# ADHD: Clinical Aspects, Neurobiology and Management


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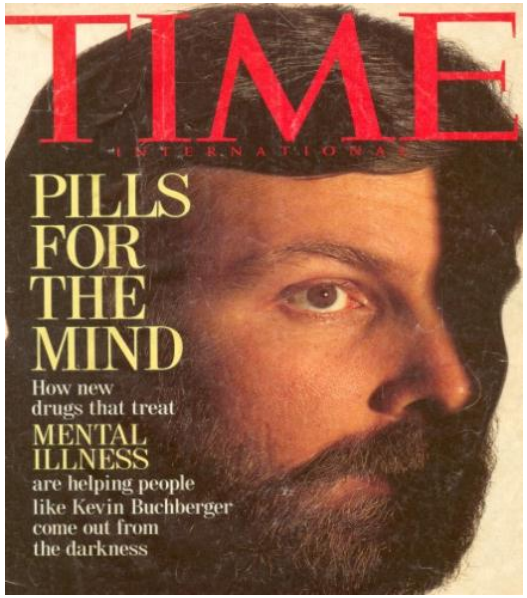
# New Science of Mind

- Mind is generated by the Brain.
- Psychiatry is the Application of  Basic Neurosciences to man's  day-to-day problems.




Psychiatry is a Branch of Medicine.

Psychiatric Disorders are Physical Disorders.

Psychiatrists are primarily Physicians.

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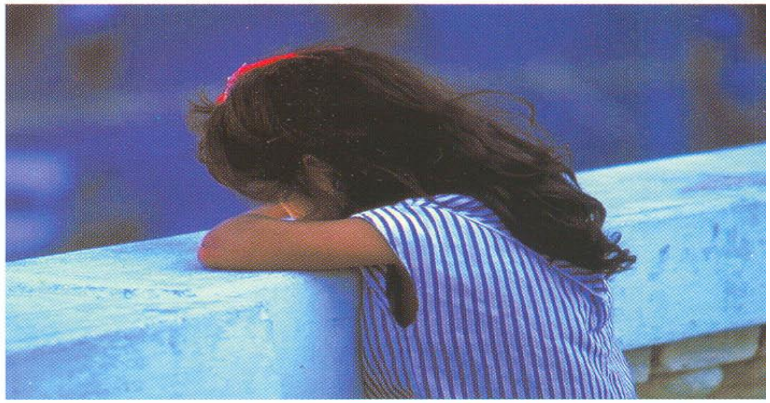
# Child Psychiatry

## -an emerging subspeciality

## Psychiatry

Psychiatry itself is a new branch of Medicine. It is now practised as the application of basic Neuro-sciences to every person's day-to-day problems; this has helped to remove the old misconceptions and stigma about psychiatric consultations.



## The Mind

Using the latest research techniques, doctors today know that the Mind is generated by the Brain; we 'think' and 'feel' inside the brain.
Mind's functions such as Thinking, Feeling, Learning, Speaking & Writing are carried out by specific biochemicals in designated areas of the Brain.

## Child Psychiatry

Any developmental delay or later disregulation in these areas can cause Learning Disorders,Attention Deficit Disorders(ADHD), Autism, Speech and Language Disorders etc. in children, as well as Behavior and Emotional Disorders.
With the rapidly-changing family and social structure in these times, Learning and Behavior problems in children have compounded.
Hence the emergence of Child Psychiatry as a subspeciality

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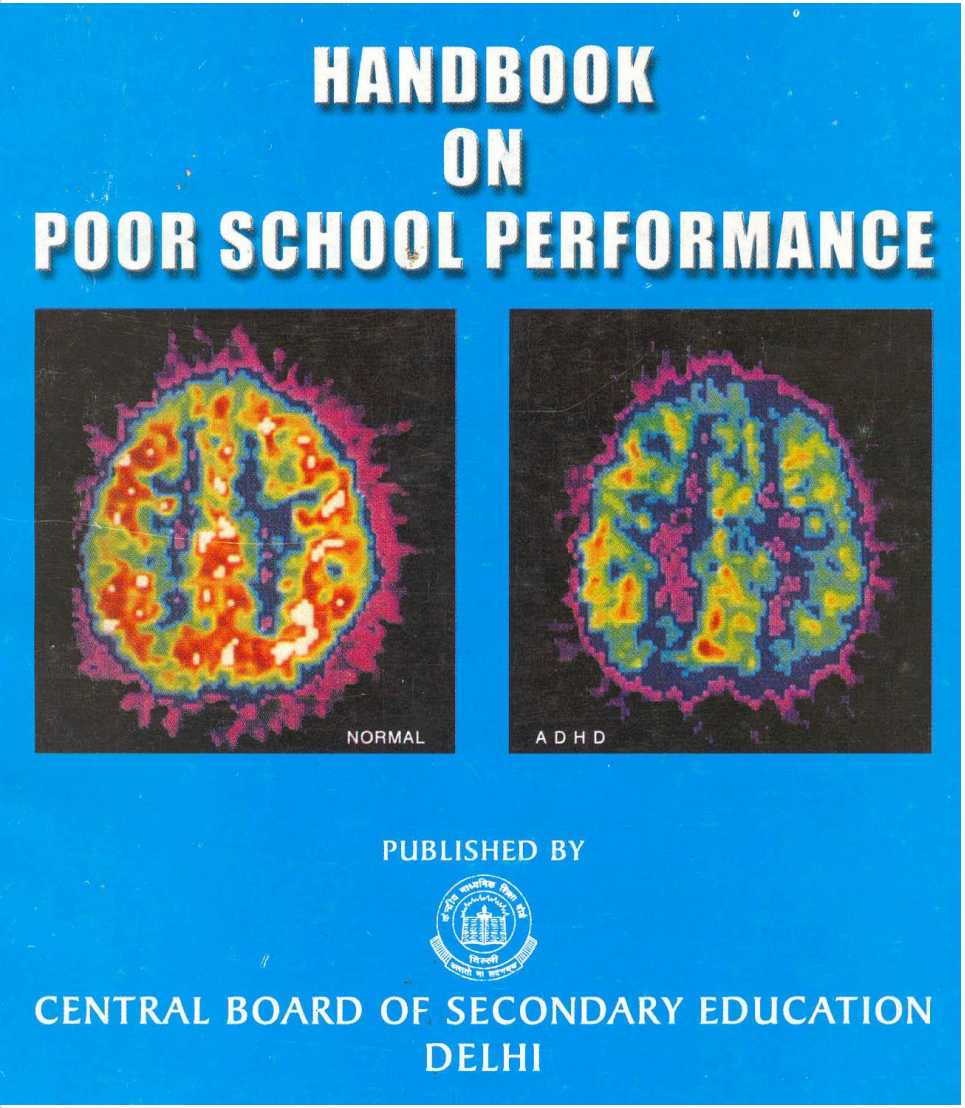


LD, ADHD…

# CBSE:

## ‘CHANGING WITH THE TIMES’

A. Ganguly, Chairman

**Philip John, Susan George**

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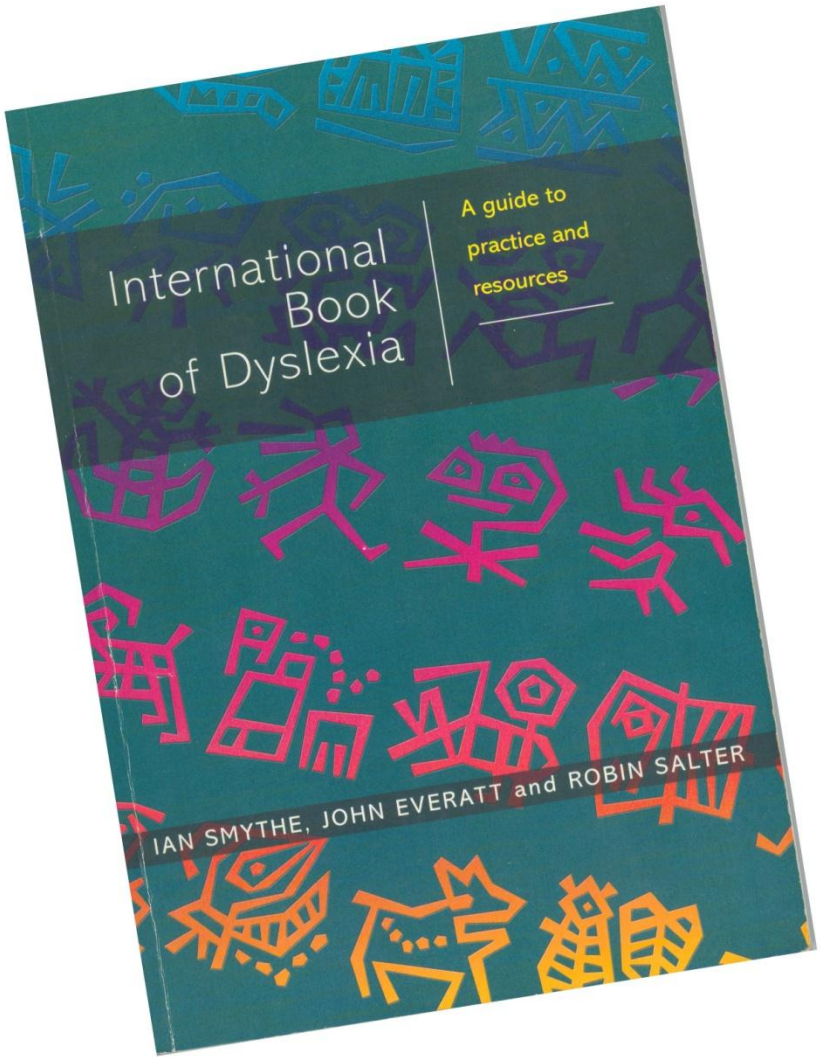


# ‘DYSLEXIA IN INDIA’

## Philip John

**JOHN WILEY & SONS,**

**LONDON**

# Presentation Format

- ADHD: ICD 10 & DSM 5
- Clinical Aspects & Symptoms
- ADHD & Co-morbidity
- Management Strategies
- Central Role of Pharmacotherapy
- Various Cognitive Enhancers
- Alternate Agents in Management
- The ‘Diet’ Story
- Conclusion

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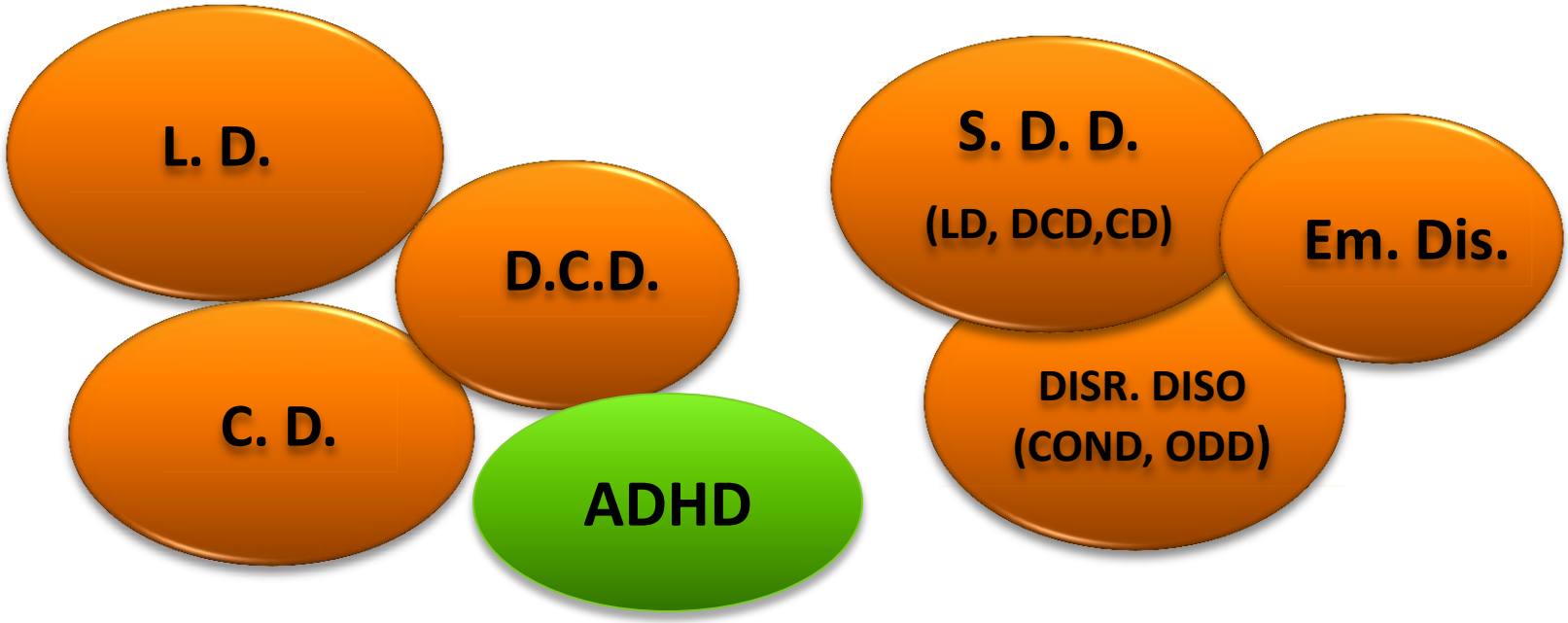
# THE CGC COCHIN EXPERIENCE

**ADHD: Paradigm Shifts:** (ICD- F80,90 and DSM 5)

## DHD & CO-MORBIDITY ?



# ICD 10

## Child Psychiatric Disorders : Overview

F 70-79 : Mental Retardation (MR)
(Intellectual Disability (ID)
Intellectual Developmental Disorder (IDD)

F 80-89 : Developmental Disorders
Neuro Developmental Disorder

F 80-83 : Specific Developmental Disorder (SDD) (Delay)

F 84 : Pervasive Developmental Disorder (PDD)
Autism Spectrum Disorder (ASD) (Deviance)

F 90-98 : Behavior & Emotional Disorders
ADHD, Conduct Diso, ODD, Anx, Dep, Tics etc

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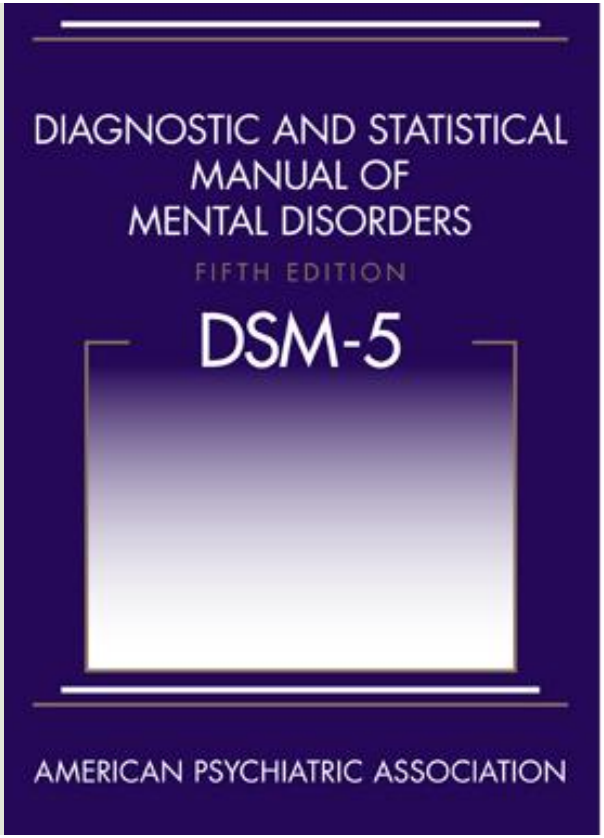
# NEURODEVELOPMENTAL DISORDERS

## Major shift in DSM 5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# DSM IV to DSM 5 : More Lenient

- Verily, under Neurodevelopmental Disorder.
  Not grouped with Disruptive Disorders (F 90) like ODD.
- Examples given for each of 18 symptoms.
- Till 17 years : 6/9 symptoms under each domain needed.
  After 17 years : 5 symptoms enough for diagnosis.
- Age of onset before 12 years, instead of 7. 'Symptoms' just need to be present, not 'impairment' itself.
- Multiple settings impairment not a must (home/ school/ work functioning.
- Severity: (Mild/ Moderate/ Severe) to be noted.
- ADHD, the Clinician's Judgment.

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# FIDGETY PHILIP (Hoffman, 1863)

"Phil, stop acting like a worm
The table's not a place to squirm."

Mother frowns and looks around,
But Philip will not take advice.

He turns, and churns
He wiggles, and giggles
Here and there, on the chair;
"Phil, these twists I cannot bear".

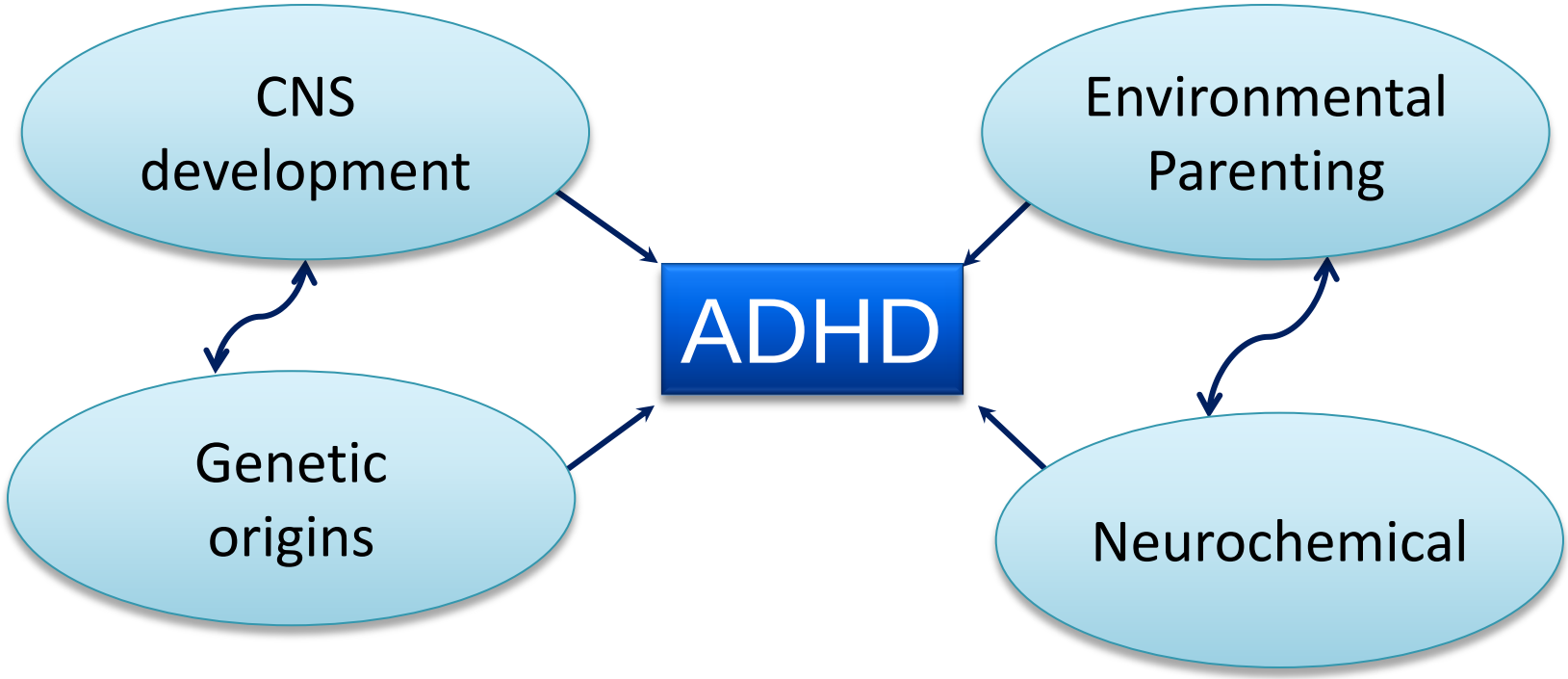
*(After which Philip leans backward in his chair and as he is falling, grabs the tablecloth – tumbling the dishes, and the chair and himself, to the floor!)*

# ADHD: Perception Change and Paradigm Shift

- From Frustration to Focus-
  - ‘Behaviour’ Disorder to ‘Brain’ Disorder.
- Central role for Pharmacotherapy in ADHD-
  - Exploiting Neuro-transmission of Cognition.

# ADHD: MULTI FACTORIAL ETIOLOGY

## Hence, Multi-modal Management Approach




- ADHD is a heterogeneous behavioral disorder with multiple possible etiologies; 8 to 12% prevalence.

# CLINICAL FEATURES
## ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADD / ADHD)

CLINICAL FEATURES (18 Symptoms listed DSM V)

1. INATTENTION (9 symptoms)
2. HYPERACTIVITY (6 symptoms)
   IMPULSIVITY (3 symptoms

- Most commonly referred disorder.
- ADHD as a Brain Disorder. Neurodevelopmental.
- Child has no control; NOT deliberate.

# ADHD : CLINICAL FEATURES

**A) INATTENTION CLUSTER** (6 or more Symptoms)

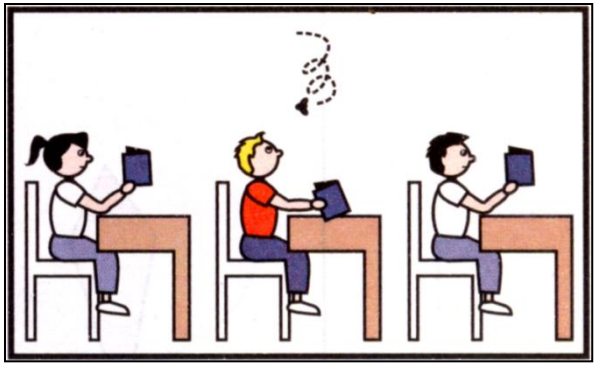
- Cannot sustain attention, premature withdrawal of attention- “Distractions”.
- ‘Careless’ mistakes in school or other work.
- Seems not to listen when spoken to directly.
- Does not follow through on instructions and fails to finish school work.

# ADHD : CLINICAL FEATURES

## INATTENTION CLUSTER (Cont'd..)

- Difficulty organising chores, tasks & activities.
- Avoids tasks that need sustained mental effort (eg. Home work).
- Often loses articles needed for tasks (toys, pencils, books).
- Easily Distracted.
- Forgetful of daily activities.

*At least 6 months*



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# ADHD : CLINICAL FEATURES

## B) HYPERACTIVITY – IMPULSIVITY CLUSTER

### HYPERACTIVITY

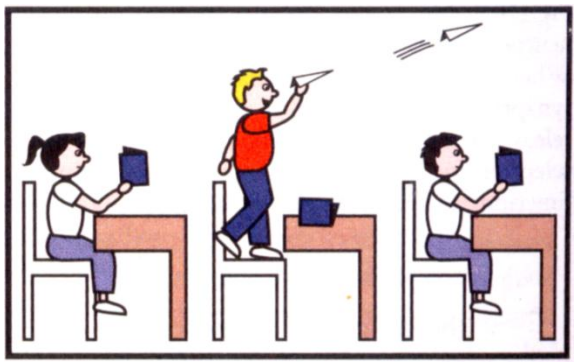
- Fidgets with hands/feet; squirms in seat, taps hands
- Leaves seat in class or where seating is norm
- Runs about/climbs inappropriately
- Difficulty playing quietly
- Continuously ‘on the go’, as if ‘driven by motor’ – accident-prone – Novelty-seeking
- Talks excessively, incongruous for age ‘unthinking breech of rules’

# ADHD : CLINICAL FEATURES

## B) HYPERACTIVITY – IMPULSIVITY CLUSTER (Contd.)

### HYPERACTIVITY

- Blurts out answers before questions have been completed.
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (butts into conversations or games)



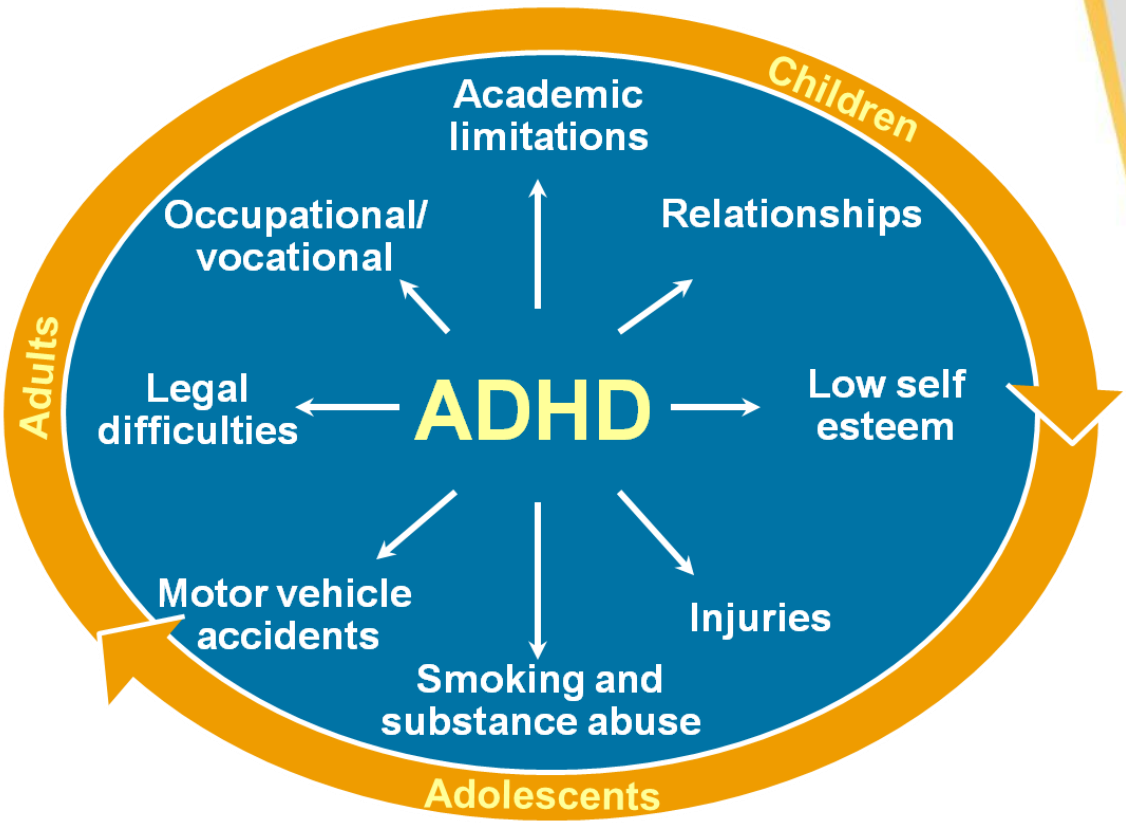
Present before age **12 years**.

2 or more settings

# ADHD: DOMAINS OF FUNCTIONAL IMPAIRMENT

## PERSISTENCE INTO ADULTHOOD :

- 60% of children with ADHD carry the disorder into adulthood.
- 85% of adults with ADHD are not diagnosed.



# PERSISTENCE INTO ADULTHOOD

## IMAGES OF ADULT ADHD

- Lack of focus
- Disorganized
- Restless (within)
- Relational difficulties
- Poor executive functions
- Perpetual search for stimulation
- Starts projects, does not finish, etc.

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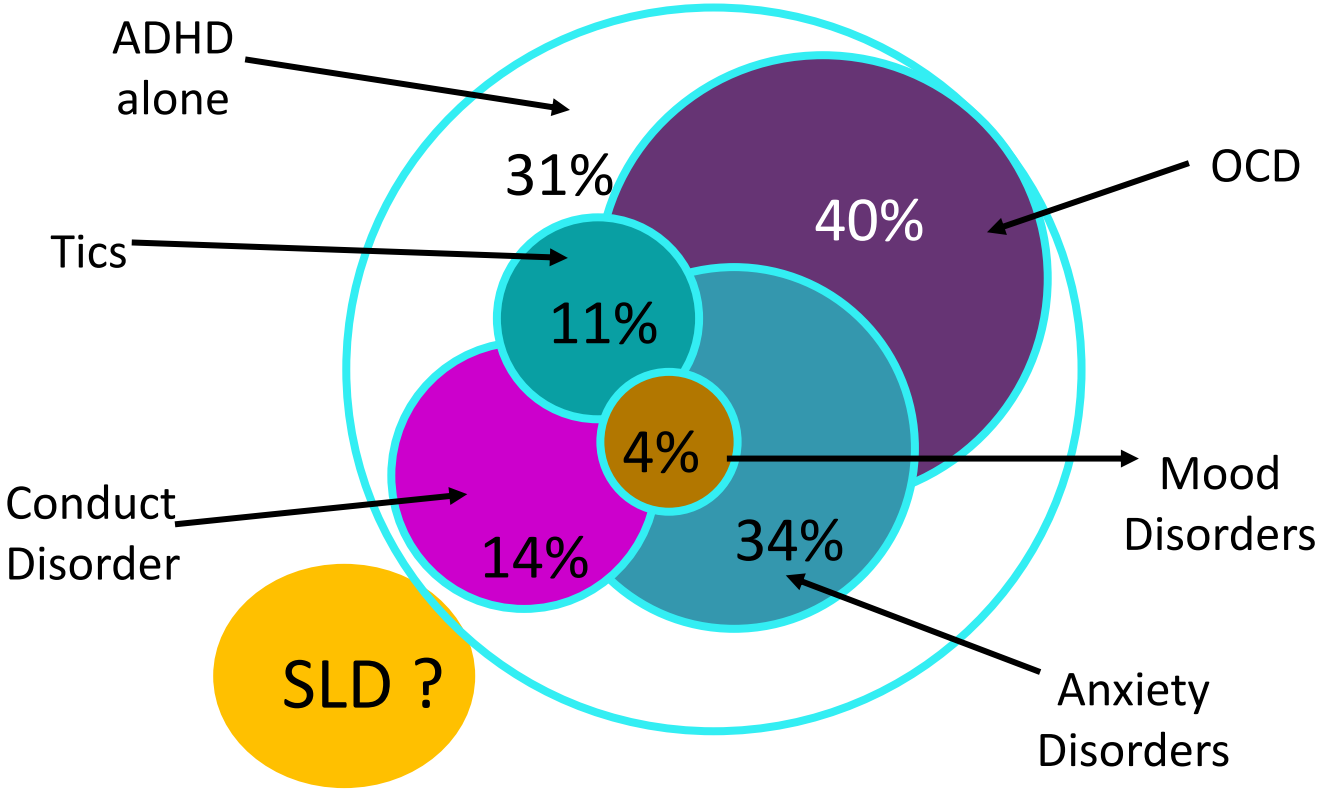
# ADHD: HETEROGENEITY & COMORBIDITY

MTA, Multimodal Treatment Study of Children with ADHD



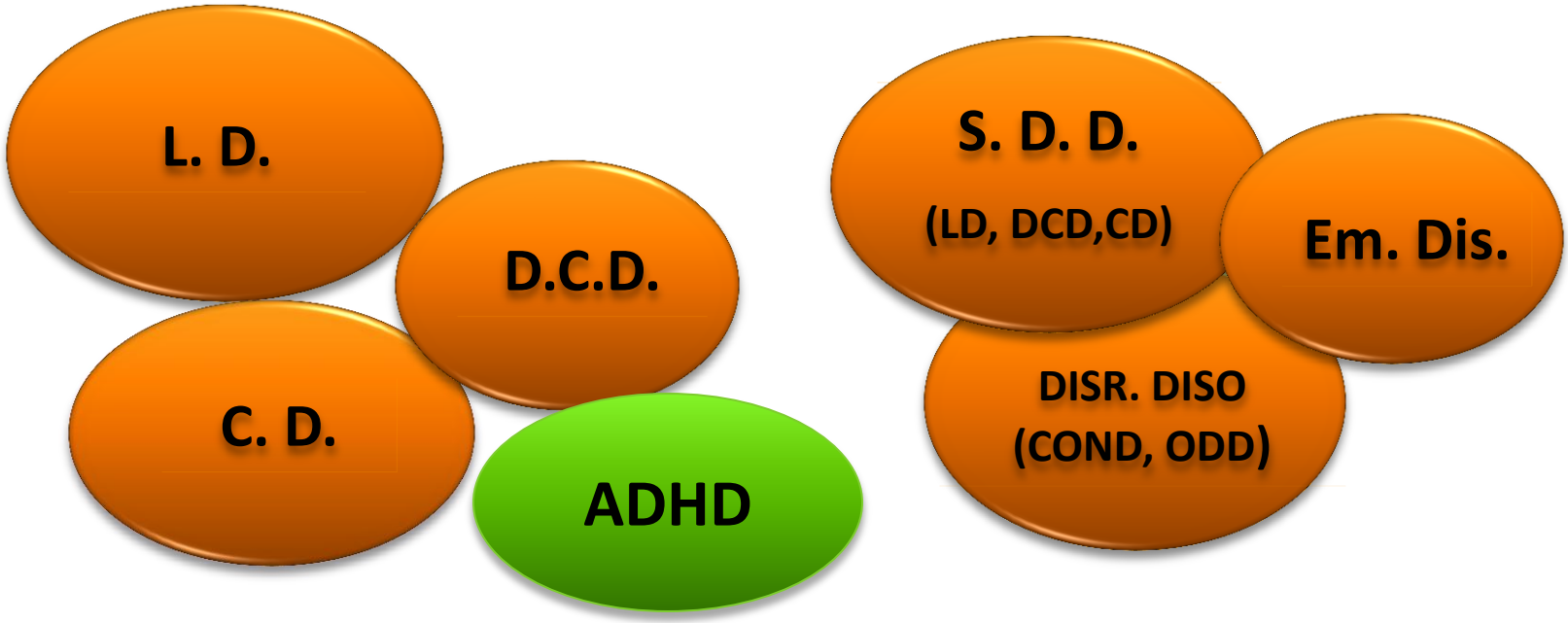

Jensen et al. J Am Acad Child Adolesc Psychiatry. 2001 Feb;40(2):147-58.

# ADHD: Paradigm Shift

## THE CGC COCHIN EXPERIENCE

## SPECTRUM-CONSTRUCT'

'Treatment of one disorder also ameliorates another.'




Neurodevelopmental Comorbidity

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# Strategies to Assessment

- Establish appropriate, firm diagnosis.
- Screen for Co-morbid disorders.
  Work on Co-morbidities; treatment of one ameliorates another: ‘spectrum hypothesis’.
- Insist on Neurological exam, EEG.
  Increased Fronto-central theta band activity is a consistent association with ADHD.
- Neuro-imaging.

# Diagnostic/ Rating Tools in ADHD

- **DSM 5 / ICD-10 Criteria**
- Conners' ADHD Rating Scale
- Barkley's ADHD Scale
- Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
- Wender Reimherr Adult Attention Deficit Disorder Scale (WRAADS)
- Brown Attention-Deficit Disorder Scale

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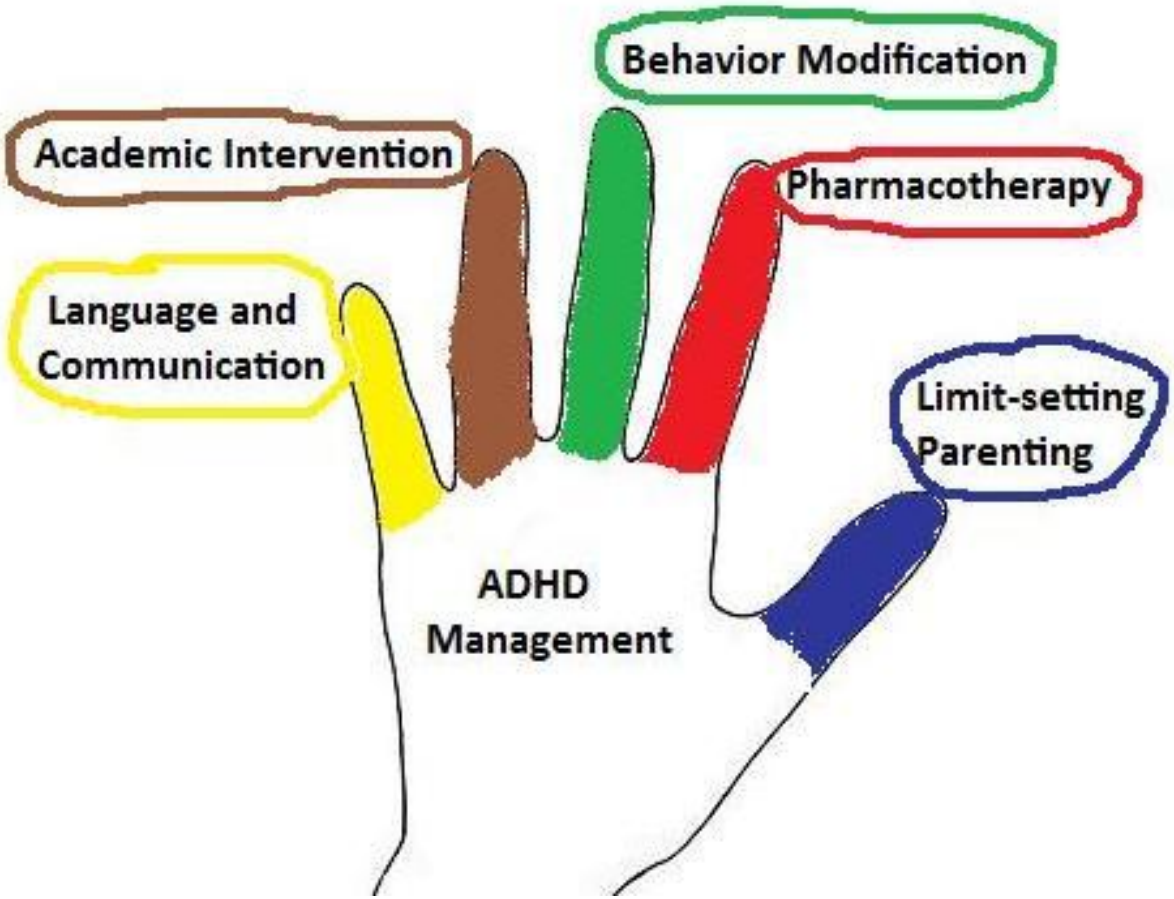
# MANAGEMENT: 5 finger approach




Five-finger Approach: Prompts for Counseling

# ADHD : PSYCHOSOCIAL TREATMENTS

- BEHAVIORAL STRATEGIES: Rewards/Punishment.
- PARENTING STRATEGIES AND DISCIPLINING.
- EDUCATIONAL AND CLASSROOM MANAGEMENT.
- MANAGING CO-MORBIDITY DISORDERS.
- **MULTI-DISCIPLINARY TREATMENT PROGRAMMES (CGC PROTOCOL).**

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# ADHD: Pharmacotherapy- beyond Symptom Control

- ***Incontrovertible*** Evidence for core role of medication in management.
- Unlike popular belief, symptom control is NOT the essence.
- Comprehensive turnaround in HRQOL.
- Enhance ‘Executive Functions’.

# ADHD – PHARMACOTHERAPY

**ENHANCE EXECUTIVE FUNCTIONS:**

- Working Memory (Verbal/Non verbal)
- Reading Comprehension
- Reconstruction (Metacognition)
- Self regulation of Emotions
- Motivation, Initiative and Drive

# MTA Cooperative Group (NIMH)
## Multimodal Treatment Study of Children with ADHD

### MTA CONCLUSIONS

- For ADHD symptoms, medication management was superior to behavioral treatment, and to routine community care that included medication.
- Combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms.

Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study. NIMH (Revised 2009)

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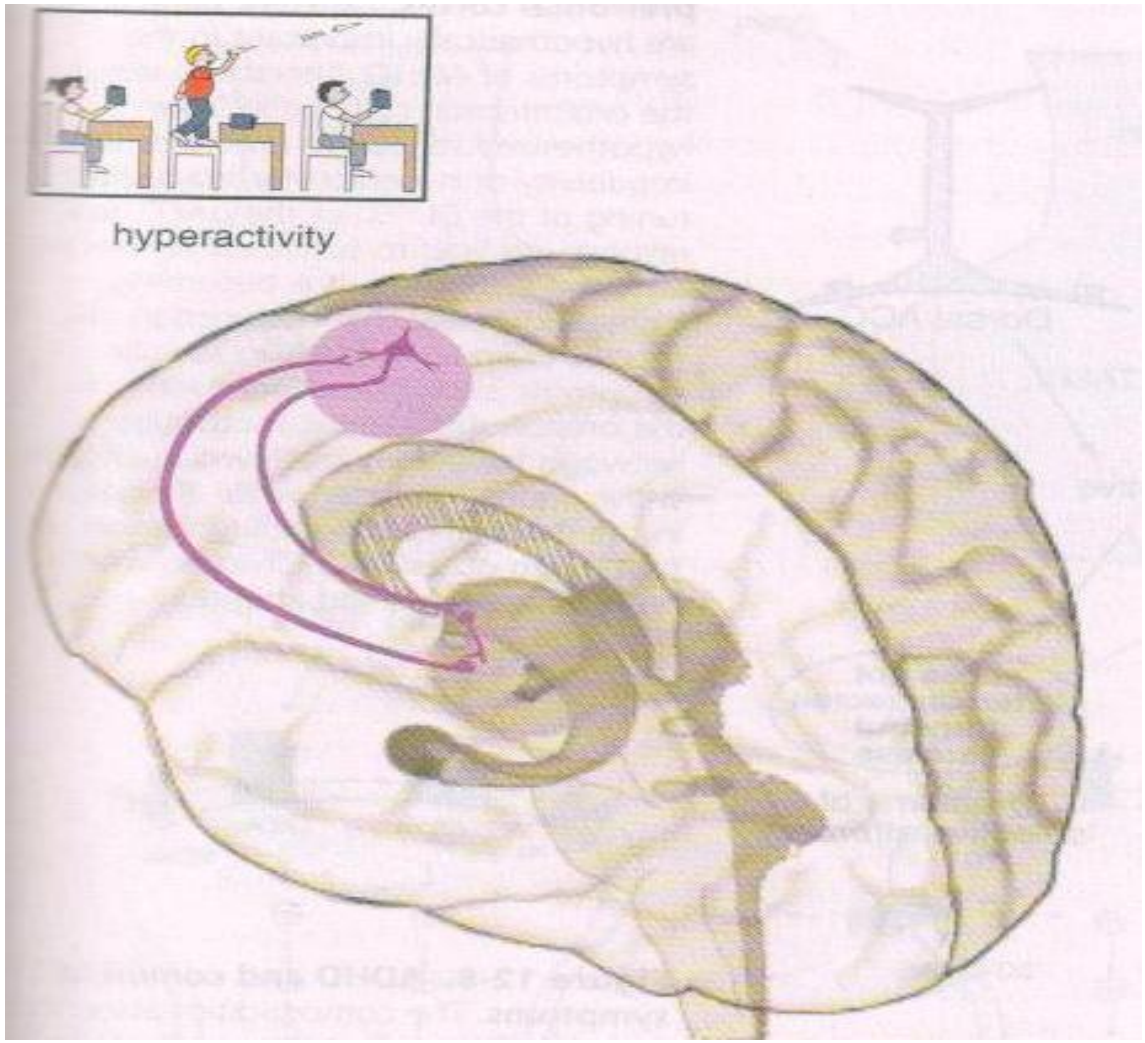
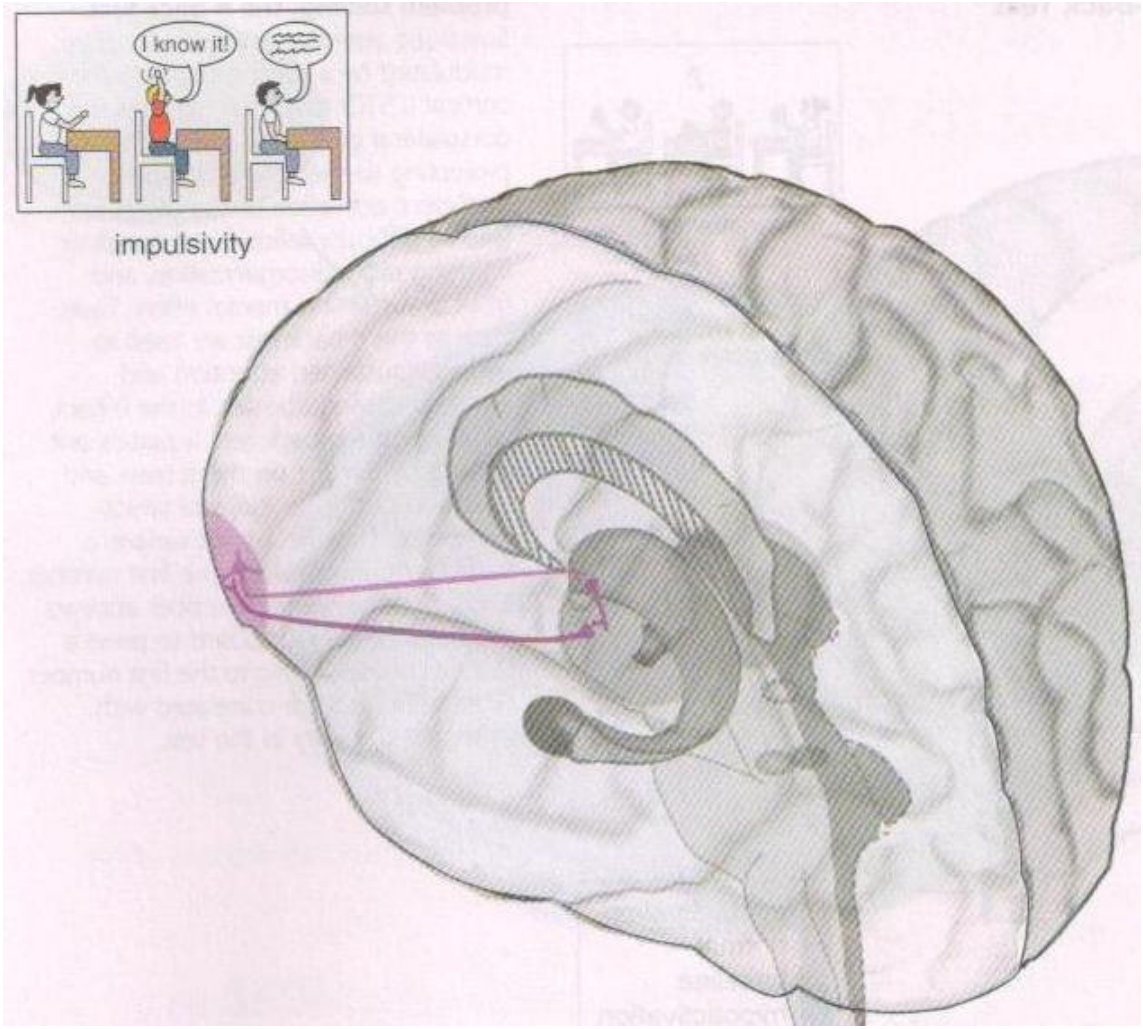
# NEURO-BIOLOGICAL BASIS OF ADHD AND MANAGEMENT WITH COGNITIVE ENHANCERS

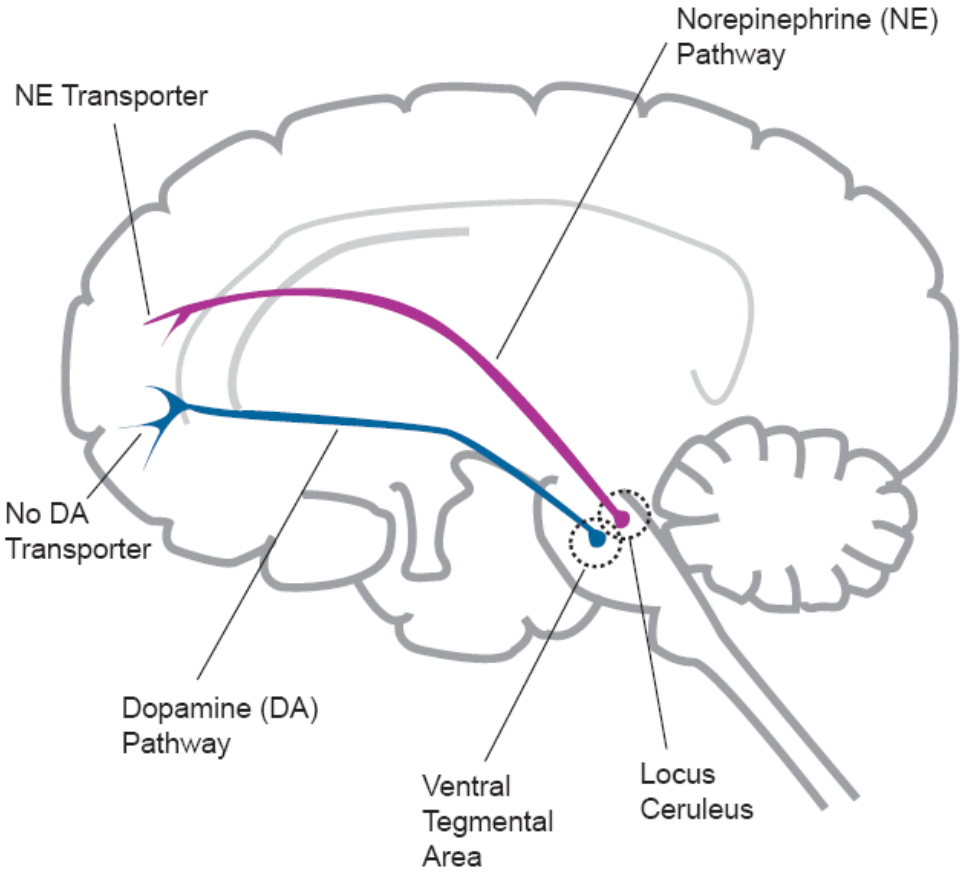



Motor Hyperactivity - Modulated by Prefrontal Cortex




Impulsivity - Modulated by Orbitofrontal Cortex

# Catecholamines in ADHD:
## Projections of NE & DA Pathways to PFC

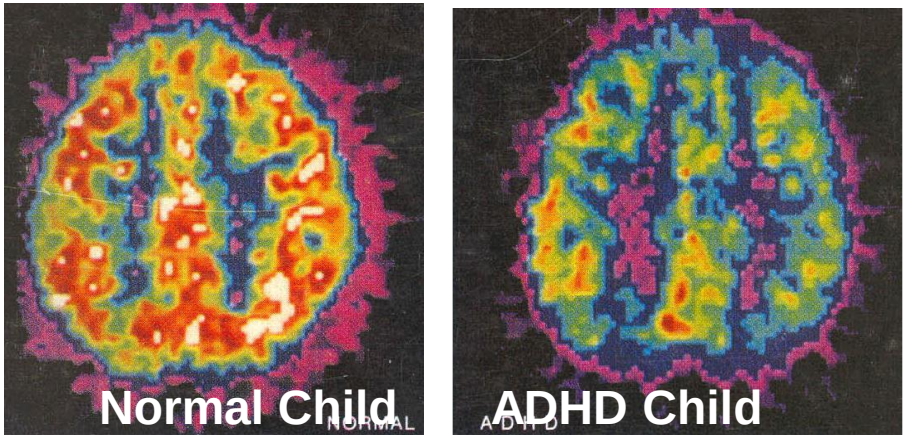



Norepinephrine projections from locus ceruleus

Dopamine projections in mesocortical pathway from ventral tegmental area

# ADHD : NEURO ANATOMICAL BASIS

## PET Data Implicates Frontal-Striatal Dysfunction




## ADHD brains fail to utilize pathways of Information Processing - Disorder of NE and DA Pathways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# ADHD: FROM CELLS TO CIRCUITS
## DOPAMINE 'HYPOFRONTALITY'

### DA & NE REUPTAKE INHIBITION

- In using Cognitive Enhancers (stimulants & non-stimulants), DA & NE Reuptake-inhibition takes place in the PFC.
- Designer Molecules for 'Smart' Neurotransmission : Methylphenidate, Atomoxetine inhibit reuptake of both DA / NE by blocking their Transporters.

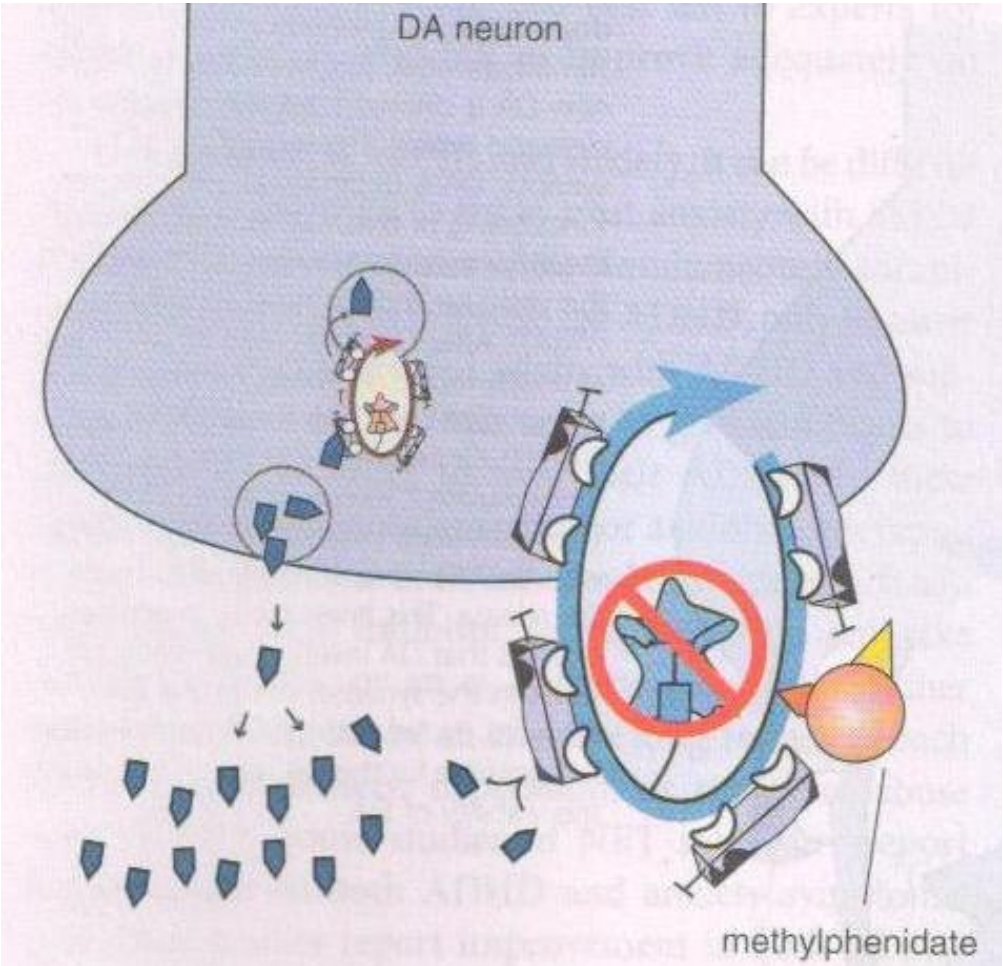
# PHARMACOTHERAPY IN ADHD

## I. STIMULANTS (Eg. Methylphenidate-MPH, Amphetamine)

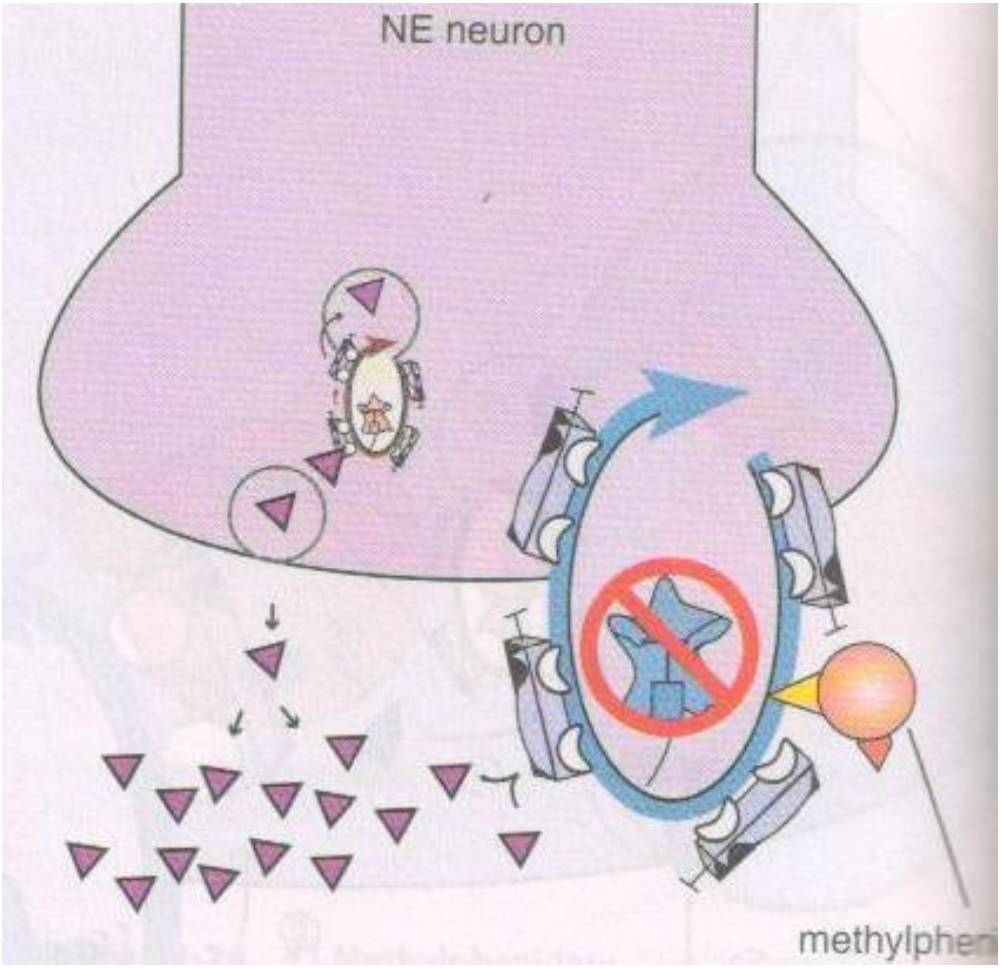
- Stimulants are more DA specific; DA / NE Releasers.
- Inhibitors of DA Transporter.
- Stimulants such as Methylphenidate and amphetamines are First-line.
- In spite of myths spread by even medical colleagues, 70-80% children improve.
- Side effects of HA, abdominal pain, insomnia, appetite loss, agitation, tics etc. are negligible.

Millions of children across the world have benefited.

# Mechanism of Action of Methylphenidate:
## DA Neurons



# Mechanism of Action of Methylphenidate:
## NE Neurons



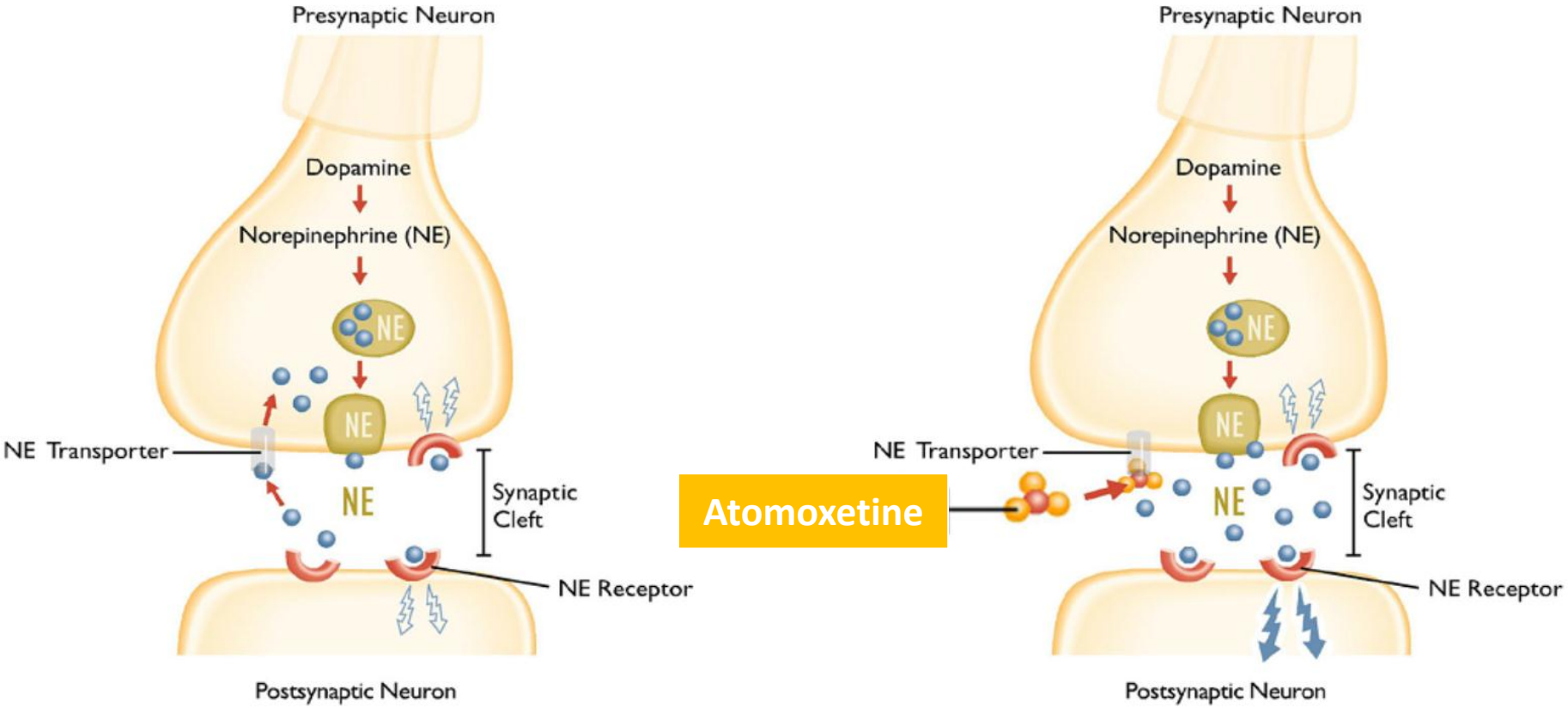
# PHARMACOTHERAPY IN ADHD

## II. NON-STIMULANTS (Eg. Atomoxetine - ATX)

- Specific, Robust NE Reuptake-blocker
- Spares DA in Subcortex, but acts on DA in the Cortex : Novel Strategy
- Action centered in Prefrontal Cortex (PFC) alone.

# NON-STIMULANT: ATOMOXETINE

## MECHANISM OF ACTION: ON NE & DA



# ADHD: Treatment vs. Non-treatment

- Without treatment, poorer morbid outcomes on long-term (Academic, Self-esteem, Antisocial, Obesity, Occupation etc.) .
- Treatment may not entirely ‘normalise’ patients, but it depends on managing comorbidities, ‘proximity-control’, and academic remediation.

Shaw et al., 2012: 351 studies on 9 parameters of outcome in 12 databases

# MPH in ADHD:
## Immediate Release (IR) vs. Extended Release (ER)

- MPH (IR): useful for about 3 hours;
  MPH (ER): lasts through 8 hours.
- MPH (ER) acts consistently through the day.
  Overall robust outcome.
- MPH (ER): No drug administration needed in school; stigma & dosing taken care of.
- MPH (ER) limits side-effects associated with fluctuations of serum concentrations, like ‘evening crash’.
  Hence better drug compliance with ER.

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# ADHD: Stimulants vs. Non-Stimulants

- Stimulant (MPH) : start IR switch to ER, may be the best choice.
- Non-stimulants (ATX) are less robust for response.
- Side effects on MPH or failure in outcome: switch to non-stimulant (ATX).
- No response to MPH : Add non-stimulant (ATX) for augmentation, or switch completely.
- Usually differential response; no need for both.

J Ch Adol Psych 23:3 (2013)
J CNSD 2013:5

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# ADHD: Alternative Agents

## Alpha-2 Adrenergic Agonists (Clonidine, Guanfacine)

- Alpha-2 agonists (antihypertensives) act in the PFC by inhibiting NE release from locus ceruleus.
  This influences DA firing rates in PFC.
- Greater use in ADHD with tics, aggression, insomnia.
- Need to r/o structural heart/ renal disorders.
- Start very low dose (1 tab = 100 micrograms).
- To be incrementally and carefully titrated.

# ADHD: Alternative Agents

## Bupropion (NDRI)

- Atypical antidepressant, blocking NE & DA reuptake.
- Response in hyperactivity, emotional control, conduct.
- Preferred for youth with ADHD & substance abuse.
- Also when stimulants & non-stimulants fail.

# ADHD: Alternative Agents

## Antidepressants

- Tricyclics
  - Of all Non stimulants, TCA most used.
  - Sobering effect on behavior too.
  - SNRI-effect: Clomipramine, Imipramine.
- SSRIs
  - 40% children – some improvement
  - Depression / anxiety / phobia / obs. anxiety improved.
- Selective NE Reuptake Inhibitor
  - Reboxetine : marginal use.

# ADHD: Alternative Agents

## Modafinil

- Non-stimulant, FDA approved for narcolepsy.
- Increases alertness through hypothalamic histamine, as well as DA & NE.
- Initial studies in ADHD appear to show robust response (78%).
- Choice in older children with Excessive Daytime Somnolence.

# ADHD: Supplemental Agents

## Poly Unsaturated Fatty Acids (PUFA)

- 50% brain weight is lipids, out of which 20% are PUFAs.
- Poly Unsaturated Fatty Acids (PUFA): 2 families – Omega-3 (Alpha Linolenic Acid) and Omega-6 (Linoleic Acid).
- Studies done by dietary supplementation in ADHD, ASD.
- PUFAs provide energy sources in membrane structures; act as mediators of immune responses.
- Influence DA & 5HT Neurotransmission & Cognition.
- (Include fish like sardines, tuna; olive and peanut oil, walnuts)

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# ADHD: The Diet Factor!

- ADHD children have CHO drive (sugary, fatty, salty…)
- Tall claims of “cure” for ADHD, Autism through diet – true web of Alternative Therapies!
- No methodologically rigorous studies or proof yet.
  - Gluten-free, Casein-free, Allergen-free, Additive-free, Sugar-free, Chocolate-free are these stories! Supplemental therapies like PUFA are different.
- ‘Pediatrics’ – the official journal of AAP emphasises this in a recent issue:
  - “These diets are complicated, disruptive to the household, impractical, expensive and have the potential to precipitate malnutrition.”

Pediatrics 2012;129;330

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# ADHD: New Horizons

- The prevalence and lifelong morbidity of ADHD is driving robust research for safe long-term remedial agents.
- Lis-dexamfetamine dimesylate (LDX) is a pro-drug that undergoes enzyme cleavage in the body to safely release amphetamine.
- LDX is thus a long-acting Pro-drug stimulant under launch.
- Several studies are underway in US & Canada, in ADHD subjects & results are reported as ‘effective’.

Adv Ther (2013) 30:472–486

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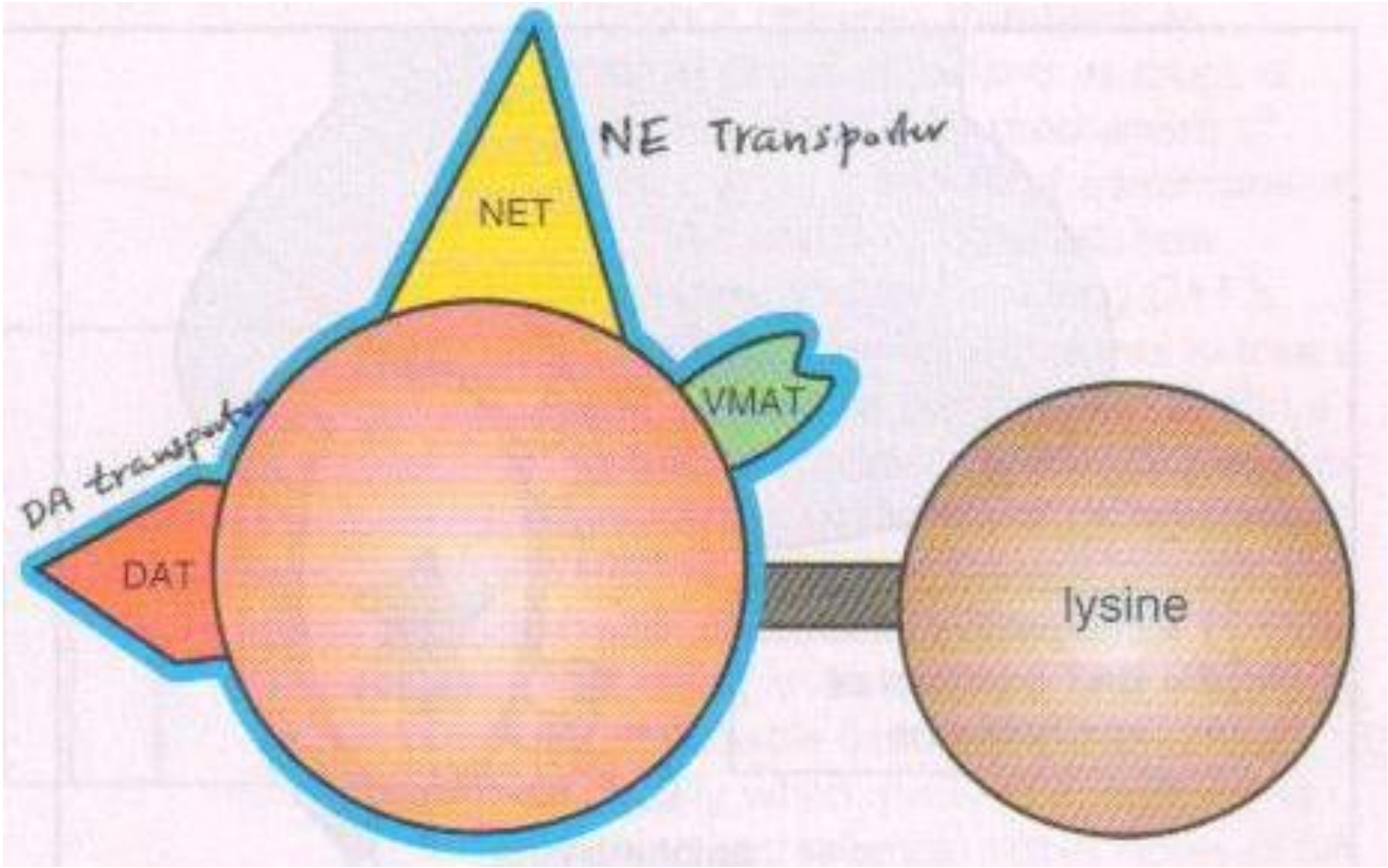
# Lis-dexamfetamine : prodrug of d-amphetamine



# ADHD: BEYOND SYMPTOM-CONTROL

- Substantial pharmacopoeia available even now, for safe and effective treatment of ADHD with evidence starting with 40 years of methylphenidate.
- “ADHD is the only so-highly prevalent non-degenerative neuropsychiatric disorder where effective medications remediate a principal cognitive disorder”

Neurotherapeutics. 2012 July; 9(3): 610–621.

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THANK YOU FOR YOUR ATTENTION