Dementia of the Alzheimer Type: the Drug Treatment Debate
I have no financial conflict of interest.

Many years ago I was given a trip to San Fran and taught to use a slide set from the drug company.

I proposed some changes.

I never heard from them again.
Imagine an elderly person who has dementia of the Alzheimer type.

What goals of treatment would be meaningful to patient or caregiver and would justify much expense and some risk?
Goals

- A better life for patient?
- Disease stabilization?
- A better life for caregiver?
- Less expense?
- Psychometric testing?
Does the patient’s quality of life improve?
Quality of Life, donepezil trials

Four trials measure this for patients

One favors donepezil at low dose, not high dose

One favors placebo

Mean difference 10 points

The scale is 350 points.
No significant differences were seen between donepezil and placebo in behavioural and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5mg and 10mg donepezil.

Courtney
Lancet 2004
Does the disease stabilize?
ADAS-cog mean change from baseline over 5 months

Mean change in ADAS-cog score

Baseline | Month 1 | Month 3 | Month 5

P < .001 vs placebo for both doses

Improvement/Maintenance

Deterioration

Adapted from Tariot et al.

Placebo

REMINYL 16 mg/day

REMINYL 24 mg/day
Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.
Evidence is insufficient to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer's disease.

“Preventing AD and cognitive decline”
12. CLINICAL PHARMACOLOGY
12.1. Mechanism of Action
Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer’s disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.
Despite intensive laboratory and clinical research over three decades, an effective treatment to delay the onset and progression of Alzheimer's disease is not at hand.

Selkoe, DJ
Preventing AD
Science; 21 Sept 2012
No significant benefits were seen with donepezil compared with placebo in institutionalisations (42% vs. 44% at 3 years; p=0.4) or progression of disability (58% vs. 59% at 3 years; p=0.4).

Courtney
Lancet 2004
Use of donepezil by AD patients resulted significant delays in NHP.
Given that treatment with a ChEI is currently recommended as the standard of care for AD patients, conducting such a study (a proper RCT) would not be ethical.
How about cognitive testing?
Cognition average 0.8 MMSE (mini-mental state examination) points better (95% CI 0.5-1.2; p<0.0001) and functionality 1.0 BADLS points better (0.5-1.6; p<0.0001) with donepezil over the first 2 years.

Courtney
Lancet 2004
MMSE favored treatment in 7 of 9 trials in which it was measured.

All differences less than 2 points
CIBIC

Average difference 0.3 to 0.5

Cummings

NEJ 2005

Minimum change that can be scored: 1 point
ADAS – cog favored donepezil in all 6 trials in which it was measured.

All differences less than 4 points
About 1 additional patient in 10 had a 4 point improvement on drug compared to placebo.

Cummings
NEJ 2004
How about Behavioral Disturbances?
“NPI-NH … no significant differences observed between the groups at any assessment”

Physical Self-Maintenance Score and MMSE – not different at study’s end (24 months) CDR-SB less than 1 point difference

Tariot JAGS 2001
“Pts treated with donepezil maintained or improved in cognition and overall dementia severity…”
“At the very least, the data in this trial demonstrate that cognition and overall dementia severity are maintained for 6 months.”
May 29, 2003: “We found the weapons of mass destruction. We found biological laboratories.”

November 12, 2005: “We do not torture.”

October 25, 2006: “Absolutely, we're winning.”
“In summary, benefits of donepezil treatment on cognition and overall dementia severity were evident in these NH patients.”

Tariot JAGS 2001
IN LONG-TERM CARE

IMPROVE BEHAVIOR WITH ARICEPT

Proven effective in more advanced Alzheimer's dementia

- Significant behavior improvements reduce staff burden
- Preserves activities of daily living (eg, eating and dressing)
- Low incidence of weight loss and other adverse events despite comorbid illnesses and concurrent medications

ARICEPT is indicated for mild to moderate dementia of the Alzheimer's type. The most common adverse events in clinical trials with ARICEPT were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anemia. In clinical trials, syncope episodes have been reported (2% for ARICEPT versus 1% for placebo).

An RCT without Pharma “guidance”

- There was no significant difference between the effects of donepezil and those of placebo on the basis of the change in CMAI scores from baseline to 12 weeks ...
There were also no significant differences between the placebo and donepezil groups in scores for the Neuropsychiatric Inventory, the Neuropsychiatric Inventory Caregiver Distress Scale, or the Clinician's Global Impression of Change.
CONCLUSIONS: In this 12-week trial, donepezil was not more effective than placebo in treating agitation in patients with Alzheimer's disease.

Howard RJ
Goals

- A better life for patient?
- Disease stabilization?
- A better life for caregiver?
- Less expense?
- Psychometric testing?
How did we get here?

Sales of these drugs are in the billions.
The talking chihuahua

(Why were we in line at Taco Bell?)

Chihuahua Number 1
“ChEIs are approved for treatment of mild-to-moderate AD and should be considered as a standard of care for patients with AD. refs 50,51”

Cummings

NEJ 2004
Pharmacologic treatment of AD.

- Cholinesterase inhibitors should be considered in patients with mild to moderate AD (Standard), although studies suggest a small average degree of benefit.

Doody, R,S.
Practice Parameter: Management of dementia
American Academy of Neurology 2001
Physicians may consider a trial of either of these agents for patients with mild to moderate AD.

**Small 1997 JAMA**

- What are these two drugs?
- Tacrine and donepezil (1 trial cited)
Recommendations for the use of ChEIs do not seem to be evidence-based.

Benefits on rating scales were minimal.

The methodological quality of the available trials was poor.

Kaduskieiwicz
BMJ 2005
Chihuahua Number 2
Doctors and caregivers need to be educated that, in the same way as the actual benefits of treating hypertension or hyperlipidemia are seen only after years of treatment, treatment of AD with donepezil needs to be maintained to see important long-term benefits.

Geldmacher 2001
And there are many chihuahuas.
Carefully manicured evidence
Abstract

First in “Results”

Final

Discussion

First

First of concluding para

Final
Rogers 1998a

Abstract

1

Discussion

1...”efficacious treating symptoms”

2

3
Rogers 1998b

Abstract
1
2...efficacious treating symptoms

Discussion
1
2
3
Burns 1999

Abstract

1

2

Discussion

1

2 ...efficacious treating symptoms

3
Abstract
1
2...well-tolerated and efficacious
Discussion
1
2...well-tolerated and efficacious
Burns 1999

Abstract
1
2 ...effective and well tolerated

Discussion
1
2 ...well-tolerated and efficacious
3 ...effective and well tolerated
Homma 2000

Abstract
1
2

Discussion
1 ...effective and well-tolerated
2
3
Abstract

1

2 ...well tolerated and effective

Discussion

1

2

3
Abstract
1
2...modestly improves cognition

Discussion
1...modest beneficial effect
2...small beneficial effect
3
Renting an office at the FDA
What would you do if your blockbuster was going off patent?

And it would become available in 5 mg and 10 mg tablets generically?
The current regulatory standard requires that the effectiveness of a treatment for Alzheimer’s Disease be demonstrated on both a cognitive and a global (or functional) primary efficacy measure...
<table>
<thead>
<tr>
<th>SIB</th>
<th>0.4</th>
<th>2.6</th>
<th>0.0001</th>
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<tbody>
<tr>
<td>CIBIC plus</td>
<td>4.2</td>
<td>4.3</td>
<td>0.18</td>
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(100-point scale)
Medical Reviewer

“I recommend that this application, which seeks the approval of Aricept in a new dose strength of 23 mg administered once daily, for the treatment of moderate to severe dementia of the Alzheimer’s type not be approved.”
“Unless there is some compelling prior reason to believe that there is a dose response between 10 mg IR (immediate release) and 23 mg SR (suspended release), the data from this trial does not seem to provide enough support for the efficacy of the 23 mg SR formulation.”
“Not only was there no statistical significance between the treatments on the primary measure of overall functioning, but there was a clear lack of significance on another accepted measure, the ADCS-ADL [a secondary endpoint].”
“There is a clear increase in the incidence of adverse events on the 23 mg dose compared to the 10 mg dose”;

“These are not trivial events in these patients; these could lead to significant morbidities and even increased mortality”;
These events “are of particular concern, given that these patients had all been receiving treatment with 10 mg once a day for at least three months. That is, even though patients had been tolerating (more or less) a dose of 10 mg for three months, the increase to 23 mg was clearly accompanied by a significant increase in the incidence of these events
Division Director

- Then he approved it.
ChEI’s and syncope

- Cohort study
- 20,000 patients on drug, 60,000 not
- Increased risks of
  - Syncope
  - Pacers
  - Hip fracture

Gill S. Arch Intern Med 2009
Cholinesterase Inhibitors and Hospitalization for Bradycardia: A Population-Based Study

More than doubled.

Laura Y. Park-Wyllie
September 2009 PLoS
Do I have time to tell you about the Geldmacher study?
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