“Enslaved in a Plausible Pseudoscience”: Big Pharma and the Chihuahuas

Tom Finucane

SHS/UHN Geriatrics Update

October 28, 2016

DISCLOSURES

None relevant

I’m on P&T committee of an insurance company

Objectives

- Review 3 blockbuster drug classes that cause widespread harm with little evidence of benefit.
- Describe some promotional techniques used by Pharma to generate the concomitant revenue.
- Recognize the clinician's role in the generalized overtreatment of the elderly.

- 80 y.o. dad with AD moves in with 55 yo daughter and her family
- She calls you because of behavior problems
- After ***non-drug interventions, which are very important***, what would you recommend?

- 1. Benzodiazepine
- 2. Second-generation antipsychotic
- 3. First-generation antipsychotic
- 4. SSRI - anxiolytic/antidepressant
- 5. Other

“Second-generation” or “atypical” antipsychotics?

First, the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction. The only second-generation antipsychotic that is obviously better than other drugs is clozapine, and this is a very old drug indeed.

Tyrer Lancet 2009

Why choose them?

There were no significant differences in incidence or change in rating scales for parkinsonism, dystonia, akathisia or tardive dyskinesia when comparing second-generation antipsychotics with perphenazine.

Miller DD 2008. Brit J Psychiatr
a randomized trial in schizophrenics

Tardive dyskinesia in the elderly

- 5.2% with second-generation antipsychotics versus 5.2% with first-generation antipsychotics (P = 0.865)

Corell. Curr Opin Psych 2008

Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: An exploratory analysis of head-to-head comparison studies of second-generation antipsychotics.

Heres Am J Psychiatry. 2006

Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor.

Flacco. J Clin Epi 2015

Safety?

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

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Efficacy?

- How would you know if the drug helped the patient or the daughter?

Results

- “There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason …”

Results

"No significant differences were noted among the groups with regard to improvement on the CGIC scale."

Schneider NEJ, 2006

- Lilly assessed penalties totaling $1.415 billion for off-label marketing of its drug, Zyprexa.
- One portion of that sum is a $515 million criminal fine, the largest criminal fine ever imposed upon an individual US corporation.
- Sales in first 6 months of 2008: $3.5 billion

usdoj.gov 1/15/09

- Analysts See Merck Victory in Vioxx Settlement - New York Times 10/10/07

- $4.85 billion loss is a victory.

List of largest pharmaceutical settlements, wiki

- Top 5 settlements >$10.4 billion.
- Every one of the these included promotional activities for drugs to neutralize elderly patients with dementia and behavioral disturbance.
- Total Zyprexa sales > $40 billion

Utilization?

- FOR decades, antipsychotic drugs were a niche product. Today, they're the top-selling class of pharmaceuticals in America, generating annual revenue of about $14.6 billion and surpassing sales of even blockbusters like heart-protective statins.

D. Wilson NYT 10/2/10

What to tell the daughter?

- They are very expensive.
- They are toxic, sometimes lethal, especially in patients like your dad.
- They are not much different, if at all, from placebo.
- They are not approved to be used for this reason.
- One reason I'm suggesting this is because of a corrupt advertising campaign.

Current evidence does not support the use of antipsychotics for prevention or treatment of delirium. Additional methodologically rigorous studies using standardized outcome measures are needed.

Neufeld. JAGS. 2016

35+ years ago


"Thank You, Doctor"

"Mom's More Like Her Former Self, Thanks to You ...and 'Stelazine'"

She hadn't expected her golden years to be tarnished by psychotic symptoms. Neither had her family. But when disturbed behavior began to disrupt family life, her physician had the solution: compassion tempered with a sympathetic ear...and a prescription for 'Stelazine'.

A 25-Year Record of Unsurpassed Antipsychotic Effectiveness

While 'Stelazine' affords relief of a broad range of psychotic symptoms, it also apparently exerts an activating effect—especially useful in withdrawn, apathetic elderly patients.

A Favorable Profile in the Elderly

Worth considering when you select an antipsychotic agent for your elderly patients is the low risk of sedation and orthostatic hypotension with 'Stelazine'. There is also low potential for anticholinergic effects—such as dry mouth, constipation, blurred vision and urinary retention. And when extrapyramidal symptoms are encountered, they generally are readily controlled.

Convenient, Economical B.I.D. Dosage

Twice-a-day dosage with distinctive blue 'Stelazine' tablets makes antipsychotic therapy easy for your patients to remember, economical for them to take. In general, dosages in the lower range are sufficient for most elderly patients.

Elderly patients should be observed closely, since they appear to be more susceptible to hypotension and neuromuscular reactions.

Stelazine®

brand of trifluoperazine HCl

Tablets: 1, 2, 5 and 10 mg.
Concentrate: 10 mg./ml.

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: For the management of the manifestations of psychotic disorders.

Possibly effective: To control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions.

'Stelazine' has not been shown effective in the management of behavioral complications in patients with mental retardation.

Final classification of the less than effective indications requires further investigation.

Contraindications: Comatose or greatly depressed states due to C.N.S. depression, blood dyscrasias, bone marrow depression, liver damage.

Warnings: Generally avoid using in patients hypersensitive (e.g., blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy.

Additive effect is possible with other C.N.S. depressants, including alcohol.

Use in pregnancy only when necessary for patient's welfare. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Use cautiously in angina. Avoid high doses and parenteral administration when cardiovascular system is impaired. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged administration of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If mental changes occur, discontinue drug. Agranulocytosis, aplastic anemia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use [illegible] in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha adrenergic blockade. Concomitant administration of phenothiazines with propranolol results in increased plasma levels of both drugs. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide.

Adverse Reactions: Dry mouth, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, visual disturbances, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions, akathisia, dystonias, parkinsonism, tardive dyskinesia. Risk of persistent tardive dyskinesia appears to be greater in elderly patients on high-dose therapy, particularly females.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or common in specific disorders (e.g., mental insufficiency or pheochromocytoma).

General oral and penile malformations, altered cerebrospinal fluid proteins, cerebral edema, prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides, nasal congestion, headache, nausea, constipation, obstruction, adynamic ileus, priapism, inhibition of ejaculation, reactivation of psychotic processes, convulsions, false pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema, reversed epinephrine effect, hyperpyrexia, mild fever after large I.M. doses, increased appetite, increased weight, a systemic lupus erythematosus-like syndrome, pigmentary retinopathy, with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits. EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually. NOTE: Sudden death of patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets, 1 mg., 2 mg., 5 mg. and 10 mg., in bottles of 100, in Single Unit Packages of 100 (intended for institutional use only). Injection, 2 mg./ml. and Concentrate (intended for institutional use only), 10 mg./ml.

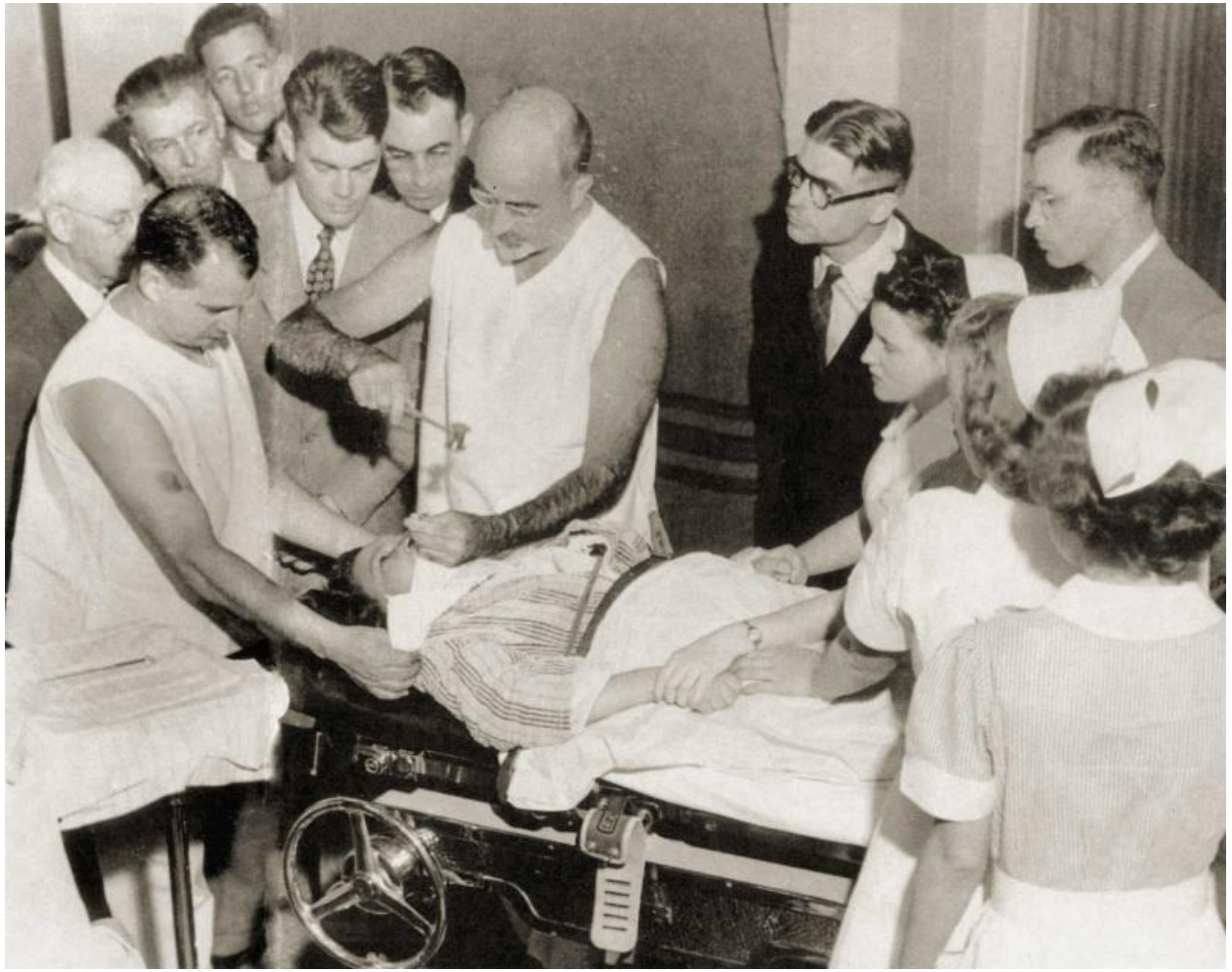
SK&F CO.

Manufactured and distributed by SK&F CO., Carolina, P.R. 00630 under Stelazine® trademark license from Smith Kline Beckman Corporation

® SK&F CO., 1981

65+ years ago

- Egas Moniz won the Nobel Prize in 1949 for developing a procedure.



Walter Freeman performs a lobotomy

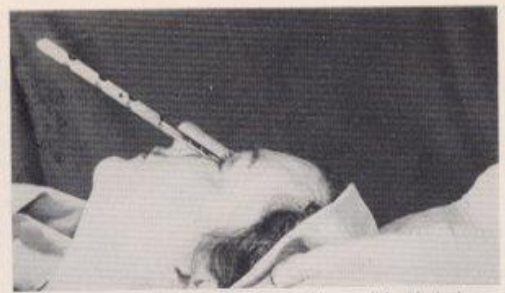


FIG. 3.—Case 490. Orbitoclast in primary position parallel with the bony ridge of the nose.

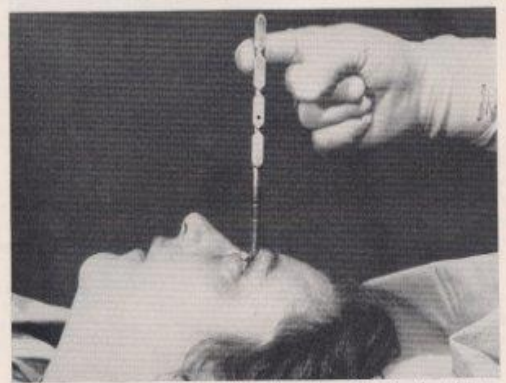


FIG. 4.—Case 490. Orbitoclast in elevated position making deep frontal cut.

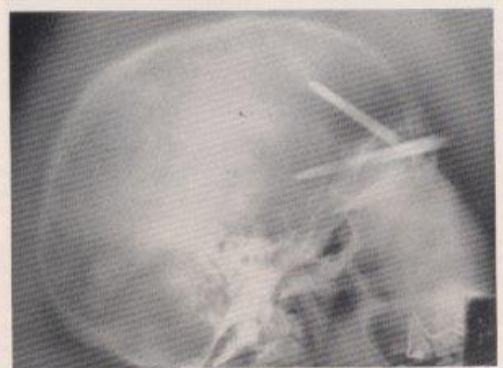


FIG. 5.—Case 490. Superimposed roentgenograms illustrating the range of movement of the orbitoclast within the frontal lobe.

Here is a Rorschach

- An overweight 70 yo woman has abdominal pain.
- She notes a several year history of a burning discomfort in the epigastric and low substernal area.
- The pain is worse lying down.
- Physical exam and labs are normal, except BMI of 31.
- What is the diagnosis?

- 1. Heartburn
- 2. Upset stomach
- 3. Stomach ache
- 4. GERD
- 5. Pyrosis
- 6. Dyspepsia
- 7. Indigestion

Are these different diseases?

- Heartburn
- Upset stomach
- Stomach ache
- GERD
- Pyrosis
- Dyspepsia
- Indigestion

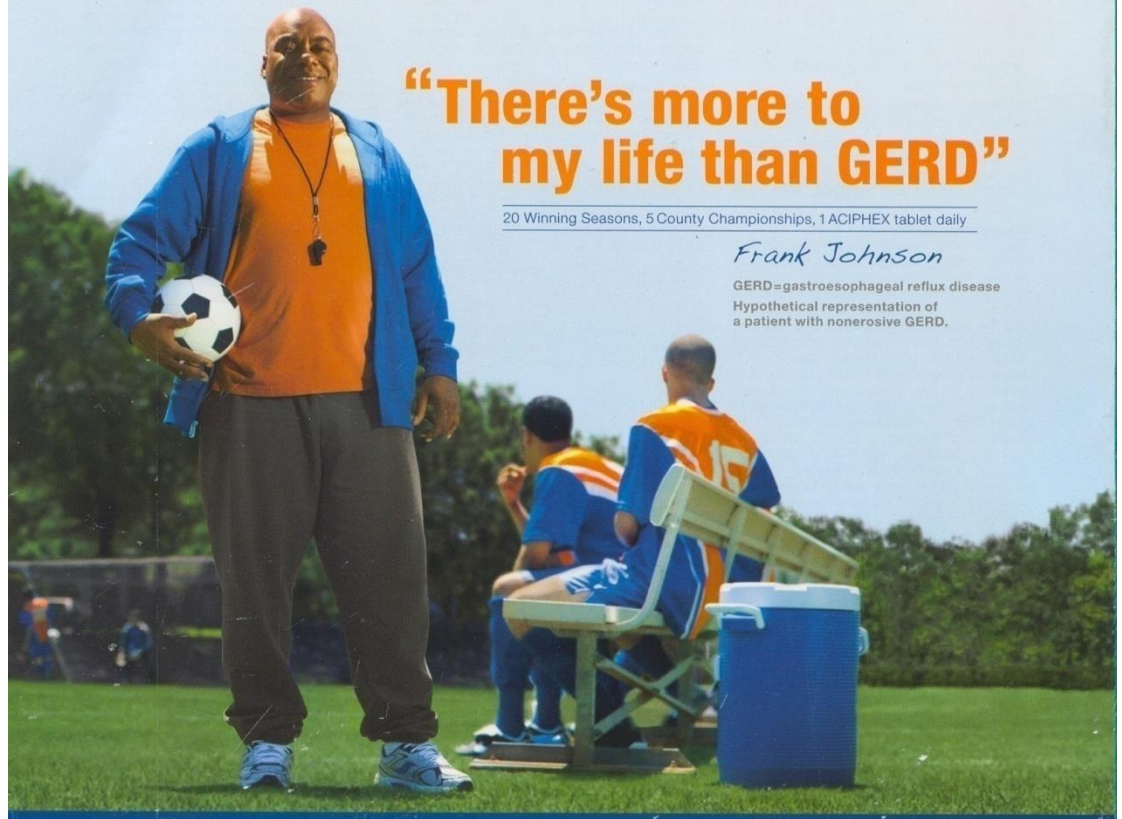
“GERD”

- Glaxo Institute for Digestive Health. 1986, trying to sell ranitidine.
- “Heartburn Across America”
- “Gastroesophageal Reflux Disease” (GERD)

TREAT HEARTBURN AND BEYOND

Prescribe ACIPHEX to relieve heartburn & other symptoms of nonerosive GERD—regurgitation, belching & early satiety, because...

TREAT HEARTBURN AND BEYOND AcipHex® rabeprazole sodium



"There's more to my life than GERD"

20 Winning Seasons, 5 County Championships, 1 ACIPHEX tablet daily

Frank Johnson

GERD=gastroesophageal reflux disease

Hypothetical representation of a patient with nonerosive GERD.

INDICATION

ACIPHEX 20 mg is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults and adolescents 12 years of age and above.

IMPORTANT SAFETY INFORMATION

In clinical trials the most common side effect assessed as possibly or probably related to ACIPHEX with a frequency greater than placebo was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

PLEASE SEE BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION ON REVERSE.

Manufactured and Marketed by

Eisai

Woodcliff Lake, NJ 07677

Marketed by

PriCara
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Raritan, NJ 08869-0602

01AX1596R2 Sep. 2008

CANCER PREVENTION?

- No serious evidence
- Some evidence of risk increase

Gastric secretion of hydrochloric acid appears to be unique to vertebrates and is almost ubiquitous in all fishes, amphibians, reptiles, birds and mammals.

Koelz HR.
Scand J Gastroenterol 1992.

- Comparative anatomy and physiology suggest that gastric acid has evolved approximately 350 million years ago. The similarity of the acid-secreting mechanism implies a major advantage for selection …

Relative risk or hazard ratio associated with PPI use; all observational

- Pneumonia
- C. diff diarrhea
- FDA drug safety communication:
  Fractures of hip, wrist, spine
- AKI
- CKD

- The avoidance of PPI medication may prevent the development of dementia. This finding is supported by recent pharmacoepidemiological analyses on primary data and …mouse models in which the use of PPIs increased the levels of β-amyloid in the brains of mice.

- Date are purely observational

Gomm. JAMA Neurol. 2016

- PPIs have an important role in treating a few real diseases of the upper GI tract.
- Gastric acidity is nearly ubiquitous in fish, reptiles, amphibians, birds and mammals.
- Long-term PPI treatment of a stomach-ache, heartburn etc is a bad idea.

- An 83 yo woman has a HbA1C of 9.4
- She has no symptoms of hyperglycemia
- You have advised her about the vital importance of weight loss and physical activity. No improvement.
- She’s on ACE, beta, statin, and maximum metformin
- What do you recommend?

- “The choice of a second medicine to add to metformin, which is often required to maintain HbA1C levels at target, is more uncertain.”

Nathans. JAMA 9/15

Nonetheless …

"The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely."

ADA guidelines 2011

“Tight Control”

A fundamental treatment strategy for diabetes, aiming to reduce glycemia toward physiologic levels …

using any drugs that have not been irrefutably shown to be lethal.

- Overall, the risk for death among people with diabetes is about twice that of people of similar age but without diabetes.

http://www.familydocs.org/f/CDC%20Diabetes%20fact%20sheet-2011.pdf

2013 Cochrane Review

- What was the risk ratio for all-cause mortality in this review of 28 RCTs comparing intensive with conventional glycemic control (almost 35,000 pts)?
- 1.00

Hemmingsen

- In UKPDS 35 the death rate increased by 21% for every 1% increase in HA1C. ($P<0.0001$)

  Observation

- UKPDS 33 No significant difference ($p=0.44$) for all-cause mortality.

  RCT

- For microvascular outcomes, often cited by proponents of intensive treatment, statistically significant benefit was seen; the risk difference for the composite microvascular outcome was 0.01, which corresponds to a NNT of 100.

Cochrane

- “All positive effects should be viewed as potentially caused by or influenced by bias (systematic error overestimating benefits). This risk does not apply to our negative findings on intensive glycaemic control.”

Cochrane

- What drugs, drug sequences, or strategies have been shown in RCTs to reduce the risk of micro or macrovascular disease or death?

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

ACCORD
NEJM

Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications with the exception of progression of albuminuria (P = 0.01)

VADT
NEJM

A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.

ADVANCE
NEJM

ADVANCE

- Median f/u 5 years
- Combined endpoint: 18.1 vs 20% (10% RRR)
- Microvascular: 9.4 vs 10.9
- Nephropathy: 4.1 vs 5.2 (20% RRR)
- Macroalbuminuria: 2.9 vs 4.1

No difference in

- Major macrovascular events
- Death from cardiovascular causes
- Death from any cause

- “We identified 16 guidelines and 328 statements. The body of evidence produced estimates warranting moderate confidence.
- This evidence reported no significant impact of tight glycemic control on the risk of dialysis/transplantation/renal death, blindness, or neuropathy. In the past decade, however, most published statements (77%–100%) and guidelines (95%) unequivocally endorsed benefit.

- “There is also no significant effect on all-cause mortality, cardiovascular mortality, or stroke; however, there is a consistent 15% relative-risk reduction of nonfatal myocardial infarction.
- Between 2006 and 2008, most statements (47%–83%) endorsed the benefit; after 2008 (ACCORD), only a minority (21%–36%) did.”

Rodriguez-Gutierrez, R

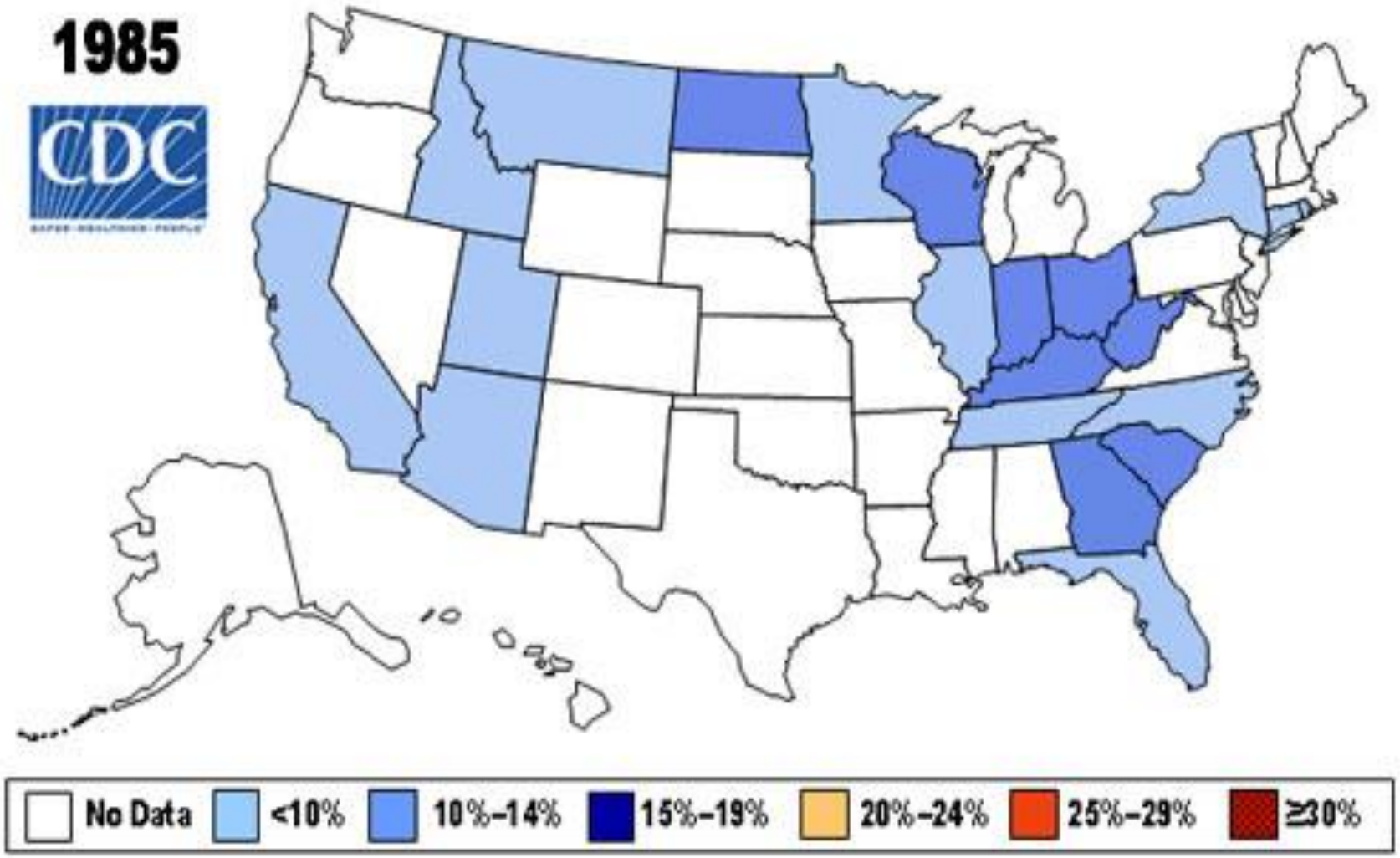
Circ Cardiovasc Qual Outcomes 2016

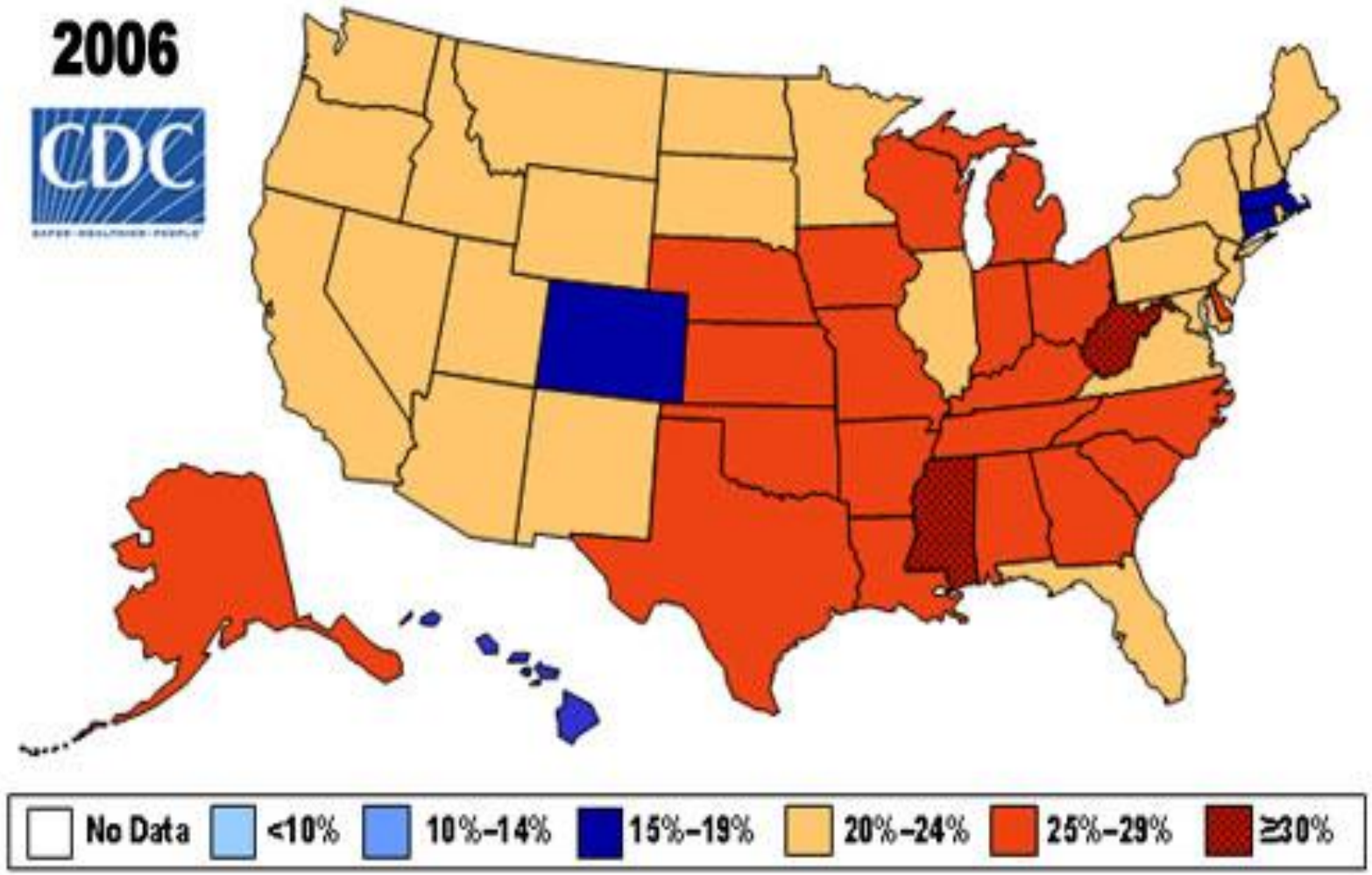
- The “preferred initial pharmacologic agent” for glycemic control in T2D is metformin (Standards of Medical Care in Diabetes—2015) even though its specific advantage “is not explicable on the basis of glycaemic control.” (UKPDS34)
- Inflammation, cancer, vascular disease …

Empagliflozin (EG), NEJM 2015

- We infer that the mechanisms behind the CV benefits of EG are multidimensional and possibly involve changes in arterial stiffness, cardiac function, and cardiac oxygen demand (in the absence of sympathetic-nerve activation), as well as cardiorenal effects, reduction in albuminuria, reduction in uric acid, and established effects on hyperglycemia, weight, visceral adiposity, and blood pressure.

1985





http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

A worldwide epidemic and novel evolutionary challenge

Chronic Sedentary

Feasting

What's wrong with CSF?

- The metabolic syndrome, including hyperinsulinemia
- Cancer: increased incidence, recurrence, progression, and death. Doubles risk of MGUS.
- Inflammation: cytokines/adipokines, CRP, neopterin, markers of oxidative stress
- Cardiovascular diseases: myocardial steatosis, heart failure, atrial fibrillation, DVT, CAD

What's wrong with CSF? (2)

- GI disease: elevated liver enzymes, NAFLD, Barrett's esophagus, GERD
- Pulmonary: asthma, sleep apnea, copd
- Other: CKD, kidney stones, hyperuricemia and gout, DJD, lymphedema, low serum vit D.
- Chronic pain, depression, disability, death
- Increased urinary levels of Bisphenol A in kids
- Oh yes. And hyperglycemia

- Sedentary, obese patients with T2D will have many of these adverse characteristics.
- Because the evolutionary challenge is novel, responses are likely to be heterogeneous.
- We don’t fully understand what’s going on.

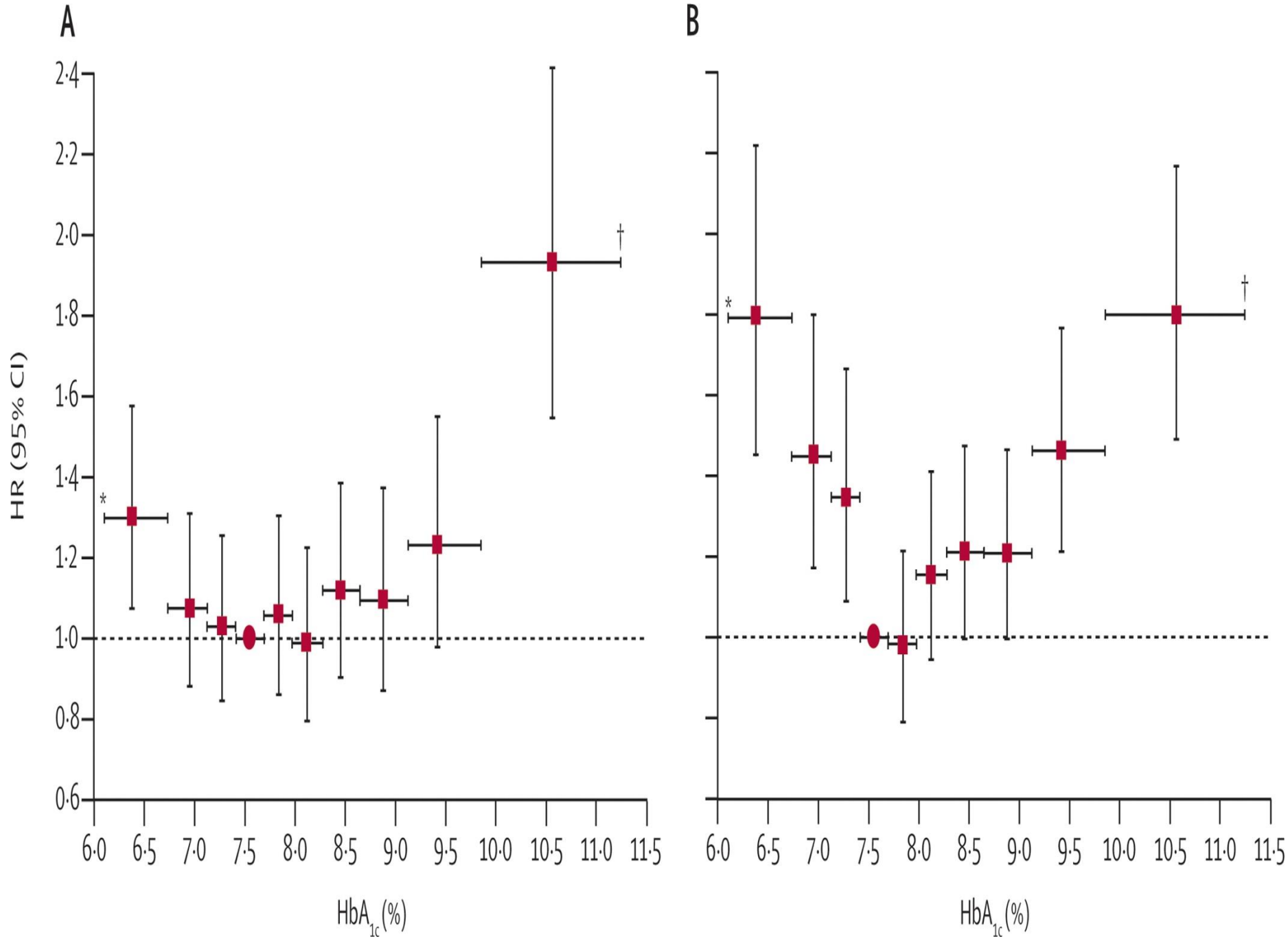
Survival as a function of HbA1C in people with Type 2 DM: a retrospective cohort study.

- Failed oral monotherapy. Mean age 64
- N = 28,000 on add-on oral agents
- N = 20,000 on insulin with or without orals
- Median f/u was 4 years

Currie CJ Lancet 2010

- From the Abstract
- HR for all-cause mortality in people given insulin-based regimens (2834 deaths) versus those given combination oral agents (2035) was 1.49 (95% CI 1.39-1.59).

Currie CJ. Lancet


A
B
HR (95% CI)
2·4
2·2
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
*
†
6·0
6·5
7·0
7·5
8·0
8·5
9·0
9·5
10·0
10·5
11·0
11·5
HbA1c (%)

- Although still limited, early evidence suggests that metformin is associated with a lower risk of cancer and that exogenous insulin is associated with an increased cancer risk.

Diabetes and cancer: A consensus report.

Giovanucci CA Cancer J Clin 2010

Where did 7% come from?

On a single day in 1997, nearly 2 million Americans became diabetic when the diagnostic fasting blood sugar level was changed from 140 to 126 mg/dl.

In the fall of 2003, 20 million people became pre-diabetic when these criteria were changed.

Every patient is a customer.

Glycemic targets in the elderly?

Mean age at randomization (approx)

- ADVANCE 66
- ACCORD 62
- VADT 60
- UKPDS 53
- UGDP 52
- Steno 2 55
- UGDP 52

This is the tip of the iceberg

- Sleeping pills
- Drugs for overactive bladder
- Anti-epileptic drugs

  Neurontin, Lyrica
- “Alzheimer” drugs
- Narcotics
- NSAIDs
- Erythropoetin

…

- Far too large a section of the treatment of disease is today controlled by the big manufacturing pharmacists, who have enslaved us in a plausible pseudoscience.

Osler, 1909

Older adults are at special risk.