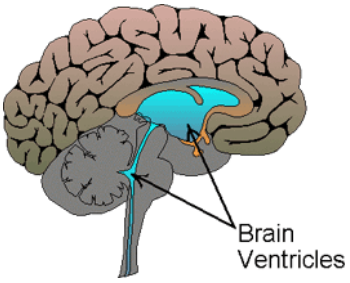
B1 = thiamine

B6 = pyridoxine

B9 = folate

B12 = cyanocobalamin

caffeine



Studies of humans and laboratory animals have repeatedly suggested a positive link between caffeine and brain health. For example, the recent CAIDE study in Finland revealed that mid-life coffee consumption (3-5 cups per day) conferred protective benefits against dementia in old age.

Scientists have identified several possible mechanisms which may account for these findings. In numerous rodent experiments, caffeinated water or caffeinated coffee has been found to reduce the synthesis of beta-amyloid (the protein which forms the core of senile plaques in Alzheimer's disease); accelerate the removal of beta-amyloid from the brain; and enhance the rate of cerebrospinal fluid production.

As dementia researchers increasingly turn their attention to the role of cerebrospinal fluid ***stasis** as a risk factor for neurodegenerative conditions, important knowledge will emerge about dietary and pharmaceutical substances which affect this process.

***stasis** = stagnation > meaning, diminished production, decreased circulation, and impaired absorption – of the fluid which bathes the brain and removes waste products and metabolites

Lifestyle

The activities which contribute to the development of a healthy brain in childhood are equally beneficial for adults.

growing a healthy brain

physical exercise
time in nature
cognitive (mental) enrichment
social engagement

Numerous studies have demonstrated the beneficial health effects -- including the dementia-preventing and dementia-reducing effects -- of the following behaviors and activities:

regular exercise training	e.g., walking, swimming, biking, strength
time in nature	exposure to plants and nature e.g., gardening, hiking, forest bathing
mental activity	e.g., reading, writing, solving puzzles, learning a new language, playing a musical instrument, creating works of art
social engagement	e.g., spending time in community of others, decreasing isolation

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

This lecture has explored some of the problems and potential solutions for individuals who have been diagnosed with mental illness.

Recipients of publicly funded mental health care, diagnosed with SMI (serious mental illness), have been suffering from multiple medical problems, in higher percentages, than individuals without SMI. On average, the seriously mentally ill patient dies 13 to 30 years earlier than expected, based upon the projected life expectancy in the USA.

Pharmaceuticals are a major part of the problem. Deaths due to adverse effects of prescription drugs are the #3 cause of death in the USA each year.

Psychiatric drugs are contributing to the current and continuing "epidemic" of dementia.

Methods to prevent or reduce the scope of these drug-induced tragedies should be a public health priority. Possible solutions include the avoidance and reduction of neurotoxic drugs; responsible prescribing practices; nutritional interventions; and the encouragement of life-enriching, health-sustaining behaviors.