What are medications supposed to accomplish *in general*?
What are medications supposed to accomplish *in dementia*?
How can we ensure that medications produce an *overall benefit*?
What role can we all play in this process?
SUMMARY

There is a reasonable scientific and ethical case for **avoiding** medications in dementia, or for **stopping** those that have been used, focusing instead on behavioral interventions and caregiver support.

You can let people know that they do not have to be using medications for dementia.

**Ultimately the decision should the patient’s and caregiver’s.**

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<table>
<thead>
<tr>
<th>Goal</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce unpleasant experience</td>
<td>Medications for itch / pain / mood / gout</td>
</tr>
<tr>
<td>Prevent disease or worsening of disease</td>
<td>Cholesterol medications, diabetes medications</td>
</tr>
<tr>
<td>Improve functioning</td>
<td>Stimulants for ADHD</td>
</tr>
<tr>
<td>Increase lifespan</td>
<td>Cardiac medications</td>
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</tbody>
</table>
Is the pill accomplishing the goal?

General Problems

“You have this condition, so you need to take this pill.” (guideline- rather than outcome-based)

All treatments involve costs and risks.

What if there is a tradeoff between goals and costs/risks?

Who gets to choose the goals?
Central problem: Dementia is a **deteriorating** condition

A **moving target** can justify any conclusions

You’re worse, but think how bad you would have been without the pills!
Dementia symptoms fluctuate

Transitional problems

- Aware of situations
- Partially aware of situations, distressed by them
- Unaware of situations, not distressed

Cognitive / Functional Status

TIME

TIME
The treatment may not be the reason for improvements

Medication Types

• Memory medications
• Medications to treat behavioral symptoms
• Medications for other psychiatric symptoms
“Memory” Medications
There are no pills that specifically improve memory.
Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine are FDA-approved for dementia.
Pills approved for dementia may improve cognitive outcomes in the short term.
These medications are not a cure.
They are nothing like a cure.

“Memory” Medications
There are no pills known to prevent dementia.
There are no medications approved for mild cognitive impairment.
“Memory” Medications

Anticipated optimal effects:

0.8 point on a 30-point cognition scale
About 1 ADL on a 17-point scale

“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”

Courtney, 2004
Memantine

![Graph showing comparison between Memantine and Placebo](image)
“Although statistical improvements were noted in the analyses, they do not necessarily translate into clinically relevant benefits for the patients receiving these drugs or for their caregivers.”

Costs

Difficult to estimate exactly
Some medications have become generic
Namenda (memantine): about $300 a month
  Total sales in 2014: $1.8 billion
Side Effects

GI upset, diarrhea

Unexpected effects (loss of energy, odd behavior, anxiety)

Most are transitory

Known Risks

• Weight loss
• Falls
• Hospitalizations
• Starting medications for urinary overflow (which then counteract the dementia medications)
• Polypharmacy
• Depression
Donepezil and Depression

130 older adults with history of depression
73 no cognitive impairment
57 mild cognitive impairment

Randomized to donepezil or placebo

Cognition and mood outcomes

Those on donepezil had far higher rates of depression recurrence compared to placebo


Explaining Negative Events in Dementia

Most people who have problems during dementia blame them on the DISEASE and not the TREATMENT. Many risks are delayed.

Exposing the effects of treatments requires careful and thoughtful examination of large amounts of data.

It has taken time and effort to establish risks.
New Drugs for Alzheimer’s

Many new drugs have been tried.

None has been approved in over 15 years.

No new drugs will be on the market any time soon.

Families and patients may be desperate.

Example: Dimebon – Phases I and II

• Antihistamine (latrepiridine) with decades-long record of over-the-counter safety in Russia.

• Animal models show cognition-enhancing effects and inhibition of cell death.

• Multi-site double-blind study in 2006-2007 in Russia
  – 183 patients followed for 6 months.
  – Active drug group shows significant improvements in functional, cognitive, and behavioral outcomes
  – Among those treated, ADAS-COG (70-point scale) increases by 1.9 points over baseline at 6 months, and by 6.9 points at 1 year

• 7/2008: “Dimebon shines as Alzheimer’s therapy”

• Pfizer invests in worldwide rights; targeted for market debut in 2012.
Example: Dimebon – Phase III

- CONNECTION Study
  - 598 patients at 63 sites in US, Europe, & South America
  - No differences in any of the endpoints
  - Placebo group has slight advantage in cognition

- 3/2010: “One swallow does not make a summer, and one positive clinical trial does not make an Alzheimer’s drug.”

- Pfizer writes off $725 million investment

- “This was a drug with no plausible mechanism that emerged from an incomprehensible series of screens.” – Samuel Gandy

AC-1204 (general claims)

AC-1204 addresses the issue of deficient glucose metabolism in AD, by inducing a mild form of ketosis by generating ketones for use in neurons. These ketones have the potential to restore the supply of adenosine triphosphate, improving neuronal metabolism and in turn cognition and function in patients with mild to moderate AD.

A Look at the Data

An improvement in cognition has been consistently shown across multiple clinical studies.
AC-1204 (Phase 2 results)

Phase 2b Study

A multi-center, double blind, placebo-controlled 90-day study in subjects with mild to moderate Alzheimer’s disease

AC-1204 (Phase 3)

Accera Announces Results of its First Phase 3 Study in Mild-to-Moderate Alzheimer’s Disease

BOULDER, Colo., Feb. 28, 2017 — Accera, Inc., a leading CNS therapeutics company, today announced results of the AC-1204 Phase 3 study for the treatment of mild-to-moderate Alzheimer’s disease. Patients treated with AC-1204 did not demonstrate a statistically significant difference at 26 weeks compared with patients treated with placebo, as measured by the Alzheimer’s disease Assessment Scale-Cognitive Subscale test (ADAS-Cog). In the study, AC-1204 was shown to be safe and

Charles Stacey, MD, the company’s President and Chief Executive Officer commented, “The trial result is disappointing for us and the millions of patients, caregivers and physicians who urgently need new treatment options for this devastating disease. This outcome is unexpected in light of the data seen in our Phase 2 study in which patients exhibited a statistically significant improvement of greater than 3 points in ADAS-Cog.”
Medications Approved by FDA to Treat Behavioral Symptoms of Dementia:

0

All medication use to treat behavioral symptoms of dementia is OFF LABEL
Antipsychotics in Dementia

1.6 times increased risk of DEATH

About 25% of people with dementia in nursing homes are prescribed an antipsychotic

**WARNING: Increased Mortality in Elderly Patients With Dementia-Related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration* of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.
Medical Breakthrough Reduces Risk of Death by 38% in Group of Dementia Patients

Antidepressants

People with dementia often seem apathetic. Antidepressants are frequently used to address negative mood states or irritability.

But antidepressants often do not work as intended.
Antidepressants
What is the therapeutic value of antidepressants in dementia? A narrative review

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Correspondence to S. Banerjee, E-mail: S.Banerjee@bsms.ac.uk

“the antidepressants tested to date show no convincing advantage over placebo for the treatment of depression in dementia.”
No evidence for use of antidepressants to address cognition, caregiver burden, cognition, psychosis, or apathy.
“We should question the use of antidepressants in dementia.”

Even Beneficial Side Effects Might Not Occur

Mirtazapine does not improve sleep disorders in Alzheimer’s disease: results from a double-blind, placebo-controlled pilot study

Francisca M. SCORALICK,¹ Luciana L. LOUZADA,¹ Juliana L. QUINTAS,¹ Janeth O.S. NAVES,² Einstein F. CAMARGOS¹ and Otávio T. NÔBREGA¹,³

→Psychotropic medications often DO NOT WORK AS EXPECTED in dementia.
**Benzodiazepines**

Benzodiazepine use increased risk of pneumonia by 30% in dementia.

Benzodiazepines increase risk of falls.

There are unclear benefits. Sometimes there is an opposite effect (disinhibition).

Watch out for alprazolam, lorazepam, diazepam, clonazepam.


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**Discontinuation**

Stopping pills is usually MORE DIFFICULT than starting them.

People often stop medications DURING difficult times -> this does **not** mean that the stopping caused problems.

When **planned carefully**, discontinuation usually causes few problems.
A Randomized Placebo-Controlled Discontinuation Study of Cholinesterase Inhibitors in Institutionalized Patients With Moderate to Severe Alzheimer Disease

Nathan Herrmann MD, Jordan O'Regan MSc, Myuri Ruthirakuhun MSc, Alexander Kiss PhD, Goran Eryavec MD, Evelyn Williams MD, Krista L. Lantctot PhD

Objectives: Cholinesterase inhibitors (ChEIs) offer modest benefits in Alzheimer disease (AD), which must be balanced against risks. Relatively few data delineate the benefits and risks of long-term ChEI administration in institutionalized patients with advanced AD. This study investigated the effects of ChEI discontinuation in institutionalized patients with AD.

Design: Institutionalized patients with moderate to severe AD (standardized Mini-Mental Status Examination ≤ 15) and treated with a ChEI for ≥ 2 years were randomized, double-blind, to ChEI continuation or placebo, with a 2-week tapering phase, for 8-weeks.

Measurements: The primary outcome of this pilot study was change on the Clinician's Global Impression of Change (CGI-C) scale. Secondary outcomes included safety, efficacy, and tolerability. Baseline (BL) predictors of clinical deterioration were also determined.

Results: Forty patients (mean ± standard deviation age = 89.3 ± 3.5 years, standardized Mini-Mental Status Examination = 8.3 ± 5.2, Neuropsychiatric Inventory–Nursing Home version total score = 21.1 ± 15.9, 80% male) were randomized to ChEI continuation (n = 21) or placebo (n = 19). There was no significant difference in clinical worsening in the ChEI continuation (28.6%) and placebo groups (36.8%) on CGI-C (odds ratio for worsening 1.58, 95% confidence interval 0.88–2.85, P = 0.1). The occurrence of adverse events was similar in both groups. There were no significant differences in any of the secondary outcome measures. In the placebo group, BL hallucinations predicted CGI-C worsening [F(1,17) = 6.4, P = 0.02], and there was a trend for BL delusions to predict CGI-C worsening [F(1,15) = 3.5, P = 0.08].

Conclusions: These results suggest that ChEI discontinuation is safe and well tolerated in the majority of institutionalized patients with moderate to severe AD. When discontinuing ChEI, the presence of hallucinations and delusions may predict clinical deterioration, suggesting the need for increased caution.

The WRONG Way to Use Medications for Dementia

“If you have dementia, you should be taking a pill for it.”

“If a pill exists to treat your condition, you should take it.”

“The pills protect you from getting worse.”

“The pills have very few risks.”

“Pills are the best way to deal with the problems in dementia.”

“If a pill worked at first, you should keep taking it.”
The RIGHT Way to Use Medications for Dementia

“Let us talk about the course of dementia.”
“What is your experience with dementia?”
“Medications can have some benefits, but also can have risks. Let’s discuss them.”
“What are we trying to accomplish? What are your values and preferences?”
“How can we know if the medication is working?”
“Let’s keep re-evaluating the effect of the medications.”
“You can try stopping. If things seem worse, you can restart.”

Agitation

Figure out what is going on before turning to medications

Main reasons for agitation:
- Delirium
  \rightarrow \text{MAIN CAUSE OF DELIRIUM: MEDICATIONS}
- Unmet needs
- Conditioning
- Natural response
GIVING PERMISSION

There is a reasonable scientific and ethical case for avoiding medications in dementia, or for stopping those that have been used, focusing instead on behavioral interventions and caregiver support.

You can let people know that they do not have to be using medications for dementia.

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