

# Chronic Traumatic Encephalopathy. Neuropsychiatric aspects.

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# DISCLOSURE



- No industry affiliation.
- No perceived conflict of interest.
- I will speak about off-label use of medications.

# AGENDA

- Pre-presentation test.
- Affective-Behavioural issues.
- Suicide.
- Treatment issues.
- Post-presentation test.
- Questions.

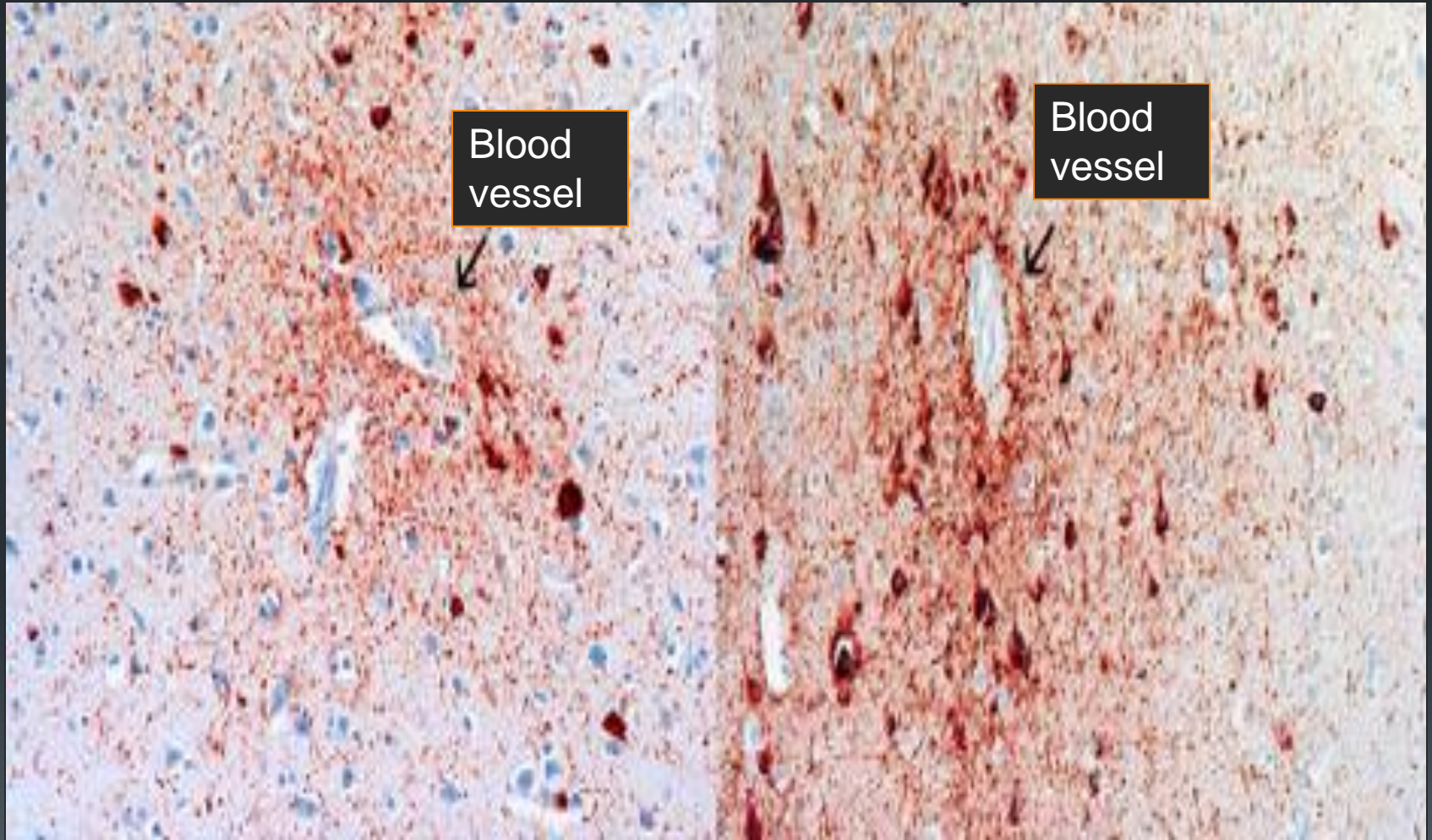
## Epidemiology

- 1.6 - 3.8 million sports concussions reported to team doctors annually
- Estimated unreported concussions 6-10 times higher

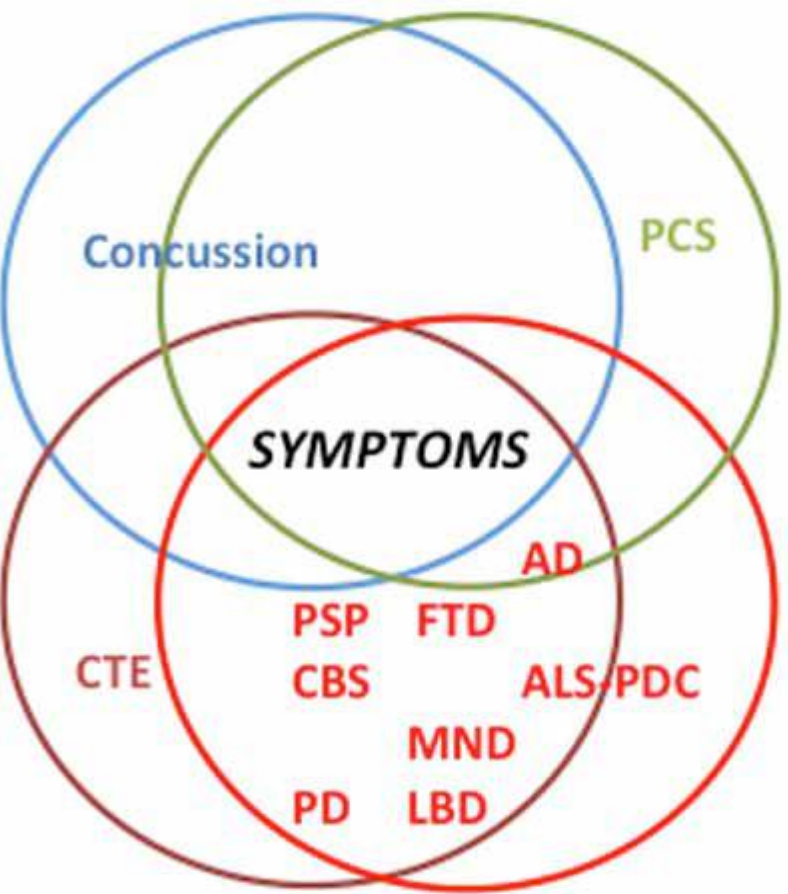


# TBI injury mechanisms

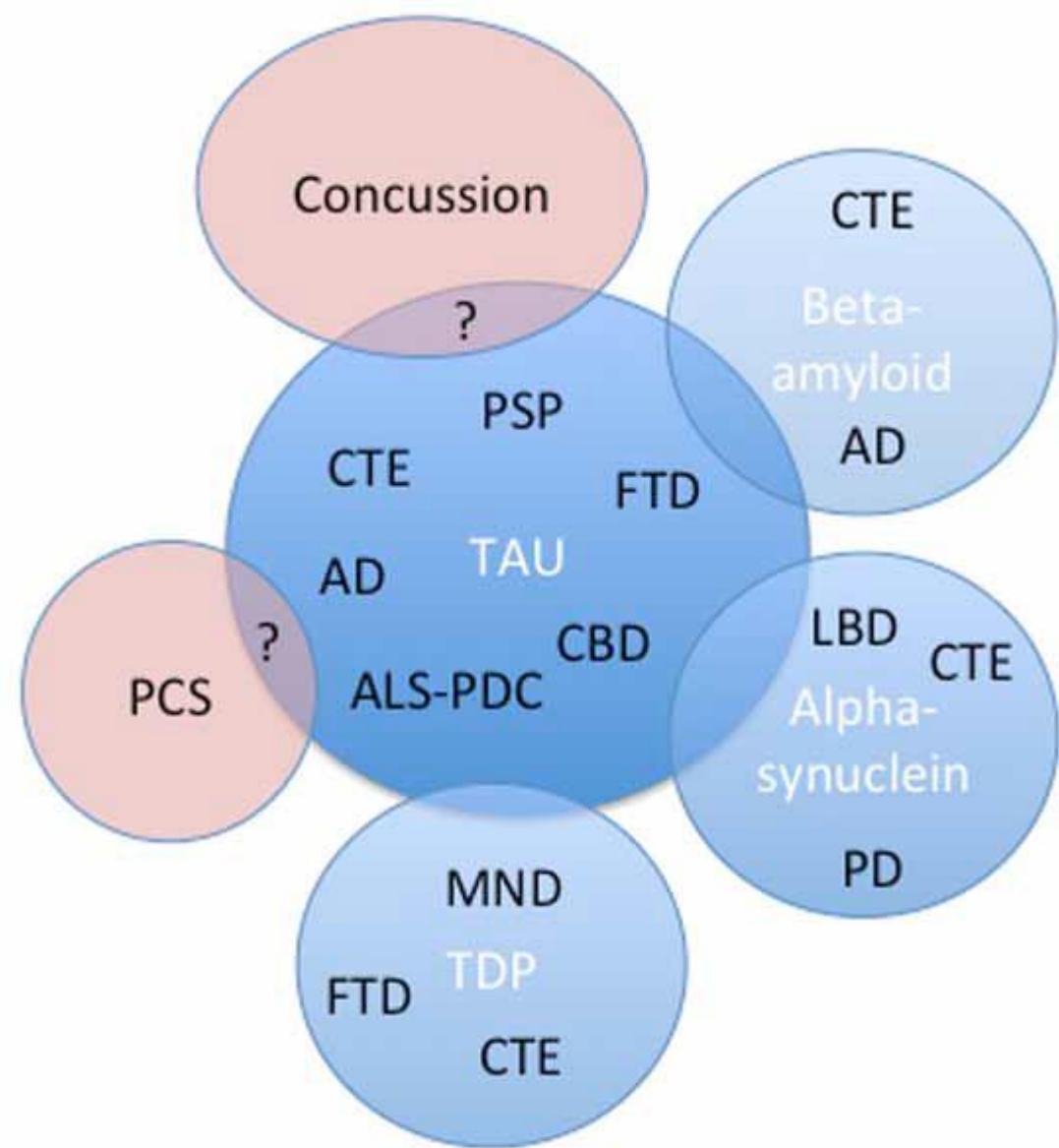
# Peri-vascular tau antibody staining



**A** Symptom overlap



**B** Pathological overlap



# CTE PRESENTATIONS

First type of clinical presentation starts with mood and behavioral symptoms earlier in life (mean age approximately 35) and progresses to include cognitive symptoms later in the disease course.

Second type of clinical presentation begins with cognitive impairment later in life (mean age approximately 60), which may progress to include mood and behavioral symptoms



# CTE FEATURES



Evidence to-date suggests that CTE presents clinically with symptoms in one or more of four possible domains:

1-Mood

2-Behaviour

3-Cognition

4-Motor

McKee et al. Brain. 2013 Jan;136(Pt 1):43-64

Smith et al. Nat Rev Neurol. 2013 Apr;9(4):222-30.

# MOOD AND BEHAVIOUR

## Commonly noted mood features include:

- Depression
- Irritability
- Hopelessness.

## Behavioral features may include:

- Impulsivity
- Explosive reactions.
- Aggression.

McKee et al. Brain. 2013 Jan;136(Pt 1):43-64

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# COGNITIVE

## Cognitive features can include:

- Memory impairment
- Executive dysfunction
- In severe cases: dementia.

McKee et al. Brain. 2013 Jan;136(Pt 1):43-64

Smith et al. Nat Rev Neurol. 2013 Apr;9(4):222-30.

# MOTOR



## Motor features include:

- Parkinsonism
- Ataxia
- Dysarthria

McKee et al. Brain. 2013 Jan;136(Pt 1):43-64

Smith et al. Nat Rev Neurol. 2013 Apr;9(4):222-30.



# Mood and Behavioural issues

# DSM V criteria for Major Depressive Disorder

- Five or more of the following:
  1. Depressed Mood most of the day, nearly every day.
  2. Anhedonia.
  3. Significant weight changes.
  4. Insomnia or hypersomnia.
  5. Psychomotor agitation or retardation nearly every day.
  6. Fatigue.
  7. Feelings of worthlessness, or inappropriate guilt.
  8. Diminished ability to concentrate or think; indecisiveness.
  9. Recurrent thoughts of death, suicidal ideation/intent.
  
- Symptoms cause significantly distress and impairment.
- Not attributable to the effects of a substance or another medical condition.
- Not better explained by a [psychotic disorder]
- Never a manic episode.

# Depression in retired athletes

Miller et al 2002

NCAA study - 21% very heavy alcohol use; 73% regular use.

Dose dependent correlation between depression and alcohol use

Backmand et al 2003

1164 retired athletes

Low physical activity associated with depression.

Schwenck et al 2007

3377 retired NFL players survey

14.7% depression

47.6% lifestyle limited by chronic pain

Adapted from McCrory, P. and:

Backmand et al. Int J Med Sport 2003; 24: 609-16

Schwenck et al. Med Sci Sports Exerc. 2007; 39: 599-605

Miller et al. J Drug Educ 2002; 32: 41-52

# Guskiewicz et al:

- Questionnaire based studies on 2552 retired NFL players:
  - 758 detailed questionnaires:
    - 61% had 1 concussion,
    - 24% had more than 3 concussions
    - 11% reported depression (Beck DI)
  - More than 3 concussions:
    - 5 times the risk of Mild Cognitive Impairment or A.D.
    - 3 times the risk of depression
    - 3 times the risk of SR memory problems



## Depression in Traumatic Brain Injury

- Most common neuropsychiatric sequelae
- Frequency ranges between 6 and 77%: methodology problems are common in these studies:
  - Different diagnostic instruments and arbitrary cut-off points in depression scales, definition of depression, symptom vs syndrome, low powered studies, etc.
- Depressive disorders more common in TBI than in a control of orthopaedic injuries.
- First year post TBI frequency: 25-50%

# Depression in Traumatic Brain Injury

- Hart et al, 2012: > 1000 TBI patients in their second year post injury.
- Approximately one fourth of patients not depressed in the first year were depressed in the second.
- 2/3 of patients depressed during the first year remained depressed during the second year.

## Axis I and II Psychiatric Disorders After Traumatic Brain Injury: A 30-Year Follow-Up Study

Salla Koponen, M.D.

Tero Taiminen, M.D., M.Sc.D.

Raija Portin, Ph.D.

Leena Himanen, M.A.

Heli Isoniemi, M.D.

Hanna Heinonen, M.D.

Susanna Hinkka, Ph.Lic., M.Sc.

Olli Tenovuo, M.D., M.Sc.D

**Objective:** Patients who had suffered traumatic brain injury were evaluated to determine the occurrence of psychiatric disorders during a 30-year follow-up.

**Method:** Sixty patients were assessed on average 30 years after traumatic brain injury. DSM-IV axis I disorders were diagnosed on a clinical basis with the aid of the Schedules for Clinical Assessment in Neuropsychiatry (version 2.1), and axis II disorders were diagnosed with the Structured Clinical Interview for DSM-III-R Personality Disorders. Cognitive impairment was measured with a neuropsychological test battery and the Mini-Mental State Examination.

**Results:** Of the 60 patients, 29 (48.3%) had had an axis I disorder that began after traumatic brain injury, and 37 (61.7%) had had an axis I disorder during their lifetimes. The most common novel disorders after traumatic brain injury were ma-

ior depression (26.7%), alcohol abuse or dependence (11.7%), panic disorder (8.3%), specific phobia (8.3%), and psychotic disorders (6.7%). Fourteen patients (23.3%) had at least one personality disorder. The most prevalent individual disorders were avoidant (15.0%), paranoid (8.3%), and schizoid (6.7%) personality disorders. Nine patients (15.0%) had DSM-III-R organic personality syndrome.

**Conclusions:** The results suggest that traumatic brain injury may cause decades-lasting vulnerability to psychiatric illness in some individuals. Traumatic brain injury seems to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances. The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury.

(Am J Psychiatry 2002; 159:1315-1321)

- Koponen et al, 2002: 60 patients with TBI followed for 30 years: 26.7% lifetime prevalence of major depression.
- Three quarters of patients with post TBI depression also had co-morbid anxiety.
- Post TBI depression is highly correlated with aggressive behaviour.

# Other neurobehavioral disorders

- Dysexecutive syndromes (“personality change”)
- Cognitive Disorders (memory, attention, processing speed)
- Psychiatric Disorders (depression, anxiety, PTSD, somatoform)

## Article

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# Depression

1. MRI Diffusion Tensor Imaging of white matter disruption correlates in depression in retired NFL players vs. controls.
2. Higher prevalence of depression (24 vs. 15%) in players vs. controls.
3. Phenomenology: more neuro-vegetative (appetite and sleep) symptoms than overt depressed mood.

# Depression in CTE

Case reports of CTE- confirmed individuals describe the presence of risk factors for depression:

- Cognitive deterioration.
- Downturn in socio-economic status.
- Bankruptcy.
- Breakdown of intimate relationships.
- Separation and divorce. spousal abuse.
- Headaches.
- Generalized aches and pain.
- Alcohol and drug abuse.

# Depression in CTE

1. Cognitive deterioration.
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8. Alcohol and drug abuse.

Similar issues are commonly seen in males with primary depression and without a history of head trauma.

# Mood issues in CTE



CTE has been associated with;

- Depression: 48% of cases
- Apathy: 9% of cases
- Early onset of mood problems in the CTE process.
- Social phobia and PTSD.
- Paranoid ideation in 42 of 51 CTE confirmed cases.
- Anxiety spectrum disorders

Omalu et al; Gavett et al; Stern et al; McKee et al; Victoroff et al; Hart et al;



# Mood issues in CTE



However, so far:

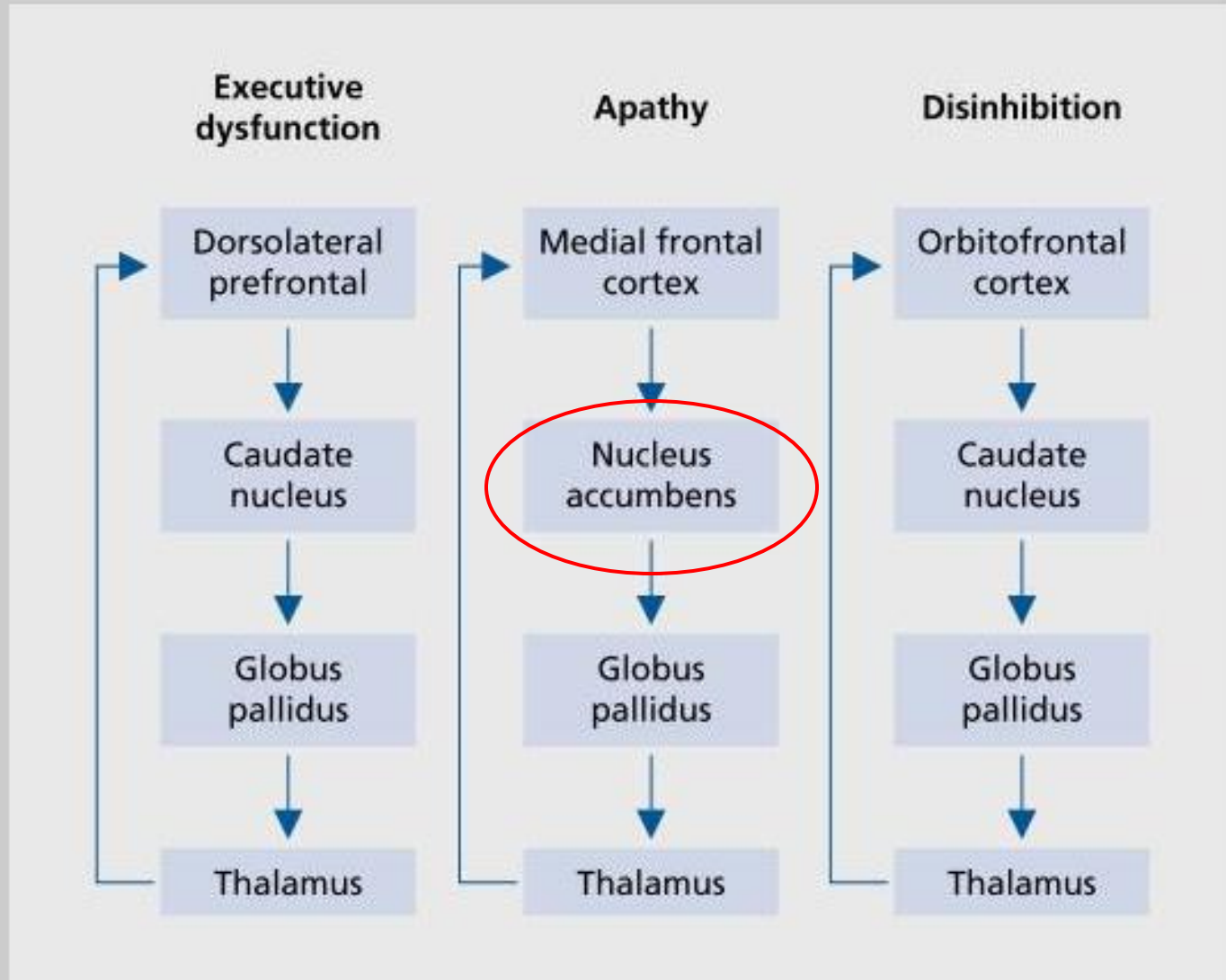
- Lack of prospective longitudinal studies.
- Case series.
- Selection bias.
- Retrospective post-mortem semi-structured interviews with relatives.
- Recall bias.
- Course of depression remains unclear.
- Not clear if presence of Tau deposits correlates with depression.

# Behavioural syndromes.



# Anatomy of frontal lobe functions

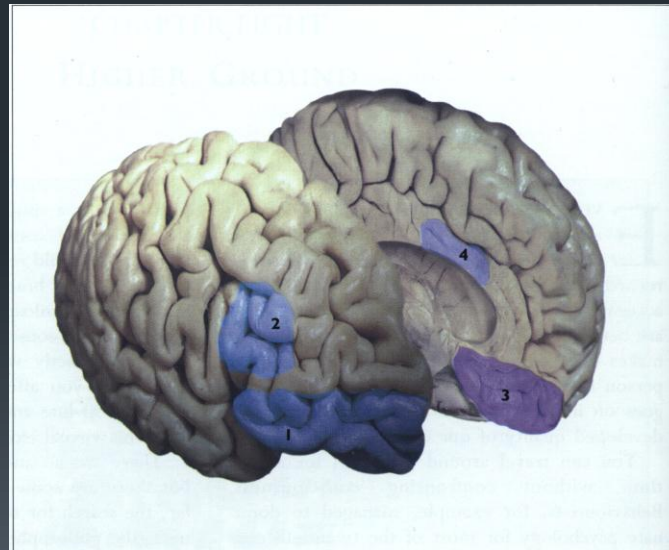
- The dorsolateral prefrontal circuit allows the organization of information to facilitate the response to information, stimuli, etc.
- The anterior cingulate circuit is required for motivated behaviour.
- The orbitofrontal circuit allows the integration of limbic and emotional information into behavioral responses.
- Impaired executive functions, apathy, and impulsivity are hallmarks of frontal-subcortical circuit dysfunction.



Bonelli, Cummings; Dialogues Clin Neurosci. 2007 Jun; 9(2): 141–151.

# Frontal Lobe Syndromes

- Dorsolateral → ■ Dysexecutive.
- Ventromedial → ■ Apathetic.
- Orbitofrontal → ■ Impulsive/aggressive



Based on :  
Alexander GE, et al. *Annu Rev Neurosci.* 1986; 9():357-81.  
Cummings, *Arch Neurol.* 1993;50(8):873-880;

# Behavioural issues in CTE



In reviews of cases of confirmed CTE:

- 70% had behavioural changes including aggression.
- 42% paranoid ideation.
- 39% irritability.
- 24% agitation.
- 5.8% hyper-sexuality.
- Definition of terms: variable.

# Behavioural issues in CTE

Possible anatomical correlates:

1. Papez circuit (hippocampal-septo-hypothalamic-mesencephalic)
2. Amygdala and mesial temporal lobe.
3. Orbito-frontal cortex.
4. Degeneration of parahippocampal gyri
5. Evidence of causality of any one anatomical region is lacking.



# Behavioural issues in CTE



Confounding factors for CTE and behavioural syndromes:

1. Premorbid personality traits
2. People involved in these sports have higher rates of impulsivity and aggression.
3. Substance abuse and addiction.
4. Socio-economic factors: Level of education , family factors, etc.



## Stats Canada, 2011

### Suicides and suicide rate, by sex and by age group (Both sexes no.)

|                             | 2007                      | 2008         | 2009         | 2010         | 2011         |
|-----------------------------|---------------------------|--------------|--------------|--------------|--------------|
|                             | <b>Both sexes</b>         |              |              |              |              |
|                             | <b>number of suicides</b> |              |              |              |              |
| <b>All ages<sup>1</sup></b> | <b>3,611</b>              | <b>3,705</b> | <b>3,890</b> | <b>3,951</b> | <b>3,728</b> |
| 10 to 14                    | 33                        | 25           | 25           | 32           | 29           |
| 15 to 19                    | 185                       | 208          | 202          | 198          | 198          |
| 20 to 24                    | 290                       | 255          | 277          | 288          | 301          |
| 25 to 29                    | 282                       | 256          | 258          | 271          | 261          |
| 30 to 34                    | 235                       | 257          | 298          | 292          | 283          |
| 35 to 39                    | 325                       | 316          | 332          | 343          | 288          |
| 40 to 44                    | 403                       | 452          | 431          | 365          | 354          |
| 45 to 49                    | 486                       | 468          | 491          | 502          | 432          |
| 50 to 54                    | 410                       | 418          | 476          | 484          | 443          |
| 55 to 59                    | 307                       | 337          | 371          | 386          | 375          |
| 60 to 64                    | 203                       | 224          | 241          | 272          | 245          |
| 65 to 69                    | 115                       | 145          | 138          | 152          | 150          |
| 70 to 74                    | 102                       | 114          | 122          | 117          | 128          |
| 75 to 79                    | 103                       | 100          | 82           | 103          | 101          |
| 80 to 84                    | 76                        | 67           | 73           | 76           | 76           |
| 85 to 89                    | 42                        | 42           | 54           | 51           | 49           |
| 90 and older                | 14                        | 21           | 19           | 19           | 13           |

# SUICIDE in CTE



- In the USA: the rate of suicide is almost twice that of homicides\*
- In the USA: persons are more likely to die from suicide than by motor vehicle accidents\*.
- In Canada: aprox. 4000 per year.\*\*
- 2011-2013: 6 NFL players commit suicide.
- Media gets interested. Increased attention.

\*Rockett, Am J Public Health 2012, 102 (1)

\*\* Stats Canada, 2011

# SUICIDE



- The question of suicide in CTE remains contentious.
- Several CTE case series have included victims of suicide.
- “However, our lack of understanding of the incidence of CTE limits our ability to attribute a complex and multifactorial behavior such as suicide to underlying CTE proteinopathy”

# SUICIDE

- The issue is further complicated considering that well established risk factors for suicide and suicidal ideation such as substance use and depression are often comorbid in cases of CTE.
- Available scientific evidence cannot wholly support the notion that CTE causes suicidal thoughts or behaviors, and such assumptions or assertions should be avoided without further evidence.

## Chronic traumatic encephalopathy and suicide: a systematic review.

Wortzel, Hal S; Shura, Robert D; Brenner, Lisa A.

Traumatic brain injury (TBI) is a global health concern, and the recent literature reports that a single mild TBI can result in chronic traumatic encephalopathy (CTE). It has been suggested that CTE may lead to death by suicide, raising important prevention, treatment, and policy implications. Thus, we conducted a systematic review of the medical literature to answer the key question: What is the existing evidence in support of a relationship between CTE and suicide?

Systematic searches of CTE and suicide yielded 85 unique abstracts.

Seven articles were identified for full text review. Only two case series met inclusion criteria and included autopsies from 17 unique cases, 5 of whom died by suicide. Neither studies used blinding, control cases, or systematic data collection regarding TBI exposure and/or medical/neuropsychiatric history.

The identified CTE literature revealed divergent opinions regarding neuropathological elements of CTE and heterogeneity regarding clinical manifestations.

Overall quality of evidence regarding a relationship between CTE and suicide was rated as very low using Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) criteria.

Further studies of higher quality and methodological rigor are needed to determine the existence and nature of any relationship between CTE and suicide.

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## Division III Collision Sports Are Not Associated with Neurobehavioral Quality of Life.

Meehan WP 3rd<sup>1,2,3,4</sup>, Taylor AM<sup>2,3,5</sup>, Berkner P<sup>6</sup>, Sandstrom NJ<sup>7</sup>, Peluso MW<sup>8</sup>, Kurtz MM<sup>9</sup>, Pascual-Leone A<sup>10</sup>, Mannix R<sup>2,4</sup>.

We sought to determine whether the exposure to the sub-concussive blows that occur during division III collegiate collision sports affect later life neurobehavioral quality-of-life measures. We conducted a cross-sectional study of alumni from four division III colleges, targeting those between the ages of 40-70 years, using several well-validated quality-of-life measures for executive function, general concerns, anxiety, depression, emotional and behavior dyscontrol, fatigue, positive affect, sleep disturbance, and negative consequences of alcohol use. We used multivariable linear regression to assess for associations between collision sport participation and quality-of-life measures while adjusting for covariates including age, gender, race, annual income, highest educational degree, college grades, exercise frequency, and common medical conditions. We obtained data from 3702 alumni, more than half of whom (2132) had participated in collegiate sports, 23% in collision sports, 23% in non-contact sports. Respondents with a history of concussion had worse self-reported health on several measures. When subjects with a history of concussion were removed from the analyses in order to assess for any potential effect of sub-concussive blows alone, negative consequences of alcohol use remained higher among collision sport athletes ( $\beta$ -coefficient 1.957, 95% CI 0.827-3.086). There were, however, no other significant associations between exposure to collision sports during college and any other quality-of-life measures. Our results suggest that, in the absence of a history of concussions, participation in collision sports at the Division III collegiate level is not a risk factor for worse long-term neurobehavioral outcomes, despite exposure to repeated sub-concussive blows.

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# Psychiatric Assessment of Depression and Behavioural syndromes in TBI

- History of present illness.
- Past psychiatric history.
- Family psychiatric and medical history.
- Medical history. Medications. Allergies.
- Substance use history.
- Social history, forensic involvement.
- Developmental and educational history.
- Mental status exam.
- MoCA, MMSE, Behavioural Neurology Assessment, etc.

# Assessment of Depression in TBI



- Beck Depression Inventory (BDI).
- Hamilton Depression Scale (HAM-D).
- Neurobehavioral Functioning Inventory Depression Sub-Scale.
- Center for Epidemiologic Studies, Scales for Depression.
- Hospital Anxiety and Depression Scale (HADS)

## Standard neuropsychological test battery to assess cognitive functioning following TBI

### Memory

Rey Auditory Verbal Learning (CDE)/California Verbal Learning Test- II (CDE)

Brief Visuospatial Memory Test-Revised (CDE)

### Processing Speed

Wechsler Adult Intelligence Scale-IV Processing Speed Index (CDE)

### Executive Functioning and Decision Making

Controlled Oral Word Association (CDE)

Trail Making Test (Trails A and B) (CDE)

Color Word Interference (CDE)

Iowa Gambling Task

### Everyday Executive Functioning

Behavioral Report Inventory of Executive Functioning—Adult

### Symptom Validity Assessment

Test of Memory Malingered (TOMM) (CDE)

*Abbreviation:* CDE, Common Data Element.

# Treatment options

- Most recommendations stem from expert opinion and consensus rather than rigorous, well powered, long term prospective RCT's

Types:

- Non pharmacological.
- Pharmacological.

# Treatment options

## Non pharmacological:

- Psycho-Education for patient, family and caregivers.
- Behavioural interventions: Differential Reinforcement of Other Behaviours:
  1. A specific schedule of reinforcement.
  2. Used to decrease the rate of behaviors that are inappropriate.
  3. Time-dependent rather than response-dependent
  4. Reinforcement is delivered after a time period of non-responding.
- Cognitive Behavioural Therapy:

Unknown effectiveness but anecdotal evidence regarding decrease of mood and anxiety symptoms

# Treatment options

## Pharmacotherapy

- General principles in acquired brain injury... not always followed
- Most medications in TBI are used “off label” as TBI patients are rarely included- if at all- in pharmacotherapy RCT’s for mood, anxiety, psychosis, mania etc.
- Start with the least invasive medication: e.g. do not use antipsychotics to treat insomnia or mild/moderate anxiety.
- Antipsychotics have very few indications in brain injury: delirium, psychosis, mania or severe behavioural problems not responsive to other interventions.
- Use the least anticholinergic/antihistaminic agent possible.

## Anticholinergic Activity of 107 Medications Commonly Used by Older Adults

Marci L. Chew, PhD,<sup>\*†</sup> Benoit H. Mulsant, MD,<sup>\*†‡</sup> Bruce G. Pollock, MD, PhD,<sup>†‡§||</sup>  
 Mark E. Lehman, PharmD,<sup>#</sup> Andrew Greenspan, MD,<sup>\*\*</sup> Ramy A. Mahmoud, MD,<sup>††</sup>  
 Margaret A. Kirshner, BA,<sup>†</sup> Denise A. Sorisio, BS,<sup>†</sup> Robert R. Bies, PharmD, PhD,<sup>\*†</sup>  
 and Georges Gharabawi, MD<sup>‡‡</sup>

The objective of this study was to measure the anticholinergic activity (AA) of medications commonly used by older adults. A radioreceptor assay was used to investigate the AA of 107 medications. Six clinically relevant concentrations were assessed for each medication. Rodent fore-brain and striatum homogenate was used with tritiated quinuclidinyl benzilate. Drug-free serum was added to medication and atropine standard-curve samples. For medications that showed detectable AA, average steady-state peak plasma and serum concentrations ( $C_{max}$ ) in older adults were used to estimate relationships between in vitro dose and AA. All results are reported in pmol/mL of atropine equivalents. At typical doses administered to older adults, amitriptyline, atropine, clozapine, dicyclomine, donepezin, L-hvoscavamine, thioridazine, and tolterodine dem-

(patients with above-average  $C_{max}$  values, who receive higher doses, or are frail may show AA). The remainder of the medications investigated did not demonstrate any AA at the concentrations examined. Psychotropic medications were particularly likely to demonstrate AA. Each of the drug classifications investigated (e.g., antipsychotic, cardiovascular) had at least one medication that demonstrated AA at therapeutic doses. Clinicians can use this information when choosing between equally efficacious medications, as well as in assessing overall anticholinergic burden. *J Am Geriatr Soc* 56:1333–1341, 2008.

**Key words:** anticholinergic activity; medications; elderly

# Treatment options

## Pharmacotherapy: Depression

- **Fluoxetine:** very long half life. Very strong inhibitor of CY-P450 system (2d6,2C19 and 3A).
- **Paroxetine:** strong anticholinergic activity; also a strong CY-P450.
- **Sertraline:** shorter half life; no anticholinergic activity. Good efficacy and safety profile.
- **Citalopram:** similar efficacy and side effect profile as Sertraline. QT-QTc issues are a concern in older patients.
- **Escitalopram:** unknown, but possible efficacy and safety profile same as Citalopram.



# Treatment options

## Pharmacotherapy: Depression, contd.

- **Unknown efficacy or safety profile on SNRI's: Venlafaxine, Desvenlafaxine and Duloxetine in ABI.**
- **Anecdotally, Venlafaxine is well tolerated and effective. Discontinuation syndrome.**
- **Duloxetine: higher anticholinergic activity and price. No head to head comparison with Venlafaxine**

# Treatment options

## Pharmacotherapy: Depression, contd.

- **MAOI's: not indicated.**
- **Tricyclics: high anticholinergic burden and unfavourable side effect profile. QT/QTc issues.**
- **Bupropion: Propensity to lower seizure threshold. Less so with the sustained release form.**
- **Stimulants: Methylphenidate, Amantadine, Modafinil.**

# Treatment options

## Behavioural dyscontrol

- Rule out comorbid medical illnesses, polypharmacy, pain, constipation, UTI's, personal need, environmental factors, etc.
- Many behavioral disturbances can be prevented by avoiding inappropriate medications and educating patient, family, caregivers, and health care providers.
- Hospitalization can be avoided and institutionalization delayed by early recognition and treatment of behavioral disturbance

# Treatment options

## Behavioural dyscontrol

- Non pharmacological treatments are the mainstay.
- First line treatments are always behavioural and environmental modification and family/caregivers education.
- Behavioural analysis: “ABC charting”, trends, triggers, timing.
- Consistency among care givers.

# Treatment options

## Behavioural dyscontrol

- Acute or chronic.
- Severity
- Location: community, hospital, long term care, etc.
- Resources: financial, social supports, etc.



## General principles in TBI

- In relatively preserved dorso-lateral prefrontal areas capable of effecting “top-down” modulation of behaviour, augmentation of these areas with stimulants ( Amantadine, Methylphenidate, Dextroamphetamine and Bromocriptine ) may reduce self injurious behaviours, agitation, aggression etc.

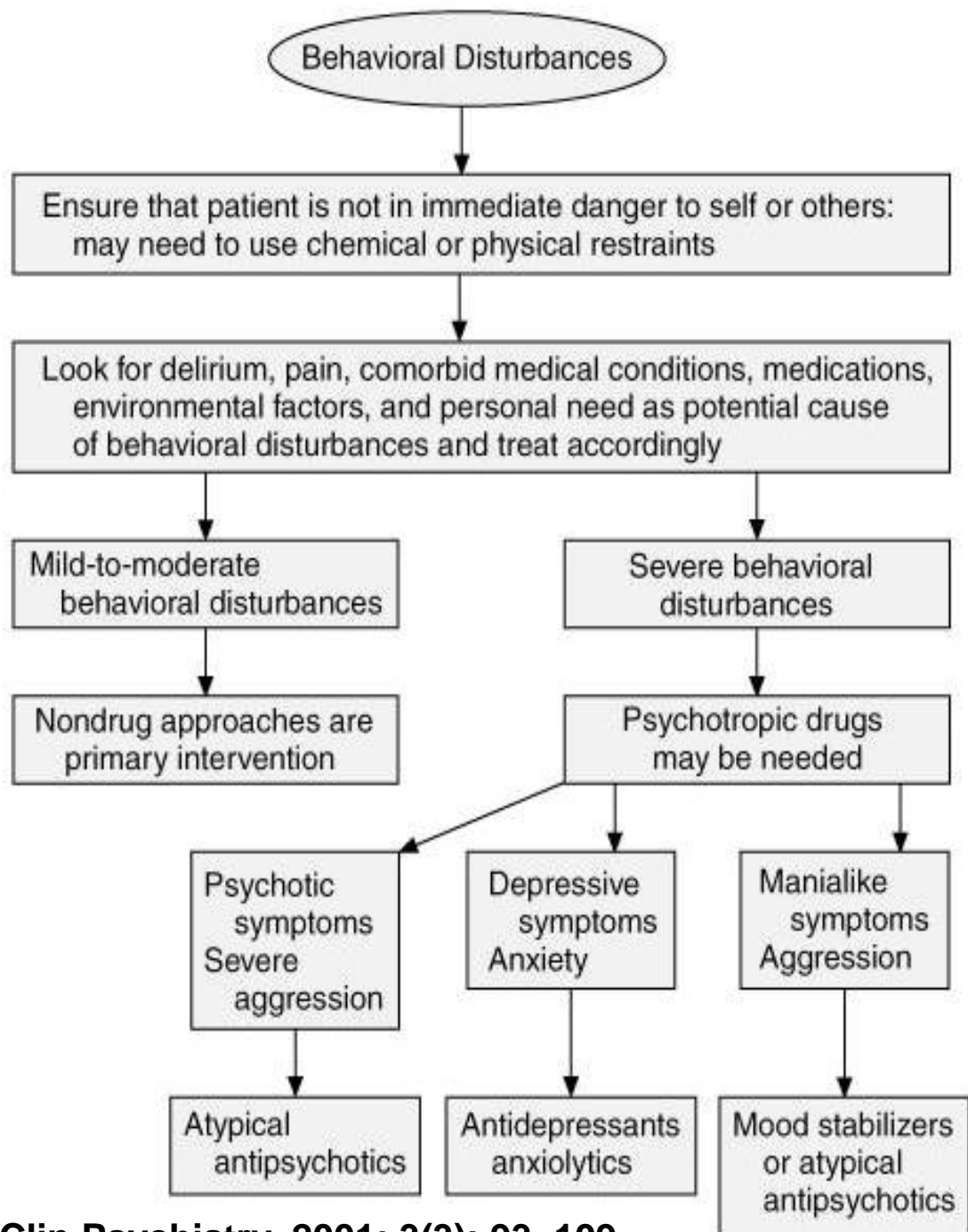
(ADHD model)

- But: risk of exacerbating behaviours if not carefully used.

## General principles in TBI

In diminished “top-down” regulation of ventral brain structures driving aggressive behaviour:

- medication that decrease limbic catecholamine function (antipsychotics or bet-blockers) or
- medications that attenuate activity in these structures (SSRI, anticonvulsants, Amantadine, atypical neuroleptics)





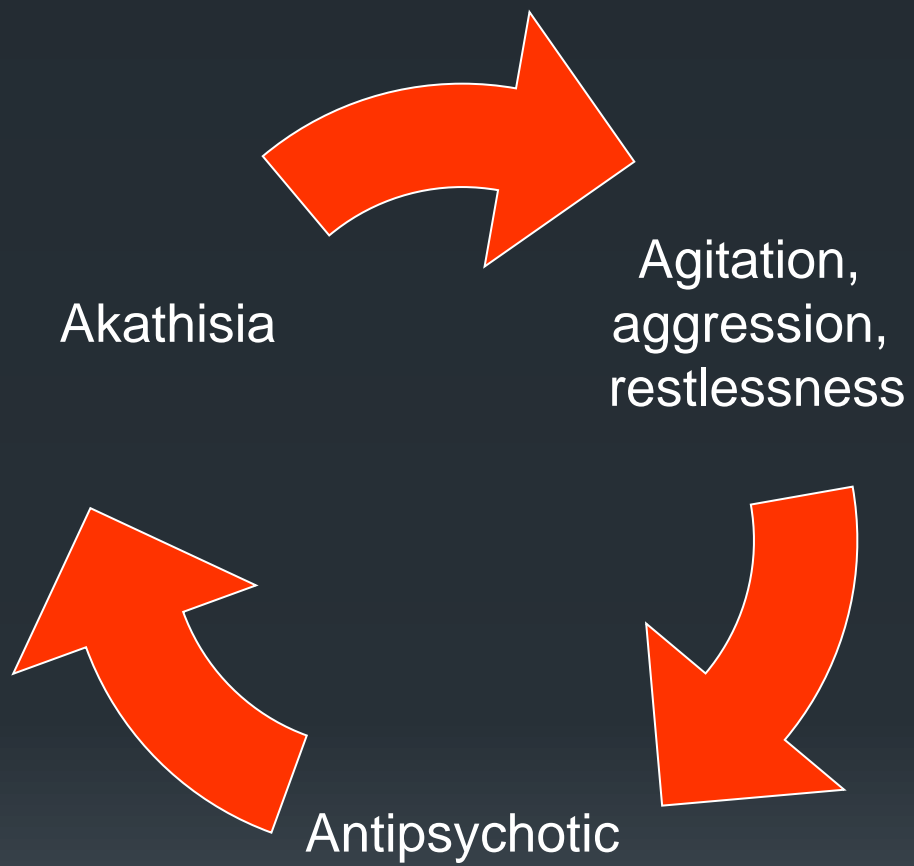
# Pharmacotherapy of acute moderate to severe behavioural dyscontrol

- First choices:
  - Lorazepam, PO/SL/IM and or
  - Haloperidol, PO/IM

## Secondary agents

- Olanzapine, Risperidone, Quetiapine.
- Trazodone.
- Anticonvulsants: Carbamazepine liquid. Divalproex.

The deadly triad...



# Pharmacotherapy of chronic behavioural dyscontrol

- First choices:
  - Beta blockers: Propanolol and Pindolol. Best evidence but poor tolerability, affective problems.
  - SSRI's: Citalopram if QTc < 450 or Sertraline. **Best option in clinical practice.**
- Secondary agents
  - Trazodone: very sedating.
  - Anticonvulsants: **Carbamazepine**, Divalproex.
  - NMDA receptor antagonist: Amantadine.
  - Tricyclics: effective but unfavourable side effect profile
  - Not enough information on Escitalopram and SNRI's but likely effective.
  - Anticholinesterase inhibitors: Donepezil. Evidence?
- Tertiary agents
  - Antipsychotics: atypical first choice. **Risperidone. Quetiapine.** Aripiprazole. Olanzapine.

# Antidepressants for agitation and psychosis in dementia.

Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P.

- To assess the safety and efficacy of antidepressants in treating psychosis and agitation in older adults with Alzheimer's disease, vascular, or mixed dementia.
- Nine trials including a total of 692 individuals were included in the review. Five studies compared SSRIs to placebo and two studies were combined in a meta-analysis for the outcome of change in Cohen-Mansfield Agitation Inventory.
- The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies.
- Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics



THANK YOU FOR YOUR  
ATTENTION