

Frontotemporal Dementia Caregiver Conference

MEDICAL MANAGEMENT

Lawrence S. Honig, MD, PhD

Taub Institute for Research, Gertrude H. Sergievsky Center,
Department of Neurology, and The Neurological Institute
Columbia University Medical Center/New York Presbyterian Hospital

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1

DISCLOSURES

Share Holder: none

Consultant: Bayer, Dainippon, Elan, Forest
Pharmaceuticals, CCNY, Isabella Geriatric Ctr, NYSDOH

Speaker's Bureau: Eisai, Forest, Johnson & Johnson,
Novartis, Ortho-McNeil, Pfizer, NYCDOHMH

Research Support: Avid, Bayer, Bristol-Myer Squibb,
Elan, Forest, Janssen, Glaxo-SmithKline, Lilly, Myriad,
Novartis, Wyeth, Alzheimer Assn, NIDDK, NIHLBI, NIA

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2

CAUSES OF DEMENTIA

- Primary neurodegenerative disorders:
Alzheimer (AD), Frontotemporal (FTD), Lewy
Body (DLB), Parkinson (PDD), PSP, CBD,
Huntington (HD), Wilson Disease (WD), CJD
- Vascular: multi-infarct, Binswanger's, CADASIL
- Inflammatory: multiple sclerosis, vasculitis
- Infectious: syphilis, Lyme, HIV, other viral, fungal
- Cancers: primary, metastatic, paraneoplastic
- Other/physical: hydrocephalus, trauma

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3

FRONTOTEMPORAL DEMENTIA

1. Prominent/early language impairment

- a) progressive reduction of speech (PPA)
- b) loss of understanding of meaning of words (SD)

2. Prominent/early behavioral (frontal) deficits

- loss of drive & interests, mental rigidity, social withdrawal
- social impropriety, disinhibition, impulsivity, distractibility
- hyperorality, stereotyped behaviors (verbal, ritual, motoric)

Early affective symptoms

depression, anxiety, somatization, asponcancy, indifference

Relative preservation of praxis & visuospatial skills

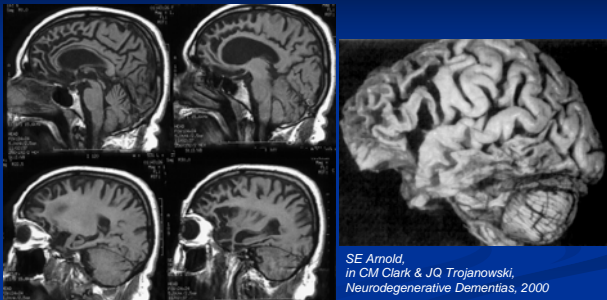
--- Presence or absence of motor neuron disease ---

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4

FRONTOTEMPORAL DEMENTIA



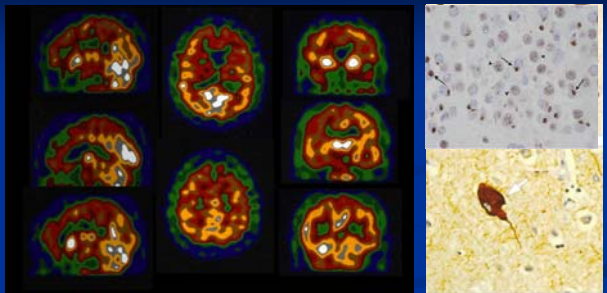
courtesy of LS Honig

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5

FRONTOTEMPORAL DEMENTIA



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6

MAJOR FUNCTIONAL SYSTEMS INVOLVED IN DEMENTIA

- MEMORY (Alzheimer's Disease [AD])
- LANGUAGE (Frontotemporal Dementia [FTD])
- BEHAVIOR (Frontotemporal Dementia [FTD])
- MOVEMENT PROGRAMS (PD, DLB, PSP, CBD)
- PRIMARY MOTOR SYSTEM (ALS, SCA)

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7

SYMPTOMS

■ SYMPTOM TYPES:

■ POSITIVE SYMPTOMS

- Agitation, Aggression, Euphoria, Mania
- Disinhibition, Hyperorality, Delusions

■ NEGATIVE SYMPTOMS

- Apathy, Indifference, Decreased energy
- Depression

■ OTHER – sleep problems, tearfulness

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8

MANAGEMENT STRATEGIES

■ NON-PHARMACOLOGIC (WITHOUT DRUGS)

■ PHARMACOLOGIC (USING DRUGS)

- SYMPTOMATIC TREATMENTS
- DISEASE-SPECIFIC TREATMENTS
- DISEASE MODIFYING TREATMENTS

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9

NONPHARMACOLOGIC

- CONTROL OF THE ENVIRONMENT
- ISOLATION vs. CROWDS
- PHYSICIANS, DENTISTS, OTHER PROVIDERS
- DIET
- MUSIC
- EXERCISE, TAI-CHI
- TV/VIDEO/COMPUTERS
- MORE HUMAN TOUCH – HELPERS
- LESS HUMAN TOUCH – STRESSORS

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10

NEUROPSYCHIATRIC DRUGS

- ANTIPSYCHOTICS
 - Typical Neuroleptics
 - Atypical Neuroleptics
- ANXIOLYTICS
- SEDATIVES
- ANTIDEPRESSANTS
- MOOD STABILIZERS
- PSYCHOSTIMULANTS

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11

SYMPTOMATIC THERAPY

POSITIVE SYMPTOMS:

agitation, aggression, disinhibition, anger, etc.

- NEUROLEPTICS
 - risperidone, olanzapine, quetiapine, clozapine, etc.
- ANTIDEPRESSANTS
 - paroxetine, sertraline, trazodone, mirtazapine, etc.
- ANXIOLYTICS/SEDATIVES
 - lorazepam, diazepam, clonazepam, etc.

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12

SYMPTOMATIC THERAPY

NEGATIVE SYMPTOMS:

apathy, depression, disinterest, staring, etc.

- ANTIDEPRESSANTS (activating)
 - fluoxetine, sertraline, bupropion, etc.
- PSYCHOSTIMULANTS
 - methylphenidate, dextroamphetamine, etc.
- OTHERS
 - modafinil, etc.

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13

AD or OTHER DRUGS IN FTD?

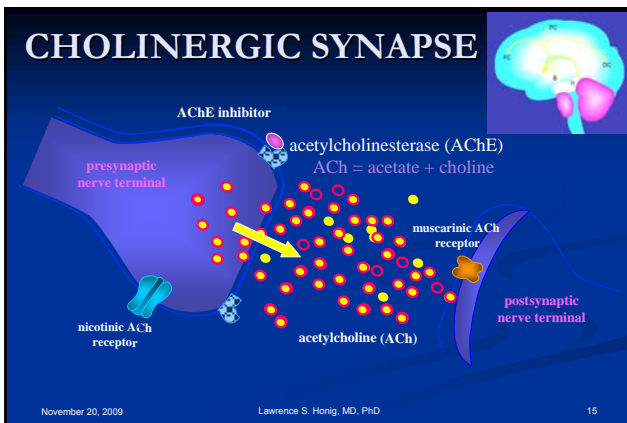
- Acetylcholinesterase inhibitor medications ?
- Memantine ?
 - a small open-label trial completed (Boxer)
 - a double-blind RPCT is currently enrolling (Boxer)
- Vitamins and hormones ?
 - Vitamins C?, E?, B?, others?, estrogen?, testosterone?
- Alternative therapies ?

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14

CHOLINERGIC SYNAPSE



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15

AD DRUGS APPROVED IN USA

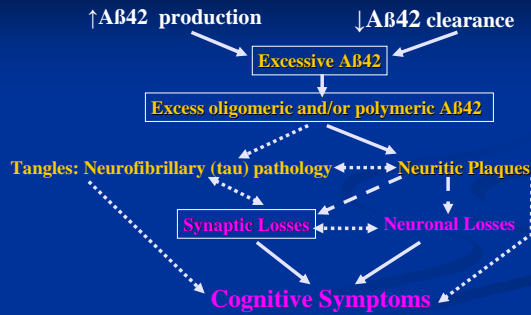
| DRUG | Year Marketed |
|------------------|---------------|
| ■ EXELON ® PATCH | 2007 |
| ■ RAZADYNE ER ® | 2007 |
| ■ RAZADYNE ® | 2007 |
| ■ NAMENDA ® | 2003 |
| ■ REMINYL ® | 2001 |
| ■ EXELON ® | 2000 |
| ■ ARICEPT ® | 1996 |
| ■ COGNEX® | 1993 |

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16

PATHOGENETIC CASCADE IN AD



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17

DISEASE-SPECIFIC DRUGS FOR FTD?

- TWO PATHOLOGIES
 - TAU PATHWAY
 - TDP43 / PROGRANULIN PATHWAY
- IDEAS ?
 - Decrease TAU or TDP43 aggregation
 - Protect Neurons from Death (neuroprotectants?)
 - Specifically: methylene blue??, memantine??, lithium??

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18

FRONTOTEMPORAL DEMENTIA MOLECULAR PATHOLOGY CLASSIFICATION

| Tau inclusions | | Non-tau pathology | |
|------------------------------|------------------|--|--------|
| Pick bodies | other | TDP43 inclusions Ubi+ (tau-syn-) inclusions | OTHERS |
| Motor neuron disease present | | | |
| TAU mutations | TDP-43 mutations | PGRN mutations | |

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19

CURRENT LISTED CLINICAL TRIALS

- Memantine 20 mg daily oral
- Amantadine oral
- Galantamine oral
- Dextroamphetamine vs Quetiapine oral
- Citalopram oral
- Tolcapone oral
- Oxytocin intranasal
- DC Polarization Brain Treatment
- Far Infrared Brain Treatment

www.clintrials.gov accessed 18 Nov 2009

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20

FUTURE TREATMENT STRATEGIES ?

- Tau – preventing aggregation ?
- Tau – preventing phosphorylation ?
- Progranulin – replacement therapy ?
- TDP43 – target alteration ?
- TDP43 – compartmentalization therapy ?
- Apoptosis prevention ?
- Neuroprotection of other sorts ?
- Nerve growth factors ?

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21

END-OF-LIFE ISSUES

- ADVANCE DIRECTIVES, LIVING WILLS
- HEALTH CARE PROXY
- FINANCIAL PROXY, WILL AND TESTAMENTS
- NUTRITION – FEEDING TUBES – yes or no?
- HOSPITALIZATIONS
- RESUSCITATION – antibiotics, drugs, CPR, intubation
- AUTOPSY

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22

AUTOPSY PROGRAMS

- Facing the end-of-life is very difficult
- Autopsy is not difficult and does not interfere with family plans
- Autopsy provides answers to the patient's family
- Autopsy information may be medically useful for the patient's descendants
- Autopsy information is vital to increasing the understanding of these diseases, and promoting the development of new therapies

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23

FRONTOTEMPORAL DEMENTIA

- EVERY AFFECTED PERSON IS AFFECTED DIFFERENTLY
- EVERY PATIENT DESERVES RESPECT AND AUTONOMY
- IT IS HARD KNOWING WHEN PATIENTS ARE NOT COMPETENT FOR A DECISION
- CAREGIVING IS THUS SPECIALLY DIFFICULT
- MAKE A PARTNERSHIP WITH YOUR HEALTHCARE PROVIDERS

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24
