Terapie Farmacologica: Limiti e Prospettive

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Neuroscience Discovery Medicine

UCB Biopharma

ROMA
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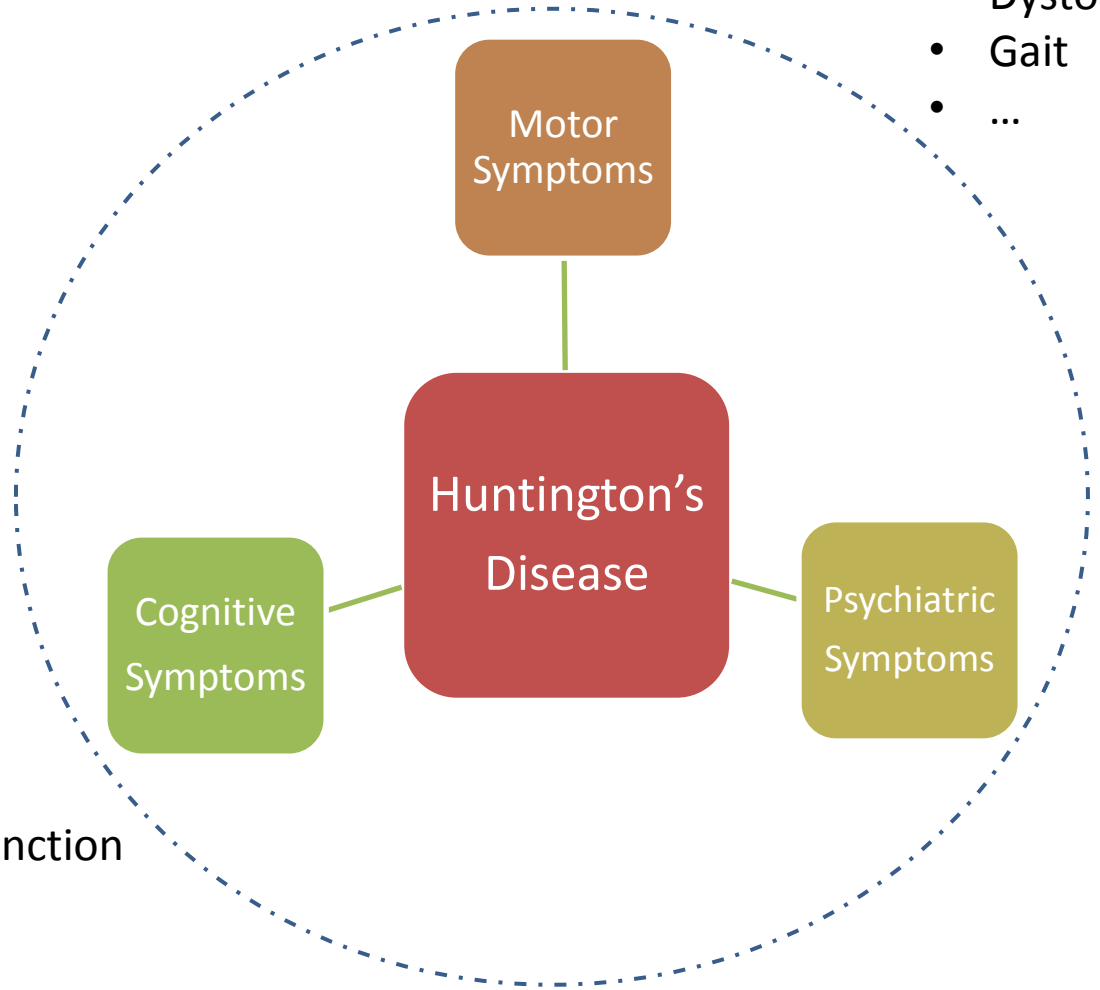
Per una corretta pratica clinica
della Malattia di Huntington

Symptomatic Treatment
while waiting for Disease Modifying Therapies



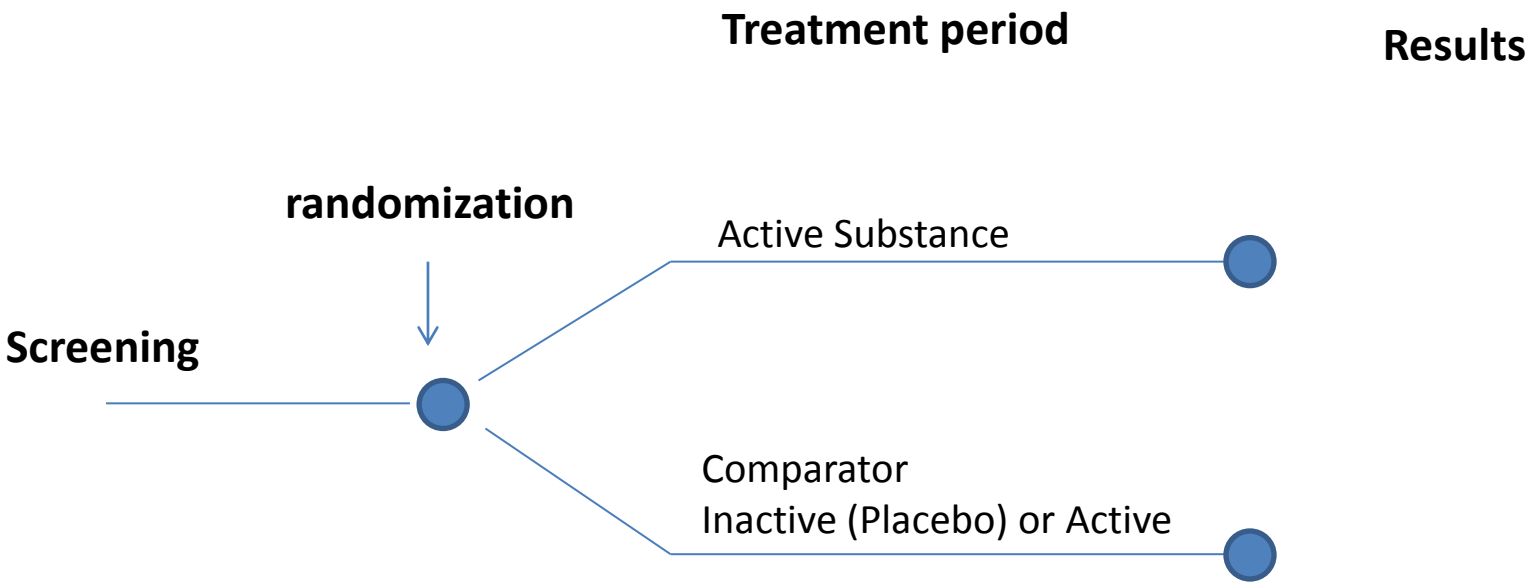
- Chorea
- Dystonia
- Gait
- …

- Executive Function
- Attention

- Anxiety
- Apathy
- Depression
- Irritability
- OCD
- Psychosis
- …

Clinical Study Designs

Randomized “double-blind” Controlled Clinical Trial Design



Un-Controlled Clinical Trial Design

A large number of drugs tested mostly in underpowered and often uncontrolled clinical studies

(Venuto et al 2012 Mov Disorders)

TABLE 1. Pharmacologic agents clinically investigated for HD

	Clinical outcome(s) investigated			
	Motor	Cognitive	Behavioral	Neuroprotection
Amantadine	Melperone	Atomoxetine	Amitriptyline	Alpha-tocopherol
Aminooxyacetic acid	Milacemide	Citalopram (phase III)	Amoxapine	Baclofen
Apomorphine	Minocycline	Epigallocatechin-gallate (phase II)	Buspirone	Coenzyme Q10 (phase III)
Arecoline	Muscimol	Donepezil	Citalopram (phase II)	Creatine (phase III)
Aripiprazole	Nabilone	Fluoxetine	Diazepam	Cysteamine
Botulinum toxin	Naltrexone	Ketamine	Fluoxetine	Idebenone
Bromocriptine	Olanzapine (phase III)	Latrepirdine	Haloperidol	Lamotrigine
Cannabidiol	Omega-3-fatty acids	Memantine (phase III)	Ketamine	Minocycline
Choline	Perphenazine	Modafinil	Leuprolide	Omega-3-fatty acids
Citalopram (phase II)	Physostigmine	Nabilone	Melperone	Remacemide
Clozapine	Pimozide	Olanzapine (phase III)	Memantine (phase III)	Riluzole
Cyproheptadine	Piracetam	Rivastigmine	Mirtazapine	Sodium phenylbutyrate
Dexamethasone	Pridopidine (phase II)	Tiapride (phase III)	Modafinil	Ursodiol
Dextromethorphan	Pramipexole		Nabilone	
Diazepam	Pyridoxine		Olanzapine (phase III)	
Dimethylaminoethanol	Quetiapine		Pindolol	
Disulfiram	Remacemide		Propranolol	
Fluoxetine	Riluzole		Quetiapine	
GABA	Risperidone		Risperidone	
Haloperidol	Sulpiride		Sertraline	
Imidazole	Tetrabenazine (phase III)[a]		Tiapride (phase III)	
Isoniazid	Thiopropazate		Venlafaxine XR	
Ketamine	Tiapride (phase III)			
L-acetyl-carnitine	Trans-dihydrolisuride			
Levodopa	Valproate			
Levetiracetam	Ziprasidone			
Lithium	Zotepine			

Phase numbers (phase I, II, and III) indicate the clinical trial phase that is currently ongoing (according to ClinicalTrials.gov in July 2011).
[a]U.S. Food and Drug Administration (FDA)-approved.
HD, Huntington disease; GABA, gamma-aminobutyric acid.

Pharmacological Treatment in Huntington's Rely almost exclusively on off-label prescription

The most commonly prescribed drugs in European HD patients, REGISTRY study (2010).

N =1468 participants from 13 countries, 1022 of which (57.9%) were on medications

Medication	n	Typical indications
Tiapride hydrochloride	148	Chorea/hyperkinesias
Olanzapine	133	Chorea/dyskinesia/aggression/psychosis
Risperidone	121	Chorea/Dyskinesia/aggression/psychosis
Citalopram hydrobromide	120	Depression/irritability
Paroxetine hydrochloride	120	Depression/irritability
Haloperidol	109	Chorea
Clonazepam	79	Anxiety
Amantadine hydrochloride	76	Chorea/dyskinesia
Mirtazapine	75	Depression/insomnia
Tetrabenazine	69	Chorea/dyskinesia
Lorazepam	54	Anxiety
Sulpiride	46	Chorea/dyskinesia/irritability

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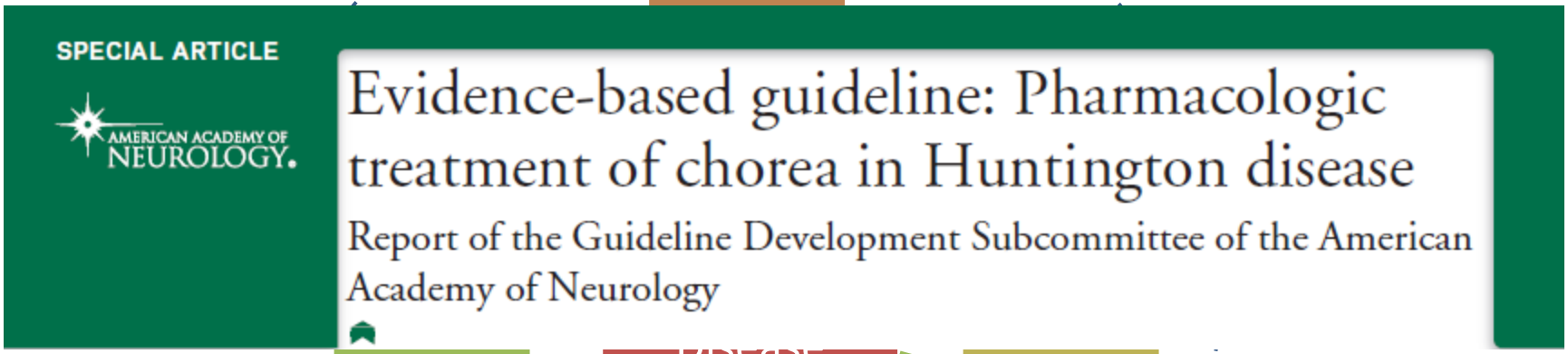
Symptomatic Treatment waiting for Disease Modifying Therapies

- Chorea
- Dystonia
- Gait

Motor Symptoms



Cognitive Symptoms

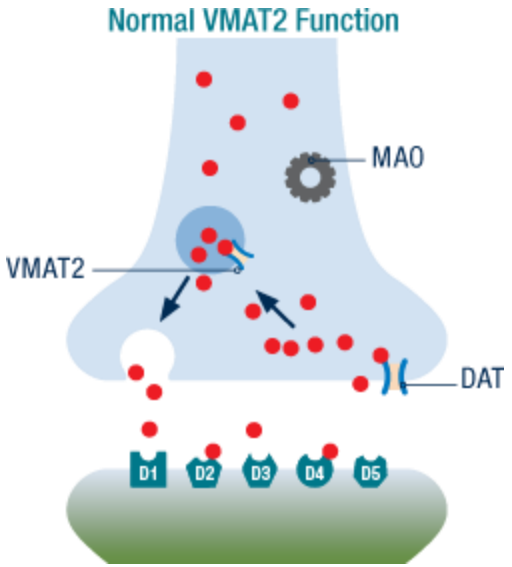
Psychiatric Symptoms

- Executive Function
- Attention

- Anxiety
- Apathy
- Depression
- Irritability
- OCD
- Psychosis

Treatment of Chorea (i)

- Tetrabenazine
  - The only approved drug
  - The better studied and most effective agents for reducing chorea
  - Decreases dopamine signaling by reversible inhibition of the Vescicular Monoamine Transporter Type 2
  - Risk of potentially serious adverse effects (depression, parkinsonisms, akatisia), titrate carefully
  - Consider CYP2D6 poor metabolizers & interactions for dose above 50 mg



Treatment of Chorea (ii)

- Riluzole
  - Based on 1 Class RCT, riluzole 200 mg/day likely moderately chorea decreases at 8 weeks. Riluzole 100 mg/day likely has no moderate antichoreic benefit but a modest benefit cannot be excluded (1 Class I RCT).
  - Riluzole100 mg/day likely fails to improve chorea at 3 years (1 Class I RCT).
- Amantadine
  - A modest amantadine effect on HD chorea could not be excluded
- Antipsychotics
  - Dopamine receptor blocking agents (antipsychotics) are commonly considered in the management of chorea although little evidence from powered and controlled studies exist on their efficacy

Source: American Academy of Neurology Guidelines 2011

A large number of drugs tested mostly in small size and often uncontrolled clinical studies

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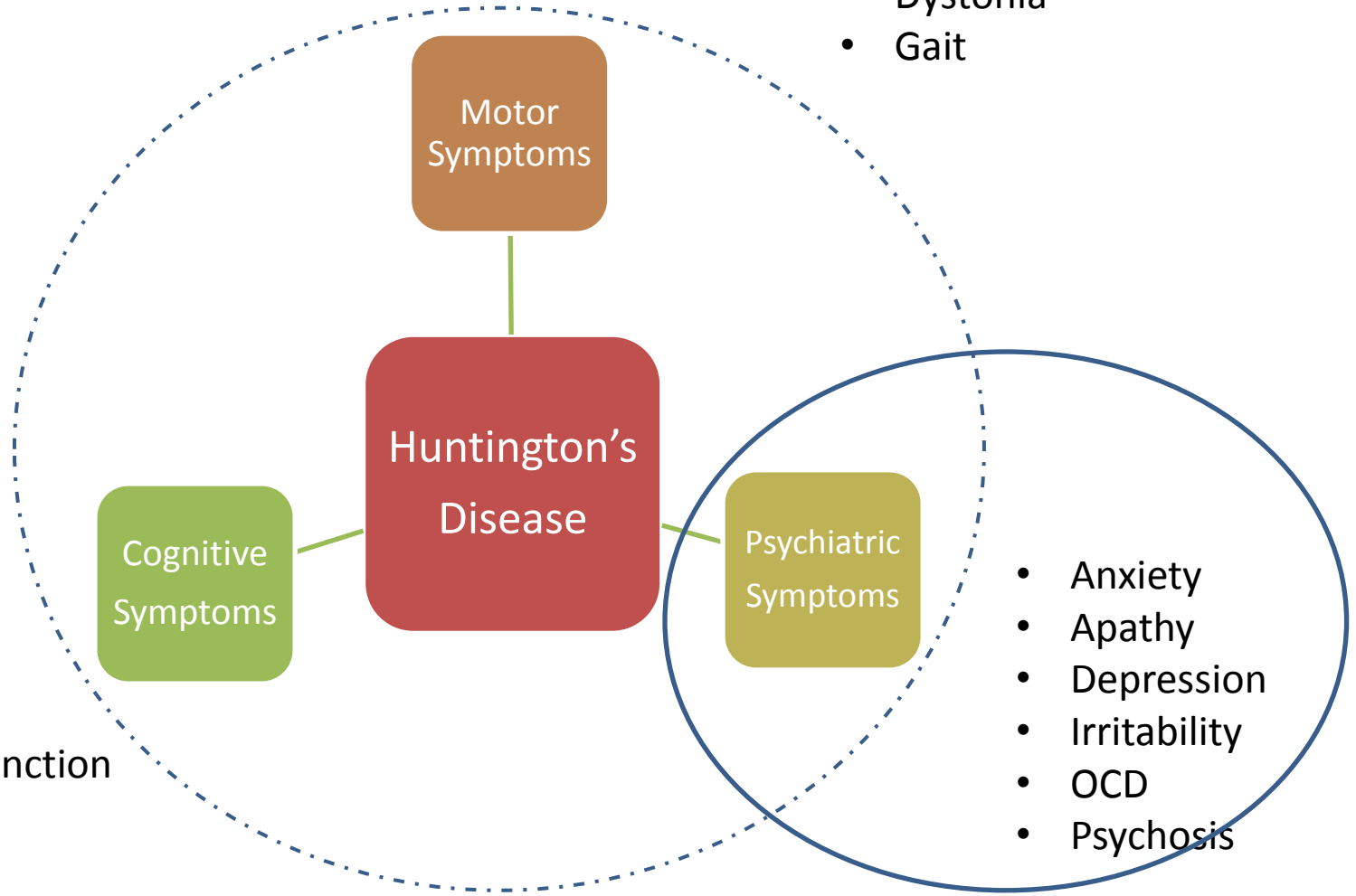
Symptomatic Treatment – Psychiatric Symptoms



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- Dystonia
- Gait

- Executive Function
- Attention

- Anxiety
- Apathy
- Depression
- Irritability
- OCD
- Psychosis

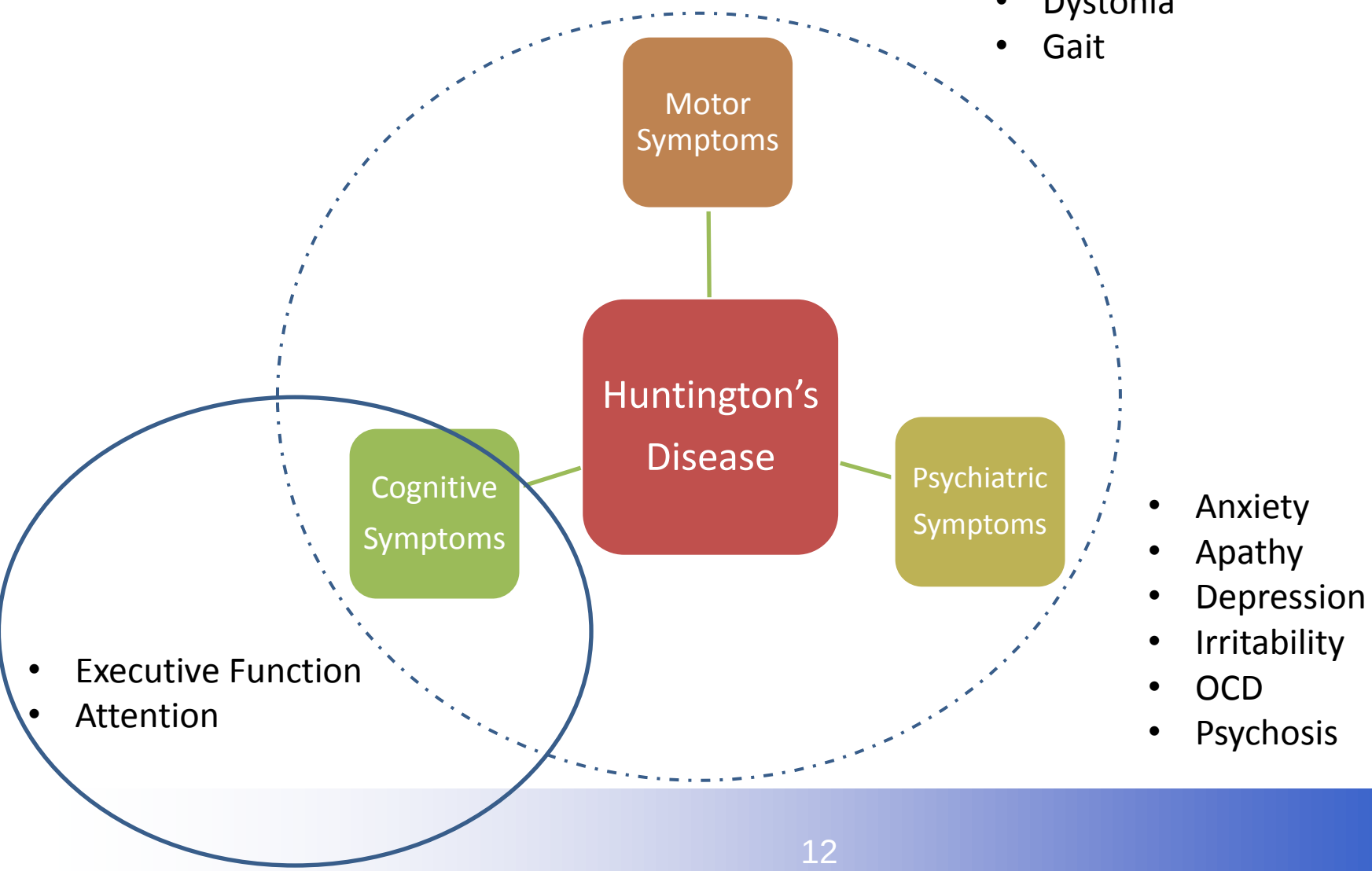
Treatment of Psychiatric Symptoms

- Anxiety
  - Poorly studied,few studies, mostly small sample size or uncontrolled, two randomised trails with floxetine, and tiapride, no evidence of effect.
  - Recommendation is to treat anxiety as you would in patients without HD.

- Depression
  - Lack of controlled studies, SSRI should be the preferred option

- Psychosis
  - Lack of controlled and robust studies
  - Antipsychotics with lower affinity/potency (e.g. quetiapine) should be preferred: less extra-pyramidal side effects (but less effect on chorea)

Symptomatic Treatment - Cognition



Pharmacological Treatment of Cognitive Impairment

No effect of any drug tested

- Donepezil

(Cubo et al 2006)

- Atomoxetine

(Beglinger et al 2009)

- Modafinil

(Blackwell et al 2008)

- Latredipine

(HORIZON, 2013)

CLINICAL TRIALS

SECTION EDITOR: IRA SHOULSON, MD

A Randomized, Double-blind, Placebo-Controlled Study of Latrepirdine in Patients With Mild to Moderate Huntington Disease

*HORIZON Investigators of the Huntington Study Group and European Huntington's Disease Network**

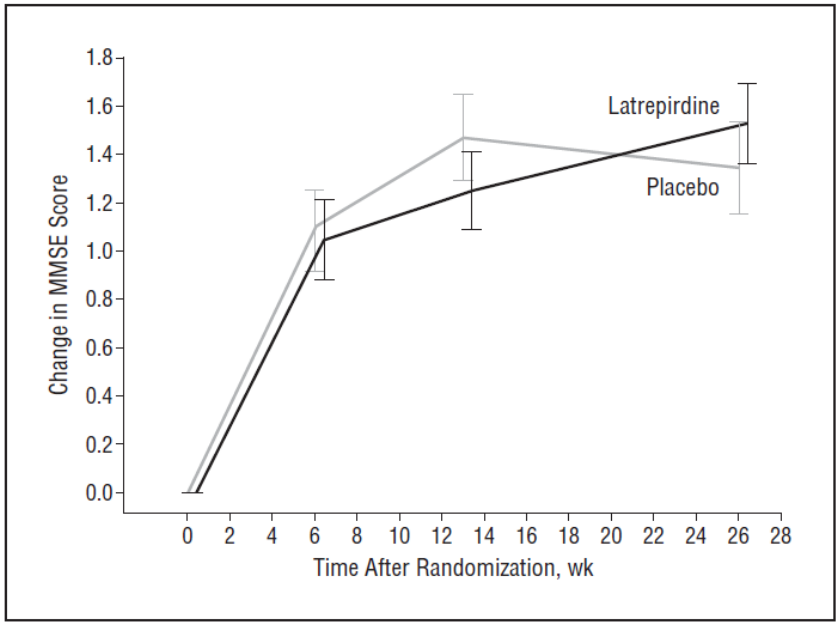


Figure 2. Change over time in the Mini-Mental State Examination (MMSE) score by treatment group. Values plotted are adjusted mean changes from baseline, estimated using a repeated-measures analysis of covariance model with week, region, treatment group, baseline MMSE score, tetrabenazine use, and the interaction between week and treatment group. See the "Statistical Analysis" subsection for details. Bars represent 1 SE of the mean.

Ongoing Clinical Trials in Huntington's Disease

Sponsor	Compound / Mechanism	Phase of Development
EnVivo Pharmaceuticals	EVP-0334 HDAC	Phase I
GSK 356278	PDE4 inhibitor	Phase I
Prana Biotechnology	PBT2 metal-binding	Phase II
Raptor Pharmaceuticals	Procysbi BDNF/mitochondria	Phase II
Omeros	OMS824 / PDE10	Phase II
Teva	Pridopidine / Dopamine	Phase II
Auspex Therapeutics	SD-809 deuterated tetrabenazine	Phase III
NIH-MGH	creatine / mitochondria	Phase III

Source: modified from Neuroprospective March 2014

Iron homeostasis in HD

- Metals (particularly Iron and Copper) have been implicated in the pahogenesis of HD
- Iron is a known cause of oxidative stress implicated in neurodegeneration and is thought to be implicated in the oligomerization of HTT that promote neurodegeneration
- A role for an altered metal homeostasis has been suggested also from recent imaging and post-mortem studies (e.g.: Rosas et al Arch Neurology 2012) that showed
  - Iron levels in specific brain areas rise before symptoms and correlate with disease severity
  - Iron levels increase with CAG repeat lenght
  - Presymptomatic iron levels predict age of onset of symptoms

Prana therapeutics and PBT2

- PBT2 is a Metal Chelant (improved drug from PBT1: clioquinol) that interphere with Copper and Zinc homeostasis.
- PBT2 has shown to mobilize ions (Cu, Zn) trapped in the Abeta deposition, reduce extracellular availability of Cu & Zn interrupting Abeta production in Alzeheimer
- PBT2 showed cognitive improvement in AD patients and currently tested in a new Phase II in AD
- PBT is neuroprotective in animal and cellular model of HD (Ngyen et al PNAS 2005)

HD - Clinical motor scores and efficacy endpoints

The Total Motor Score, TMS

- The motor part of the Unified HD Rating scale (UHDRS)
- Measures 15 items related to motor symptoms
- Disease progression: ~4-5 pts increase p.a.

1. Occular pursuit
2. Saccade initiation
3. Saccade velocity
4. Dysarthria
5. Tongue protrusion
6. Finger taps
7. Pronate/supinate hands
8. Fist-hand-palm sequencing
9. Rigidity - arms
10. Body bradykinesia
11. Dystonia
12. Chorea
13. Gait
14. Tandem walking
15. Retropulsion pull test

Eye movements

– 3 items from the TMS

Involuntary movements

– 2 items from the TMS

The modified Motor Score, mMS

– A measure of voluntary motor symptoms
– 10 items from the TMS
– Disease progression: ~2 pts increase p.a.

Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial

Justo Garcia de Yebenes, Bernhard Landwehrmeyer, Ferdinando Squitieri, Ralf Reilmann, Anne Rosser, Roger A Barker, Carsten Saft, Markus K Magnet, Alastair Sword, Åsa Rembratt, Joakim Tedroff, for the MermaiHD study investigators

Lancet Neurol 2011; 10: 1049–57

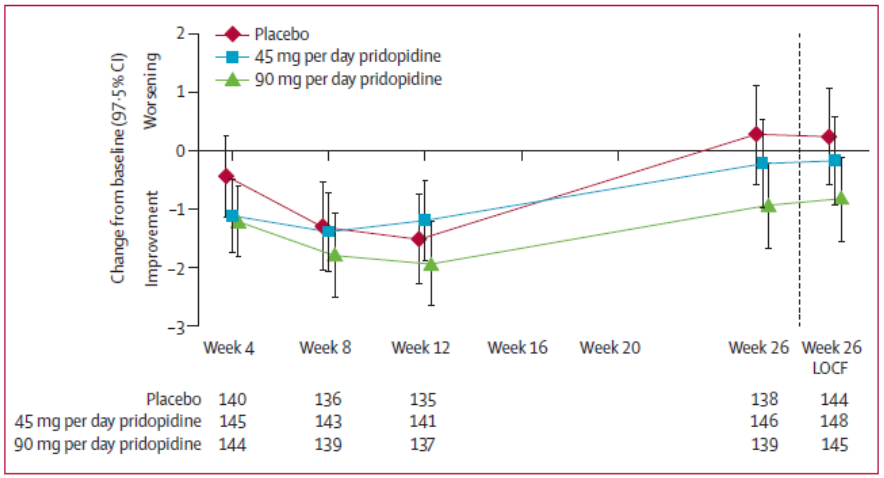


Figure 2: **Mean change from baseline in the modified motor score**
Data at week 26 are also shown after adjustment for non-completers with last observation carried forward (LOCF).

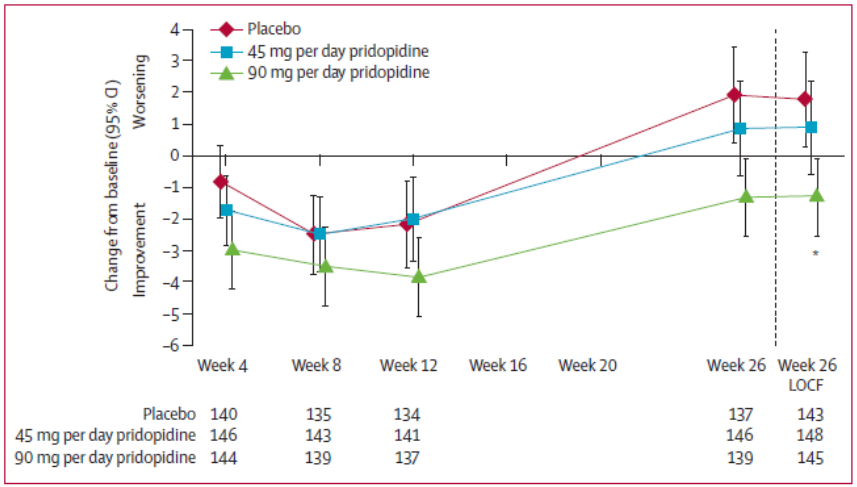


Figure 3: **Mean change from baseline in the UHDRS–TMS**
Data at week 26 are also shown after adjustment for non-completers using last observation carried forward (LOCF). UHDRS–TMS=unified Huntington's disease rating scale total motor score. *p=0·004 for the between-group difference (90 mg per day pridopidine *vs* placebo).

RESEARCH ARTICLE

A Randomized, Double-Blind, Placebo-Controlled Trial of Pridopidine in Huntington's Disease

The Huntington Study Group HART Investigators

Movement Disorders, Vol. 28, No. 10, 2013

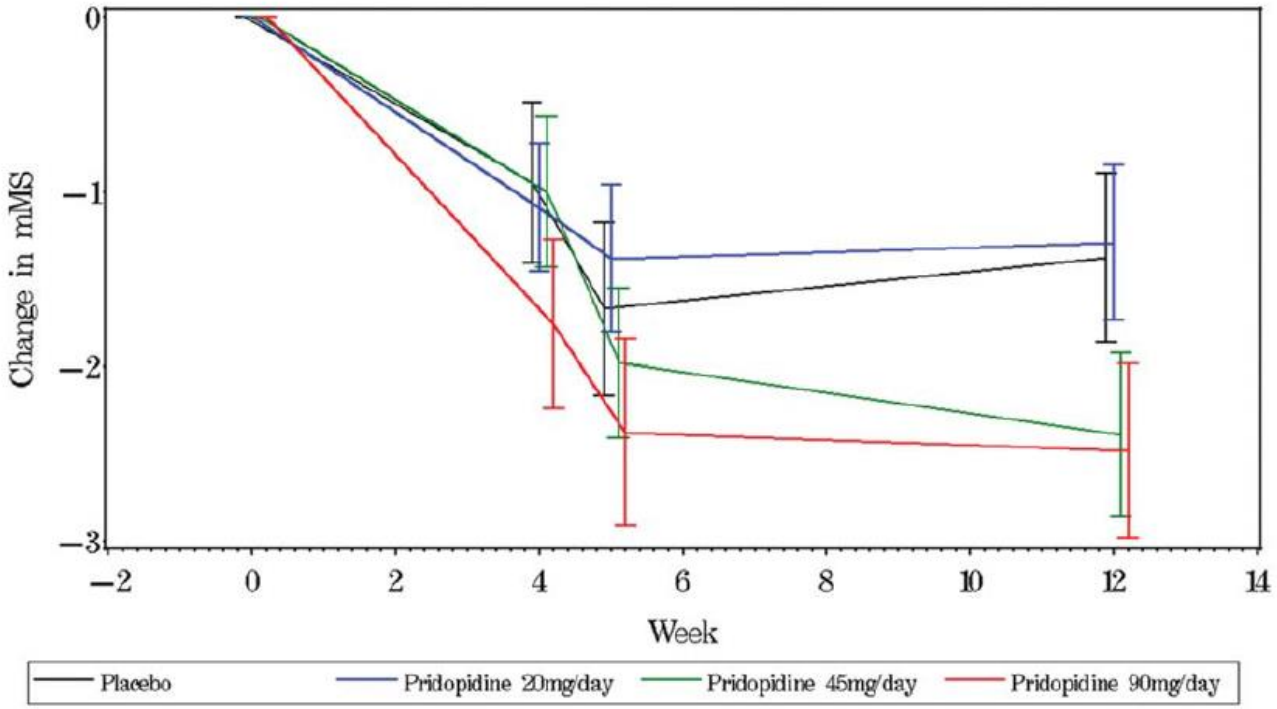


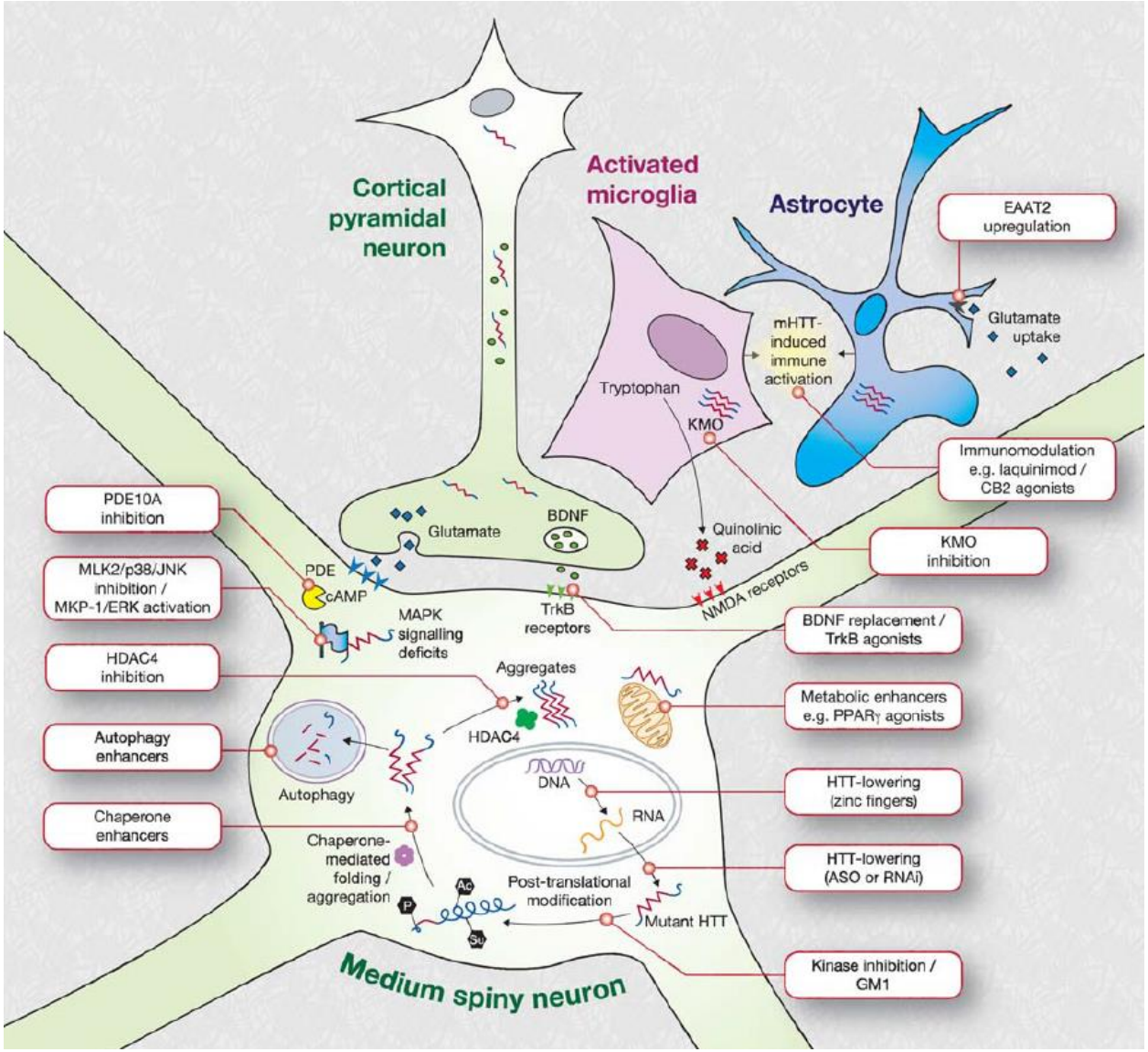
FIG. 2. Total Motor Score and Modified Motor Score Changes for Placebo and Treatment Groups Over 12 Weeks.

HD Programs in Development

Company	Compound	Phase	Target
Adamas Pharmaceuticals	Nurelin	PhII (PD-LID)	amantadine CR
Albany Molecular (with CHDI)		discovery	JNK inhibitors
Alnylam	duplex RNA	discovery	huntingtin production
Alnylam (with Medtronic)		preclinical	RNAi
Auspex Therapeutics	SD-809	PhIII	deuterated tetrabenzaine
Biocrea		preclinical	PDE10
Biogen-Idec (with Proteostasis Therapeutics)		preclinical	clearance
Biomarin (from Repligen)	RG2833	PhIb (FA)	HDAC
Buck Institute		discovery	caspase inhibition
Cambria Pharmaceuticals	CMB-21805	preclinical	aggregation
Chaperone Therapeutics	HSF1a	discovery	protein misfolding
Cornell		discovery	DRP1/mitochondria
EnVivo Pharmaceuticals	EVP-0334	PhI	HDAC
Evotec (with CHDI)		discovery	undisclosed
Gladstone Institute	10-NCP	discovery	autophagy/clearance
GSK	356278	PhI	PDE4
Harvard	methazolamide	preclinical	mitochondria
Harvard		discovery	USP14--proteostasis
Johnson & Johnson		discovery	HDAC inhibition
Isis Pharmaceuticals (with Roche)	antisense	discovery	antisense
Kyowa Hakko	istradefylline	PhIII (PD)	adenosine 2a
Lundbeck (with U.Mass)		discovery	RNAi
NeuralStem	stem cells	preclinical	
Neurocrine Biosciences	NBI-98854	PhII (TD)	VMAT2
NeuroPhage		discovery	fusion protein
NIH-MGH	creatine	Phase III	mitochondria
NIH-MGH	Coenzyme Q10	Phase III	mitochondria
Omeros	OMS824	PhII-HD cognition	PDE10
Pfizer (from FoldRx)		discovery	mHtt
PharmaTrophix		preclinical	BDNF mimetics
Prolexys		discovery	Huntingtin interactions
Prana Biotechnology	PBT2	PhII	metal-binding
Proteostasis Therapeutics (with Biogen-Idec)		preclinical	clearance
Raptor Pharmaceuticals	Procysbi	PhII	BDNF/mitochondria
Raptor Pharmaceuticals	transglutiminase inhbitors	preclinical	mitochondria
ReNeuron	cell implants	discovery	replacement
Riken Institute		discovery	Hsp70
Roche (with Isis Pharmaceuticals)	antisense	discovery	antisense
Sangamo Biosciences	ZFP	preclinical	zinc-finger transcription
Teva (from NeuroSearch)	pridopidine/Huntexil	Phase II	DA
Vybion	INT41	preclinical	mHtt aggregation
Zenobia Therapeutics	caspase-6 inhibitors	discovery	anti-apoptotic
Zenobia Therapeutics	PDE10 inhibitors	discovery	symptomatic

Source:
Neuroprospective March 2014

Key Mechanisms with potential in Huntington's Disease in Pre-Clinical & Research Stage



Three main Approaches for “Gene Silencing” Aiming to lowering expression of mutated Huntingtin

- Transcription repression
- Antisense Oligonucleotides (ASOs)
- RNA interference

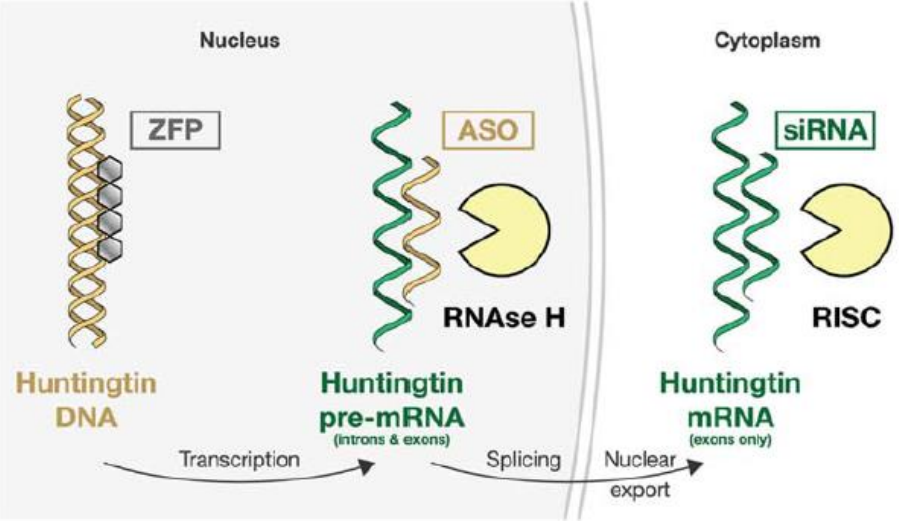


FIG. 2. Schematic illustration of the three main approaches to lowering huntingtin expression. Zinc finger protein (ZFP) therapeutics aim to reduce transcription of the huntingtin gene. Translational repression can be attempted at the pre-mRNA level using DNA-based antisense oligonucleotides (ASOs) or on mature mRNA using short interfering RNA (siRNA) compounds. Different cellular mechanisms degrade the bound mRNA.[4]

Movement Disorders, Vol. 29, No. 11, 2014

Summary

- Lack of controlled studies for symptomatic effect of drugs approved for other neuropsychiatric indications
- Increasing number of sponsored studies in clinical phase
- Larger investment (and cautious optimism) for a number of novel therapies aiming to lower expression of mutated Huntingtin