A NEW OR FALSE HOPE: A Review of Recent Agents Investigated for the Treatment of Agitation and Aggression in Dementia.

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OBJECTIVES:

1. Discuss pathophysiology and characteristics of neuropsychiatric symptoms of dementia.
2. Discuss limitations of current treatments for agitation and aggression in dementia patients.
3. Review recent literature regarding pharmacotherapy for agitation and aggression in dementia.
4. Discuss potential place in therapy of recently studied treatment options for agitation and aggression in dementia.

OVERVIEW OF DISEASE STATE:

I. **Neurocognitive Disorder (NCD)[1,2]**

a. Decline in cognitive functioning from baseline causing significant impairment in cognitive performance and interference with daily activities

b. Domains of cognition affected:

i. Complex attention
ii. Executive function
iii. Learning
iv. Memory
v. Language
vi. Perceptual-motor
vii. Social

Table 1: Types of Neurocognitive Disorder[1]

	Alzheimer's Disease (AD)	Lewy Body Dementia (LBD)	Frontotemporal Lobar Degeneration (FTD)	Vascular Dementia (VD)
% of Dementia Cases:	60-90%	1.7-30.5%	5%	
Usual Age of Onset:	70s – 80s	Mid 70's	< 65	Any age following stroke
Clinical Course:	Insidious onset Slow, gradual progression	Insidious onset Slow, gradual progression	Gradual progressive	Step wise progression
Core Features:	Early impairment of memory and learning Gradual progression of cognitive and behavioral symptoms Later impairment of visuospatial, language, and motor function	Fluctuating cognition, attention, and alertness Recurrent vivid and detailed hallucinations Spontaneous features of parkinsonism Rapid eye movement sleep behavior disorder Severe neuroleptic sensitivity	Behavioral impairment: • Behavioral disinhibition • Apathy or inertia • Stereotyped behaviors Language impairment • Speech production • Comprehension	Personality and mood changes Abulia Depression Emotional lability Late-onset depressive symptoms and psychomotor slowing
Physical Markers:	Accumulation plaques and tangles	Lewy Body accumulation in cortex	Atrophy in frontal and temporal lobes	Evidence of brain injury or infarcts

II. **Neuropsychiatric symptoms (NPS)**[3]
   a. Also called behavioral and psychological symptoms of dementia(BPSD)
   b. Most common:
      i. Agitation
      ii. Depression
      iii. Apathy
      iv. Repetitive questioning
      v. Psychosis
      vi. Aggression
      vii. Sleep problems
      viii. Wandering
      ix. Socially inappropriate behaviors
   c. Consequences of NPS
      i. Significant stress and lower quality of life for caregivers
      ii. Early placement in nursing homes
      iii. Accounts for 1/3 dementia care costs
      iv. Agitation and aggression[4]
         1. Occurs in up to 80% of patients with Alzheimer's disease
         2. Leading cause of nursing home admissions

III. **Review of Current Treatments Guidelines for Agitation and Aggression in Dementia Patients**[5,6,7,8]
   a. No FDA approved agent indicated for treatment of NPS
   b. Rule out/Treat underlying causes:
      i. General medical condition (neurological conditions, infection, dehydration, delirium, fecal impaction, injury)
      ii. Psychiatric disorder (depression, psychosis, anxiety, sleep disorders, substance/medication abuse, withdrawal)
      iii. Undetected pain or discomfort
      iv. Medication side effects/interactions
      v. Religious beliefs or cultural identity
      vi. Psychosocial factors
      vii. Physical environmental factors
   c. Non-Pharmacological Treatments are first-line in absence of imminent danger or severe distress
      i. Actives therapy
      ii. Modification of activities of daily living (ADLs)
      iii. Environmental modification
      iv. Behavioral theory treatment
      v. Social contact interventions
      vi. Aromatherapy
      vii. Multisensory stimulation
      viii. Therapeutic use of music and/or dancing
      ix. Animal-assisted therapy
      x. Massage
   d. Pharmacological therapy should be reserved for when behavioral or environmental measures are not successful or severe distress or immediate risk of harm to the person or others
      i. There are no FDA approved agents for the treatment of NPS

Table 2: Comparison of Major Guidelines Addressing Pharmacological Treatment of Agitation and Aggression

	NICE 2012[5]	APA 2007/2014[6,7]	AGS/AAGP 2003[8]
Recommended Pharmacological Agents	Antipsychotics AChEI Memantine	Antipsychotics PRN BZD Anticonvulsants Antidepressants	Antipsychotics
Pharmacological Agents Recommended Against Use	IM Diazepam IM Chlorpromazine AChEI (in VD)	AChEI Memantine Valproic acid	
Recommendations for use of Antipsychotics	Avoid over-sedation Use lowest effect dose Avoid drug combinations Avoid IV formulations	Use lowest effect dose	Attempt to taper or discontinue every 6 months once stable

NICE: National Institute of Health and Care Excellence; **APA**: American Psychiatric Association; **AGS/AAGP**: American Geriatric Society/American Association for Geriatric Psychiatry; **AChEI**: acetylcholinesterase inhibitors; **PRN**: as needed; **BZD**: benzodiazepines, **IV**: intravenous

Table 3: Limitations of Current Recommended Pharmacological Treatments[6,7,8]

Agent	Pros	Cons	ADEs
Atypical Antipsychotics	Most evidence for short-term efficacy	Black Box Warning for increased all-cause mortality when used for behavioral disturbances in dementia patients. NNH ranges from 27 to 50[9]	Excess mortality, cerebrovascular events, sedation, falls, cognitive impairment, metabolic syndrome, parkinsonism, tardive dyskinesia
BZDs[7]	Benefit over placebo in RTC	Not as effective as antipsychotics in reducing behavior problems	Sedation, falls, cognitive impairment, dependency, withdrawal, respiratory depression
AChEI[7,10,11,12]	Modest benefit for behavioral symptoms	No demonstrated benefit for agitation or aggression Clinically significant benefit unclear	Agitation, insomnia, parkinsonism, diarrhea, nausea, vomiting
Anticonvulsants[6,7,10]	Carbamazepine shows modest benefit for agitation at low doses	Carbamazepine not routinely recommended due to drug-drug interactions and poor tolerability	Sedation, hyponatremia, blood dyscrasias, cognitive changes, hepatitis
Antidepressants	Citalopram 30mg/day shown to improve agitation in patients with dementia in RCT[13]	Citalopram dose used in RCT exceeds FDA max recommended dose in patients $\geq$ 60 years of age Evidence for other antidepressants is mixed NNH approximately 166[9]	QTc prolongation, nausea, vomiting, headaches, sleep changes, diarrhea, tremor, hyponatremia

ADEs: Adverse Drug Event; **NNH**: Number needed to harm; **RTC**: Randomized Controlled Trial; **FDA**: Food and Drug Administration

REVIEW OF CURRENT LITERATURE:

I. Methods of Literature Search

a. PubMed search conducted using MeSH terms “dementia”, “behavioral symptoms”, “agitation”, and “aggression”
b. Filters used: “last 5 years”, “English”, “Humans”
c. Inclusion Criteria: randomized trial, data for agitation/aggression presents (NPI subscale for agitation/aggression [NPI A/A] or Cohen Mansfield Agitation Inventory [CMAI]; see Appendix B and C), pharmacological intervention

d. Exclusion Criteria: case series trials, agitation/aggression specific data not published or available in supplementary documents, post-hoc studies, and pooled data analysis.

Table 4: Randomized Trials of Pharmacological Agents to Treat Agitation and Aggression in Dementia from Last 5 years

Agent	Study	Positive/Negative Findings
Dextromethorphan-Quinidine	**Cummings 2015**[14]	Positive
Δ9-Tetrahydrocannabinol	**van den Elson 2015**[15]	Negative
Antidepressants	Proteinsson 2014[13]	Positive
	Banergjee 2013[16]	Negative
	Teranishi 2014[17]	Positive
Memantine	Cumbo 2014[18]	Positive
	Hermann 2013[19]	Negative
	Choi 2011[20]	Negative
	Fox 2012[21]	Negative
AChEI	Cumbo 2014[18]	Positive
Mibampator	**Trzepacz 2012**[22]	Negative
Yokukonsan	Teranishi 2013[17]	Positive
Oxytocin	**Jesso 2011**[23]	Negative

II. **Dextromethorphan-Quinidine**[14]

a. Brand Name: Nuedexta®

b. Class: N-Methyl-D-Aspartate (NMDA) Receptor Antagonist

c. FDA Approved Indications: Pseudobulbar affects (PBA)

d. Proposed Mechanism of Action: Dextromethorphan modulates activity at glutamate and serotonin receptors. Quinidine acts as a specific inhibitor of cytochrome CYP2D6 to increases the systemic bioavailability of dextromethorphan.

General Study Overview	
Citation	Cummings J.L., Lyketsos C.G., Peskind E.R., Porsteinsson A.P., Mintzer J.E., et al. Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia: A Randomized Clinical Trial. *JAMA*. 2015;314(12):1242-54.[14]
Purpose	Efficacy and safety of dextromethorphan-quinidine for moderate to severe agitation in AD.
Methods	
Design	10-Week, multi-center, randomized, double-blind, placebo-controlled study • Sequential parallel comparison design – 2 consecutive 5-week stages
Subjects	Inclusion Criteria: • 50 to 90 years of age • Probable AD per 2011 National Institute on Aging-Alzheimer Association criteria[24] • Clinically significant agitation defined as poorly organized and purposeless psychomotor activity characterized by aggressive verbal, aggressive physical, and or nonaggressive physical behaviors. • Behavioral symptoms interfere with daily routine and are severe enough to warrant pharmacological treatment • Clinical Global Impression Severity (CGIS) scale for agitation score ≥ 4 • Mini-Mental Status Examination (MMSE) score of 8 to 28 Exclusion Criteria: • Non-AD dementia • Agitation not secondary due to AD • Hospitalization in a mental health care facility • Significant depression defined as a Cornell Scale for Depression in Dementia (CSDD) score ≥ 10 • Presence of schizophrenia, schizoaffective disorder, or bipolar disorder • Presence of myasthenia gravis

	• History of complete heart block, QT prolongation, or torsade de pointes or family history of congenital QT prolongation • History of postural or unexplained syncope within the last year • History of substance or alcohol abuse within the last 3 years
Endpoints	Primary Outcome • Change in NPI A/A from baseline Select Secondary Outcomes • NPI total score and individual domain scores • NPI composite score for agitation/aggression, aberrant motor behavior, and irritability/liability domain plus either anxiety domain (NPI4A) or disinhibition domain (NPI4D) • NPI Caregiver Distress score (NPI-CD) for each positively endorsed NPI domain • Psychotropic medication changes • Use of rescue lorazepam • MMSE Safety Outcomes • ADE • Vital signs • Clinical laboratory test results • Electrocardiographic findings
Intervention	Stage 1: Subjects randomized 3:4 to one of two treatment arms • Dextromethorphan-quinidine (DEX-QUIN) 20/10mg every morning plus placebo in evening for 1 week, then increased to 20/10mg twice a day for 2 weeks, then increased to 30/10mg twice a day • Placebo twice day with similar pill count Stage 2: • Subjects randomized to DEX-QUIN group continued at 30/10mg twice a day • Subjects randomized to placebo group were stratified by treatment response and re-randomized in 1:1 ratio to one of two treatment arm Oral lorazepam up to 1.5mg/day and 3 days/week allowed as rescue medication
Statistics	• A sample of size of 196 subjects needed to detect a mean difference of 2.5 points between groups to achieve a power of 90% • Efficacy Endpoints o Data from both 5 week stages with 1:1 weighting using ordinary least squares and including all subjects in stage 1 and only the re-randomized placebo non-responders in stage 2. o Difference between treatment groups: analysis of co-variance (ANCOVA) with treatment as the fixed effect and baseline as the covariant o Sensitivity analysis performed on primary endpoint using repeated-measures model excluding those re-randomized in stage 2 and using unrelated regression method in the sequential parallel comparison design o Exploratory analysis on primary endpoint using sequential parallel comparison method including those re-randomized in stage 2

Results

Baseline Characteristics

Table 5: Select Baseline Characteristics from Cummings 2015 Table1 on page 1247.

	DEX-QUIN (n = 93)	Placebo (n = 127)
Mean age, years	77.8	77.8
Female, %	55.9	58.3
Caucasian, %	90.3	92.9
Residence, %		
Outpatient	88.2	87.4
Assisted living	5.4	7.9
Nursing home	6.5	4.7
Concomitant Medications, %		
AChEIs	72.0	74.8
Memantine	46.2	52.0
Antidepressants	61.3	51.2
Antipsychotics	17.2	22.8
Benzodiazepines	6.5	9.5
Benzodiazepine like derivatives	6.5	9.5
Baseline NPI total score	40.1	38.0
Agitation/Aggression	7.1	7.0
Aberrant Motor Behavior	4.0	2.0
Irritability/Liability	5.8	5.4
NPI4A	20.9	20.1
NPI4D	19.8	18.5
Baseline MMSE	17.4	17.2

DEX-QIN: Dextromethorphan-Quinidine; **AChEI**: Acetylcholinesterase inhibitors; **CGI-S**: Clinical Global Impression Severity Scale; **NPI**: Neuropsychiatric Inventory, **NPI4D**: NPI composite score for agitation/aggression, aberrant motor behavior, and irritability/liability domain plus disinhibition domain; **NPI4A:** NPI composite score for agitation/aggression, aberrant motor behavior, and irritability/liability domain plus anxiety domain; **MMSE**: Mini Mental Status Examination.

Efficacy Outcomes

Table 6: Select Efficacy Data from Cummings 2015 Table 2 on page 1248-9.

Outcome Measure and Study Stage	Change from Baseline, mean DEX-QUIN (n = 93)*	Placebo (n = 125)*	P-Value by Stage	Least Squares Mean Treatment Difference (95% CI)	P-Value by SPCD
NPI A/A					
Stage 1	-3.3	-1.7	<0.001	-1.5 (-2.3 to -0.8)	
Stage 2	-2.0	-0.8	0.02	-1.6 (-2.9 to -0.3)	<0.001
Week 10	-3.6	-1.9	0.001	-1.8 (-2.8 to -0.7)	0.03
NPI Total Score					
Stage 1	-13.5	-8.5	0.03	-4.2 (-8.0 to -0.4)	
Stage 2	-6.0	-2.5	0.15	-3.8 (-9.0 to 1.4)	0.01
Week 10	-16.0	-10.1	0.02	-5.7 (-10.7 to -0.7)	N/A
NPI4A Composite					
Stage 1	-7.3	-4.5	0.03	-2.4 (-4.6 to -0.2)	
Stage 2	-4.8	-1.4	0.01	-3.9 (-7.0 to -0.9)	0.001
Week 10	-8.5	-5.0	0.01	-3.4 (-6.1 to -0.7)	N/A
NP14D Composite					
Stage 1	-7.6	-4.0	0.006	-3.0 (-5.1 to -0.9)	
Stage2	-4.6	-1.9	0.02	-3.5 (-6.5 to -0.5)	<0.001
Week 10	-8.3	-5.0	0.02	-3.0 (-5.5 to -0.4)	N/A

DEX-QIN: Dextromethorphan-Quinidine; **SPCD**: Sequential parallel comparison design analysis, combined results from all patients in stage 1 and from placebo non-responders re-randomized in stage 2 based on 50/50 weighting of the NPI A/A for each stage of the study; **NPI A/A**: Neuropsychiatric Inventory Agitation/Aggression domain; **NPI4D**: NPI composite score for agitation/aggression, aberrant motor behavior, and irritability/liability domain plus disinhibition domain; **NPI4A**: NPI composite score for agitation/aggression, aberrant motor behavior, and irritability/liability domain plus anxiety domain

*Total number of subjects randomized in stage 1 included in primary SPCD analysis, total number of non-responders re-randomized at stage 2 and included in primary SPCD analysis DEX-QUIN (n =44) Placebo (n=45)

- Significant statistical difference also for:
  - NPI Aberrant Motor Behavior at stage 2 and week 10 (p-value 0.04 and 0.03) and SPCD (p = 0.03)
  - NPI irritability/liability at SPCD (p =0.03)
  - NPI Caregiver distress agitation score at stage 1 (p < 0.001) and SPCD (p =0.01)
  - NPI Caregiver distress total score at SPCD (p = 0.01).
  - Caregiver Strain Index (CSI) for stage 1 and at week 10 (p = 0.3 and 0.4)
  - CSDD for stage 1 and at week 10 (p = 0002 and 0.03) and SPCD (p = 0.01)
  - Alzheimer Disease Cooperative study Clinical Impression of Change (ADCS-CGIC) score for agitation at Stage 1 and week 10 (p = <0.001 and 0.02) and SPCD (p < 0.001)
  - Patient Global Impression of change (PGIC) for stage 1, stage 2, and week 10 (p = 0.001, 0.04, and 0.007) and SPCD (p = 0.001)
  - Alzheimer Disease Assessment Scale – Cognitive Subscale (ADAS-CS) week 10 (p = 0.07)
- No significant statistical difference for:
  - Quality of Life – Alzheimer's Disease score (QoL-AD) rated by patient or caregiver
  - Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL)
  - MMSE

Safety Outcomes

Table 7: Summary of Treatment-Emergent Adverse Events (TEAEs) from Cumming 2015

	DEX-QUIN (n = 152)	Placebo (n = 127)
TEAEs, n (%)	93 (61.2)	55 (43.4)
SAEs, n (%)	12 (7.9)	6 (4.7)
Treatment discontinuation due to TEAEs, n (%)	8 (5.3)	4 (3.1)
Treatment discontinuation due to SAEs, n (%)	4 (2.6)	2 (1.6)

DEX-QUIN: Dextromethorphan-quinidine; **TEAE**: Treatment-Emergent Adverse Events; **SAE**: Serious Adverse Event

- Most common TEAEs in DEX-QUIN group (>3% and > placebo): falls (8.6 vs. 3..9%), diarrhea (5.9% vs. 3.1%), urinary tract infection (5.3% vs. 3.9%), and dizziness (4.6% vs. 2.4%)
- SAEs in DEX-QUIN group: chest pain (n = 2), anemia (n = 2), acute myocardial infarction (n = 2), bradycardia (n = 1), kidney infection (n = 1), femur fracture (n = 1), dehydration (n = 1), colon cancer (n = 1), cerebrovascular accident (n = 1), aggression (n = 1), and hematuria (n = 1)
- No clinically significant differences in ECG findings between groups
  - Mean change in QTcF in DEX-QUIN group was 5.3 ms (SD 14.06)

Author's Conclusions

- Dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation in Alzheimer disease with moderate to severe agitation

Clinical Significance

- Large, RCT study
- Minimum clinically important difference (MCID) for NPI total score (decrease in 4 points or a 30% reduction in baseline score)
- MICD for NPI A/A unknown
- Improvement in caregiver distress seen but not improvement in QoL or ADLs.

Strengths	Weaknesses
• Randomized, double-blind, controlled trial • Sequential parallel comparison design to reduce placebo effect • Sufficient sample size • NPI Agitation/Aggression domain at primary outcome • Results consistent with sensitivity analysis	• Short trial duration • Funded by Avanir Pharmaceuticals Inc. which had a role in design, data collection and analysis, interpretation of results, and decision to submit for publication.

e. Future Studies:

i. NCT02442765: 15-AVP-786-301

1. Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety, and Tolerability of AVP-786 (Deuterated [d6]-Dextromethorphan Hydrobromide [d6-DM]/Quinidine Sulfate [Q]) for the Treatment of Agitation in Patients With Dementia of the Alzheimer's Type

2. Study Contacts: Nguyen, U. and Shin, P.
3. Current Status: Enrolling
4. Estimated Date of Completion: July 2018
5. Study Design: 12 week multicenter, randomized, placebo-controlled study
6. Primary Outcome Measure: NPI Agitation/Aggression Domain

ii. NCT02442778 : 15-AVP-786-302

1. Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety, and Tolerability of AVP-786 (Deuterated [d6]-Dextromethorphan Hydrobromide [d6-DM]/Quinidine Sulfate [Q]) for the Treatment of Agitation in Patients With Dementia of the Alzheimer's Type.
2. Study Contacts: Nguyen, U. and Shin, P.
3. Current Status: Enrolling
4. Estimated Date of Completion: July 2018
5. Study Design: 12 week multicenter, randomized, placebo-controlled study
6. Primary Outcome Measure: NPI Agitation/Aggression Domain

iii. NCT02446132: 15-AVP-786-303

1. Title: Long Term, Extension Study of the Safety and Efficacy of AVP-786 (Deuterated [d6] Dextromethorphan Hydrobromide [d6-DM]/Quinidine Sulfate [Q]) for the Treatment of Agitation in Patients With Dementia of the Alzheimer's Type
2. Study Contacts: Nguyen, U. and Shin, P.
3. Current Status: Enrolling
4. Estimated Date of Completion: July 2019
5. Study Design: Extension study of the Phase 3 Studies 15-AVP-786-301 and 15-AVP-786-302, which also allows patients from the Phase 2 Study 12-AVR-131 to be included.
6. Primary Outcome Measure: Treatment Emergent Adverse Event, SAE, Clinical Laboratory Assessments, 12-lead electrocardiograms (ECGs)

III. **Δ9-Tetrahydrocannabinol (THC)[15]**

a. Brand Name: Namisol®
b. Class: Natural cannabinoid
c. FDA Approved Indications: none
   iv. Synthetic THC dronabinol (Marinol®) approved in US for use in appetite stimulation in AIDS patient and chemotherapy-induced nausea and vomiting
d. Proposed Mechanism of Action: Activation of CB_1 receptors leading to modulation of emotion, cognition and behavior. Proposed activity at acetylcholine, dopamine, norepinephrine, y-aminobutyric acid, glutamate, serotonin, prostaglandin, and opioid receptors.

General Study Overview	
Citation	van den Elsen G.A., Ahmed A.I., Verkes R.J., Kramers C., Feuth T., et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. *Neurology*. 2015 Jun 9;84(23): 2338-2346. [15]
Purpose	Efficacy and safety of low dose tetrahydrocannabinol (THC) in dementia related neuropsychiatric symptoms.
Methods	
Design	3-Week Randomized, double-blind, placebo-controlled, multicenter, phase II trial
Subjects	Inclusion Criteria: • Diagnosis of AD, VD, or mixed dementia per National Institute on Aging-Alzheimer's Association[26] or National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche en l'Enseignement en Neurosciences (NINDS-AIREN) criteria[1] • NPI total score ≥ 10 with reported symptoms of agitation, aggression, or aberrant motor behavior existing at least 1 month prior to screening • Caregiver available at least twice a week Exclusion Criteria: • Current major psychiatric disorders • Any severe or instable concomitant illness (particularly seizures) • Arrhythmia necessitating treatment other than Beta-blocker or digoxin • Severe heart failure • Any concomitant disease necessitating treatment changes • History of frequent falling due to hypotension • History or current alcohol or drug abuse • Use of tricyclic antidepressants (TCAs), fluoxetine, or carbamazepine NOTE: Original protocol specified recruitment of patients with behavioral disturbances and persistent pain complaints however was amended after first 8 subjects were enrolled due to low number of eligible patients.
Endpoints	Primary Outcome: • Change in total NPI score from baseline at day 14 and 21 Secondary Outcomes: • CMAI • Barthel Index – activities of daily living • QOL-AD • Caregiver Clinical Global Impression of Change (CCGIC)
Intervention	• Subjects randomized in 1:1 allocation ratio to one of two treatment arms stratified per center and minimized for baseline NPI score, dementia severity, sex, and current opioid use o THC 1.5mg tablets three time a day for 3 weeks (total 4.5mg/day) o Placebo with similar pill burden • All patients also received 1000mg acetaminophen three times a day in case of pain complain or suspected pain in non-communicative patients • Concurrent psychotropic medications were continued provided that dose and frequency were kept stable within 2 weeks prior to and after trial
Statistics	• Sample size of 130 subjects required for power of 80% to detect a difference in NPI scores of 4 points with a standard deviation (SD) of 12 points using two-sided testing at 0.05. • Efficacy Outcomes o Intent-to-treat analysis ▪ Mean difference in NPI total score from baseline and sub-items, and other secondary outcomes measures – linear mixed model with center, baseline NPI, clinical dementia rating score, sex, current opioid use, and time as fixed factors. o Post-Hoc Analysis: ▪ Efficacy in ambulatory vs. inpatient subjects • Safety Outcomes: o Difference in incidence of ADE between groups – Chi-square o Difference in severity of ADE between groups – Mann-Whitney U

Results

Baseline Characteristics

Table 8: Select Baseline Characteristics from van den Elsen 2015 Table1 on page 2341.

	Total (N=50)	THC (N=24)	Placebo (N=26)
Men (%)	50	45.8	53.8
Mean age (years)	78.4	79.0	78.0
Domestic Situation (%)			
Community dwelling	24	13	11
Specialized dementia care unit	13	4	9
Nursing home	13	7	6
Caucasian (%)	100	100	100
Type of Dementia			
Alzheimer	34	16	18
Vascular	7	3	4
Mixed	9	5	4
Mean MMSE	14.8	15.9	14.0
Concomitant Psychotropic Medication (%)			
Antipsychotics	20	**29.2**	**11.5**
Antidepressants	40	37.5	42.3
Benzodiazepines	42	33.3	50
Anticonvulsants	0	0	3.8
Cholinesterase inhibitors	16	20.8	11.5
Memantine	6	8.3	3.8
Melatonin	26	20.8	30.8

THC: tetrahydrocannabinol

Efficacy Outcomes

Table 9: Select Efficacy Data from van den Elsen 2015 Table 2 on page 2343.

	THC			Placebo			Mean Difference at Day 21 (95% CI)
	Baseline	Day 14	Day 21	Baseline	Day 14	Day 21	
NPI Total Score	37.4	31.0*	27.8*	25.6	26.1	23.9	3.2 (-3.6 to 10.0)
NPI A/A	5.7	4.1	4.5	6.2	5.0	4.4	-0.1 (-2.0 to 1.9)
NPI Aberrant motor behavior	4.5	4.9	3.6	5.2	4.3	3.7	0.3 (-1.0 to 1.7)
CMAI	58.8		56.6	61.6		53.7	4.6 (.3.0 to 12.2)
CCGIC	3.7		3.5	3.4		3.2	0.2 (-0.5 to 0.9)

NPI: Neuropsychiatric Index**; NPI A/A:** NPI agitation/aggression domain; **CMAI**: Cohen-Mansfield Agitation Inventory; **CCGIC**: Caregiver Clinical Global Impression of Change
* Indicates change from baseline was statistically significant, p = < 0.05

- No benefit seen in community dwelling patients (5.0, 95% CI: -1.8 to 11.7) or inpatient patients (1.5, 95% CI: -10.0 to 13.1)
- No significant difference between groups for Barthel Index or QoL-AD
- Four patients in THC group received escape medication (BZDs) and 2 patients in placebo groups (p=0.33)

Safety Outcomes

Table 10: Summary of TEAEs from van den Elsen 2015

	THC (n=24)	Placebo (n=26)
One or more TEAEs	16 (66.7%)	14 (53.8%)
SAEs	0 (0.0%)	0 (0.0%)
Common TEAEs*		
Dizziness	4 (16.7%)	4 (15.4%)
Cognitive disorder	3 (12.5%)	1 (3.8%)
Restlessness	2 (8.3%)	1 (3.8%)
Pneumonia	2 (8.3%)	0 (0.0%)

THC: Δ9-Tetrahydrocannabinol; **TEAE**: Treatment-Emergent Adverse Events; **SAE**: Serious Adverse Events
*TEAS with an incidence >1 in THC group and occurring more often in THC groups than placebo group.

- No difference in incidence of ADE between groups
- 2 subjects discontinued due side effects – pneumonia (THC), persistent nausea (placebo)
- No significant differences between groups regarding changes in safety measurements

Author's Conclusions

- No benefit seen with 4.5mg/day of oral THC treatment on behavioral disturbances, QOL, or ADL in patients dementia.

Clinical Significance	
• Largest RTC of THC for NPS in dementia	
Strengths	**Weaknesses**
• Randomized controlled trial • Sample population consistent with dementia population • Subjects had clinically relevant NPS at baseline • NPS as primary outcome	• Small sample size, did not meet power • Larger number of subjects in THC group were also receiving antipsychotic medications

e. Future Studies:
   i. NCT02351882: 318-2013
      1. Title: Safety and Efficacy of Nabilone in Alzheimer's Disease: a Pilot Study
         a. Nabilone = Δ9-tetrahydrocannabinol (THC) analogue
      2. Primary Investigators: Lanctôt K.L, Herrmann, N.
      3. Current Status: Enrolling
      4. Estimated Date of Completion: October 2017
      5. Study Design: 14-week randomized, cross-over trial
      6. Primary Outcome Measure: Change in agitation per CMAI

IV. **Mibampator**[22]
   a. Brand Name: LY451395
   b. Class: Biarylpropylsulfonamide α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) potentiator
   c. FDA Approved Indications: none
   d. Proposed Mechanism of Action: Potentiation of glutamatergic neurotransmission

General Study Overview	
Citation	Trzepacz P.T., Cummings J., Konechnik T., Forrester T.D., Chang C., et al. Mibampator (LY451395) randomized clinical trial for agitation/aggression in Alzheimer's disease. *Int Psychogeriatr.* 2013 May; 25(5):707-19.[22]
Purpose	Efficacy and safety of mibampator in patients with Alzheimer's disease and clinically significant agitation/aggression symptoms.
Methods	
Design	12-week, multicenter, randomized, double-blind, placebo-controlled, phase II trial
Subjects	Inclusion Criteria • Age ≥ 60 years • Male or non-fertile female • Community dwelling • MMSE score 6-26 • Probable AD per Diagnostic and Statistical Manual –IV-R (DSM-IV-R) and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) criteria • NPI total score ≥ 10 • NPI A/A score ≥ 4 on one domain at screening visit and randomization visit • Clinically significant and persistent agitation/aggression for at last 3 days per week for at least 4 weeks • Reliable caregiver available Exclusion Criteria • CT or MRI scan within the last 2 years inconsistent with AD • Modified Hachinski Ischemia Scale >4 • Meet DSM-IV-TR criteria for delirium and/or Delirium Rating Scale-Revised-98 (DRS-R98) score ≥ 18 • Unstable medical problems or other major neurological or psychiatric disorder
Endpoints	Primary Outcome • Change in NPI A/A score from baseline at 12 weeks Secondary Outcomes

	• Frontal Systems Behaviors Scale (FrSEBe) • NPI-10 • CMAI-C • CSDD • CGI-S Agitation/Aggression • CGI-S Global Functioning • ADAS-CS • ADCS-ADL

Intervention	• Psychotropic medications were discontinued prior to randomization
	  ○ Stable doses of sertraline, citalopram, escitalopram, and fluoxetine were allowed
	  ○ Use of AChEIs and memantine were allowed
	• 3 – Study periods
	  ○ 3 to 28 day screening period
	  ○ 12-week, double-blind treatment period
	  ○ 1-week single-blind washout period
	• Subjects Randomized in 1:1 manner into one of two treatment arms and stratified by investigation site and severity of NPS in block sizes of four
	  ○ Mibampator 3mg twice a day
	  ▪ One time dose reduction to 1mg twice a day allow due to intolerability
	  ○ Placebo twice a day with similar pill burden
	• Rescue doses of lorazepam 0.5mg up to 3 doses/day and 6 doses in 3-weekperiod were allowed for severe agitation
	  ○ Rescue dose not allowed within 24 hours proceeding a clinic visit

Statistics	• Sample size of 75 subjects per treatment arm needed to obtain power of 80% for primary outcomes
	• Primary and Secondary Outcomes:
	  ○ Intent-to-treat population
	  ○ Continue measures – likelihood based, mixed-effects model repeated measures analysis (MMRM) with fixed categorical effects of treatment, investigator, baseline NPS severity, visit, and treatment-by-visit interaction and continuous covariates of baseline score, and baseline score-by-visit interaction score
	  ▪ Baseline severity was stratified in high NPS (NPI-10 $\geq$ 30) and low NPS (NPI-10 < 30)
	  ○ Categorical measures – Fisher's exact test

Results	
Baseline Characteristics	**Table 11: Select Baseline Characteristics from Trzepacz 2013 Table1 on page 18.**

	Mibampator (n = 63)	Placebo (n = 69)
Female, %	49.2	52.2
Age, years	77.2	77.7
Caucasian, %	84.1	89.9
Years of formal education	13.4	13.3
Baseline MMSE, %		
Mild (20 – 26)	33.3%	39.1%
Moderated (11-19)	41.3%	50.7%
Severe (6-10)	25.4%	10.1%
Psychosis per NPI, %	33.3%	29.0%
Current AChEI or memantine use, %	73.0%	71.0%
Current antidepressant use	**4.8%**	**18.8%***
Baseline NPI A/A	18.8	18.1
Baseline NPI-10	31.9	29.7
Baseline CMAI-C	**73.6**	**64.7***
Baseline FrSBe Total T-Score	92.4	89.1

MMSE: Mini Mental Status Examination**; NPI:** Neuropsychiatric Inventory**; AChEI:** acetylcholinesterase inhibitor**; NPI:** Neuropsychiatric Inventory**; NPI A/A:** Neuropsychiatric Inventory Agitation/Aggression Domain**; NPI D-A/A:** Neuropsychiatric Inventory Distress score for Agitation/Aggression**; CMAI-C:** Cohen-Mansfield Agitation Inventory Caregiver version**; FrSBe:** Frontal Systems Behaviors Scale
* indicates p-value < 0.05

	• Mean mibampator dose 2.75mg • 20 subjects withdrew from each treatment arm

Efficacy Outcomes	• Change in NPI A/A scores from baseline
	  ○ No significant difference between groups (p = 0.593), both groups improved by 5 points after 3 weeks and sustained improvement to week 12
	  ○ No significant difference between groups in secondary analysis (APOE-4 allele status, sex, type of caregiver, concomitant AchEI or memantine use, functional status, comorbid medical conditions, etc.)
	• Secondary Outcomes
	  ○ No significant difference in change from baseline scores for ADAS-CS, ADCS-ADL, CMAI-C or CSDD scores between groups
	  ○ Statistically significant improvement in FrSBe Total T-score in mibampator group compared to placebo (p = 0.007), as well as Apathy (p = 0.04) and executive dysfunction (p = 0.018) subscale T-scores
	  ▪ Trend towards significance on disinhibition subscale T-score (p = 0.052)
	  ○ Statistically significant improvement in NPI apathy (p = 0.039) in mibampator group
	  ○ More subjects in mibampator group received lorazepam doses (36.5% vs. 18.8%, p = 0.031).

Safety Outcomes	• Incidence of TEAEs were similar between groups
	  ○ mibampator 57.14% vs. placebo 55.07%
	• No significant difference in incidence SAEs between groups
	  ○ SAEs in mibampator group – pseudocyst (n=1), non-cardiac chest pain (n = 1), pneumonia (n=1), transient ischemic attack (n=1), and psychotic disorder (n=1)
	  ○ No SAEs were attributed to mibampator
	• No significant difference between discontinuation due to AEs, TEAEs, or TEAEs possibly related to study drug between groups
	  ○ Mibampator group: back pain (n=1), myalgia (n=1), dizziness (n=1), depression (n=1), and psychotic disorder (n=1)
	  ○ Placebo group: pneumonia (n=1), spinal column stenosis (n=1), anxiety (n=1)
	• No TEAEs led to a dose reduction in either treatment group

Author's Conclusions
• No efficacy advantage of mibampator over placebo for agitation/aggression symptoms in AD

Clinical Significance
• RCT specifically designed to investigate efficacy of mibampator on NPS symptoms of agitation and aggression based upon secondary outcome of previous trial

Strengths	Weaknesses

• RCT with primary outcome specifically measuring agitation/aggression
• Met sample size necessary per power calculations
• Adequate trial period to determine effects
	• Baseline differences
	  ○ Greater antidepressant use in placebo group
	  ○ Higher CMAI scores in mibampator group
	• Possible inflated baseline scores due to caregiver bias
	• Caregiver education given at start of study may impacted results

e. Future Studies:
   ii. No future registered studies

V. **Oxytocin**[24]
   a. Brand Name: Pictocin®
   b. Class: Oxytocic agent
   c. FDA Approved Indications: induction of labor, postpartum hemorrhage, termination of pregnancy
   d. Proposed Mechanism of Action: enhanced prosocial behaviors

General Study Overview	
Citation	Jesso S., Morlog, D., Ross. R., Pell M.D., Pasternak S.H., et al. The effects of oxytocin on social cognition and behavior in frontotemporal dementia. *Brain*. 2011: 134; 2493-2501.[23]
Purpose	Efficacy of oxytocin to improve performance on emotion recognition tasks and caregiver reports of social functioning.

<table>
<tr><th colspan="2">Methods</th></tr>
<tr><td>Design</td><td>1-Week, Randomized, double-blind, placebo-controlled, cross-over study</td></tr>
<tr><td>Subjects</td><td>Inclusion Criteria:
• Meet criteria for behavioral variant FTD per Neary 1998[26] and FTD consensus criteria per Rascovksy 2011.[27]
• MRI, CT, or single-photon emission CT imaging consistent with diagnosis
• Presence of emotional blunting features
Exclusion Criteria:
• Comprehension deficits or language impairment that would preclude completion of study tasks
• History of stroke, tumor or other focal brain lesions
• History of other neurological or psychiatric disorder that could account for patient's symptoms
• Uncontrolled hypertension
• Current use of prostaglandins
• Use of any investigational or experimental drug or device within 60 days prior to screening</td></tr>
<tr><td>Endpoints</td><td><u>Primary Outcome</u>: Emotion recognition
• Facial expression recognition task
• Auditory emotion recognition task
• Mind in the Eye Theory of Mind task
<u>Secondary Outcomes</u>: Behavioral Improvement
• NPI
• Frontal Behavioral Inventory (FBI)</td></tr>
<tr><td>Intervention</td><td>• 3 experimental visits 2 weeks apart with a follow up call 1 week after each experimental visit
o Visit 1: Baseline visit; Visit 2: oxytocin/placebo; Visit 3: placebo/oxytocin
• Study Medications
o One dose of 24 IU of intranasal oxytocin (3 puffs per nostril, 4 IU per puff)
o Saline mist (placebo)
• Measures
o Emotion processing tasks completed 20 minutes after receiving dose
o Caregiver ratings on NPI and FBI completed evening of medication administration and at 1 week follow up</td></tr>
<tr><td>Statistics</td><td>• Primary Outcome – Emotion recognition tests
o Repeated-Measures ANOVA with emotion, intensity, and treatment was within-subject factors for percentage of correct responses for each task
• Secondary Outcome – Behavioral ratings
o Paired-sample t-test for NPI and FBI total scores</td></tr>
<tr><th colspan="2">Results</th></tr>
<tr><td>Baseline Characteristics</td><td>
Table 12: Select Baseline Characteristics from Jesso 2011 Table 1 page 2495.
<table>
<tr><th></th><th>Total Population
(n =20)</th></tr>
<tr><td>Age, mean years</td><td>64.4</td></tr>
<tr><td>Education, mean years</td><td>12.85</td></tr>
<tr><td>Illness duration, mean years</td><td>4.96</td></tr>
<tr><td>Baseline MMSE mean score</td><td>23.4</td></tr>
<tr><td>Baseline FBI mean score</td><td>37.68</td></tr>
<tr><td>Baseline NPI mean score</td><td>32</td></tr>
<tr><td colspan="2">MMSE: Mini-Mental Status Examination; FBI: Frontal Behavioral Inventory; NPI: Neuropsychiatric inventory</td></tr>
</table>
• 20 subjects enrolled in study
o 2 subjects withdrew due to inability to complete emotion recognition tasks
o 18 subjects completed the study
</td></tr>
</table>

Efficacy Outcomes

Table 13: Select Efficacy Data from Jesso 2011 Table 2 page 2498 and Table 3 2499

	Baseline	Oxytocin Day 1	Placebo Day 1	Oxytocin Week 1	Placebo Week 1
NPI Total	**32 ± 12.9**	**28.1 ± 12.2**	**30.8 ± 12.5**	32.8 ± 13.4	31.0 ± 12.8
Agitation/aggression	2.3 ± 2.5	2.3 ± 2.5	2.4 ± 2.7	2.8 ± 3.2	2.4 ± 2.8
Irritability	3.9 ± 3.1	1.7 ± 2.2	2.5 ± 3.0	2.5 ± 2.9	2.4 ± 2.8
Disinhibition	6.4 ± 2.8	3.7 ± 3.4	4.0 ± 3.3	3.9 ± 3.4	3.8 ± 3.3
FBI Total	13.8 ± 4.6	12.9 ± 4.3	14.1 ± 4.8	14.2 ± 4.2	13.6 ± 4.6
Aggression	0.7 ± 1.1	0.5 ± 0.9	0.7 ± 1.1	0.6 ± 1.0	0.7 ± 1.1
Irritability	1.3 ± 1.2	1.2 ± 1.1	1.4 ± 1.3	1.3 ± 1.2	1.5 ± 1.2
Inappropriateness	2.0 ± 0.9	1.9 ± 9.0	2.1 ± 0.9	2.1 ± 0.9	2.1 ± 0.8
Impulsivity/poor judgment	2.1 ± 1.1	2.1 ± 1.2	2.1 ± 1.1	2.3 ± 1.0	2.0 ± 1.2

NPI: Neuropsychiatric Inventory**; FBI:** Frontal Behavioral Inventory

- Significantly greater improvement from baseline NPI score with oxytocin compared to placebo on day 1. (13% vs. 3% improvement, estimated score difference of -2.70 [95% CI: -5.29, -0.11], p = 0.05)
  - No significant different at week 1
  - No significant difference in NPI sub-item scores
- Nonsignificant trend toward improvement in raw FBI scores with oxytocin compared to placebo on day 1 (9% vs. 3% improvement, p = 0.08)
  - No significant difference at week 1
  - No significant difference in FBI sub-time scores

Safety Outcomes

- No significant adverse reactions attributed to study medication reported
- Reported ADRs after administration of study drug include: soft stool (n=1) , visual hallucinations (n=1), palpitations and idiopathic hypokalemia (n=1)
- Reports ADRs after administration of placebo include: fatigue (n=3), irritability and restlessness (n=3), hand tremor (n=1)

Author's Conclusions

- Results show a potential therapeutic benefit of oxytocin on FTD symptomology and social cognition and suggest oxytocin may be a potential symptomatic treatment for FTD however, longer duration trials with larger patient populations are needed to warrant use of oxytocin in FTD.

Clinical Significance

- First RCT to examine the potential effects of oxytocin on negative social behaviors in FTD.

Strengths	Weaknesses
• Randomized, double-blind, placebo-controlled, cross-over study • Dosing based on significant effects on emotion recognition tasks in prior studies in healthy adults and patients with autistic spectrum disorder • Use of validated behavioral scale - NPI	• Small sample size • Short study duration, no repeat dosing data • Behavioral results are secondary outcomes and post-hoc analysis of sub-items • Caregiver rating open to bias • Duration of benefit unclear with weekly assessment • Limited to FTD • Caregivers known to patient, may not be generalizable to nursing staff/non-kin caregivers

e. Future studies: none

VI. Other agents being studied:

f. Atypical antipsychotics: aripiprazole, brexpirpazole

g. Mood stabilizers: lithium

h. Alpha-2C antagonists : ORM-12741 (potent and selective alpha-2C adrenoceptor (AR)-antagonist)

i. Alpha-1 antagonists: prazosin

j. Amyloid anti-aggregation agents: ELND005 (Scyllo-inositol)

CONCLUSIONS:

1. Need for safe and effective pharmacological treatment for agitation and aggression in dementia.
2. Current recommended pharmacological treatments lack in efficacy or safety.
    a. Atypical antipsychotic remain first-line treatment for short-term use.
    b. Antidepressants are a safer alternative if long-term treatment is indicated.
3. Sufficient evidence to recommend newer agents under investigation is lacking.
    a. Data for dextromethorphan-quinidine is promising but long-term safety data is needed prior to recommending routine use.

APPENDIX A

List of Abbreviations	
NCD	Neurocognitive Disease
AD	Alzheimer's disease
VD	Vascular Dementia
FTD	Frontotemporal Neurocognitive Disorder
LBD	Lewy Body Dementia
NPS	Neuropsychiatric Symptoms
BPSD	Behavioral and Psychological Symptoms of Dementia
ADL	Activities of Daily Living
NICE	National Institute of Health and Care Excellence
APA	American Psychiatric Association
AGS	American Geriatric Society
AAGP	American Association for Geriatric Psychiatry
AChEI	Acetylcholinesterase inhibitors
PRN	as needed
BZD	Benzodiazepines
IV	Intravenous
ADE	Adverse Drug Event
RTC	Randomized Controlled Trial
FDA	Food and Drug Administration
NPI	Neuropsychiatric Inventory
NPI A/A	Neuropsychiatric Inventory Agitation/Aggression Subscale
CMAI	Cohen Mansfield Agitation Inventory
PBA	Pseudobulbar affects
CGI-S	Clinical Global Impression Severity Scale
MMSE	Mini-Mental Status Examination
CSDD	Cornell Scale for Depression in Dementia
NPI-CD	Neuropsychiatric Inventory Caregiver Distress
DEX-QUIN	Dextromethorphan-Quinidine
ANCOVA	Analysis of co-variance
SPCD	Sequential parallel comparison design
CSI	Caregiver Strain Index
ADCS-CGIC	Alzheimer Disease Cooperative Study-Clinical Impression of Change
PGIC	Patient Global Impression of Change
ADAS-CS	Alzheimer Disease Assessment Scale –Cognitive Subscale
QoL-AD	Quality of Life-Alzheimer Disease score
ADCS-ADL	Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory
TEAE	Treatment Emergent Adverse Event
SAE	Serious Adverse Events
THC	Tetrahydrocannabinol
TCA	Tricyclic antidepressant
CCGIC	Caregiver Clinical Global Impression of Change
DSM-IV-R	Diagnostic and Statistical Manual – IV-Revised
DRS-R98	Delirium Rating Scale-Revised-98
FrSEBe	Frontal Systems Behaviors Scale
MMRM	Mixed-effects model repeated measures analysis
FBI	Frontal Behavioral Inventory

APPENDIX B

Neuropsychiatric Inventory (NPI)[28]:

- Used to assess behavioral changes in patients with AD and other dementias.
- Usually completed by caregiver regarding behaviors that are new since onset of disease and have been present for the past four weeks or other defined period
- Contains 10 behavioral and 2 neurocognitive domains
  - Delusions
  - Hallucinations
  - Depression/Dysphoria
  - Agitation/Aggression
  - Anxiety
  - Elation/Euphoria
  - Apathy/Indifference
  - Disinhibition
  - Irritability/Lability
  - Aberrant motor behavior
  - Sleep and Nighttime Behavior Disorders
  - Appetite and Eating Disorders
- Each domain is rated on frequency, severity, and distress
  - Frequency: Rarely (less than once per week), sometimes (about once per week), often (several times per week but less than every day), very often (once or more per day)
  - Severity: mild (produces little distress in the patient), moderate (more disturbing to the patient but can be redirected by caregiver), severe (very disturbing to the patient and difficult to redirect)
  - Distress: Not at all, minimally (almost no change in work routine), mildly (some change in work routine but little time re-budgeting required), moderately (disrupts work routine, requires time re-budgeting), severely (disruptive, upsetting to staff and other residents, major time infringement), very severely or extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities).
- Scoring:
  - Four scores for each domain: frequency, severity, total (frequency x severity), and caregiver distress
  - Total NPI score= sum of total scores of first 10 domains
  - Total distress score = sum of distress scores

Neuropsychiatric Inventory Agitation/Aggression Domaine (NPI A/A)[28]:

- Upset with caregiver
- Resists ADLs
- Stubbornness
- Uncooperative/ resists help
- Hard to handle
- Cursing or shouting angrily
- Slams doors/kicks/throws things
- Hits or harms others
- Other

APPENDIX C

Cohen-Mansfield Agitation Inventory (CMAI)[29]:

- Used to assess the frequency of agitated behaviors in elderly persons
- Developed for use in nursing homes
- Completed by caregiver regarding behaviors in the two proceeding weeks
- Consists of 29 agitated behavior items
  - Pacing and aimless wandering
  - Inappropriate dressing or disrobing
  - Spitting (including while feeding)
  - Cursing or verbal aggression
  - Constant unwarranted request for attention or help
  - Repetitive sentences or questions
  - Hitting (including self)
  - Kicking
  - Grabbing onto people or things inappropriately
  - Pushing
  - Throwing things
  - Making strange noises
  - Screaming
  - Biting
  - Scratching
  - Trying to get to a different place
  - Intentional falling
  - Complaining
  - Negativism
  - Eating or drinking inappropriate substances
  - Hurting self or others
  - Handling thing inappropriately
  - Hiding things
  - Hoarding things
  - Tearing things or destroying mannerisms
  - Performing repetitious mannerisms
  - Making verbal sexual advances
  - Making physical sexual advances or exposing genital
  - General restlessness
- Each item is rated on a 7-point scale: never, less than once a week, once or twice a week, several times a week, once or twice a day, several times a day, several time an hour.

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