Program

DEMENTIA: A Comprehensive Update
May 27 – 30, 2020
Livestream

Friday, May 29, 2020

8:30 - 8:35  Morning PreTest……………………………………………………………………………………………………..A. Atri, MD, PhD

2020 Annual Plenary Session 2: Recognition and Management of Neuropsychiatric and Behavioral Issues in Dementia
8:35 - 9:30  Non-Pharmacological Approaches to Neuropsychiatric Symptoms and Problem Behaviors in Dementia..H.Kales, MD
9:30 - 10:25 Pharmacological Management of Behavioral Problems in Dementia……………C. Ballard, MDB ChB, MRCPsych, MD
10:25 - 10:40  Morning Coffee Break
10:40 - 11:25  Practical & Ethical Considerations for Disclosure of Demetia-Related Diagnosis and Risk….J. Karlawish, MD
11:25 - 12:05pm  Caregiving in Dementia: Impact, Consequences & Opportunities…………………………….M. Mittelman, DrPH
12:05 - 12:40  Morning Post-Test, Panel Discussion and Q & A…………………………………………………..Morning Faculty
12:40 - 1:40  Lunch Break
1:40 - 1:45  Afternoon PreTest…………………………………………………………………………………………………..B. Dickerson, MD, MMSc
1:45 - 2:00  Community Advocacy and Activism For Dementias……………………………………..K. Brandt, MM
2:00 - 2:45  Chronic Traumatic Encephalopathy (CTE) & Dementia…………………………………R. Stern, PhD
2:45 - 3:00  Afternoon Coffee Break
3:00 - 4:00  Delirium, Encephalopathies and Uncommon Dementias…………………………………..J. Schmahmann, MD
4:00 - 4:45  Afternoon Post-Test, Panel Discussion, Q&A and Conclusions………………Drs. Atri, Dickerson, and Course Faculty
Non-Pharmacological Approaches to Neuropsychiatric Symptoms and Problem Behaviors in Dementia

Helen Kales, MD
Moving evidence-informed assessment and management of behavioral symptoms out of the ivory tower and into the real world: The DICE Approach and the WeCareAdvisor

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### Topics covered

- What prevents families and people with dementia from “living well”?  
  - Behavioral and psychological symptoms are among the most difficult aspects of living with dementia  
  - Resources are not coordinated  
  - Lack of personalization and precision of current dementia care  
  - Workforce largely without specialized training

- The DICE Approach

- The WeCareAdvisor

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Currently, the **5 million** people with dementia and their **15 million** family caregivers often find themselves navigating without resources or training.
The critical role of the family caregiver

- 15 million family caregivers of people with dementia in the US
- Assesses and reports on symptoms, carries out recommendations, evaluates their effect
- Managing BPSD one of the most challenging aspects of dementia care
- Caregivers of people with BPSD
  - more distressed and depressed than those not managing behaviors
  - does caregiver distress drive outcomes?

Dementia and BPSD

- Devastating syndrome affecting 5 million people in US, 16 million by 2050
- Cognitive impairment is the clinical hallmark

- However, non-cognitive behavioral and psychological symptoms of dementia (BPSD) are universal (>98%)
  - often dominate the disease course
Dementia behaviors (BPSD) and their consequences

- Depression
- Anxiety
- Apathy
- Psychosis
- Agitation
- Aggression
- And many more

- Greater functional impairment
- Worsened quality of life
- Excess morbidity and hospitalizations
- Earlier nursing home placement
- Major source of caregiver burden and reduced caregiver income
- $10,000/year additional care costs
- Shorter time to severe dementia
- Accelerated mortality

Dementia Care for BPSD: Big problem #1

- Big problem #1 = Inability to access relevant resources precisely when needed
  - Few specialists, concentrated in academic centers
  - Primary care physicians with too little training
  - Dementia is more than a “medical” illness, there are multiple other spheres it impacts (legal, financial, functional, social)
  - Resources are available but can be hard for caregivers to find and access
Lack of resources impacts on family caregivers and people with dementia

Caregiver themselves:
- Stress
- Burden
- Depression
- Burnout
- Lost income

To the person with dementia:
- Unoptimized health and function
- Limited social engagement
- Lack of tailored activities

Within the dyad:
- Lack of understanding about dementia (“he’s doing this on purpose”)
- Poor communication (yelling, negative communications)
- Expecting too much for the person’s dementia stage

Dementia Care for BPSD: Big problem #2

- Personalized medicine=treatment focusing on patients based upon their individual clinical characterization
- Precision medicine=focus on identifying which treatment approaches will be effective for which patients

- **Big problem #2=Current dementia care is neither personalized nor precise**
  - Given the lack of a cure for dementia, the current focus is on day to day management
  - Much of that management is focused on the ubiquitous and extremely challenging behaviors that accompany dementia
  - Current real-world care (community or NH) for behaviors is largely centered on medicating/sedating people with dementia
Current Real-World “Assessment” of Behavioral and Psychological Symptoms of Dementia

![Diagram showing the relationship between agitation and psychotropic medication types.]

- Caregiver dealing with a behavior:
  - “Joe is agitated”
  - “I need something to calm Joe down”
  - “Can we get an order for Risperdal 0.5 BID?”

- Physician:
  - “I’ll write for the Risperdal now”

- Family caregiver dealing with a “physical” symptom:
  - “Joe has shortness of breath”

- PCP:
  - “I’ll write for the antibiotic now”

Dementia Care: Big problem #3

- Medications not very effective (1950’s treatment for 21st century patients)
- In most cases, medications do not treat the underlying problem, but cover it over (e.g. sedate)
- Medications are associated with significant side effects including mortality
- Efforts by national policy bodies to limit use of one medication (e.g. antipsychotics) drive up use of others (e.g. anticonvulsants)
- Behavioral and environmental treatment strategies if selected appropriately (precision medicine) are more effective

<table>
<thead>
<tr>
<th>Medication</th>
<th>Risk Difference, % (95% CI)</th>
<th>NHN (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant (Reference)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>12.3 (8.6-16.0)</td>
<td>8 (6-12)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7.0 (4.2-9.8)</td>
<td>14 (10-24)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3.2 (1.6-4.9)</td>
<td>31 (21-62)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6.1 (4.1-8.2)</td>
<td>16 (12-25)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>5.1 (1.8-8.4)</td>
<td>20 (12-56)</td>
</tr>
</tbody>
</table>
Antipsychotic use HAS declined—but does that mean that fewer people with dementia are being medicated with psychiatric drugs?

- Programs such as CMS’ National Partnership have driven down nursing home AP use.
- Unintended consequences?: Shift to other psychotropics with less evidence of benefit and similar risks?

Maust, Kales et al
JAMA Internal Med 2018

Kales et al
Conceptual Model

- Consequence of neurodegeneration associated with dementia
- Creates an increased vulnerability to stressors
- Stressors include patient, caregiver and environmental factors
- No one-size-fits all solution
- Need for personalization and precision

Kales, Gitlin, Lyketsos BMJ 2015
NIA/NIMH Panel, 2017
Kales, Gitlin, Lyketsos JAMDA 2019
Neurodegeneration Associated with Dementia

- Disrupts brain circuits
  - DIRECT effect
    - Apathy is a good example of a symptom that is caused by a direct impact of disruption of brain circuitry
- Changes the ability of the person with dementia to interact with others and with the environment
  - INDIRECT effect
    - Other symptoms may be caused by underlying brain disease but need to be triggered by person with dementia, caregiver or environmental factors

Person with dementia factors

- Psychiatric problems/personality issues from earlier in life
  - Schizophrenia
  - Bipolar disorder
  - Anxiety
  - Depression
  - Personality disorder
- Acute medical problems
  - Infection, constipation, dehydration, medication interactions
- Unmet needs
  - Pain, sleep problems, fear, boredom, loss of control or purpose
Caregiver factors

• Stress, burden, depression
• Lack of understanding about dementia and its stages, or how brain disease impacts behavior (“he’s doing this on purpose”)
• Communication issues (yelling, negative communications)
• Expecting too much for the person’s dementia stage

Environmental Factors

• Too noisy (TV or stereo blaring)
• Chaotic (people coming and going)
• Lack of stimulation (nothing to look at or enjoy)
• Lack of activity that interests the person
• Lack of structure/routines (person does not know what to expect from day to day)
Spot the triggers!

Does how we treat behaviors currently make sense?
Non-pharmacologic treatment

- Numerous expert bodies recommend as first-line
- May be better stated as “ecobiopsychosocial” interventions
- Largely NOT been translated to real-world care and clinical settings
  - Lack of scalable training programs for caregivers and providers
  - Time required
  - Lack of guidelines—what strategy to use and when?
  - So many interventions (e.g. acupuncture, music therapy, reminiscence)—what works?

- Big problem #3: Lack of training among caregivers (or providers) on how to use proven non-pharmacological strategies to manage behavioral symptoms
  
  Molinari et al, 2010;
  Cohen-Mansfield et al, 2013

Family Caregiver Interventions: Meta-analysis

- Brodaty meta-analysis of 23 RCTs with family caregivers; outcomes related to frequency/severity of behaviors and caregiver well-being
  - effect size (magnitude of treatment effect) is LARGER for family caregiver interventions for behaviors in dementia than for antipsychotics OR for cognitive enhancers for cognitive symptoms

Non-pharmacologic approaches: best evidence

• Behavioral, environmental, and caregiver supportive interventions that have a growing evidence base

• Most significant evidence base for family caregiver interventions that train caregivers to:
  • Use problem-solving skills to manage behaviors
  • Increase tailored activity for the person with dementia
  • Enhance communication in the dyad
  • Reduce environmental complexity
  • Simplify tasks for the person with dementia

• Big problem #1=Inability to access relevant resources precisely when needed
• Big problem #2=Current dementia care is neither personalized nor precise
• Big problem #3: Lack of training among caregivers (or providers) on how to use proven non-pharmacological strategies to manage behavioral symptoms
How can we solve Big Problems #1, 2 and 3?

With innovation, “packaging” and technology

The DICE Approach

- Program for Positive Aging organized and funded a 2011 meeting of national experts across disciplines
  - Consider possible etiologies
  - Include caregiver in process
  - Integrate pharmacologic and non-pharmacologic
  - Build in flexibility to use in various care settings
  - Goal to avoid knee-jerk prescribing without assessment of underlying causes

- *We need to better PACKAGE non-pharmacologic approaches

Kales, Gitlin, Lyketsos JAGS 2014
- **Describe** a behavior that challenges; who, what, where, when, and how the behavior occurs
- **Investigate** thinking like a detective and explore the person with dementia, the caregivers, and environment for possible clues to triggers underlying possible causes of behavior
- **Create** a prescription in collaboration with your team to help prevent and manage behaviors
- **Evaluate** and review prescription effectiveness, and modify or restart the process as needed

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**How does DICE differ from other approaches out there?**

- Approach is algorithmic
  - Simple but elegant
  - Designed to be easy to remember and to help create “good habits”
- Integrates pharmacologic and non-pharmacologic approaches
- Expands the discussion of medications beyond psychiatric medications to other medications (for pain, infection, constipation, etc)
- Strategies are tailored to the PWD, caregiver and environment
Gemma

- 85-year old woman who emigrated from Italy fifty years ago. Now living in an assisted living facility
- Generally good-natured, but gets agitated in the afternoons, asking staff to “go home” or saying that she “has to get to church”
- Staff tries to “reason” with her and tells her to “calm down”, but Gemma continues to escalate, following staff in her wheelchair, repeatedly asking them to go home or be taken to church
- Because Gemma interferes with their work flow and “won’t listen to reason”, staff will administer a “prn” dose of an antipsychotic

DESCRIBE

- Full and accurate description of the behavior
- Critical step often left out
  - Do we treat “shortness of breath” with antibiotics without history, physical or labs?
- Full description leads to underlying cause possibilities
- Clinical scenario: Gemma, the 85 year old assisted living resident, getting “agitated” in the afternoon.
- Learn to “play it back like a scene from a movie”
**DESCRIBE the problem behavior**

**Gemma:**
- Asking to “go home” or saying “I have to get to church”
- Typically starts in the late afternoon
- Will begin to follow staff in her wheelchair

**Assisted Living Staff:**
- Try to “reason” with her and “give her reality”
  - “This is NOT your home”
  - “You live here in the facility now”
  - “We are not going to church”
- Staff feel that Gemma’s behavior is interfering with their workflow

**Environment**
- Group activities are going on in the afternoon, Gemma does not seem to enjoy these and will try to leave the group

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**INVESTIGATE**

- Another “left out” step
- This step is led by the clues from DESCRIBE
- Play “detective” to search for underlying causes/triggers of behavioral symptoms
- Triggers often come from >1 of three categories

![Diagram showing Triggers, Person with dementia, Environment, Caregiver]
Patient Factors

<table>
<thead>
<tr>
<th>Problem</th>
<th>What you might notice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>• Holding or rubbing part of body</td>
</tr>
<tr>
<td></td>
<td>• Fast breathing</td>
</tr>
<tr>
<td></td>
<td>• Groaning or moaning</td>
</tr>
<tr>
<td></td>
<td>• Tension</td>
</tr>
<tr>
<td></td>
<td>• Pushing away when touched</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Pain and difficulty opening bowels</td>
</tr>
<tr>
<td></td>
<td>• Hard poo</td>
</tr>
<tr>
<td></td>
<td>• Pain on touching stomach</td>
</tr>
<tr>
<td>UTI (Urinary Tract Infection)</td>
<td>• Burning pain on passing urine</td>
</tr>
<tr>
<td></td>
<td>• Urinating more frequently</td>
</tr>
<tr>
<td></td>
<td>• Cloudy or different smelling urine</td>
</tr>
<tr>
<td>Recent changes in medication</td>
<td>• Dose changes in long-standing medications</td>
</tr>
<tr>
<td></td>
<td>• New medications causing behavioral changes (e.g. Benadryl, Ditropan)</td>
</tr>
</tbody>
</table>

Caregiver Factors

- “Doing this on purpose”
- Reacting harshly
- Offering too many choices
- Expecting more than possible
- Feeling stressed, anxious, depressed
- Family, facility or cultural expectations

Environmental Factors

INVESTIGATE underlying causes

**Gemma:**
- No prior psychiatric history, although family states that when Gemma got anxious she would be very “action-oriented” (cleaning, cooking)
- Gemma was a regular church-goer all her life, attending Catholic mass daily
- She also ran an Italian family restaurant for years and loves to cook and talk about food
- She loves Italian music from the 1940’s (but calls “American” music “noise”)
- Used to say that many “American activities” are a “waste of time” (“why they exercise? They should do work instead”)

**Staff:**
- Did not know much of Gemma’s history
- Couldn’t understand why she couldn’t see “that they were busy”
- Frustrated that she won’t participate in group activities like music and exercise group, “why won’t she go along with the program?”

**Environment**
- Daily groups are a mismatch for her interests and preferences
CREATE-Six general strategies

- Manage any physical problems
- Provide family/staff education/support
- Improve communication
- Create meaningful and tailored activities
- Simplify tasks
- Ensure the environment is safe

Create/implement collaborative treatment plan

Gemma:
- Rule out acute medical issues

Staff:
- Educate staff about BPSD and “broken brain”
- Reinforce communication strategies that are more effective (e.g. reasoning is not working)
- Taking some time to brainstorm tailored activities will save time in the long run
- Redirect calmly and with humor, occasionally incorporate Gemma in the staff routine as time/work permit

Environment
- Create routines and activity for Gemma that are safe, not overstimulating and meaningful/tailored to her interests, start them BEFORE she usually gets agitated
- Consider activities incorporating Italian food/music or religious practices
- Allow to wander safely
Don’t forget to evaluate!

Best way to tell if something is working may be to do a formal assessment at baseline and after a trial of an intervention.

NPI Q is a nice tool to measure symptoms.

Evaluate the interventions

Gemma:
- Evaluate effect of non-pharmacologic strategies

Staff:
- What approaches did staff try? Were there any that they were resistant to? If so, why?
- What worked?
- What didn’t?
- Were there any unintended consequences or “side effects” noted?

Environment:
- What changes were made? Were new routines instituted? Any issues with that?
Medications in the DICE Approach

- Off-label use of medication is not necessarily a bad thing (e.g. rare diseases and cancer)
- However, with psychiatric medications in dementia, there is no FDA indication because the **risks** (many side effects and even death) outweighs the **benefits** (modest efficacy at best) in many cases
- *The DICE Approach does not prohibit medications*
- But rather, we encourage **careful consideration of the risks and benefits in EVERY case**

Safety first!

- Always assess safety as part of the DESCRIBE step!
- If anyone’s safety is at risk, they should call their doctor immediately

- Psychiatric medications as a first-line therapy in **THREE cases**
  - **Major (clinical) depression with or without suicidal thoughts**
  - **Aggression with risk of harm to self or others**
  - **Psychosis with risk of harm to self or others**

- Note: People with chronic mental illness
A Goal of the DICE Approach

- Avoid the “knee-jerk” use of medications without assessing the possible underlying causes
- Knee-jerk medication use (“agitation”=Risperdal) causes many problems
  - Worsening of symptoms
  - Ignoring the underlying cause (pain, urinary tract infection)
  - Unnecessary sedation and other side effects (including falls, worsened memory)
  - Worsened quality of life
  - Death
- Expand the consideration of “medications” with behavior to non-psychiatric medications
  - Pain control
  - Antibiotics for infections
  - Bowel regimens for constipation

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**DESCRIBE**
- Consider psychiatric medication use only if there is concern for harm/risk including significant person with dementia distress

**INVESTIGATE**
- Consider psychiatric medication use if behavior is not allowing a full investigation to occur (e.g. fear of aggression preventing blood draw or urine sample)

**CREATE**
- Consider psychiatric drug use as a first-line if there is serious depression, psychosis or aggression with risk

**EVALUATE**
- If medications were used, how well did they work? Evaluate for adverse effects, whether there is still risk and whether medications could be tapered and discontinued
We’ve “Packaged” the Approaches Via DICE, How do we Deliver Them?

- **Pilot of DICE Training:** 1 day; 8 modules with 1.5 hour brainstorming session
  - **Wisconsin:** 1 statewide training n=125, results pending
  - **Michigan:** 3 trainings (Grand Rapids, Ann Arbor, East Lansing)
    - Mix of family and professional (RN, LPN, CNA, PT, RT, SW) caregivers
    - N=182
    - Both groups with significant improvement from pre to post

- **Most helpful aspects:**
  - Use of workshop materials (case studies, role playing, time to talk to other providers)
  - Combining paid professionals and home/family care givers for interaction and learning
  - Use of simple framework (DICE) that is understandable to all
  - Covering medication issues (effect on older adult, family, paid caregivers)
  - Handouts to take home

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**Michigan Health Endowment Funding (MHEF)**

- **Pilot of DICE Trainings:** 1 day; 8 modules with 1.5 hour brainstorming session
  - Creation of DICE manual
  - Michigan: 3 trainings (Grand Rapids, Ann Arbor, East Lansing)
    - Mix of family (n=40) and professional (RN, LPN, CNA, PT, RT, SW; n=142) caregivers; a number of the professional caregivers were also family caregivers
    - N=182
### Michigan Training Results

<table>
<thead>
<tr>
<th></th>
<th>Family Caregivers (n=40)</th>
<th>Professional Caregivers (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand feelings of PWD</td>
<td>1.67 (0.81-3.41) NS</td>
<td>1.46 (0.66-3.35) NS</td>
</tr>
<tr>
<td>Understand way the PWD interacts with others and their environment</td>
<td>2.78 (1.30-5.95) <em>p&lt;0.009</em></td>
<td>2.78 (1.18-6.52) <em>p&lt;0.02</em></td>
</tr>
<tr>
<td>Use information about past interests</td>
<td>1.67 (0.81-3.41) NS</td>
<td>1.81 (0.80-4.13) NS</td>
</tr>
<tr>
<td>Protect the dignity of the PWD</td>
<td>2.13 (0.92-4.92) NS</td>
<td>2.93 (1.11-7.71) <em>p&lt;0.03</em></td>
</tr>
<tr>
<td>Deal with behavior of the PWD</td>
<td>5.60 (2.16-14.50) <em>p&lt;0.0004</em></td>
<td>3.92 (1.40-10.98) <em>p&lt;0.01</em></td>
</tr>
<tr>
<td>Decide about risk in PWD</td>
<td>2.44 (1.13-5.31) <em>p&lt;0.03</em></td>
<td>1.53 (0.64-3.65) NS</td>
</tr>
<tr>
<td>Offer stimulation to the PWD</td>
<td>2.78 (1.30-5.95) <em>p&lt;0.009</em></td>
<td>1.35 (0.57-3.20) NS</td>
</tr>
<tr>
<td>Offer choices to the PWD</td>
<td>3.29 (1.41-7.66) <em>p&lt;0.006</em></td>
<td>2.62 (1.03-6.67) <em>p&lt;0.05</em></td>
</tr>
<tr>
<td>Engage PWD in creative activities</td>
<td>3.00 (1.35-6.68) <em>p&lt;0.008</em></td>
<td>1.55 (0.63-3.80) NS</td>
</tr>
<tr>
<td>Understand the causes of behaviors</td>
<td>4.50 (1.86-10.90) <em>p&lt;0.0001</em></td>
<td>1.95 (0.74-5.18) NS</td>
</tr>
<tr>
<td>Understand how to assess and manage BPSD</td>
<td>10.33 (3.16-33.80) <em>p&lt;0.0001</em></td>
<td>4.88 (1.39-17.09) <em>p&lt;0.02</em></td>
</tr>
<tr>
<td>Understand PWD, caregiver, environmental factors and BPSD</td>
<td>4.80 (1.83-12.58) <em>p&lt;0.002</em></td>
<td>3.55 (1.24-10.18) <em>p&lt;0.02</em></td>
</tr>
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### Qualitative Feedback

- “The whole approach organizes a complicated medical problem -brain disease -into something more manageable. Each aspect of the training was illuminating for me as a caregiver. I have found great comfort today -education really is empowering.”
- “The DICE approach incorporates front line staff to help describe and investigate and be included in the process.”
- “I liked the different steps in DICE and how simple the acronym is. I also like how it focuses on the person and how to help them and the caregiver through situations rather than just accept the disease.”
DICE Trainings

- Most helpful aspects:
  - Use of workshop materials (case studies, role playing, time to talk to other providers)
  - Combining paid professionals and home/family caregivers for interaction and learning
  - Use of simple framework (DICE) that is understandable to all
  - Covering medication issues
  - Handouts to take home

DICE Website: Now available for training!
The WeCareAdvisor

- The WeCareAdvisor contains a comprehensive “Caregiver Survival Guide” that includes vetted medical, legal, financial, functional and social information. It also includes linkage to additional outside resources.

- Daily supportive/motivational messaging for caregivers

Big Problem #1 = Inability to access relevant resources precisely when needed

Big Problem #2 = Current dementia care is neither personalized nor precise

- Personalized peer navigator to lead caregivers through the tool

- Use of the **DICE Approach** within the tool to figure out the individual reasons for behavioral and functional changes (personalized care)
After using the DICE approach within the WeCareAdvisor (to figure out the underlying causes of behaviors), an individualized “prescription” is created for the caregiver and person with dementia (precision medicine).

Using a proprietary algorithm, (based on caregiver input during DICE) treatment strategies are selected from over 1000 contained in the tool.

**Nice. But does it work?**

- Randomized controlled trial of the WeCareAdvisor in comparison to wait-list control (BMC Geriatrics, 2017)
- During brief (one-month) use of the tool:
  - Family caregivers had significant reductions on the primary outcome of DISTRESS
  - Distress is associated with most of the negative outcomes of dementia caregiving (hospitalizations, NH placement)
  - Trends to decreased dementia behaviors **Caregiver Distress**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T0)</th>
<th>Month 1 (T1)</th>
<th>Month 2 (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WeCare</td>
<td>17.7</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Waitlist</td>
<td>15.4</td>
<td>13.6</td>
<td>9.9</td>
</tr>
</tbody>
</table>
Caregiver Feedback

- “Wonderful new tool in my caregiving arsenal”
- “DICE structures my thinking”
- “Survival guide is comprehensive”
- “I shared the tool with my support group and everyone was impressed by the content and ease of use”
- “Love the feeling of support”
- “Ease of use if very nice”
- “Daily tips are awesome”
- “I wish I would have had this a long time ago”
- “I learned a great deal more about dementia and the skills to use in dealing with related behaviors”
- “This week my spouse had a UTI and the WeCareAdvisor helped to trigger in my mind that something was wrong and he should see the doctor”
- “We can go to the doctor, go to support groups, but I see the value of having this daily. This is advice every day”

Summary

- The number of people with dementia and their family caregivers is large and growing every day with the aging of the population
- Living well with dementia is the goal
- Current care systems are inadequate and lead to multiple poor outcomes
- Innovative solutions like the DICE Approach with delivery methods including a manual, training and website and the web-based WeCareAdvisor can put the key components of good dementia care at the fingertips of the people who need it most
Additional Opportunities for DICE Training


- DICE Website: [https://diceapproach.com](https://diceapproach.com)

- In-person trainings: by arrangement with the PPA

- DICE certification: Coming 2020
Pharmacological Management of Behavioural and Psychological symptoms in People with Dementia

Professor Clive Ballard
MBChB MMedSci MRCPsych MD FMedSci
University of Exeter, UK

Leiden ranking 2019 –world top 20 for research quality
## Risperidone Efficacy: BEHAVE-AD

Ballard & Howard 2006 Nature Neuroscience Reviews

<table>
<thead>
<tr>
<th>Target symptom</th>
<th>Mean Difference from placebo</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risperidone 1mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>-0.79</td>
<td>p=0.03</td>
<td>-1.31 to -0.27</td>
</tr>
<tr>
<td><strong>Risperidone 1mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td>-0.84</td>
<td>p=0.0002</td>
<td>-1.28 to -0.40</td>
</tr>
<tr>
<td><strong>Risperidone 2mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression</td>
<td>-1.50</td>
<td>p&lt;0.0001</td>
<td>-2.05 to -0.95</td>
</tr>
</tbody>
</table>

## STAR TRIAL: Zhong et al 2007

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Quetiapine 200mg (N=114)</th>
<th>Quetiapine 100mg (N=120)</th>
<th>Placebo (N=92)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS-EC</td>
<td>-5.7 (0.9)</td>
<td>-4.9 (0.8)</td>
<td>-3.9 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>NPI (total)</td>
<td>-9.7 (2.2)</td>
<td>-8.9 (2.1)</td>
<td>-8.2 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>NPI (agitation)</td>
<td>-1.1 (0.5)</td>
<td>-0.9 (0.5)</td>
<td>-1.2 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>NPI (psychosis)</td>
<td>-2.5 (0.9)</td>
<td>-1.8 (0.8)</td>
<td>-2.5 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>CGIC</td>
<td>3.0 (0.2)</td>
<td>3.2 (0.2)</td>
<td>3.6 (0.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Major Adverse Outcomes with antipsychotics over 6-12 weeks
(FDA, Schneider et al 2005, Ballard et al 2009)

- Parkinsonism
- Sedation
- Gait disturbance
- Increased respiratory infections
- Oedema
- Accelerated cognitive decline (2-4 fold)
- Stroke (>3 fold)
- Other thrombo-embolic events (up to 80%)
- Mortality (1.5-1.7 fold)

No Benefit and Accelerated Cognitive Decline with Quetiapine

<table>
<thead>
<tr>
<th></th>
<th>rivastigmine</th>
<th>quetiapine</th>
<th>placebo</th>
<th>Chi v plac</th>
<th>Nip v plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>N=24 (15 completed SIB)</td>
<td>N=26 (14 completed SIB)</td>
<td>N=29 (17 completed SIB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diff CMAI</td>
<td>-8.3 ± 18.4</td>
<td>-4.7 ± 17.3</td>
<td>-6.2 ± 17.2</td>
<td>T=0.4 P=0.67</td>
<td>T=0.3 P=0.74</td>
</tr>
<tr>
<td>Diff SIB</td>
<td>+4.2 ± 15.4</td>
<td>-10.5 ± 14.8</td>
<td>+2.8 ± 15.5</td>
<td>T=0.3 P=0.80</td>
<td>T=2.4 P=0.02*</td>
</tr>
<tr>
<td>Week 26</td>
<td>N=24 (16 completed SIB)</td>
<td>N=26 (15 completed SIB)</td>
<td>N=29 (17 completed SIB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diff SIB</td>
<td>-1.1 ± 21.1</td>
<td>-11.6 ± 15.6</td>
<td>+2.3 ± 18.1</td>
<td>T=0.5 P=0.61</td>
<td>T=2.3 P=0.03*</td>
</tr>
<tr>
<td>Diff CMAI</td>
<td>-10.5 ± 20.4</td>
<td>-4.4 ± 15.7</td>
<td>-7.9 ± 16.6</td>
<td>T=0.5 P=0.62</td>
<td>T=0.1 P=0.87</td>
</tr>
</tbody>
</table>

AGIT-AD Ballard et al 2005 BMJ
Responses to atypical antipsychotics

• Response** based on CGIC score at 12 weeks:
  – 32% Olanzapine group
  – 26% Quetiapine group
  – 29% Risperidone group
  – 21% placebo group
• Overall comparison: p=0.22

** A response was defined as continued treatment with the original phase 1 study drug and at least minimal improvement on the CGIC.


Change from Baseline to 6 months DART AD

Ballard et al PLOS Medicine 2008

<table>
<thead>
<tr>
<th>Total NPI</th>
<th>(n=56)</th>
<th>(n=33)</th>
<th>-2.4 (-8.2 to 3.5)</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUPDRS</td>
<td>(n=54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5 (17.4)</td>
<td>4.0 (2.2)</td>
<td>1.3 (-0.4 to 3.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Bristol AD</td>
<td>(n=52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8 (8.9)</td>
<td>0.2 (7.2)</td>
<td>1.7 (-1.2 to 4.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Change in FAST*</td>
<td>(n=53)</td>
<td>(n=33)</td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>-2</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGIC*</td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Very much improved</td>
<td>(n=48)</td>
<td>(n=48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much improved</td>
<td>3 (7%)</td>
<td>3 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally improved</td>
<td>7 (15%)</td>
<td>14 (29%)</td>
<td>14 (29%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>18 (37%)</td>
<td>10 (21%)</td>
<td>10 (21%)</td>
<td></td>
</tr>
<tr>
<td>Minimally worse</td>
<td>9 (19%)</td>
<td>10 (21%)</td>
<td>10 (21%)</td>
<td></td>
</tr>
<tr>
<td>Much worse</td>
<td>7 (15%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very much worse</td>
<td>3 (6%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DART AD: Differential Survival
Ballard et al Lancet Neurology 2009


Reduced Antipsychotic Use and Stroke Incidence in people with Dementia
Sultana et al 2019 Drug Safety

OBJECTIVE:
• The aim of this study was to measure the change in stroke incidence after two safety warnings in both the UK and Italy.
• METHOD:
  • A cohort study was conducted using electronic medical records representative of the UK (The Health Improvement Network) and Italy (Health Search-IQVIA Health LPD), containing data on 11 million and 1 million patients, respectively.
• RESULTS:
  • In the UK and Italy, 6342 and 7587 elderly antipsychotic initiators were identified.
  • A 42% stroke incidence reduction was seen in the UK after the first safety warning [42.3 (95% confidence interval (CI) 35.2-50.8) vs. 24.4 [95% CI 19.0-31.2] events per 1000 person-years (PYs)], while there was a 60% stroke incidence reduction after the second warning (16.9 [95% CI 12.2-23.4] events per 1000 PYs) compared to before the first warning. There was no significant reduction in stroke incidence in Italy.
2 RCTs of Brexpiprazole
Grossberg et al Am J Ger Psych 2020

**DESIGN:**
- Two 12-week, randomized, double-blind, placebo-controlled, parallel-arm studies (NCT01862640; NCT01922258).

**PARTICIPANTS:**
- Patients with AAD (Study 1: 433 randomized; Study 2: 270 randomized) in a care facility or community-based setting. Stable Alzheimer disease medications were permitted.

**INTERVENTION:**
- Study 1 (fixed dose): brexpiprazole 2 mg/day, brexpiprazole 1 mg/day, or placebo (1:1:1) for 12 weeks. Study 2 (flexible dose): brexpiprazole 0.5-2 mg/day or placebo (1:1) for 12 weeks.
- In Study 1, brexpiprazole 2 mg/day demonstrated statistically significantly greater improvement in CMAI Total score from baseline to Week 12 than placebo (adjusted mean difference, -3.77; confidence limits, -7.38, -0.17; t_(316) = -2.06; p = 0.040; MMRM).
- Brexpiprazole 1 mg/day did not show meaningful separation from placebo (0.23; -3.40, 3.86; t_(314) = 0.12; p = 0.90; MMRM).
- In Study 2, brexpiprazole 0.5-2 mg/day did not achieve statistical superiority over placebo (-2.34; -5.49, 0.82; t_(230) = -1.46; p = 0.15; MMRM).

---

Clinical Trials of Person Centred Care Interventions in Care Homes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chenoweth, L et.al. 2009 (Australia)</td>
<td>RCT: 15 NH 289 residents 194 care staff</td>
<td>Quality of life, Antipsychotics, Agitation</td>
<td>CMAI QUALID Falls</td>
<td>Agitation was lower in sites providing DDC and PCC. No change on QOL or antipsychotics</td>
</tr>
<tr>
<td>Brooker, DJ et.al. 2011 (UK)</td>
<td>Quasi-Experimental design: 10 extra care housing schemes n=293</td>
<td>Quality of life, depression</td>
<td>QOLAD GDS DSSI DCM</td>
<td>Significant decrease in depression after 18 months in the intervention group</td>
</tr>
</tbody>
</table>
WHELD Factorial RCT: Key Results

*Ballard et al Am J psychiatry 2016*

- AR significantly reduced antipsychotic use by 50% (OR 0.17, 95% CI 0.05 to 0.60, p=0.006).
- AR and SI significantly reduced mortality (OR=0.36, 95% CI 0.23 to 0.57, p<0.001)
- Benefits in mortality were achieved without a worsening of neuropsychiatric symptoms in people receiving AR and SI (-0.44, CI -4.39 to 3.52, p=0.82)
- EX significantly improved depression (-4.74, CI 0.76 to 8.72) and neuropsychiatric symptoms (-4.01, 95% CI -7.91 to -0.10, p=0.045).
- SI significantly improved quality of life (6.04, 95% CI 0.24 to 11.84, p=0.042)
- Combination of both SI and AR (p<0.04) and EX and AR (P<0.02) also significantly improved apathy
WHELD dementia champion RCT

- 847 residents with dementia in 69 nursing homes
- 9 month cluster RCT
- Key outcomes:
  - Quality of Life (DEMQOL proxy)
  - Agitation (CMAI)
  - Cost
- Results: Significant benefits in quality of life and agitation for WHELD at lower cost compared to treatment as usual
- No reduction in antipsychotic use without primary care education programme

WHELD Parallel group RCT  
Ballard et al PLOS Medicine 2018

| Outcome measure  | Adjusted effect (SE)* | p-Value  | Mean difference (SEM) | 95% CI of mean difference | Effect size (Cohen's D) | Number needed to treat
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMQOL-Proxy (n = 553)</td>
<td>R = 0.12; Z = 2.82</td>
<td>0.0042</td>
<td>2.54* (0.88)</td>
<td>0.81, 4.28</td>
<td>0.24</td>
<td>9</td>
</tr>
<tr>
<td>CMAI (n = 553)</td>
<td>R = 0.11; Z = 2.68</td>
<td>0.0076</td>
<td>4.27* (1.59)</td>
<td>−7.39, −1.15</td>
<td>0.23</td>
<td>6</td>
</tr>
<tr>
<td>NPI-NH (n = 547)</td>
<td>R = −1.5; Z = 3.52</td>
<td>&lt;0.001</td>
<td>4.55* (1.28)</td>
<td>−7.07, −2.02</td>
<td>0.30</td>
<td>9</td>
</tr>
</tbody>
</table>

The quality of interactions of positive care between care staff and residents with dementia (QUIS) was collected as a care-home-level assessment in 62 of the participating care homes. There was a statistically significant 19.7% greater increase in the proportion of positive care interactions from baseline to 9 months in the WHELD group compared to the TAU group (SEM 8.94; 95% CI 2.12, 37.16, p = 0.03; Cohen's D 0.55). AU: Comparison unclear here: increase from baseline to 9 months? Or is this a comparison of WHELD versus TAU (in which case the term “increase” may lead readers astray)? Please clarify.

19.7 greater increase from baseline to month 9 in the WHELD group than in the TAU group
DOMINO: Estimates of mean NPI and GHQ-12 by visit and treatment arm
Howard et al NEJM 2012

CitAD: JAMA 2014

- **OBJECTIVE:** To evaluate the efficacy of citalopram for agitation in patients with Alzheimer disease.

- **DESIGN, SETTING, AND PARTICIPANTS:** CitAD was a randomized, placebo-controlled, double-blind, parallel group trial with 186 patients with probable AD and clinically significant agitation.

- **INTERVENTIONS:** Patients were randomized to receive a psychosocial intervention plus either citalopram (n = 94) or placebo (n = 92) for 9 weeks. Dosage began at 10 mg per day with planned titration to 30 mg per day over 3 weeks based on response and tolerability.
Citalopram: Citalopram for Agitation in AD (CitAD) - Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment effect (95% CI)</th>
<th>P-val</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBR-A</td>
<td>-0.93 (-1.80, -0.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>mADCS-CGIC</td>
<td>2.13 (1.23, 3.69)</td>
<td>0.007</td>
</tr>
<tr>
<td>CMAI</td>
<td>-2.38 (-4.13, -0.63)</td>
<td>0.008</td>
</tr>
<tr>
<td>NPI-agitation</td>
<td>-0.78 (-1.77, 0.21)</td>
<td>0.12</td>
</tr>
</tbody>
</table>


Limitations for Citalopram in AD Agitation

• CitAD Trial Results
  • Worsening of cognition (-1.05 points; 95% CI, -1.97 to -0.13; P = .03)
  • QT interval prolongation (18.1 ms; 95% CI, 6.1-30.1; P = .01)

• Package insert for citalopram recommends maximum dose of 20 mg for elderly population, less than the 30 mg dose found to improve agitation symptoms in CitAD study
Aggressive Behaviour and Neuroleptic Medication are associated with Increased Number of Alpha1-Adrenoceptors in Patients with Alzheimer Disease

Sharp, Sally I.; Ballard, Clive G, Chen, Christopher P-L; Francis, Paul T. American Journal of Geriatric Psychiatry 2007

**Objective:** Aggressive behavior in dementia is a major clinical management problem.

**Method:** Postmortem brain tissue was obtained from 24 patients with Alzheimer disease (AD) and 25 comparison cases. [3H] Prazosin binding to α1-AdR was determined.

**Results:** Aggressive behavior was significantly correlated with α1-adrenoceptor number in patients with AD (R²=0.454, N=24). Furthermore, patients receiving ongoing neuroleptics had significantly higher Bₘₐₓ for [3H] prazosin (21 ± 2, N=9) than those who were not (16 ± 1, N=15).

**Conclusions:** Upregulation of α1-AdR is associated with aggressive behavior and chronic treatment with neuroleptic medication.

---

**Behavioural Responses to Prazosin versus Placebo:**

**Behaviour Scores Presented as Mean ± Standard Deviation**

(Wang et al 2009)

<table>
<thead>
<tr>
<th>NPI</th>
<th>Baseline (n=22)</th>
<th>Change from baseline for participants remaining at each time point</th>
<th>Mean group change</th>
<th>Test statistic</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1 (n=22)</td>
<td>Week 2 (n=19)</td>
<td>Week 4 (n=15)</td>
<td>Week 6 (n=13)</td>
<td>Week 8 (n=13)</td>
</tr>
<tr>
<td>Prazosin</td>
<td>49 ± 16</td>
<td>-20 ± 19</td>
<td>-16 ± 23</td>
<td>-16 ± 25</td>
<td>-15 ± 24</td>
</tr>
<tr>
<td>Placebo</td>
<td>43 ± 18</td>
<td>-5 ± 17</td>
<td>-2 ± 21</td>
<td>4 ± 17</td>
<td>-1 ± 14</td>
</tr>
<tr>
<td>BPRS</td>
<td>Prazosin</td>
<td>45 ± 8</td>
<td>-9 ± 8</td>
<td>-8 ± 10</td>
<td>-7 ± 13</td>
</tr>
<tr>
<td>Placebo</td>
<td>44 ± 7</td>
<td>-3 ± 7</td>
<td>-5 ± 7</td>
<td>-2 ± 6</td>
<td>-3 ± 8</td>
</tr>
<tr>
<td>CGIC</td>
<td>Prazosin</td>
<td>2.6 ± 1.0</td>
<td>Z=2.57</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.5 ± 1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cost-effectiveness analyses for mirtazapine in dementia: randomised controlled trial *British Journal of Psychiatry, 202: 121-128*

Mirtazapine

– centrally active presynaptic α2-antagonist

HTA SADD RCT (339 participants randomised and 326 with costs data (111 placebo, 107 sertraline, 108 mirtazapine). Taking the top 50% of raw NPI scores (ie those with appreciable BPSD)

– there was a 7.1 point difference in NPI score (95%CI -0.50 to 14.68; p=0.067) between mirtazapine and placebo and a 13.2 point difference between mirtazapine and sertraline (95%CI 4.47 to 21.95; p=0.003).

– from the cost effectiveness analyses, the time spent by unpaid carers caring for participants in the mirtazapine group was almost half that for patients in the placebo group (6.74 vs 12.27 hours per week) and sertraline group (6.74 vs 12.32 hours per week).

– SYMBAD trial now ongoing in the UK

---

Dextromethorphan/Quinidine (DM/Q)

*JAMA 2015*

- 220 patient randomized to Dextromethorphan/Quinidine (DM/Q) or placebo in 10 week trial
- Complicated 3:4 randomization design with re-randomization of placebo non-responders after 5 weeks
- 88% completed trial
- Significant benefits in agitation/aggression and CGIC, with benefits evident from week 1
- Falls and diarrhoea were the main emergent adverse events (both <10%)
RESEARCH

Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial

Bettina S Husebo postdoctoral fellow1, Clive Ballard professor2, Reidun Sandvik registered nurse1, Odd Bjarte Nilsen statistician3, Dag Aarsland professor4

1Department of Public Health and Primary Health Care, University of Bergen, 5020 Bergen, Norway; 2Wolfson Centre for Age-Related Diseases, Wolfson Wing and Hodgkin Building, Guy’s Campus, King’s College, London SE1 1UL, UK; 3Department of Psychiatry, Stavanger University Hospital, 4011 Stavanger, Norway; 4Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Karolinska Institute-Alzheimer Disease Research Center, Novum, Stockholm, Stavanger University Hospital, Department of Psychiatry, Stavanger, Norway, and University of Oslo, Oslo, Norway.

Table 3] Comparison of Cohen-Mansfield agitation inventory (CMAI) total score between control and intervention (stepwise protocol for treatment of pain) groups using repeated measures analysis of covariance (ANCOVA)*

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean (SD) CMAI total score</th>
<th>Effect of intervention on CMAI total†</th>
<th>Intraclass correlation coefficient‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>Intervention group</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>62.2 (16.1), n=177</td>
<td>66.5 (15.2), n=175</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>53.9 (17.0), n=161</td>
<td>52.0 (19.5), n=158</td>
<td>-3.6 (-0.5 to -6.7)</td>
</tr>
<tr>
<td>4</td>
<td>52.5 (16.3), n=160</td>
<td>49.4 (19.0), n=148</td>
<td>-4.1 (-0.9 to -7.4)</td>
</tr>
<tr>
<td>8</td>
<td>52.8 (16.8), n=157</td>
<td>46.9 (18.7), n=147</td>
<td>-7.0 (-3.7 to -10.3)</td>
</tr>
<tr>
<td>12</td>
<td>52.5 (16.0), n=152</td>
<td>50.3 (20.3), n=142</td>
<td>-3.2 (0.1 to -6.4)</td>
</tr>
</tbody>
</table>

*Baseline score as covariate and least squares weighted by number of patients within cluster; P value from multivariate test of intervention was 0.002, and cross effect between week and intervention was <0.001.
†Variable estimate by week of effect of intervention on CMAI score from estimated model.
‡Proportion of total variance between clusters, and measured within framework of ANCOVA.
Genetic Associations of Psychosis in AD

Proportion of studies finding significant associations with major symptoms:

<table>
<thead>
<tr>
<th></th>
<th>DEPRESSION</th>
<th>PSYCHOSIS</th>
<th>AGITATION/AGGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT2A T102C</td>
<td>1/5</td>
<td>6/9</td>
<td>1/5</td>
</tr>
<tr>
<td>5HT2C CYS23SER</td>
<td>1/4</td>
<td>1/4</td>
<td>0/4</td>
</tr>
<tr>
<td>5HTTLPR</td>
<td>0/7</td>
<td>4/9</td>
<td>2/8</td>
</tr>
<tr>
<td>5HTTVNTR</td>
<td>0/4</td>
<td>2/4</td>
<td>1/4</td>
</tr>
</tbody>
</table>


Pollock et al: 5HT polymorphisms predict reduced response and increased adverse events to risperidone and citalopram

Pimavanserin for AD psychosis

• 12 week RCT of people with AD in nursing homes with clinically significant psychosis (N=179)
• Primary outcome NPI psychosis at 6 weeks
• Key Secondary Outcome safety (cognition, function, parkinsonism, adverse events, mortality)
• Significant benefit in NPI psychosis at 6 weeks (Cohen’s D 0.32) with good tolerability
• Benefits even more substantial in people with severe psychosis (NPI combined delusion and hallucination score ≥12) Cohen’s D 0.73
• No increase of SAEs or mortality and no cognitive or functional decline compared to placebo
Significant improvement over placebo at primary endpoint of Week 6
Pimavanserin maintained improvement to Week 12

* p<0.05 placebo vs pimavanserin

LS Mean Difference in NPI-NH PS Change from Baseline (PIM – PBO)

Overall
NPI-NH Psychosis Score

Subgroups
Baseline NPI-NH Psychosis Score ≥12 (n=57)
Baseline NPI-NH Psychosis Score <12 (n=121)
Prior Antipsychotic Use (n=16)
No Prior Antipsychotic Use (n=162)
SSRI Use (n=41)
No SSRI Use (n=137)
Baseline Agitation/Aggression Score ≥6* (n=85)
Baseline Agitation/Aggression Score <6* (n=93)
Baseline NPI-NH Psychosis Score ≥12 & Agitation/Aggression Score ≥6* (n=38)

* Post-hoc analyses

Indicates the more severe patient sub-group
Acceptable Tolerability With No New Safety Observations

Summary of Adverse Events (AEs)

<table>
<thead>
<tr>
<th></th>
<th>PBO (N=91) n (%)</th>
<th>PIM (N=90) n (%)</th>
<th>TOTAL (N=181) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>85 (93.4)</td>
<td>88 (97.8)</td>
<td>173 (95.6)</td>
</tr>
<tr>
<td>Any Serious AE</td>
<td>10 (11.0)</td>
<td>15 (16.7)</td>
<td>25 (13.8)</td>
</tr>
<tr>
<td>Any AE Leading to DC</td>
<td>11 (12.1)</td>
<td>8 (8.9)</td>
<td>19 (10.5)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (4.4)</td>
<td>4 (4.4)</td>
<td>8 (4.4)</td>
</tr>
</tbody>
</table>

Citad Study: Secondary Outcomes including Psychosis
Leonpacher et al 2016 Am J Psych

METHOD:
• planned secondary analysis of the Citalopram for Agitation in Alzheimer's Disease study (CITAD),
• Evaluated effect of citalopram on the Neuropsychiatric Inventory (NPI) domains.
• Compared NPI scores at week 9 in patients receiving citalopram (30 mg/day) or placebo with regard to both the presence or absence of individual neuropsychiatric symptoms and individual domain scores (reflecting severity) in participants who had symptoms at week 9.

RESULTS:
• At week 9, participants treated with citalopram were significantly less likely to be reported as showing delusions (odds ratio=0.40), anxiety (odds ratio=0.43), and irritability/lability (odds ratio=0.38).
• At week 9 there were significant differences on NPI domain scores favoring citalopram for hallucinations.
Emerging Treatments

• Non-Drug
  – Sensory impairments
  – Specific psychological therapies for psychosis
• Drugs
  – M1 and M4 agonists
  – Epigenetic regulators
  – Cannaboids
  – 5HT6 regulators
  – New dextromethorphan combinations

Representative heat map images highlighting the difference in immunoreactivity of phosphorylated microtubule-associated protein tau (AT8 antibody) in the dorsolateral prefrontal cortex, between Alzheimer’s disease with psychosis (AD+P) and Alzheimer’s disease without psychosis (AD−P) subjects at lower (IV) and higher (VI) Braak stages. Blue and red colors represent lower and higher immunofluorescence intensities, respectively. Images captured at 60 magnification.

Farber et al 2000: Significant association between psychosis and increased neurofibrillary tangle area density across neocortical regions but not in medial temporal lobe structures.

Murray et al 2013: Increased concentrations of phosphor MAPT aggregates have also been identified in the dorsolateral prefrontal cortex of people with AD and psychosis compared to those without psychotic symptoms.
## Treatment of Psychosis in PD, PDD, DBL Friedman et al 2010, Aarsland et al 2012

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Clinical Practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treating underlying medical</td>
<td>Anecdotal/best</td>
<td>Good practice for newly presenting symptoms but limited utility for symptoms</td>
</tr>
<tr>
<td>causes/delirium</td>
<td>practice guide</td>
<td>present for &gt; 4 weeks</td>
</tr>
<tr>
<td>Reducing Parkinson's</td>
<td>Anecdotal</td>
<td>Can sometimes be effective in clinical practice, but limited evidence base and</td>
</tr>
<tr>
<td>medications</td>
<td></td>
<td>can lead to worsening of motor symptoms</td>
</tr>
<tr>
<td>Atypical Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>2 RCTs</td>
<td>Both RCTs show significant benefit in psychosis without worsening of motor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms. Possible increase of deaths in 1 study. Black box warning for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>agranulocytosis with mandatory monitoring. Cohen’s D &gt;0.7</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Limited evidence</td>
<td>Parkinsonian side effects too severe to consider in clinical practice</td>
</tr>
<tr>
<td></td>
<td>from open clinical trials</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2 RCTs</td>
<td>Worsening of motor symptoms too severe for olanzapine to be a viable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5 RCTs</td>
<td>The 4 RCTs in people without dementia and the only RCT in people with dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>indicated no benefit in the overall treatment of psychosis. One study showed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>some benefits in secondary analysis of hallucinations.</td>
</tr>
</tbody>
</table>

### Frequency of Neuroleptic Sensitivity Reactions:
Leading to Severe Parkinsonism, Impaired Consciousness, Rhabdomyolysis, Renal Failure and often Death

<table>
<thead>
<tr>
<th></th>
<th>DLB</th>
<th>PDD</th>
<th>PD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>36</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>No NSR</td>
<td>2(13%)</td>
<td>16(44%)</td>
<td>15(58%)</td>
<td>10(59%)</td>
</tr>
<tr>
<td>Mild NSR</td>
<td>5(33%)</td>
<td>6(17%)</td>
<td>4(15%)</td>
<td>7(41%)</td>
</tr>
<tr>
<td>Severe NSR</td>
<td>8(53%)*</td>
<td>14(39%)*</td>
<td>7(27%)*</td>
<td>0</td>
</tr>
</tbody>
</table>

* chi square = 12.4, df=3, p=0.006

* Including clozapine

Aarsland et al. et al 2005 J Clin Psych
<table>
<thead>
<tr>
<th>Treatment-emergent Adverse Event</th>
<th>No APD (N=357; PY = 557)</th>
<th>Concurrent APD (N=66; PY =74)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pt. with TEAE [1]</td>
<td>Proportion (%)</td>
</tr>
<tr>
<td>Death</td>
<td>25</td>
<td>7.0</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>99</td>
<td>27.7</td>
</tr>
<tr>
<td>Any APD Related Event [4]</td>
<td>194</td>
<td>54.3</td>
</tr>
<tr>
<td>CVA/Stroke Related Events</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Cognition Related Events</td>
<td>25</td>
<td>7.0</td>
</tr>
<tr>
<td>Fall Related Events</td>
<td>92</td>
<td>25.8</td>
</tr>
<tr>
<td>Infection Related Events</td>
<td>76</td>
<td>21.3</td>
</tr>
<tr>
<td>Oedema Related Events</td>
<td>23</td>
<td>6.4</td>
</tr>
</tbody>
</table>

### Cholinergic Function and Psychosis in DLB

<table>
<thead>
<tr>
<th>Visual Hallucinations</th>
<th>Yes (12)</th>
<th>No (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline Acetyl Transferase</td>
<td>$1.7\pm0.6$</td>
<td>$2.5\pm0.7^*$</td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>122.3±31.6</td>
<td>106.3±44.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delusions</th>
<th>Yes (14)</th>
<th>No (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline Acetyl Transferase</td>
<td>$1.9\pm0.6$</td>
<td>$1.9\pm0.8$</td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>131.0±31.4</td>
<td>93.5±27.7**</td>
</tr>
</tbody>
</table>

* $p=0.02$, ** $p=0.01$  
Ballard et al Annals of Neurology 2000
RCTs of Cholinesterase inhibitors in DLB

3 placebo controlled RCTs (McKeith et al 2000, Mori et al 2012, Ikeda et al 2015) all 120-150 participants over 5-6 months

– McKeith: Oral rivastigmine was well tolerated, with no worsening of parkinsonism and 77% of participants completed the trial. Significant benefit in cognition and non-significant trends favouring rivastigmine with respect to NPI4 (a measure combining delusions, visual hallucinations, depression and apathy) and global outcome.

– Mori: Oral donepezil, 3 doses (3-10mg). Significant benefits on the NPI 4 and suggested a specific benefit for the treatment of hallucinations and delusions in a secondary analysis. There was also a numerical benefit on the NPI for depression and anxiety with the 10mg dose.

– Ikeda: Less conclusive overall results, but confirmed a treatment effect of donepezil 10mg on psychosis (Ikeda et al 2015).

Primary efficacy results: NPI Items (1) Patients with Visual Hallucinations

<table>
<thead>
<tr>
<th>NPI Items</th>
<th>Rivastigmine (n = 110)</th>
<th>Placebo (n = 64)</th>
<th>ITT+RDO analysis *p &lt; 0.05 versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>-0.4</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>-1.2</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>-0.4</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>-0.6</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.8</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>Depression/Dysphoria</td>
<td>-0.8</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>Euphoria/Elation</td>
<td>0.0</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Apathy/Indifference</td>
<td>0.0</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.0</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Irritability/ Irritability</td>
<td>0.0</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>0.0</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>
RCTs of Cholinesterase Inhibitors in PDD

2 RCTs: Emre et al 2004, Dubois et al 2012

Emre N=541:
- Oral rivastigmine v placebo
- Significant but modest overall improvement in neuropsychiatric symptoms. No specific secondary analysis focussing on psychosis

Dubois N=550: Oral donepezil v placebo
- Less convincing overall benefits
- No specific benefits in neuropsychiatric symptoms

5HT Polymorphisms and Delusions in DLB Creese et al 2014 Am J Ger Psychiatry

- PARTICIPANTS:
  - A total of 187 individuals, recruited from centres in Norway, Sweden, and the United Kingdom were included in this study; 97 with clinically or neuropathologically diagnosed DLB/PDD and 90 cognitively normal individuals as a comparison group.

- MEASUREMENTS:
  - All participants with dementia underwent serial evaluation of neuropsychiatric symptoms to assess the presence of persistent delusions and hallucinations using the Columbia University Scale for Psychopathology in Alzheimer disease, the Neuropsychiatric Inventory, or the Present Behavioural Examination. Severity of cognitive impairment was measured using the Mini Mental State Examination (MMSE). Individuals were genotyped for the 5HTTLPR polymorphism.

- RESULTS:
  - Logistic regression demonstrated that homozygosity for the L/L genotype and lower MMSE were associated with an increased risk for delusions (odds ratio: 11.5 and 1.16, respectively). Neither was significantly associated with hallucinations.

- CONCLUSIONS:
  - This study is the first to demonstrate the 5HTTLPR polymorphism is associated with delusions in Lewy body dementias, with important implications regarding the mechanisms underlying this symptom across the AD/DLB/PDD spectrum. Further studies are warranted to investigate this relationship further and examine treatment opportunities.
-020 Study: Pimavanserin Demonstrated Highly Significant Antipsychotic Efficacy *(Lancet Feb 2014)*

SAPS-PD (primary endpoint)
(ITT, N=185; change from baseline)

-020 Study: Pimavanserin Improved Nighttime Sleep and Daytime Wakefulness

-020 Study: Pimavanserin Improved Nighttime Sleep and Daytime Wakefulness
### SAPS-PD Score and Change from Baseline Subgroup Analysis (OC) (ITT Analysis Set) Subgroup: Screening MMSE < 25

#### Change from Baseline to Day 43

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pimavanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td><strong>Mean (SE)</strong></td>
<td>-0.47 (1.89)</td>
<td>-7.11 (1.81)</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>2.00</td>
<td>-8.00</td>
</tr>
</tbody>
</table>

#### Treatment-emergent Adverse Event

<table>
<thead>
<tr>
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</tr>
<tr>
<td>Oedema Related Events</td>
<td>23</td>
<td>6.4</td>
</tr>
</tbody>
</table>
What is Mild Behavioural Impairment (MBI)?

**MCI**
- Impairments in cognition above normal but not making a significant impact to daily functioning
  - Amnestic MCI
  - Non-amnestic MCI

**MBI**
- Neurobehavioral syndrome
  - apathy/drive/motivation
  - mood/affect/anxiety
  - impulse control/agitation/reward
  - social appropriateness
  - thoughts/perception
Factor structure of the MBI checklist

Prevalence

MBI total scores categorised as followed (based on previous research)

- 0 = No MBI
- 1-8 = Intermediate MBI
- >8 = MBI

Prevalence of MBI in the general, cognitively normal population is 9.44% (95% CI: 8.88-10.02)
MBI is associated with cognitive decline over 1 year

- **Simple reaction time speed**
- **Digit vigilance speed**
- **Choice reaction time**

- **Simple RT Cov**
- **Digit vigilance Cov**
- **Choice RT Cov**

- **p=0.009**
- **p<0.0001**

**Genetics: Schizophrenia polygenic score associated with psychotic symptoms (N=3200)**

- SCZ PRS associated with psychotic experiences in cognitively normal older adults in the PROTECT cohort
- Consistent with our data showing polygenic score for SCZ associated with psychosis, particularly delusions (light grey bar), in AD

- Creese et al. (2019) bioRxiv
Conclusions

• Non-pharmacological interventions provide a safe and effective intervention for agitation

• Antipsychotics have a limited role in the short term management of severe aggression and possibly psychosis. The best evidence base is for short term treatment with risperidone for aggression. Longer term efficacy is limited and the serious adverse risks are considerable.

• Non drug treatments are safe and effective as alternatives to pharmacological treatment and to aid withdrawal of antipsychotics.

• Recent evidence reinforces the potential value of analgesia

• Pimavanserin appears to be a safe and effective treatment for psychosis in AD, PD and PD dementia

• Emerging evidence highlights potential efficacy of citalopram and dextromethorphan combinations for neuropsychiatric symptoms in AD

• Alpha adrenergic agents and 5HT6 agents are also emerging as candidate therapies for agitation

• Emerging evidence is highlighting importance of MBI and the potential opportunities for precision medicine
Practical & Ethical Considerations for Disclosure of Demetia-Related Diagnosis and Risk

Jason Karlawish, MD
Practical & Ethical Considerations for Disclosure of Dementia-Related Diagnosis and Risk

Jason Karlawish, MD
University of Pennsylvania
Penn Memory Center – www.pennmemorycenter.org
@jasonkarlawish

Disclosures

• Site PI for clinical trials jointly funded by NIA and Norvartis (Generation Program), and NIA and Lilly (A4 Study).
Outline of the talk

• Significance of the topic

• Overall key concepts and points
  • Respect for autonomy of persons with and without disabilities
  • Relationships among mood and well-being and cognitive symptoms
  • The stigmas of Alzheimer’s disease

• Points to consider with disclosing a diagnosis of dementia, MCI, or preclinical AD

Ethical & Practical Significance of Diagnostic Disclosure

• The professional responsibility to be a good teacher and to do no harm, and to remember how, in matters of taste there can be no disputes
• Autonomy as capacity, identity, privacy – a sense of self that is embedded in public and private relationships
• Knowledge of diagnosis allows people to make sense of symptoms, plan and organize their lives, and avoid harms from disabling cognitive impairments (fraud and exploitation, Rx errors, financial errors, etc...)
• Symptoms of cognitive impairment, depression and anxiety are key determinants of self-ratings of well-being – more so than the severity of functional and cognitive impairments
• The experience of stigma affects behavior; this further impairs sense of self (identity and capacity) and well-being
Overall Key Concepts & Points

• The decisional abilities of understanding and appreciation

The ability to understand

• Definition: Comprehend the meaning of information, know the facts

• Most common standard for competency used by the law and in theory of informed consent
The ability to understand

• “Can you tell me in your own words what are the [factual concept under assessment: risks / benefits / reasons to do / reasons not to do]?”

• Any parrot can repeat verbatim — you are looking for the person to paraphrase the meaning of the facts.

The ability to appreciate

• Definition: recognize how facts apply to you.
• You have the problem at hand (e.g. illness), evaluate its effects upon you (e.g. prognosis) and the effects of risks and benefits of options for taking care of the problem (e.g. loss of privacy in adult day activity program)
• Requires the person to assign values to info
  – Are the values coherent & consistent?
• Impaired by illnesses that distort the perception of reality
Comparison of AD patient and CG insight into patient diagnosis.

<table>
<thead>
<tr>
<th>Question</th>
<th>Patients (n=68)</th>
<th>Caregivers (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1) Do you have any problems with memory or thinking?</td>
<td>41 (60%)</td>
<td>27 (40%)</td>
</tr>
<tr>
<td></td>
<td>68 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>2) Will your memory or thinking problems get worse*</td>
<td>24 (35%)</td>
<td>44 (65%)</td>
</tr>
<tr>
<td></td>
<td>66 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>3) Do you have AD or dementia</td>
<td>23 (36%)</td>
<td>40 (63%)</td>
</tr>
<tr>
<td></td>
<td>66 (99%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Patients with mild to moderate AD (MMSE 30 to 12)

*Question asked of patients who responded yes to problems or mild problems with memory or thinking.

*1*Wording of questions changed for CGs. E.g. “Does your relative have problems with memory or thinking?”
Making an AD dementia treatment decision: appreciation of Rx risk & benefit

<table>
<thead>
<tr>
<th>Measure and score</th>
<th>AD Patients (n=48)</th>
<th>Caregivers (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciate risk</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>48%</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>13%</td>
</tr>
<tr>
<td>0</td>
<td>19</td>
<td>40%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.6 (0.7)</td>
<td>1.8 (0.5)</td>
</tr>
<tr>
<td>Appreciate benefit</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>33%</td>
</tr>
<tr>
<td>0</td>
<td>25</td>
<td>52%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.9 (0.9)</td>
<td>1.6 (0.6)</td>
</tr>
</tbody>
</table>

Overall Key Concepts & Points

• The decisional abilities of understanding and appreciation
• Persons with MCI and mild stage dementia do have symptoms of cognitive impairment, depression and anxiety that associate with well-being
Awareness of diagnosis correlates to impairments in quality of life (QOL)

- 259 older adults (MCI, AD, normal cognition)
- Patients were asked 3 diagnosis-related items
  - Do you have a diagnosis of ["Alzheimer’s disease" / "Mild Cognitive Impairment"]?
  - "What about a little bit of Alzheimer’s disease?"
  - "What about dementia?"

Awareness of diagnosis correlates to impairments in quality of life (QOL)


Patients with similar cognitive impairment

![Graph showing MoCA, MMSE, and CCS scores for different diagnosis groups](image-url)
Awareness of diagnosis correlates to impairments in mood and stress

Diagnosis awareness correlates to lower QOL and being unaware relates to more positive views of physical wellbeing
Self-reported cognitive symptoms relate to lower QOL

![Graph showing health-related quality of life (QOL) and cognitive difficulties across Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), and Normal Cognition (NC). The graph indicates that high cognitive difficulties are associated with lower QOL.]

AD = Alzheimer's Disease; MCI = Mild Cognitive Impairment; NC = Normal Cognition

Self-reported cognitive symptoms relate to higher stress

![Graph showing stress levels (PSS) across Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), and Normal Cognition (NC). The graph indicates that high cognitive difficulties are associated with higher stress levels.]

AD = Alzheimer's Disease; MCI = Mild Cognitive Impairment; NC = Normal Cognition

Self-reported cognitive symptoms relate to greater depression

Overall Key Concepts & Points

• The decisional abilities of understanding and appreciation
• Persons with MCI and mild stage dementia do have symptoms of depression and anxiety
• The stigmas of Alzheimer’s disease affect both persons with the disease and their caregivers
  • Self stigma
  • Public stigma
Perceived Stigma in Dementia: Patient Perspectives

Presented by:
Sandy Burgener, Ph.D., R.N., F.A.A.N.
Associate Professor Emerita
University of Illinois College of Nursing
Kathleen Buckwalter, Ph.D., R.N., F.A.A.N.
Professor, OUHSC College of Nursing

Qualitative Interview: Person with Memory Loss and Family Caregiver

• Data reported for n=22 persons with memory loss
• Interview: 11 questions reflecting common aspects of perceived stigma
• Data collected: Responses audio-recorded and handwritten
• Validity: Content analysis by 2 researchers and research assistant: agreement >95%

Sandy Burgener and colleagues. GSA 2018
Describe how you feel about talking about diagnosis with family & friends

- No problem: 58%:
  - "They (family/friends) should know"
  - "No reason to hide it"
  - "It feels better to talk about it"
- Some difficulty, have not disclosed: 42%:
  - "Don’t like the word, “dementia”, but “It’s better than cancer”.
  - Disclosed diagnosis to family and, “That’s where the stigma gets in trouble”
  - "I don’t want to talk about the future."
  - Fear disclosure would lead to their no longer being able to live alone and they would be sent to a facility.
  - In general, children seemed to have most difficulty accepting the diagnosis.

Sandy Burgener and colleagues. GSA 2018

Have you disclosed your diagnosis to family and/or friends

- No problem. Have disclosed diagnosis: 64%
  - Qualified response to “good friends only”.
  - Some note that most of their friends have the same problem.
  - The subject ‘doesn’t come up’, perhaps suggesting denial on everyone’s part.
- Have not disclosed: 36%
  - “Don’t feel it’s necessary to announce to everyone.”
  - Felt it wasn’t necessary or would tell if asked.
  - Another respondent wanted to “keep it private” to avoid jokes about “senior moments”.

Sandy Burgener and colleagues. GSA 2018
What about your diagnosis are you most uncomfortable discussing?

- Nothing: 56%
  - “Very comfortable with people in church.”
- Some discomfort: 44%
  - “I’m very uncomfortable. I don’t want anyone to know”
  - Becoming dependent/need help: “I was the one in charge.”
  - What the future will bring (unknown)
  - Feels like “I’m going backwards.”
  - People talk about him “like he’s not there. They forget that I still have feelings and can hear.”

Sandy Burgener and colleagues. GSA 2018

Do family members treat you differently since your diagnosis?

- No: 48%
  - No reports of being treated differently
- Yes: 52%
  - “My children treat me like a baby”
  - “They took all my credit cards away”
  - Some say their children avoid contact
  - “My son does not want to talk about my diagnosis”
  - My children say “I can’t do this or that”, “I shouldn’t live alone”

Sandy Burgener and colleagues. GSA 2018
How has your quality of life been affected by your memory loss and diagnosis?

- Not at all: 33%
  - “My quality of life is nice”
  - “I have fewer obligations”
- Negatively affected: 67%
  - Common themes: Becoming more dependent, loss of freedom, loss of driving privileges
  - Being dependent more difficult if “didn’t suit their personality” or “used to being in charge”
  - Worried about future (self, spouse, children) and health of spouse
  - “I become exasperated when I forget things”
  - “I’m afraid of making mistakes”

Sandy Burgener and colleagues. GSA 2018

Who are you most comfortable interacting with at present?

- Most common responses:
  - Family and close friends
  - Church associates
- Other responses:
  - Small groups, because “I don’t like to feel like an outcast”
  - People in their day care program
  - Activity groups (e.g. water aerobics)
  - Volunteer groups
  - Neighbors

Sandy Burgener and colleagues. GSA 2018
What changes have you made in your social networks?

- No changes in social networks: 47%
  - One person who claimed “no changes in social networks” also stated she “hasn’t been as social”.
- Changes in social networks: 53%
  - “I’m only liking to talk to friends on the phone now.”
  - Interact now when “people come to him”.
  - “Haven’t been as social.”
  - “I connect more with others with the same diagnosis; “I’m ‘hooked onto the goofy tree.’”
  - Common response: “I can’t drive now, so can’t get out as much.”

Sandy Burgener and colleagues. GSA 2018

What drives public stigma in response to a person with mild stage dementia?

Public stigma means…

“To what extent do you think that OTHER PEOPLE take the following actions towards Mr. Andrews…

… pity
… social distance

The key points of this study are…
Public stigma responses to a person with mild stage dementia are driven by the prospect of decline, the future is decline, not the cause (Alzheimer’s disease, TBI or no cause)

Public Stigma is affected by expectations of the future


What’s the experience of a biomarker based diagnosis of Alzheimer’s disease?
A majority of elevated participants reported that the amyloid PET scan result was unlike other medical test results.

- Many elevated participants (16 of 33 [48%]) felt that the amyloid PET scan result had unique implications for their sense of self:
  - “A colonoscopy isn’t going to change who I am . . . This is my brain involved.”
  - “[The result] speaks to who I am . . . My brain is a very critical part of me.”

- Some (9 of 33 [27%]) worried about the potential social consequences of the amyloid PET scan result:
  - “Losing your mental faculties is regarded by people differently than eye sight or hearing or anything else because they are seeing you as less of a person.”
  - “Alzheimer’s has a negative stigma to it.”
Learning an amyloid PET scan result—whether “elevated” or not—affects perceptions of memory.

**Elevated**
- A third (18 of 50 [36%]) reported having felt their memory was impaired prior to the amyloid PET scan. Learning their result validated their memory-related concerns.
- Another third (16 [32%]) reported becoming more aware of and more worried about memory issues after learning their result.
  - “I’m starting to question more whether these ‘senior moments’ are related to amyloid plaques.”

**Not-Elevated**
- Roughly half (16 of 30 [53%]) described re-interpreting memory lapses as normal aging.
  - “[The result] made me think that any memory problems I was having was just normal age related rather than . . . Alzheimer’s.”
- At T2, several expressed frustration because they lacked an explanation for perceived memory issues.
  - “[K]nowing that I don’t have any amyloids, I’m saying, ‘Well, what can it be?’”

Disclosure of an “elevated” result led to negative emotions, but not clinically significant levels of distress. A “not elevated” result led to relief.

**Elevated**
- Participants expressed diverse feelings about the future.
  - Bleak future (24%) – “I know . . . several people [with] Alzheimer’s . . . They were more like vegetables. I don’t look forward to that.”
  - Bright future (28%) – “I’m convinced they’ll find a cure.”
  - Future unknown (54%) – “Well, . . . there are just a lot of question marks.”

**Not-Elevated**
- Two-thirds (19 of 30 [63%]) reported their future was bright, two-thirds (19 [63%]) reported relief. Nearly half [13 [43%]] reported feeling both.
People will look at me differently

- I had thought about telling other people, but I didn't want to because I'm concerned that on some level when I share the results people will look at me differently. Then I have those senior moments they'll be saying, "Oh, she shouldn't be working, or she shouldn't be the chairperson of this group, or she shouldn't be in charge of this or that." I don't want people to think that. I want to go out in my own time. Do you know what I mean? [Female, aged 68. 0711]

Vision of future

- On decision to not tell her daughter her amyloid status:
  - I don't want to upset her. There's no need for her to know that I'm going to dwindle and decline before it becomes obvious and necessary... No, I have not shared it with my children. Oh, my God. [Female, aged 68. 0711]
Disclosing a diagnosis of dementia

- Review the patient’s chief complaint/concern; their answer to your question, “How can I help you? What’s the problem?”
- Have in hand your assessment of their mood, e.g. GDS
  - “Do you have more problems with memory than most?”
- Have in hand your assessment of their awareness of cognitive problems and subjective experience
  - “Are you having problems with your memory? Do they bother you? How do you cope with them?”
- The above assessments will assist in identifying a patient at risk of a catastrophic reaction, or who lacks insight
Disclosing a diagnosis of dementia

- Assess willingness to have their chief complaint answered, to learn the cause of their cognitive problems
  - “Would you like to learn what is the cause of your [chief complaint language]? Would you like to find out why [chief complaint]?”
- Ask what they think is the cause...
  - “What do you think is the cause of [patient’s chief complaint]?”
- Assess what they know about the common causes of memory loss, what is dementia, what is Alzheimer’s disease (or Lewy Body Disease, etc)
  - “One of the common causes of memory loss is Alzheimer’s disease. What do you know about that disease? One cause of memory loss is Lewy Body disease. What do you know about that disease?”
  - Ask if they would want to know if they had Alzheimer’s disease (or LBD, etc) and to explain their answer

Disclosing a diagnosis of dementia

- Disclose the diagnosis in plain English in a manner that incorporates what the person told you about what they know and what you then taught them
  - “Based on all the information I have about you, the most like cause of your [adapted language of chief complaint] is Alzheimer’s disease.”
- Assess how the person is feeling
  - “How are you feeling right now?”
  - Use silence, the three second pause...
- Promote the value of education and support for patients and caregivers
Disclosing a diagnosis of MCI

- Many of the same considerations as with dementia
- A picture may be worth a thousand words, that is a picture of the risk over time of conversion from MCI to dementia
- If you have obtained AD biomarkers that adds a wrinkle
  - Dementia and Alzheimer’s disease are tightly linked concepts
  - You ought to have assessed the desire to know the cause prior to ordering the biomarker test
  - A negative result can be more mysterious than a positive test result

Disclosing a diagnosis of preclinical AD

- Matters of capacity impairments as a result of cognitive impairments are not an issue
  - But the need to assess understanding and appreciation are
- The challenge here is that you are not answering a chief complaint, but instead you are, in a sense, creating a chief complaint.
  - Doctor as teacher – you are asking the person to grasp novel concepts (Ad as a biomarker diagnosis) and think about unusual, peculiar, topics
  - Prompt the person to think about their future self: impact on memory, sharing with others (family, friends, work), impact in plans (work, residence, leisure, money...)
Selected references


Caregiving in Dementia: Impact, Consequences & Opportunities

Mary Mittelman, DrPH
Caregiving in Dementia: Impact, Consequences & Opportunities

Mary S. Mittleman, DrPH
Research Professor
Psychiatry and Rehabilitation Medicine
NYU School of Medicine

The Burden of Care for People with Dementia

- Worldwide costs of dementia exceeded 1 percent of global GDP in 2015, at $818 billion, US.*
  - Direct medical costs are $159.2 billion, 19.5%
  - Societal care costs are $327.9 billion, 40.1%
  - Informal care costs are $330.8 billion, 40.4%
- Caregivers provide many hours of care for people with dementia **
  - Friends and family in the USA provided 18.6 billion hours of care a year, an average of 48 hours of care per week
  - Unpaid care in the US valued at $244 billion (at $13.11/hour).

* World Alzheimer Report 2015, prepared by Alzheimer’s Disease International
** Alzheimer's Association: 2020 Alzheimer's Disease Facts and Figures
Rationale for Interventions for Family Members of People with Dementia

- There is currently no drug to reverse or halt the progression of the disease
- Well-being of person with dementia dependent on caregiver well-being
- Family caregivers are at risk of stress, depression and physical illness
  - 59% rate emotional stress as high
  - 30-40% suffer from depression; 44% suffer from anxiety
  - More likely than other caregivers to say their health is fair or poor and to say their health was worse since they began caregiving
  - More likely than other caregivers to have high levels of stress hormones, reduced immune function, slow wound healing, new hypertension and new coronary heart disease
  - 56% report financial stress; 53% report family conflict
  - The physical and emotional impact of caregiving on family members of people with dementia is estimated to result in $11.8 billion in increased healthcare costs in the United States in 2018

Note, however, that 45% of caregivers reported caregiving was very rewarding.

Alzheimer’s Association: 2020 Alzheimer’s Disease Facts and Figures

Family Caregivers Differ in Many Ways

- Demographics
  - Gender, age, race, ethnicity, acculturation, income, urban or rural
- Availability of other family members
- Cultural characteristics
  - Norms about caregiving, involvement of other family members
- Relationship to the person with dementia
  - Adult child caregivers, spouse caregivers, other
- Competing roles
  - Work, other family members needing care, school
- Living arrangements
  - With the person with dementia or separately
  - Caring for a person with dementia at home, in someone else’s home, in residential care
Psychosocial Interventions for Caregivers

- Education
- Skills training
- Improving coping strategies
- Support
- Formal services (paid help, day care)
- Multicomponent interventions
- Interventions including the person with dementia with the family caregiver
  - Couples interventions
  - Enjoyable shared activities

Characteristics of Effective Psychosocial Interventions for Caregivers

- Family caregivers actively involved
- Tailored and flexible
- Enhance caregiver competency
- Offer emotional support
- Meet needs of both caregivers and people with dementia


Liew TM, Lee CS. Reappraising the efficacy and acceptability of multicomponent interventions for caregiver depression in dementia: The utility of network meta-analysis. Gerontologist 2019;59(4):e380-e392
What Made Us Think Support and Counseling Would Work?

Clinical experience at NYU
- 1980-85

The Stress Process Model
- 1990

The Stress Process Model

# The NYU Caregiver Intervention (NYUCI)

- A multi-component intervention including counseling, support and education
- Individualized to the needs of each family
- Emphasizes support for the primary family caregiver
- Includes the caregiver and other family members
- Available when needed and as long as needed
- Geared to the stage of dementia and the strengths and limitations of the person with dementia and the family caregivers.

## The Implementation Process

There are several components to the NYU Caregiver Intervention delivered at key times during the intervention process. This timeline illustrates the components and general timing of these components.

<table>
<thead>
<tr>
<th>Intake Assessment</th>
<th>First Individual Session</th>
<th>Family Counseling Sessions</th>
<th>Second Individual Session</th>
<th>*Follow-up Assessments</th>
<th>*Intervention support can continue as needed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intake Assessment</strong></td>
<td><strong>First Individual Session</strong></td>
<td><strong>Family Counseling Sessions</strong></td>
<td><strong>Second Individual Session</strong></td>
<td><strong>Follow-up Assessments</strong></td>
<td><strong>Intervention support can continue as needed</strong></td>
</tr>
</tbody>
</table>

*Initial contact can be email, call, or letter. Contact and screening can be two separate steps.

*The Assessment process changes when the person with AD enters a nursing home or dies.

**As determined by clinician or agency practice.*
Why is Individual Counseling Helpful to Family Caregivers?

- Counselor can tailor treatment to needs of individual caregiver
- Counseling can occur in a time and place convenient for caregiver
- Caregiver can establish a relationship with counselor that makes it possible to seek further advice and support when needed
- Caregiver becomes aware of need to involve other family members in patient care

Why is Family Counseling Helpful to Caregivers?

- Family members understand that person with dementia is ill
- Family members understand that person with dementia is no longer a sufficient source of social support for caregiver
- Family members learn about the needs of the primary caregiver
- The primary caregiver learns what kind of support other family members would like to give.
Why is Family Counseling Helpful to Caregivers?

- Family members can talk objectively about current problems
- Family conflict about caregiving can be resolved
- Communication among family members improves
- Family members are aware of counseling services.

Why are Support Groups Helpful to Caregivers?

- Caregivers can provide each other with ongoing emotional support
- Caregivers benefit from talking to others who have gone through similar experiences
- Caregivers can get information about how to solve the problems they are currently facing.
Why is Ad Hoc Counseling Helpful to Caregivers?

- Caregivers know that a counselor will be available when needed
- Caregivers can receive help without leaving home
- Effects of dementia change over course of illness; when a new problem arises, help is available
- In a crisis, there is someone to call.

NYU Caregiver Intervention
Original Randomized Controlled Trial Participants

- 406 spouse-caregivers of people with Alzheimer’s disease
- Enrolled from August 1987 to February 1997
- Followed for up to 18 years
- Living with the person with AD at intake
- At least 1 close relative in the area.

Results of Original RCT of NYUCI (1987-2010; n=406 spouse caregivers)

- The NYUCI Improved the well-being of family caregivers
  - Improved support for caregiver
  - Reduced caregiver depression
  - Reduced caregiver stress reaction to behavior of person with dementia
  - Improved caregiver self rated health
  - Reduced caregiver depressive symptoms and burden during the transition to a nursing home
  - Effects on depression persisted through bereavement

- Mediator of all other outcomes is social support
- Note: Fewer than 5% dropped out while the person with dementia was still living at home.

Time to Nursing Home Placement of People with Dementia is Delayed by Counseling and Support of Caregivers

The Minnesota Economic Model of Healthcare Cost
Savings with the NYU Caregiver Intervention

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>All Persons with Dementia</th>
<th>Residential Facility</th>
<th>Community Residence</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td>$288,964,986</td>
<td>$461,172,862</td>
<td>$172,207,876</td>
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<tr>
<td>10</td>
<td>$673,127,779</td>
<td>$1,072,761,818</td>
<td>$399,634,039</td>
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<tr>
<td>15</td>
<td><strong>$996,033,190</strong></td>
<td>$1,618,120,046</td>
<td>$622,086,856</td>
</tr>
</tbody>
</table>

NOTE: Direct costs include medical and facility costs. Residential facility includes assisted living facilities and nursing homes. All costs are in discounted 2011 dollars.

Long KH, Moriarty JP, Mittelman MS and Foldes SS. Potential Cost Savings With the NYU Caregiver Intervention in Minnesota. Health Affairs Health Affairs 2014 Apr: 596-604.

Next Steps: Dissemination, Translation, Extension

- Replicated randomized controlled trial in other communities
- Provided the NYUCI in community settings
- Expanded the evidence base for the NYUCI to adult child caregivers
- Developed and evaluated training in the NYUCI for providers
  - Published manual
  - Online training and certification
- Developed teleconferencing version of the NYUCI (now being evaluated)
- Used social support paradigm for other interventions
- Received funding from NY State to provide free supportive services for family caregivers in New York City
Enrollment in NYUCI Translations and New RCTs

Translations

<table>
<thead>
<tr>
<th>Years</th>
<th>Place</th>
<th>Screened</th>
<th>Enrolled</th>
<th>Dropped</th>
<th>Complete*</th>
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<tr>
<td>5.5</td>
<td>AsA Minnesota</td>
<td>206</td>
<td>238</td>
<td>37</td>
<td>137</td>
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<tr>
<td>3</td>
<td>AsA California</td>
<td>200</td>
<td>140</td>
<td>29</td>
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<tr>
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<td>AsA Georgia</td>
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<td>59</td>
<td>63</td>
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<tr>
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<td>AsA Florida</td>
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<td>173</td>
<td>16</td>
<td>103</td>
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<tr>
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<td>AsA Utah</td>
<td>150</td>
<td>109</td>
<td>16</td>
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<td>AsA Wisconsin</td>
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<td>VA Bedford MA</td>
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<td>13</td>
<td>3</td>
<td>10</td>
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<tr>
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<td>VA Manhattan NY</td>
<td>61</td>
<td>4</td>
<td>1</td>
<td>3</td>
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<td>EmblemHealth</td>
<td>71</td>
<td>15</td>
<td>6</td>
<td>1</td>
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<td>1</td>
<td>U Queensland, Australia</td>
<td>7</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1500</td>
<td>936</td>
<td>186</td>
<td>565</td>
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</table>

New RCTs

<table>
<thead>
<tr>
<th>Years</th>
<th>Place</th>
<th>Screened</th>
<th>Enrolled</th>
<th>Dropped</th>
<th>Complete*</th>
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<tbody>
<tr>
<td>3</td>
<td>US, UK and Australia</td>
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<td>158</td>
<td>32</td>
<td>135</td>
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<td>Washington Heights</td>
<td>282</td>
<td>139</td>
<td>23</td>
<td>118</td>
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<tr>
<td>2</td>
<td>Israel</td>
<td>137</td>
<td>101</td>
<td>21</td>
<td>80</td>
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<td>5</td>
<td>Minnesota NYUCI-AC</td>
<td>126</td>
<td>107</td>
<td>1</td>
<td>106</td>
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<tr>
<td>0</td>
<td>Paris, France</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>64+</td>
<td>506</td>
<td>77</td>
<td>439</td>
</tr>
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</table>

* Complete means at least one follow-up assessment completed

Evidence-based Interventions for People with Dementia together with their Family Caregivers Studied at NYU

Couples Counseling

Museum Experiences

The Unforgettables Chorus
Couples Counseling: Rationale

- Focus on the couple as a unit when the person with AD is still in the mild stage of dementia
- Provides a supportive environment in which the couple can share their emotional reactions to the diagnosis
- Help them address their current reactions, and consider future plans and needs

The NYU Couples Counseling Intervention

- Intervention: Six counseling sessions for each couple within a two-month period plus “ad hoc” counseling
- Study: Randomized wait-list control trial (All participants receive “ad hoc” counseling)
  - 41 couples
  - Comprehensive written assessment at baseline, 2- and 4-month follow-ups
- Results
  - Significant improvement in relationships at the first follow-up maintained at the second follow-up.
  - Goals achieved (goal attainment scaling)
  - Improved communication observed and reported.
The Unforgettables: A Chorus for People with Dementia with their Family Members

- Few pleasurable activities available for this population.
- We observed that participating together in a museum program had positive effects on both people with dementia and their family members.
- We thought that a music-based program might yield even greater benefits.
- A chorus may provide an opportunity for people in the early and moderate stages of dementia and their family caregivers to share a stimulating and social activity that can improve their quality of life.
- To our knowledge, when I founded the chorus in 2011 there were no rigorous studies of participating in musical activities for people with dementia together with their family members.

Eligibility Criteria

- People with dementia in the early to middle stage
- A caregiver/family member who will commit to attending all the rehearsals and the concert.
### Quantitative Results: Caregiver (n=10)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time 1 Mean (SD)</th>
<th>Time 2 Mean (SD)</th>
<th>Test statistic, p value</th>
<th>Effect size Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-8 (Quality of Life)</td>
<td>15.10 (4.79)</td>
<td>13.30 (4.27)</td>
<td>t=1.42, NS</td>
<td>0.45</td>
</tr>
<tr>
<td>Social Support</td>
<td>56.80 (12.93)</td>
<td>61.20 (12.99)</td>
<td>t=1.32, NS</td>
<td>0.42</td>
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<tr>
<td>Depression</td>
<td>13.40 (1.65)</td>
<td>13.30 (1.89)</td>
<td>t=0.17, NS</td>
<td>0.05</td>
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<tr>
<td>Communication with person with dementia</td>
<td>41.50 (3.44)</td>
<td>41.60 (3.66)</td>
<td>t=0.93, NS</td>
<td>0.29</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>33.40 (3.31)</td>
<td>35.10 (3.57)</td>
<td>t=2.15, p=0.060</td>
<td>0.68</td>
</tr>
</tbody>
</table>


### Quantitative Results: Person with Dementia (n=10)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time 1 Mean (SD)</th>
<th>Time 2 Mean (SD)</th>
<th>Test statistic, p value</th>
<th>Effect size Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL-AD (Quality of life)</td>
<td>35.60 (5.4)</td>
<td>38.90 (5.4)</td>
<td>t=2.28, p=0.048</td>
<td>0.72</td>
</tr>
<tr>
<td>DEMQoL (Quality of life)</td>
<td>93.0 (9.39)</td>
<td>98.1 (9.48)</td>
<td>t=1.85, p=0.098</td>
<td>0.59</td>
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<tr>
<td>Communication with Cg</td>
<td>39.78 (5.14)</td>
<td>43.89 (6.39)</td>
<td>t=1.97, p=0.085</td>
<td>0.62</td>
</tr>
<tr>
<td>Self Esteem</td>
<td>29.50 (3.50)</td>
<td>30.90 (4.95)</td>
<td>t=1.00, p=0.34, NS</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Observations

- Participants attended rehearsals in spite of harsh weather conditions
- People in the middle stage, as well the early stage, seemed to enjoy themselves and learn from the experience, although they could not respond to the questionnaires
- Participants were so eager to continue the chorus that they have been contributing to its costs since the pilot study ended in September 2011
- Caregivers and people with dementia from all cultures and backgrounds can support each other and bring joy to the community
- There are now two Unforgettables choruses in New York City, rehearsing weekly online. Those who moved away have rejoined – there are 100 people rehearsing!

THE NYU LANGONE ALZHEIMER’S DISEASE AND RELATED DISORDERS FAMILY SUPPORT PROGRAM

An Opportunity to Provide Comprehensive Counseling and Support to Dementia Caregivers in New York City

One of Ten Family Support Programs Funded by New York State in 2016
NYU Family Support Program

- Consultation and support personalized to the needs of each caregiver
  - Individual consultation
  - Family consultation
- Ongoing support in person, by telephone, video conferencing and email
- Consistent access to care team throughout the course of caregiving
- Education about caregiving and dementia
- Referral to community services that can address the often complex needs of caregivers
- Unique features: A Buddy Program for people with dementia, “A Place for Us” – a community program for people in the early stage of dementia provide respite for caregivers; supportive workshops in music, creative writing and weaving for caregivers,
- No cost to families, except for reimbursable outside services to which we make referrals.

Funded by New York State Department of Health: January 1, 2016 – December 31, 2020

Schematic of Structure for Providing Caregiver Services

Notes: Blue shapes indicate service provided directly by NYU; Green shape is service provided by subcontractor to NYU; Yellow shapes provided by others. Blue arrow indicates caregiver referral. Red arrow indicates patient referral.

NYU Dementia Patient Services (CEAD, Barlow, ADC, Geriatric Medicine) Diagnosis, evaluation and treatment Clinical trials

NYU Social Workers (LCSWs)

NYU Community Health Reps

NYU Family Support Program Administration

Reimbursable Interventions
SkillsCare Psychotherapy

Nonreimbursable Interventions
Care consultation Family Consultation Evidence based Interventions NYUCI

Education
Caregiver and community

CaringKind
Respite connection and scholarships Support groups

New Models of Respite for Caregivers of People in the Early Stage of Dementia Buddy Program Photo workshops A Place for Us Music Ensemble

Community Services
NYC OFTA Caregiver Services Programs: local services, support groups, Medicaid apps, etc. Meals on Wheels, etc.
The NYU Family Support Program During COVID-19

- The need is greater than ever
  - Increased stress caused by worry about vulnerability to the disease and risk of serious illness and death for self and person with dementia
  - Physically isolated either with the person with dementia or away
  - Unable or unwilling to have family or paid help in their homes
  - Respite not available - day care centers and senior centers are closed
  - Caregivers of people in residential care are not able to see their relatives or help with their daily activities.

- The Family Support Program provides almost all its activities online or by phone
  - Individual and family counseling
  - Support groups, including a new group for “Caring from Afar”
  - Workshops and seminars
  - A Place For Us now more frequent than before
  - Museum tours and memory cafes for people with dementia with their family members every other week.

A Place for Us Dress-Up Party Online – May 2020
Some Thoughts about the Implications of My Work

• The public and the medical professional should reframe the meaning of care in dementia.

• In our culture, treatment of the sick is the job of physicians and other medical professionals.

• A more holistic approach has demonstrated benefits in dementia.

• Social support is essential

• Dementia is one example, but what we have learned can be useful for treatment of almost all diseases, even when there are available drugs.

To learn more about the NYU Family Support Program, call 646-754-2277 or visit our website at: 
http://nyulangone.org/memorydisordersupport

To contact:
Mary Mittelman
E-Mail: mary.mittelman@nyumc.org
Community Advocacy and Activism For Dementias

Katie Brandt, MM
A Community-Based Model for Caregiver Support:

The Power of Advocacy and Community Events

KATIE BRANDT, MM
DIRECTOR OF CAREGIVER SUPPORT SERVICES AND PUBLIC RELATIONS
FRONOTEMPORAL DISORDERS UNIT
MASSACHUSETTS GENERAL HOSPITAL
WWW.FTD-BOSTON.ORG

Disclosures

No Disclosures
Where We Are Today

There are no approved treatments to slow or stop the degeneration process.

Today we have a cure for the isolation and loneliness that comes with a diagnosis.

Caregiver support is treatment for dementia.

Communication

**Connections** through a website or social media are ways for families to learn more about the programs and services you offer. It can help them to feel connected to you between appointments.

**Educate** families through blog posts, twitter chats and publications about upcoming events, novel therapeutic approaches or disease information.

**Support** families through an online support group, publication of caregiver and patient voices or notifications of community events.
Community Events

Support can happen for families through established community agencies (Alzheimer’s Association, senior center, library) and they can also be created for specific cohorts of patients.

Fundraisers can be a powerful outlet for families and community members who are looking for a place to focus their energy while bringing joy into their lives in a safe way.

Advocacy has the powerful ability to shine a light on the lived experience, even the little known experience, as a way to educate through empathy.

Advocacy

Advocacy is an activity by an individual or group which aims to influence decisions within political, economic and social systems and institutions.

An advocate is someone who provides advocacy support to people who need it.

Activism consists of efforts to promote, impede, or direct social, political, economic or environmental reform with the desire to make improvements in society. Activism may range from writing letters to hosting rallies and utilizing social media to facilitate collective action.
Micro and Macro-Level Advocacy Applications

**Being a Voice for Another**
Family caregivers advocate for loved ones for care and resources every day

**Impacting Public Policy**
National Alzheimer's Project Act (NAPA) Advisory Council on Alzheimer’s Research, Care and Services

**Leveraging Partnerships**
Alzheimer’s Association, Association for Frontotemporal Degeneration, Cure PSP, Lewy Body Dementia Association, etc.

Advocacy can be virtual!


---

How to Integrate Clinic and Community: The Three E’s

**Establish** Opportunities for Advocacy and Volunteerism
- Identify specialized skill sets
- Create a range of micro and macro-level events
- Seek partnerships for success

**Engage** Patients and Families Outside of Clinic
- Bringing clinic to community
- Offer both passive and active engagement

**Empower** Patients and Families
- Opportunities for new titles and roles
- Leadership and participatory roles
- Nametags and business cards provide legitimacy
Research

Recognizing the connection between grassroots community initiatives and advancements in research helps families feel like they are part of the search for a cure.

Acknowledging the role of the Citizen Scientist and the Community Ambassador gives prestige and purpose to a role that is chosen.

Explaining to families that all research doesn't happen under a microscope. By explaining the importance of participation in natural history studies and caregiver research, we can give our families hope that the cure of tomorrow is not so far from the care of today.

Where life ends, love does not.
Diagnosis: Superhero

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Bonnie Wong, PhD/ABPP-CN
Alzheimer’s Association
Association for Frontotemporal Degeneration
Boston-area FTD Support Group
MassBio
National Alzheimer’s Project Act (NAPA) Advisory Council
Persons Living With A Diagnosis, Care Partners & Family
Members in our Dementia Community
Chronic Traumatic Encephalopathy (CTE) & Dementia

Robert A. Stern, PhD
Disclosures

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• Biogen (Alzheimer’s Advisory Board)
• King Devick Technologies (Board of Directors)
• National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation (Medical Science Committee)
• Psychological Assessment Resources, Inc. (Royalties for Published Tests)
• Powering Precision Health (Advisory Board)
• Funding from NIH, DoD, Concussion Legacy Foundation
Concussion:

- Results from linear, lateral, and rotational forces on the brain; rotational likely to cause most shearing
Concussion

- **Definition** (1 of ~150 published):
  - Broglio, Cantu, Gioia, et al., 2014

- Concussions occur from forces applied directly or indirectly to the skull that result in the rapid acceleration and deceleration of the brain.

- The sudden change in cerebral velocity elicits neuronal shearing, which produces changes in ionic balance and metabolism.

- When accompanied by clinical signs and symptoms, changes at the cellular level are commonly referred to as mild traumatic brain injury, or concussion.
Neurometabolic Cascade of Concussion (Giza & Hovda, 2001)

1. Widespread depolarization and neurotransmitter release

2. Potassium efflux

3. Calcium in the cell impairs ATP production in mitochondria, worsening energy crisis

4. Calcium influx also causes axonal swelling and decreased axonal function

SYNAPSE

Ca$_{2+}$

K$^+$

Glut

Glut
Concussion

• Does not require a loss of consciousness; Less Than 10%
• Does require symptoms
• No “structural” abnormalities seen on routine neuroimaging (CT, MRI)
• Diffusion Tensor Imaging (DTI) and other MRI methodologies may detect changes, including diffuse axonal injury
• New research with blood and saliva biomarkers (microRNA, S100B, GFAP, Tau) looks promising
• Helmets do not protect the brain from concussion; helmets prevent skull fractures
Great Strides in Sports Concussion Prevention, Awareness, Detection, and Management
Disclosures - Continued

• I know very little about concussions!
  – My area of expertise is “neurodegenerative disease.”

• I’m not very concerned about concussions when it comes to later life neurodegenerative disease
Repetitive Head Impacts

Moderate-to-Severe TBI

Concussion

Subconcussive Trauma
Subconcussive Impacts

• Impact to brain with adequate force to have an effect on neuronal functioning
  – including: neurometabolic cascade, neuroimmune response, breakdown of blood brain barrier, release of toxic proteins
• BUT… No Immediate Symptoms of Concussion
• Some sports and positions very prone
Measuring Subconcussive Impacts

- Using helmet accelerometers, high school football players received an average of 652 hits to head in excess of 15 g of force. One player = 2,235 hits! (Broglio et al., 2011). Studies with college players higher.

- Growing evidence that even after one season, repetitive subconcussive trauma can lead to cognitive, physiological, metabolic, and structural changes.
  - Abbas et al., 2015; Davenport et al., 2014; Koerte et al., 2012, 2014; McAllister et al., 2012; Pasternack et al., 2014; Robinson et al., 2015; Breedlove et al., 2012; Poole et al., 2015; Stewart et al., 2017; Slobounov et al., 2017; Penchal et al., 2018; Jang et al., 2019; Di Virgilio et al., 2019; Papa et al., 2019; Hirad et al., 2019; O’Keefe et al., 2020; and more!
A common neural signature of brain injury in concussion and subconcussion

Adnan A. Hirad¹,², Jeffrey J. Bazarian¹, Kian Merchant-Borna¹, Frank E. Garcea³,⁴, Sarah Hellbronner⁵,⁶, David Paul⁷, Eric B. Hintz⁸, Edwin van Wijngaarden⁹, Giovanni Schifitto¹⁰, David W. Wright¹¹, Tamara R. Espinoza¹¹, Bradford Z. Mahon¹²,¹³,¹⁴,*

Repetitive Subconcussive Impacts in College
Microstructural alterations of cortical and deep gray matter over a season of high school football revealed by diffusion kurtosis imaging

Nan-Jie Gong, Samuel Kuzminski, Michael Clark, Melissa Fraser, Mark Sundman, Kevin Guskiewicz, Jeffrey R. Petrella, Chunlei Liu
Repetitive Subconcussive Impacts in Youth

Subconcussive Head Impact Exposure and White Matter Tract Changes over a Single Season of Youth Football

Naeim Bahrami, PhD
Dev Sharma, PhD
Scott Rosenthal, BS
Elizabeth M. Davenport, PhD
Jillian E. Urban, PhD
Benjamin Wagner, BS
Youngkyoo Jung, PhD
Christopher G. Vaughan, PsyD
Gerard A. Gioia, PhD
Joel D. Stitzel, PhD
Christopher T. Whittle, MD, PhD, MHA
Joseph A. Maldjian, MD

Radiology: Volume 281: Number 3—December 2016
Subconcussive Impacts: Blood Biomarkers

Association of Increased Serum S100B Levels With High School Football Subconcussive Head Impacts

Fluctuations in blood biomarkers of head trauma in NCAA football athletes over the course of a season

Evaluating glial and neuronal blood biomarkers GFAP and UCH-L1 as gradients of brain injury in concussive, subconcussive and non-concussive trauma: a prospective cohort study

NFL blood levels are moderated by subconcussive impacts in a cohort of college football players
Repetitive Subconcussive Impacts: Long-Term Consequences
Cumulative Head Impact Exposure

• Estimation of an individual’s cumulative head impact exposure through *Exposure Science* modeling

• *Cumulative Head Impact Index (CHII)*
  – Based on data from previously published studies of youth, high school, and college football players with helmet accelerometers
  – Average hits per season by position and level of play
• 93 former high school (n = 17) and college (n = 76) football players from the BU LEGEND Study; no other contact sport; mean age = 47.3

• **Dose-Response relationship** between cumulative head impacts and later life cognitive, mood, and behavioral impairment

• With each additional 1000 hits, the risk of later life impairments increased significantly
Montenigro et al (2017)
Risk of Clinically Elevated Depression

![Graph showing risk of depression across different CHII dose ranges with p-value < 0.0001 and threshold at 1801 dose.]
Montenigro et al (2016)
*Risk of Clinically Relevant Cognitive Impairment*
Fluid and Neuroimaging Biomarker Correlates of Estimated Cumulative Head Impact Exposure
More RHI Exposure Significantly Associated with Higher Plasma Total Tau $(p = 0.014)$
More RHI Exposure Significantly Associated with Higher CSF Total Tau (p = 0.024)
More RHI Exposure Significantly Associated with MRI White Matter Signal Abnormality (WMSA) Volume (p=.021)
Do Repetitive Concussive and Subconcussive Head Impacts Lead to Neurodegeneration?
Long-Term Consequences of Repetitive Head Impacts in Boxing

- **Punch Drunk:**
  - Martland, *JAMA*. 1928
  - “goofy,” “slug-nutty”
  - Later on, “institutionalized in an asylum”...for dementia

- **Dementia Pugilistica:**
  - Millspaugh, 1937

- **Chronic Traumatic Encephalopathy:**
  - Bowman & Blau, 1940; Critchley, 1957
Long-Term Consequences of Repetitive Head Impacts in American Football

- Mike Webster (who died in 2002) was the First American Football Player with Neuropathologically Diagnosed Chronic Traumatic Encephalopathy
  - Omalu et al., 2005
  - Began increased media attention to CTE
Chronic Traumatic Encephalopathy
same as Dementia Pugilistica

- Neurodegenerative disease, similar to Alzheimer’s disease but it is a unique disease
- Associated with a history of repetitive head impacts, including concussions and subconcussive trauma
- The repetitive trauma appears to start a cascade of events in the brain that eventually leads to progressive destruction of brain tissue
Neuropathology of CTE

• Like Alzheimer’s and other neurodegenerative diseases, CTE can currently only be diagnosed through postmortem examination of brain tissue.

• Neuropathology of CTE first described by Corsellis et al., in 1973 – “The Aftermath of Boxing”

• Dr. Ann McKee at BU has examined more brains with CTE than any other neuropathologist; BU has the largest CTE brain bank (VA-BU-CLF Brain Bank) in the world – >500 brains examined.
CTE Neuropathology

- Characterized by abundance of an abnormal form of tau protein (hyperphosphorylated tau or p-tau)
Microtubule-Associated Protein Tau

Healthy Neuron

CTE Neuron

- Healthy Neuron: Microtubules are intact, with stabilizing Tau molecules.
- CTE Neuron: Microtubules are disintegrating, with disintegrating microtubules and tangled clumps of Tau proteins.
Unique Pathology of CTE *Pathognomonic Lesions*

1. Perivascular foci of p-tau immunoreactive neurofibrillary tangles, astrocytes and neurites in the neocortex
2. Irregular distribution of p-tau lesions at the depths of cerebral sulci
3. NFTs located preferentially in the superficial layers of cortex (a feature often most pronounced in temporal lobe)
<table>
<thead>
<tr>
<th>Stage of Tau Pathology</th>
<th>Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>mean age: 28.3 ± 13 years</td>
</tr>
<tr>
<td>Stage II</td>
<td>mean age: 44.3 ± 16 years</td>
</tr>
<tr>
<td>Stage III</td>
<td>mean age: 56.0 ± 14 years</td>
</tr>
<tr>
<td>Stage IV</td>
<td>mean age: 77.4 ± 12 years</td>
</tr>
</tbody>
</table>
Pathologically CTE p-tau is distinct from AD
• CTE is a disease
• It is unique from other tauopathies (e.g., AD, PSP, CBD, FTLD, ARTAG) or normal aging (PART)
• It is only seen in people with a history of previous brain trauma, usually repetitive
Scientific Growth versus Media and Public Attention

• Dr. McKee’s groundbreaking work on the neuropathology of CTE has had a tremendous impact on public awareness of CTE and the long-term consequences of repetitive brain trauma, especially in football.
Number of Publications in PubMed with “Chronic Traumatic Encephalopathy” as Keyword
Total = 748

Number of Publications
Year of Publications

216 Projected for 2020 based on 36 in first two months
Is CTE a Unique Neuropathological Disease?
The CTE fold supports the hypothesis that conformers of filamentous tau define distinct tauopathies. We previously showed that tau filaments from Alzheimer’s and Pick’s diseases adopt different folds\(^{12-14}\), which establishes the existence of molecular conformers. In contrast to Pick’s disease, filaments in CTE have the same composition of tau isoforms as in Alzheimer’s disease, showing that the same protein sequences can also form different conformers or aggregate strains. The results presented here provide a unifying neuropathological criterion, and confirm that dementia pugilistica and CTE are the same disease. The structures will aid in the design of specific tracer compounds, which are crucial for early diagnosis and thus allow for timely therapeutic intervention.
Not Just p-Tau

- As with most neurodegenerative diseases, in later stages of the disease, it is not uncommon to have multiple proteinopathies.
- From Mez et al., JAMA 2017:

<table>
<thead>
<tr>
<th>CTE Stage</th>
<th>No. of Brain Donors</th>
<th>Age at Death, Median (IQR), y</th>
<th>Neuropathological Features, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aβ</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>36 (25-56)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>49 (29-65)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>67 (57-78)</td>
<td>45 (59)</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>76 (69-82)</td>
<td>52 (91)</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>67 (53-78)</td>
<td>107 (61)</td>
</tr>
</tbody>
</table>
Heterogeneous cohort of deceased athletes and military veterans with neuropathologically diagnosed CTE ($n = 114$, mean age at death = 60)

- Aβ deposition, either as diffuse or neuritic plaques, was present in 52% of CTE subjects
- Aβ deposition in CTE occurred at accelerated rate and with altered dynamics in CTE compared to a normal aging population (OR = 3.8, $p < 0.001$)
- Clear pathological and clinical dichotomy between CTE cases with/without Aβ plaques
  - Aβ deposition significantly associated with the presence of the APOE ε4 allele ($p = 0.035$), older age at symptom onset ($p < 0.001$), and older age at death ($p < 0.001$)
  - Controlling for age, neuritic plaques were significantly associated with increased CTE tauopathy stage ($\beta = 2.43$, $p = 0.018$), co-morbid Lewy body disease (OR = 5.01, $p = 0.009$), and dementia (OR = 4.45, $p = 0.012$).
• 269 Contact Sports Athletes (UNITE Study)
• 164 Community Cohort (Framingham Heart Study)
• 261 Boston University Alzheimer Disease Center
• Individuals with CTE and LBD were more likely to have b-amyloid deposition, dementia, and parkinsonism than CTE alone (p<0.05)
• Clinically, dementia was significantly associated with neocortical LBD, CTE stage, and AD; parkinsonism associated with LBD pathology but not CTE stage
• Contact sports participation may increase risk of developing neocortical LBD, and increased LBD frequency may partially explain extrapyramidal motor symptoms sometimes observed in CTE.
In a convenience sample of 202 American football players at all levels of play, whose brains were donated for research:

- 87% were diagnosed with CTE using strictly defined criteria
- 3 of 14 high school football players (21%)
- 48 of 53 college football players (91%)
- 110 of 111 NFL players (99%)
BU-VA-CLF Brain Bank has a **Biased** Sample Based on Who Donates Brain Tissue

- The goal is NOT to examine the epidemiology of CTE
- The goal is to describe the neuropathology and clinico-pathological correlations
- Need for a large-scale brain bank (not focused on CTE or athletes, etc.) to examine CTE neuropathology
• Mayo Clinic Brain Bank (Dickson)
• 1700 male brains examined for CTE neuropathology
• CTE found in 21 brains, all were amateur contact sport athletes (primarily football)
• ~1/3 of contact sport athletes in the brain bank had changes of CTE
• CTE not seen in matched controls (no contact sport Hx)
• CTE not seen in brains of people with single TBI
The More Exposure to Repetitive Head Impacts, The More Risk for CTE
• 266 deceased football players from the VA-BU-CLF and Framingham Heart Study Brain Banks
• More years of football played was associated with having CTE
• The odds of having CTE double every 2.6 yr of football played
• Multiple simulation analyses conducted to address selection biases: even under conditions of extreme selection into the brain bank, the OR for the relationships between duration played and CTE outcomes had consistent magnitudes
CTE Does NOT Occur Without History of Repetitive Head Impact Exposure
Aging-Related Tau Astrogliopathy
ARTAG

- A small number of recent papers have argued that “CTE” pathology is found in individuals without any history of repetitive brain trauma (Ling et al., 2015; Puvenna et al., 2016; Iverson et al., 2019)
- In all cases, diagnostic CTE neuropathology features were NOT found and were confused with ARTAG
ARTAG Misinterpreted as CTE
from McKee, *Seminars in Neurology*, in press

10-μm paraffin-embedded tissue sections immunostained for phosphorylated tau (AT8) (Pierce Endogen). **A,B.** P-tau immunoreactive thorn-shaped astrocytes found at glial limitans at the depths of the sulcus are features of ARTAG that may be found in CTE, but are not diagnostic for CTE, **A.** magnification x 200, **B.** X 100. **C.** Perivascular clusters of p-tau positive astrocytes surrounding thin-walled vessel in the superficial regions of the sulcal depths also represent ARTAG, magnification x 200. **D,E,F.** Common forms of perivascular p-tau immunoreactive astrocytic pathology (ARTAG) in white matter, magnification x 200.
Abstract

This study determined the prevalence of chronic traumatic encephalopathy (CTE) and cortical aging-related tau astrogliopathy (ARTAG) in a European community-based population (n = 310). The frontal, parietal, and temporal cortices, representing initial stages of CTE were assessed. No case fulfilling CTE consensus criteria was found. However, isolated astroglial or neuronal tau pathologies were recognized in the depths of cortical sulci (<2%). A single case (female, 85 years) without a history of traumatic brain injury (TBI) showed combined tau-immunoreactive features confined to frontal sulci without perivascular accumulation. Another 24 cases had single tau pathologies in cortical sulci. ARTAG was identified in 117 cases (38%), with a similar regional prevalence. Gray matter ARTAG was the most common followed by subpial, white matter, and perivascular. The presence of any type of ARTAG was strongly associated with having another type of ARTAG in the same region (p < 0.05). In summary, although isolated tau pathologies in the depths of cortical sulci were identified, no case fulfilled diagnostic criteria of CTE. Cortical ARTAG in this population is common and contrasts the high prevalence of CTE in individuals with repeated mild TBI. ARTAG in isolation might not be indicative of CTE although commonalities in pathogenesis should be considered.
well-characterized cohort of AD cases enriched for atypical presentations. In our cohort, ARTAG pathology is frequent and correlates with older age and higher Braak stage. ARTAG subtypes exhibit distinct distribution patterns with subpial and subependymal deposition occurring in the amygdala, while white and grey matter astrocytic deposition are distributed throughout cortical regions. However, ARTAG pathology is equally prevalent in cases with typical and atypical clinical presentations.

patency into the white matter and categorized as subependymal ARTAG in our study. Similar to Forrest et al, sulcal accentuation of TSA pathology was also identified in our cohort, albeit at higher frequencies (12% overall compared with <2% in their study) and we did not find any pathology fulfilling CTE consensus criteria (39).
How Does CTE Tau Deposition Begin?

• Why sulcal depths?
Figure 5. Water Hammer Illustration of the mechanism whereby traumatic impact to the skull results in transmission of force to the cerebrospinal fluid (CSF). As the elastic brain impacts the non-compressible calvarium, the non-compressible CSF is driven into the sulci. The base of the sulcus receives the major force of the CSF impulse. The alignment of the axons in the gray matter at the base of the sulcus is oriented parallel to the vector force while the U fiber bundles at the base are oriented perpendicular to the vector. Differing rigidity features of the gray and white matter result in shearing at that interface. The areas of red intensity at the base of the sulci represent sites of major force dissipation. The intense linear red at the interface between the gray matter and the U fiber bundles represents areas of bleeds from vascular injury.
Computational results for American football. (A) Time history of head accelerations; (B) strain and strain rate contours within the brain; (C) the predicted strain and strain rate measured at the grey-white matter interface and overlaid onto an ‘inflated’ brain image (gyral regions light grey and sulcal dark grey)

How Does CTE Tau Deposition Begin?

• Very little really known, but initial evidence suggesting the following:
  – Meningeal vascular injury
  – Arterioles are damaged at depths of sulci
  – p-tau accumulates primarily in neurons surrounding the arterioles
  – Astrocytes around arterioles mostly disappear, but some accumulate p-tau
  – **Loss of blood-brain barrier integrity**; leakage of proteins
  – **Microglial inflammation** leads to further tau accumulation
  – Breakdown of glymphatic clearance system of the brain

• Repetitive nature of injuries overwhelm the natural clearance systems
  – e.g., Russo et al., *Nature Immunology*, 19:442–452
Hypothetical Mechanism of Blood-Brain Barrier Involvement in Initiation of Pathogenesis of Neurodegeneration

Single severe TBI
Mild repetitive TBI

Modifying factors:
APOE*ε4, Age, CVD

Chronic neurodegenerative dementia syndrome

Alzheimer’s disease
Chronic traumatic encephalopathy

Chronic neuropathology:
- Increased concentration of Aβ & tau in brain interstitial fluid/intracellular
- Aβ deposition in vasculature (CAA) and parenchyma (plaques)
- p-tau pathology (neuronal, glial), cell dysfunction and death

Chronic neuroinflammation, cognitive impairment, dementia

Acute-to-chronic pathophysiology:
- Leakage of serum proteins into brain parenchyma
- Perivascular inflammation
- Impaired clearance of Aβ and p-tau
- Aβ and p-tau accumulation and aggregation
- Impaired cerebral blood flow, brain ischemia

Altered BBB components:
- Endothelium
- Junctional proteins
- Basement membranes
- Pericytes
- Astrocytes
- Transporters
- Cell-cell signaling

From Abrahamson and Ikonomovic (2020) Exp. Neurology
How Does CTE p-Tau Spread?  
Seeding and Propagation

"Prion" spread

Woerman, AL; Aoyagi, A; Patel, S; Kazmi, SA; Lobach, I; Grinberg, LT; McKee, AC; Seeley, WW; Olson, SH; Prusiner, SB. Tau prions from Alzheimer's disease and chronic traumatic encephalopathy patients propagate in cultured cells. PNAS, 2016
Seeding and Propagation of Tau Aggregates

Mechanisms of Cell-to-Cell Transfer of Pathological Tau Protein

Microglial Activation and Neuroinflammation

• Each day there are new papers describing the key role of microglial activation and inflammation in the propagation and neurodegenerative processes of Alzheimer’s disease and other tauopathies.

• It will likely be a critical piece of the CTE puzzle.
Critical Next Step: Diagnose CTE During Life

- Understand how common it is
- Determine risk factors (head impact exposure, genetics, vascular, lifestyle)
- Begin clinical trials of medications to treat and hopefully prevent CTE
Diagnosis of CTE During Life

Step One

Describe the clinical features associated with neuropathologically confirmed CTE
John Grimsley - Died at Age 45

- Houston Oilers 1984-1990; Miami Dolphins 1991-1993; Linebacker; Pro-Bowl, 1988
- Hunting/Fishing guide post NFL
- For the 5 years prior to death at age 45, he experienced worsening memory and cognitive functioning, as well as increasing “short fuse.”
- Died of accidental gunshot to chest while cleaning gun.
Grimsley - Neuropathology

65 yr old healthy control

Grimsley 45 yr old CTE

73 yr old boxer with dementia and CTE
Dave Duerson – Age 50
November 28, 1960 – February 11, 2011
Duerson’s Clinical History

• Successful businessman post NFL
• ~5 years prior to death, he had worsening short-term memory difficulties
• Increasingly out of control:
  – Short fuse, hot tempered, physically abusive, verbally abusive; lost business, marriage
• Committed suicide Feb 2011, shooting self in chest to avoid hurting brain.
Neuropathological Diagnosis:
Chronic Traumatic Encephalopathy Stage 3 of 4
CTE in Older Patient Can Mimic AD Dementia
J.D.: 66 yo Former NFL Center

• Exposure History
  – 17 years of American football
  – Age of first exposure: 10
  – 6 years in the NFL as a Center
  – Approx. 50 concussions, 1 with brief LOC, no hospitalizations

• Clinical Course
  – Late 20s: angry outbursts
  – Mid 50s: mild memory impairment, but continued to work
  – Age 64: retired, experienced apathy, depression and anxiety
  – Mid 60s: progression of memory impairment, more outbursts, problems with navigation, word finding difficulty, phonemic paraphasias, gait instability, masked facies, mild impairment in iADLs, dementia diagnosis

• Cause of death: myocardial infarction
J.D.: 66 yo Former NFL Center

- Neuropathological diagnosis
  - Chronic Traumatic Encephalopathy, Stage 4 of 4
  - No other neurodegenerative disease present; no immunopositivity for Aβ, TDP-43 or α-synuclein.
What are the Clinical Features Associated with CTE

- Based on retrospective reports of next-of-kin of deceased individuals
- Features are diverse and nonspecific
Clinical Features Associated with CTE

• Changes in Neurobehavioral Regulation
  – Apathy, Agitation, Rage, Short Fuse, Impulsivity, Aggression

• Changes in Cognitive Functioning
  – Poor Episodic Memory (cannot make new memories, rapid forgetting, repeats stories)
  – Executive Dysfunction (poor judgment and decision-making, impaired organizational and planning skills, poor multi-tasking)
Clinical Features Associated with CTE

- **Dementia**
  - Not “Alzheimer’s disease”
  - Dementia = cognitive impairment significant enough to impact daily functioning, independence
  - CTE dementia can easily be misdiagnosed as AD Dementia

- **Motor Impairment** (more common in boxers)
  - Parkinsonism, dysarthria, gait disturbance, falls
Are there Subtypes of the Clinical Features of CTE?

Clinical presentation of chronic traumatic encephalopathy

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ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects’ histories and clinical presentations. These interviews were conducted blind to the subjects’ neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. Neurology 2013;81:1-8

AD = Alzheimer disease; CTE = Center for the Study of Traumatic Encephalopathy; CTE = chronic traumatic encephalopathy; p-tau = hyperphosphorylated tau; RBT = repetitive brain trauma; TBI = traumatic brain injury.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau). To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to blast injuries, and patients with head injury in the absence of structural brain injury. CTE presents a growing challenge to the medical community, with estimated prevalence of 1.8 million athletes in the United States and 10 million military personnel. As a result, the Centers for Disease Control and Prevention has designated CTE as a public health priority.
Stern et al. (2013) *Neurology*

- 36 Neuropathologically-confirmed cases of CTE (mean age = 56.8; SD = 21.9; range = 17–98)
- All athletes (81% football)
- No comorbid findings, i.e., only CTE
- Extensive semi-structured interviews (psychological autopsy) and medical record review; Blind to neuropath findings
- 33 of 36 symptomatic
Consistent with previous case reports of boxers, two different initial clinical presentations:

1. **Behavior and/or mood changes**
2. **Cognitive impairment**

- The behavior/mood group demonstrated symptoms at a significantly younger age \( (M=34.5) \) than the cognition group \( (M=58.5) \).
- Motor features relatively uncommon
Clinical Subtypes

• Two subtype presentations supported by subsequent studies:
Impaired Signs and Symptoms of Concussions with prolonged PCS

Cognitive Presentation of CTE

Diagnostic Difficulty: What is CTE? What is AD, FTLD, DLB, other?

Behavior/Mood Presentation of CTE

Diagnostic Difficulty: What is PCS? Idiopathic depression? Non-CTE WM damage? CTE?
Diagnosis of CTE During Life

Step Two

Develop and begin to refine clinical research diagnostic criteria
Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H Montenigro¹, Christine M Baugh², Daniel H Daneshvar³, Jesse Mez⁴, Andrew Eudson⁴,⁵, Rhoda Au²,⁶, Douglas I Katz²,⁷, Robert C Cantu⁸,⁹ and Robert A Stern¹,⁴,²,⁸*
The term, "Traumatic Encephalopathy Syndrome" (TES) was selected to describe the clinical presentation of CTE as well as other possible long-term consequences of repetitive head impacts (RHI) – e.g., chronic or progressive axonopathy without tauopathy.

Based on:
- Exposure to Brain Trauma
- Clinical Features
- Course
- Biomarkers
The Provisional Research Diagnostic Criteria for TES include five General Criteria, three Core Clinical Features, and nine Supportive Features, that are used to define subtypes of TES, including:

- Behavioral/Mood Variant
- Cognitive Variant
- Mixed Variant
- TES Dementia
  - Behavioral/Mood
  - Cognitive
  - Mixed
First NINDS Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome (TES)  
April 15, 2019 – Phoenix, Arizona
Results of Round One Consensus Voting
Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome
Diagnosis of CTE During Life

Step Three

*Develop and validate *in vivo* biomarkers to detect the underlying pathophysiology*
Similar to Alzheimer’s Disease, Biomarkers, in Addition to Clinical Evaluation, will Lead to Accurate Detection and Diagnosis of CTE During Life
Biomarkers for Pre-Clinical Detection

• Biomarkers can provide accurate early- or pre-clinical detection/diagnosis.

• Like, AD, it is likely that pathophysiological process of CTE begin years or decades prior to clinical symptoms.

• If progressive, it is critical to develop disease modifying treatments and to initiate prior to destruction of brain tissue. So, preclinical detection is critical.
What Should a CTE Biomarker Test For?

- Initial abnormal tau protein in brain
- Spread of abnormal tau protein
- Destruction of brain tissue (neurodegeneration) and atrophy
- Changes to white matter
- Blood vessel (vascular) integrity
- Inflammation
What Should a CTE Biomarker Test For?

- **Screening**
  - Highly “sensitive”
- **Diagnostic**
  - Highly “specific”
- **Response to treatment**
Biomarkers for Pre-Clinical Detection

• Biomarkers can provide early- or pre-clinical detection/diagnosis when there may be no clinical symptoms.

• Like AD, it is likely that brain changes of CTE begin years or decades prior to clinical symptoms.

• If progressive, it is critical to develop disease modifying treatments and to initiate prior to destruction of brain tissue. So, preclinical detection is critical.
As with AD, Early **CTE** Disease Modification = Prevention

- **Pre-Clinical CTE**
- **Mild CTE**
- **Function**
- **CTE Dementia**

**New Disease Modifying Drugs, e.g., Anti-Tau Compounds**
Two-Step Clinical Diagnostic Approach

Step 1: Meets Criteria for *Traumatic Encephalopathy Syndrome* (TES)

Biomarker Positive

Step 2: Meets Criteria for *Probable CTE with Biomarker Evidence of...*
Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests
“Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers”

Goal:
To Develop Biomarkers to Diagnose CTE During Life

Principal Investigator: R.A. Stern
NIH R01 Grants R01NS078337 and R56NS078337
funded by:
National Institute of Neurologic Diseases and Stroke
National Institute of Aging
National Institute of Childhood Health and Development
DETECT Study - Subjects

- ~100 former NFL players (CTE High Risk)
  - ages 40-69
  - positions with highest exposure to RHI
  - currently symptomatic
- 30+ controls (CTE No Risk)
  - same age
  - no brain trauma exposure
Several Promising Findings from DETECT Study Using Fluid Biomarkers: Blood and Cerebrospinal Fluid (CSF)
More RHI Exposure Significantly Associated with Higher CSF Total Tau (p = 0.024)
Repetitive head impact exposure and later-life plasma total tau in former NFL players

Michael L. Alosco\textsuperscript{a,b}, Yorghos Tripodis\textsuperscript{a,c}, Johnny Jarnagin\textsuperscript{a}, Christine M. Baugh\textsuperscript{a,b,d}, Brett Martin\textsuperscript{a,e}, Christine E. Chaisson\textsuperscript{a,c,e}, Nate Estochen\textsuperscript{f}, Linan Song\textsuperscript{f}, Robert C. Cantu\textsuperscript{a,b,g}, Andreas Jeromin\textsuperscript{f}, Robert A. Stern\textsuperscript{a,b,g,h,*}
Repetitive head impact exposure and later-life plasma total tau in former NFL players

Michael L. Alosco\textsuperscript{a,b}, Yorghos Tripodis\textsuperscript{a,c}, Johnny Jamagin\textsuperscript{a}, Christine M. Baugh\textsuperscript{a,b,d}, Brett Martin\textsuperscript{a,e}, Christine E. Chaisson\textsuperscript{a,c,e}, Nate Estochen\textsuperscript{f}, Linan Song\textsuperscript{f}, Robert C. Cantu\textsuperscript{a,h,g}, Andreas Jeromin\textsuperscript{f}, Robert A. Stern\textsuperscript{a,b,g,h,i}
Exosomes in Blood and CSF

- Exosomes are cell-derived “nanovesicles” present in biological fluids, including blood, saliva, cerebrospinal fluid and urine.
- Mirror the features of the parent cell, including the proteins inside (e.g., p-tau from neurons!)
- Very stable and make a “liquid” biopsy possible.
- And...they cross the blood-brain barrier!
Preliminary Study of Plasma Exosomal Tau as a Potential Biomarker for Chronic Traumatic Encephalopathy

Robert A. Stern\textsuperscript{a,b,c,d,*}, Yorghos Tripodis\textsuperscript{a,c}, Christine M. Baugh\textsuperscript{a,1}, Nathan G. Fritts\textsuperscript{a,2}, Brett M. Martin\textsuperscript{a,f}, Christine Chaisson\textsuperscript{a,c,f}, Robert C. Cantu\textsuperscript{a,b,c,g}, James A. Joyce\textsuperscript{h}, Sahil Shah\textsuperscript{i}, Tsuneya Ikezu\textsuperscript{b,j}, Jing Zhang\textsuperscript{k}, Cicek Gercel-Taylor\textsuperscript{i,3} and Douglas D. Taylor\textsuperscript{i,3}
Plasma Exosomal Tau Study

- NFL group had higher exosomal tau than the control group
Plasma Exosomal Tau Study

- Within the NFL group, higher exosomal tau associated with worse cognitive functioning
- Very preliminary! Many limitations and need for refinement (assure derivation from brain and from specific cell types, antibodies for specific tau isoforms), replication, and post-mortem validation, with proteomics; currently underway with Dr. Tsuneya Ikezu and others
Proteomic Profiling of Extracellular Vesicles Isolated From Cerebrospinal Fluid of Former National Football League Players at Risk for Chronic Traumatic Encephalopathy

Satoshi Muraoka, Mark P. Jedrychowski, Harutsugu Tatebe, Annina M. DeLeo, Seiko Ikezu, Takahiko Tokuda, Steven P. Gygi, Robert A. Stern and Tsuneya Ikezu

ORIGINL RESEARCH
published: 09 October 2019
doi: 10.3389/fnins.2019.01059

CRABP1 (2) CPNE7 (1) S100A9 (12) CTSD (9)
SLC44A1 (1) ENPP6 (7) CST3 (8)
GSN (22) CYBRD1 (1) ABCD2 (1) LTF (6)
A2M (1) FXYD1 (2) HSPA1A (5)
AGT (3) CD14 (5) S100A8 (4)
ALDH1L1 (8) ITGB2 (3) HPN (2)
ATP1A2 (10) SPP1 (2) FCER1G (1)
SLC39A12 (18) MFGE8 (37)
Several Promising Findings from our NIH-Funded DETECT Study Using Advanced MRI Techniques
Cavum Septi Pellucidi in Symptomatic Former Professional Football Players

Inga K. Koerte,1,2,,* Jakob Hufschmidt1,3,* Marc Muehlmann1,2 Yorghos Tripodis,4,6 Julie M. Stamm1,5,7 Ofer Pasternak,1 Michelle Y. Giwerc,1 Michael J. Coleman1, Christine M. Baugh5,8 Nathan G. Fritts5, Florian Heinen3, Alexander Lin1,9,10 Robert A. Stern5,6,7,11,12+ and Martha E. Shenton1,9,12,+

\[ \text{Ratio of CSP / septum length} \]

\[ p = 0.03 \]

\[ W = -2.17 \]
Volumetric MRI Assessment of Limbic Structures
Lepage, Muehlmann et al., 2018, *Brain Imaging and Behavior*

- Former NFL group had significantly smaller volumes of the amygdala, hippocampus, and cingulate gyrus, compared to controls
- Within the NFL group, reduced cingulate gyrus volume was associated with worse attention/psychomotor speed ($p<0.001$)
- Reduced right hippocampal volume was associated with worse visual memory ($p=0.027$)
More RHI Exposure Significantly Associated with MRI White Matter Signal Abnormality (WMSA) Volume (p=.021)
A magnetic resonance spectroscopy investigation in symptomatic former NFL players

Michael L. Alosco¹ · Yorghos Tripodis² · Benjamin Rowland³ · Alicia S. Chua² · Huijun Liao³ · Brett Martin⁴,⁵ · Johnny Jarnagin¹ · Christine E. Chaisson¹,²,⁵ · Ofer Pasternak⁶ · Sarina Karmacharya⁷ · Inga K. Koerte⁷,⁸ · Robert C. Cantu⁹,¹⁰ · Neil W. Kowall¹¹,¹² · Ann C. McKee¹¹,¹³,¹⁴ · Martha E. Shenton⁶,¹³ · Richard Greenwald¹⁵,¹⁶ · Michael McClean¹⁷ · Robert A. Stern¹⁸ · Alexander Lin³
A magnetic resonance spectroscopy investigation in symptomatic former NFL players

Michael L. Alosco¹ · Yorghos Tripodis² · Benjamin Rowland³ · Alicia S. Chua² · Huijun Liao³ · Brett Martin⁴,⁵ · Johnny Jarnagin¹ · Christine E. Chaisson¹,²,⁵ · Ofer Pasternak⁶ · Sarina Karmacharya⁷ · Inga K. Koerte⁷,⁸ · Robert C. Cantu⁹,¹⁰ · Neil W. Kowall¹¹,¹² · Ann C. McKee¹¹,¹³,¹⁴ · Martha E. Shenton⁶,¹³ · Richard Greenwald¹⁵,¹⁶ · Michael McClean¹⁷ · Robert A. Stern¹⁸ · Alexander Lin³

Table 2  Cognitive and neuropsychiatric test performance

<table>
<thead>
<tr>
<th></th>
<th>Former NFL Players</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle Component Factor Scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioral/Mood</td>
<td>0.35 (0.93)</td>
<td>-0.92 (0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychomotor Speed/Executive Function</td>
<td>-0.03 (0.84)</td>
<td>0.27 (0.68)</td>
<td>0.75</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-0.08 (0.89)</td>
<td>0.35 (1.22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>0.01 (0.90)</td>
<td>0.29 (0.74)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Can We “See” the Abnormal Tau in the Brain During Life?

- Positron Emission Tomography (PET) Scans
PET Scan for **Amyloid Plaques in Alzheimer’s Disease**

- Three FDA-approved PET “radiotracers” for beta amyloid **neurotic** plaques as a biomarker for Alzheimer’s disease
PET Scans for Abnormal Tau in Alzheimer’s Disease and Other Tauopathies

• PET tracers that bind to specific p-tau “species” is a major area of research in Alzheimer’s disease, PSP, FTD, and other tauopathies

• Flortaucipir (T807, AV1451) PET tracer designed to detect abnormal tau in Alzheimer’s disease
What About PET for CTE Tau?

- Flortaucipir (T807, AV1451) PET radiotracer designed to detect abnormal PHF tau (3R/4R) in AD
- Is it appropriate for CTE tau???
Cerebral $[^{18}F]T807/AV1451$ retention pattern in clinically probable chronic traumatic encephalopathy resembles pathognomonic distribution of CTE tauopathy

Figure 4. PET Imaging from a 39-year-old retired NFL player. (a) structural MRI image, (b) $[^{18}F]florbetapir$ PET, (c) $[^{18}F]T807/AV1451$ PET from a healthy age-matched control subject. Note that the $[^{18}F]florbetapir$ image was negative for amyloid accumulation, while the $[^{18}F]T807/AV1451$ image shows extensive cortical ligand retention, especially at the junction of the gray and white matter, as is characteristic of the distribution of tauopathy in CTE. The PET scales represent ligand uptake in Becquerel per ml. CTE, chronic traumatic encephalopathy; MRI, magnetic resonance imaging; PET, positron emission tomography.
Tau and Amyloid PET for CTE

- Amyloid neuritic plaques are uncommon until late stage CTE, so Florbetapir amyloid PET would not be expected to be elevated in CTE
PET Scans for Tau: The Gold Standard?

- PET tracers that bind to specific p-tau species is a major area of research in Alzheimer’s disease, PSP, FTD, and other tauopathies.
- Flortaucipir (T807, AV1451) PET tracer designed to detect abnormal tau in Alzheimer’s disease.
Tau Positron-Emission Tomography in Former National Football League Players

Robert A. Stern, Ph.D., Charles H. Adler, M.D., Ph.D., Keweı Chen, Ph.D.,
Michael Navitsky, M.S., Ji Luo, M.S., David W. Dodick, M.D.,
Michael L. Alosco, Ph.D., Yorghos Tripodis, Ph.D., Dhruven D. Goradia, Ph.D.,
Brett Martin, M.S., Diego Mastroeni, Ph.D., Nathan G. Fritts, B.A.,
Johnny Jarnagin, B.A., Michael D. Devous, Sr., Ph.D., Mark A. Mintun, M.D.,
Michael J. Pontecorvo, Ph.D., Martha E. Shenton, Ph.D., and Eric M. Reiman, M.D.

DOI: 10.1056/NEJMoa1900757
Methods

• Participants
  • 26 symptomatic former NFL players
    – 40-69 years, > 2 yrs in NFL, > 12 yrs total tackle football, and self-reported complaints of cognitive, behavioral, and mood symptoms reported at telephone screening
  • 31 asymptomatic controls
    – male, 40-69 years, no cognitive symptoms, and no history of traumatic brain injury
Methods

• Clinical Measures
  – All participants were administered the MMSE
  – Former NFL players also administered a series of neuropsychological tests and neuropsychiatric measures.
    • A subset of six tests of executive functioning (Trail Making Test Part B, Category [Animal] Fluency), episodic memory (Neuropsychological Assessment Battery List Learning Test), and emotional regulation (Beck Depression Scale-II, Beck Hopelessness Scale, Barratt Impulsivity Scale) was used for the analyses as measures of functions reported to affected by CTE.

• Imaging
  – Each participant had flortaucipir (FTP) tau PET, florbetapir amyloid PET, and T1-weighted volumetric brain MRI.
    • FTP PET was performed on PET/CT systems using an intravenous bolus of 370 MBq (10 mCi; +/- 10%) of FTP; CT scan used to correct for radiation attenuation and scatter. Dynamic emission PET data collected over a 20 min period beginning 80 min after radiotracer administration were used for analysis. All PET images were smoothed using an 8 mm Gaussian kernel.
Statistical Parametric Maps of Flortaucipir Positron-Emission Tomography (PET). The maps show voxels with higher regional cerebellar gray-matter flortaucipir standard uptake value ratios (SUVRs) among former National Football League (NFL) players than among controls (P<0.005, uncorrected for multiple regional comparisons).
Three-Dimensional Stereotactic Surface Projection Maps of Flortaucipir PET.

Higher flortaucipir SUVRs in the former-player group than in the control group were found in the bilateral superior frontal (Panel A), bilateral medial temporal (Panel B), and left parietal (Panel C) regions of the brain. The regions shown in red in these surface projection images correspond to the statistical parametric maps after restriction of the map to those clusters of at least 100 contiguous voxels associated with higher regional cerebellar gray-matter flortaucipir SUVRs in the former-player group than in the control group (P<0.005, uncorrected for multiple regional comparisons).
Results

• Florbetapir Amyloid PET: Although all the former NFL players in the study reported cognitive symptoms, and more than 35% had impaired delayed-recall scores on an objective memory test, they did not have a higher proportion of positive florbetapir PET scans or higher amounts of amyloid-beta deposition as measured by the florbetapir SUVR than the controls
  – Cognitive difficulties reported by the former players were not related to AD neuritic plaque deposition

• Off-Label Binding to Melanocytes: No difference on medial temporal FTP SUVRs between 14 self-identified black former players and the 11 self-identified white former players (P>0.05)
Results

• **Clinical Measures:** There were NO significant relationships between flortaucipir Tau PET levels and the clinical measures of memory, executive functioning, or mood/behavior

• **Possible explanations:**
  – Insufficient power due to small sample size and the patchy, focal distribution of tau deposition observed in postmortem studies of CTE
  – Exclusion of asymptomatic former NFL players from the study may have reduced the ability to detect a relationship between flortaucipir uptake and clinical features of CTE
  – Flortaucipir may not be that specific to CTE p-tau
Conclusion: AV-1451 may have limited utility for in vivo selective and reliable detection of tau aggregates in CTE. The existence of disease-specific tau conformations may likely explain the differential binding affinity of this tracer for tau lesions in different tauopathies.
Tau PET and multimodal brain imaging in patients at risk for chronic traumatic encephalopathy


Abstract

Objective: To characterize individual and group-level neuroimaging findings in patients at risk for Chronic Traumatic Encephalopathy (CTE).

Methods: Eleven male patients meeting criteria for Traumatic Encephalopathy Syndrome (TES, median age: 64) underwent neurologic evaluation, 3-Tesla MRI, and PET with $^{18}$FDG, florbetapir (FTP, tau-PET) and $^{11}$C-Pittsburgh compound B (PIB, amyloid-PET). Six patients underwent $^{18}$F-fluorodeoxyglucose-PET (FDG, glucose metabolism). We assessed imaging findings at the individual patient level, and in group-level comparisons with modality-specific groups of cognitively normal older adults (CN). Tau-PET findings in patients with TES were also compared to a matched group of patients with mild cognitive impairment or dementia due to Alzheimer's disease (AD).

Results: All patients with TES sustained repetitive head injury participating in impact sports, ten in American football. Three patients met criteria for dementia and eight had mild cognitive impairment. Two patients were amyloid-PET positive and harbored the most severe MRI atrophy, FDG hypometabolism, and FTP-tau PET binding. Among the nine amyloid-negative patients, tau-PET showed either mildly elevated frontotemporal binding, a “dot-like” pattern, or no elevated binding. Medial temporal FTP was mildly elevated in a subset of amyloid-negative patients, but values were considerably lower than in AD. Voxelwise analyses revealed a convergence of imaging abnormalities (higher FTP binding, lower FDG, lower gray matter volumes) in frontotemporal areas in TES compared to controls.

Conclusions: Mildly elevated tau-PET binding was observed in a subset of amyloid-negative patients at risk for CTE, in a distribution consistent with CTE pathology stages III-IV. FTP-PET may be useful as a biomarker of tau pathology in CTE but is unlikely to be sensitive to early disease stages.
Tau PET and multimodal brain imaging in patients at risk for chronic traumatic encephalopathy

Orit H Lesman-Segev1,2, Renaud La Joie1, Melanie L Stephens1, Ida Sonni2, Richard Tsai1, Viktoria Bourakova1, Adrienne V Visani3, Lauren Edwards1, James P O’Neil4, Suzanne I Baker2, Raquel C Gardner (MD)1,2, Mustafa Janabi3, Kiran Chaudhary3, David C Perry5, Joel H Kramer1, Bruce L Miller3, William J Jagust1,2, Gil D Rabinovici1,2,6

A B S T R A C T

Objective: To characterize individual and group-level neuroimaging findings in patients at risk for Chronic Traumatic Encephalopathy (CTE).

Methods: Eleven male patients meeting criteria for Traumatic Encephalopathy Syndrome (TES, median age: 64) underwent neurologic evaluation, 3-Tesla MRI, and PET with [18F]-Flortaucipir (FTP, tau-PET) and [11C]-Pittsburgh compound B (PIB, amyloid-PET). Six patients underwent [18F]-Fluorodeoxyglucose-PET (FDG, glucose metabolism).

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A. Frequency maps

% subjects with t-score > 1.645 in each voxel

11 TES

13 with dementia due to AD

9 PIB negative TES

9 with MCI due to AD

67 CN

Abnormality Frequency
20% 40% 60%

B. Voxelwise analysis

11 TES Vs. 67 CN

9 PIB Negative TES Vs. 67 CN

Cohen’s D effect size
0.6 1.5

Lesman-Segev et al., NeuroImage: Clinical 24 (2019) 102025
**Results of Stern et al. (2019) NEJM**

- **Clinical Measures**: There were NO significant relationships between flortaucipir Tau PET levels and the clinical measures of memory, executive functioning, or mood/behavior.

- **Possible explanations**:
  - Insufficient power due to small sample size and the patchy, focal distribution of tau deposition observed in postmortem studies of CTE.
  - Exclusion of asymptomatic former NFL players from the study may have reduced the ability to detect a relationship between flortaucipir uptake and clinical features of CTE.
  - Flortaucipir may not be that specific to CTE p-tau.
  - Tau pathology alone may not be associated with the neuropsychiatric symptoms and cognitive impairment described in former American football players, boxers, and others with a history of extensive repetitive head impact exposure.
CTE Clinical Features: Is p-tau the sole culprit?

- What clinical features are specifically related to p-tau pathology?
  - Initial sulcal depth p-tau deposition
  - Later medial temporal involvement
  - p-tau-related neurodegeneration

- Recent study at UCSF with flortaucipir in AD showed that p-tau (but not Abeta) predicted future neurodegeneration and was not associated with baseline clinical deficits (La Joie et al., *Sci Transl Med*, 2020). Relationship between p-tau pathology and clinical presentation partly mediated by brain degeneration (Bejanin et al., *Brain*, 2017)
CTE Clinical Features: Is p-tau the sole culprit?

– Or…related and/or unrelated pathology
  • Inflammatory responses
  • Chronic or progressive changes from single moderate-severe TBI
  • White matter damage (arteriosclerosis vs rarefaction)
  • Comorbid AD, other neurodegenerative diseases, proteinopathies
    – TDP-43
    – beta amyloid
    – cerebral amyloid angiopathy
    – alpha synuclein
We Now have **Potential CTE Biomarkers**
DIAGNOSE CTE
Research Project

Diagnostics, Imaging, And Genetics Network
for the Objective Study & Evaluation of
Chronic Traumatic Encephalopathy
"Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors"

$17 Million grant funded by the National Institute of Neurological Disorders & Stroke (U01NS093334)

7-Year Multicenter Study

Principal Investigators
Robert Stern, Ph.D., Boston University (Contact PI)
Jeffrey Cummings, M.D., Cleveland Clinic
Eric Reiman, M.D., Banner Alzheimer’s Institute
Martha Shenton, Ph.D., Brigham & Women’s Hospital

40 Collaborators
10 Research Institutions
Goals of the Study

DIAGNOSE CTE Research Project

1. Collect and analyze neuroimaging and fluid biomarkers for the *in vivo* detection of CTE
2. Characterize the clinical presentation of CTE
3. Examine the progression of CTE over a three-year period
4. Refine and validate diagnostic criteria for the clinical diagnosis of CTE
5. Investigate genetic and head impact exposure risk factors for CTE
6. Share project data with researchers across the country and abroad
Who is being studied?

- Males between 45-74 years old
- Three groups based on history of exposure to repetitive head impacts
  - 120 Former NFL Players
    - No Symptoms
    - Mild Symptoms
    - Dementia (impaired daily functioning)
  - 60 Former College Football Players (no other contact sports)
    - No Symptoms
    - Mild Symptoms
    - Dementia
  - 60 Controls (no contact sports, TBI, mTBI, Military)
    - No Symptoms

240 Participants
Where are participants being evaluated?

<table>
<thead>
<tr>
<th>Arizona</th>
<th>Boston</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic-Scottsdale</td>
<td>BU School of Medicine</td>
</tr>
<tr>
<td>• PET scans at Banner Alzheimer’s Institute, Phoenix</td>
<td>• MRI’s at Brigham and Women’s Hospital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Las Vegas</th>
<th>New York</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland Clinic Lou Ruvo Center for Brain Health</td>
<td>New York University Langone Medical Center</td>
</tr>
</tbody>
</table>
High Exposure Group
120 Former NFL Players
Asymptomatic, Symptomatic, Dementia

Medium Exposure Group
60 Former College Players
Asymptomatic, Symptomatic, Dementia

Control Group
60 No-Contact Sport/no-TBI Controls
All Asymptomatic

Exposure

Baseline
Clinical Exams
Neurocognitive, Mood, Behavior, & Motor Tests

Biomarkers
Fluid: CSF & Blood, Saliva
Neuroimaging: MRI, DTI, fMRI, MRS, PET-amyloid, & PET-tau

Clinical Diagnosis
Traumatic Encephalopathy Syndrome
Behavior/Mood, Cognitive, Mixed, Dementia Subtypes &
Chronic Traumatic Encephalopathy
Probable, Possible, Unlikely

Risk Assessment:
Head Impact Exposure & Genetic Polymorphisms

Disease Course:
Clinical and Biomarker Characteristics

Consensus Statement on Diagnostic Criteria

3 Yr Follow-up
Clinical Exams

Biomarkers
Fluid Neuroimaging

DIAGNOSE CTE Research Project
Study Design Overview
Future Research

• Once we can diagnose CTE during life, we will be able to begin clinical trials for treatment.
• And, if we can detect it early in the disease course, prior to symptoms, we can conduct clinical trials for prevention!
## Acknowledgments

*All the athletes and families who participate in our research*

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- Ron Killiany
- Neil Kowall
- Brett Martin
- Mike McClean
- Ann McKee
- Jesse Mez
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### DIAGNOSE CTE Research Project Coordinating Center

- Courtney Diamond
- Nicole Gullotti
- Olivia Haller
- Megan Mariani
- Brian Mayville
- Megan Mariani
- Kathleen McLaughlin
- Taylor Platt
- Fiona Rice

### Others

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Delirium, Encephalopathies and Uncommon Dementias

Jeremy D. Schmahmann, MD
Disclosures

• Book Publishers
  – Academic Press
  – Elsevier
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  – MacKeith Press
  – Springer

• Licensing
  – BARS, CCAS / Schmahmann Scale, CNRS; with MGH

• Consulting
  – Cadent Pharma
2

Neuroanatomy and Behavioral Neurology of Subcortical Systems
Jeremy D. Schmahmann and Deepak N. Pandya

15

The Differential Diagnosis of Rapidly Progressive and Rare Dementias
A Clinical Approach
Jeremy D. Schmahmann

Acute confusional state (Delirium; encephalopathy)

Minutes to Hours

Confusional state = medical emergency

Mental state characterized by waxing and waning level of arousal and attention

Meningitis, encephalitis, intracranial hemorrhage, stroke, acute toxic / metabolic, seizure (convulsive or non-convulsive)
Subacute Dementia

Weeks to Months

The time course is THE MAJOR consideration, and limits the differential diagnosis.
Neurodegenerative dementias

Months to Years

The clinical differential diagnosis is highly determined by the pattern of elementary deficits and the nature of the cognitive decline (the domains of cognition affected)
Diagnoses in patients initially suspected of having Creutzfeldt-Jakob Disease


UCSF Non-prion diagnoses in 67 patients initially suspected of having CJD

- **Neurodegenerative** N=26; 39%
  - CBD 8, FTD 7, DLB 4, AD 5, PSP 2
- **Autoimmune** N = 15, 22%
  - Hashimoto 4, MS 1, Antibody mediated 9
- **Unknown** N = 8; 12%
- **Infectious** N = 4; 6%
- **Psychiatric** N = 4; 6%
- **Malignancy** N = 4; 6%
- **Toxic/metabolic** N = 3; 4%
- **Vascular** N = 3; 4%

<table>
<thead>
<tr>
<th>Category</th>
<th>University of California, San Francisco (UCSF), Cohort N = 104 (21)(^b)</th>
<th>German Cohort(^7) N = 124 (37)(^b)</th>
<th>National Prion Disease Pathology Surveillance Center (NPDPSC) Cohort(^8) N = 304 (304)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune/antibody-mediated(^c)</td>
<td>13</td>
<td>27</td>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Unclassified dementia</td>
<td>13</td>
<td>16</td>
<td>Vascular disease</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>12</td>
<td>9</td>
<td>Immune mediated</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>8</td>
<td>8</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Encephalitis, not otherwise specified</td>
<td>8</td>
<td>5</td>
<td>Infections</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>8</td>
<td>5</td>
<td>Unspecified degenerative disease</td>
</tr>
<tr>
<td>Frontotemporal dementia with or without motor neuron disease</td>
<td>7</td>
<td>2</td>
<td>Frontal lobe degeneration</td>
</tr>
<tr>
<td>Corticobasal syndrome or corticobasal degeneration</td>
<td>6</td>
<td>2</td>
<td>Metabolic</td>
</tr>
<tr>
<td>Alzheimer disease(^d)</td>
<td>5</td>
<td>2</td>
<td>Hippocampal sclerosis</td>
</tr>
<tr>
<td>Central nervous system vasculitis</td>
<td>3</td>
<td>2</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td>Encephalopathy, not otherwise specified</td>
<td>3</td>
<td>2</td>
<td>Tauopathy, not otherwise specified</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>3</td>
<td>2</td>
<td>Hereditary diffuse leukoencephalopathy with spheroids</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>3</td>
<td>2</td>
<td>Progressive supranuclear palsy</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>2</td>
<td>2</td>
<td>Other(^e)</td>
</tr>
<tr>
<td>Other(^e)</td>
<td>8</td>
<td>Total</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Subacute Dementia

• **Weeks to Months**
• The time course is THE MAJOR consideration, and limits the differential diagnosis.
• Consider neurodegenerative disorders in this category only after other identifiable conditions have been excluded.
What **ELS** do you need to know to make the diagnosis?

**Exam**
- Time course
- Nature of the progression
- Medical / Elementary neurologic features
- Cognitive profile

**Lab**
- Blood, urine, CXR, LP when indicated

**Scan**
- MRI, CT, as indicated
Subacute Dementia: A broad approach to differential diagnosis by category and disease

- TRAUMA
- INFLAMMATION/INFECTION
- NEOPLASTIC
- METABOLIC
- VASCULAR
- AUTOIMMUNE
- DRUGS/TOXINS
- DEMYELINATING
- OBSTRUCTIVE
- DEGENERATIVE
Here's how this really works...

- **Something obvious**
  - Exam diagnostic
    - Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - Metabolic derangement on first line labs
    - Na, Ca, UTI, pneumonia, pO2…
  - Imaging diagnostically abnormal and easy
    - stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    - NPH, MELAS, ADEM, stroke that didn’t make sense until now

- **Something not so obvious** – if you don’t think of it you won’t diagnose it
  - DON'T MISS THIS BECAUSE:
    - A) Your patient may die if you miss it, because it’s lethal and treatable, or
    - B) Patients and families need to know the diagnosis, even though you may not be able to cure it

- First line labs are fine
- Imaging is normal, not clearly abnormal, non-specific, or missed
- **THE BIG FOUR**: Drugs / toxins / metabolic / infectious
  - Limbic encephalitis (paraneoplastic / immune mediated)
  - Hashimoto encephalopathy
  - Creutzfeld-Jakob disease
- **EVERYTHING ELSE**
Something not so obvious – if you don’t think of it you won’t diagnose it

DON’T MISS THIS BECAUSE:

A) Your patient may die if you miss it, because it’s lethal and treatable

or

B) Patients and families need to know the diagnosis, even though you may not be able to cure it
Drugs / toxins / metabolic derangements

**Medications**
- Benzodiazepines – use or withdrawal
- Anticonvulsants – keppra in the elderly
- Dopaminergic agents – sinemet confusion
- Neuroleptics
- Anticholinergics
- Polypharmacy

**Alcohol**
- Acute
- Chronic (Korsakoff, Marchiafava-Bignami)

THE BIG FOUR: Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld
THE BIG FOUR: Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld

Drugs / toxins / metabolic derangements

Wernicke encephalopathy (B1, thiamine)
(If it’s Korsakoff, it’s probably too late)
Confusion, ataxia, nystagmus, extraocular nerve palsy
– VI most common

Vitamin B12 deficiency
Dementia +/- pernicious anemia, myelopathy
(subacute combined degeneration of the spinal cord)

Vitamin B3 deficiency (nicotinic, niacin)
Pellagra = dementia +/- dermatitis, diarrhea
Pellagra encephalopathy (vitamin B3)

- Rapidly progressive dementia
- Fluctuating cognition, frontal disinhibition, release phenomena
- Startle myoclonus, decreased arousal
- Cerebellar motor syndrome
- Hyperreflexia
- Peripheral neuropathy
- Autonomic dysfunction
- Cranial neuropathies
- In the alcoholic patient, differentiate alcohol withdrawal from the acute and persistent confusional state, disorientation, agitation, irritability, paranoia, and hallucinations of pellagra.

Ishii and Nishihara, 1981
In, Schmahmann, 2014
Drugs / toxins / metabolic derangements

Hypothroid
  Myxedema madness (? Relationship to Hashimoto)

Adrenal insufficiency
  Addison's disease

Vitamin E deficiency
  Encephalopathy with neuropathy, ataxia
Drugs / toxins / metabolic derangements

Carbon monoxide, cyanide – globus pallidus lesions
Marijuana psychosis
Heroin – intravenous drug use
  “Chasing the Dragon” leukoencephalopathy
Phencyclidine (PCP)
Mescaline
Heavy metals: lead, mercury, arsenic
Herpes simplex encephalitis

Fever, confusion, often with aphasia
Herpes simplex encephalitis

THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld
Limbic Encephalitis

Voltage-gated K⁺ channel antibody syndrome (VGKC-Ab)

Memory loss, confusion, seizures; low serum sodium

Treat with immune modulation (steroids, plasmapheresis, IVIG)
### THE BIG FOUR:
Drugs / toxins / metabolic / infectious; **Limbic encephalitis**; Hashimoto; Creutzfeld

#### TABLE 15.4 Well-Characterized Onconeuronal Antibodies and Paraneoplastic Neurological Syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Predominant Tumors</th>
<th>Most Common PNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu (ANNA1)</td>
<td>SCLC</td>
<td>Encephalomyelitis, limbic encephalitis, brainstem encephalitis, PCD; sensory neuronopathy, gastrointestinal pseudoobstruction</td>
</tr>
<tr>
<td>CV2 (CRMP5)</td>
<td>SCLC, thymoma</td>
<td>Same as Hu, and chorea, optic neuropathy, isolated myelopathy, and mixed neuropathies</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Breast SCLC</td>
<td>Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis, sensory neuronopathy</td>
</tr>
<tr>
<td>Ri (ANNA2)</td>
<td>Breast, SCLC</td>
<td>Brainstem encephalitis, opsoclonus myoclonus</td>
</tr>
<tr>
<td>Yo (PCA1)</td>
<td>Ovary, breast</td>
<td>PCD</td>
</tr>
<tr>
<td>Ma2</td>
<td>Testicular</td>
<td>Limbic and brainstem encephalitis</td>
</tr>
<tr>
<td>Tr</td>
<td>Hodgkin’s</td>
<td>PCD</td>
</tr>
</tbody>
</table>

PCD, paraneoplastic cerebellar degeneration; PNS, paraneoplastic neurological syndromes; SCLC, small-cell lung cancer.

*Source: From Graus and Dalmau (2012); reproduced with permission.*

#### TABLE 15.5 Antibodies Against Cell Surface or Synaptic Antigens Associated With Paraneoplastic Neurological Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;4&lt;/sub&gt; R</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>CASPR2</td>
<td>Morvan’s syndrome</td>
</tr>
<tr>
<td>AMPAR</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>VGCC</td>
<td>PCD</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Limbic encephalitis</td>
</tr>
</tbody>
</table>

AMPAR, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein 2; GABA<sub>4</sub> R, γ-aminobutyric acid-B receptor; mGluR5, metabotropic glutamate receptor type 5; NMDAR, N-methyl-D-aspartate receptor; PCD, paraneoplastic cerebellar degeneration; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.

*Source: From Graus and Dalmau (2012); reproduced with permission.*
LGI-1 Ab encephalitis
Faceo-brachial dystonic seizures

Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia

Sarosh R. Irani,1,2* Sian Alexander,1,2 Patrick Waters,1 Kleopas A. Kleopa,2 Philippa Pettingill,1 Luigi Zuliani,1 Elor Peles,2 Camilla Buckley,1 Bethan Lang1 and Angela Vincent1

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E-mail: angela.vincent@nmon.ox.ac.uk

ABSTRACT

Purpose: To describe clinical and electrographic characteristics of seizures LGI1-antibody encephalitis, and their correlations with two-year outcomes.

Methods: Video-electroencephalography recordings were performed on a cohort of 16 consecutive patients with LGI1-antibodies from two UK neuroscience-centres over five years.

Results: From 14 of 16 patients (13 males; age range 53–92 years), 86% focal/limbic dystonic seizures were recorded at a median frequency of 0.4 per hour (range 0.1–4.9), and 85% EEG changes accompanied focal onset events. In addition, 11/16 patients showed 53 other seizures – subclinical (n = 18), motor (n = 16), or sensory (n = 19) – at a median of 0.1 per hour (range 0.001–1.2) associated with temporal and frontal discharges. The sensory events were most commonly thermal sensations or body-shivering, and the motor events were frequently automatism or vocalisations. Furthermore, multifocal interictal epileptiform discharges, from temporal, frontal and parietal regions, and interictal slow-wave activity were observed in 25% and 60% of patients, respectively. Higher observed seizure frequency correlated with poorer functional recovery at two years (p = 0.001).

Conclusions: Multiple frequent seizure semiologies, in addition to numerous subclinical seizures and interictal epileptiform discharges, are hallmarks of LGI1-antibody encephalitis. High overall seizure frequency may predict more limited long-term recovery. These observations should encourage closer monitoring and proactive treatment of seizure activity in these patients.

1. Introduction

LGI1-antibodies are closely associated with a limbic encephalitides (LE) which is characterised by confusion, disorientation and seizures, frequently with medial temporal lobe inflammation on imaging [1]. The seizures include typical medial temporal lobe events [2–4], and more distinctive semiologies including bradykardia, piloerection, and faciobrachial dystonic seizures (FBDS) [2,4–7]. These multiple seizure descriptions appear in several separate reports, largely based on retrospective histories. As patients often show some amnesia for the acute illness, and these reports lack the gold-standard of video-EEG monitoring [2,5,8], our aim was to systematically describe and quantify the electrophysiological characteristics of seizures in patients with LGI1-antibodies, with a focus on seizure localisation, semiology and frequency, from consecutive patients attending video-EEGs.
Facio-brachial dystonic seizures

- [https://www.youtube.com/watch?v=1vdsNa6Qk8k](https://www.youtube.com/watch?v=1vdsNa6Qk8k)
- [https://www.youtube.com/watch?v=QlEHp8oYhsQ](https://www.youtube.com/watch?v=QlEHp8oYhsQ)
Hashimoto encephalopathy

Roma origin. Grade 3 education. Grew up “in the carnival”.
Active housewife, sociable, respectful and aware of social conventions.

Age 47, dizziness, tiredness, anxiety, intermittent shaking of hands and legs, episodes of slurring of speech and confusion.
Age 48, over 3 months, change in personality with decreased conversation, not following the thread of conversation.
Personality change - inconsiderate of other people’s feelings, "talking dirty", reporting she was smelling bad things, restriction of her activities, refused to shower, spent much of her day sleeping, did not brush her teeth, liberal with profanities.

Thyroid problem began 15 years ago. On levothyroxine
Thyroid peroxidase (TPO) 301 (0-34 IU/mL)
Thyroglobulin Ab >3,000 (<40 IU/mL)
Hashimoto encephalopathy

Elementary exam unremarkable

- Fluent language
- Unable to learn words
- Cannot repeat 3 numbers forwards, or understand reverse digit span
- Confabulates. Frequent profanities. Utilization behavior
- Asked to draw a picture – produces female nude
- Perseverates with Luria diagram, and copying 2-loop diagram
- Draw-to-stimulus with copying 2-D figure
THE BIG FOUR: 
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld

Hashimoto encephalopathy

9/2010

9/2014

48 year-old woman. Confusion, profound disinhibition, aphasia.
65 yr woman. 4 months of unsteady gait, lethargy, confusion, forgetfulness

**Creutzfeld-Jakob disease**
Ataxia, dementia, myoclonus

DWI - MRI
Creutzfeld-Jakob disease

54-yr woman. 6 week history. Vertigo, unsteady gait, cortical visual loss, alexia, agraphia, apraxia, aphasia (output > comprehension), amnesia, confusion
Sporadic CJD

- **Dementia**
  - concentration, memory, judgment, personality, depression/disinhibition

- **Ataxia**
  - impaired gait (not necessarily typically cerebellar)

- **Myoclonus**
  - with startle in 90%

- Also: extrapyramidal, corticospinal (40 – 80%), cerebellar, occipital (Heidenhein), thalamic, basal ganglia

THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld
THE BIG FOUR:
Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeld

EEG in CJD
Periodic triphasic waves

67 – 95% of cases
Sensitivity 67%
Specificity 86%
• CSF in CJD
  – 14-3-3 protein
    • Sensitivity 53 to 85%, Specificity 95%
  – RT-QuIC (Real-time quaking-induced conversion: amplify, detect, and quantify prion protein)

• CJD Pathology – spongiform encephalopathy

THE BIG FOUR: Drugs / toxins / metabolic / infectious; Limbic encephalitis; Hashimoto; Creutzfeldt

Courtesy Matthew Frosch, MD, PhD
Normal Pressure Hydrocephalus
Normal Pressure Hydrocephalus

Before VP shunt

After VP shunt

Schwartzschild M, Rordorf G, Bekken K, Buonanno F, Schmahmann JD.
Normal Pressure Hydrocephalus with Misleading Features of Irreversible Dementias. A Case Report.
Normal pressure hydrocephalus
Following intraparenchymal hemorrhage
Normal Pressure Hydrocephalus
Acute callosal angle at the level of the posterior commissure
Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response


ABSTRACT

Objective: We evaluated evidence for utility of shunting in idiopathic normal pressure hydrocephalus (iNPH) and for predictors of shunting effectiveness.

Methods: We identified and classified relevant published studies according to 2004 and 2011 American Academy of Neurology methodology.

Results: Of 21 articles, we identified 3 Class I articles.

Conclusions: Shunting is possibly effective in iNPH (96% chance subjective improvement, 83% chance improvement on timed walk test at 6 months) (3 Class III). Serious adverse event risk was 11% (1 Class III). Predictors of success included elevated $R_0$ (1 Class I, multiple Class II), impaired cerebral blood flow reactivity to acetazolamide (by SPECT) (1 Class I), and positive response to either external lumbar drainage (1 Class III) or repeated lumbar punctures. Age may not be a prognostic factor (1 Class II). Data are insufficient to judge efficacy of radionuclide cisternography or aqueductal flow measurement by MRI.

Recommendations: Clinicians may choose to offer shunting for subjective iNPH symptoms and gait (Level C). Because of significant adverse event risk, risks and benefits should be carefully weighed (Level B). Clinicians should inform patients with iNPH with elevated $R_0$ and their families that they have an increased chance of responding to shunting compared with those without such elevation (Level B). Clinicians may counsel patients with iNPH and their families that (1) positive response to external lumbar drainage or to repeated lumbar punctures increases the chance of response to shunting, and (2) increasing age does not decrease the chance of shunting being successful (both Level C). Neurology® 2015;85:2063–2071
Figure 1  Percentage of patients improving with shunting in each of the 10 described studies

Halperin et al. Neurology 2015
72 year PhD physicist
Bedridden, confused and incontinent after a 1 year decline
Videos
Diagnosing NPH
The take-home message

• Suspect it from the clinical triad
  – Gait impairment (not always with small stuttering steps, magnetic gait, but that makes you think of it)
  – Bladder difficulties
  – Cognitive change, including neuropsychiatric

• Review the MRI for acute callosal angle

• Large volume LP as test
  – With quantitative metrics, usually with PT help
Diagnosing NPH
The take-home message

• The clinical triad alone is not sufficient
  – Differential includes Binswanger, multifactorial gait disorder, unrelated bladder issues

• The MRI alone is not sufficient
  – Large ventricles may be life-long

• Large volume LP is essential
  – The response may be delayed, can occasionally be long-lasting, and guides the need for shunt
  – You may need to repeat the LP if there is diagnostic uncertainty
Cerebellar Cognition
Cerebellar Cognitive Affective Syndrome

23-yr woman post gangioglioma resection

I am a young girl who is twenty-three.

The young girl went into her closet.

62-yr man

Schmahmann and Sherman 1998
Cerebellar Cognitive Affective Syndrome (CCAS)

- Executive Function
  Planning, set-shifting, verbal fluency, abstract reasoning, working memory
- Spatial Cognition
  Visual spatial organization and memory
- Language Deficits
  Agrammatism, aprosodia, anomia
- Personality Change
  Blunting of affect, disinhibited and inappropriate behavior

Schmahmann and Sherman. Brain, 1998

Schmahmann’s syndrome - identification of the third cornerstone of clinical ataxiology
Mario Manto and Peter Mariën. Cerebellum and Ataxias 2015;2:2
Functional topography of human cerebrocerebellar connections as determined by resting state fcMRI

Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke

CCAS / Schmahmann Scale
Hoche, Guell, Sherman, Vangel, Schmahmann. Brain, 2018

CEREBELLAR COGNITIVE AFFECTIVE / SCHMAHAMN SYNDROME SCALE (CCAS-Scale)
VERSION 1A.

DATE: 
NAME: 
ID #: 

SEMASTIC FLUENCY
Score = total correct words up to a maximum of 26 words, Fail if score 15 or less.
(Use space bottom right for notation).
Please name as many animals or living creatures as you can in one minute

PHONEMIC FLUENCY
Score = total correct words up to a maximum of 19 words, Fail if score 9 or less.
(Use space bottom right for notation).
Please name as many words as you can in one minute that start with the letter F. Do not use names of people or places or repeat the same word in different forms.

CATEGORY SWITCHING
Score = total number of correct alternating words up to a maximum of 15 alternations. Repeated or not correct errors are not scored. Fail if score 9 or less.
(Use space bottom right for notation).
Please name a type of vegetable and then a type of profession or job, and then another vegetable and another profession, and so on, switching between the two lists. Name as many as you can in one minute.

VERBAL REGISTRATION
This test is not scored. (The test for 4 attempts in learn 5 words raises concerns for cerebellar involvement).
I am going to read you a list of words which I would like you to learn. Please repeat these words. I am going to ask you to give them back in a few minutes. (Read 5 words at rate of 1 / second. Subject repeats them once, then repeats them again. Repeat trials until subject recalls all 5 words. Stop after 4 attempts.)

DIGIT SPAN FORWARD
Score = maximum string of numbers correctly repeated. Fail if score 5 or less.
I am going to read you some numbers. Please repeat them in exactly the same order. (Read aloud at a rate of 1 per second. Start with * and administer previous items if subject fails to repeat *).

DIGIT SPAN BACKWARD
Score = maximum string of numbers correctly repeated. Fail if score 3 or less. Inability to reverse 2 digits fails.
Now please say these numbers backwards, in reverse order. (Give example, then start with *).

CUBE (DRAW)
Score = 15 points if 12 lines present and diagram is 3-dimensional. If 12 lines not present or diagram is not 3-dimensional, administer "CUBE (COPY)."
Please draw a cube – a six-sided box, make it transparent or see-through. (Use space bottom left).

CUBE (COPY)
Score = 12 points, 1 for each line. Deduct 1 point if not 3-D, 1 point for each line not drawn; 1 point for each additional line >12. Fail if score 11 or less.

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### TOTAL SCORE

Calculate total raw score (1st column) and total number of failed tests (2nd column).
1 failed test = Possible CCAS; 2 failed tests = Probable CCAS; 3 or more failed tests = Definite CCAS.

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**VERBAL RECALL**
Spontaneous recall: 2 points per word, category: 2 points, multiple choice: 1 point. Score = total points. Fail if score 18 or less. Inability to recall more than 1 word from multiple choice raises concern for cerebellar involvement.

What were the words you asked to learn earlier? (Subject recalls the words learned previously. Use cues and multiple choice alternatives bottom left if needed).

- **Spontaneous recall:**
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]

- **Recall with category cue:**
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]

- **Recall with multiple choice:**
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]
  - [ ] [ ] [ ] [ ] [ ]

**SIMILARITIES**
Correct answer (conceptual) = 2 points, partial answer (concrete) = 1 point, incorrect answer / no answer = 0 points. Score = total points. Fail if score < 6 or low key-bottom right.

How are the following words alike; what is the same about them? (Provide example, then test items).
(e.g., Ball/Moon = Round)

**GO NO-GO**
2 points for no errors, 1 point for one error, 0 points for two or more errors.
I am going to tap the table. When I tap once, please raise your finger then put it back down again. When I tap twice, don’t do anything. (Give an example of each condition to make sure subject understands).

**AFFECT**
Score 6 points if none are present. Subtract 1 for each item present. Fail if score 4 or less. (Rater assesses if the following are present, incorporating input from patient and/or caregiver)

- Difficulty with focusing attention or mental flexibility
- Emotionally labile, incongruous emotions, appears hopeless or depressed
- Shows easy sensory overload or avoidant behaviors
- Expresses illogical thoughts or paranoia
- Lacks empathy, is apathetic, or has blunted affect
- Angry or aggressive, irritable, oppositional, difficulty with social cues and social boundaries

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| TOTAL SCORE | RAW 120 | PASS 1  |

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**CUES AND MULTIPLE CHOICE ITEMS FOR VERBAL RECALL TEST**

<table>
<thead>
<tr>
<th>Test word</th>
<th>Flower</th>
<th>Robert</th>
<th>Courage</th>
<th>Speak</th>
<th>Yellow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note:</td>
<td>Get's at the garden</td>
<td>Boy's name</td>
<td>Trait or virtue</td>
<td>Way of communicating</td>
<td>Color</td>
</tr>
<tr>
<td>Cues:</td>
<td>Green</td>
<td>Stephe</td>
<td>Brave</td>
<td>Speak</td>
<td>Red</td>
</tr>
<tr>
<td>Multiple choice items:</td>
<td>Bush</td>
<td>Michael</td>
<td>Courage</td>
<td>Talk</td>
<td>Green</td>
</tr>
<tr>
<td>Flower</td>
<td>Joseph</td>
<td>Honesty</td>
<td>Sing</td>
<td>Blue</td>
<td></td>
</tr>
<tr>
<td>Robert</td>
<td>Grass</td>
<td>Robert</td>
<td>Patience</td>
<td>Shoot</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

---

**SIMILARITIES**
Correct conceptual answers (examples) = 2 points, partial correct / concrete answers (examples) = 1 point, incorrect answer / no answer = 0 points.

- Nose/Ear: Sense of smell
- Sheep/Elephant: Mammals, animals
- Lake/River: Bodies of water
- Airplane/Motorcycle: Vehicles, transportation

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Hoche, Guell, Sherman, Vangel, Schmahmann. Ataxia Unit, Cognitive Behavioral Neurology Unit, Schmahmann Laboratory for Neuropsychology and Cerebellar Neurology, Department of Neurology, Massachusetts General Hospital. © 2015 The General Hospital Corporation. All Rights Reserved.
Thalamus
Tuberothalamic artery territory infarction

- Fluctuating arousal and orientation
- Impaired learning, memory, autobiographical memory
- Personality changes, apathy, abulia
- Executive failure, perseveration
- True to hemisphere – language if VL involved on left; hemispatial neglect if right sided
- Emotional facial, acalculia, apraxia

Paramedian artery territory infarction

- Decreased arousal (coma vigil if bilateral)
- Impaired learning and memory, confabulation, temporal disorientation, poor autobiographical memory
- Altered social skills and personality, including apathy, aggression, agitation
- Aphasia if left sided, spatial deficits if right sided

Thalamic nuclear groupings

- RETICULAR
- INTRALAMINAR (CL, CM-Pf, Pcn)
- LIMBIC (AD, AV, AM, LD, parts of MD, PM)
- SPECIFIC SENSORY (VPL, VPM, VPI, LGN, MGN)
- EFFECTOR (VL, VA)
- ASSOCIATIVE (MD, Pulvinar, LP)

Schmahmann, 2003
• **Something obvious**
  - Exam diagnostic
    • Asterixis; alcohol on breath; diagnostically abnormal general / neuro exam
  - metabolic derangement on first line labs
    • Na, Ca, UTI, pneumonia, pO2…
  - imaging diagnostically abnormal and easy
    • stroke, hemorrhage, subdural, tumor, infection
  - Imaging clearly abnormal but not easy
    • NPH, MELAS, ADEM, stroke that didn’t make sense until now

• **Something not so obvious** – if you don’t think of it you won’t diagnose it
  - DON’T MISS THIS BECAUSE:
    • A) Your patient will die if you miss it, because it’s lethal and treatable, or
    • B) Patients and families need to know the diagnosis, even though you may not be able to cure it

  - First line labs are fine
  - Imaging is normal, not clearly abnormal, non-specific, or missed
  - THE BIG FOUR: Drugs / toxins / metabolic / infectious
    Limbic encephalitis (paraneoplastic / immune mediated)
    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
  - EVERYTHING ELSE
Here’s how this really works…

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  - EVERYTHING ELSE
Anterior Cerebral Artery Infarct

Watershed infarction
(Triple borderzone)
Anomia, verbal memory impairment, hemianopsia - the “silent confusional state” from LEFT occipitotemporal infarction

Case 1

Case 2
Prosopagnosia and visual disorientation from RIGHT medial temporal lobe (and thalamic) stroke
Posterior reversible encephalopathy syndrome (PRES)

hypertensive encephalopathy, eclampsia, cyclosporin, uremia
Primary CNS vasculitis

Presenting features
- Headache
- Seizure
- Psychosis
- Stroke

Disease entities
- Primary angiitis of the CNS
- Giant cell arteritis
- ABRA: Aβ-related angiitis
  - vasculitis superimposed upon CAA / inflammatory amyloid

Alterations in mental status (59%)
- Headaches (35%)
- Seizures, focal neurological deficits (24%)
- Hallucinations (12%)

Primary angiitis of the central nervous system (PACNS) has varied imaging characteristics. Cerebral angiography shows beading of arteries, and focal narrowing.
Here’s how this really works…

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    - Hashimoto encephalopathy
    - Creutzfeld-Jakob disease
  - EVERYTHING ELSE
Hypertension vs Cerebral amyloid angiopathy (CAA)?

64 yr woman, hemorrhagic stroke, cognitive change

Susceptibility sequence
(SWI/SWAN/gradient echo)

FLAIR sequence
Cerebral amyloid angiopathy and ischemic leukoencephalopathy
Cerebral amyloid angiopathy - lobar hemorrhage, microbleeds. White matter signal, dementia.

Cortical superficial siderosis

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    Hashimoto encephalopathy
    Creutzfeld-Jakob disease
  – **EVERYTHING ELSE**
Solitary lung metastasis

Gliomatosis cerebri

Solitary splenium metastasis causing amnesia
Intraventricular tumor resection. Delayed post-surgery seizure, with amnesia, and transient DWI signal hyperintensity in splenium.
Here’s how this really works…

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  - Imaging is normal, not clearly abnormal, non-specific, or missed
  - **THE BIG FOUR:** Drugs / toxins / metabolic / infectious
    - Limbic encephalitis (paraneoplastic / immune mediated)
    - Hashimoto encephalopathy
    - Creutzfeld-Jakob disease
  - **EVERYTHING ELSE**
Toxoplasmosis with trophozoites
Here’s how this really works…

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MELAS (Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes)

FLAIR

DWI

ADC

Lactate in serum and on MR spectroscopy, muscle biopsy, A3243G mutation or others on gene testing
Acute disseminated encephalomyelitis

2007 - Height of illness

2009 - Recovered following treatment with IVIG
Tumefactive MS
Progressive Multifocal Leukoencephalopathy
(JC virus attacks oligodendroglia)
Cerebral Autosomal Dominant Arteriopathy with Stroke-like episodes and Ischemic Leukoencephalopathy

CADASIL

52 yr. man with progressive cognitive decline
Left hemineglect from infarct in genu of right internal capsule

Schmahmann, 1984
Binswanger disease – progressive subcortical ischemic leukoencephalopathy
Intravascular lymphoma
HIV encephalitis

Multinucleated giant cell

Microglial nodule
Methotrexate leukoencephalopathy
Chasing the Dragon – Inhaled heroin leukoencephalopathy

Kriegstein et al. 1999
Hippocampal involvement due to heroin inhalation—“Chasing the Dragon”
Heroin

21 year-old woman
Recovering addict ~ 1 year
Heroin relapse. Developed confusion, repeating questions, agitation.

Exam:
**Profound anterograde amnesia**
Preserved autobiographical memory, relatively preserved long term recall

Impaired reverse digit span (3), unable to spell WORLD backwards

Normal:
Attention span (DSF 8), language, drawing/copying, praxis, abstract reasoning, calculation, affect
Delayed post-hypoxic leukoencephalopathy

2010 - At start of illness; 3 weeks after initiating event

2012 - Stable, chronically disabled
Chronic Traumatic Encephalopathy

McKee, 2009
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  - EVERYTHING ELSE
Case Study Examples
Subacute sclerosing panencephalitis
(late complication of measles virus)

Pregnant 20-yr woman. 2 weeks of dizziness, emesis, weak left side, impaired gait. Progressed to being combative, confused, short-term memory loss, disorientation. Over 1 month became mute with minimal reaction to environment. EEG with FIRDA.
CNS Whipple’s Disease
(Tropheryma whippelli)

Dementia/psychiatric, vertical gaze palsy, hypothalamic-autonomic, rhythmic movements of face and eyes (oculomasticatory myorhythmia)
Susac syndrome - Autoimmune arteriopathy
Branch retinal artery occlusion, sensorineural hearing loss, encephalopathy
Sagging Brain Syndrome — mimics frontotemporal dementia

Scharff, Buchbinder, Schmahmann, unpublished
Adrenoleukodystrophy
Metachromatic Leukodystrophy
Globoid Cell Leukodystrophy
Vanishing White Matter Disease

42 yr F: Adult Onset Leukodystrophy with Neuroaxonal Spheroids

Huntington’s disease
Movement disorder, cognitive, psychiatric manifestations

COGNITIVE FEATURES

Slowed learning
Impaired delayed free recall
Decreased use of organizational strategies (clustering of semantically related words)
Difficulty completing multi-step sequences
Impaired organizational and sequential planning
Fragile X Tremor Ataxia Syndrome

(ataxia, tremor, cognitive failure / dementia, incontinence, ED)
Gordon Holmes Syndrome
(ataxia, hypothalamic hypogonadism, dementia)
Spinocerebellar ataxia type 2
Langerhans cell histiocytosis

Mild ataxia, but prominent impulsivity, aggression, dysexecutive function

Age 8

Age 25
Neuropsychiatry in Chiari malformation: Association vs cause?