BXCL501 Focused Virtual KOL Day:
A Potential Treatment for Agitation and Opioid Withdrawal Symptoms

February 19, 2021

NASDAQ: BTAI

Introduction & Agenda

Frank Yocca, Ph.D.
Chief Scientific Officer, BioXcel Therapeutics

Agenda

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Vimal Mehta, Ph.D.,
Chief Executive Officer & Founder,
BioXcel Therapeutics

Will Kane
Chief Commercial Officer
BioXcel Therapeutics

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Scott Zeller, M.D.

III. Dementia Related Agitation

Larry Ereshefsky, PharmD, FCCP, BCPP
Alan Breier, M.D.

IV. Opioid Withdrawal Disorder

Thomas R. Kosten, M.D.

V. Delirium Related Agitation

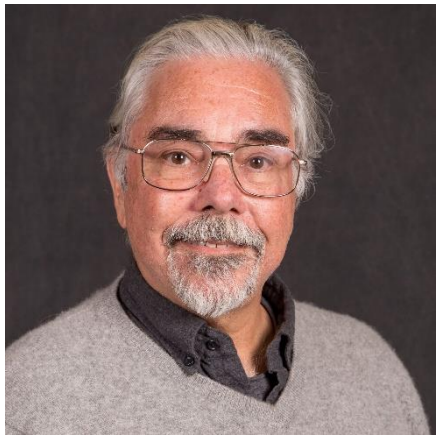
E. Wesley Ely, M.D., MPH

VI. Q&A

KOL Presenters

Scott Zeller, MD

Schizophrenia/Bipolar Disorder Related Agitation



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Dementia Related Agitation

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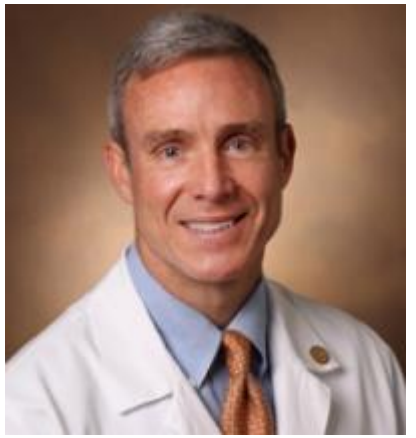
Opioid Withdrawal Symptoms



E. Wesley Ely, MD, MPH

Delirium Related Agitation

Overview of BioXcel

Vimal Mehta, Ph.D.
Chief Executive Officer & Founder, BioXcel Therapeutics

Forward-Looking Statements

This presentation includes "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements in this presentation include, but are not limited to, statements that relate to the advancement and development of BXCL501 and BXCL701, anticipated milestones, clinical development plans, including registrational studies for BXCL501 in dementia patients, the availability and results of data from clinical trials, planned commercialization, expected demand for BXCL501 and potential market size and other information that is not historical information. When used herein, words including "anticipate", "being", "will", "plan", "may", "continue", and similar expressions are intended to identify forward-looking statements. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon BioXcel's current expectations and various assumptions. BioXcel believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain.

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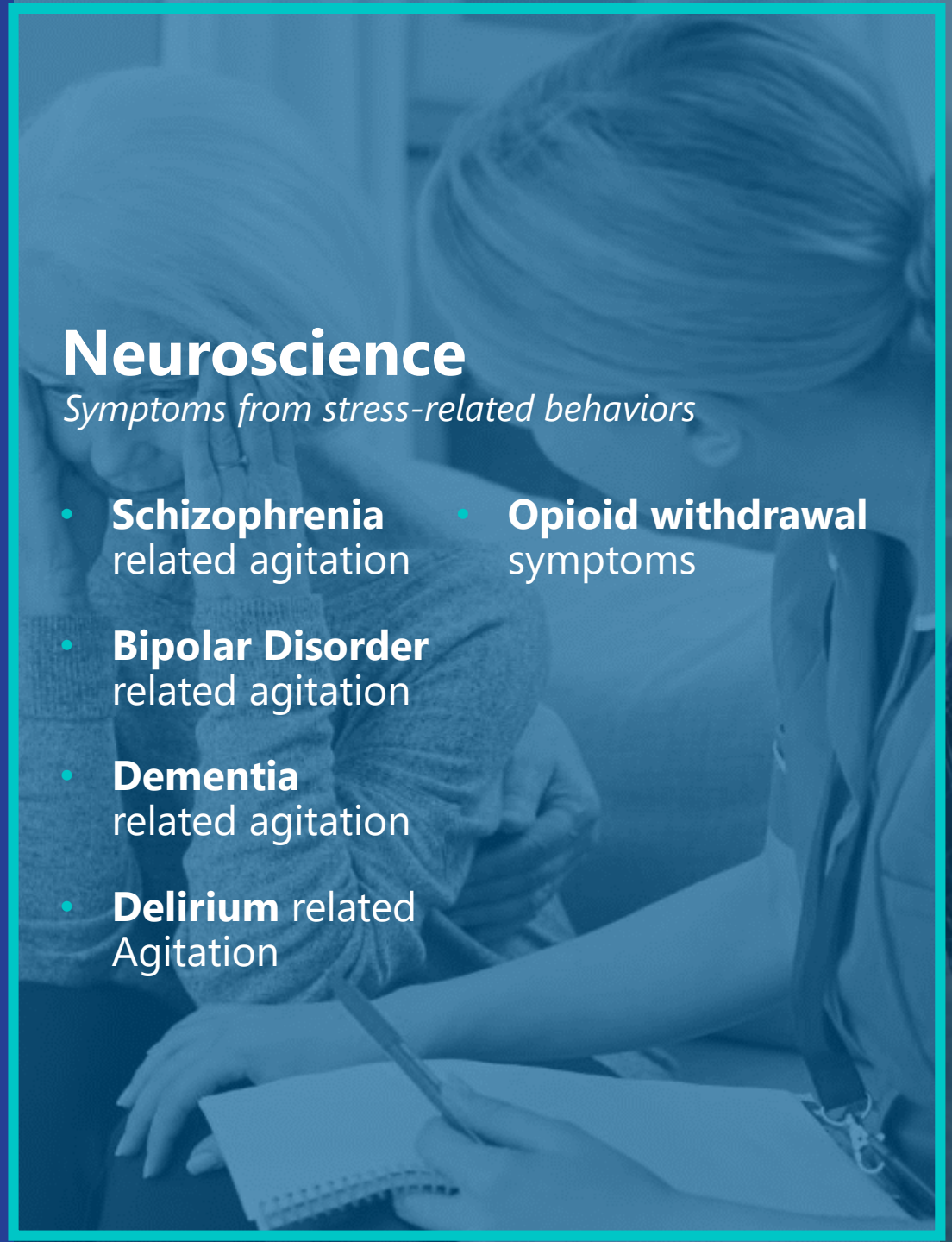
bioxcel therapeutics

Our mission:

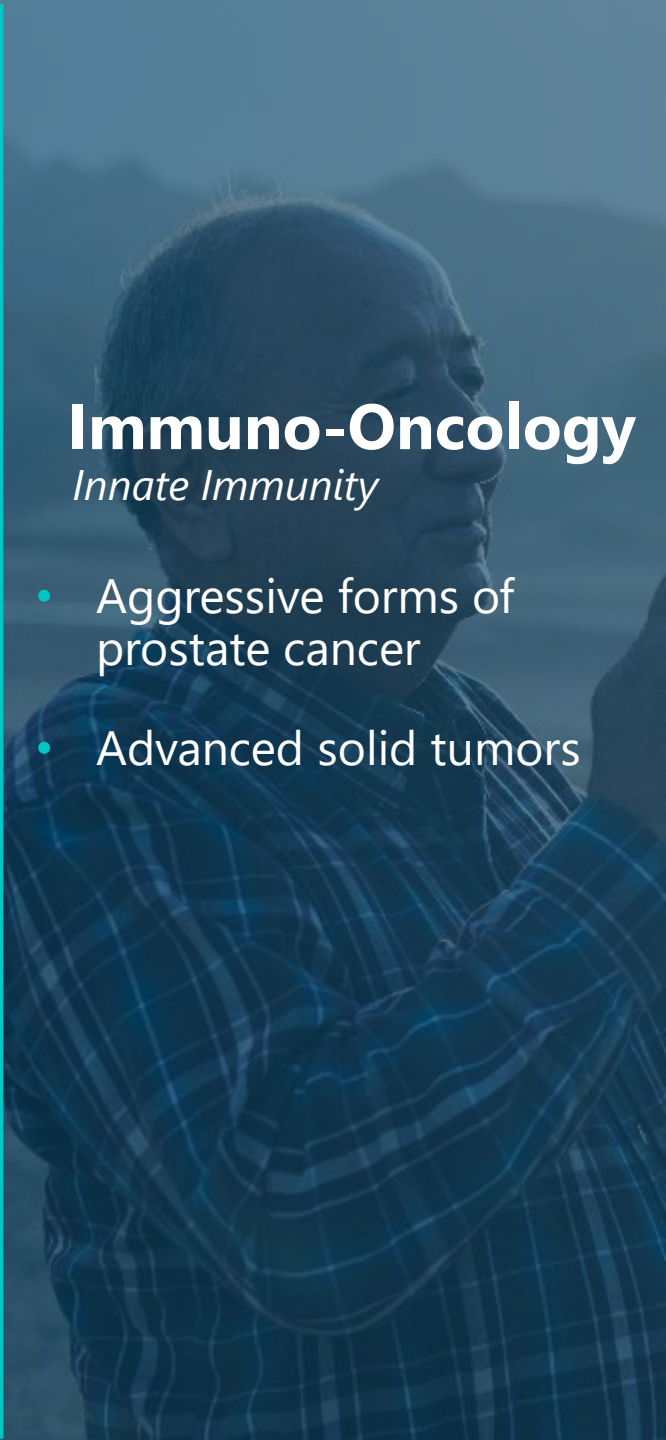
Utilizing AI approaches to develop transformative medicines



Neuroscience

Symptoms from stress-related behaviors

- **Schizophrenia** related agitation
- **Bipolar Disorder** related agitation
- **Dementia** related agitation
- **Delirium** related Agitation
- **Opioid withdrawal** symptoms



Immuno-Oncology

Innate Immunity

- Aggressive forms of prostate cancer
- Advanced solid tumors

Our Strategy – Leveraging AI for Greater Predictability and Efficiency

BXCL501 – First-in-Human to Pivotal Data in 20 Months

Multiple Candidates Screened By AI

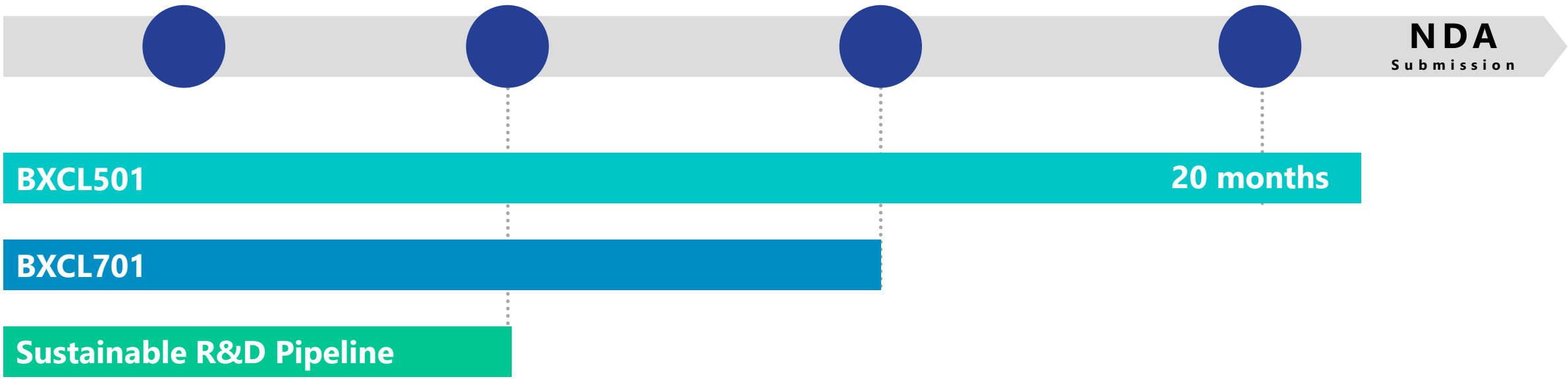
Selection of Best Candidates

Translational Team

Candidate Validation

Clinical Development Team & Regulatory Team

Human Proof of Concept & Registration Trials



Overview of Lead Neuroscience Program

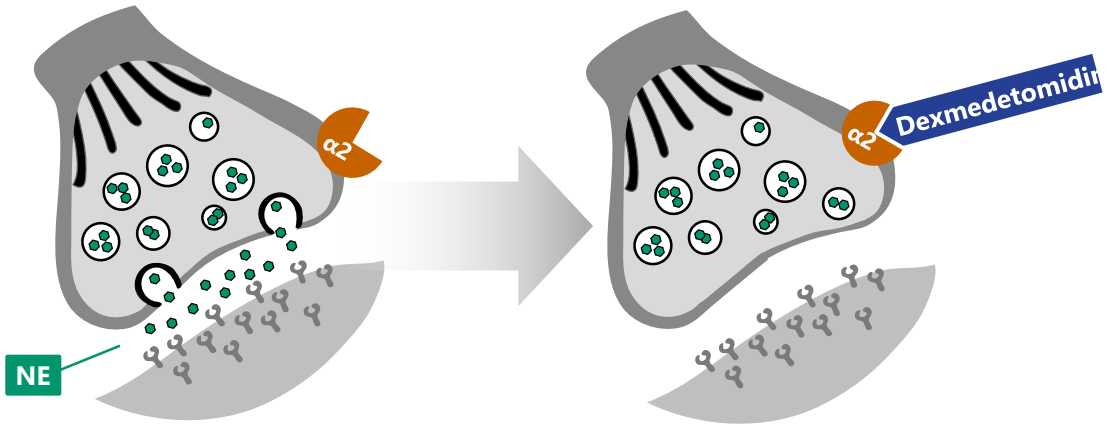
Will Kane

Chief Commercial Officer, BioXcel Therapeutics

BXCL501: Novel Mechanism Potentially Targets Causal Agitation

Positive Trials in Three Distinct Indications Support Underlying MoA

Dexmedetomidine MoA



(+) Agitation **(-) Agitation**

Norepinephrine (NE)

*Dexmedetomidine

Highly Differentiated from Current Treatments

- ✓ Easy to administer thin film, sublingual or buccal
- ✓ Non-invasive
- ✓ Non-traumatic
- ✓ Self-administered by patients

Patent Portfolio

- ✓ U.S. patent (No. 10,792,246) issued
- ✓ IP protection expected until 2039
- ✓ Multiple patent applications

Agitation: Debilitating for Patients and Threatening for Healthcare Providers

A Common and Difficult to Manage Symptom

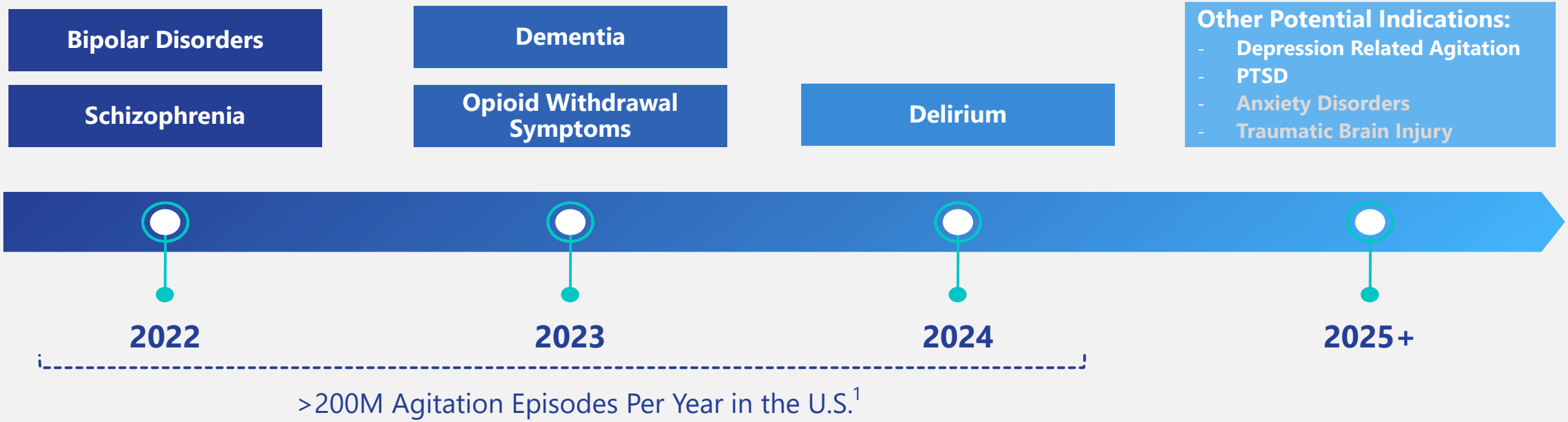
- Agitation is a common occurrence in most neuropsychiatric disorders
- Characterized by recurring episodes requiring frequent treatments
- Over 150M people globally [1] with schizophrenia, bipolar disorder, dementia, delirium and opioid use disorder
  - Over 13M patients in the U.S.[1] experience agitation within these disease areas
  - More than 200M agitation episodes per year in the U.S.[1]
  - Multi-billion dollar healthcare burden
- Current treatment options are suboptimal
  - Physically restraining patients
  - Over-sedating therapies such as antipsychotic and benzodiazepines
  - Antipsychotic drugs have black box warnings for elderly
- BXCL501 offers a novel mechanism and a highly differentiated approach

1. Internal company estimates

BXCL501: Neuroscience Franchise Plan Across Multiple Indications

Total Disease Prevalence Across Multiple Indications >50M patients in U.S.[1]

Anticipated Launch Timing



Value Drivers

- Treatment settings: institutional to community
- Broad spectrum of agitation: acute to chronic

1. Internal company estimates

bioxcel therapeutics

Debra Swingle, DNP APN PMHNP-BC

BioXcel Therapeutics

Director, Medical Science Liaison,
New York/New Jersey

Schizophrenia/Bipolar Disorder Related Agitation:

Current state of evaluation and acute treatment

Scott Zeller, MD*

Vice-President, Acute Psychiatry Vituity, Emeryville, CA; Assistant Clinical Professor, Univ. of California, Riverside; Past Chair, National Coalition on Psychiatric Emergencies; Past President, American Association for Emergency Psychiatry

*Dr. Zeller is a paid consultant to BioXcel

My Experience with Agitated Patients

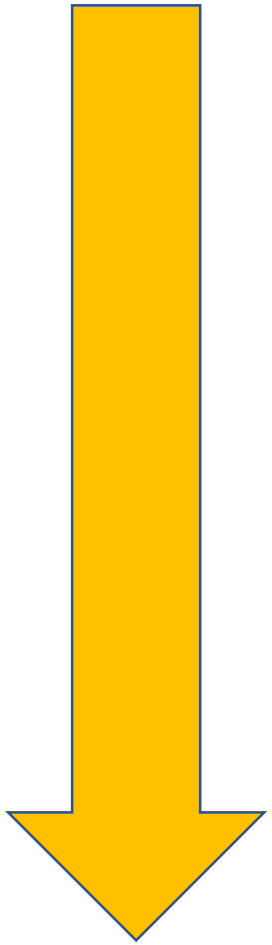
Work in Psychiatric Emergency Services

- 1500-1800 emergency psychiatric patients coming to unit/month, ~90% on involuntary police-initiated holds as danger to self/ others
- >20% (300-400 patients/month) are agitated during their stay
- >50% (750-900 patients/month) have conditions at risk for agitation
- Prompt interventions lead to good outcomes; 78% of patients can be discharged within 24 hours of arrival
- Personally have treated over 90,000 emergency psychiatric patients; all levels of agitation from mild to severe – great majority are mild-to-moderate

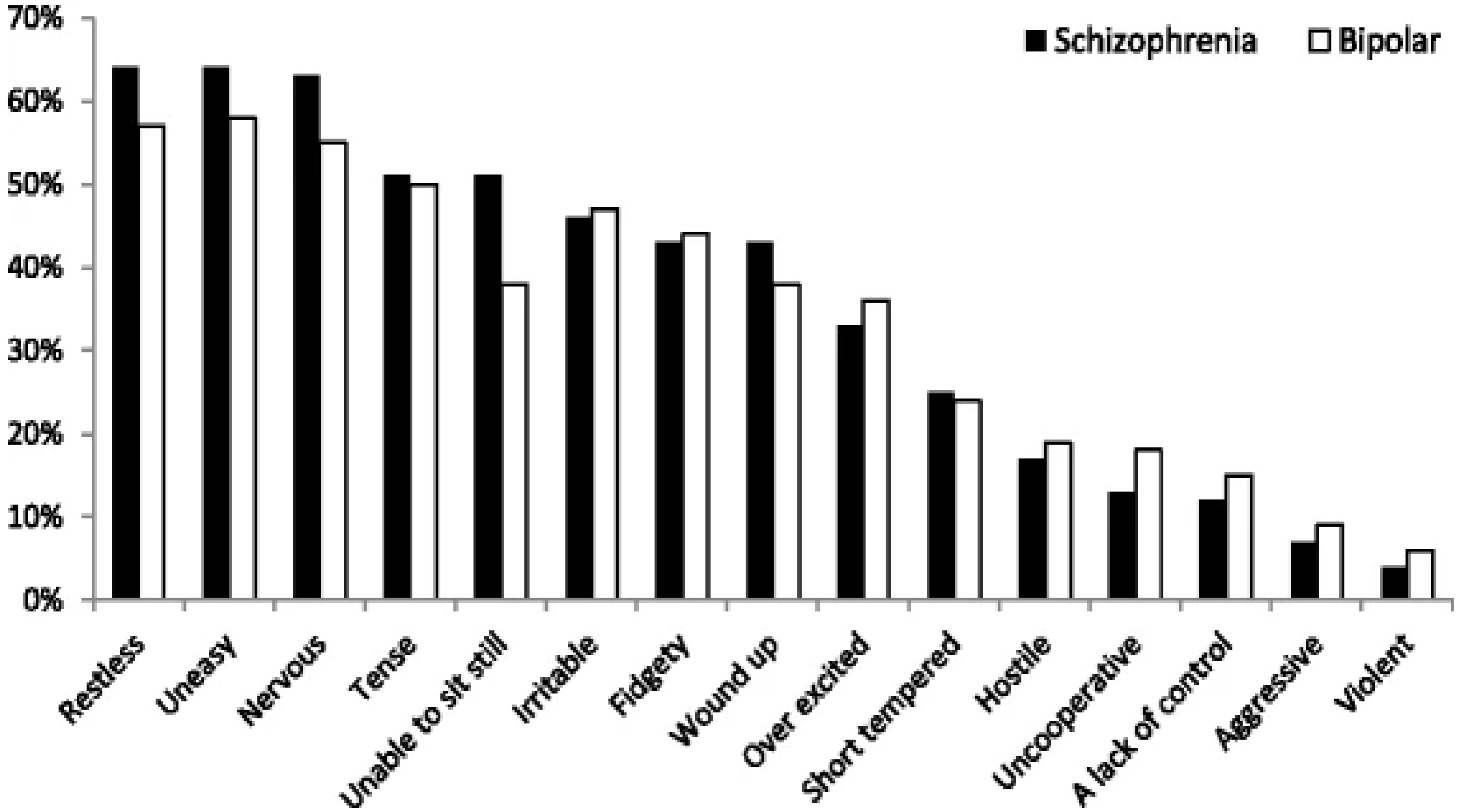
Disease State of Agitation

- Agitation is excessive verbal and/or motor behavior
- Agitation can present in a wide spectrum, from restlessness to combativeness; best to intervene early as possible before symptoms progress – most patients are mild to moderate, but even severely agitated individuals can respond to interventions and willingly accept medications

Increasing Escalation – Signs of Agitation:



- Pacing
- Irritability
- Sarcastic/hostile comments
- Affective lability
- Verbal outbursts
- Clenching of the fists or jaw
- Threatening or destructive behavior, such as slamming doors and banging walls
- Screaming
- Combative, violence, fighting



From Roberts J. BMC Psychiatry 2018

Agitation in the U.S.

- Of psychiatric emergency visits, twenty to fifty percent might involve patients at risk for agitation
- Up to 20 percent of patients seen in psychiatric emergency settings might be agitated or violent during their evaluation
- 2 million medical emergency room visits in USA per year may involve agitated patients
- One-third of patient assaults on staff are random, while two-thirds occur during containment procedures

From: Garriga M, World J Biol Psychiatry 2016

Zeller's Six Goals of Emergency Psychiatric Care

- Exclude medical etiologies of symptoms and ensure medical stability
- Rapidly stabilize the acute crisis
- Avoid coercion
- Treat in the least restrictive setting
- Forge a therapeutic alliance
- Formulate an appropriate disposition & aftercare plan

From: Zeller, Primary Psychiatry, 2010

Acute Care Goals of Treating Agitation

- Reduce dangerous behaviors, anguish, and agitation
- Rapid calming, regaining control, and reduction in symptoms while minimizing side effects, without oversedation
- Avoid use of physical restraints
- Treat while creating therapeutic alliance with patient

BXCL501 may be a novel treatment option to manage schizophrenia related and bipolar disorder related agitation, as demonstrated in the SERENITY I & II trials

The six Project BETA articles are the most downloaded and most cited articles in the history of the Western Journal Of Emergency Medicine, cited over 1,000 times to date in the academic literature.

The guidelines are currently in active use in hospitals on all six continents.

Project BETA Approach

- Agitation is an acute behavioral emergency requiring immediate intervention
- The preferred intervention for calming the agitated patient is verbal de-escalation
- Medication can help, and offering medication is part of verbal de-escalation
- With de-escalation, most patients will accept oral medications willingly and voluntarily

Many hospitals now require annual training in de-escalation and agitation management for all their clinical staff!

Benefits of De-Escalation and Avoiding Coercion

- Verbal de-escalation usually takes less time than the process of restraint and involuntary medication; it's worth attempting de-escalation in all psychiatric patients, no matter how severely agitated
- Avoiding "containment" procedures will result in less injuries to both staff members and patients
- Patients are more trustful when not restrained or forcibly medicated
- Receiving facilities may be more willing to accept a patient who has not been restrained, improving throughput

Improving Emergency Department Throughput

- Restraint use leads to a length of stay of psychiatric patients in EDs averaging 4.2 hours longer than that of patients not requiring restraints [1]

1. Weiss AP et al, Annals of Emergency Medicine 2012

Expert Consensus Guideline Series Treatment of Behavioral Emergencies 2005

- The goals of emergency intervention include:
  - Calming the patient without sedation (preferred goal)
  - Mild sedation to the point of drowsiness but not sleep*

- Some of the most important factors in selection of medication include:
  - Acute (immediate) effect on behavioral symptoms
  - Speed of onset
  - Patient's history of response to the medication
  - Limited risk of side effects
  - Patient preference
  - Ease of administration (no need for lab tests, simple dosing requirements)

* The panel did not endorse sleep or heavy sedation as an appropriate goal of intervention.

Allen MH, et al. J Psychiatr Pract. 2005; 11 (suppl 1): 5-108

Project Beta – General Medication Recommendations

- Medications are not chemical restraints, but appropriate agents chosen to treat symptoms
- Medication is used to calm, not induce sleep
- Patients should be involved in the process of selecting medication when possible
  - Oral medications are preferred over IM

Benzodiazepines: Benefits and Limitations

Benefits

- Well accepted

Limitations

- Oversedation
- Masking Symptoms
- Untreated Underlying Causes/Psychosis

Oral Antipsychotics: Benefits and Limitations

Benefits

- Patients take collaboratively, without coercion
- Rapidly dissolving formulations can work more quickly
- Less side effects than injected antipsychotics

Limitations

- Slower onset compared to injectables, typically 45-60 minutes to onset
- Patient may spit out or cheek oral tablet

Older IM Medications: Benefits and Limitations

Options

- Conventional antipsychotics
- Benzodiazepines
- Combination treatment— B-52: Haldol/Ativan cocktail

Benefits

- Faster onset of action than po, but still 30-60 minutes for effect

Limitations

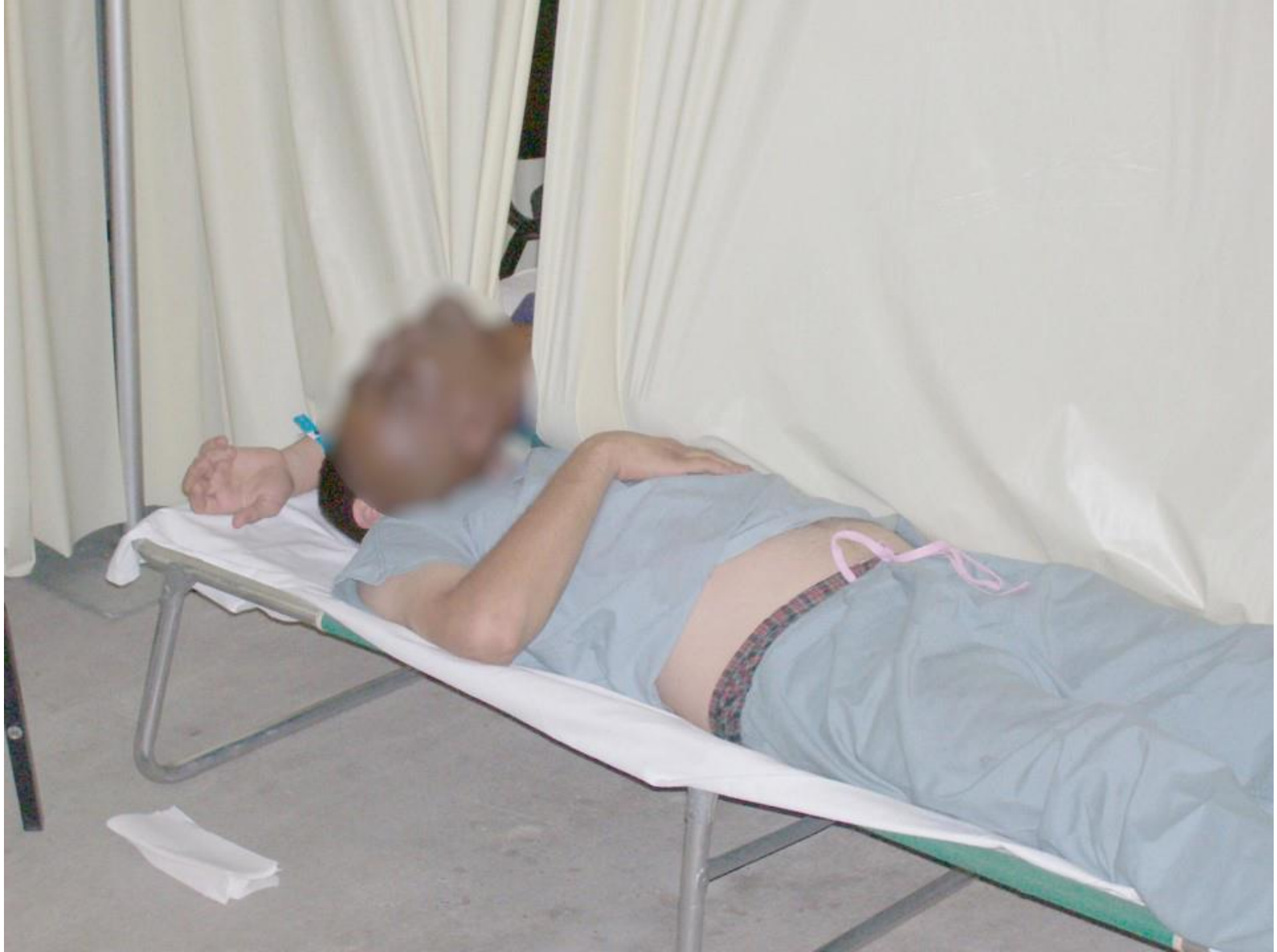
- Acute Dystonia
- Akathesia
- EPS
- Dysphoria
- Oversedation
- Patients dislike

IM Atypical Antipsychotic (SGA) Agents

- IM SGA less caustic, preferred by patients over IM haloperidol
- Faster relief of agitation and distress
- Still coercive, requires restraints, risk for needlestick
- Can be oversedating if combined with benzodiazepine; too often done by habit
- Approved by FDA IM SGA medications for agitation:
  - Ziprasidone – Brand name Geodon
  - Olanzapine – Brand name Zyprexa
  - Aripiprazole – Brand name Abilify

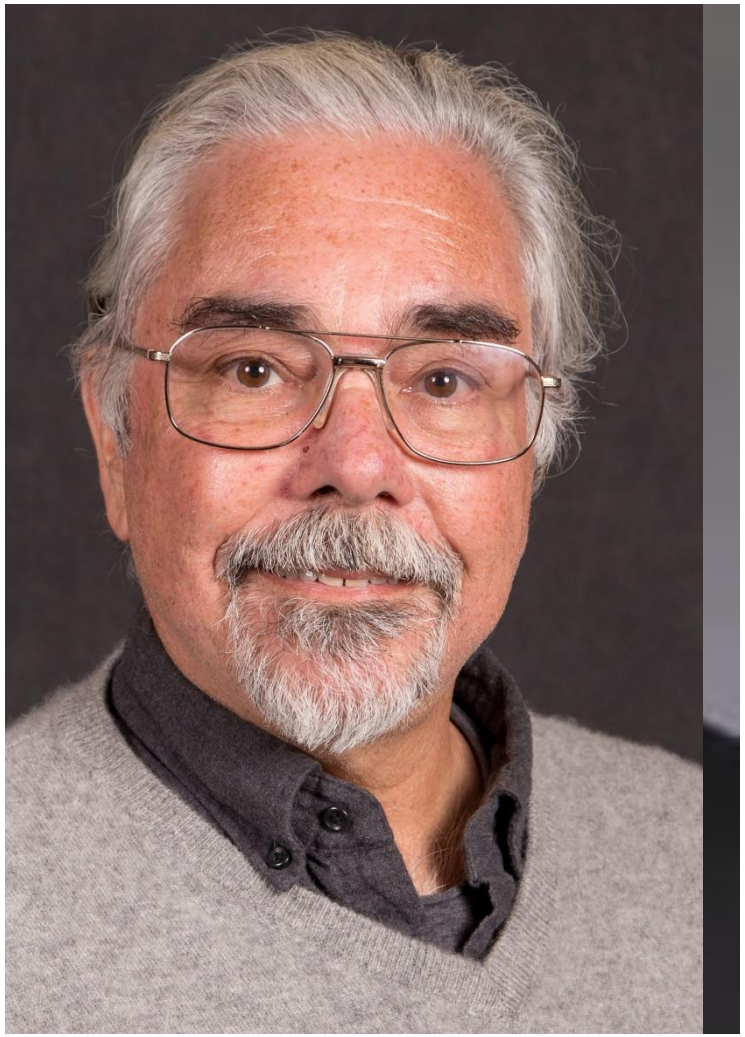
Complications of Oversedation

- Prevents ability to do full medical/psychiatric evaluation, and can mask medical comorbidities
- Patients unable to answer questions
- Patients unable to keep self hydrated, other self care
- Psychiatric consultant will typically not come to evaluate until patient is awake
- Receiving hospitals/programs unwilling to consider patient transfers until alert, leading to boarding, dispositional delays
- Unconscious patient not receiving treatment but taking up vital space in ED – thus not helping patient while preventing other ED patients from treatment



The Search for the Ideal Agent for Agitation

- Prompt onset of calming, allows patient to regain control, maintain safety
- Not oversedating while effective throughout evaluation
- Collaborative, not coercive
- Well tolerated, minimal or no side effects
- Safe to administer, yet patient can't "cheek"
- Helps build trust, therapeutic alliance
- Patients will request it earlier in agitation spectrum, prevent serious problems of untreated agitation
- **Emergency Psychiatrists have been seeking this for many years**



Dementia Related Agitation:
Overview and Pipeline

Larry Ereshefsky PharmD, FCCP, BCPP*

Retired Professor, Psychiatry, Pharmacology, and Pharmacy, The University of Texas;

Founding member of the International Society for CNS Clinical Trials and Methodology; Chair of the Behavioral and Psychological Symptoms of Dementia working group; Co-Chair for the Agitation and Apathy sub-groups;

Chief Scientific Officer, APEX Innovative Sciences and Follow the Molecule

*Dr. Ereshefsky is a paid consultant to BioXcel

Alzheimer's Disease: Rapidly Increasing Prevalence

- An estimated 5.8 million Americans age 65 and older are living with Alzheimer's dementia in 2020.
- Eighty percent are age 75 or older
- One in 10 people (10%) age 65 and older has Alzheimer's dementia
- Numbers of patients with Alzheimer's is expected to grow significantly over the next 30 years

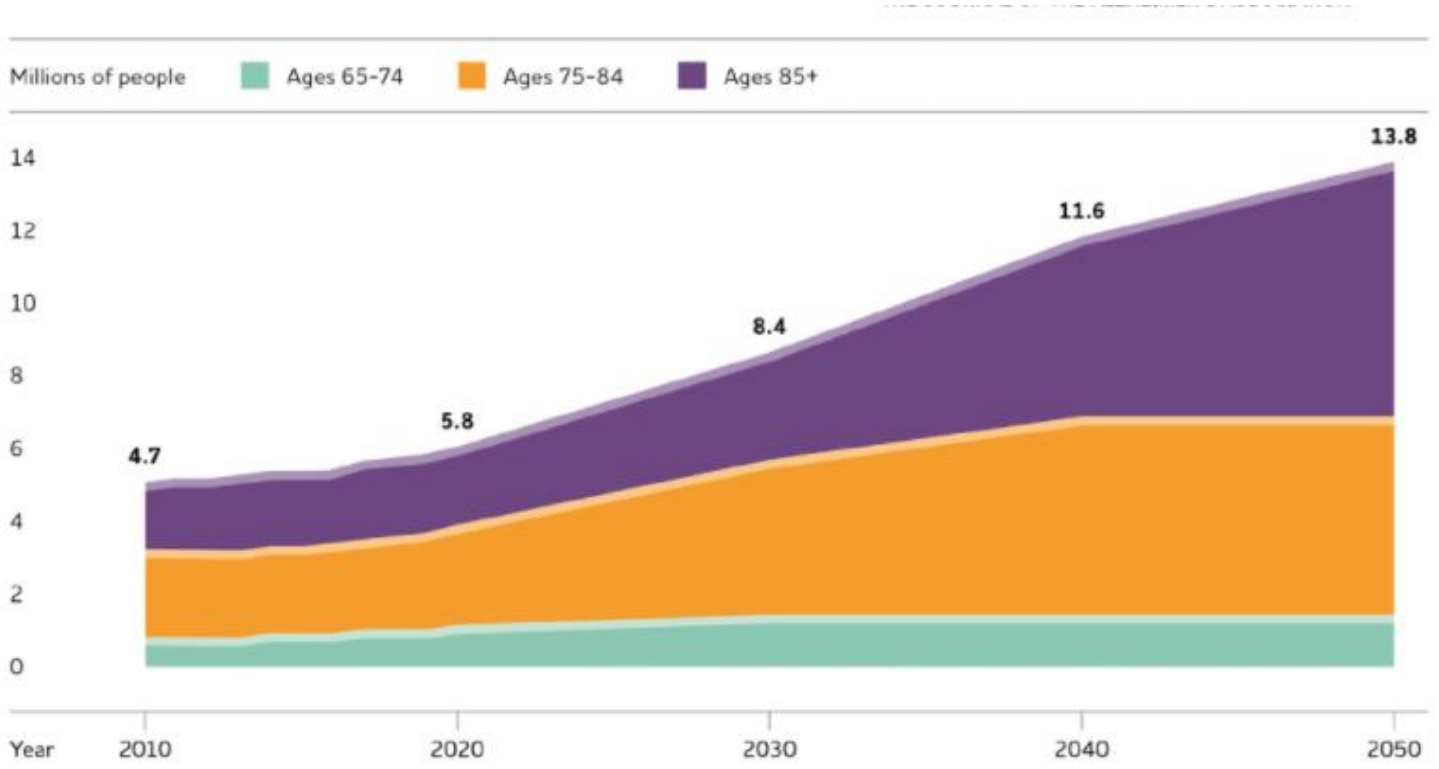
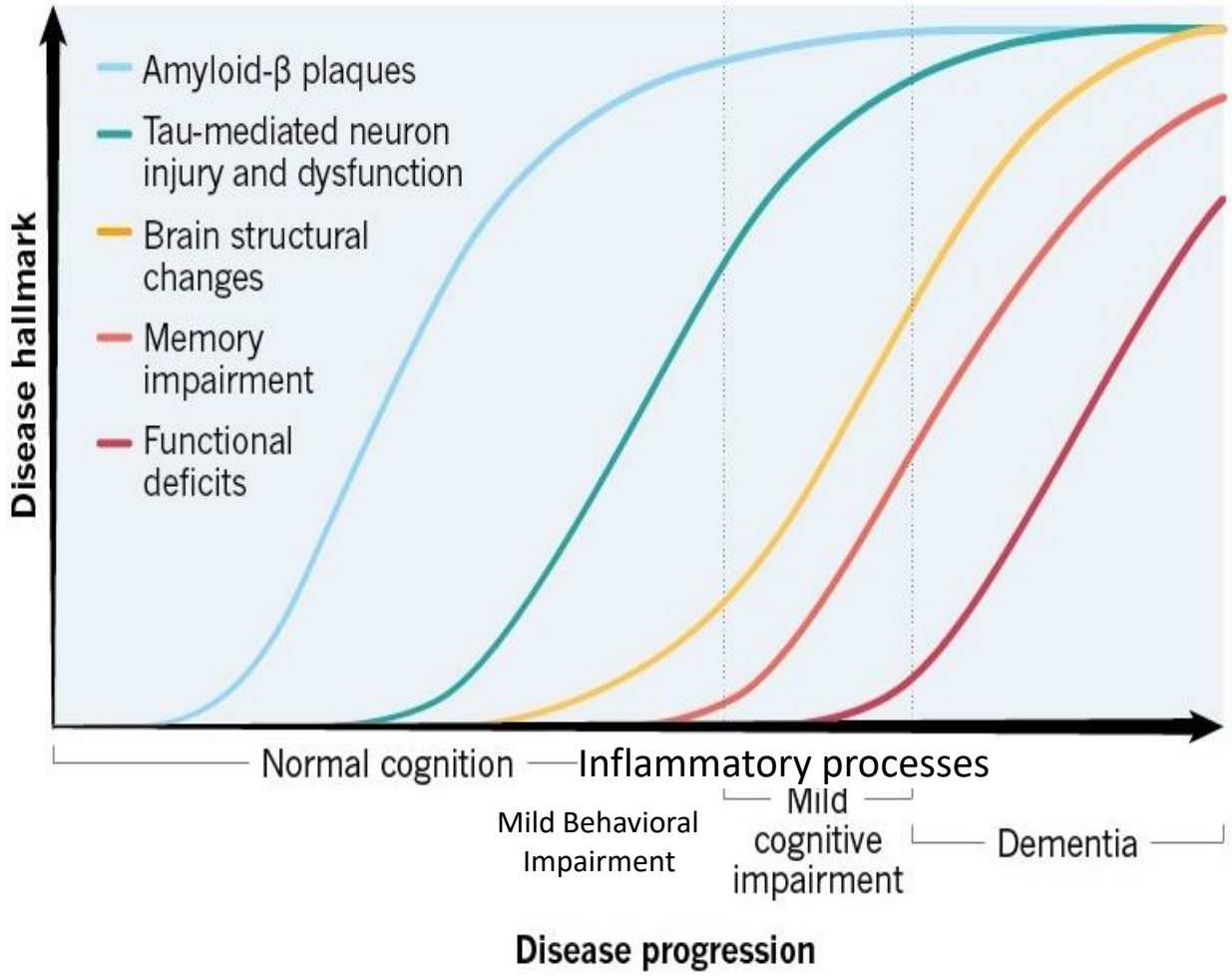


FIGURE 5 Projected number of people age 65 and older (total and by age) in the U.S. population with Alzheimer's dementia, 2010 to 2050. Created from data from Hebert et al.[A9.62]

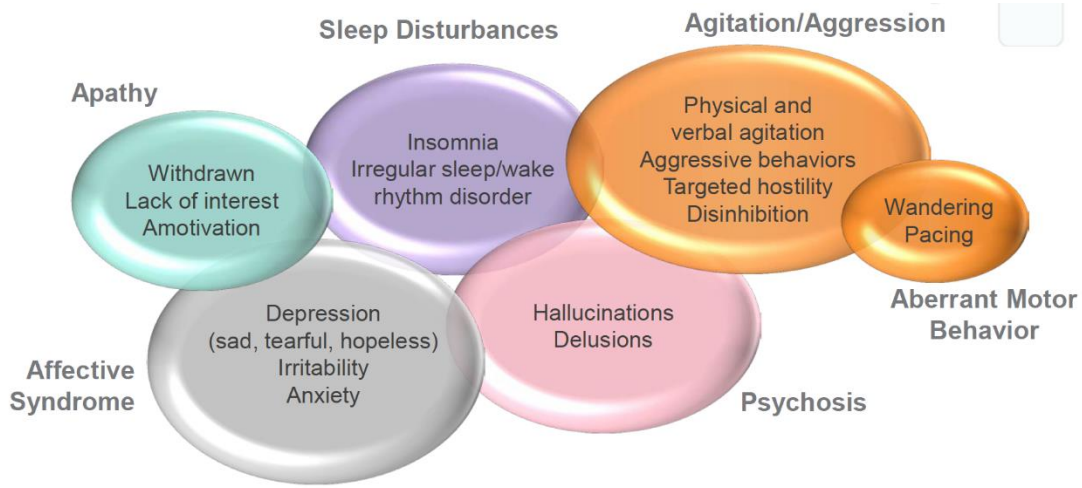
Neuropathology Progression Leads to Neuropsychiatric Symptoms (NPS)

- AD progresses over years with accumulation of 2 markers in the brain: amyloid plaques and tau phosphorylation and filament formation
  - MCI progression to dementia (functional deficits)
- There also is considerable evidence for inflammatory processes co-occurring
- In addition to cognitive deficits, neuropsychiatric symptoms become apparent
- Mild Behavioral Impairment (MBI) (NPS-PIA AAIC)
  - Acquired in late life
  - Early-stage evidence of neurodegenerative processes
  - Sustained/Impactful
  - Can present in advance of any cognitive impairment or along with MCI
  - Agitation and apathy are key symptoms



Neuropsychiatric Symptoms: Highly Prevalent and Burdensome

- NPS are Highly Prevalent ~90% cumulative risk in patients with AD; Point prevalence 60-80% [1]
- 60% of patients have cumulative risk for agitated and/or aggressive behaviors [2]
- Agitation/aggression seen in 45% of AD patients over a 5 year period
- Agitation/Aggression is clinically significant in ~ 20% of people with dementia in community settings and in nearly 50% in assisted/long-term care facilities [3]
- AD Europe Care Survey: Behavioral symptoms cited more often than cognitive loss as most problematic [4]
- Enormous distress for patient, family, caregivers (work and psychological) make NPS legitimate [5] object for intervention



1. Lyketsos CG, Miller DS. *Alzheimers Dement*. 2012;8(1):60-64; 2. Lyketsos CG, et al. *Int J Geriatr Psychiatry*. 2001;16:1043-1053; 3. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608; 4. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608 (Appendix C: Ancoli-Israel S, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-03.docx; Appendix D: Sultzer DL, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-04.docx. Accessed November 3, 2014).

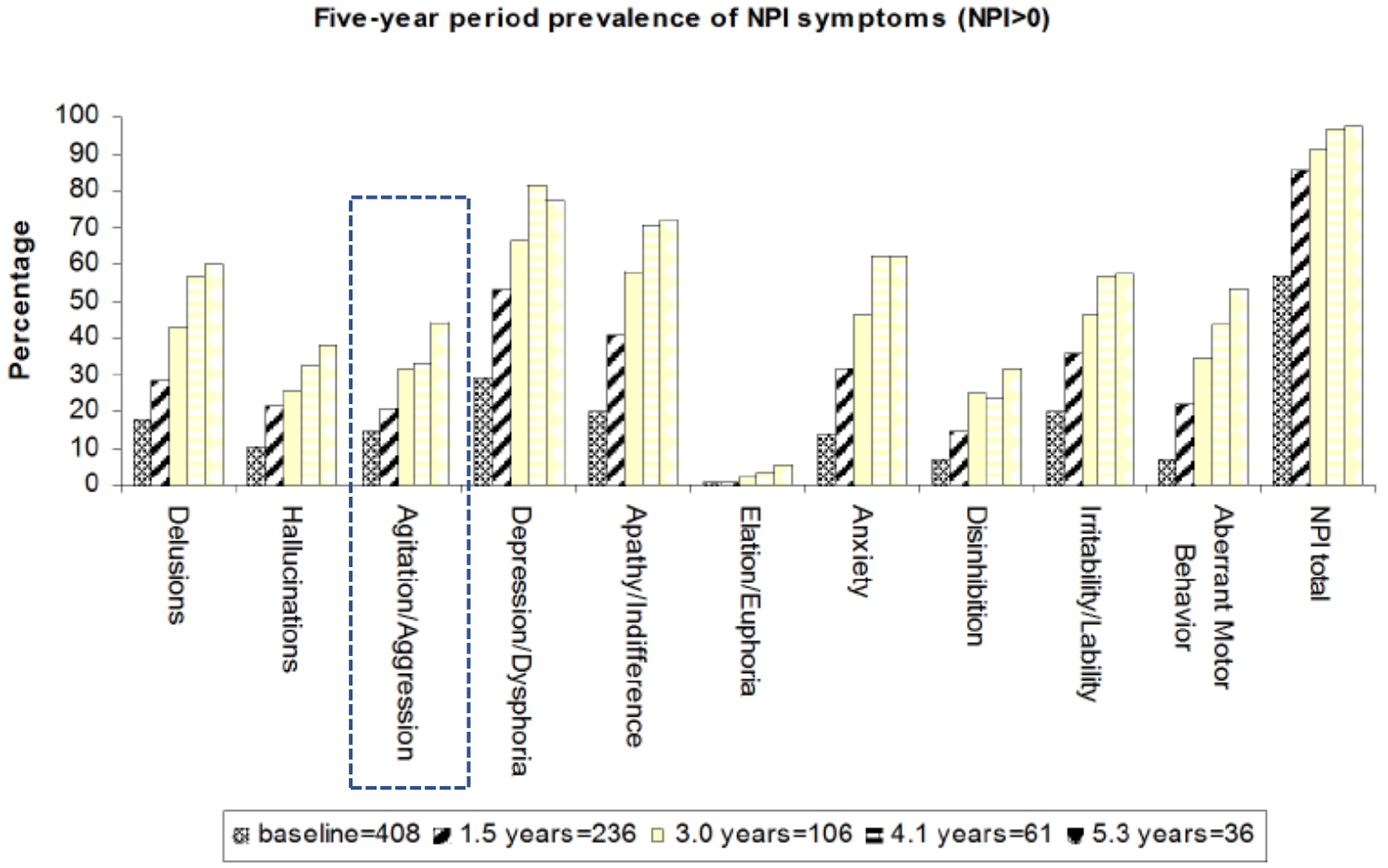
Agitation → Aggression Spectrum: Physical and verbal agitation, motor restlessness, verbal outbursts, resistance to care, overt aggressive behaviors, violence to self and others

Dynamic interaction of underlying neurodegenerative vulnerability with environmental triggers/stress

1. Sternberg 2008; 2. Craig 2005; 3. Lobo 2000; 4. Georges 2008; 5. Banerjee 2008

Natural History of Neuropsychiatric Symptoms

- Sources of Information
  - Informant; Patient Observation; Technological Devices
- 365 individuals in Cache County Study [1] with dementia and agitation/aggression and psychosis, were associated with more rapid progression to severe dementia (hazard ratio 2-3) and with earlier death (hazard ratio 1.4-2.0)
- 497 patients mild to moderate AD follow up mean of 4.4 years who had 'disruptive behavioral symptoms" were associated with greater cognitive and functional decline, and institutionalization to nursing facilities [2]



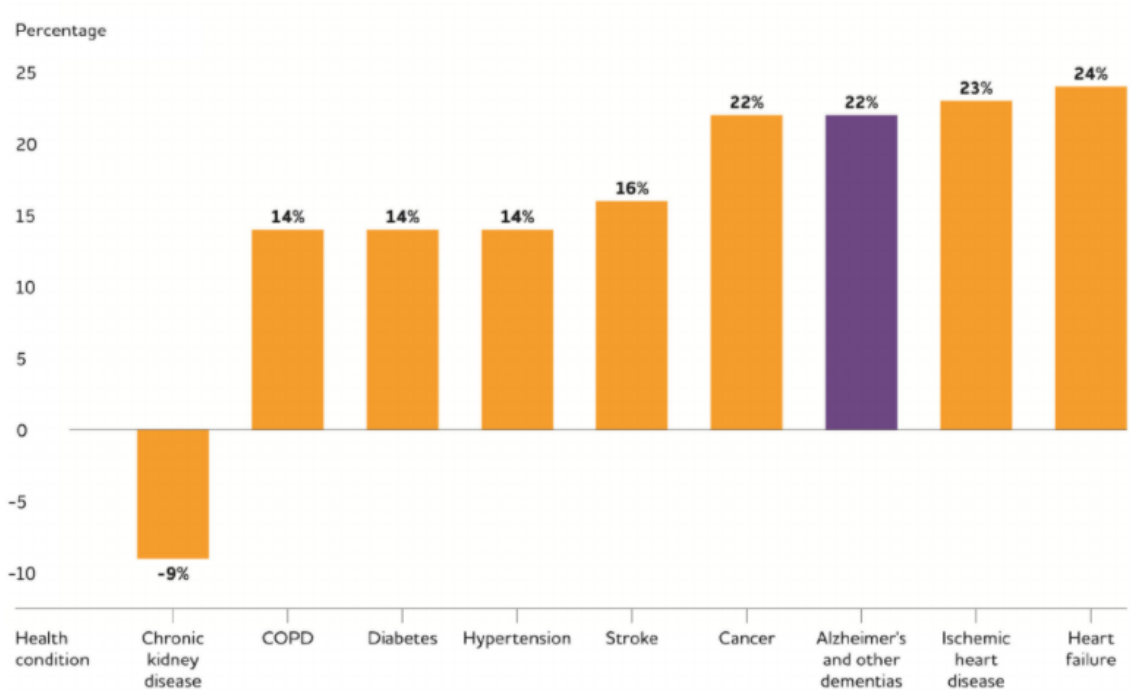
Cache County Dementia Progression Study

1. Peters 2015. 2. Scarmeas 2007

NPS Impacts Morbidity and Mortality in Dementia

- NPS ALSO has strong association[1] with:
  - Impairment of activities of daily living (ADLs)
  - Quality of life of patient
- MCI plus NPS results in higher conversion rate to AD
- A 1 point increase in Neuropsychiatric Inventory score can result in substantial increase in direct costs
- 70% of Nursing Home patients with dementia and NPS were at higher care levels
- NPS were associated with costs of $4115 per patient per year in community based AD study

Percentage Changes in emergency department visits per 1,000 fee-for service Medicare beneficiaries for selected health conditions between 2007 and 2017



Includes Medicare beneficiaries with a claims-based diagnosis of each chronic condition. Beneficiaries may have more than one chronic condition. Created from data from U.S. Centers for Medicare & Medicaid Services.

1. Lyketsos Alz Dementia 2012; Yaffee J AM Med Assoc 2002
2. Murman DL Neurology 2002; O'Brien Int Psychogeriatr 2000; Beeri MS Int J Geriatr Psych 2002; Tampi Neurology 2011; Cerejeira Front Neurol 2012

Care Progression and Increasing Cost Burden for Dementia Patients

- It is behavior, not worsening cognition, that is drives transitions to more expensive care
- Effective and safe treatment of agitation will impact healthcare costs significantly by delaying transition to nursing homes and reducing visits of nursing home patients to hospitals

SETTING	PERCENTAGE with Dementia	COSTS
Adult day services	31%	$25K per year
Home health services	32% of patients using home care have dementia	$56K per year
Residential care facilities	42%	$48.6K per year
Nursing home care	48%	$102K per year
Alzheimer's special care units	100%	Similar to nursing homes

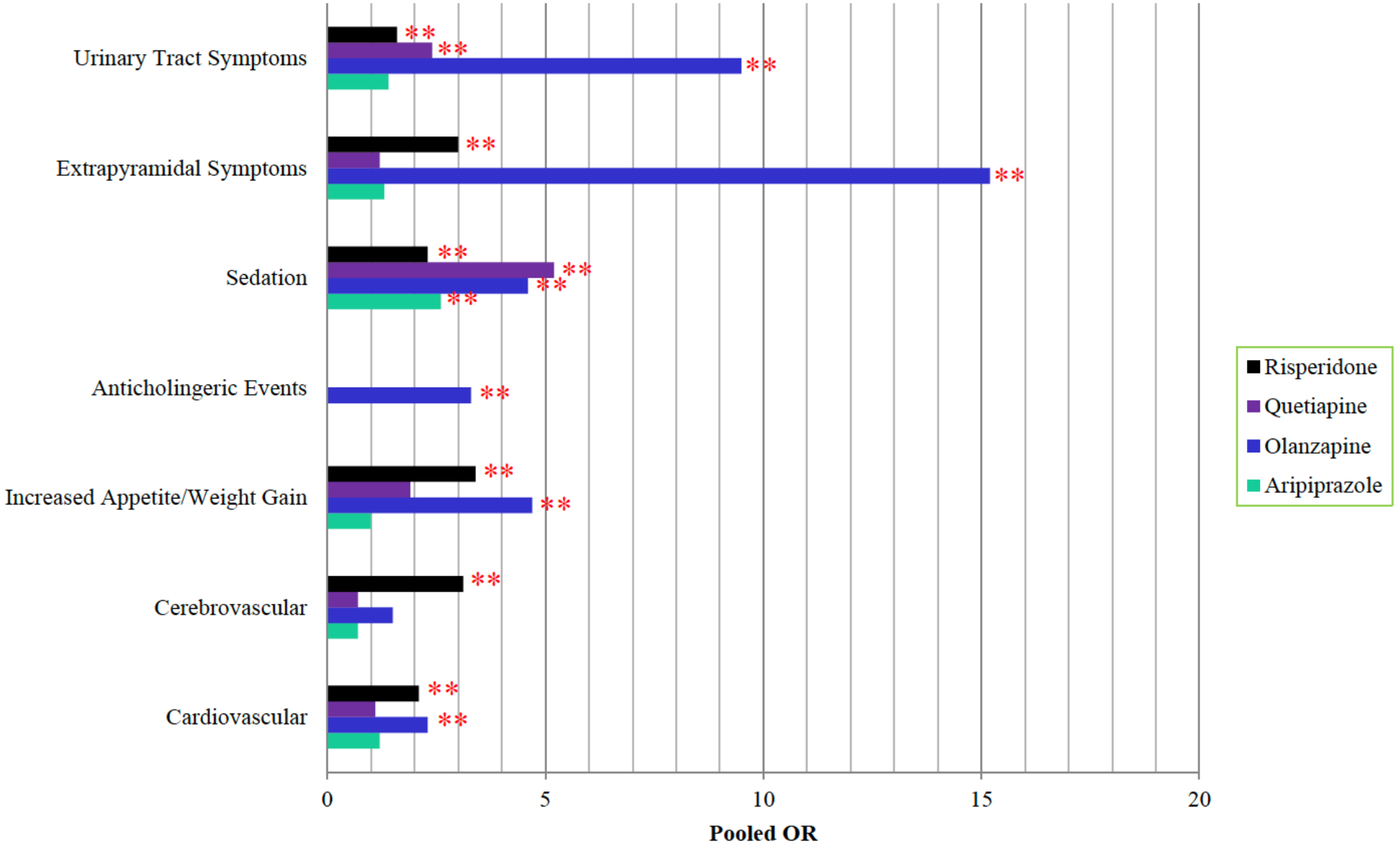
Adapted from Alzheimer's Association. 2020 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2020;16(3):391

Current Treatment Options are Suboptimal

- No approved treatments for agitation in dementia
- Commonly used agents pose management challenges
- Antipsychotics (black box warning)
  - Impaired cognition
  - Stroke, death
  - Metabolic syndrome
- Benzodiazepines (black box warning)[1]
  - Falls
  - Cognitive impairment
- SSRIs (Citalopram), Porsteinsson JAMA 2014
  - Impaired cognition
  - QTc prolongation

1. Salzman Int J Geriatr Psych 1992; Ray J Am Geriatr Soc 2000; Sgadari J Clin Psychopharm 2000

Adverse Events Associated with Atypical Antipsychotics in Elderly Dementia Patients

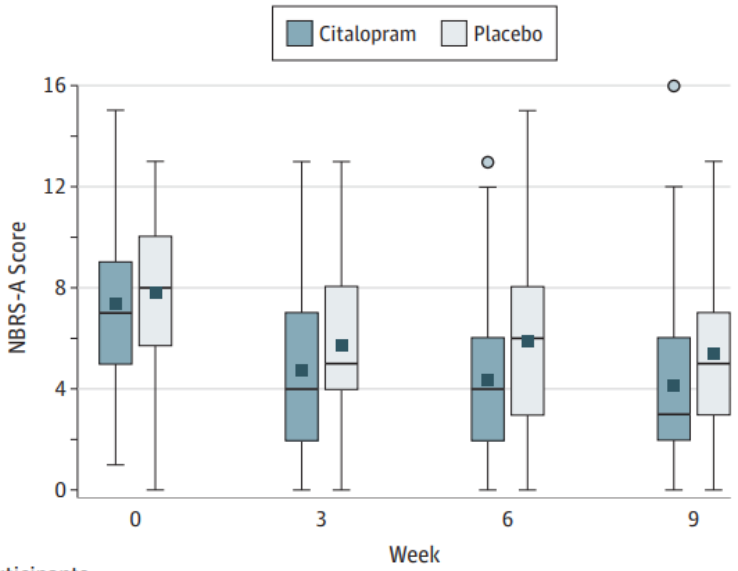


Effect of Citalopram on Agitation in Alzheimer's Disease

The CitAD Randomized Clinical Trial

- Setting: CitAD enrolled 186 patients from eight academic centers in the US and Canada from August 2009 to January 2013
- Patients had AD and clinically significant agitation1) occurring `very frequently' or 2) occurring `frequently' with `moderate' or `marked' severity on the agitation/aggression domain of the Neuropsychiatric Inventory (NPI)
- Outcome measures were the agitation subscale of the Neurobehavioral Rating Scale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC)
- Participants showed significant improvement compared to placebo on both primary outcome measures at week 9
- Anorexia, diarrhea, upper respiratory infection, fever, falls Cit >PBO
- Worsening of cognition and prolongation of QTc Cit>PBO

Figure 2. Neurobehavioral Rating Scale (NBRS)-Agitation Subscale



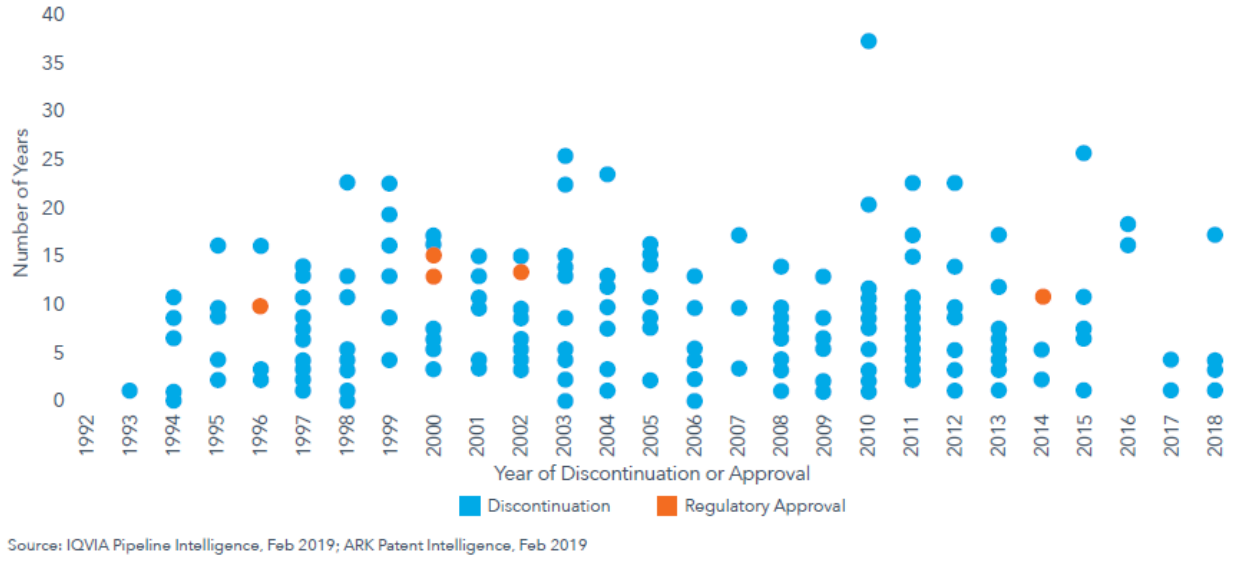
No. of participants				
Citalopram	94	87	85	86
Placebo	92	84	84	81

Higher NBRS scores indicate more severe symptoms. The horizontal bar inside the boxes indicates the median, the square in the boxes indicates the mean, and the lower and upper ends of the boxes are the first and third quartiles. The whiskers indicate values within 1.5 × the interquartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 × the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.

Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014 Feb 19;311(7):682-91. doi: 10.1001/jama.2014.93. PMID: 24549548; PMCID: PMC4086818.

Drug Development Landscape for Treatment of Alzheimer's Disease

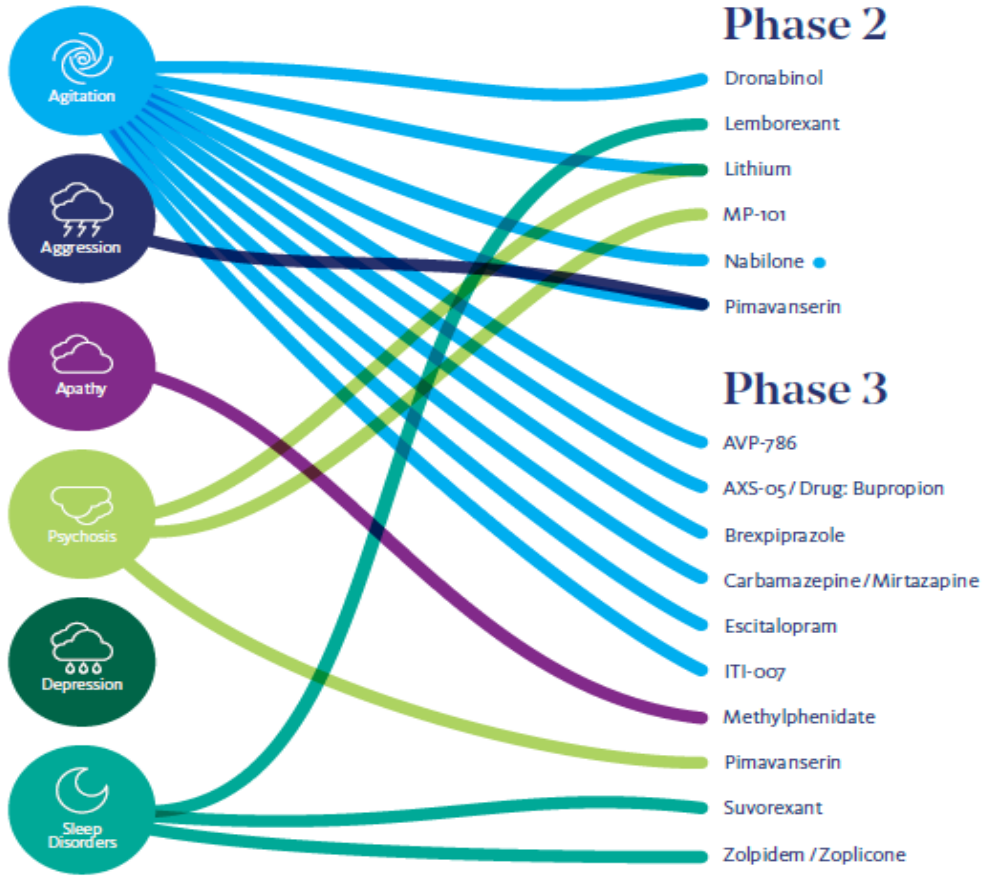
Drugs in Development for Alzheimer's



Source: IQVIA Pipeline Intelligence, Feb 2019; ARK Patent Intelligence, Feb 2019

- Over 85 failures including both disease-modifying and symptomatic treatments
- Approved drugs are symptomatic drugs such as cholinesterase inhibitors (Aricept, e.g.) and memantine
- Some disease-modifying treatments are still active (Aducanumab from Biogen, e.g.)
- Currently more emphasis is on finding drugs to treat neuropsychiatric symptoms

Drugs in Development for NPS



Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA. 2014 Feb 19;311(7):682-91. doi: 10.1001/jama.2014.93. PMID: 24549548; PMCID: PMC4086818.

ISCTM BPSD Working Group*
Evaluating Agitation and Apathy in Dementia: Can Clinical Trials be Done? Yes!

The Journal of Prevention of Alzheimer's Disease - JPAD
Volume 7, Number 4, 2020

A Framework for Developing Pharmacotherapy for Agitation in Alzheimer's Disease: Recommendations of the ISCTM* Working Group

C. O'Gorman[1], R. Khoury[2], A. Anderson[3], M. Carter[4], F. DiCesare[5], S. Dubé[6], L. Ereshefsky[7], G. Grossberg[2], N. Hefting[8], S. Khan[4], S. Lind[8], H. Moebius[9], T. Shiovitz[10], P. Rosenberg[11]

- Use Established (or develop validated) Diagnostic Criteria
- Acknowledge subtypes and disease course progression
- Carefully select outcome measure(s)
- Evaluate single NPS symptoms or in combo with other NPS (e.g. – agitation/psychosis, depression/apathy)?
- Agitation as a single event vs Agitation as a persistent NPS
- Address issues around placebo response
- Standardize Non-Pharmacologic Interventions
- Appreciate the source for determining ratings

**Larry Ereshefsky is founder of ISCTM BPSD Working Group*
ISCTM: The International Society for CNS Clinical Trials and Methodology
BPSD: Behavioral and Psychiatric Symptoms in Dementia

Guidelines for Prescribing for the Elderly with NPS

- Target the drug to the symptom
  - Hallucinations and delusions are likely to be responsive to antipsychotics or pimavanserin
  - Agitation and anxiety may respond to drugs with anxiolytic effects; benzodiazepines not appropriate
  - Persistent insomnia might indicate a short-term role for a hypnotic; usually trazadone over GABA drugs
- Start low, go slow with doses; ‘rule of thumb’ is psychotropic doses should be started at ¼ to ½ adult dose
- Use one drug at a time, at the lowest effective dose
  - Many elderly are taking several drugs (polypharmacy) with high likelihood of interactions and adverse effects
  - Low dose drugs that are not primarily inhibited by CYP enzymes should be preferred
  - Drugs that don’t depress respiration should be preferred
- Review early, and often, for the emergence of adverse effects. Older people have a greater likelihood of developing extrapyramidal effects, which often emerge during treatment rather than when starting a drug
- Federal requirements for monitoring of nursing home patients reflect the above as ‘Regulation’

Agitation & Dementia:
Unmet Need, Advances in Treatment

Alan Breier, M.D.*

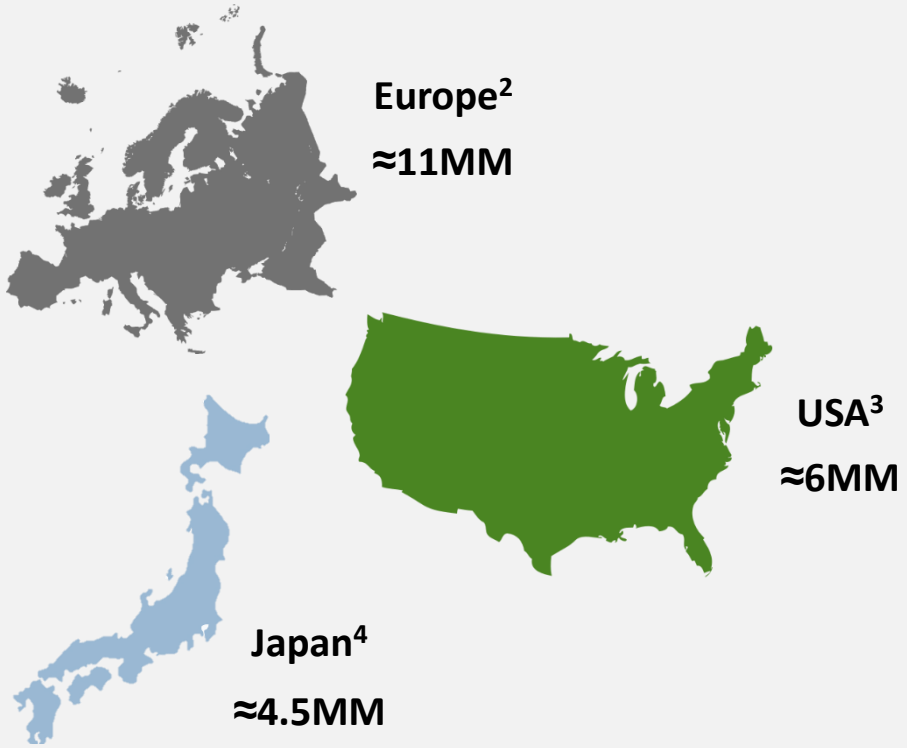
Indiana University Mental Health Research and Education, Senior Professor of Psychiatry; Vice-Chair for Clinical Research; Chief, IU Psychotic Disorders Program; Director, Prevention and Recovery Center; Indiana University School of Medicine

*Dr. Breier is a paid consultant to BioXcel

Dementia and Related Agitation to Substantially Increase

Highly prevalent global condition, with incidence increasing rapidly

2020 Dementia Global Prevalence ≈ 50MM[1]



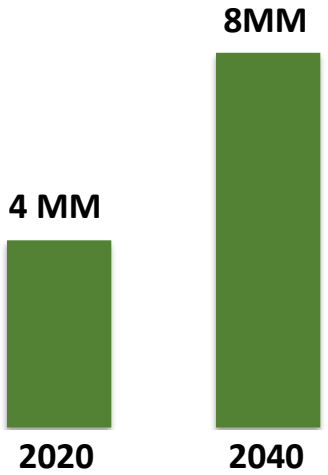
>40% of population in priority regions/countries

American 65+ with Alzheimer's Disease[2] to double by 2040[3]

Up to 70%

Experience agitation[5]

Estimated Number of U.S. Patients with Agitation



Sources: [1]WHO 2020, [2]Alzheimer's Europe Yearbook 2019; [3]Alzheimer's Association, [4]Alz.org Japan;; [5]Tractenberg, R Neuropsychiatry Clin Neuroscience 14:1, Winter 2002; [6]Internal company estimate based on market research

Implications of Agitation in Dementia

- Agitation is a common and difficult to manage symptom
- Characterized by restless behavior, improper physical and verbal actions, resulting in:
  - Endangerment to patients and others
  - Caregiver burden and burnout
  - **Early Institutionalization and frequent ED visits**
- Dementia prevalence over 50M worldwide, with~6M in the U.S.
  - Up to 80% have Alzheimer's Disease
  - Up to 70% of patients experience agitation
  - In U.S., approximately 100M agitation episodes per year*
- **Agitation worsens as severity of dementia progresses**
- The causes include both neurobiological factors and environmental triggers

Alzheimer's Association. 2020 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2020;16(3):391

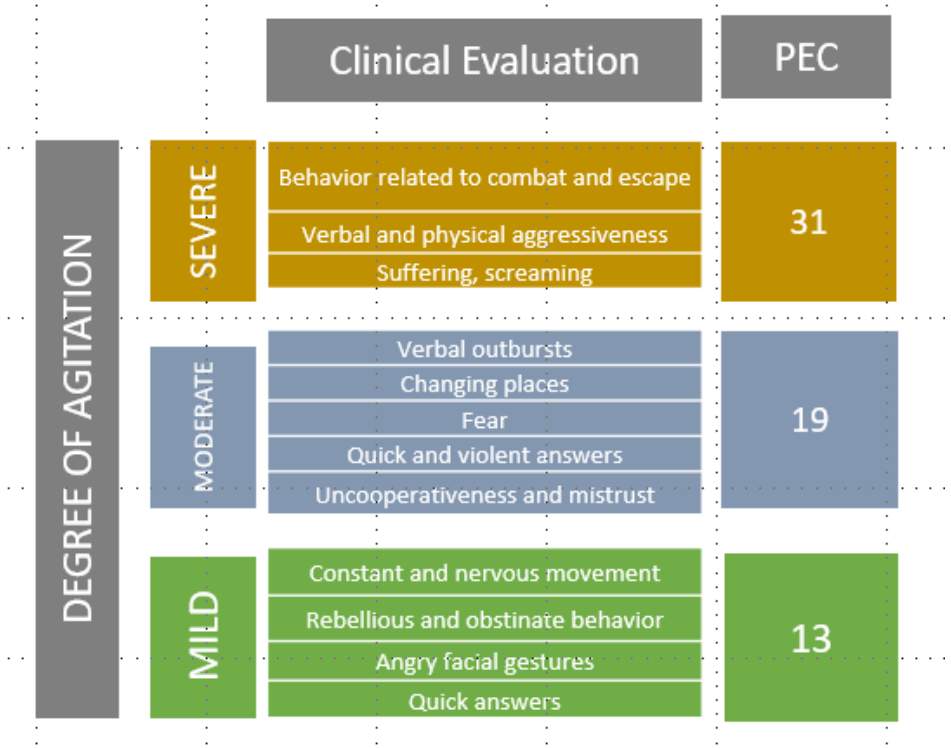
Substantial Unmet Medical Need

- No FDA approved treatments for agitation in Dementia
- Commonly used agents are fraught with safety concerns
  - Benzodiazepines
    - Black box warning
    - Disorientation, falls, respiratory suppression, excessive somnolence, abuse
  - Antipsychotic Drugs
    - Black Box, heightened mortality
    - Extrapyramidal symptoms, akathisia, acute dystonia
    - Disorientation, falls, respiratory suppression, excessive somnolence

Clinical Scales Used to Evaluate Agitation and Calmness

PEC : PANSS Excitatory Component

5 items: excitement, tension, hostility, uncooperativeness, and poor impulse control.
The 5 items from the PANSS-EC are rated from 1 (not present) to 7 (extremely severe)



PAS: Pittsburgh Agitation Scale

Four behavior groups: aberrant vocalizations, motor agitation, aggressiveness and resisting care, scored from 0 (not present) -4 (extremely loud screaming or yelling, highly disruptive, unable to redirect).

CMAI: Cohen Mansfield Agitation Inventory

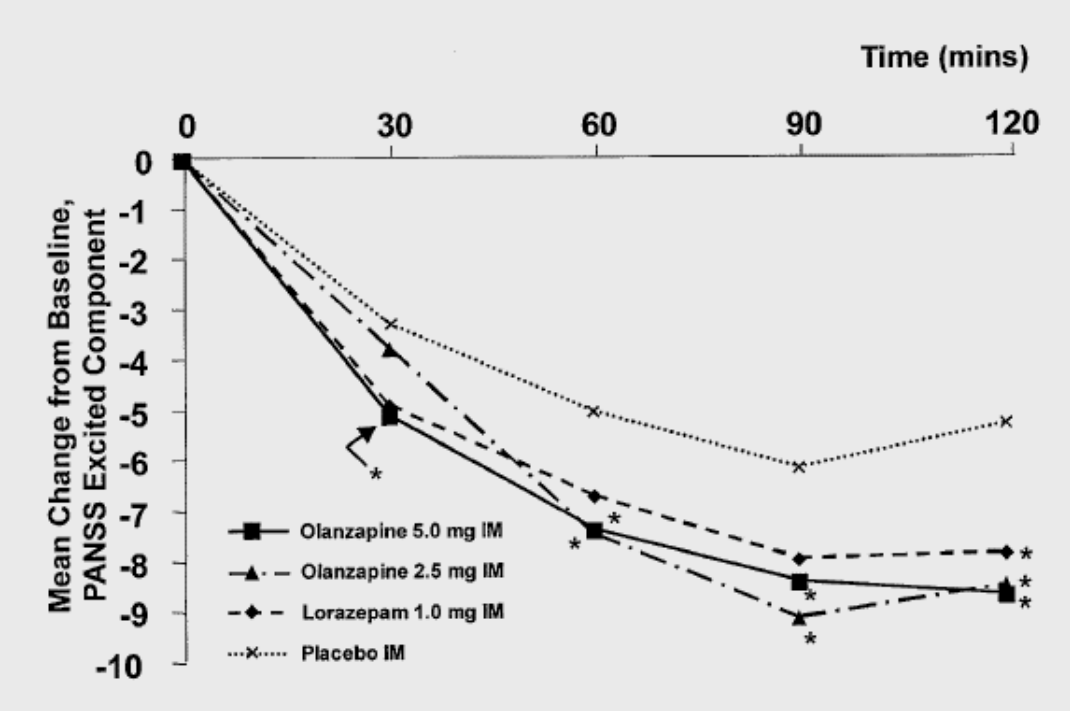
Measures an inventory of agitated behaviors on a 29 item scale over a 2 week period

ACES: Agitation and Calmness Evaluation Scale

9 points scale to measure calmness from
1- Marked Agitation to 9 Unarousable: Sleeping deeply)

IM Olanzapine and Lorazepam for Acute Treatment of Agitation in Patients with Dementia

Double-blind, Randomized Study in Acutely Agitated Patients with Dementia



Meehan KM, Wang H, David SR, Nisivoccia JR, Jones B, Beasley CM Jr, Feldman PD, Mintzer JE, Beckett LM, Breier A. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology. 2002 Apr;26(4):494-504.

Table 2. Additional Measures of Efficacy—Mean Change from Baseline at 2 and 24 Hours Post First Intramuscular Injection (LOCF)

Variable	Olanzapine 2.5 mg ($n = 71$)	Olanzapine 5.0 mg ($n = 66$)	Lorazepam 1.0 mg ($n = 68$)	Placebo ($n = 67$)
	2 Hours Post First IM Injection, Mean (*SD*)			
CMAI	−3.77 (2.93)	−3.97 (3.89)*	−4.18 (3.52)*	−2.78 (3.40)
ACES	1.80 (1.61)*	1.88 (1.86)**	2.19 (1.83)**	1.04 (1.66)
	24 Hours Post First IM Injection, Mean (*SD*)			
PANSS-EC	−6.44 (6.00)*	−6.29 (6.75)*	−5.75 (5.99)	−3.81 (6.20)
BPRS Total	−10.51 (11.50)	−10.59 (11.31)	−9.12 (10.27)	−10.29 (11.72)
BPRS Positive	−1.72 (3.50)	−1.86 (3.39)	−1.32 (3.32)	−2.09 (3.80)
CMAI	−2.82 (3.21)	−3.36 (3.92)	−2.82 (3.08)	−2.21 (3.57)
ACES	0.90 (1.19)	1.29 (1.49)**	1.07 (1.12)*	0.63 (1.14)
CGI-S	−0.38 (0.80)	−0.47 (0.89)	−0.46 (0.80)	−0.59 (0.92)
MMSE Total	0.31 (2.29)	0.10 (3.01)	0.08 (3.04)	0.37 (3.62)

*$p < .05$ relative to placebo, analysis of variance, uncorrected for multiplicity.
**$p < .01$ relative to placebo, analysis of variance, uncorrected for multiplicity.
***$p < .001$ relative to placebo, analysis of variance, uncorrected for multiplicity.
Abbreviations: ACES, Agitation–Calmness Evaluation Scale; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impressions – Improvement of Illness Scale; CGI-S, Clinical Global Impressions – Severity of Illness Scale; CMAI, Cohen-Mansfield Agitation Inventory; LOCF, last observation carried forward; MMSE, Mini-Mental State Exam; PANSS-EC, Positive and Negative Syndrome Scale–Excited Component subscale.

Table 3. Treatment-Emergent Adverse Events Reported during 24 Hours Post First Intramuscular Injection (incidence ≥3% in any treatment group)[a]

COSTART Term	Olanzapine 2.5 mg ($N = 71$) *n* (%)	Olanzapine 5.0 mg ($N = 66$) *n* (%)	Lorazepam 1.0 mg ($N = 68$) *n* (%)	Placebo[b] ($N = 67$) *n* (%)
Accidental Injury	1 (1.4%)	2 (3.0%)	3 (4.4%)	0 (0.0%)
ECG Abnormal	1 (1.4%)	2 (3.0%)	0 (0.0%)	0 (0.0%)
Headache	2 (2.8%)	2 (3.0%)	1 (1.5%)	0 (0.0%)
Hypertension	0 (0.0%)	2 (3.0%)	2 (2.9%)	1 (1.5%)
Somnolence	3 (4.2%)	2 (3.0%)	7 (10.3%)	2 (3.0%)
Vasodilatation	0 (0.0%)	2 (3.0%)	0 (0.0%)	0 (0.0%)
Sinus Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)

[a] No statistically significant differences were seen among treatment groups.
[b] Excludes data subsequent to third injection for crossover placebo patients.

Harvard Project Treatment Algorithm for Agitation (Dementia)

Note: No drugs approved for this indication

ALGORITHM : Use these treatments in order of preference

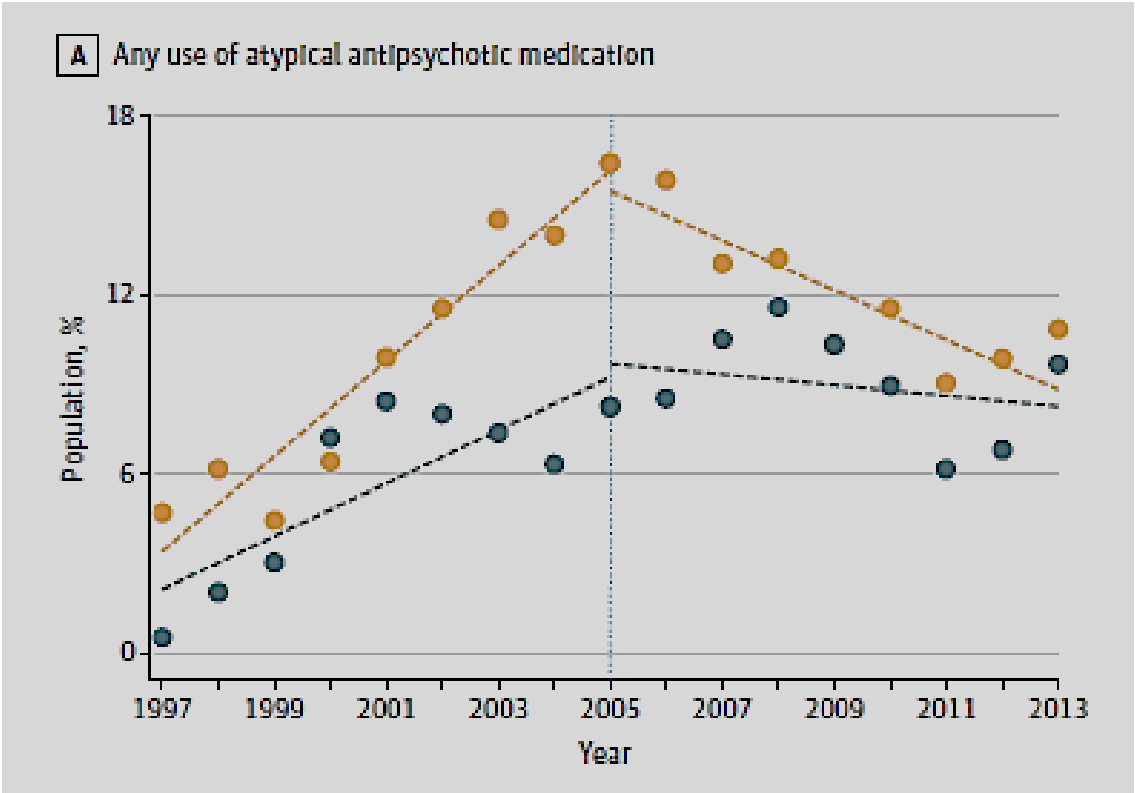
EMERGENT	URGENT	NON-EMERGENT
• Olanzapine (IM)	• Aripiprazole (oral)	• Sleep optimization, trazadone
• Haloperidol (IM)	• Risperidone (oral)	• AChE Is: Donepezil, Memantine
• Lorazepam (IM)	• Prazosin (oral)	• SSRIs: Escitalopram, Sertraline
	• Consider ECT	• Antipsychotics
		• Prazosin
		• Carbamazepine

"**emergent**" BPSD needing immediate help with their agitation, "**urgent**" cases where agitation needs to be treated but there is space to wait a few days up to a few weeks for improvement, "**non-emergent**" cases whose symptoms may be only moderately disruptive

Chen A, Copeli F, Metzger E, Cloutier A, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An update on management of behavioral and psychological symptoms in dementia. Psychiatry Res. 2021 Jan;295:113641. doi: 10.1016/j.psychres.2020.113641. Epub 2020 Dec 13.

Decreasing Use of Antipsychotics for Dementia

- Antipsychotics include olanzapine and haloperidol
- 2005: FDA issued a boxed warning regarding increased mortality associated with the use of AAPs in elderly patients with dementia-related psychosis
- After 2005, use of antipsychotics has decreased
- Use of other non-approved drugs with poor safety profiles (benzodiazepines, opioids, anti-epileptics) increased[1]



Use of antipsychotics as measured by medical expenditures (blue) and medical care surveys (orange)

1. Rubino A, Sanon M, Ganz ML, Simpson A, Fenton MC, Verma S, Hartry A, Baker RA, Duffy RA, Gwin K, Fillit H. Association of the US Food and Drug Administration Antipsychotic Drug Boxed Warning With Medication Use and Health Outcomes in Elderly Patients With Dementia. JAMA Netw Open. 2020 Apr 1;3(4):e203630

Benzodiazepines to be Avoided for Dementia Patients

DRUGS	RATIONALE	RECOMMENDATION	QUALITY OF EVIDENCE	STRENGTH OF RECOMMENDATION
Benzodiazepines	• Older adults have increased sensitivity to benzodiazepines • benzodiazepines increase risks of cognitive impairment, delirium, falls, fractures	AVOID	MODERATE	STRONG

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

- 2020: The FDA required the Boxed Warning be updated for all benzodiazepine medicines
- Addresses risks of abuse, addiction, physical dependence, and withdrawal reactions, **even when taken at recommended dosages**
- Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioid pain relievers, alcohol, or illicit drugs.
- Physical dependence can occur when benzodiazepines are taken steadily for several days to weeks, even as prescribed.
- Stopping them abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening.

Need for Novel Mechanism of Action to Treat Agitated Patients Safely

DRUG CLASS	EXAMPLE	MECHANISM
Antipsychotics	Haloperidol	Dopamine D2 Receptor antagonist
Atypical Antipsychotics	Olanzapine Risperidone	D2 antagonist/5-HT2A antagonist
Benzodiazepines	Lorazepam	GABA positive modulator

- Targeting noradrenergic signaling may be a novel pathway to address dementia related agitation

Ideal Drug Profile for Acute Treatment of Agitation in the Elderly

- Rapid onset of action
- Ease of administration
- High percentage of responders
- Dose dependent responses
- Not overly sedating, no/low risk of falls
- Minimal drug:drug interactions

Chen et al., 2021

Conclusions

- Acute agitation in elderly with dementia commonly treated with benzodiazepines and antipsychotics (IM)
- Both classes of drugs have box warnings on their use by the FDA
- Drugs with new mechanisms needed
- New drugs should work as quickly as IM drugs and have minimal safety concerns when administered to elderly patients

Opioid Withdrawal

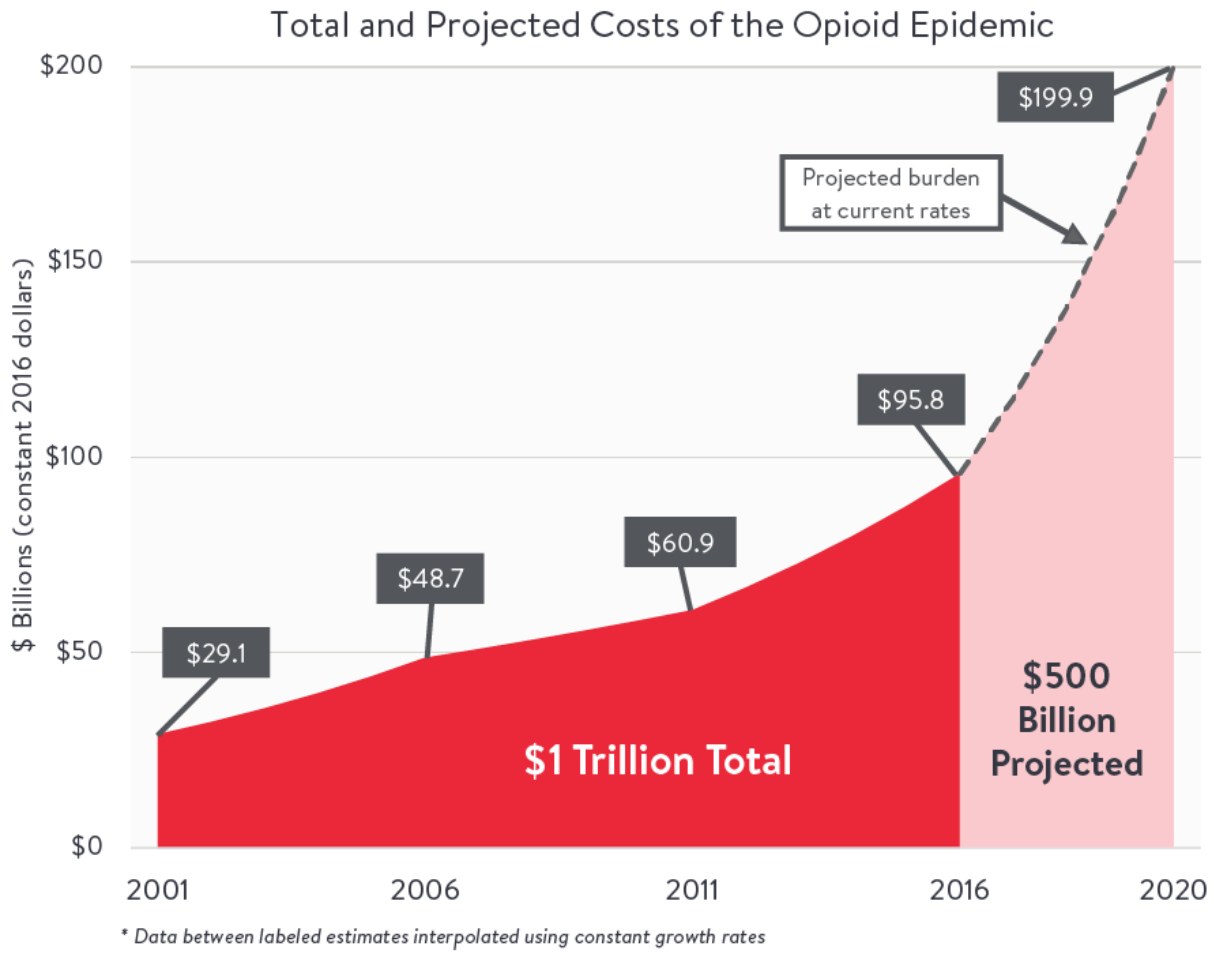
Thomas R. Kosten, MD

JH Waggoner Chair and Professor of Psychiatry, Pharmacology, Immunology, Pathology, and Neuroscience of the Dan Duncan Institute for Clinical and Translational Research,
Baylor College of Medicine

*Dr. Kosten is a paid consultant to BioXcel

OUD: High Prevalence with High Financial and Societal Cost

- ~2M individuals with opioid use disorder (2018)
- 5 lives lost to opioid overdose every hour



Includes treatment, lost wages and tax revenues

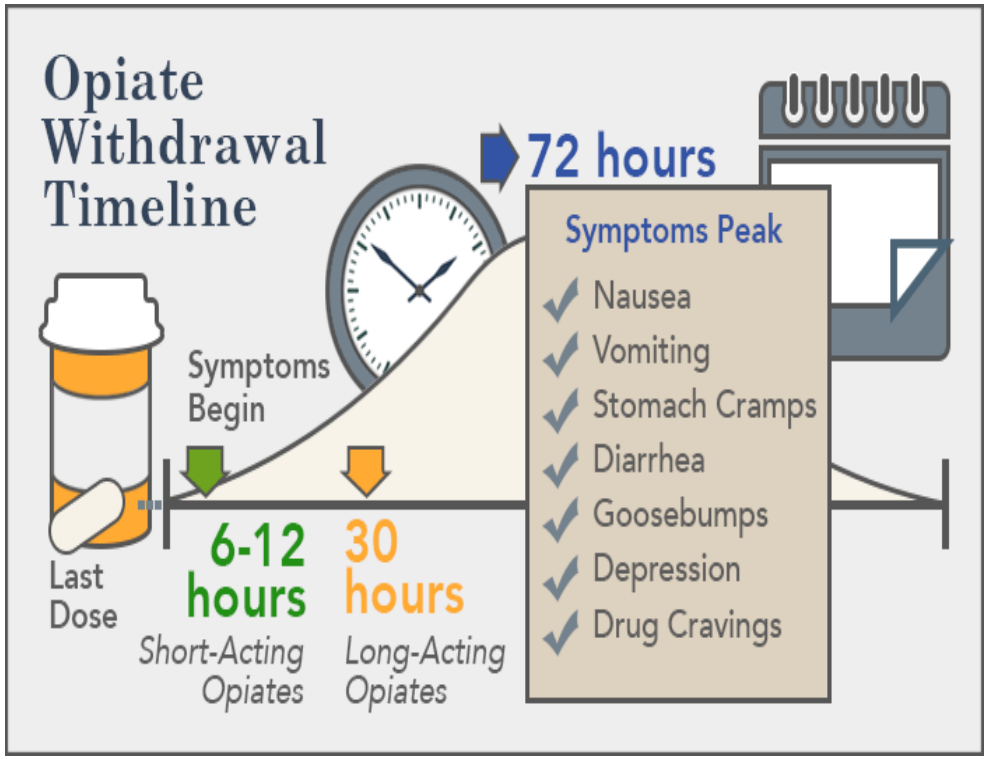
https://altarum.org/news/economic-toll-opioid-crisis-us-exceeded-1-trillion-2001

Kosten, T. Review Article: Effective Management of Opioid Withdrawal Symptoms: A Gateway to Opioid Dependence Treatment. The American Journal on Addictions, 28: 55-62, 2019

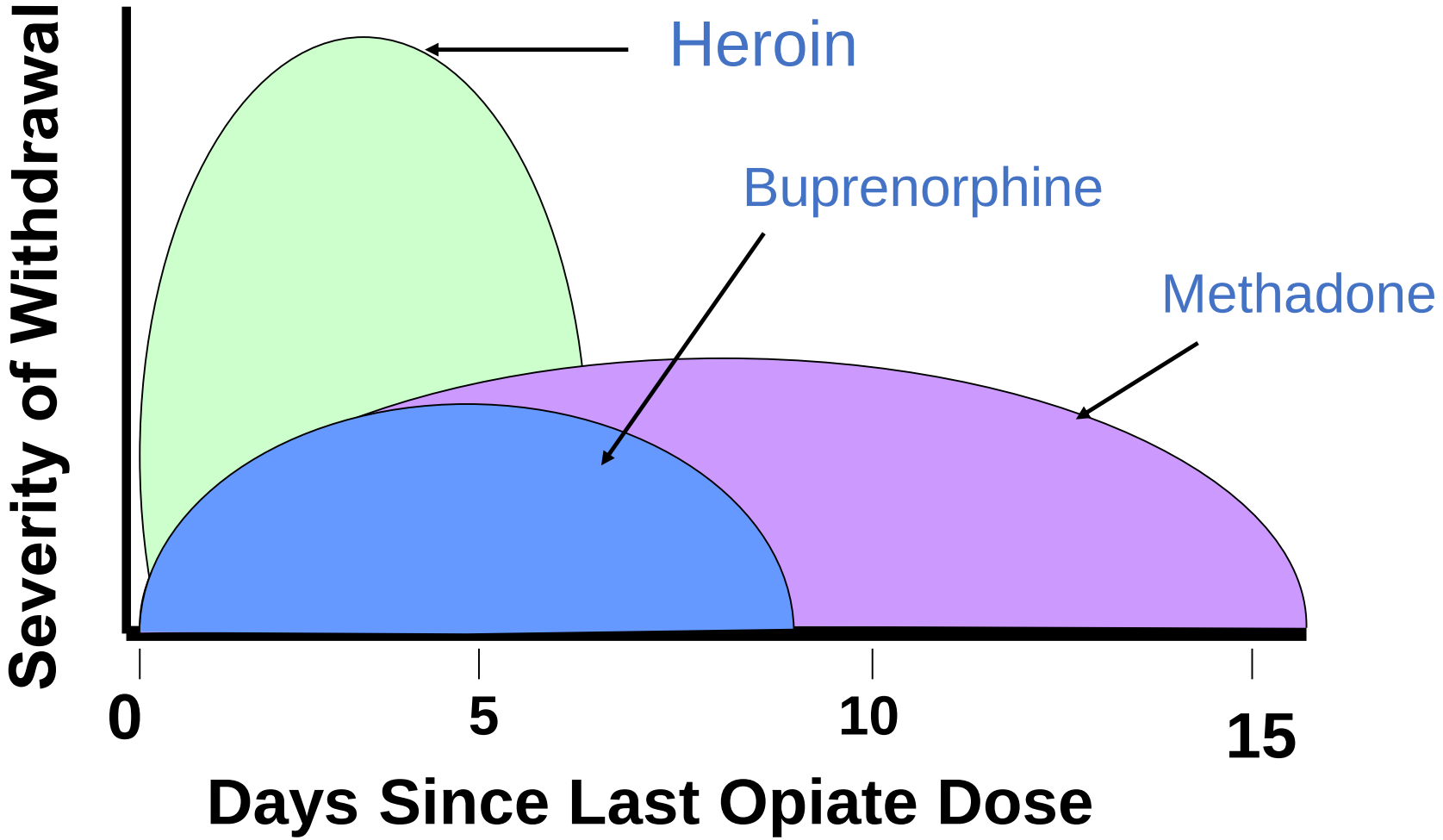
Opioid Withdrawal Symptoms

TABLE 2. Opioid withdrawal symptoms[13,14]

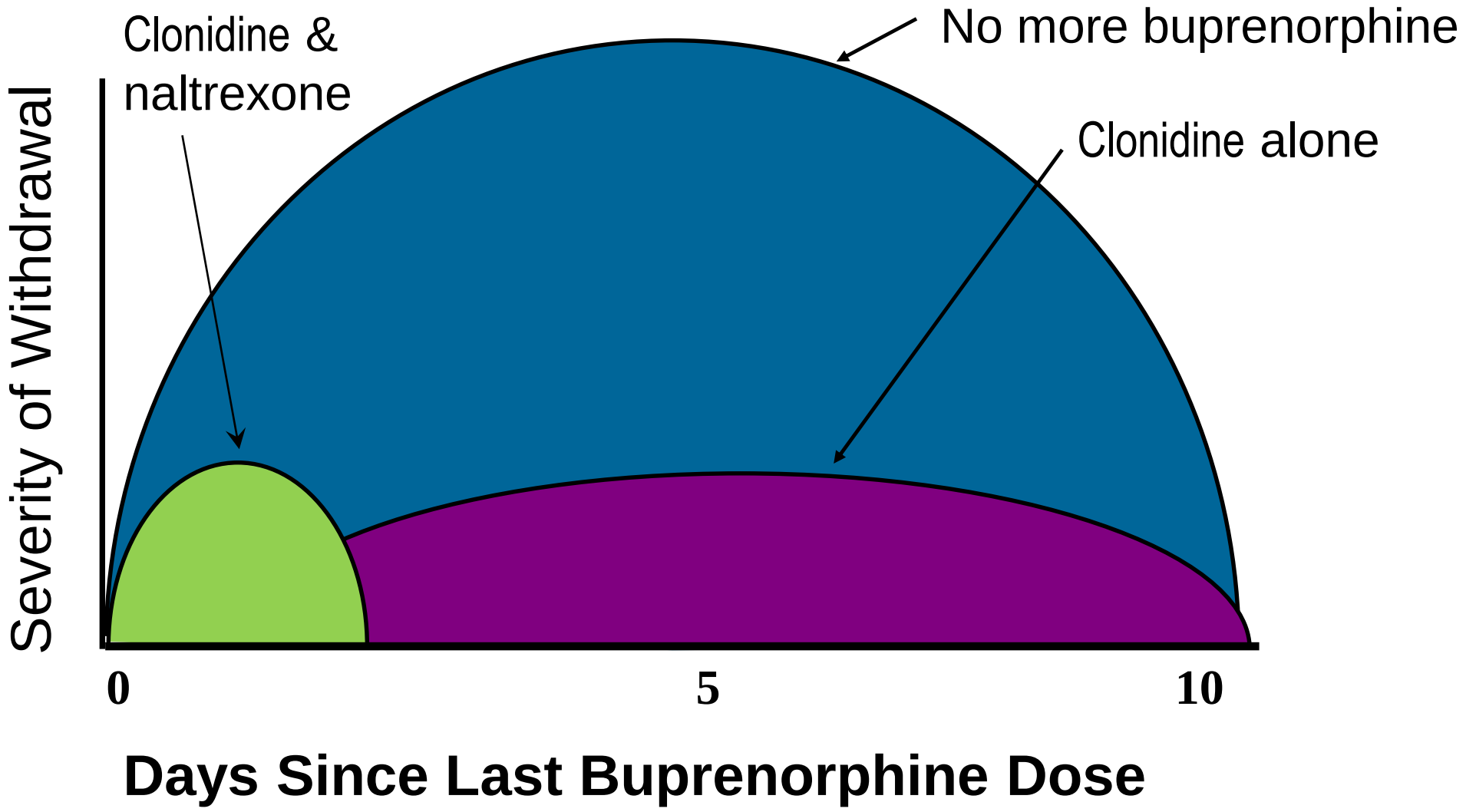
- Aches/pain
- Muscle spasms/twitching/tension
- Tremor
- Abdominal cramps
- Nausea/vomiting/diarrhea
- Anxiety/restlessness
- Irritability
- Insomnia
- Hot flashes/chills
- Heart pounding
- Lacrimation
- Sweating
- Rhinorrhea
- Pupillary dilatation
- Yawning
- Gooseflesh



Opioid Withdrawal Severity at Equivalent Doses

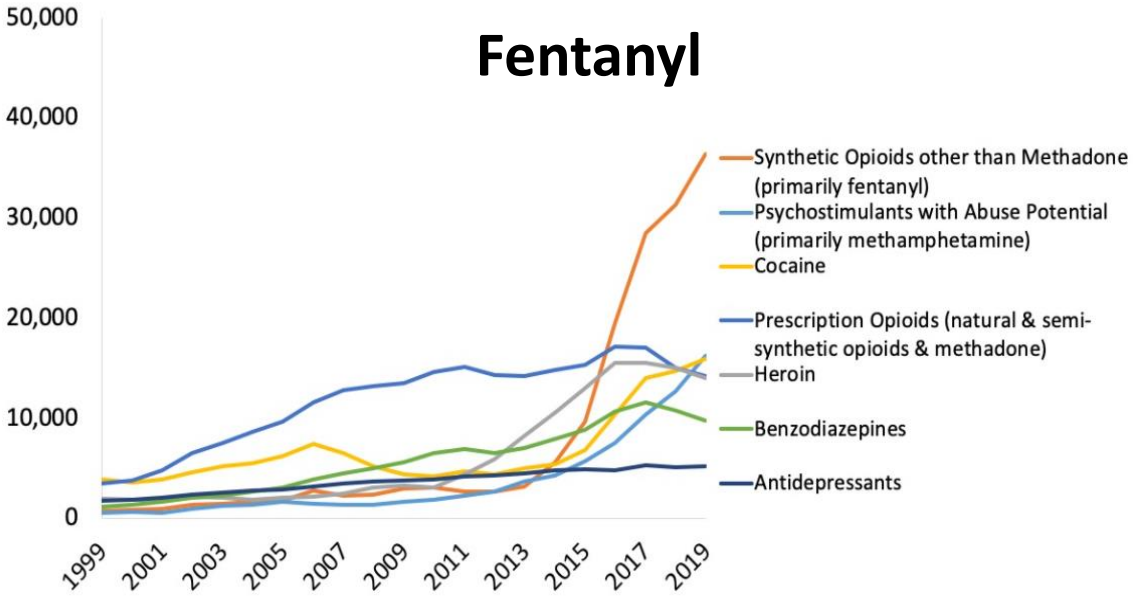


Abruptly Stopping Buprenorphine (<8 mg daily)

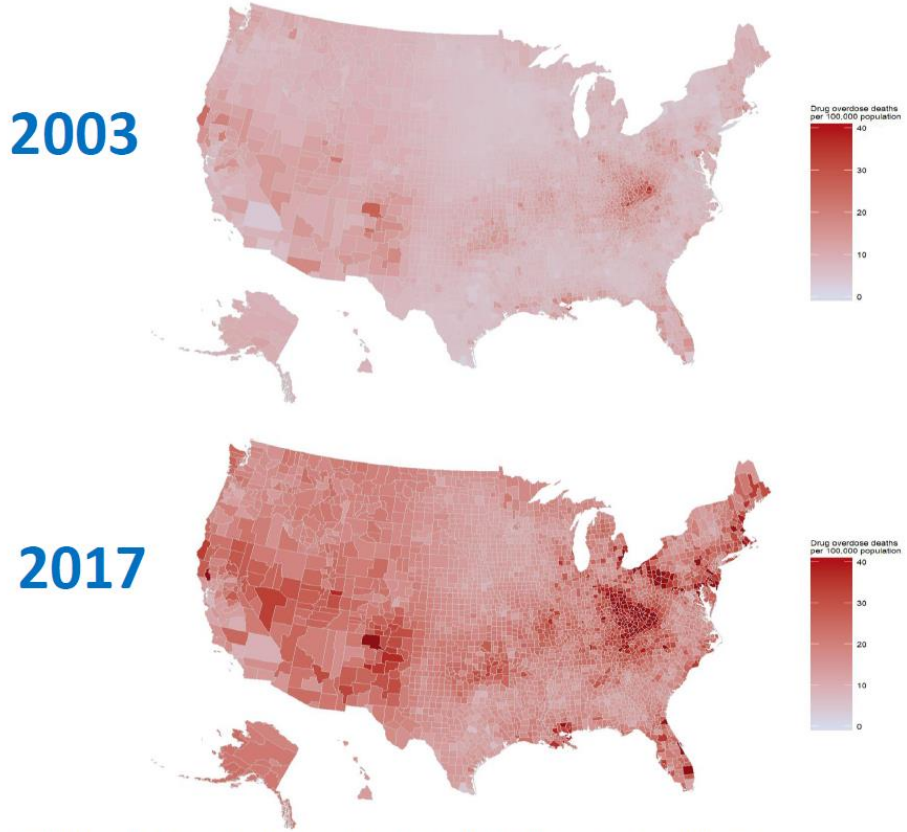


Evolving Landscape of Opioid Epidemic

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2019



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

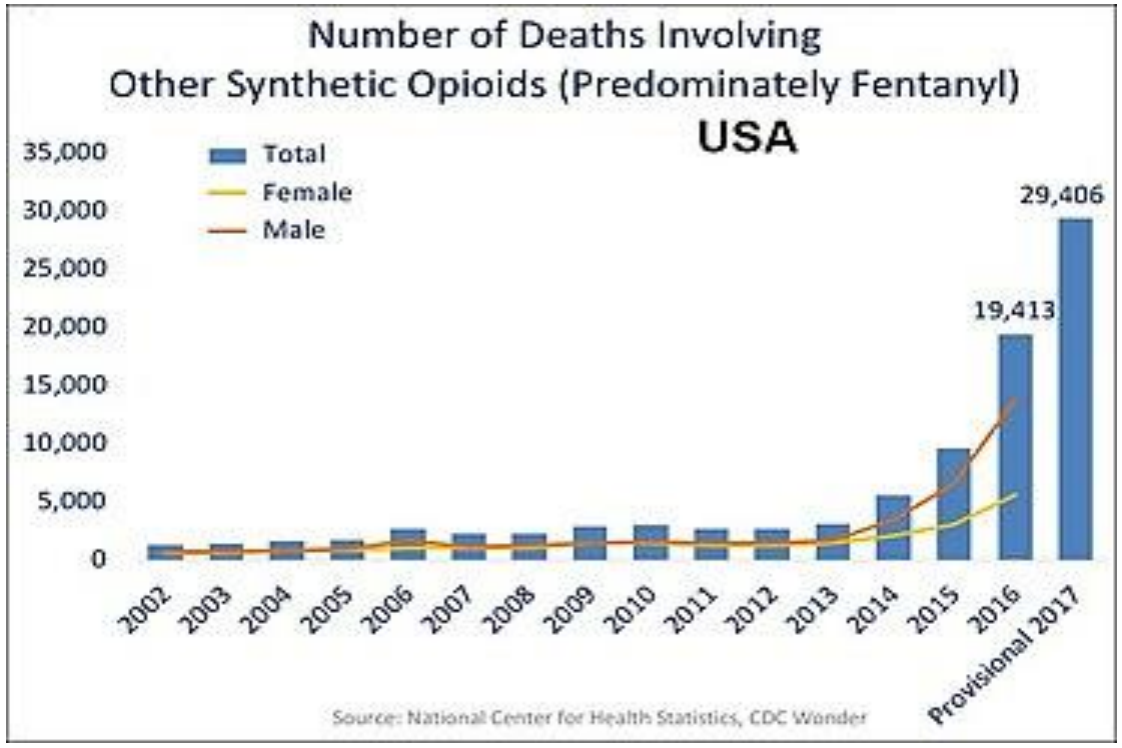


- **SOURCE:** National Center for Health Statistics, National Vital Statistics System, mortality data (http://www.cdc.gov/nchs/deaths.htm).

Opioid Epidemic: Lethality from Fentanyl

Fentanyl- What is it?

- Fentanyl is a synthetic opioid that is 80-100 times stronger than morphine and heroin
- Pharmaceutical fentanyl is for managing pain in cancer patients
- Fentanyl is added to heroin to increase its potency



Street Names

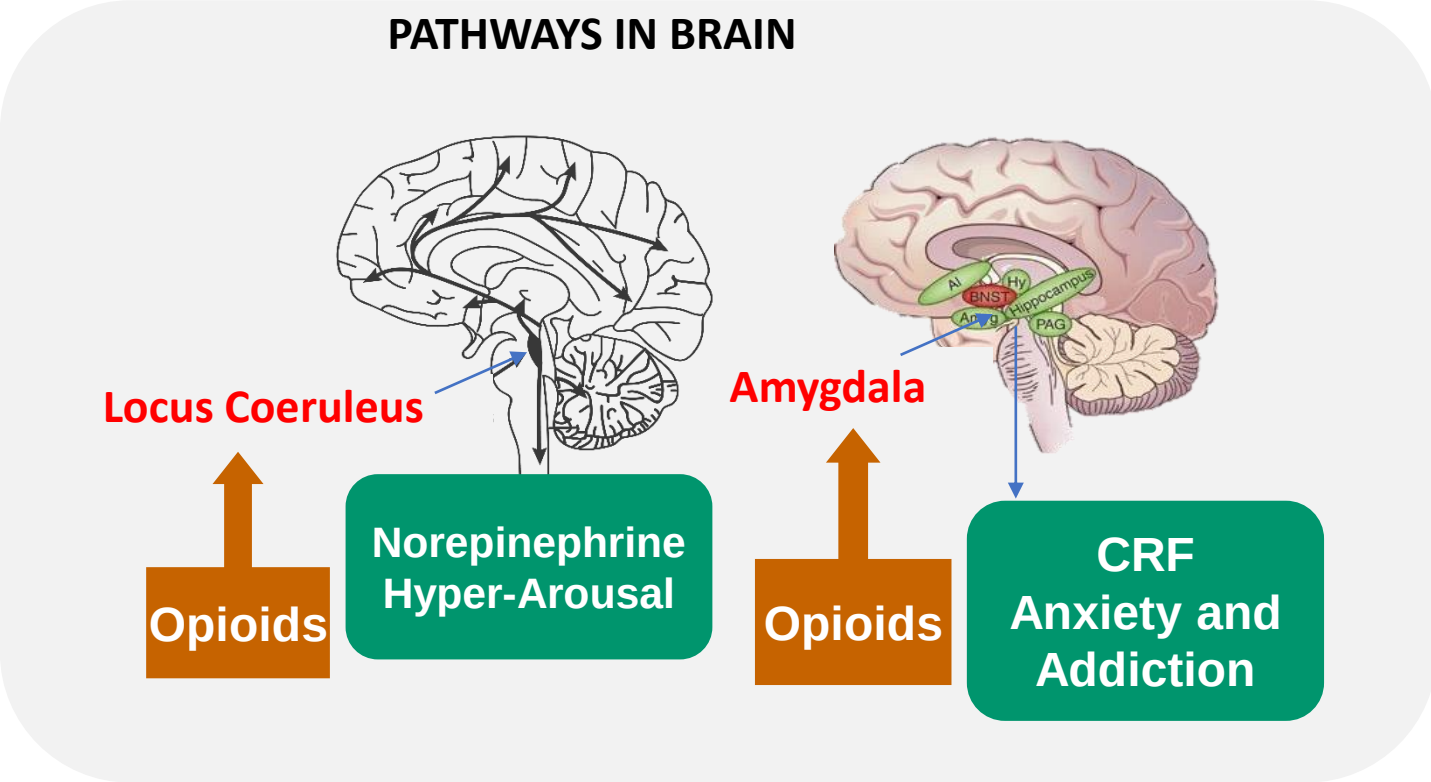
- Apace, China Girl, China Town, China White, Dance Fever, Goodfellas, Great Bear, He-Man, Poison and Tango & Cash

Patient Types and Treatment Goals

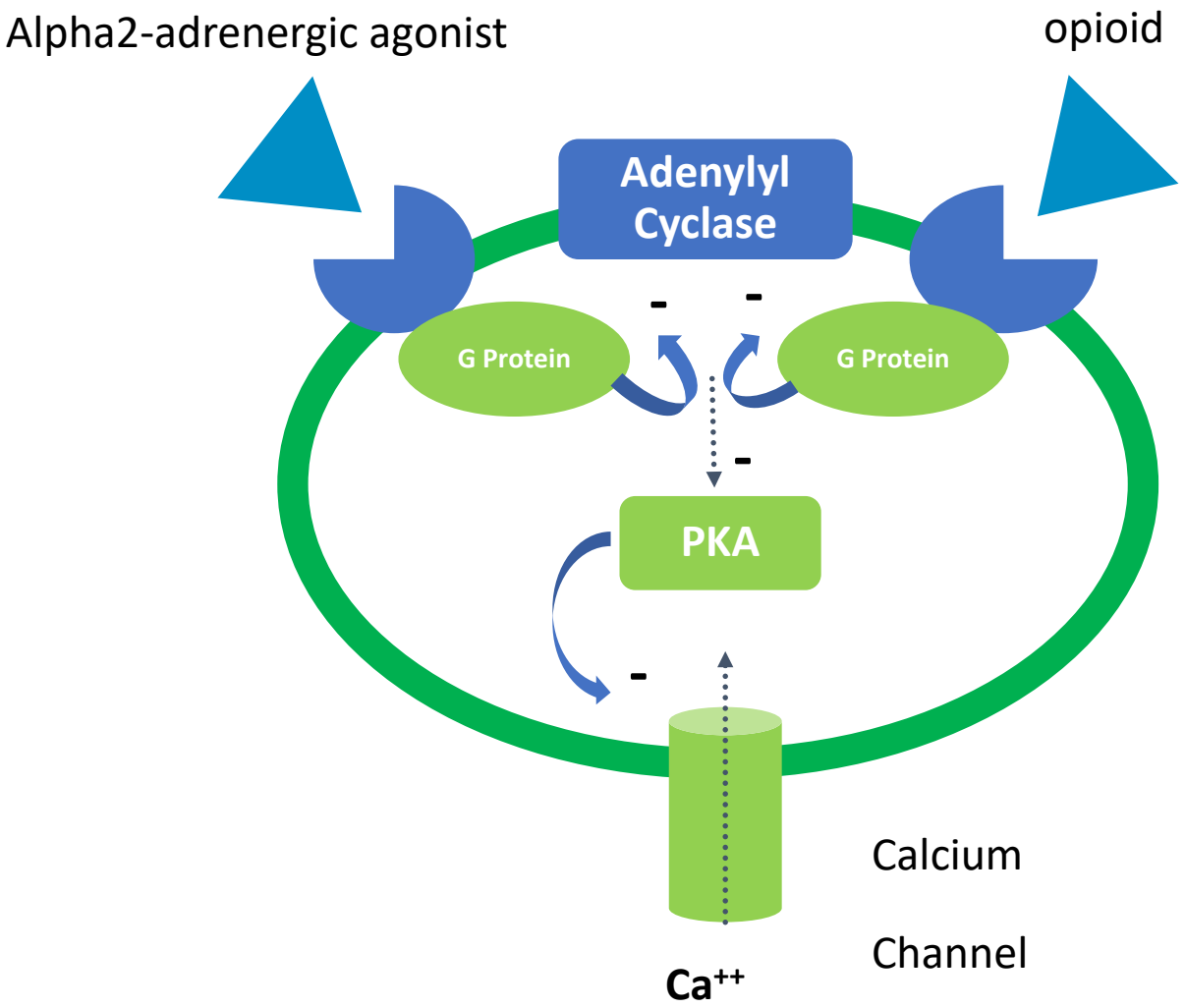
Patient Type:	Treatment Goal:
• Prescription opioid abuse • Illicit heroin abuse • Post-opioid overdose • Buprenorphine maintained • Chronic pain • Stop long-term analgesia	<u>WITHDRAWAL AT END:</u> • Buprenorphine maintained <u>WITHDRAWAL FIRST STEP:</u> • Naltrexone maintained • Drug-free residential • Transition to non-opioid analgesia

Neurobiology of Withdrawal & Alpha-2-Adrenergic system

- Opioids affect 2 regions of the brain, the **Locus Coeruleus** and **Amygdala**, that mediate withdrawal when opioid use stops
- Alpha-2-Adrenergic receptors modulate brain activity in **both regions**



Shared Opioid & Alpha-2 Adrenergic Receptor Actions



Optimal Features for a Non-Opioid Drug to Treat Withdrawal

Feature	Lofexidine	Comments
Fast acting, consistent delivery with low PK variability in patients	Tablets ingested, subject to problems with absorption in GI tract and liver changes	Hepatic dysfunction from alcohol, acetaminophen or hepatitis can inhibit bioavailability
Minimal Risk of DDIs	Lofexidine primarily metabolized by CYP2D6, which has slow & fast metabolizers	Non-CYP mediated metabolism preferred
Able to treat patients who cannot swallow or are vomiting	New formulation required (syrup or rectal suppository) for patients who cannot swallow	Mucosal formulation will minimize problems from vomiting and diarrhea or patients that cannot swallow
Minimal number of administrations daily	4 doses per day	Compliance is a significant problem among substance abusers
Promotes natural sleep	Not tested	Dexmedetomidine shows good sleep benefits using polysomnography[1]

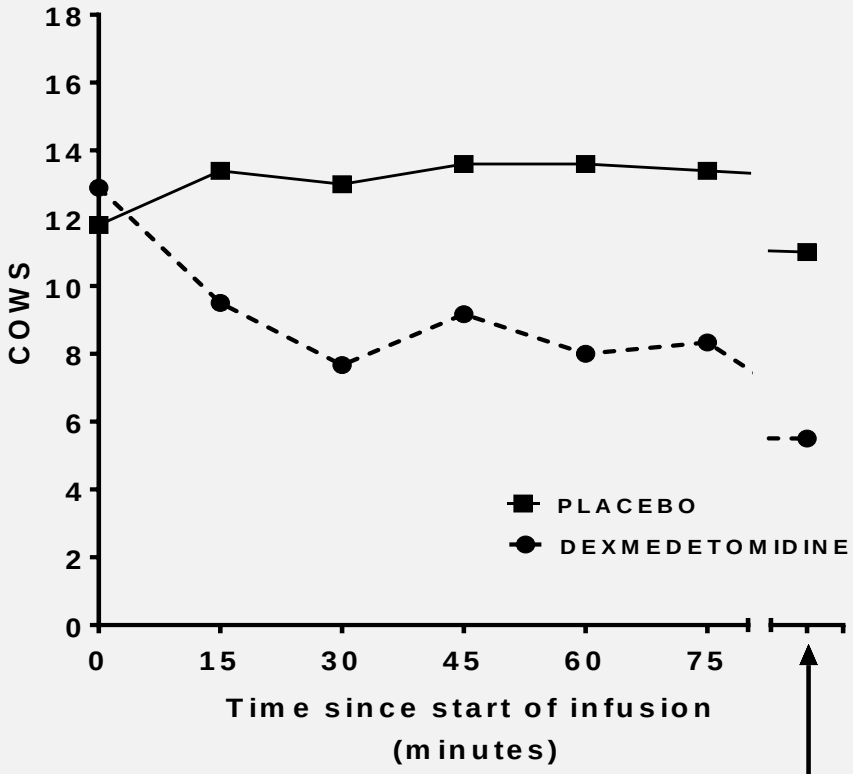
[1] Belur et al. Predicting Deep Hypnotic State From Sleep Brain Rhythms Using Deep Learning: A Data-Repurposing Approach. Anesth Analg. 2020 May;130(5):1211-1221

IV Dexmedetomidine (Precedex):

Effective in Reducing Symptoms of Opioid Withdrawal

- Randomized DB PC Proof-of-concept trial with IV Dexmedetomidine in 16 Opiate SUD
- All patients had DSM5 opioid use disorder
- Entry COWS at screening: from 9 to 15 pts
- Stepwise escalation of IV infusion rate until stopping criterion were met
    - Mimic a sublingual PK profile
- Stopping Criterion: 50% drop in COWS

Precedex Treatment of Opioid Withdrawal



Conducted by BioXcel Therapeutics

Advantages of a Non-Opioid Treatment for Withdrawal

Non-Opioid:

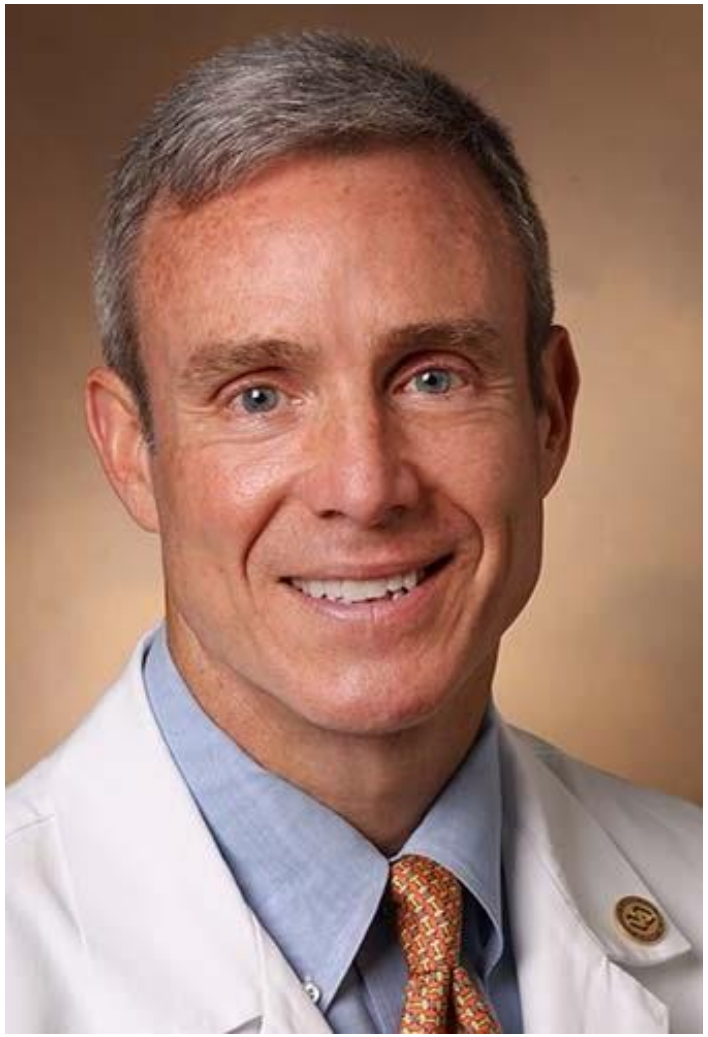
- Lower risk of abuse & diversion
- No respiratory depression
- Safe & effective
- Reduces symptoms rapidly
- Manageable side effects
- No limiting off-target effects at non-alpha2 adrenergic receptors

Usage:

- Rapid onset
- Once/Twice daily administration
- Ease of administration

Broader Access:

- Not scheduled, no license required
- Easier access



Delirium Related Agitation

E. Wesley Ely, MD, MPH

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Co-director, Critical Illness, Brain Dysfunction and Survivorship (CIBS) Center

Agenda Topics

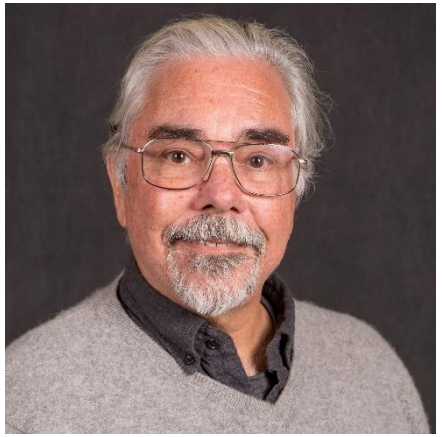
- Delirium Fundamentals
  - Definition
  - Manifestation in Different Hospital Settings
- Assessing Delirium: Multifactorial Etiology
- Delirium Protocol
  - Monitoring Delirium and Agitation Associated with It
- Preventing Delirium
  - Nonpharmacologic Approaches
- Managing Agitation Associated with Delirium
  - Current Guidelines
  - BXCL501 Clinical Development

Q&A Session

KOL Presenters

Scott Zeller, MD

Schizophrenia/Bipolar Disorder Related Agitation



Larry Ereshefsky, PharmD, FCCP, BCPP

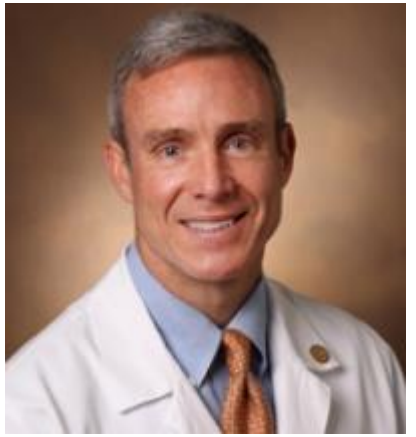
Dementia Related Agitation

Alan Breier, MD

Dementia Related Agitation

Thomas R. Kosten, MD

Opioid Withdrawal Symptoms



E. Wesley Ely, MD, MPH

Delirium Related Agitation