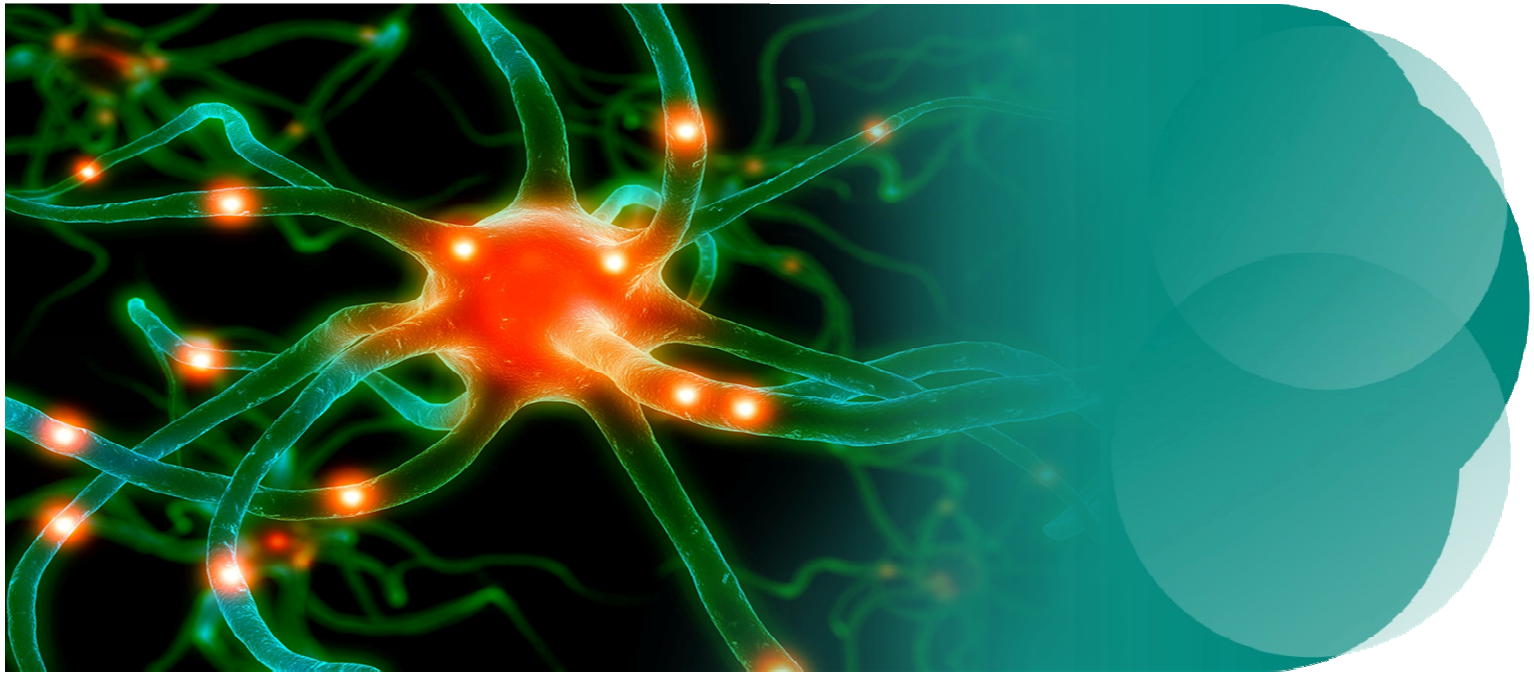


Challenges in Neuroscience Discovery and Development

What has Changed and Where are We Headed?

Darryle D Schoepp, Ph.D.

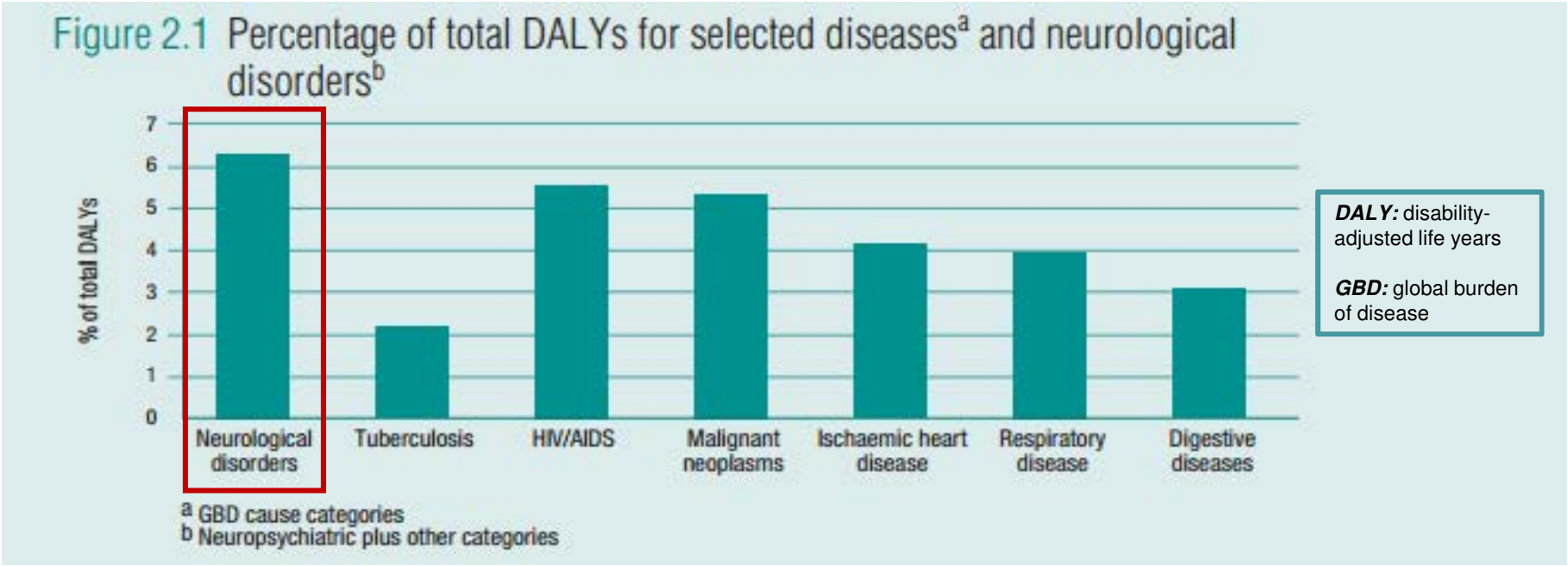
Vice President and Therapeutic Area Head, Neuroscience

MSD
Be well

Summary of Talk

- Historically how successful have we been in Neuroscience Therapeutics?
- What has led to / defined past success?
- What is different now?
- What does future success look like?
- What we now need to do?
- Recent example: Belsomra (Suvorexant) "*Trifecta* of Target Validation"

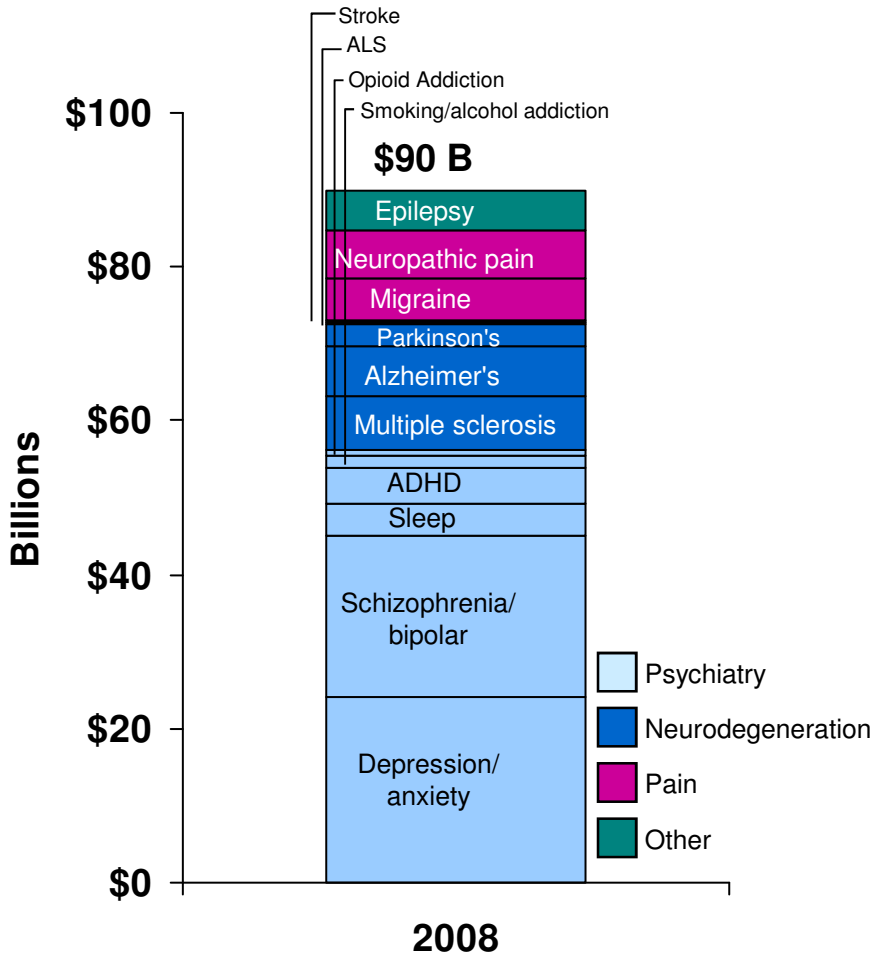
Global burden of neurologic and psychiatric disorders



- The **disability-adjusted life year** (**DALY**) is a measure of overall disease burden
- Each DALY represents 1 year lost due to ill-health, disability or early death
- WHO estimates that in the United States between 2000 and 2012, disorders of the nervous system accounted for 7 of the 20 highest causes of DALYs [1]

[1] WHO global health estimates 2014
http://www.who.int/healthinfo/global_burden_disease/en/

2008 Neuroscience Overview



- **Psychiatry**
  - Largest value accounting for ~ 48% of all CNS sales
  - Significant unmet need especially in schizophrenia and depression / bipolar where opportunity still exists for novel drugs
- **Neurology**
  - Growing sector of CNS need as aging population drives prevalence in neurodegenerative disorders

What can we say about these classes of drugs?

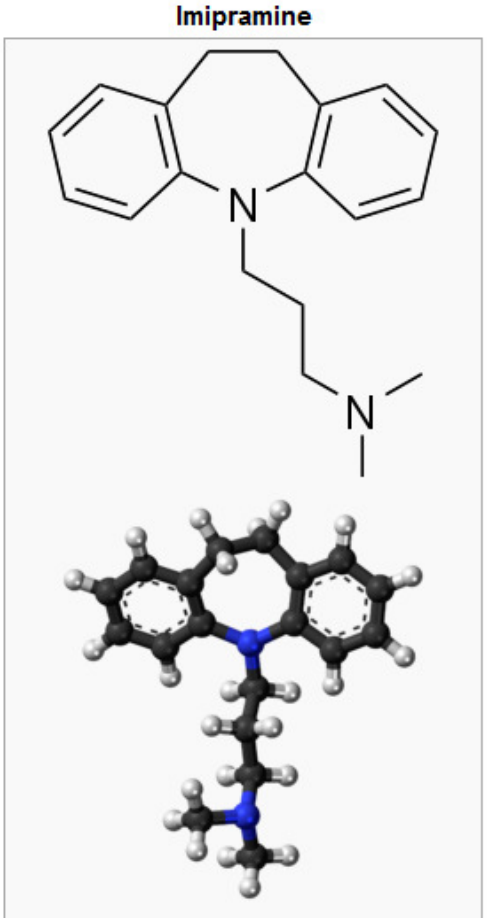
*Source: Merck Commercial data and input; IMS 2008; CNS Market Outook to 2012, Business Insights; Datamonitor CNS Market Overview April 2008

Neuroscience Therapeutic Mechanisms in 2010

Neurotransmitter Class	System / Function	Drugs Approved	# of Top 60 Drugs
Amino Acids • GABA • Glutamate	• Fast onset • Excitability/plasticity • Widespread • Multiple targets	▪ Sedative hypnotics ▪ Benzodiazapenes ▪ Anticonvulsants ▪ Memantine ▪ Ketamine	6 / 60
Biogenic amines • Dopamine • Norepinephrine • 5-HT • Histamine	• Modulatory • Widespread • Multiple targets	▪ L-DOPA, dopaminergics ▪ **Antipsychotics** ▪ **Tricyclics, SSRIs, SNRIs** ▪ Stimulants ▪ Triptans	14 / 60
Cholinergic / purinergic • Acetylcholine • Adenosine / ATP	• Modulatory • Widespread • Multiple targets	▪ Acetylcholine esterase inhibitors ▪ Nicotine Patch ▪ Chantix	2 / 60
Neuropeptides • Substance P • CGRP • Orexins • Enkephalins	• Perturbed homeostasis • Dynamic regulation • Selective distribution • Targeted function	▪ Substance P / EMEND ▪ Opiates	1 / 60

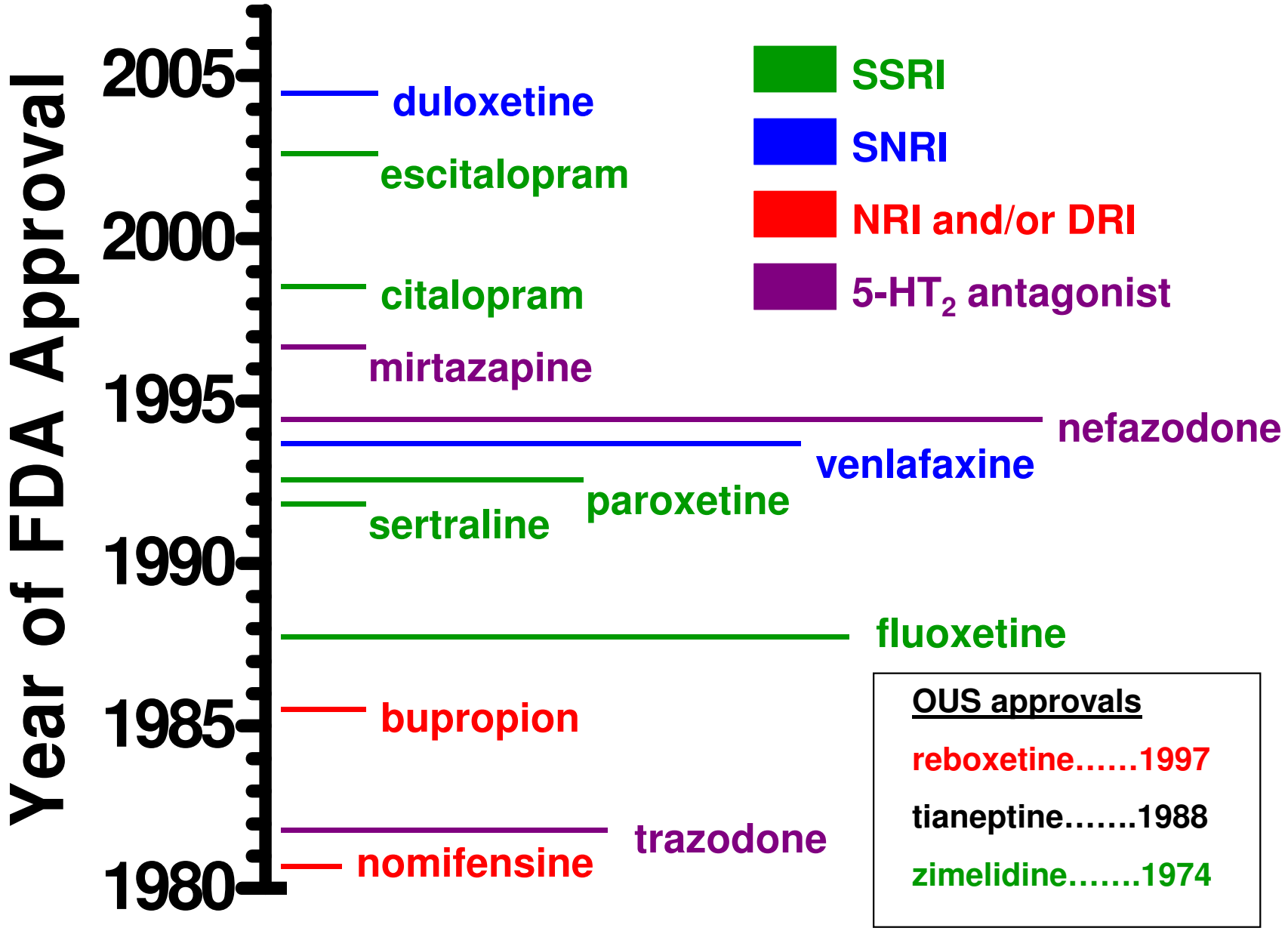
Source: Verispan, VONA, Drugs.com

First the Molecule , then the Mechanism…



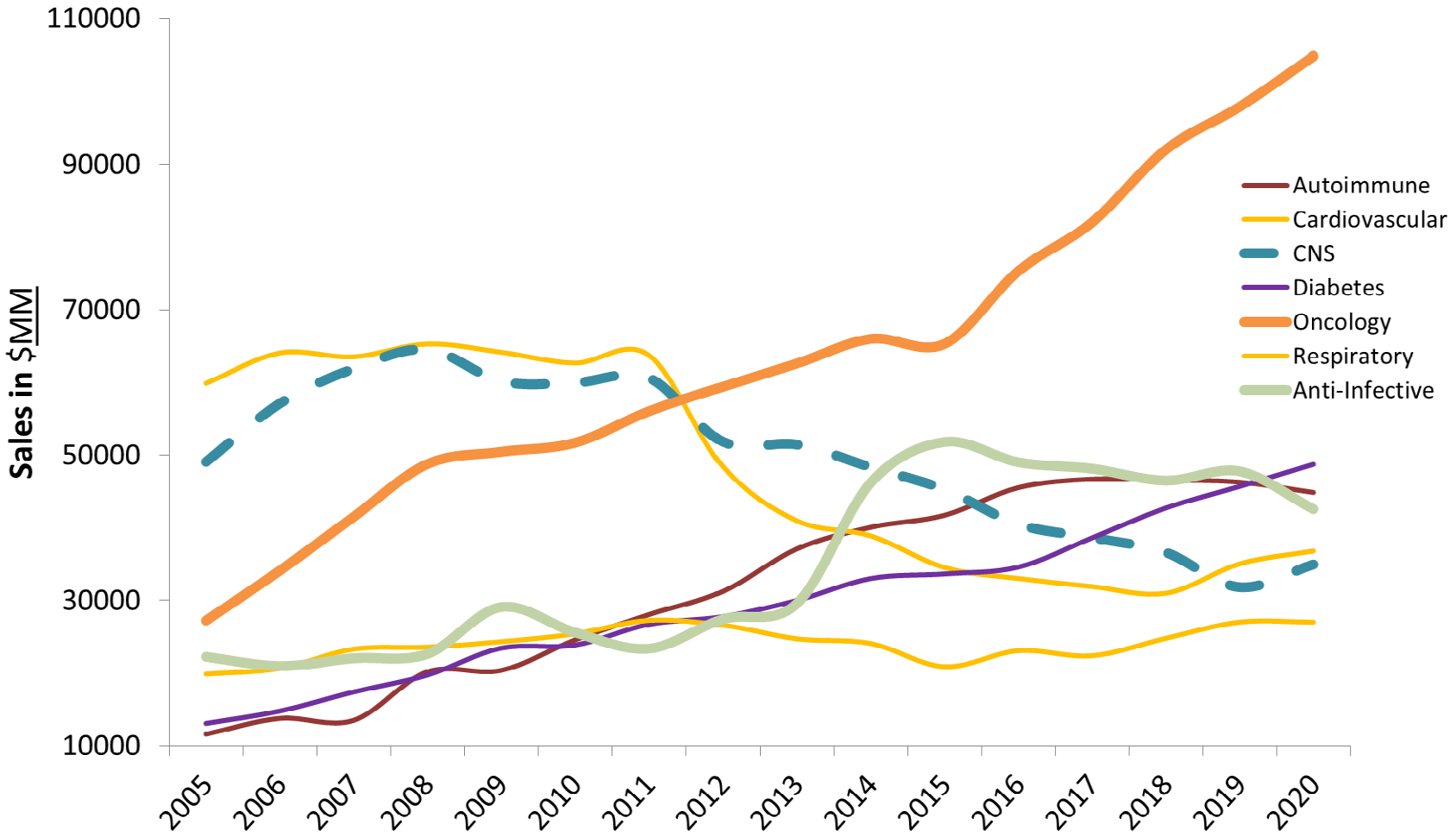
- Imipramine was first tried against psychotic disorders such as schizophrenia, but proved insufficient.
- At the first international congress of neuro-pharmacology in Rome, September 1958 Dr Freyhan from the University of Pennsylvania discussed as one of the first clinicians the effects of imipramine in a group of 46 patients, most of them diagnosed as "depressive psychosis".
- The patients were selected for this study based on symptoms such as depressive apathy, kinetic retardation and feelings of hopelessness and despair.
- In 30% of all patients, he reported optimal results, and in around 20%, failure.

Antidepressant New Drug Approvals –Iteration of Serendipity



Drug Sales for Major Therapeutic Areas – 2005-2020

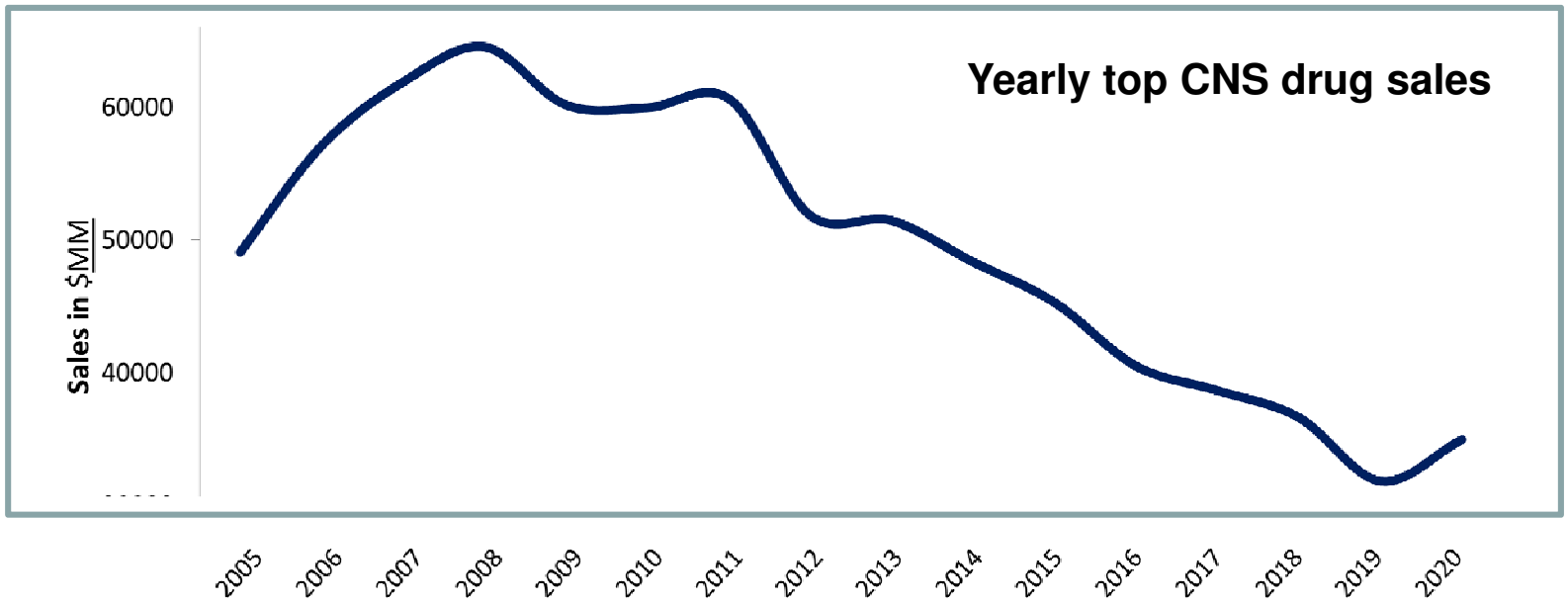
Top 200 Drugs

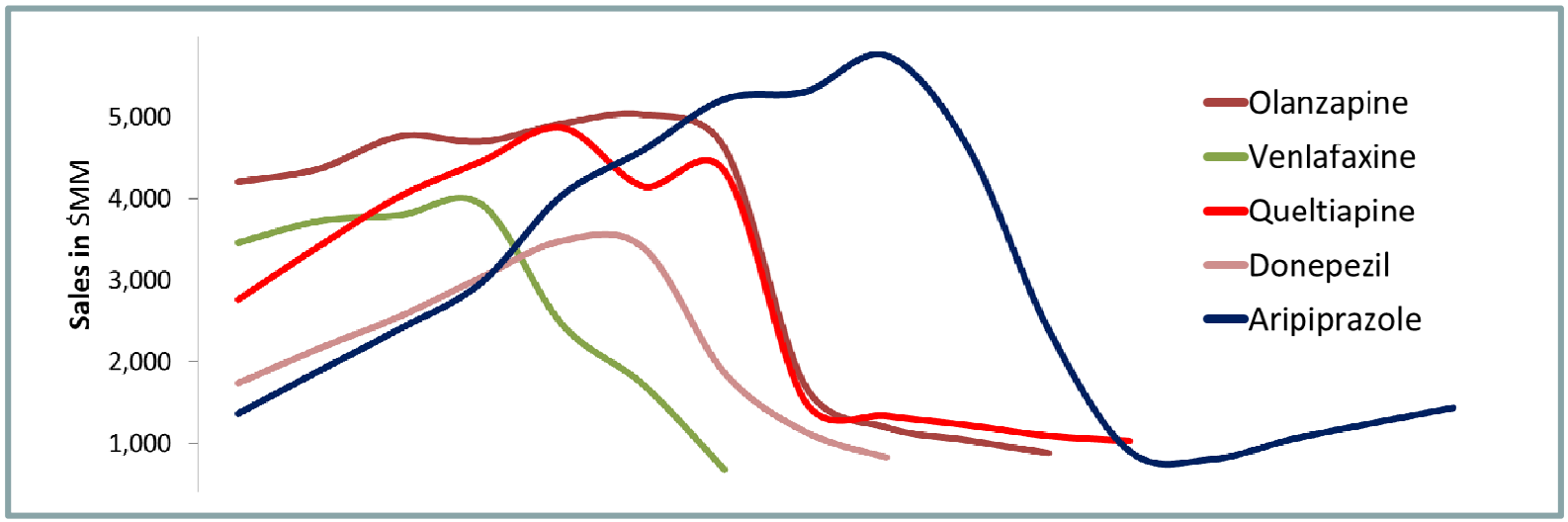


Public

Source: EvaluatePharma

Neuroscience Drugs Patent Cliff - Top Contributing Drugs





Source: EvaluatePharma

Challenges in Neuroscience Discovery and Development

- ✓Historically how successful have we been in Neuroscience Therapeutics?
- ✓What has led to / defined past success?
- **What is different now?**
- **What does future success look like?**
- **What we now need to do?**
- Recent example: Belsomra (Suvorexant) "*Trifecta* of Target Validation"

WELCOME TO THE FDA CENTER FOR DRUG EVALUATION AND RESEARCH'S (CDER) FOURTH ANNUAL NOVEL NEW DRUGS SUMMARY.

- Each year, CDER approves hundreds of new medications, most of which are variations of previously existing products……..These new products contribute to quality of care, greater access to medication, more consumer choice, and a competitive marketplace that enhances affordability and public health.
- However, products in a small subset of these new approvals, which we refer to as novel new drugs, are among the more truly innovative products that often help advance clinical care to another level.
- At the end of each calendar year, CDER summarizes these new products.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
www.fda.gov/drugs

IMPACT · INNOVATION

NOVEL NEW DRUGS 2014 SUMMARY

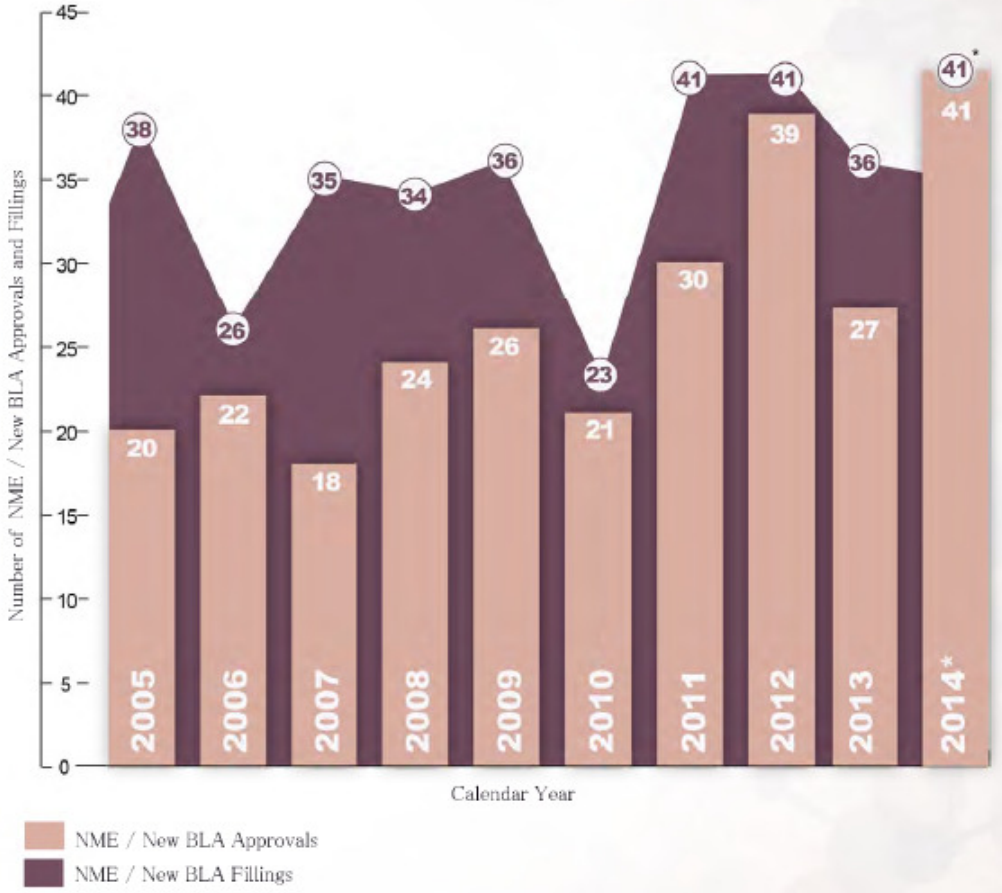
JANUARY 2015

41 NOVEL NEW DRUG APPROVALS IN CY 2014 IS MORE THAN THE AVERAGE NUMBER APPROVED ANNUALLY DURING THE PAST DECADE

FROM 2005 THROUGH 2013 CDER HAS AVERAGED

25

NOVEL NEW DRUG APPROVALS PER YEAR



Public

Class of 2014: 41 Novel New Drug US Approvals Innovation in Neuroscience is "Still" Rare

NOVEL NEW DRUGS

2014

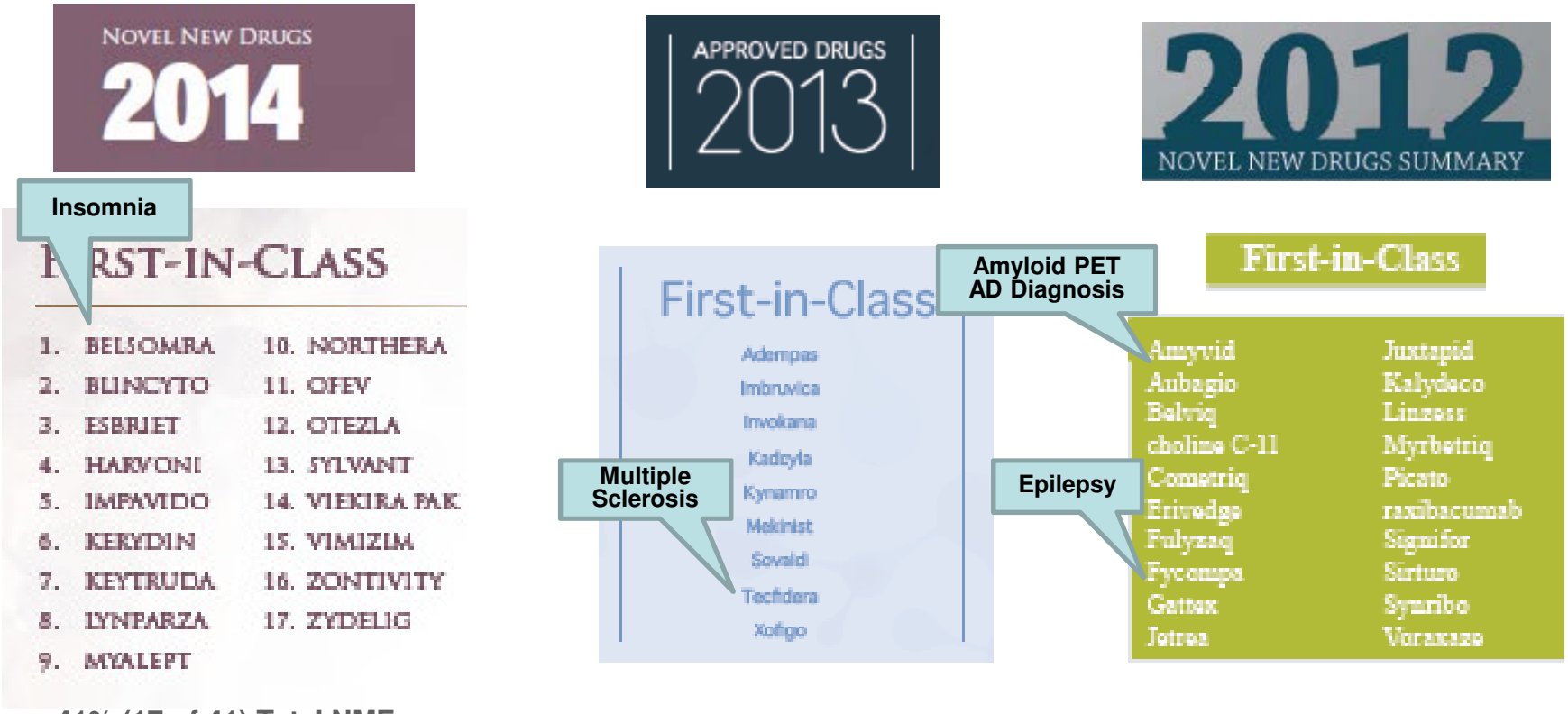
AKYNZEO
BELEODAQ
BELSOMRA
BLINCYTO
CERDELGA
CYRAMZA
DALVANCE
ENTYVIO
ESBRIET
FARXIGA
HARVONI
HETLIOZ
IMPAVIDO
JARDIANCE
JUBLIA
KERYDIN
KEYTRUDA
LUMASON
LYNPARZA
MOVANTIK
MYALEPT
NEURACEQ
NORTHERA
OFEV
OPDIVO
ORBACTIV
OTEZLA
PLEGRIDY
RAPIVAB
SIVEXTRO
STRIVERDI RESPIMAT
SYLVANT
TANZEUM
TRULICITY
VIEKIRA PAK
VIMIZIM
XTORO
ZERBAXA
ZONTIVITY
ZYDELIG
ZYKADIA

FIRST-IN-CLASS

1. BELSOMRA
2. BLINCYTO
3. ESBRIET
4. HARVONI
5. IMPAVIDO
6. KERYDIN
7. KEYTRUDA
8. LYNPARZA
9. MYALEPT
10. NORTHERA
11. OFEV
12. OTEZLA
13. SYLVANT
14. VIEKIRA PAK
15. VIMIZIM
16. ZONTIVITY
17. ZYDELIG

- **Only ONE Neuroscience compound on first-in-class list**
- **Two on entire list of 41 but one was a PET diagnostic (Neuraceq / 18F-florbetaben)**

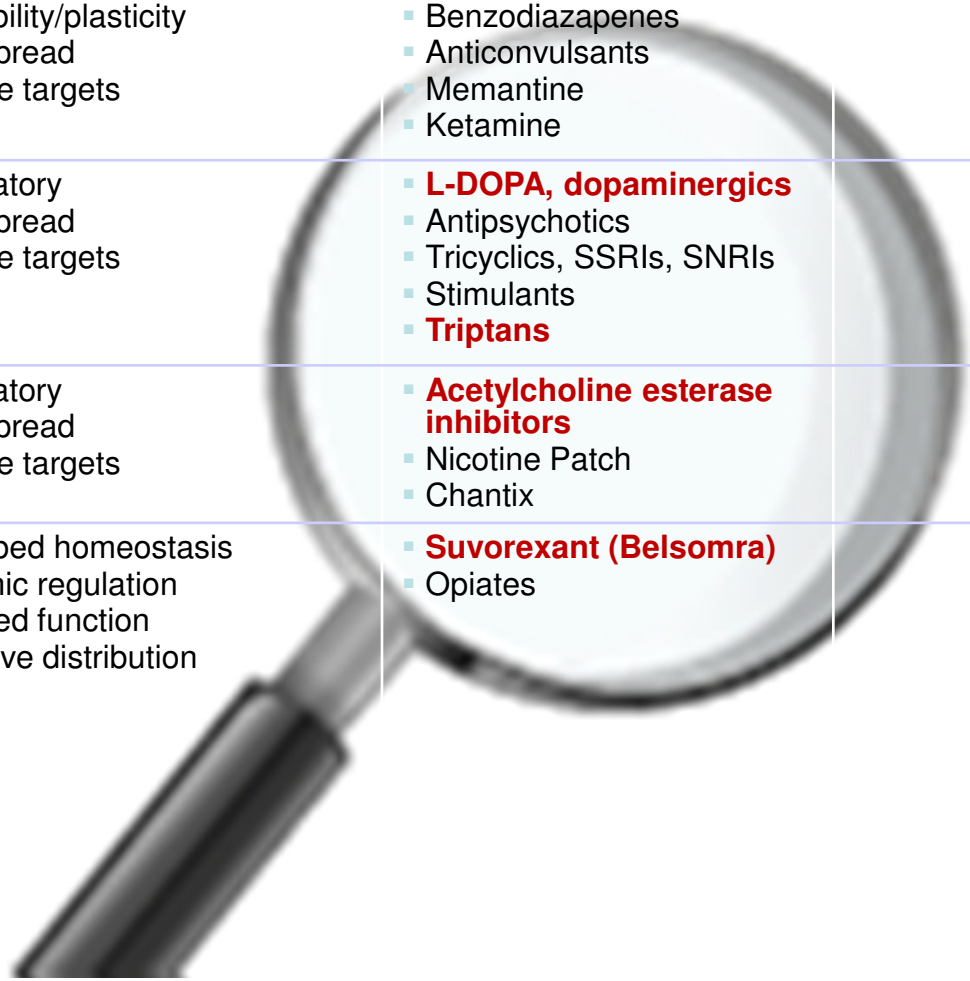
Novel New Drug US Approvals by Year
Innovation in Neuroscience is "Still" Rare



How many Neuroscience compounds on first-in-class lists?

Rationally Designed Fundamentally New Neuroscience Mechanisms are Rare Events

Neurotransmitter Class	System / Function	Drugs Approved
Amino Acids • GABA • Glutamate	• Fast onset • Excitability/plasticity • Widespread • Multiple targets	▪ Sedative hypnotics ▪ Benzodiazapenes ▪ Anticonvulsants ▪ Memantine ▪ Ketamine
Biogenic amines • Dopamine • Norepinephrine • 5-HT • Histamine	• Modulatory • Widespread • Multiple targets	▪ **L-DOPA, dopaminergics** ▪ Antipsychotics ▪ Tricyclics, SSRIs, SNRIs ▪ Stimulants ▪ **Triptans**
Cholinergic / purinergic • Acetylcholine • Adenosine / ATP	• Modulatory • Widespread • Multiple targets	▪ **Acetylcholine esterase inhibitors** ▪ Nicotine Patch ▪ Chantix
Neuropeptides • Orexins • CGRP • Enkephalins	• Perturbed homeostasis • Dynamic regulation • Targeted function • Selective distribution	▪ **Suvorexant (Belsomra)** ▪ Opiates



Parkinson's Disease: History of Innovation

L-DOPA: First Rationally Designed CNS Drug?

1910: Dopamine synthesized

1913 : L-DOPA isolated from Fava beans

1938: L-Dopa Decarboxylase Discovered

1957: Brain dopamine is involved in motor function

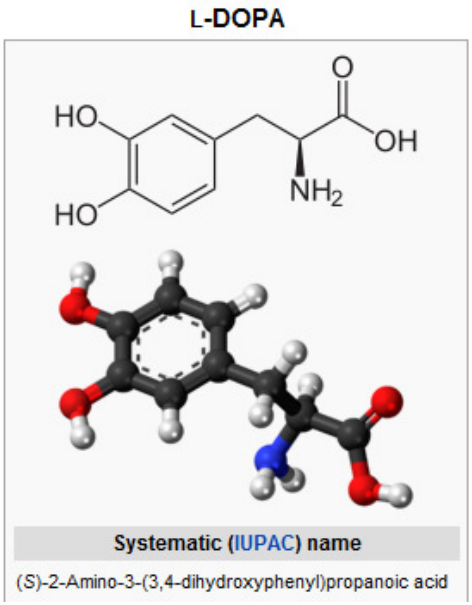
1959: Dopamine enriched in striatal / motor brain regions

1960: Severe dopamine depletion in Parkinson's brain

1961: L-DOPA clinical trial for dopamine replacement

1967: High dose chronic L-DOPA therapy introduced

1969: L-DOPA plus DOPA decarboxylase inhibitor therapies introduced



Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets

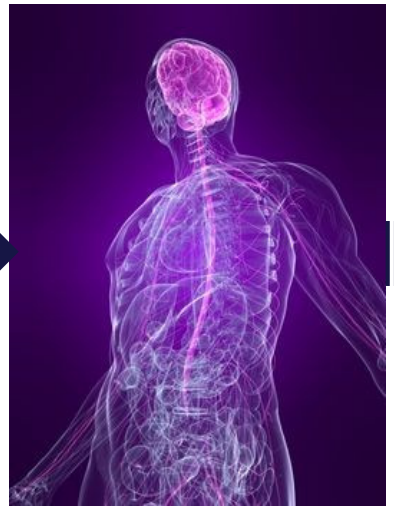
What's in our toolbox?

Genetics

Pathophysiology

Pharmacology

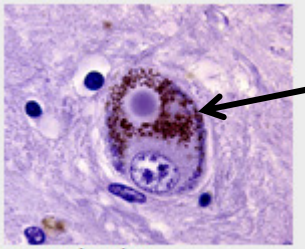
Understanding of human disease



New ideas for drug targets

1. Modify/prevent disease

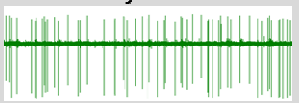
Target Pathophysiology



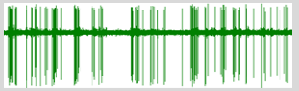
2. Restore function

Subthalamic Nucleus Neuronal Firing Rate Increases with Parkinson's Disease Progression

STN activity: Naïve Rat



STN activity: 6-OHDA Lesioned Rat



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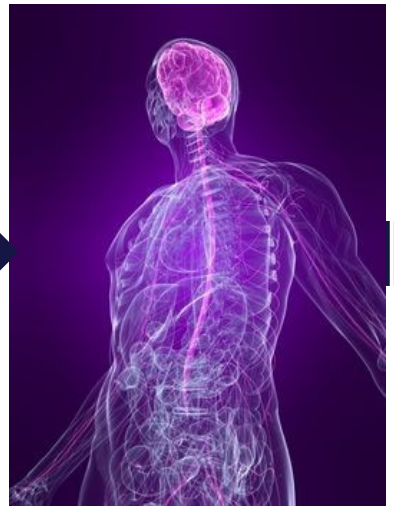
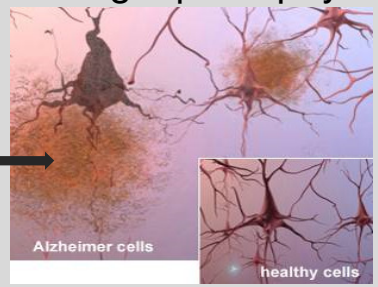


New ideas for drug targets

1. Modify/prevent disease

Example: target pathophysiology

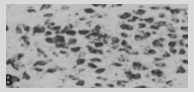
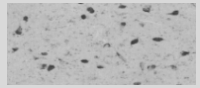
Amyloid →

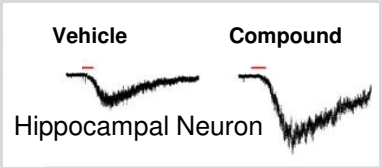


BACE INHIBITION – MK8931

2. Restore function

Example: Restoring acetylcholine signaling

	Normal Brain	Alzheimer's Brain
Cholinergic Neurons		



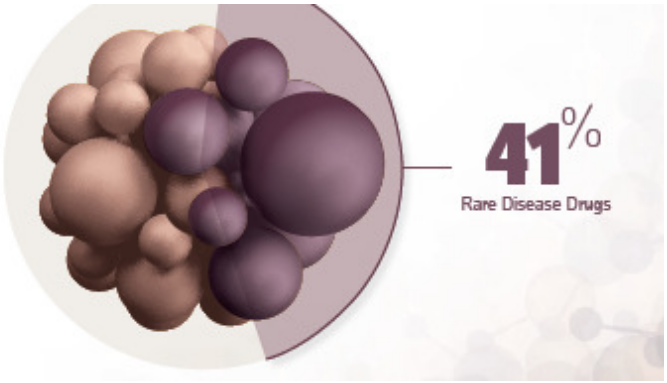
Receptor PAMs
Nicotinic
Muscarinic

Class of 2014: Many New Drugs for Orphan Diseases

NOVEL NEW DRUGS

2014

AKYNZEO
BELEODAQ
BELSOMRA
BLINCYTO
CERDELGA
CYRAMZA
DALVANCE
ENTYVIO
ESBRIET
FARXIGA
HARVONI
HETLIOZ
IMPAVIDO
JARDIANCE
JUBLIA
KERYDIN
KEYTRUDA
LUMASON
LYNPARZA
MOVANTIK
MYALEPT
NEURACEQ
NORTHERA
OFEV
OPDIVO
ORBACTIV
OTEZLA
PLEGRIDY
RAPIVAB
SIVEXTRO
STRIVERDI RESPIMAT
SYLVANT
TANZEUM
TRULICITY
VIEKIRA PAK
VIMIZIM
XTORO
ZERBAXA
ZONTIVITY
ZYDELIG
ZYKADIA



RARE DISEASES

1. BELEODAQ
2. BLINCYTO
3. CERDELGA
4. CYRAMZA
5. ESBRIET
6. HETLIOZ
7. IMPAVIDO
8. KEYTRUDA
9. LYNPARZA
10. MYALEPT
11. NORTHERA
12. OFEV
13. OPDIVO
14. SYLVANT
15. VIMIZIM
16. ZYDELIG
17. ZYKADIA

About 41% of the novel new drugs approved in 2014 (17 of 41) were approved to treat rare or "orphan" diseases that affect 200,000 or fewer Americans. This is significant because patients with rare diseases often have few or no drugs available to treat their conditions.

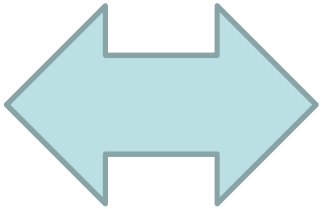
What does this mean for the Neuroscience area?

Neuroscience Diseases– What to Chose?

Major Diseases

Alzheimer's Disease
Parkinson's Disease
Pain / Migraine
Schizophrenia
Depression
Insomnia

Consider:
- Supporting science
- Ability to translate
- Address medical needs
- Major markets



"Rare" / Orphan Diseases

- Well defined patient populations
- Broader applications may also be possible
- Means to interrogate a novel mechanism

- Tauopathies (e.g. FTLD / PSP)
- Lewy Body Dementia
- ALS
- Gauchers Disease
- Narcolepsy
- Others…..

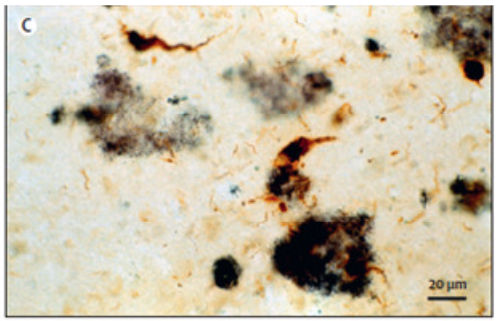
Consider:
- Very strong supporting science
- Increased POS
- Benefit versus risk more favorable
- Very high medical need
- Faster path to POC / Registration

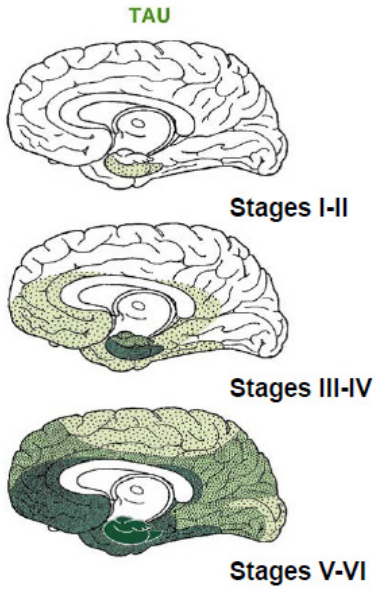
Tau pathology and neurodegeneration

Panel: **Diseases with tau inclusions**

- Alzheimer's disease
- Amyotrophic lateral sclerosis and parkinsonism-dementia complex
- Argyrophilic grain disease
- Chronic traumatic encephalopathy
- Corticobasal degeneration
- Diffuse neurofibrillary tangles with calcification
- Down's syndrome
- Familial British dementia
- Familial Danish dementia
- Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by *MAPT* mutations)
- Frontotemporal lobar degeneration (some cases caused by *C9ORF72* mutations)
- Gerstmann-Sträussler-Scheinker disease
- Guadeloupean parkinsonism
- Myotonic dystrophy
- Neurodegeneration with brain iron accumulation
- Niemann-Pick disease, type C
- Non-Guamanian motor neuron disease with neurofibrillary tangles
- Pick's disease
- Postencephalitic parkinsonism
- Prion protein cerebral amyloid angiopathy
- Progressive subcortical gliosis
- Progressive supranuclear palsy
- SLC9A6-related mental retardation
- Subacute sclerosing panencephalitis
- Tangle-only dementia
- White matter tauopathy with globular glial inclusions

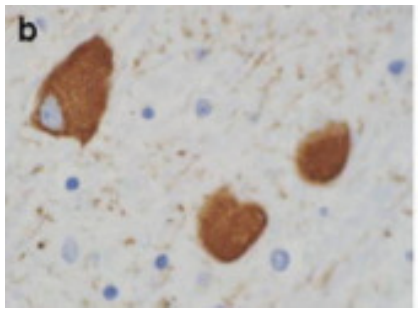
Alzheimer's Disease





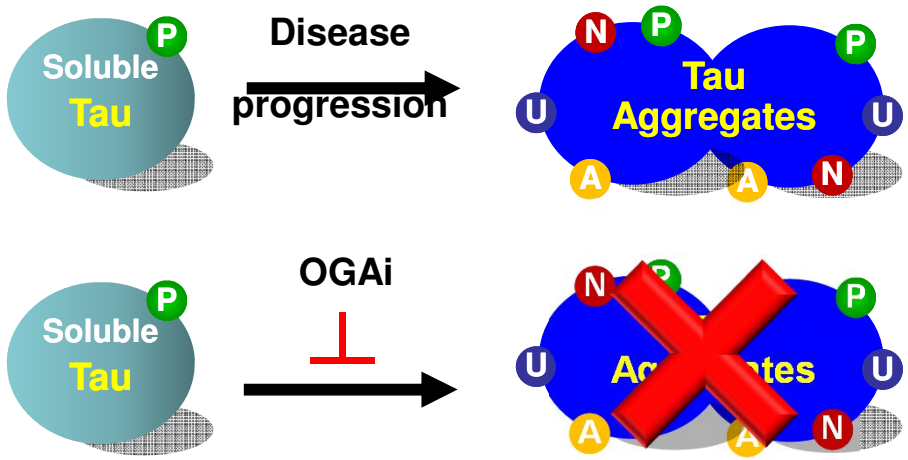
Goedert M et al., 2010

Progressive supranuclear palsy



OGA Inhibitors Increase Tau O-GlcNAcylation and Reduce Formation of Toxic Tau Species

- In adult brain, tau is O-GlcNAcylated at several sites
- OGA inhibitors increase tau O-GlcNAcylation



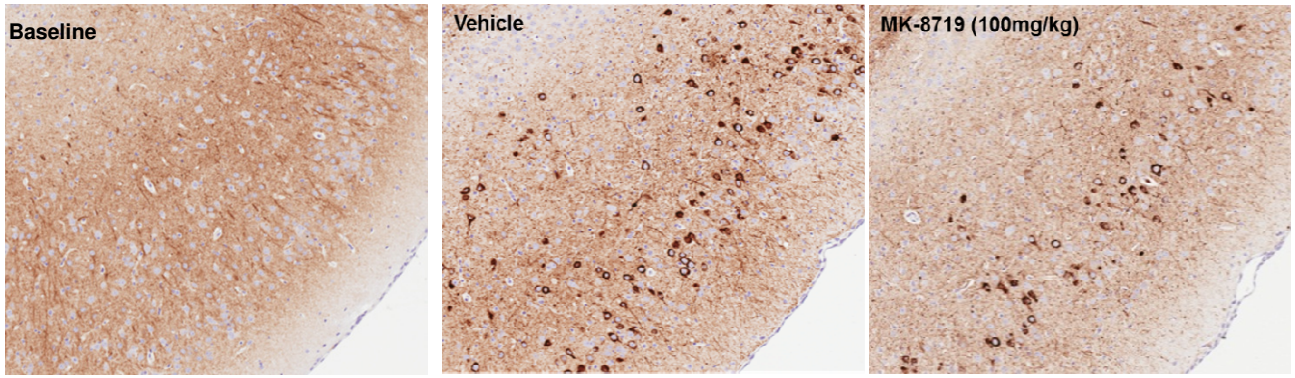
Pathological tau aggregates

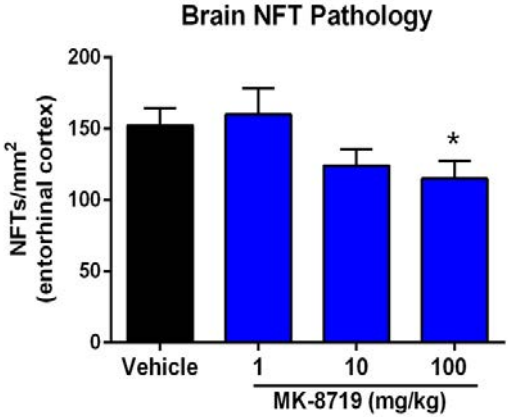
Modified in various ways:

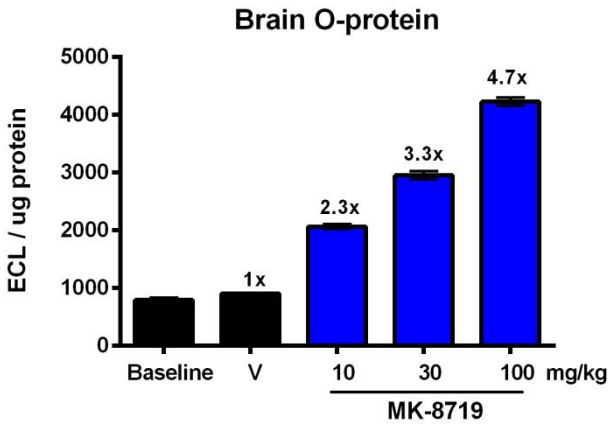
- **Hyperphosphorylated (P)**
- **Acetylation (A)**
- **Nitrated (N)**
- **Ubiquitinated (U)**

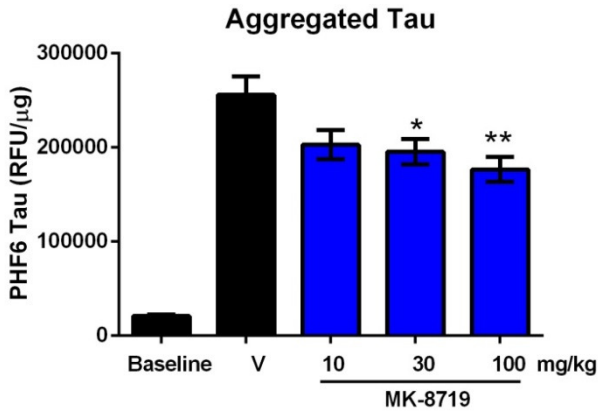
- OGA inhibitors block formation of pathological tau

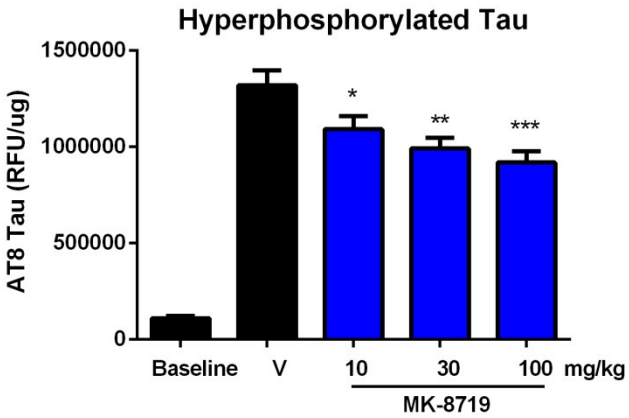
The OGA Inhibitor MK-8719 Reduces NFTs and Pathological Tau in Tg4510 Mice











** p<0.05, **p<0.01 ***p<0.001*

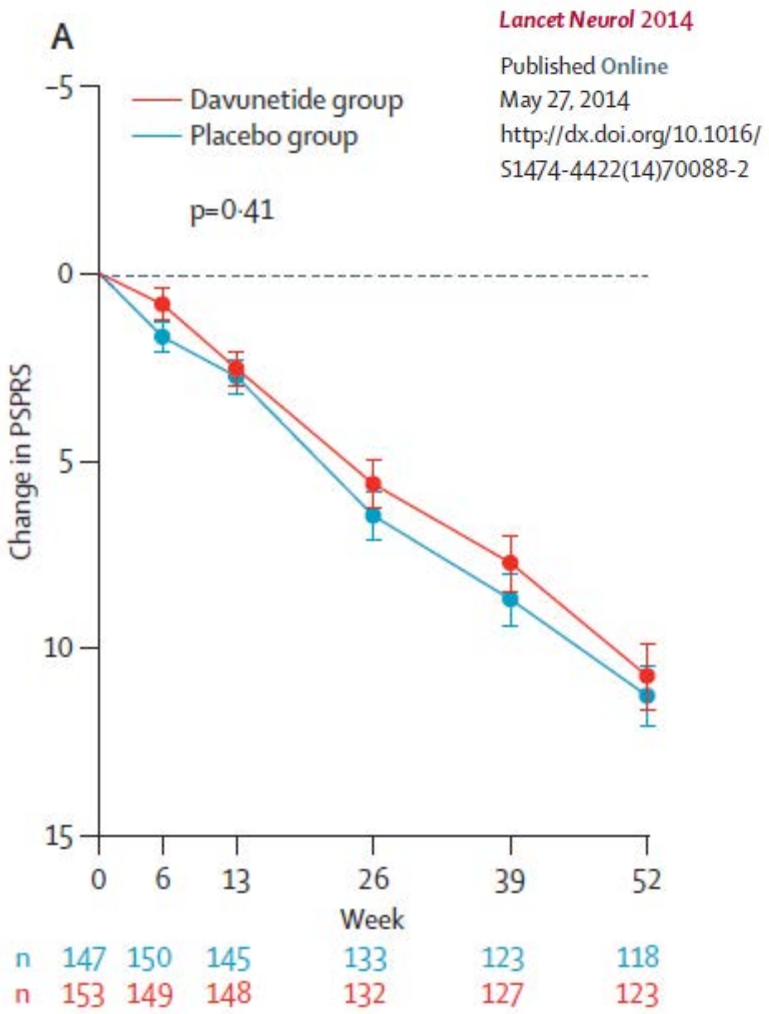
- Preclinical data demonstrated that MK-8719 dose dependently elevated brain O-GlcNAclaytion and reduced pathological tau in the brains of Tg4510 mice

MSD
Be well

Contrasting Clinical Approaches for "Anti-Tau" POC

- **Merck's First-in-Class BACE inhibitor (MK-8931) – Initiated 2012**
- ~2,000 patients with Mild to Moderate Alzheimer's Disease
  - Primary Endpoint: Change from Baseline in AD Cognitive and Functional measures
  - 78 weeks of treatment with estimated study completion date in 2017
- ~1,500 patients with Prodromal Alzheimer's Disease
  - Collaborations with GE Healthcare (PET-flutemetamol) and Luminex (CSF tau/Aβ) collaborations for patient selection
  - Primary Endpoint: CDR-Sum of boxes
  - 104 weeks of treatment with estimated study completion in 2018

Clinical POC Trial in Progressive Supranuclear Palsy (PSP)



Public

Challenges in Neuroscience Discovery and Development

- ✓Historically how successful have we been in Neuroscience Therapeutics?
- ✓What has led to / defined past success?
- ✓What is different now?
- ✓What does future success look like?
- ✓What we now need to do?
- ➢ **Recent success example: Belsomra (Suvorexant) "*Trifecta* of Target Validation"**

Public

Introducing

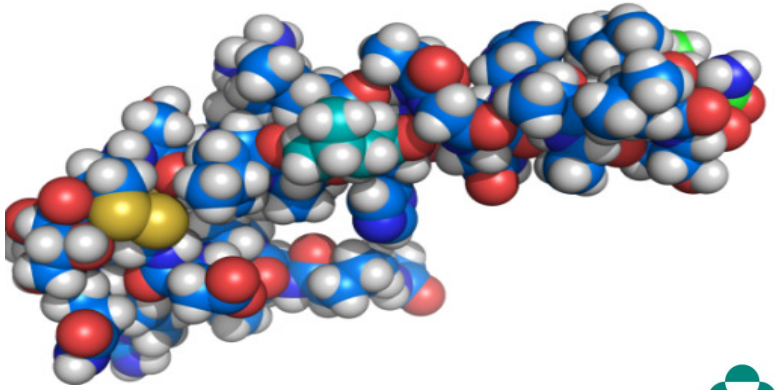
A DIFFERENT APPROACH TO TREATING INSOMNIA

FDA APPROVED*

Belsomra®

(suvorexant)

5, 10, 15, 20 mg tablets



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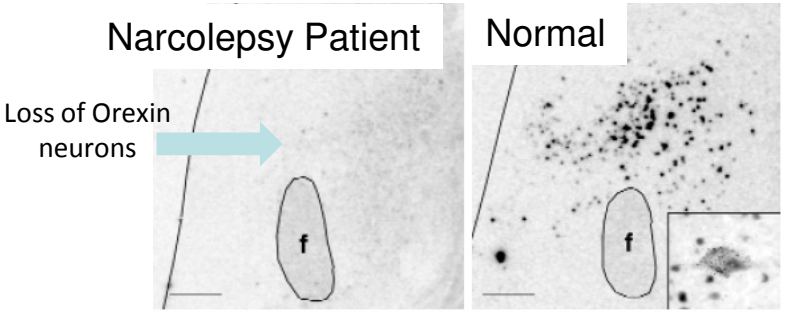
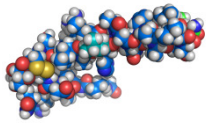
Belsomra: genetics, pathophysiology and pharmacology



1998 — Discovery of Orexin (hypocretin) peptides



1999 — Orexin 2 receptor Identified as cause of canine narcolepsy

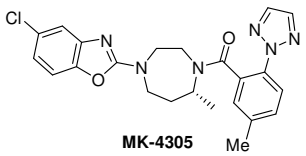
2000 — Orexin Antagonist Discovery Programs ----------→

Loss of Orexin neurons in Narcolepsy patients

Orexin peptide KO mice show sleep phenotype

2005

2007 — First Human Dose



MK-4305

2008 — PhII Suvorexant

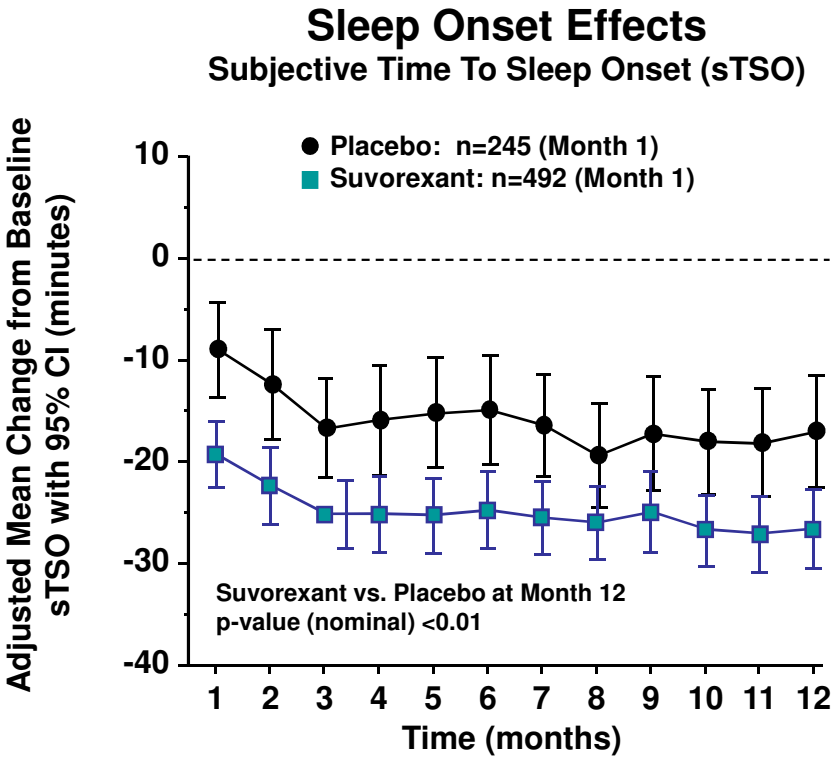
2009 — Suvorexant PhIII

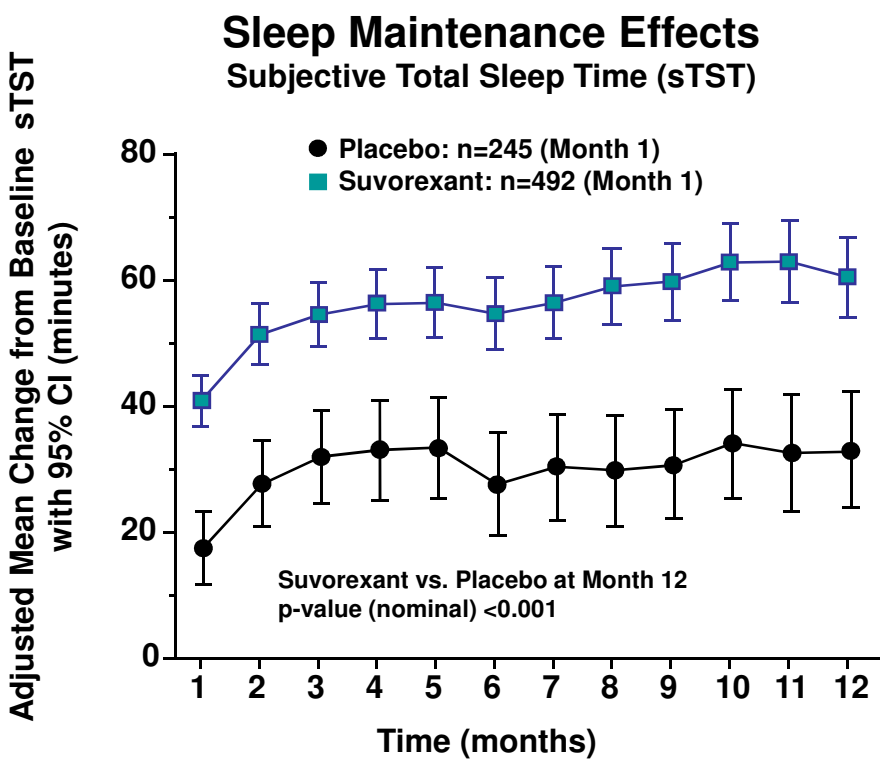
2014 — Suvorexant Approval

Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial

Lancet Neurol 2014; 13: 461–71

David Michelson, Ellen Snyder, Erin Paradis, Mary Chengan-Liu, Duane B Snavely, Jill Hutzelmann, James K Walsh, Andrew D Krystal, Ruth M Benca, Martin Cohn, Christopher Lines, Thomas Roth, W Joseph Herring





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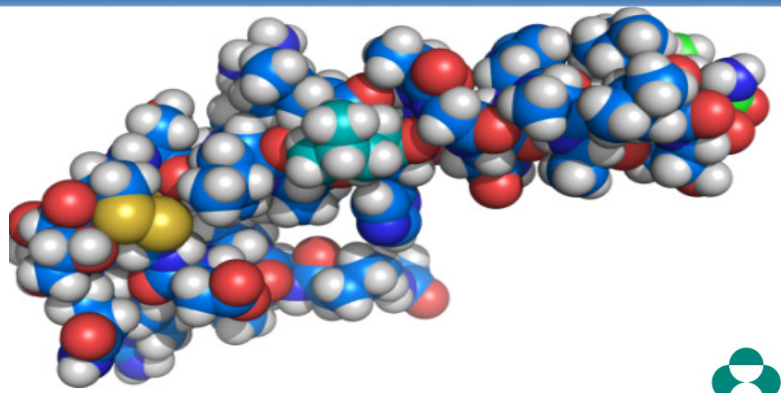
Introducing

A DIFFERENT APPROACH TO TREATING INSOMNIA

FDA APPROVED*

Sleep architecture (Gotter et al., 2014 BMC Neurosci; Winrow et al. 2012 Neuropharm.)
qEEG by sleep stage analysis (Fox et al., 2013 Neuropsychopharm.; Ma et al., 2014 Sleep)
Locomotor performance (Ramirez et al., 2013 Front Neurosci.)
Alcohol interaction (Ramirez et al., 2013 Front Neurosci.)
Effects on cognition (Uslaner et al., 2013 Science Transl. Med; Winrow & Renger 2014 BJP)
Salience gating and arousability (Tannenbaum et al., 2014 Front Behav Neurosci)

Belsomra®
(suvorexant)
5, 10, 15, 20 mg tablets



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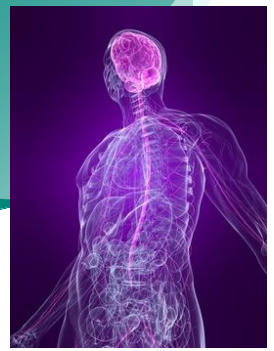
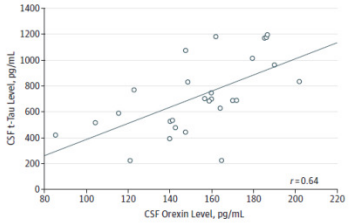
Using Human Biology to Shape Therapeutic Approaches: Orexin Future Areas



Target
Orexin Hyper-activity

Orexinergic System Dysregulation, Sleep Impairment, and Cognitive Decline in Alzheimer Disease



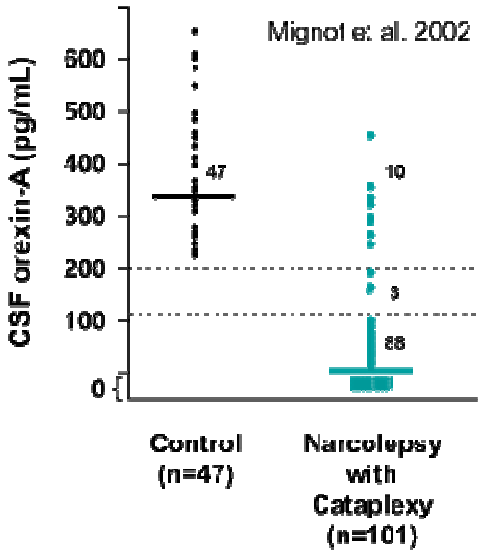
" The orexinergic system seems to be dysregulated in AD, and its output and function appear to be overexpressed along the progression of the neurodegenerative process."

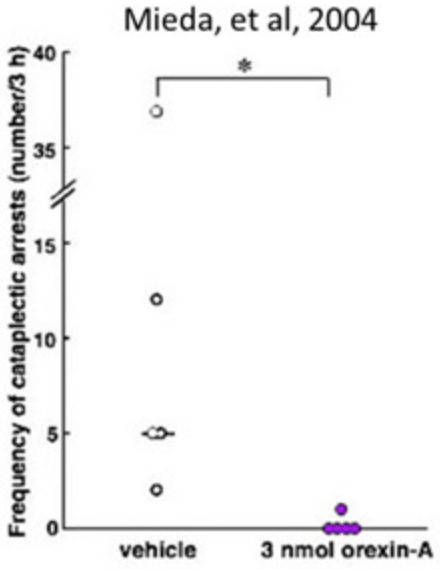
"..we hypothesize that, …..orexin receptor antagonists will be used as potential drugs targeting ....the management of sleep disturbances in AD patients

Liguori et al., 2015 *JAMA Neurol.* 2014

Target
Orexin Hypo-Activity

Agonist Replacement Therapy Narcolesy





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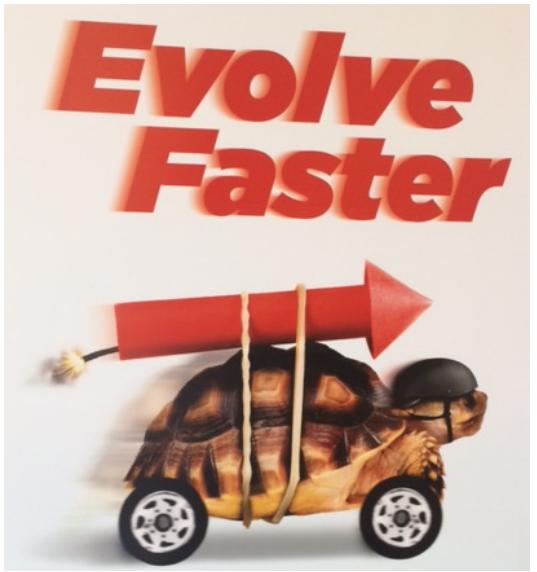
Conclusions: Opportunities in Neuroscience Therapeutics

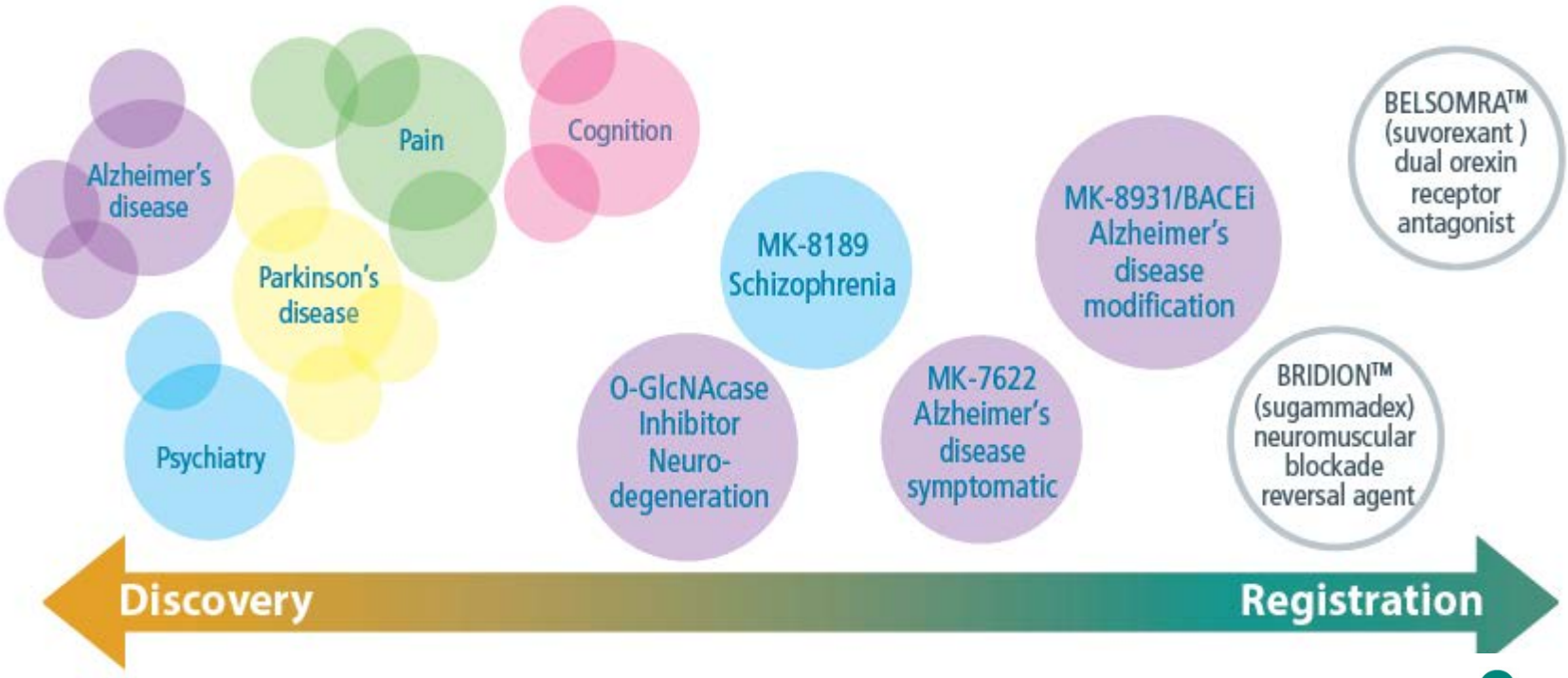
- **YES….** Neuroscience disorders are complex and there is much we do not yet know….
- **BUT……** The need for therapies to treat nervous system disorders are now even greater and ….
- **TODAY…..** Understanding of human biology / pathophysiology of the nervous system is advancing rapidly and ….
- **LOOKING AHEAD….** promising new approaches, drug targets and biomarkers for disease will continue to advance so that ….
- **NEW THERAPIES WILL COME….** from new approaches linked to our increasing understanding of human disease biology



Merck Neuroscience Pipeline Approach to Increase POS and Patient Value

- High quality molecules and positioning to test important disease hypotheses
- Development approaches that provide the greatest opportunities of demonstrating meaningful clinical advantages

Industry Leading First-in-Class Development Candidates and Products



Thank You!

Merck Orexin Team – MK4305 Suvorexant – Many, many contributors
Special Thanks……..Well Done!!!!!!

John Renger
Paul Coleman
Chris Winrow
Tony Gotter
Pam Tannenbaum
Jason Uslaner
Richard Hargreaves
Joe Herring
David Michelson
Carol Sable
Eric Luthi
……..

Merck OGA Team /Alectos – MK8719

Merck BACE Team – MK8931

My Special Thanks to Samer Eid

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