Will we ever have effective treatments for dementia?

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The hubris of the Daily Express
We beat dementia twice weekly
Objectives of presentation

Review evidence for treatments for
(i) cognitive symptoms and function
(ii) behavioural symptoms and psychosis
(iii) potential disease modification in AD

Hope – 2 reasons to be optimistic about the future
What the evidence shows for cholinesterase inhibitor treatment of cognition and function

Mild, moderate and severe AD – modest improvements in cognitive function and ADLs

No effect on overall decline

Withdrawal effect involving worsening cognition and function and earlier nursing home placement
Donepezil vs. placebo and MMSE score over 2 years in the AD2000 trial

[Graph showing change from baseline over time for Donepezil and Placebo treatments with treatment effect and statistical significance noted.]

Number at risk:
- Donepezil: 282 245 211 185 165 154 94
- Placebo: 283 263 229 192 168 160 87
Change in MMSE in first 12 weeks of AD2000 for Donepezil and Placebo

**Donepezil**
Mean 0.93 (SD 3.24)

**Placebo**
Mean 0.00 (SD 2.96)
What happens when cholinesterase inhibitor therapy is stopped? The DOMINO trial
Nursing home placement in the DOMINO trial
Kaplan-Meier survival curve
What the evidence shows for treatment of behavioural symptoms and psychosis

Only risperidone is convincingly superior to placebo in treatment of agitation, aggression and psychosis in AD

Psychosis returns when treatment stops

Dementia drugs ineffective in AD
Pivotal risperidone trial data and the difficulties of evaluating treatment of behavioural symptoms

Figure 3. Mean BEHAVE-AD score shifts from baseline at each time point: (A) total, (B) aggressive. Risperidone versus placebo comparisons were two-tailed and determined at week 12 and at endpoint. *Significant change from baseline (see table 3).
What happens when you stop an antipsychotic in an individual patient?
Dementia drugs no better than placebo in treatment of agitated behaviours in AD
Disease modification in AD. It should have been so easy....... The Hubris of Neuroscience
Results of the Rember trial sounded amazing, but the data were never published...
Disease modification in Alzheimer’s disease
An elusive Holy Grail

No shortage of translationally-identified targets

Anti-amyloid (immunotherapy, anti-aggregation, γ- and β-secretase inhibitors)
Neurotransmitter-based
Metabolic and neurotrophic drugs
Regenerative approaches
Glial cell modulators
Anti-tau proteinopathy

The difficult truth is that everything (so far) has failed
Data from Phase 3 Bapineuzumab trials showed failure on primary outcome as usual
Hope 1. Almost all psychiatric treatments discovered through serendipity

Let it find you.

SERENDIPITY
the effect by which one accidentally stumbles upon something truly wonderful, especially while looking for something entirely unrelated.

www.MyBeautifulWords.com
Repurposing trials are perfect for NHS
Hope 2 – Adult hippocampal neurogenesis

Figure 1 Development of newly generated granule cells in the adult hippocampus. Neural progenitors.
In conclusion

Current symptomatic treatments make modest but measurable differences to cognition and function.

Behavioural disturbance and psychosis have an evidence-based and licensed treatment.

Difficult to predict timetable for discovery of disease modifying drugs or lifestyle interventions with impact, but live in hope.