DRUG THERAPY CHOICES
FOR THE DEMENTED PATIENT
Past, Present and Future

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INTRODUCTION

EPIDEMIOLOGY
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Figure 1

Prevalence - A greater burden in poorer countries
DEMENTIA STATISTICS

• Number of persons with dementia is increasing globally
  – Incidence vs. prevalence

• One third of older persons die with dementia
EPIDEMIOLOGY OF DEMENTIA IN CANADA

NEUROLOGICAL DISEASES AND COGNITIVE IMPAIRMENT

• Alzheimer’s Disease

• Parkinson’s Disease

• Vascular Dementia
DEMENTIA STAGES

General Classification
- Preclinical
  - Cognitively normal
- Mild Cognitive Impairment
- Clinical Dementia
  - Mild
  - Moderate
  - Severe

FDA Guidance - draft 2018
- Stage 1 – cognitively normal – biomarkers?
- Stage 2 – subtle abnormalities with neuropsychological testing – no functional impairment
- Stage 3 – Stage 2 + functional impairment
- Stage 4 – overt dementia – mild, moderate, severe
Pathology present even in brains where cognitive function was normal. However, degree of pathology increased with diagnosed severity of disease.
PAST AND PRESENT
CURRENTLY RECOMMENDED STRATEGIES FOR DEMENTIA PREVENTION

• Treat hypertension
• Increase childhood education
• Maintenance of social engagement
• Reduce smoking – for multiple pathologies
• Manage comorbidities such as diabetes, depression and obesity
INTERVENTION STRATEGIES

• Cognitive
• Exercise
• Medication
MEDICATION STRATEGIES

• Cholinesterase inhibitors and Memantine

• Nonsteroidal anti-inflammatory drugs

• Statins

• Vitamins

• Ginkgo biloba
ISSUES

• **Key Definitions**
  
  – **Efficacy** – Does the intervention work?
  
  – **Effectiveness** – Efficacy in actual practice
MILD COGNITIVE IMPAIRMENT

• A recent review of the literature concluded that there is no evidence for efficacy of cholinesterase inhibitor drugs at the stage of mild cognitive impairment.

(Lancet 2017, See reference citation on previous slides)
DRUGS FOR DEMENTIA

• **Cholinesterase Inhibitors**
  – Donepezil HCl  *(Aricept®)*
  – Galantamine HBr  *(Reminyl®)*
  – Rivastigmine tartrate  *(Exelon®)*
    - For mild to moderate dementia

• **N-Methyl-D-Aspartate (NMDA) Receptor Antagonists**
  – Memantine HCl  *(Ebixa®)*
    - For moderate to severe dementia

(CPS 2014)
TESTS OF COGNITIVE FUNCTION

- **ADAS cog** – Score out of 70 – Categorical
  - Initial clinically important difference “10 points”
  - After drug studies reduced to “4 points”
  - Many interventions “3 points”

- **MMSE** – Score out of 30 – Categorical
  - Lower score worse. Dementia only if score < 24

- **ADS-CGIC** – Seven point scale – Categorical
  - Lower score better
  - Score of “4” = no change
Optimum dose on cognition – similar finding on global assessment
Only suggestion of modest benefit in mild to moderate disease
– statistical analysis – clinical benefit??

Lancet 2017
ADVERSE EFFECTS – CHOLINESTERASE INHIBITORS

- **Bradycardia**
  - Vagal effect – caution in cardiac and/or cardiovascular disease. Increased risk of falls and hip fracture

- **Gastrointestinal**
  - Increased ulcer risk especially with NSAIDs, nausea, vomiting diarrhea – most common with start of therapy and with dose escalation

- **Genitourinary**
  - Bladder outflow obstruction ?

- **Neurologic**
  - Reduced seizure threshold

- **Pulmonary**
  - Caution in asthma and COPD

- **Mortality**
  - Higher death rate in patients treated with donepezil
HEALTH CANADA ALERT

• Issued January 21, 2015

  – Alzheimer’s drug Aricept (donepezil) – New warnings on the serious risks of muscle breakdown (rhabdomyolysis) and a neurological disorder (neuroleptic malignant syndrome)
Donepezil (Aricept®)

- **Rhabdomyolysis symptoms** – a combination of fever, muscle or joint pain, weakness, nausea, and dark (tea-like) urine

- **Neuroleptic Malignant Syndrome symptoms** – high fever, muscle stiffness or rigidity, mental changes including delirium and agitation, and irregular heartbeat and pulse
Rivastigmine

• The only cholinesterase inhibitor drug with approval for treatment of mild to moderate Parkinson’s disease.
MEMANTINE

Optimum dose on cognition – modest efficacy by statistical analysis – clinical efficacy ??

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Figure 8
ADVERSE EFFECTS – NMDA RECEPTOR ANTAGONISTS

- Fatigue
- Pain
- Dizziness
- Abnormal Gait
- Headache
- Constipation
- Hypertension
- Anorexia
- Anxiety
- Hallucinations
- Dyspnea
DURATION OF EFFICACY

• Almost no data on efficacy in patients older than 85 years

• No demonstration of efficacy in vascular dementia

• Data on use for more than one year are lacking
RECOMMENDATIONS FOR DEMENTIA THERAPY

• Currently available drugs do not stop, slow or reverse neurodegeneration
• Anticholinesterase inhibitors may modestly improve symptoms for mild to moderate disease
• Memantine may provide modest benefit in moderate to severe disease
• Although attempted, adding memantine to anticholinesterase therapy remains to be demonstrated as increasing efficacy
Suggested decision tree
Suggested decision tree
NEUROPSYCHIATRIC SYMPTOMS AND DEMENTIA

• Common in dementia and increase with disease severity
• Visual hallucinations more common with Lewy body dementia
• Psychosis – persists for months with delusions most common and associated with more rapid cognitive decline
• Vulnerable to delerium
CONFOUNDING FACTORS IN DIAGNOSIS OF AGITATED BEHAVIOUR IN THE DEMENTED PERSON

• Pain

• Delerium
“The use of second generation antipsychotics (i.e., risperidone, olanzapine, quetiapine), benzodiazepines, and related medications in older adults in Manitoba is increasing; and it is especially high in residents of personal care homes, despite recommendations to avoid these agents, whenever possible, in older adults with dementia. By 2008/09, 27% of older adults residing in personal care homes received a prescription for a second generation antipsychotic (the most commonly used agent was risperidone). Use of high dose second generation antipsychotics is less than optimal due to an increased risk for dose related adverse effects, such as falls and movement disorders. It is good news that from 2002/03–2007/08, only 10.2% of new users of second generation antipsychotics received high doses of these agents within the first year of therapy. Users of high dose second generation antipsychotics were younger and more likely to be male, have psychosis or dementia (taking medications to treat dementia), and be taking fewer other medications. No prescriber or environment characteristics (including PCH environment and type of PCH) predicted this less than optimal prescribing”

Manitoba Ctr for Health Policy 2010
DRUG TREATMENT OF PSYCHOSIS

• Drug therapy is controversial
  – Risk of adverse events and death greater in the first 30 days of therapy and with higher doses
  – Evidence for efficacy is scarce
  – Causes more cognitive impairment than placebo
  – In most Alzheimer disease patients risk outweighs benefit
  – Discontinuation more risky in the presence of agitation and distress
Management of the neuropsychiatric symptoms of dementia including agitation, low mood, or psychosis is usually psychological, social, and environmental, with pharmacological management reserved for individuals with more severe symptoms.

(Lancet 2017 – See Lancet citation in earlier slides)
CHOICE OF ANTIPSYCHOTIC

• Resperidone has best evidence for efficacy at doses of <1 mg/day but only for 12 weeks.
  
  – Withdrawal trials showed no change in behaviour except in those with the most severe symptoms
THE FUTURE
BIOMARKERS

• Depending on age, 10 – 30% of cognitively healthy persons have abnormal levels of tau protein or amyloid beta in their cerebrospinal fluid
  – Only a few progress to mild cognitive impairment or Alzheimer dementia over the next three years.

• Ethical issues ?? Use as a biomarker for inclusion in clinical trials?
CURRENT DRUG TRIALS

• Mostly disappointing with many failures in Phase 3 clinical trials
  – Phase 2 studies of aducanumab – an antibody targeting aggregated amyloid beta reduced brain amyloid beta in prodromal or mild Alzheimer disease persons in a dose-dependent manner and is suggested to slow clinical decline. A Phase 3 study currently under way.
• Highly speculative with a weak evidence base that it will result in improved medications in the near future
  – Hope that the biomarker approach can identify higher risk cohorts for recruitment into clinical trials.
Experimental design model showing difficulty in demonstrating drug efficacy in reducing the occurrence of dementing diseases
Venn diagram showing suggested potential mechanisms for prevention of dementia
THERAPEUTIC PROBLEMS IN THE ELDERLY

• Multiple pathology is a common phenomenon among the elderly
• The problem of multiple pathology fosters the practice of multiple drug therapy
• Multiple drug therapy is particularly hazardous for the elderly patient
• Side effects increase with the number of drugs prescribed
Adverse Drug Events Presenting to Emergency Departments

Estimated annual incidence of presentation to an Emergency Department of a US hospital for adverse drug responses as a function of age. Only Figure in this publication
HIGH RISK DRUGS FOR THE ELDERLY
INTERNET WEBSITES

Drugs of Concern for Older Persons


DEMENTIA AND COGNITIVE IMPAIRMENT

Drugs to Avoid – Beers Criteria

Anticholinergics

Benzodiazepines

Antihistamines

Zolpidem

Antipsychotics
TOP FIVE BEERS DRUGS IN 2005-2006

• Oral conjugated estrogens—hormone replacement

• Amitriptyline—an antidepressant**

• Digoxin—a treatment for heart conditions

• Oxybutynin—a treatment for incontinence**

• Temazepam—a treatment for sleep disorders**

**Asterisk identifies drugs affecting cognition
ISSUES – DRUG THERAPY IN THE ELDERLY

• Is drug therapy really necessary? Are alternate treatments with acceptable outcome available? Interaction with OTCs to produce observed symptoms?

• What are the goals of drug therapy?

• What other concurrently ingested drugs may alter your choice for drug therapy? E.g. benefit:risk ratio, short-acting vs long-acting drug

• Is the dose schedule confusing or conflicting with other concurrently ingested therapies? Is the formulation convenient? Are the instructions clear? Adherence problems? Dose modification due to concurrent confounding factors?

• Have you waited long enough to insure that the patient is at steady-state before increasing the dose or changing the drug therapy?
CONCLUSIONS

- In most situations, the risk of an important adverse drug interaction is small

- There are identifiable settings in which these interactions are more likely to occur

- Recognition of these settings and understanding the mechanism will reduce the likelihood of their occurrence
THE END

Questions ?