Delirium

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Conflict of Interest

- **None, except that I am a researcher working in this area**

Delirium

- **I have spoken on DELIRIUM on three of the previous occasions in Mumbai**

Neuropathogenesis of Delirium: Current Understanding

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3rd Global Conference of Biological Psychiatry, 23-26th Aug 2018

Delirium & Psychiatry

Dy Patil Medinspire Conference in 15-17th Feb, 2019

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A,B, C……. of Delirium

Mid-terms CME of IAGMH, 7th April 2019

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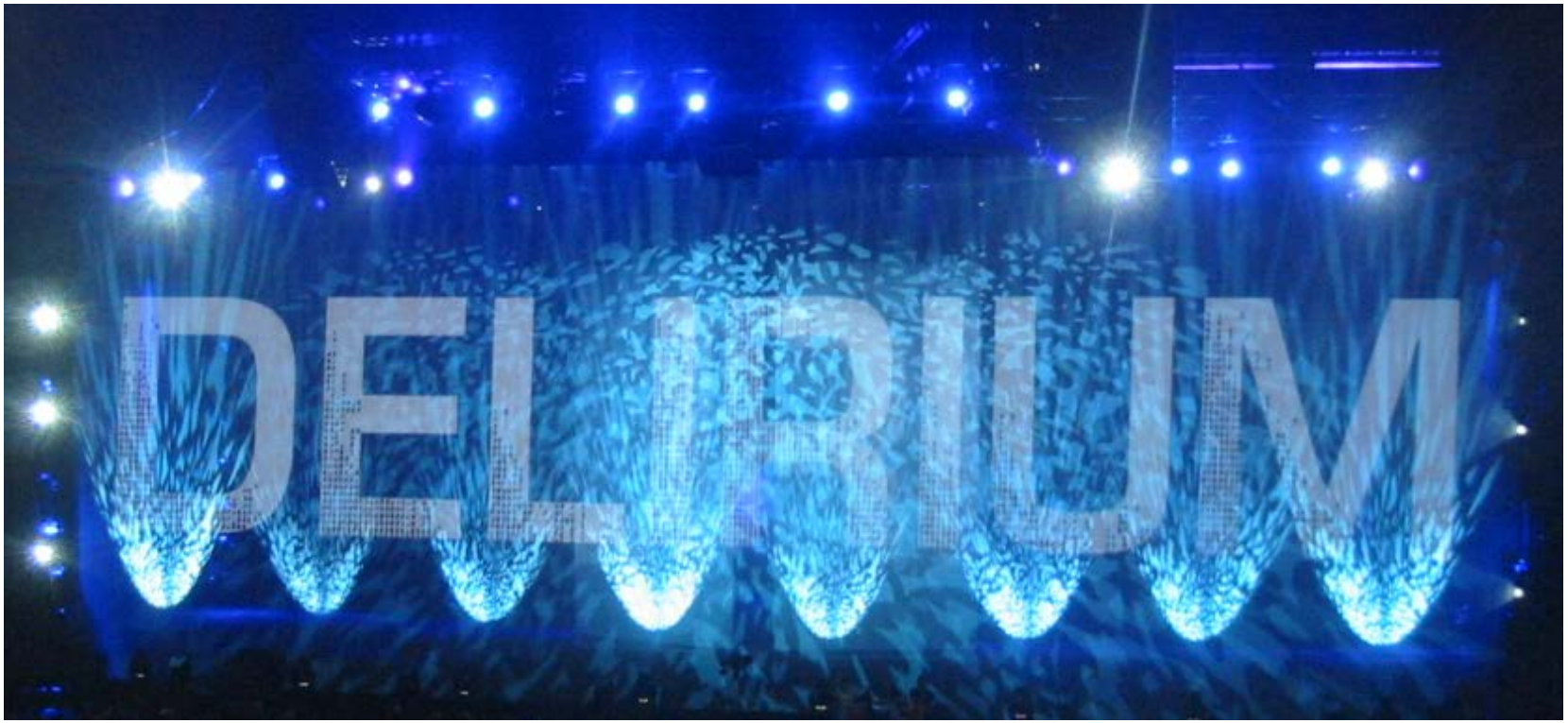
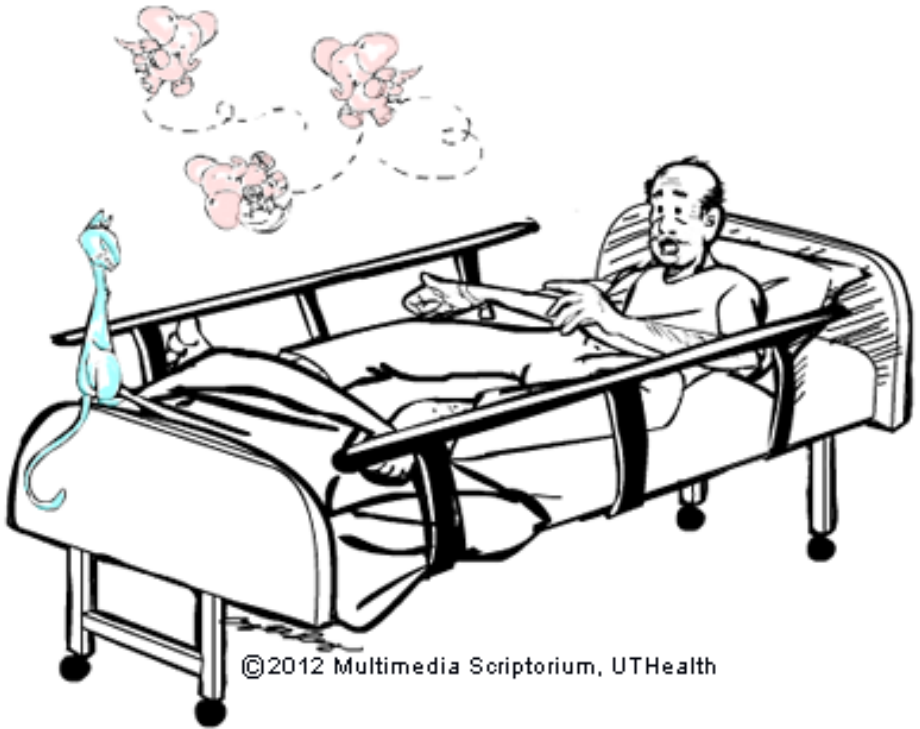

DELIRIUM

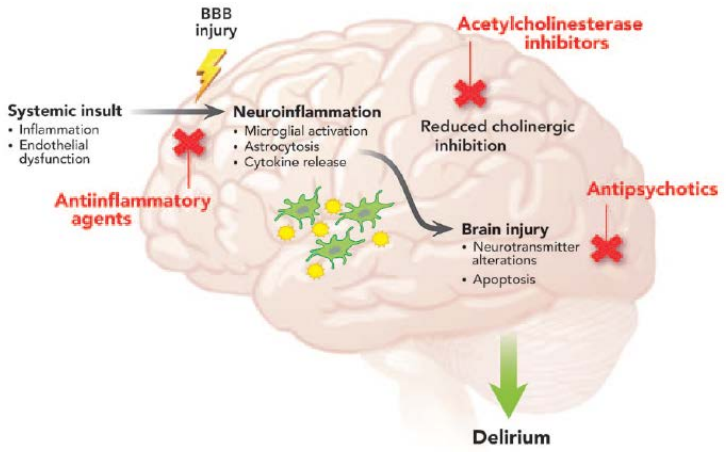
Introduction: Delirium

- Possibly the most common psychiatric morbidity seen in patients with acute medical illnesses
- Psychiatric manifestations are purely of organic etiology
- Often under-recognised
- Often under-treated



What is Delirium ?

- Complex Neuropsychiatric syndrome
- Due to one or more **structural and/or physiological abnormalities** directly or indirectly affecting the brain- **BRAIN FAILURE**
- Potentially **reversible** brain dysfunction
- **Acute** onset and fluctuating course

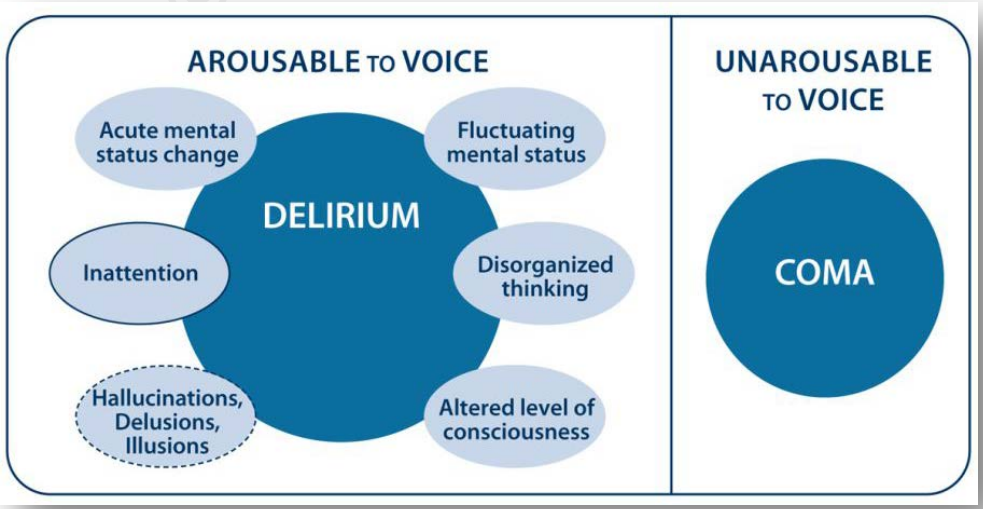


[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

What is Delirium ?

- **The altered mental state in delirium is considered to be on the continuum between**

Wakefulness **Delirium** **Coma**



[Morandi et al. Intensive Care Medicine 2008; 14: 1907-15]

Terminology

- Acute brain failure
- Postoperative psychosis
- Cerebral insufficiency
- Acute confusional state
- Toxic psychosis
- Encephalopathy
- Acute organic syndrome
- ICU psychosis
- Terminal agitation

[Meagher D. Delirium: the role of psychiatry. Advances in Psychiatric Treatment 2001; 7: 433–443]

How common it is ?

Prevalence of Delirium across various settings & age groups

	Adult	Elderly
Community	**0.4%**	**1.1%**
General hospital	11 to 42%	10-42%
Medical inpatients	10-24%	10-31%
Surgical inpatients	37-46%	
Post operative		20-40%
ICU	**15-52%** **9.27 to 59.6%****	**60-80%** **26.21 to 83.33%****
General wards - Psychiatry referrals	**10.3%-18.2%** **30.77 - 38.95%***	**28.5%** **48.72%***
Cancer	**10-35%**	**28-85%**

Ola et al, 2010; Schellhorn et al, 2009; Folstein et al,1991; Dasgupta et al, 2006; Fong et al., 2009; Saxena et al, 2009; Mittal et al, 2011; Burn et al, 2004; Khurana et al, 2002; Khurana et al, 2011; Grover et al, 2009; Sharma et al, 2012; Lahariya et al, 2014; Grover et al, 2018

Why it is important to recognise?

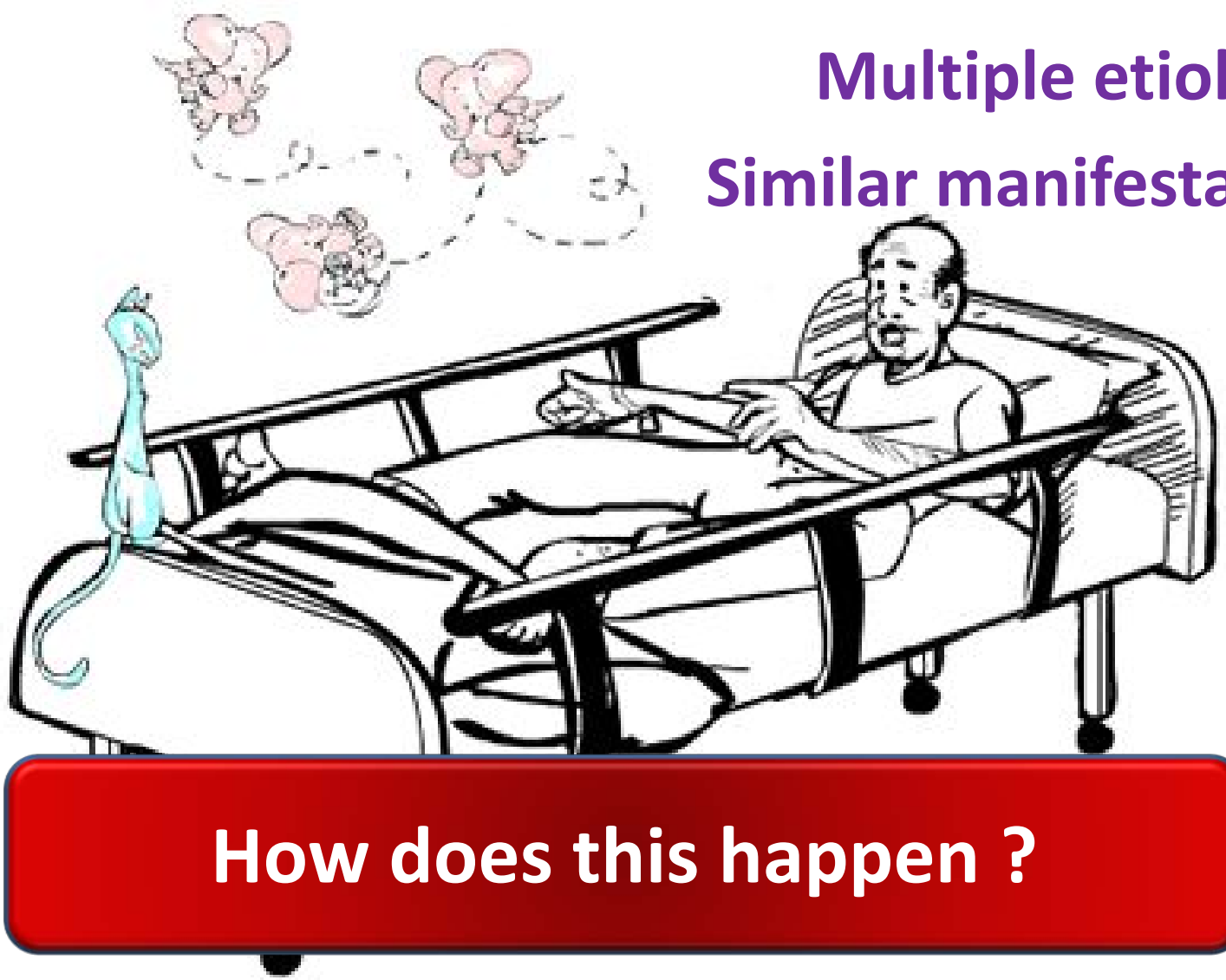
- Associated with high mortality rate (twice that of matched controls)
- Significant increase in the length of hospital stay
- Increased healthcare costs
- Institutional care, functional decline
- Important risk marker for dementia
- Experience is distressing for patients & caregivers

Grover S, Kate N. Delirium Research: Contributions from India. In: Developments in Psychiatry in India: Clinical, Research and Policy Perspectives. Eds: Savita Malhotra, Subho Chakrabarti. Springer (India) Pvt. Ltd., 2015; pp 463-492.

Understanding Delirium

Multiple etiologies

Similar manifestations



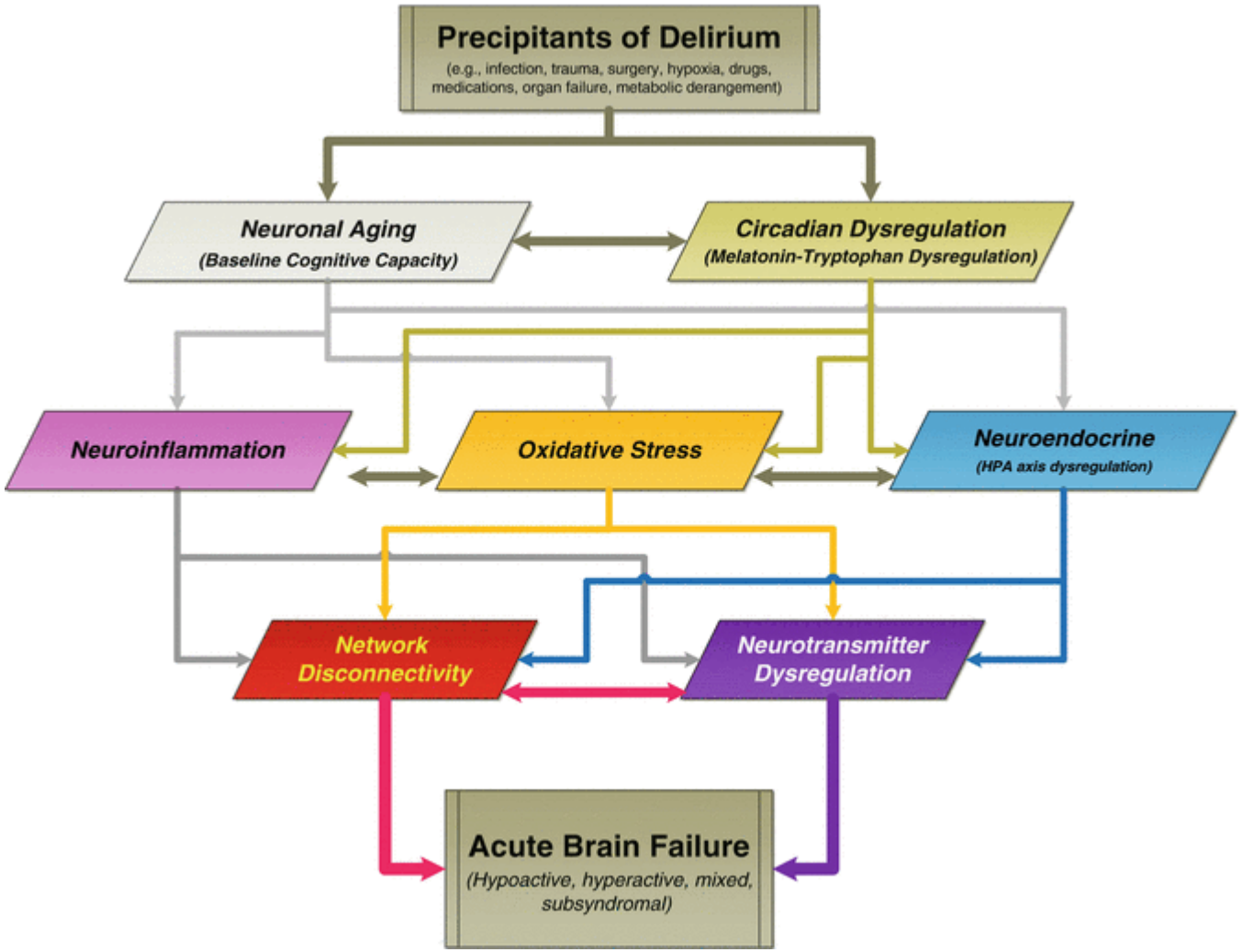
How does this happen ?

Why does delirium occur ?

- Neuro-inflammatory hypothesis
- Neuronal aging hypothesis
- Oxidative stress hypothesis
- Neurotransmitter deficiency hypothesis
- Neuroendocrine hypothesis
- Diurnal dysregulation hypothesis
- Network dis-connectivity hypothesis

[Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013 Dec;21(12):1190-222]

Why does delirium occur ?



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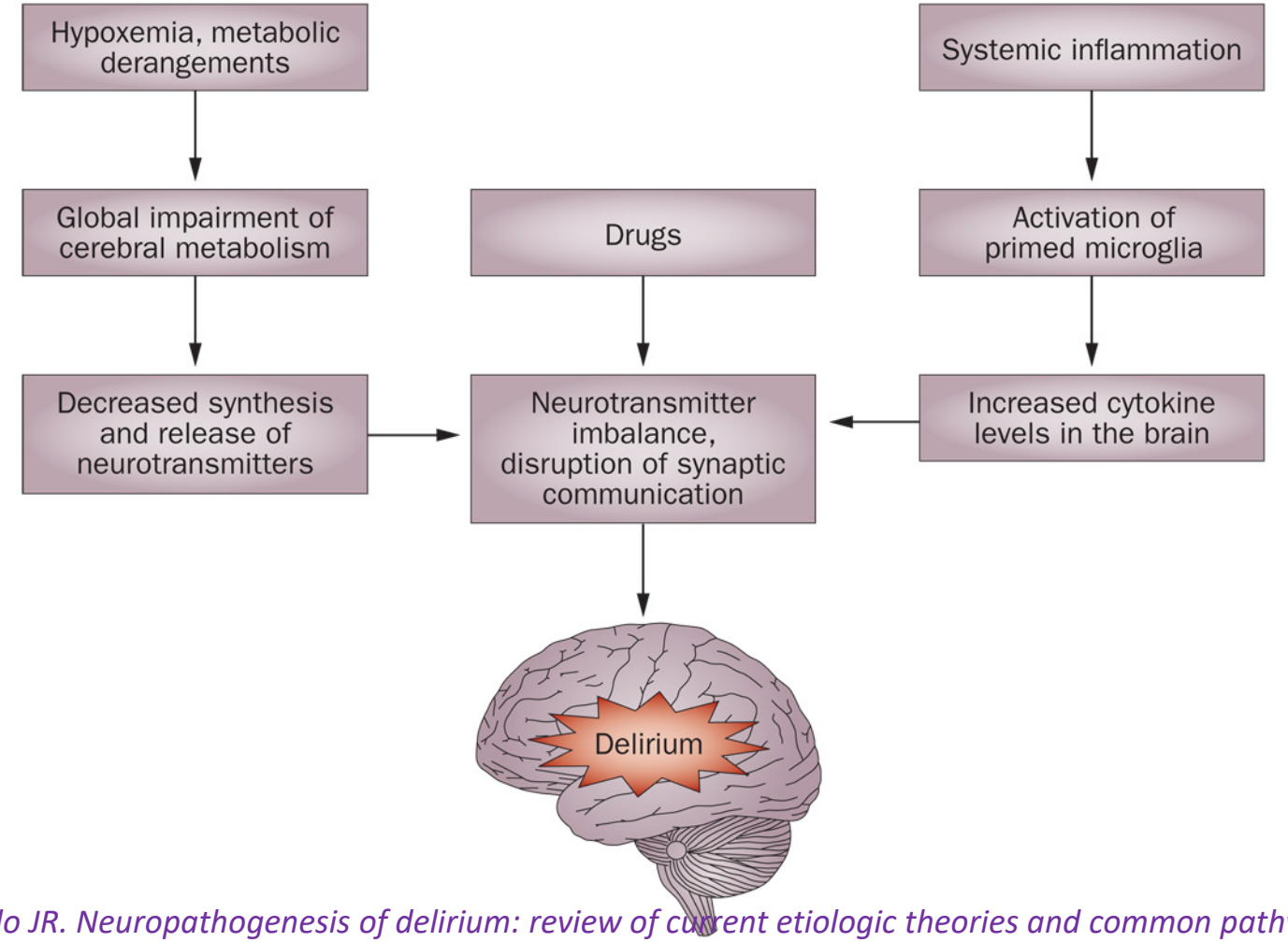

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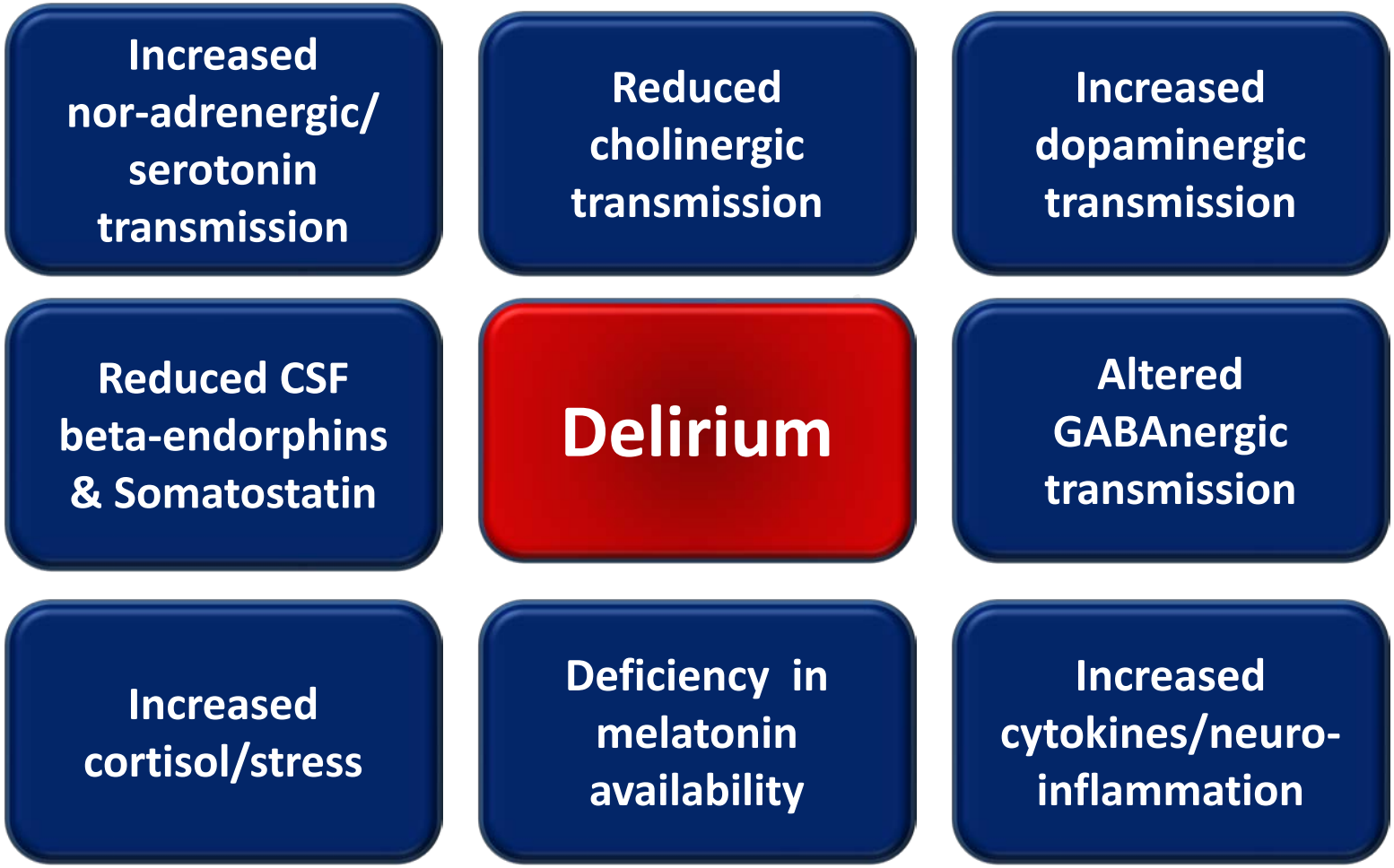
Pathogenesis of Delirium



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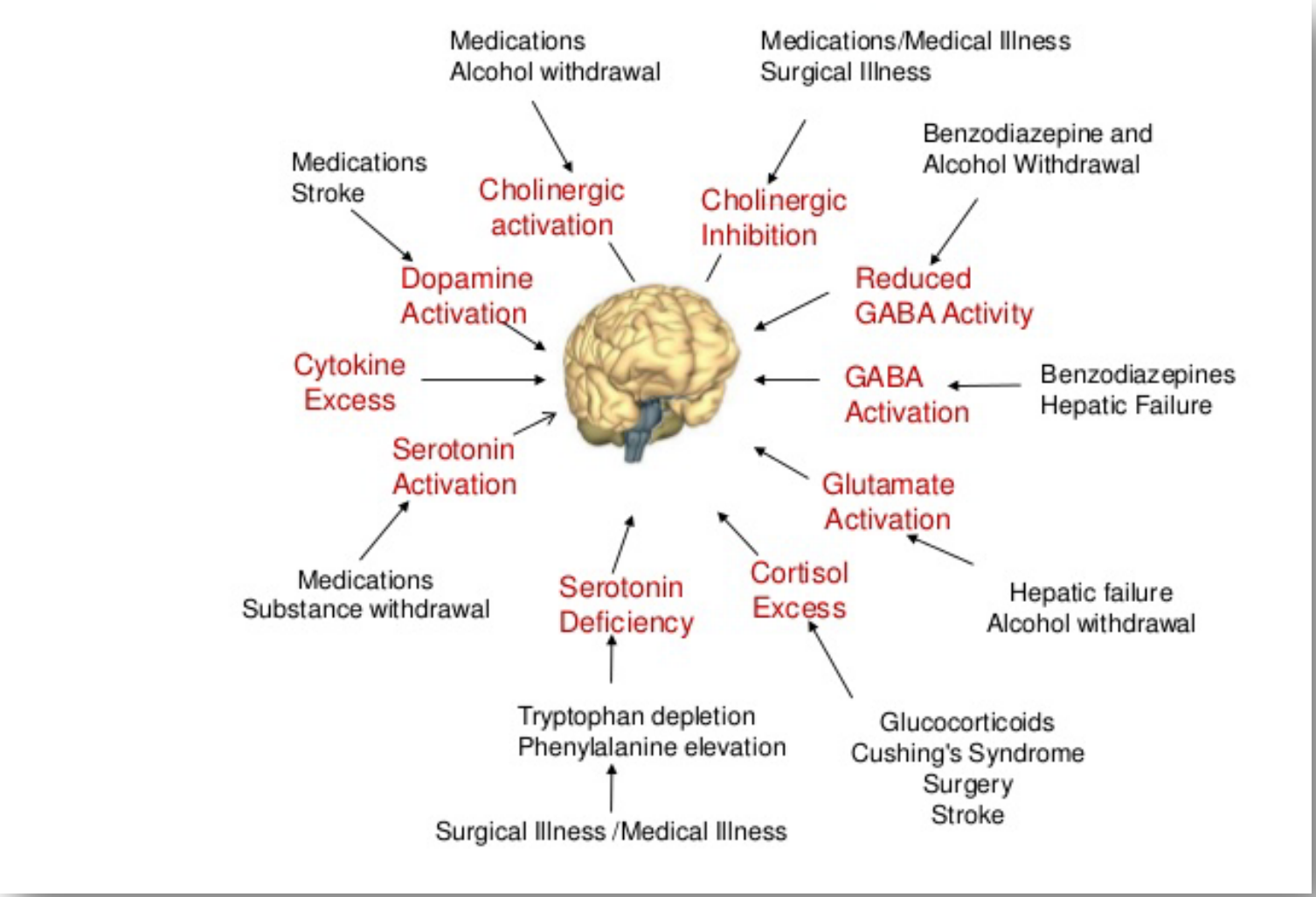
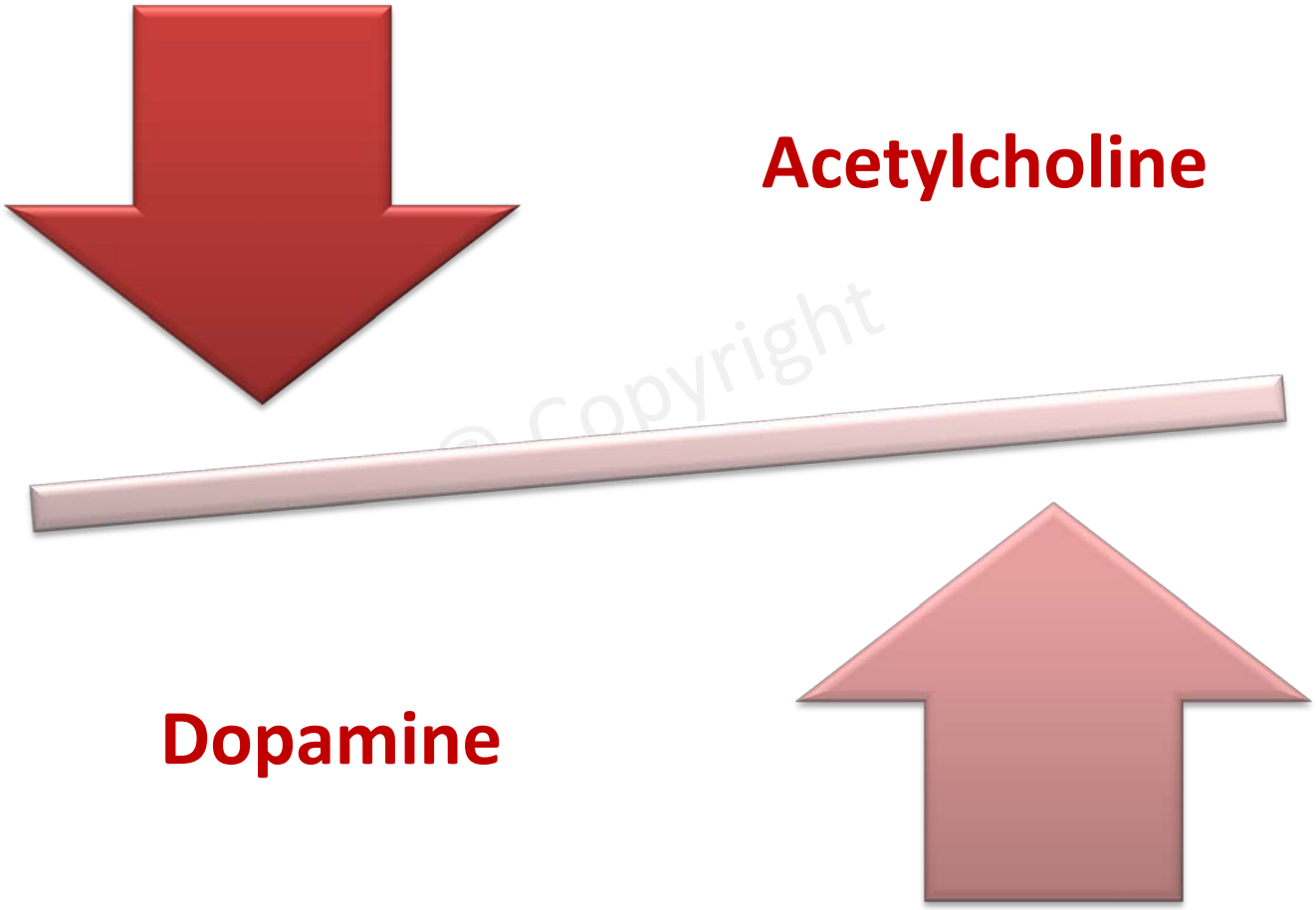


[Flacker JM, Lipsitz LA. Serum anticholinergic activity changes with acute illness in elderly medical patients. J Gerontol A Biol Sci Med Sci. 1999;54:M12-6]

Pathogenesis of Delirium



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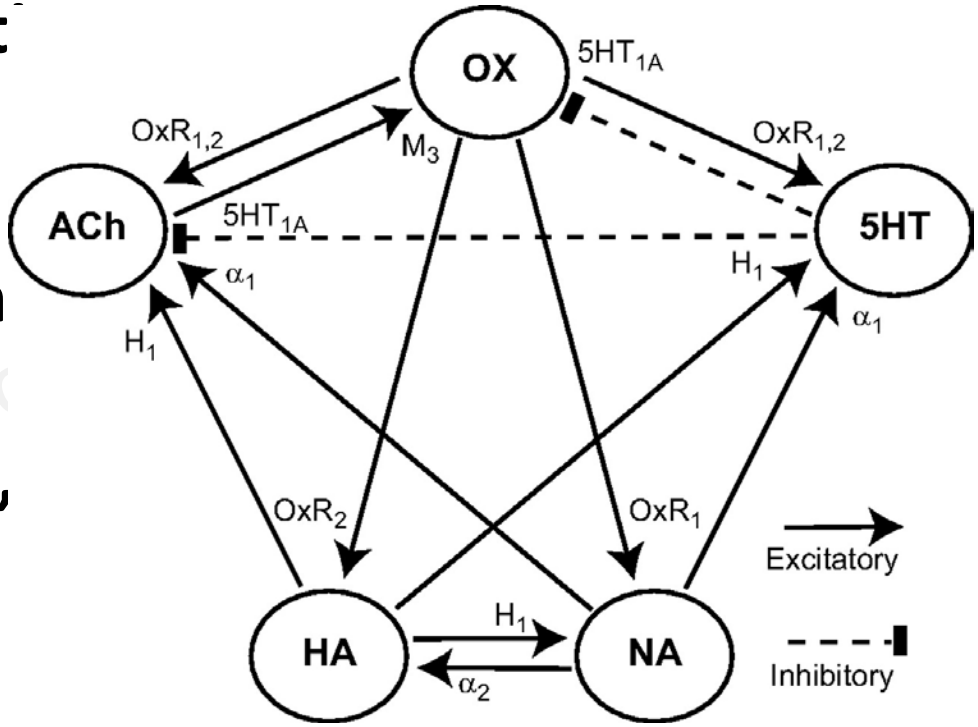
Pathogenesis of Delirium

- **It is not just the interact of acetylcholine and dopamine, which is responsible for delirium but these systems also interact with glutamate, GABA, Opioids**



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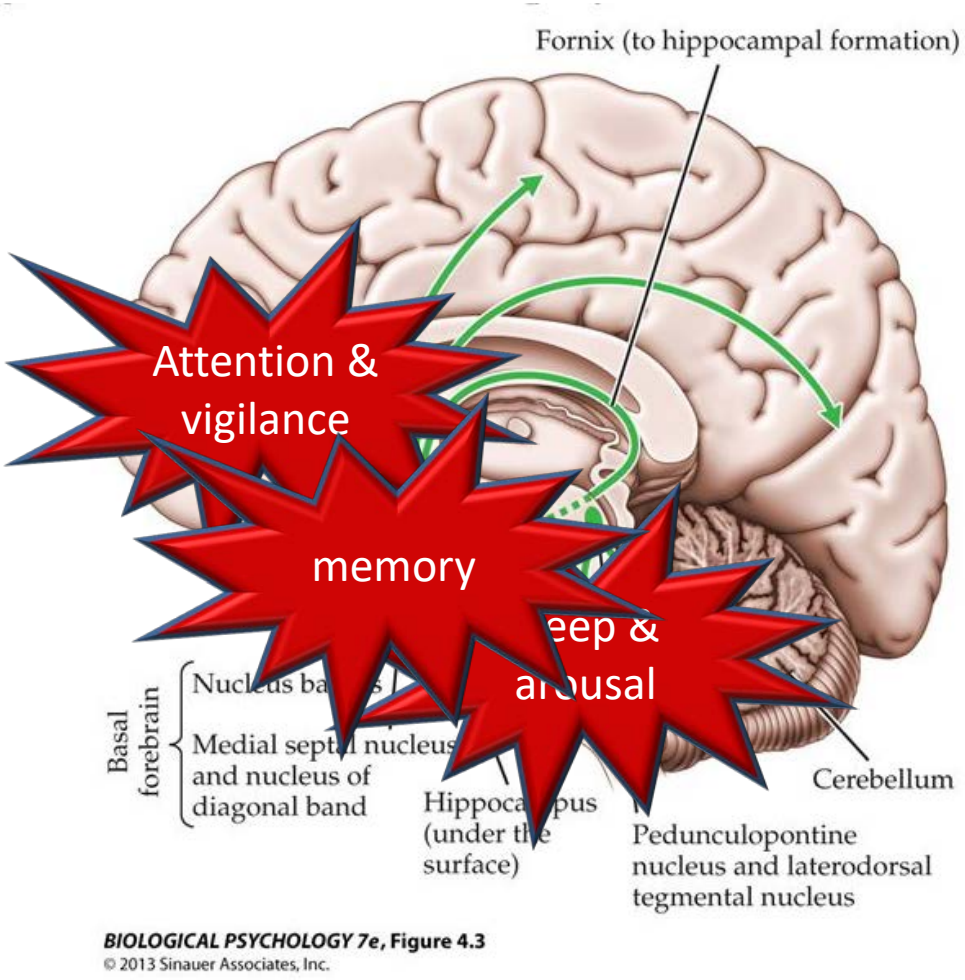

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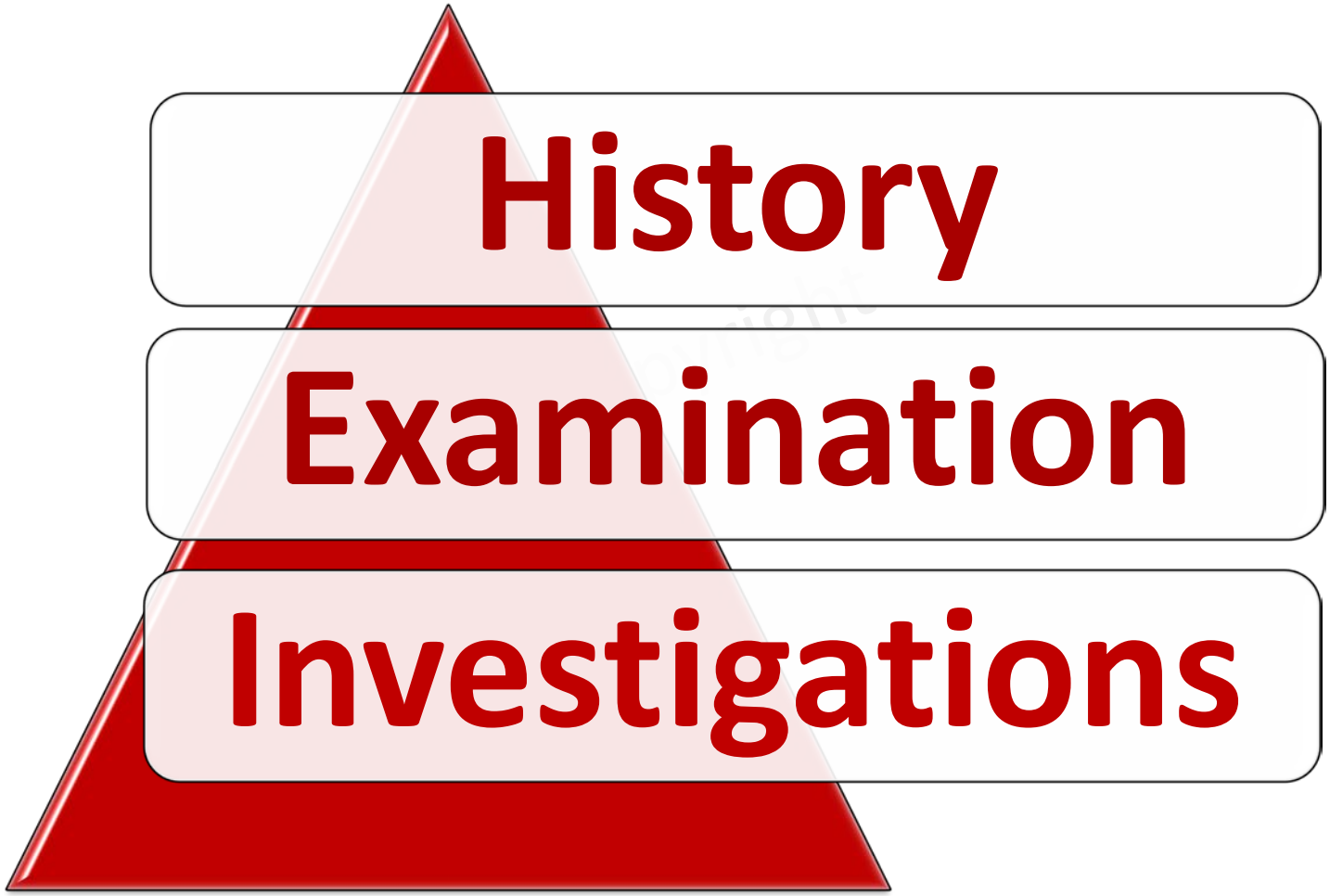
Assessment for Delirium



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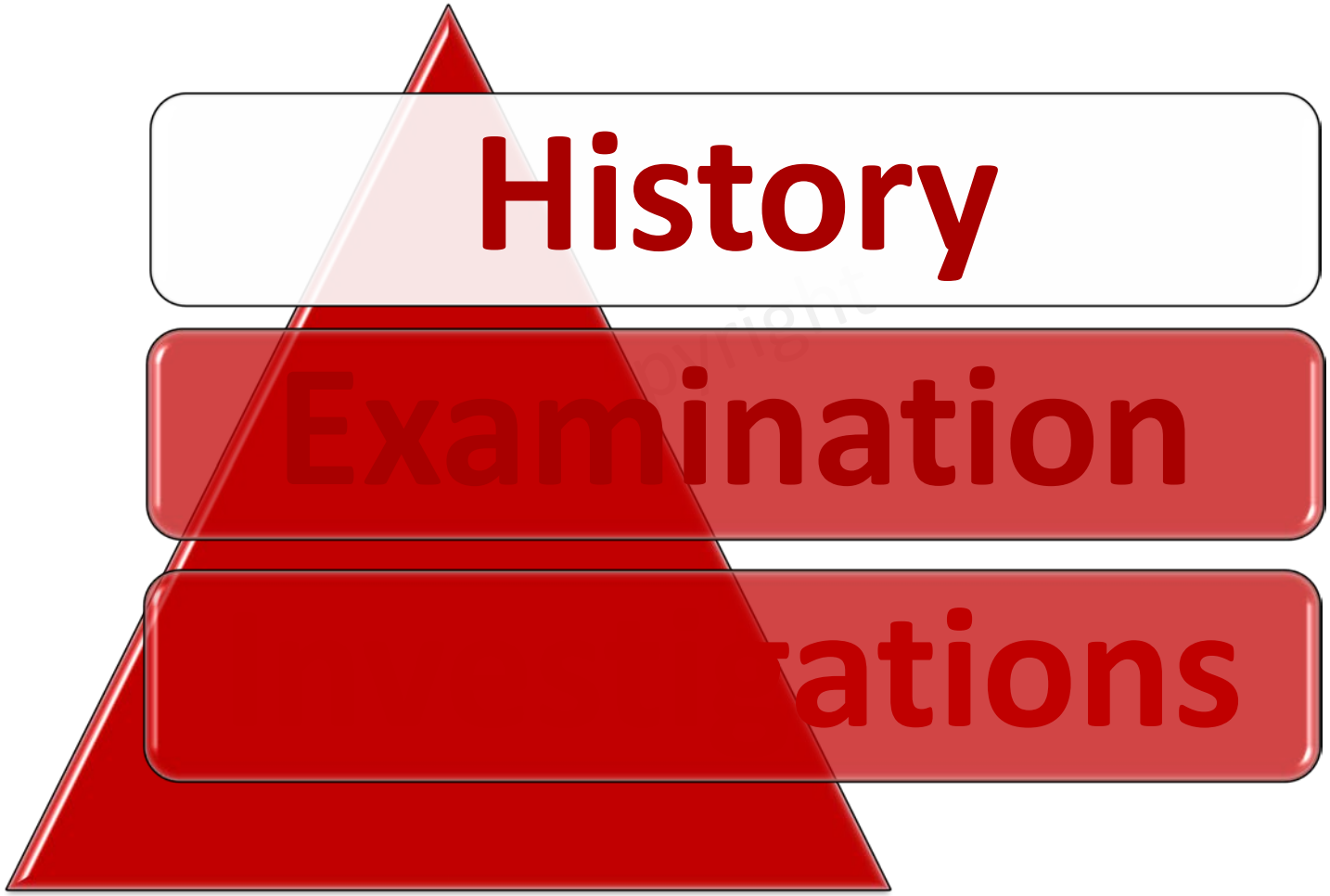


Assessment for Delirium

History

- Focus on the onset & course of symptoms
- Focus on evaluation of symptoms
- Look for the predisposing factors and precipitating factors
  - ✓ Past & current medical-surgical history
  - ✓ Pre-morbid cognitive status
  - ✓ Past psychiatric history
  - ✓ Current medications- prescription & non-prescription
  - ✓ Substance use – type, last intake

[Canadian Coalition for Seniors' Mental Health (CCSMH). National Guidelines for Seniors' Mental Health - The Assessment and Treatment of Delirium. Canadian Coalition for Seniors' Mental Health, Toronto, 2006]

How does it manifest ?

- Disturbance of consciousness
- Inattention
- Disruption of sleep and wakefulness
- Emotional disturbance
- Fluctuation
- Psychomotor disturbance
- Disorders of thought
- Disorders of language
- Disorders of memory and orientation
- Perceptual disturbances

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

- Cognitive
- Non-Cognitive Symptoms

How does it manifest ?

Disturbance of consciousness

- Falling asleep during interview
- Conflicting reports about awake mental state of the patient provided by various caregivers

Inattention

Forgets instructions
Distraction to seemingly irrelevant stimuli
Repeatedly asks the same question(s)
Gives different replies to same question

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

Disorders of memory and orientation

- Forgetting about meals, medicines, visitors, *etc*
- Forgetting about things recently discussed/mentioned
- Not aware about the time, place, person
- Misidentifying people around/familiar persons
- Talking as if at home
- Talking about dead relatives, or relatives who are not present around the patient at that time

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

Visuospatial Difficulties

Constructional apraxia: difficulty in constructing- drawing, copying, designs, copying 3D models

Topographical disorientation: difficulty finding one's way in the environment

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

Disruption of sleep and wakefulness

- Not able to sleep at night
- Fragmentation/disruption of sleep
- Reversal of sleep-wake cycle (sleeping in day & awake at night)
- Vivid dreams and nightmares - difficulty distinguishing dreams from real perceptions

Emotional disturbance

May demonstrate fluctuations in emotional state varying from anxiety, sadness, fearfulness to euphoria during the same interview or over the multiple interactions in a day

How does it manifest ?

Fluctuation in symptoms

- **Unpredictable** – during the course of interview, over the period of 1 or more days
- **Intermittent**
- Often **worse at night**
- **Periods of lucidity** - may function at "normal" level

Agitation: Try to get out of bed repeatedly, wander around in the ward/house, try to pull out the tubes/drains/ catheters repeatedly, frequent postural changes while in bed

Retardation: Apathy and withdrawal, Minimal activity in bed, Minimal/reduced verbal output

How does it manifest ?

Disorders of thought

Abnormalities in form & content of thinking are prominent

- Impaired organization & utilization of information
- Thinking may become bizarre or illogical
- Content may be impoverished or psychotic
- Delusions of persecution are common
- Judgment & insight may be poor

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

Disorders of language

- Slow and slurred speech, Pressure of speech
- Word-finding difficulties
- Difficulty with writing
- Incoherent or rambling or irrelevant speech
- Inability to understand what is being said

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

How does it manifest ?

Perceptual disturbances

- ***Visual hallucinations*** (seeing things which others do/can not)
- ***Tactile hallucinations*** (report crawling sensation over the body as if some insects are present OR can be seen as if trying to remove insects over their body)
- ***Auditory hallucinations*** (hearing things which others do/can not)
- ***Misinterpretation*** (loud noise of machines may be interpreted as gunshot, alarm of a machine may be interpreted as police siren)
- **Illusions** (interpret folds of bed sheets/blankets as animate objects; can be seen trying to clean the bed sheet/blanket in order to remove them)

How does it manifest ?

Core symptoms

- Attention deficits (97–100%)
- Thought process abnormalities (54–79%)
- Disorientation (76–96%)
- Memory deficits (88–96%)
- Sleep–wake cycle disturbances (92–97%)
- Motoric alterations (24–94%)
- Language disturbances (57–67%)

Non-core symptoms

- Perceptual disturbances (50–63%)
- Delusions (21–31%)
- Affective changes (43–86%)

[Gupta et al, 2008]

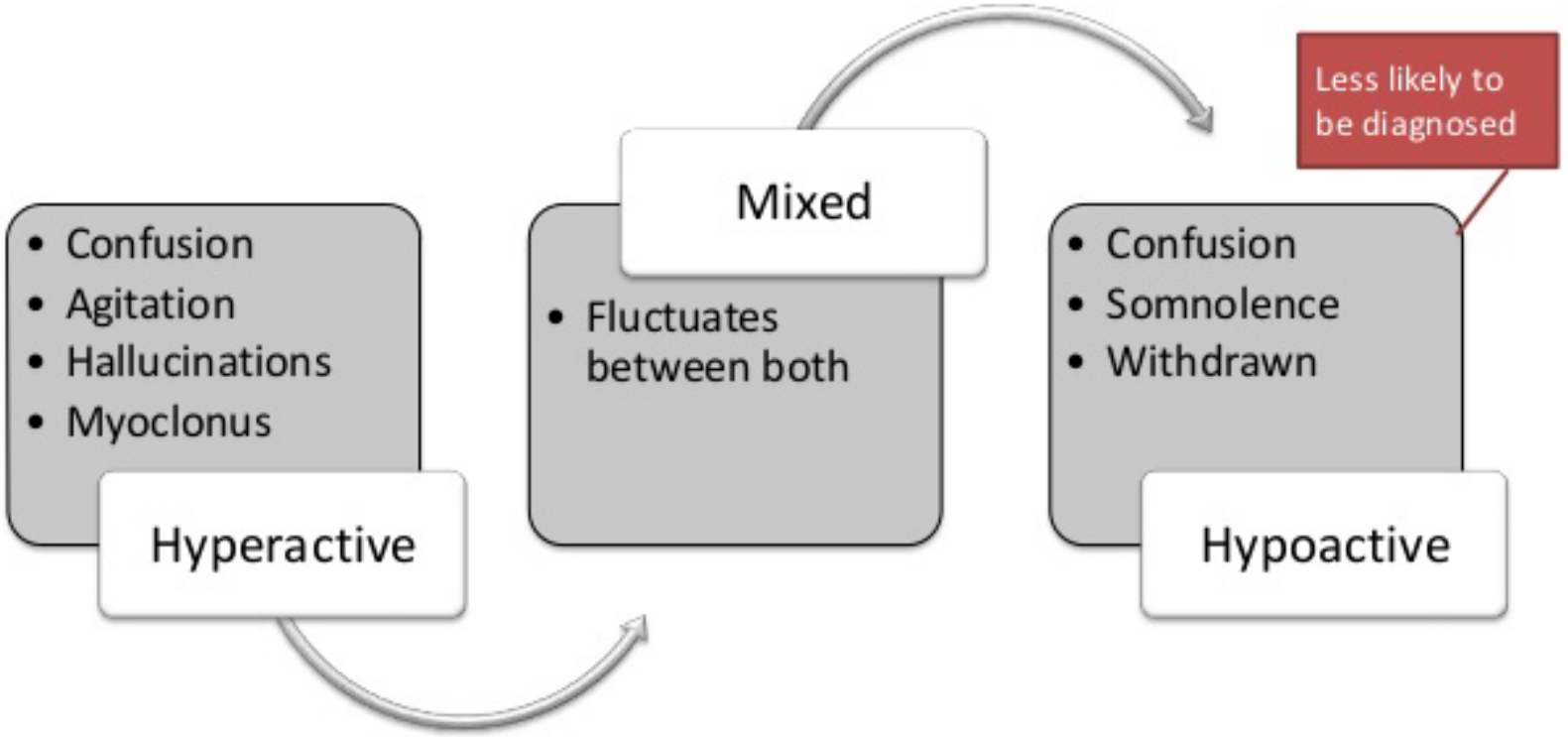
How does it manifest ?

Based on the activity level, subtypes of delirium include

- Agitated, fidgety
- Withdrawn, not responding, talking minimally, drowsy

[Meagher D. Motor subtypes of delirium: past, present and future. Int Rev Psychiatry. 2009;21:59-73]

How does it manifest ?



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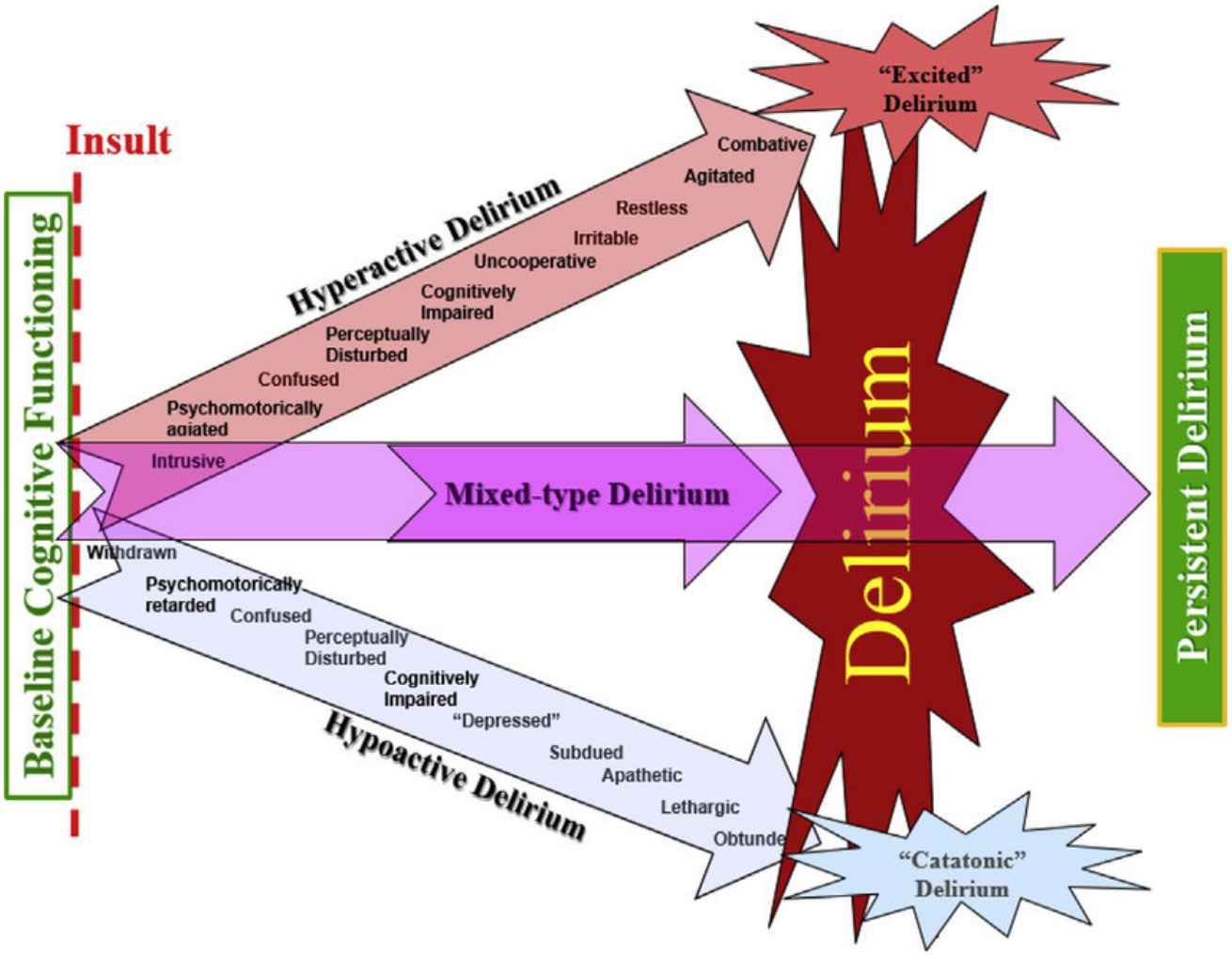
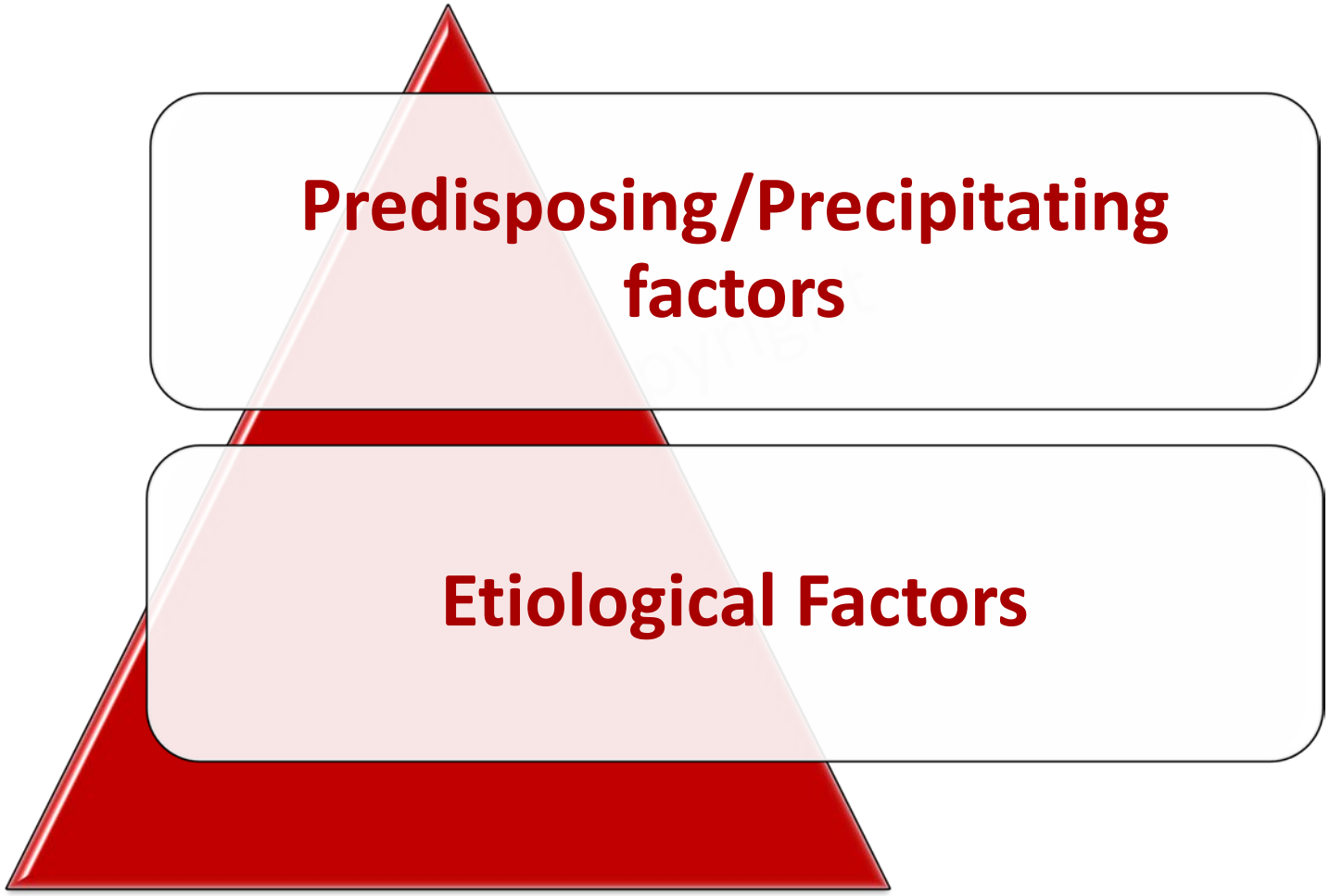
How does it manifest ?

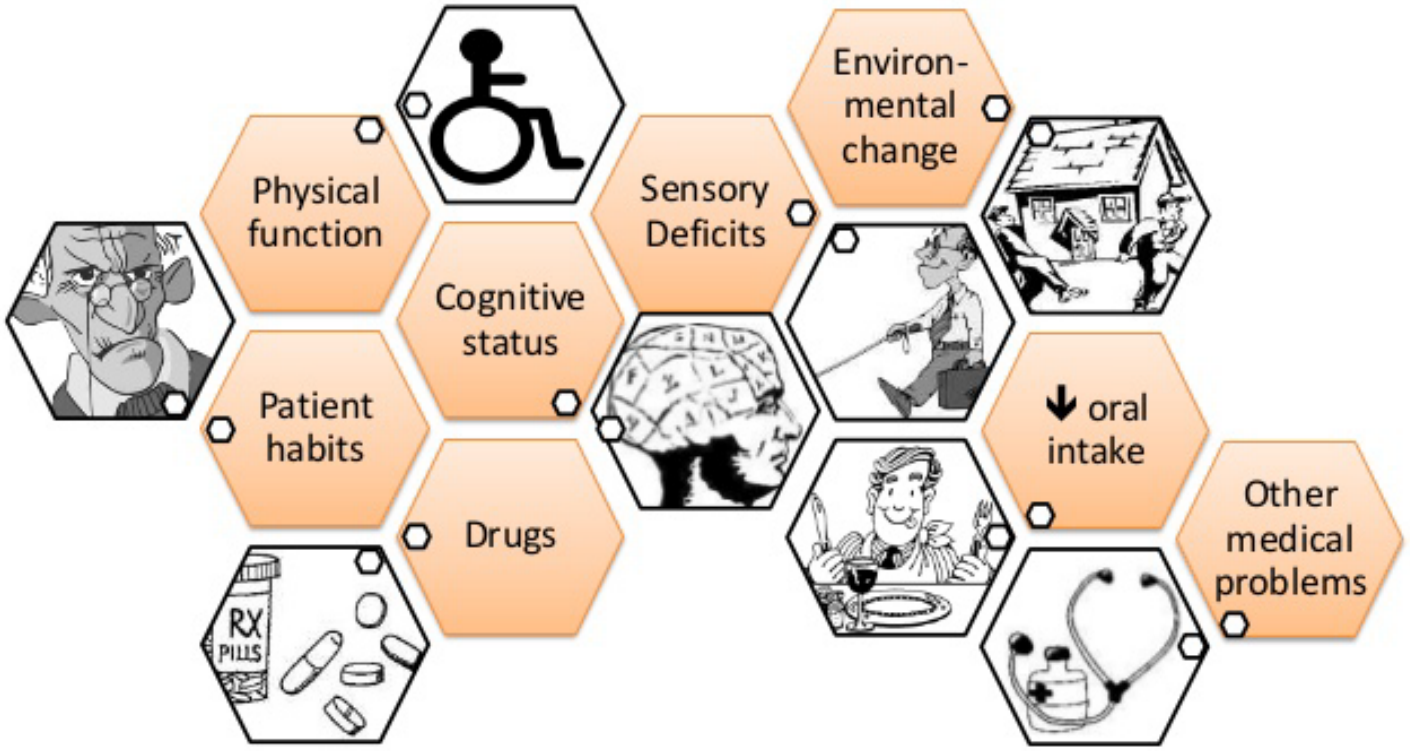


Risk factors for Delirium



Predisposing factors for Delirium

Which patients are at risk ?



Predisposing factors for Delirium

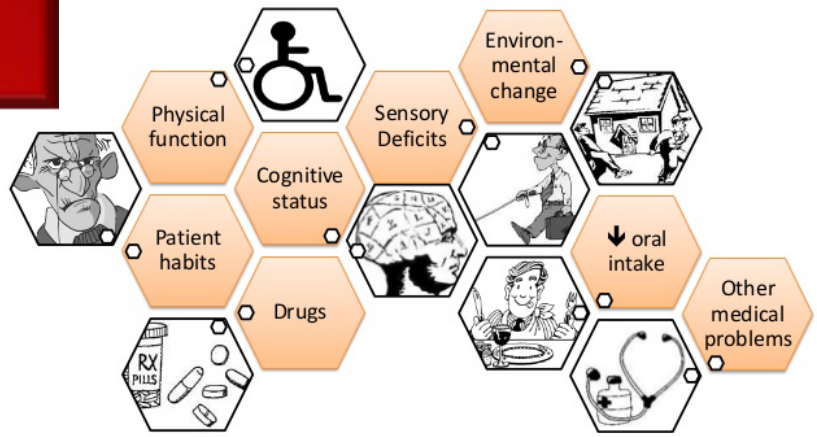
SUSPECT CAM

- **S**ensory impairment- visual
- **U**se of over the counter Medication
- **S**everity of illness
- **P**oorer functional ability
- **E**lderly
- **C**ognitive decline/dementia
- **T**reatment (prescribed drugs)

Co-morbid illnesses

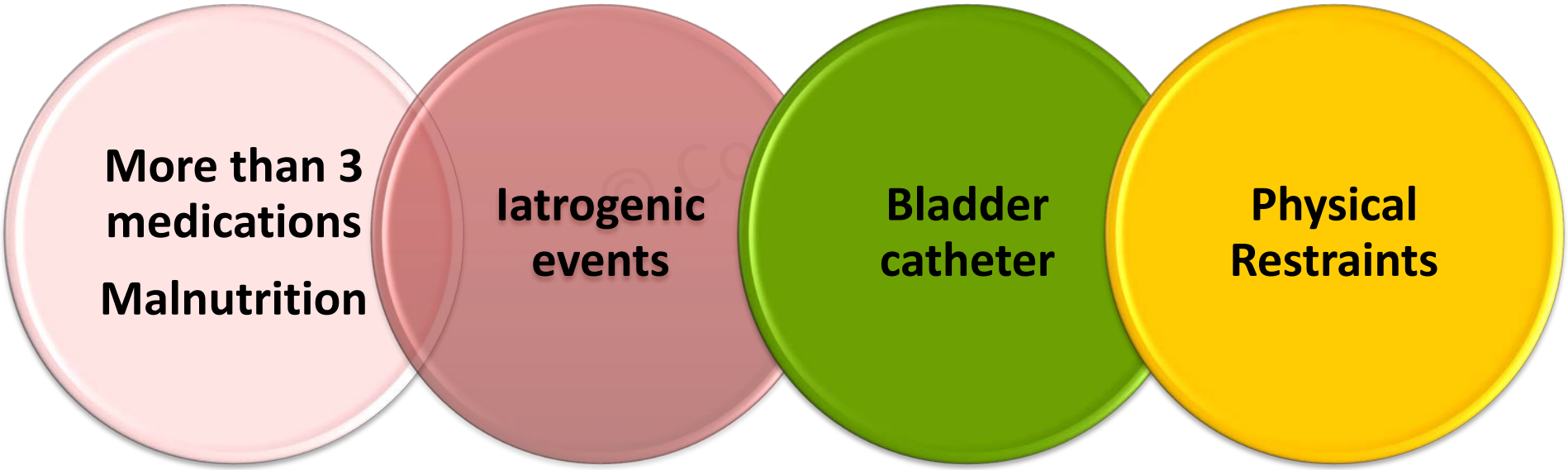
Alcohol abuse

Male gender



Precipitating factors for Delirium

3MMICR



Etiological factors for Delirium

- **I**nfections

I

- **W**ithdrawal
- **A**cute metabolic
- **T**rauma
- **C**NS pathology
- **H**ypoxia

WATCH

- **D**eficiencies (nutritional)
- **E**ndocrinopathies
- **A**cute vascular
- **T**oxins/drugs
- **H**eavy metals

DEATH

Etiological factors for Delirium

Drugs
Electrolyte Imbalance
Lack of Drugs (drug withdrawal)
Infection
Reduced sensory Inputs (visual & hearing)
Intracranial (e.g., CVA, subdural)
Urinary retention/ fecal impaction
Myocardial/ Pulmonary

Etiological factors for Delirium

Etiological factors for Delirium

Etiological factors for Delirium

Wernicke's encephalopathy

Withdrawal

Hypertensive crisis

Hypo-perfusion/hypoxia of brain

Hypoglycemia

Hyper/hypothermia

Intracranial process/ infection

Metabolic/meningitis

Poison

Status Epilepticus

Life threatening Causes of Delirium

High Risk Medications

Sedative/hypnotics

- Benzodiazepines
- Barbiturates
- Antihistamines

Anticholinergic drugs

- Oxybutynin
- TCAs
- Antipsychotics
- Warfarin
- Furosemide (Lasix)

Narcotics/opioids

Histamine blocking agents

- Ranitidine

Anticonvulsants

- Phenytoin

Antiparkinsonian agents

- Dopamine agonists
- Levodopa-carbidopa
- Benztropine

- Cumulative effect of Medications
- > 3 medications

High Risk Medications

ACUTE CHANGE IN MS

Antibiotics
Cardiac Drugs
Urinary Incontinence drugs
Theophylline
Ethanol

Insomnia Drugs
NSAIDS

Muscle relaxant
Seizure medications

Corticosteroids
H_2 Blockers
Antiparkinsonian agents
Narcotics
Geriatric psychotropic agents
ENT Drugs

Medications with Anticholinergic activity ?

- **Antiarrythmics:**
  - Disopyramide, Procainamide, Quinidine
- **Antiemetics:**
  - Dimenhydrinate, Meclizine, Trimethobenzamide, Prochlorperazine
- **Antihistamines:**
  - Azatadine, Chlorpheniramine, Clemastine, Diphenhydramine, Promethazine
- **Antiparkinson Agents:**
  - Benztropine, Biperiden, Procyclidine, Trihexyphenidyl
- **Antipsychotics:**
  - Chlorpromazine, Clozapine, Mesoridazine , Olanzapine, Promazine, Quetiapine, Thioridazine
- **Antispasmotics:**
  - Atropine, Dicyclomine, Flavoxate , Hyoscyamine, Oxybutynin, Scopolamine, Tolterodine
- **Skeletal muscle relaxants:**
  - Carisoprodal , Chlorzoxazone ,
  - Cyclobenzaprine , Methocarbamol, Orphenadrine
- **Tricyclic Antidepressants:**
  - Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline

Grading of Anticholinergic activity

Drugs with ACB Score of 1

Generic Name	Brand Name
Alimemazine	Theralen™
Alverine	Spasmonal™
Alprazolam	Xanax™
Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Nefopam	Nefogesic™
Oxcarbazepine	Trileptal™
Pimozide	Orap™

Categorical Scoring:

- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

Aging Brain Care

www.agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Medication Review

Review Medication Chart:

- **Look for the agents which can contribute to delirium- discuss with the primary physician to stop it**
- **Stop the non-required medications**

[Canadian Coalition for Seniors' Mental Health (CCSMH). National Guidelines for Seniors' Mental Health - The Assessment and Treatment of Delirium. Canadian Coalition for Seniors' Mental Health, Toronto, 2006]

Steps in Assessment & Management of Delirium

Call from a physician-surgeon

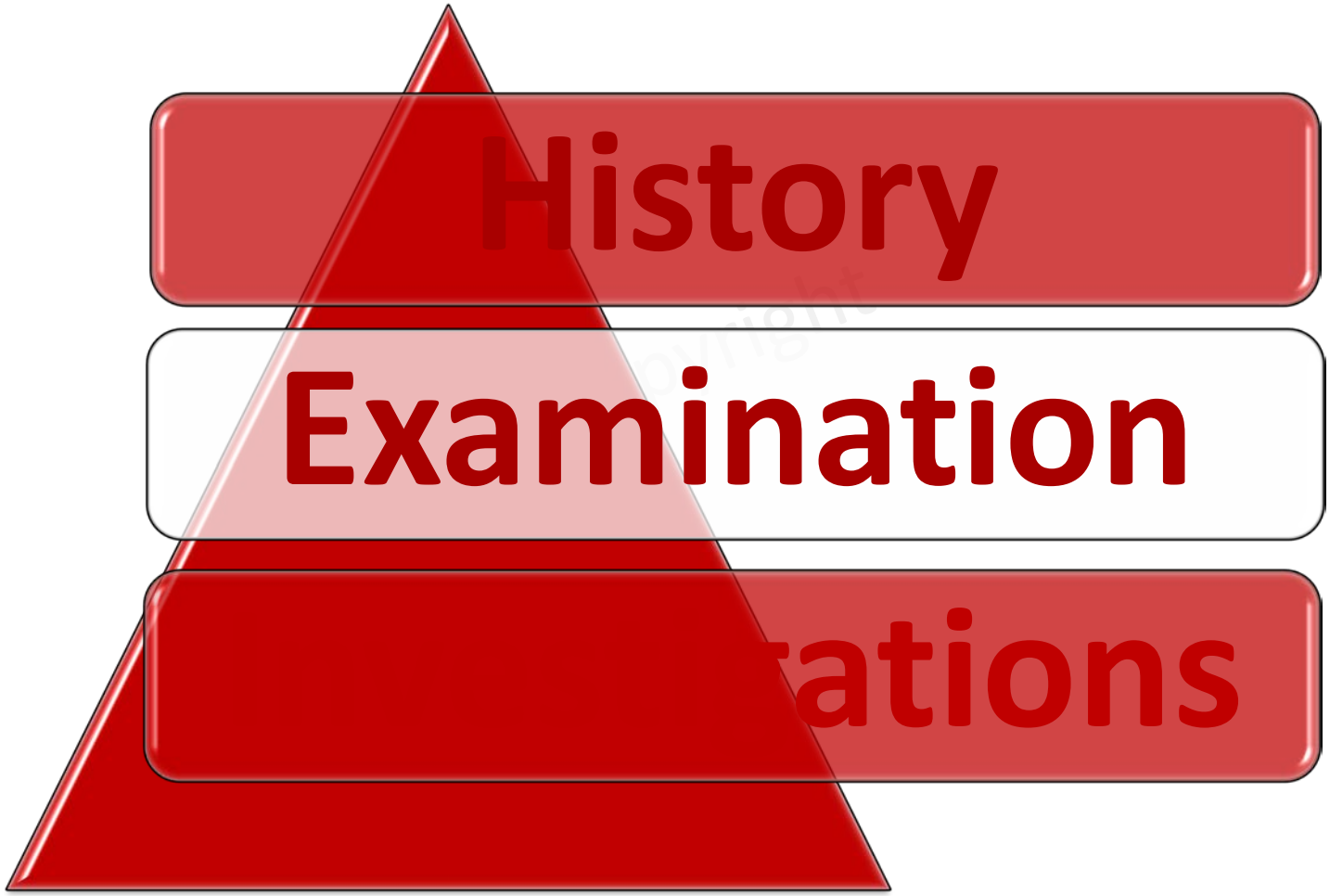
- Uncooperative patient
- Pulling out tubing
- Speaking irrelevantly
- Agitated/lethargic
- Not sleeping at night
- Misrecognition
- Disoriented
- Forgetfulness
- Hallucinating

- Ascertain the sudden change in the mental state
- Fluctuating clinical picture
- Cognitive disturbances
- Motoric disturbances/ Psychotic features

- Review the history – physical illness, any precipitating factor, medication/drug abuse history

- Diagnosis of delirium

Assessment for Delirium



Examination in a patient with Delirium

Examination

- Physical examination
- Assess hydration, nutritional status
- Evidence of sepsis
- Consider differential diagnosis
- Confirm the diagnosis
- Rate the severity of delirium
- Rate the Cognitive functions
- Rate the Subtype of delirium

[Canadian Coalition for Seniors' Mental Health (CCSMH). National Guidelines for Seniors' Mental Health - The Assessment and Treatment of Delirium. Canadian Coalition for Seniors' Mental Health, Toronto, 2006]

Examination in a patient with Delirium

Physical Examination

- **Head:** look for evidence of head trauma
- **Pupil**: fixed & dilated (Intracranial insult or raised intracranial pressure), miosis (opioids toxicity), mydriasis (anticholinergic toxicity)
- **Fundus:** papilledema
- **Extraocular movements:** ophthalmoplegia (WE), nystagmus
- **Neck:** Thyromegaly, neck rigidity
- **Neurological examination:** focal deficits
- **Skin:** fever, dehydration, injection marks, marks of use of patches, evidence of liver dysfunction etc

Han & Suyama. Delirium and Dementia. Clin Geriatr Med 2018; 34: 327–354

Examination in a patient with Delirium

Physical Examination

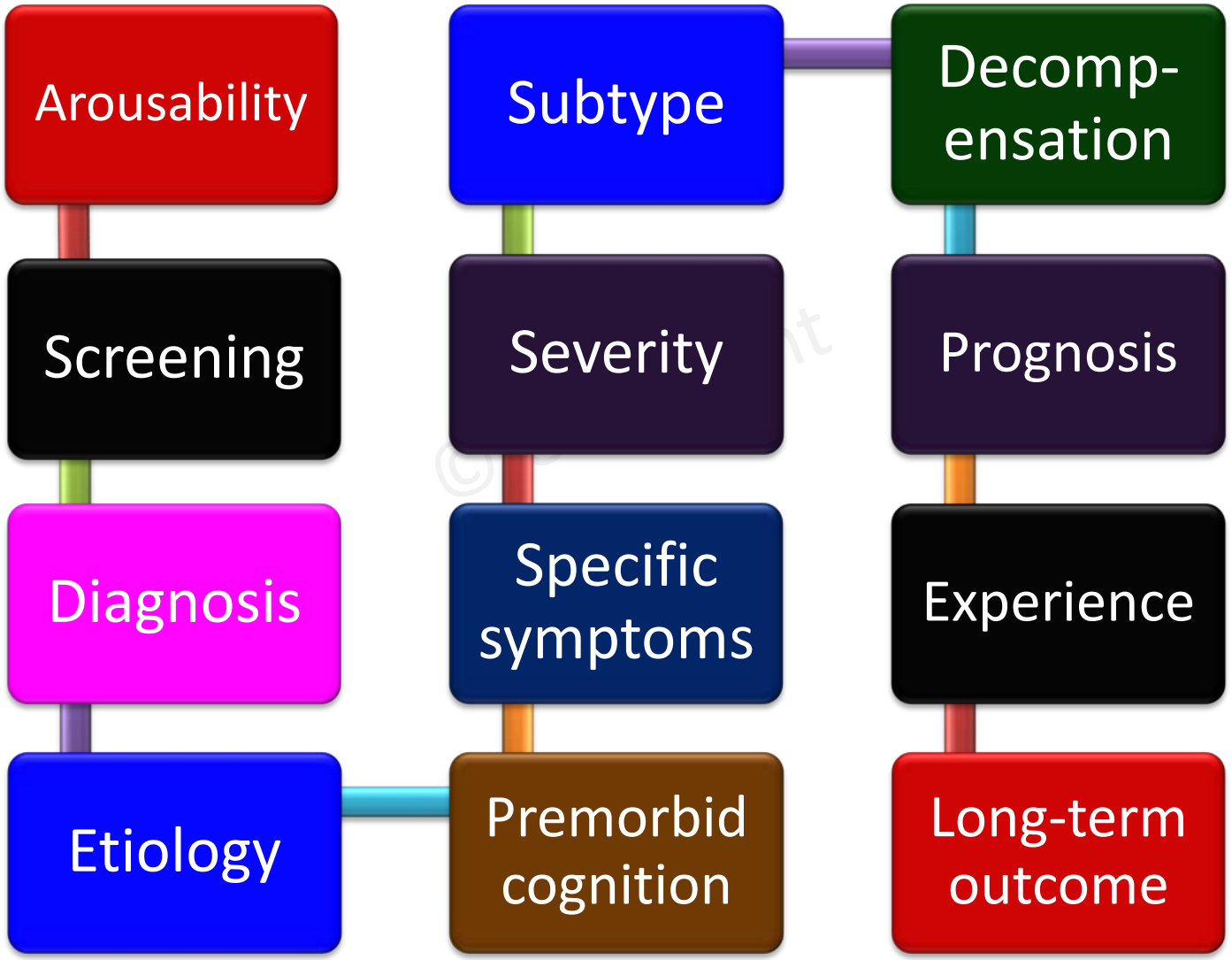
- **Lungs:** crepts, wheeze
- **Cardiac:** murmur
- **Abdomen:** mass, tenderness
- **Genitourinary:** urinary retention, local discharge
- **Rectum:** faecal mass, haemorrhoids etc

Han & Suyama. Delirium and Dementia. Clin Geriatr Med 2018; 34: 327–354

Assessment for Delirium

- Assessment of arousability
- Screening for premorbid cognitive disturbances
- Scales for screening for delirium
- Diagnostic instrument
- Scale for severity rating
- Scale for cognitive functions
- Scale for assessment of motor activity
- Scale for assessment of etiologies
- Scale for assessment of experience/distress due to symptoms of delirium
- Scales to assess severity of physical illnesses

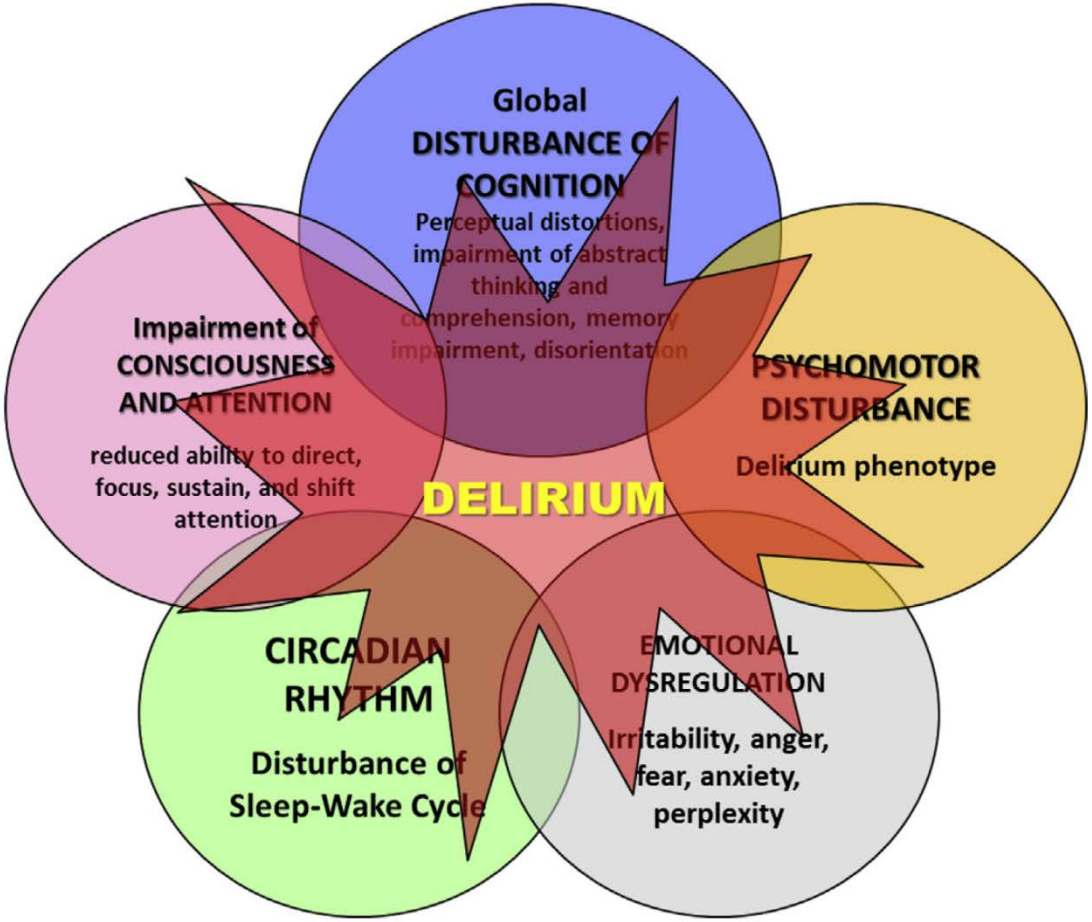
What all do you need to rate



Scales for Delirium

Instruments for assessment of arousability of the patient	Richmond Agitation and Sedation Scale (RASS)
Instruments for screening for premorbid cognitive disturbances	Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
Screening instruments	NEECHAM Confusion Scale Nursing Delirium Screening Scale (Nu-DESC) Delirium Observation Screening Scale (DOSS) Delirium Observation Scale (DOS) Intensive care delirium screening checklist (ICDSC) Pediatric Anesthesia Emergence Delirium (PAED) scale Global Attentiveness Rating
Diagnostic instruments	Delirium Symptom Interview Saskatoon Delirium Checklist Delirium Rating Scale-revised version (DRS-R-98) Memorial Delirium Assessment Scale (MDAS) Confusion Assessment Method (CAM) Confusion Assessment Method for Intensive Care Unit assessment tool (CAM-ICU) Paediatrics CAM-ICU Clinical Assessment of Confusion – A and B (CAC- A and B)
Instruments for Assessment of severity of delirium	Delirium Rating Scale Delirium Rating Scale-Revised-98 Confusion Assessment Method (CAM) Confusion Assessment Method for Intensive Care Unit assessment tool (CAM-ICU) Delirium-O-Meter Delirium Index Memorial Delirium Assessment Scale (MDAS) Confusional State Evaluation (CSE) Scale Delirium Assessment Scale Delirium Severity Scale
Instruments for assessment of cognitive symptoms only	Mini Mental Status Examination (MMSE) Cognitive Test for Delirium (CTD) Clock Drawing test Digit Span Test Vigilance “A” Test Mental state Questionnaire (MSQ) Short Portable Mental Status Questionnaire (SPMSQ)
Motor symptoms	Delirium Motor Checklist, Delirium Motor Symptom Scale Richmond Agitation and Sedation Scale (RASS) Motoric items of DRS, DRS-R-98, MDAS
Etiology, risk factors	Delirium Etiology Checklist
Paediatric delirium	Pediatric Anesthesia Emergence Delirium (PAED) scale
Distress with delirium experience	Delirium Experience Questionnaire
Instruments for assessment of severity of physical illness and prediction of mortality	Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores Glasgow Coma scale (GCS) Sequential Organ Failure Assessment score (SOFA score) Simplified Acute Physiology Score (SAPS-II & III) Charlson Comorbidity index Paediatric Index of Mortality (PIM)

How to Diagnose



Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management & Sequelae of Delirium. Crit Care Clin. 2017; 33: 461-519.

Nosology: DSM-5

- **A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)**
- **B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day**
- **C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)**
- **D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma**
- **E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies**

[DSM-5]

Nosology: DSM-5

DSM-IV	DSM-5
A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.	A. A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day	B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.	C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
	D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.	E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies.

[DSM-5]

Nosology: ICD-10

Box 3.1 The ICD–10 criteria features of delirium (World Health Organization, 1992)

Impairment of consciousness and attention (on a continuum from clouding to coma; reduced ability to direct, focus, sustain and shift attention)

Global disturbance of cognition (perceptual distortions, illusions and hallucinations most often visual; impairment of abstract thinking and comprehension with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and of recent memory but with relatively intact remote memory; distortion of time as well as, in more severe cases, of place and person)

Psychomotor disturbances (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction)

Disturbance of the sleep-wake cycle (insomnia or, in severe cases, total sleep loss or reversal of the sleep–wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares which may continue as hallucinations after awakening)

Emotional disturbances, (e.g. depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity)

How to Diagnose

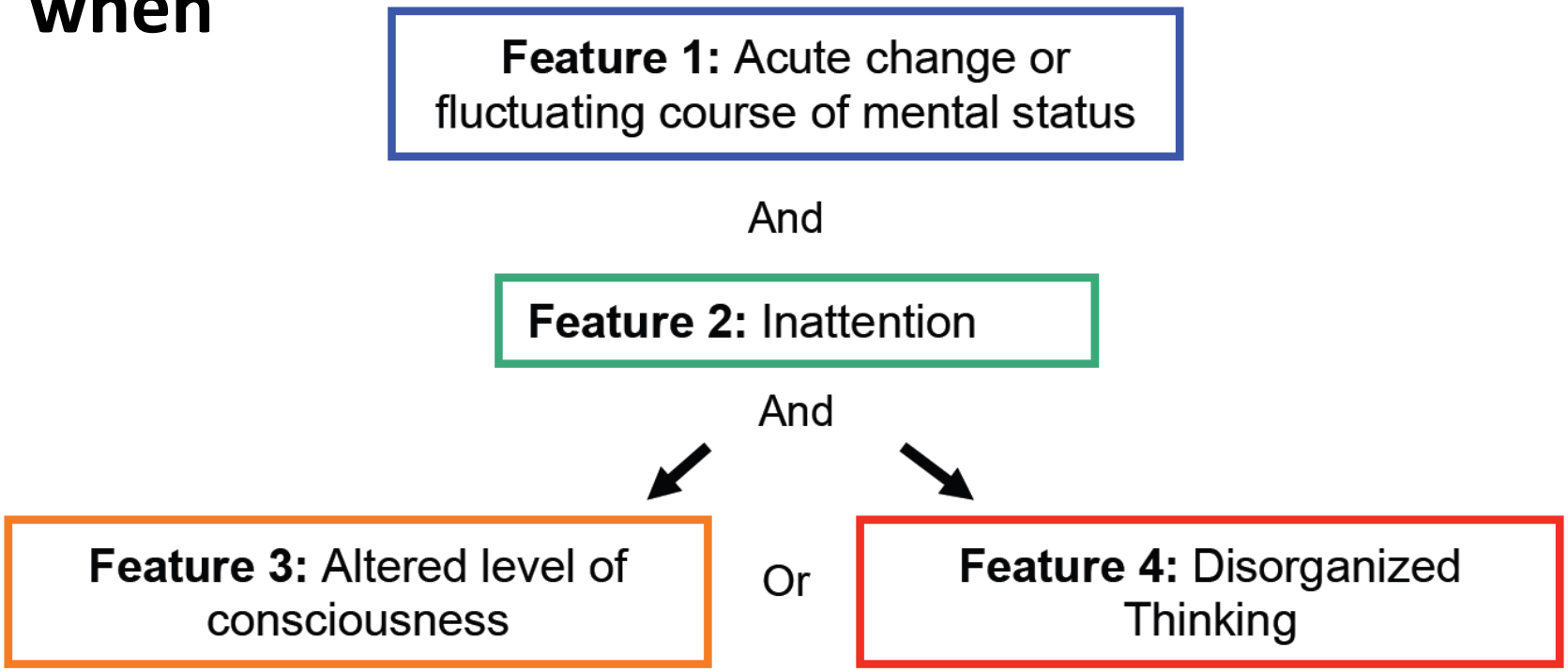
- Many screening and diagnostic instruments are available, depending on the treatment setting (ICU/Non-ICU set-up), age etc
- Most popular
  - CAM
  - CAM-ICU
  - DRS-R-98

Confusion Assessment Method (CAM)

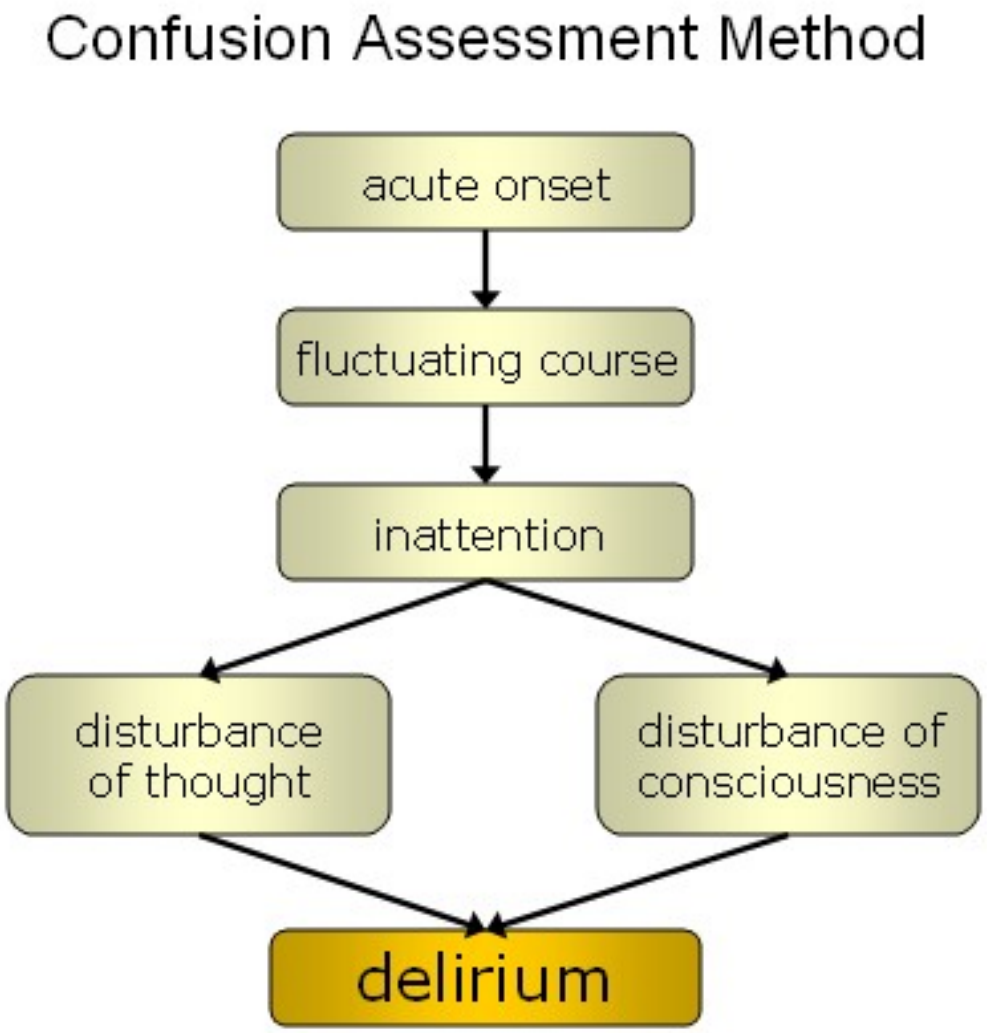
- **Confusion Assessment Method (CAM) designed by Sharon Inouye in 1990**
- **Bedside assessment tool usable by non-psychiatrists by to assess for delirium**
- **The CAM-ICU is an adaptation of this tool for use in ICU patients (e.g., critically ill patients on or off the ventilator)**

Confusion Assessment Method (CAM)

- **Delirium is defined in terms of four diagnostic features, and is deemed positive when**



Confusion Assessment Method (CAM)



[Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-948]

Confusion Assessment Method (CAM)

Confusion Assessment Method

Feature 1: Acute Onset and Fluctuating Course	Obtained from a family member or nurse: • Is there evidence of an acute change in mental status from the patient's baseline? • Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2: Inattention	• Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3: Disorganized thinking	• Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4: Altered Level of consciousness	• Overall, how would you rate this patient's level of consciousness? alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

[Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-948]

Confusion Assessment Method (CAM)

Table 2

Confusion Assessment Method for the diagnosis of delirium

Criteria	Evidence
1. Acute change in mental status, **AND**	Observation by a family member, caregiver, or primary care physician
2. Symptoms that fluctuate over minutes or hours, **AND**	Observation by nursing staff or other caregiver
3. Inattention	Patient history Poor digit recall, inability to recite months of the year backwards
PLUS	
4. Altered level of consciousness, **OR**	Hyperalertness, drowsiness, stupor, or coma
5. Disorganized thinking	Rambling or incoherent speech

Note: The first 3 criteria plus criterion 4 or 5 must be present to confirm a delirium diagnosis

Source: Reference 5

[Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941-948]

CAM-ICU

First-Step of Assessment

- **The first step to** assess **level of consciousness**
- **This is best done using a validated** sedation/level of consciousness scale
- The Richmond Agitation-Sedation Scale **(RASS)**

CAM-ICU

First-Step of Assessment

Scale	Label	Description
+4	COMBATIVE	Combative, violent, immediate danger to staff
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive
+2	AGITATED	Frequent non-purposeful movement, fights ventilator
+1	RESTLESS	Anxious, apprehensive, movements not aggressive
0	ALERT & CALM	Spontaneously pays attention to caregiver
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact)

VOICE

If RASS is ≥ -3 proceed to CAM-ICU (Is patient CAM-ICU positive or negative?)

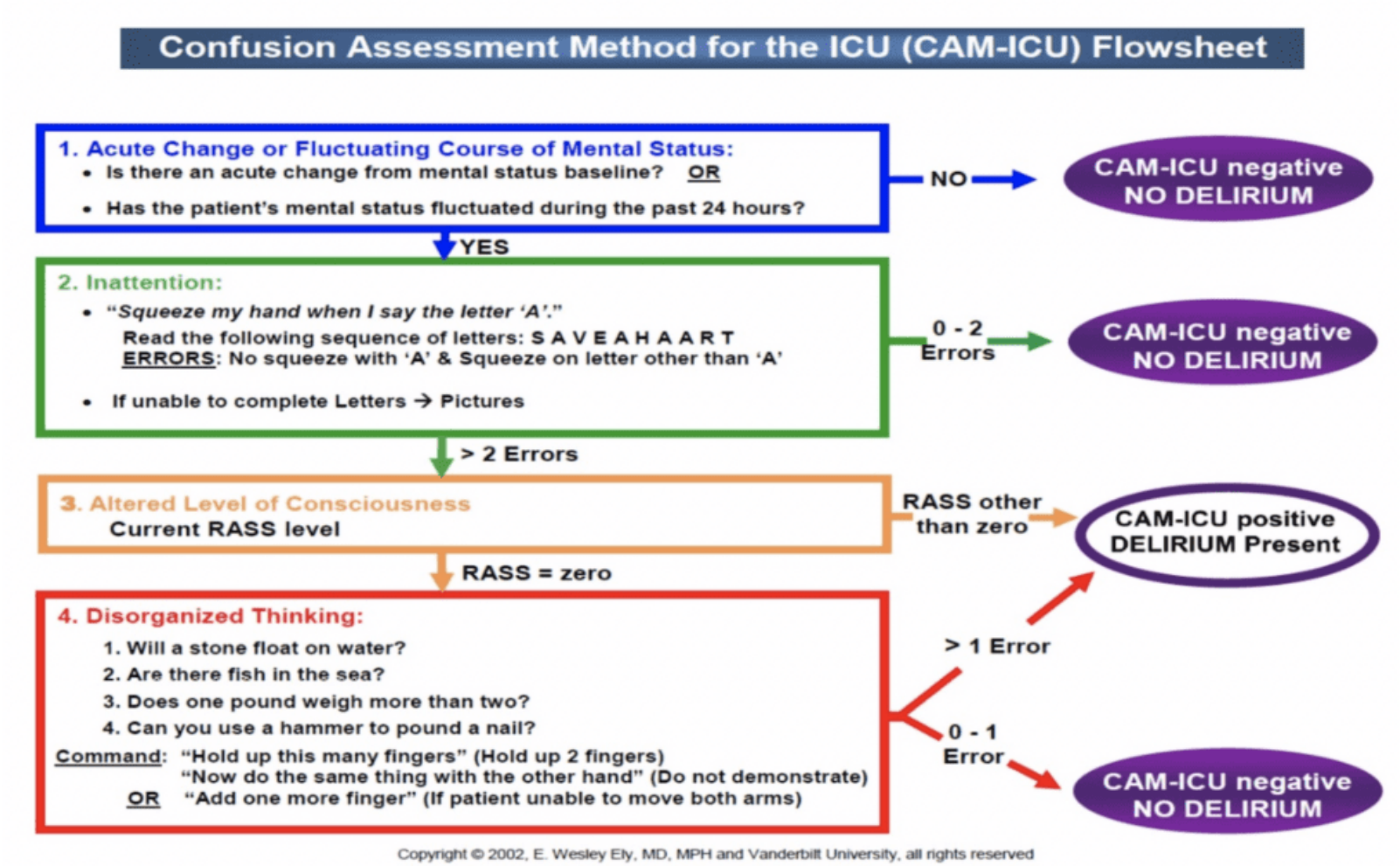
-4	DEEP SEDATION	No response to voice, but movement or eye opening to physical stimulation
-5	UNAROUSABLE	No response to voice or physical stimulation

TOUCH

If RASS is -4 or -5 → STOP (patient unconscious), RECHECK later

CAM-ICU

Assessment on CAM-ICU



CAM-ICU

Inattention

2. Inattention:

- "*Squeeze my hand when I say the letter 'A'.*"

  Read the following sequence of letters: S A V E A H A A R T
  ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'

- **If unable to complete Letters → Pictures**

Read at the rate of a letter @ 3 sec

Scoring: Errors are counted when the patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A"

CAM-ICU

Inattention

2. Inattention:

- "*Squeeze my hand when I say the letter 'A'.*"

  Read the following sequence of letters: S A V E A H A A R T
  ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'

- If unable to complete Letters → Pictures

- **If the patient never squeezed then the patient is inattentive**
- **Also be suspicious for inattention when you have to repeat the instructions more than twice**

CAM-ICU

Inattention

2. Inattention:

- "*Squeeze my hand when I say the letter 'A'.*"

  Read the following sequence of letters: S A V E A H A A R T
  ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'

- If unable to complete Letters → Pictures

- One way to think about this is if there is eye opening or movement to voice, then the "lights are on"
- These concepts also apply to a patient who is agitated (i.e., RASS +1 thru +4) and therefore not participating in assessment or comprehending your instructions

CAM-ICU

Inattention

अक्षर ध्यान परिक्षण (पर्याय तस्वीरों के लिए प्रशिक्षण पुस्तिका देखें)

दिशानिर्देश- रोगी से कहें " मैं आपको १० अक्षरों की एक श्रृंखला पढ़कर सुनाऊंगा| उसमें से आप जब भी 'अ' अक्षर सुने, तब मेरा हाथ दबाकर बताए|

निम्नलिखित अक्षर सूचि में से अक्षरों को ३ सेकंड के अंतर पर सामान्य आवाज में पढ़े|

स अ व इ अ ह अ अ र त

त्रुटियाँ गिनी जाती है जब रोगी 'अ' अक्षर पर हाथ न दबाए एवं 'अ' अक्षर से भिन्न अक्षरों पर हाथ दबाए|

Scoring: Errors are counted when the patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A"

CAM-ICU

Inattention

- I am going to show you pictures of some common objects
- Watch carefully and try to remember each picture because I will ask what pictures you have seen

Pictures

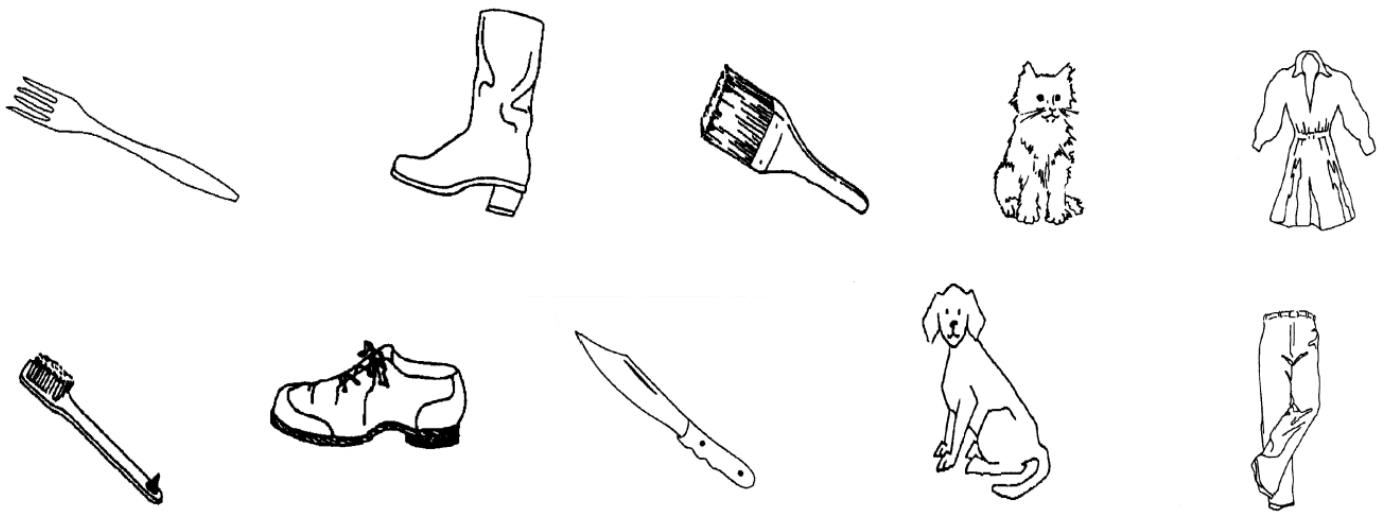
Step 1

CAM-ICU

Inattention

- Now I am going to show you some more pictures
- Some of these you have already seen and some are new
- Let me know whether or not you saw the picture before by nodding your head yes (demonstrate) or no (demonstrate)

Step 2

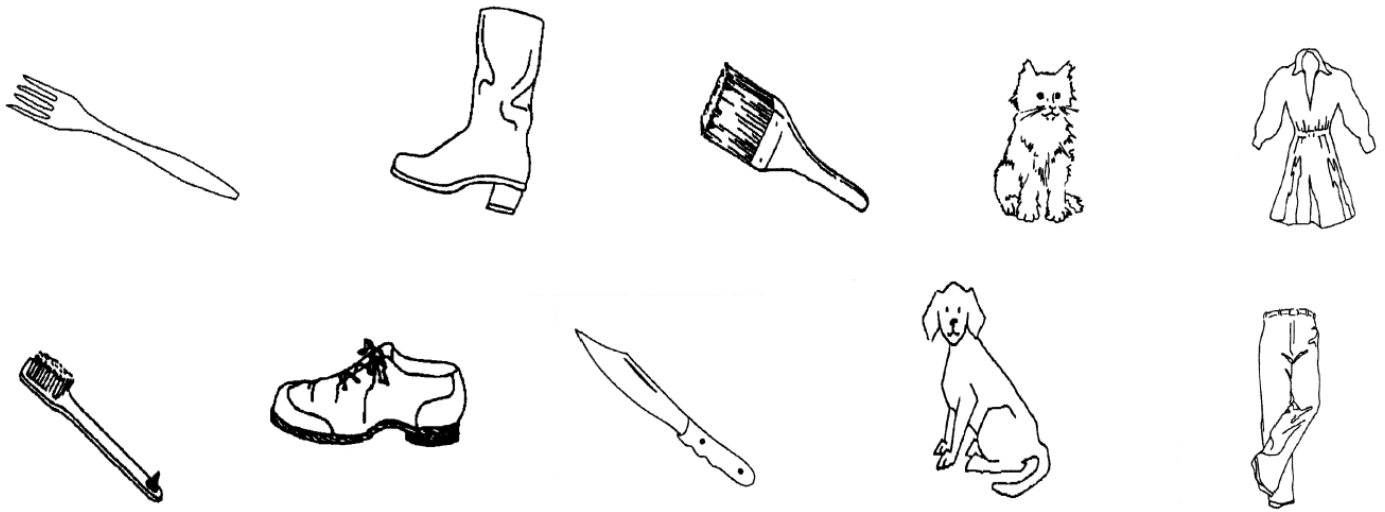


CAM-ICU

Inattention

- Then show 10 pictures (5 new 5 repeat) for 3 seconds each (Step 2 of Packet A or B, depending upon which form was used in Step 1 above)

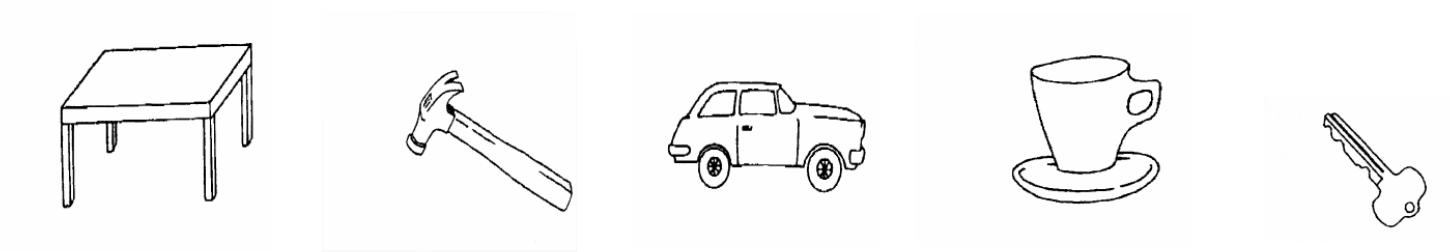
Step 2



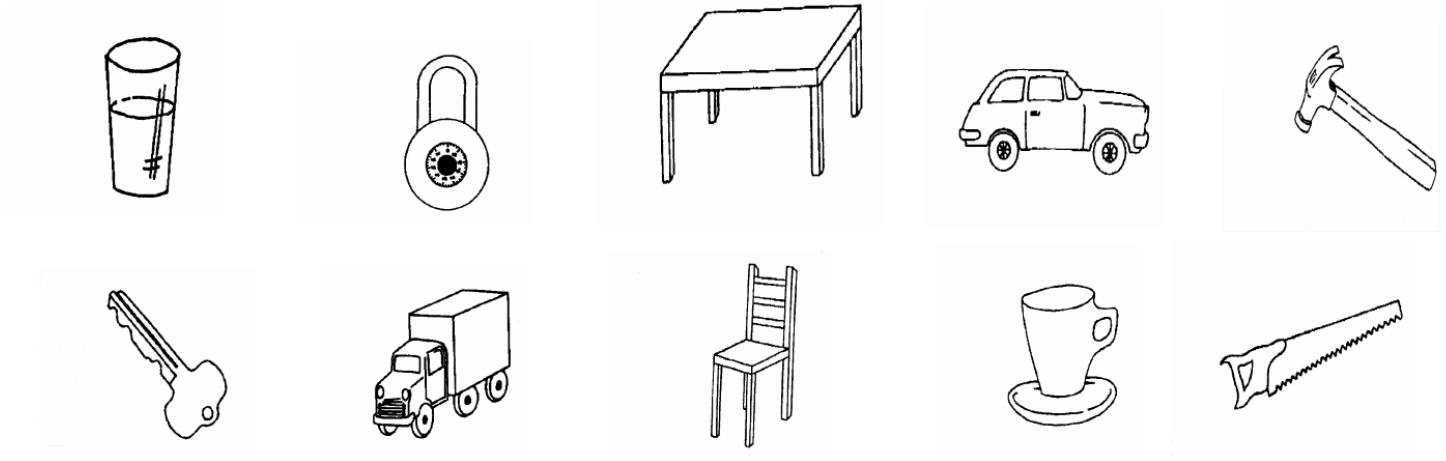
CAM-ICU

Inattention

Step 1



Step 2



CAM-ICU

Inattention

- Scoring: Errors are counted with the patient incorrectly indicates ‘yes’ or ‘no’ for a picture during the second step
- In order to improve the visibility for elderly patients, the images are printed on 6”x10” buff-colored paper and laminated with a matte finish

CAM-ICU

Disorganized Thinking

- If Features 1 & 2 are absent, you do not need to proceed with this Feature

4. Disorganized Thinking:

1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weigh more than two pounds?
4. Can you use a hammer to pound a nail?

Command: "Hold up this many fingers" (Hold up 2 fingers)
"Now do the same thing with the other hand" (Do not demonstrate)
Or: "Add one more finger" (If patient is unable to move both arms)

CAM-ICU

Disorganized Thinking

<u>हाँ /ना सवाल</u> (पर्याय प्रश्नावली के लिए प्रशिक्षण पुस्तिका देखें)

१. क्या एक पत्थर पानी में तैरेगा?

२. क्या समुद्र में मछलियाँ होती है?

३. क्या एक पाउंड वजन दो पाउंड से ज्यादा होता हैं?

४. क्या आप खिला ठोकने के लिए हतोड़े का इस्तमाल कर सकते है?

त्रुटियाँ गिनी जाती है रोगी सवालों का गलत जबाब देता हैं|

आदेश:- रोगी से कहे "इतने अंगुलियाँ उठेएं" (रोगी से सामने डॉ अंगुलियाँ उठएं)

"अब यही चीज दुसरे हाथ से करें" (अंगुलियों की संख्या को दोहराएँ नहीं)

* यदि रोगी दोनों हाथो को हिलाने में असमर्थ है तो, आदेश के दुसरे भाग के लिए रोगी को यह कहें "एक और अंगुली जोड़ दें"

CAM-ICU

Disorganized Thinking

- Alternate Questions
- Will a leaf float on water?
- Are there elephants in the sea?
- Do two pounds weigh more than one?
- Can you use a hammer to cut wood?

CAM-ICU

Disorganized Thinking

- If a patient cannot move his/her arms or is blind, score solely on Feature 4 questions
- Therefore, Feature 4 is present if the patient misses more than one question (>1 error)

CAM-ICU

STEP 1 - RASS

What is her current RASS Score? ____

Proceed with Step 2 – CAM-ICU assessment?

☐ **Yes** (it is possible to assess delirium at this level)

☐ **No** (the patient is comatose and cannot be assessed for delirium)

STEP 2 - CAM - ICU

Feature 1: Acute Change or Fluctuating Course of Mental Status

Is there an acute change from mental status baseline? Yes ☐ No ☐

Has mental status fluctuated during the past 24 hours? Yes ☐ No ☐

Feature 1: Present ☐ Absent ☐

Proceed with Feature 2? Yes ☐ No ☐

Feature 2: Inattention

Letters > 2 Errors: Yes ☐ No ☐

Pictures > 2 Errors: Yes ☐ No ☐ Not needed ☐

Feature 2: Present ☐ Absent ☐

Proceed with Feature 3? Yes ☐ No ☐

Feature 3: Altered Level of Consciousness

Current RASS (Think back to level of consciousness assessment in Step 1)

Feature 3: Present ☐ Absent ☐

Proceed with Feature 4? Yes ☐ No ☐

Feature 4: Disorganized Thinking

Combined number of Errors > 1 Yes ☐ No ☐

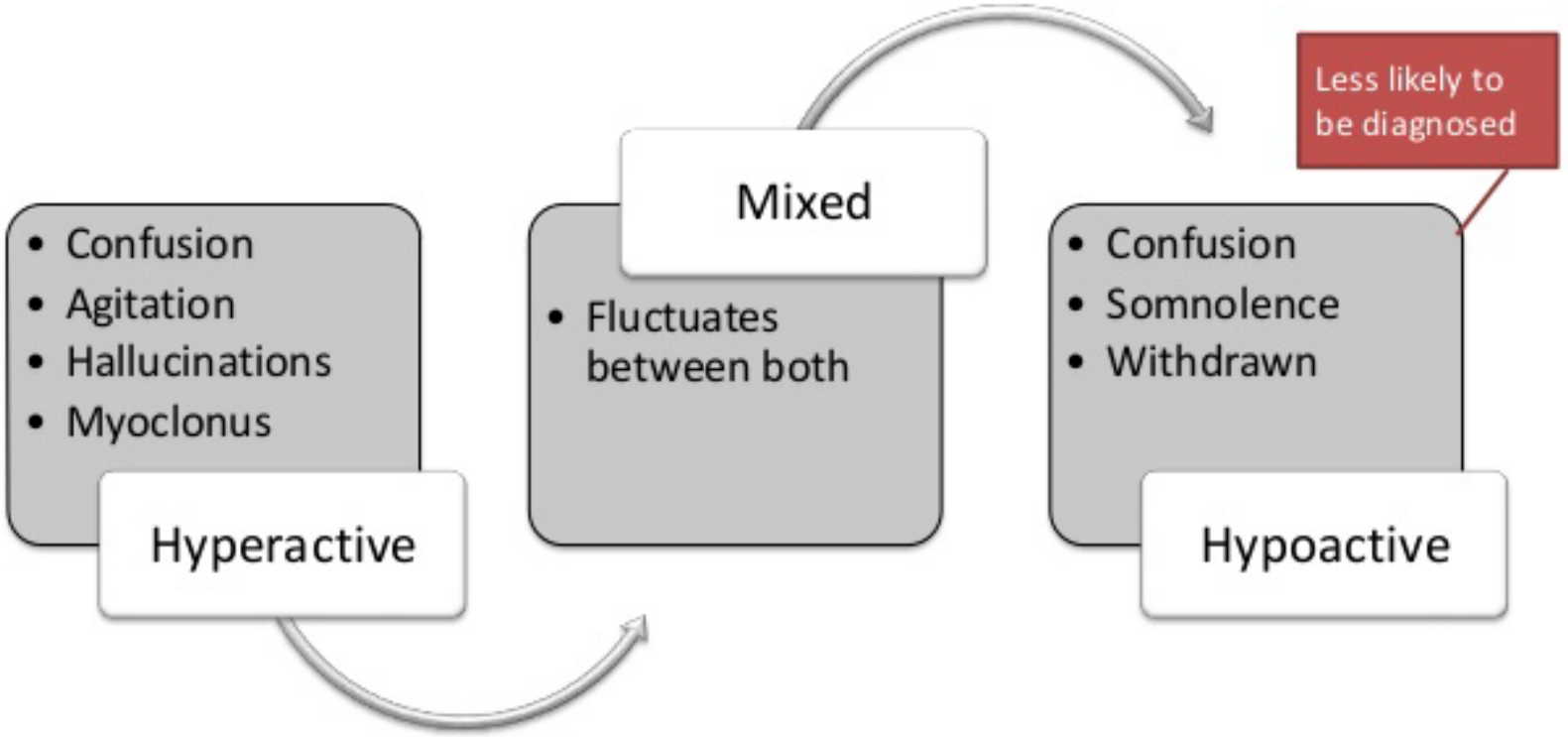
Feature 4: Present ☐ Absent ☐

Overall CAM-ICU:

☐ **Positive (Feature 1 and 2 and either 3 or 4 present)**

☐ **Negative**

How to assess the subtypes ?



[Meagher D. Motor subtypes of delirium: past, present and future. Int Rev Psychiatry. 2009;21:59-73]

How to assess the subtypes ?

Hyperactive Subtype if definite evidence in the previous 24 hours of (and this should be a deviation from pre-delirious baseline) at least two of:

- Increased quantity of motor activity
- Loss of control of activity
- Restlessness
- Wandering

Hypoactive Subtype if definite evidence in the previous 24 hours of (and this should be a deviation from pre-delirious baseline) two or more of:*

- Decreased amount of activity
- Decreased speed of actions
- Reduced awareness of surroundings
- Decreased amount of speech
- Decreased speed of speech
- Listlessness
- Reduced alertness/withdrawal

*Where at least one of either decreased amount of activity or speed of actions is present

Mixed Motor Subtype if evidence of both hyperactive and hypoactive subtype in the previous 24 hours

No Motor Subtype if evidence of neither hyperactive or hypoactive subtype in the previous 24 hours

[Meagher, D., Moran, M., Raju, B., et al. (2008a). A new data-based motor subtype schema for delirium. The Journal of Neuropsychiatry and Clinical Neurosciences, 20(2), 185–193]

How to assess the subtypes ?

Delirium Motor Subtype Scale (DMSS)

Hyperactive Subtype if definite evidence in the previous 24 hours of (and this should be a deviation from the pre-delirious baseline) at least two of the following:

- **Increased quantity of motor activity**
- **Loss of control of activity**
- Restlessness
- Wandering

- **Mixed Motor Subtype if evidence of both hyperactive and hypoactive subtype in the previous 24 hours**
- **No Motor Subtype if evidence of neither hyperactive or hypoactive subtype in the previous 24 hours**

Hypoactive Subtype if definite evidence in the previous 24 hours of (and this should be a deviation from pre-delirious baseline) two or more of the following:*

- Decreased amount of activity
- **Decreased speed of actions**
- Reduced awareness of surroundings
- **Decreased amount of speech**
- Decreased speed of speech
- Listlessness
- Reduced alertness/withdrawal

* Where at least one of either decreased amount of activity or speed of actions is present.

[Meagher D. Motor subtypes of delirium: past, present and future. Int Rev Psychiatry. 2009;21:59-73]

Differential Diagnosis

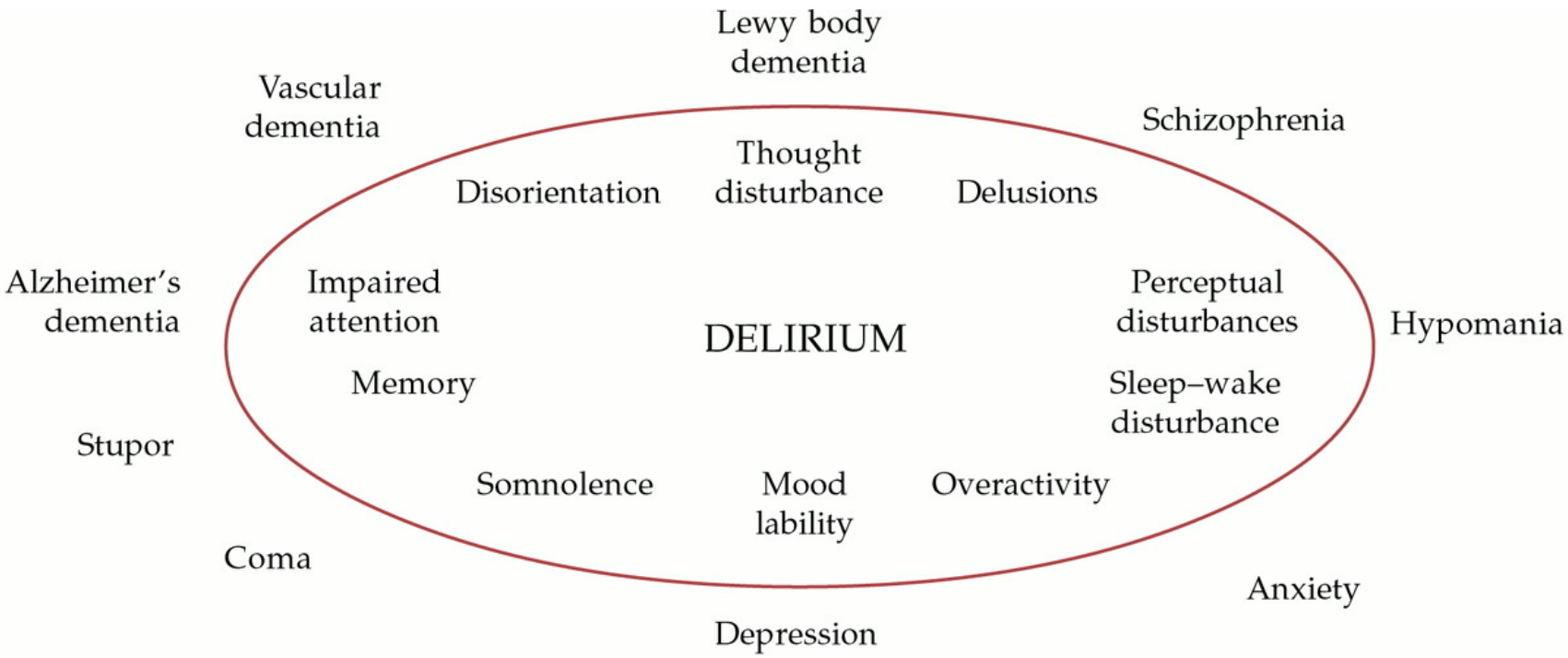


Fig. 1 The differential diagnosis of delirium reflects its broad symptom profile

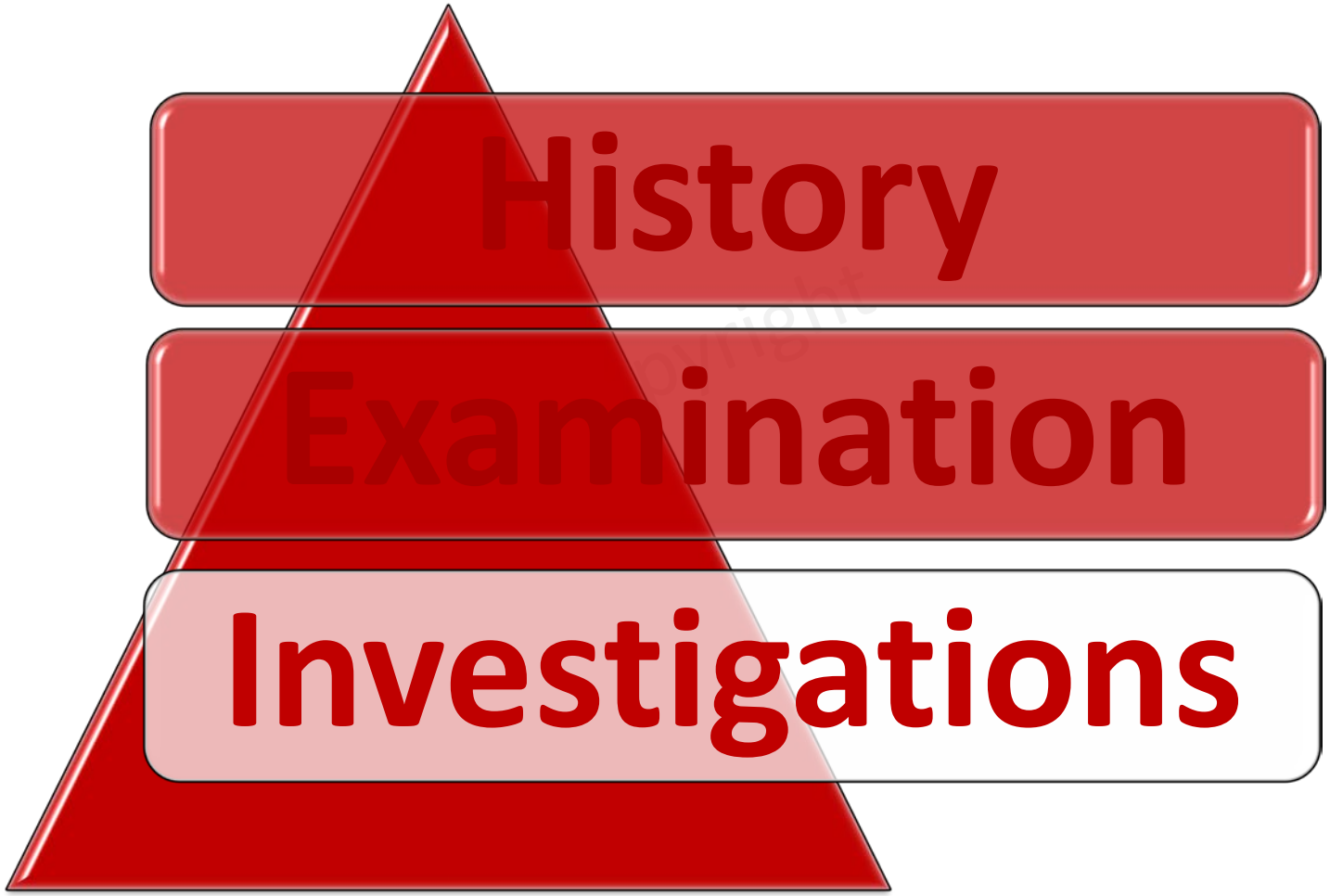
[Meagher D. Delirium: the role of psychiatry. Advances in Psychiatric Treatment 2001; 7: 433–443]

Differential Diagnosis

Features	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious	Variable	Variable
Consciousness	Marked Fluctuations	Clear till late stages	Generally no impairment	Generally no impairment
Attention	Impaired	Impairment-late stages	Poor attention	Poor attention
Orientation	Disoriented	Disoriented – later stages	Usually oriented	Usually oriented
Memory	Poor short term memory	Poor short & Long term memory	Usually intact	Usually intact
Diurnal fluctuation	Fluctuations common	May be present	Morning worsening	Usually not seen
Psychotic Sx	Fleeting, simple	Less common	Less common	Persistent, complex
Hallucinations	V>A; T	Usually absent	If present, A	Mostly A
Mood	Fluctuating	Flat, apathetic	Sadness	Apathy/flat

[Mattoo SK, Grover S, Gupta N. Delirium in General Practice. Indian J Med Res 2010; 131: 387-398]

Assessment for Delirium

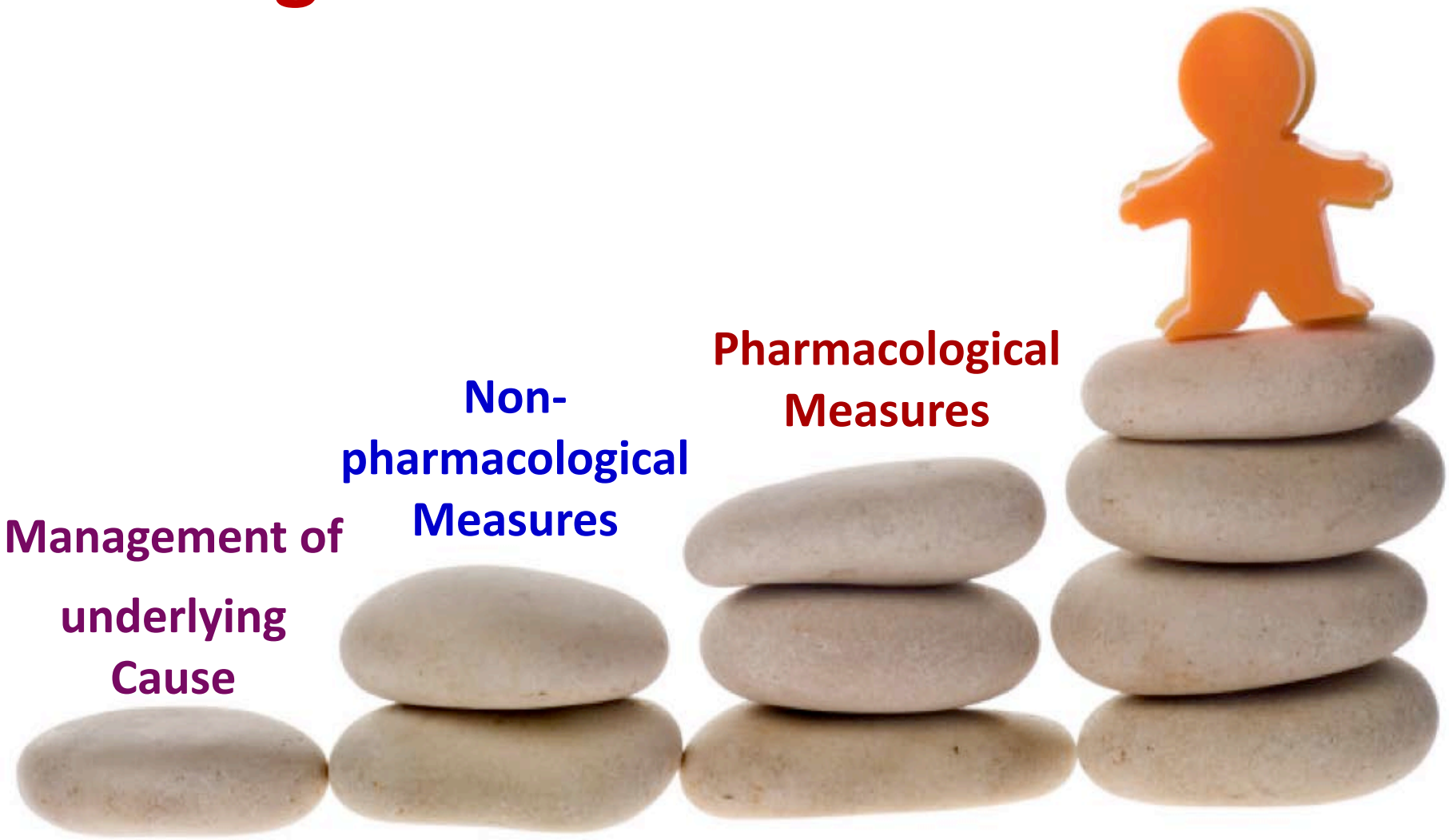


Assessment for Delirium

Investigations:

- Routine investigations- to rule out other causes
- Basic investigations like serum electrolytes, RFT, LFT, Haemogram, ABG – must
- Other investigations – as indicated
- If required – neuroimaging, EEG
- Monitor the abnormalities closely

Management of Delirium

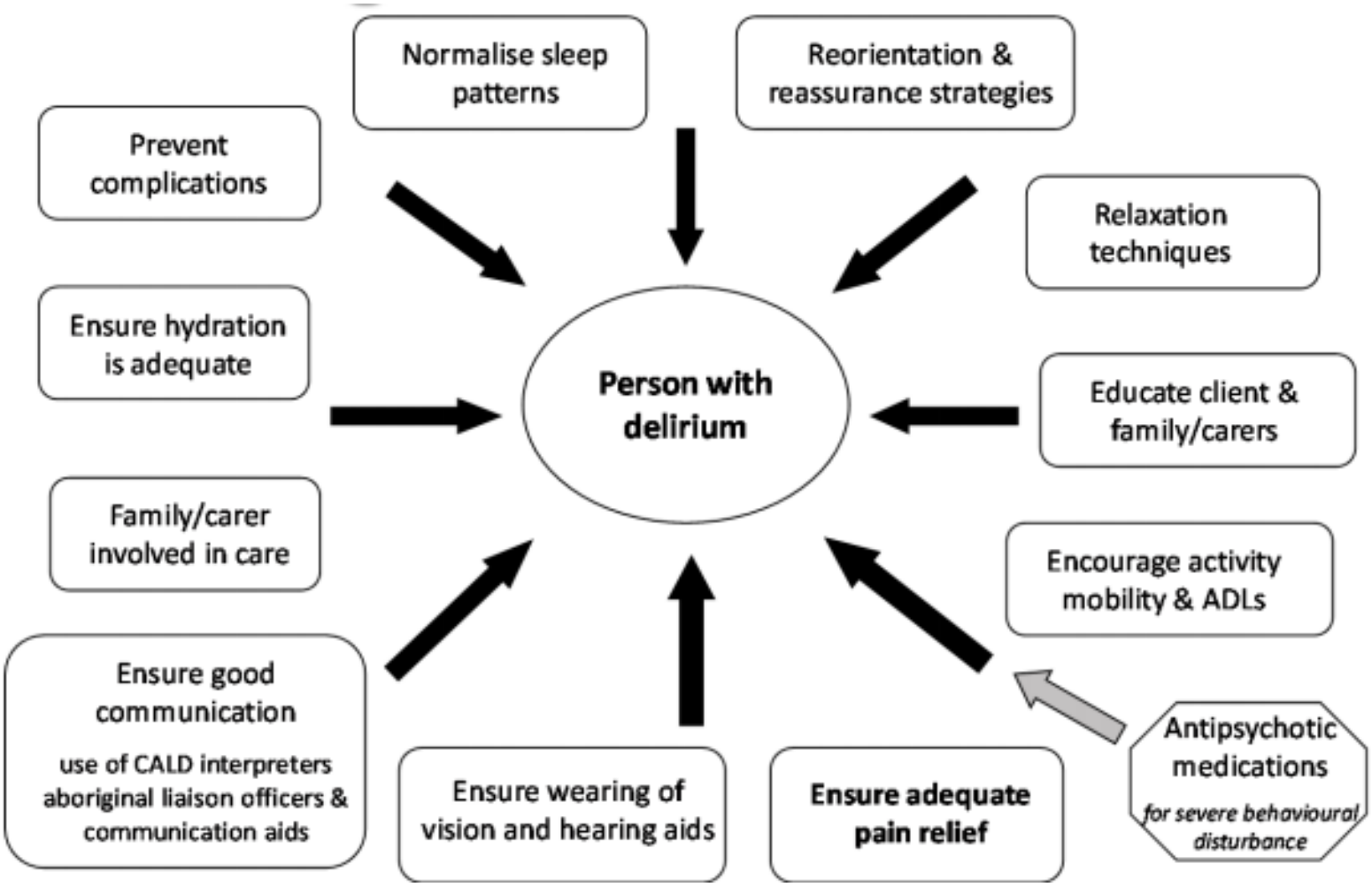


Management of Cause

- Remove the offending agent (s) associated with development of delirium
- Use scales like Anticholinergic Burden Classification (ABC) to evaluate the anticholinergic propensity of all the prescribed drugs which patient is receiving and minimize the anticholinergic load
- Remove all the unnecessary medications
- Treat underlying infections with appropriate antibiotics
- Poisoning and Intoxication: use appropriate antidote
- Delirium related to Alcohol Withdrawal: Benzodiazepines, Thiamine

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment



Nonpharmacological Treatment

Supportive Care

- Ensure safety of the patients
- Close observation and monitor the vital signs, temperature, oxygenation, hydration, electrolytes, glucose level, nutrition, input/output
- Regularly evaluate the patients and take measure to avoid development of pressure sores
- Reduce immobility – encourage performance of self-care activities on their own, allow free movements
- Remove the catheter as soon as possible
- Monitor bladder and bowel habit and maintain normal elimination patterns
- Monitor the prescription with special focus on evaluation of potential adverse drug-drug interactions and drug-disease interactions

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

Providing an unambiguous environment

- **Simplify care area by removing unnecessary objects; allow adequate space between beds**
- **Consider using single rooms to aid rest and avoid extremes of sensory experience;** reduces the disturbance caused by staff attending other patients in the same room
- **Do not frequently change the patient's bed location -** frequent changes may increase disorientation
- **Avoid using medical jargon in front of the patient as it may encourage paranoia**
- **Making eye contact, frequent touching, and using clear verbal instructions when talking to patients**
- **Encourage family and caregiver involvement**

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

Providing support

- **Encourage family/caregivers to bring in client's personal and familiar objects**
- **Lighting appropriate to time of day** – windows with a view to outside, curtains and blinds open during the day, and minimal lighting at night may reduce disorientation
- **Ensure that lighting is adequate; provide a 40–60 W night light to reduce misperceptions**
- **Quiet environment especially at rest times** – noise reduction strategies (e.g.: use of vibrating pagers/phones rather than call bells)
- **Control sources of excess noise (such as staff, equipment, visitors): aim for <45 decibels in the day and <20 decibels at night**
- **Keep room temperature between 21°C and 23.8°C**

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

Providing orientation

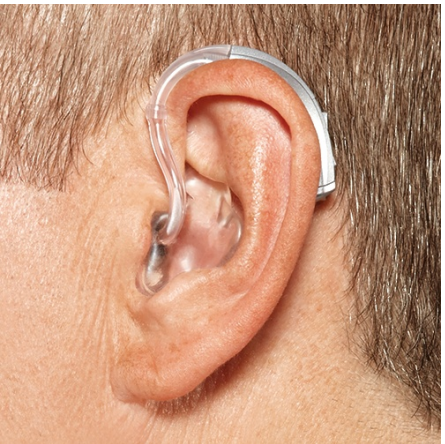
- **Communicate clearly and concisely:** give repeated verbal reminders of the day, time and location, and identify key individuals, such as members of the treatment team and relatives
- **Provision of clock and calendar that clients can see**

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

Maintaining competence

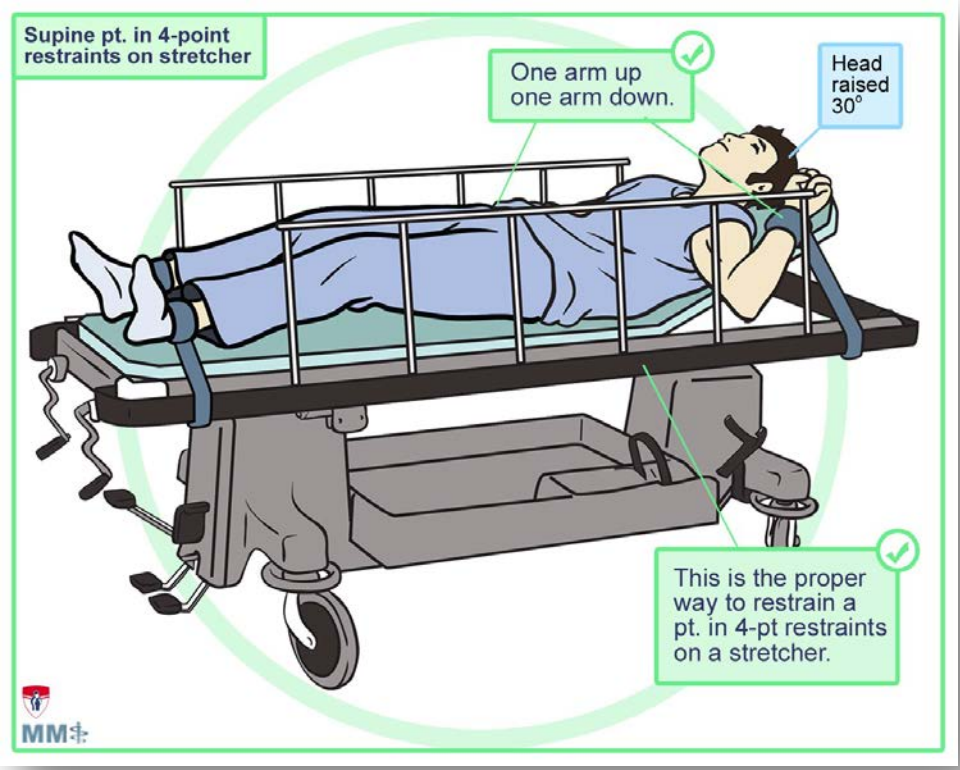
- Identify and correct sensory impairments: ensure patients have their glasses, hearing aid and dentures
- Consider an interpreter if needed
- Encourage self care and participation in treatment (for example have the patient give feedback on pain)
- Arrange treatment



Nonpharmacological Treatment

Providing support and orientation

- **Avoid physical restraints, if possible**



[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

Ensure good uninterrupted sleep:

- Schedule treatment/interventions/ Intravenous fluids in such a way that patient can have maximum periods of uninterrupted sleep (use a sleep protocol to promote quiet hours)

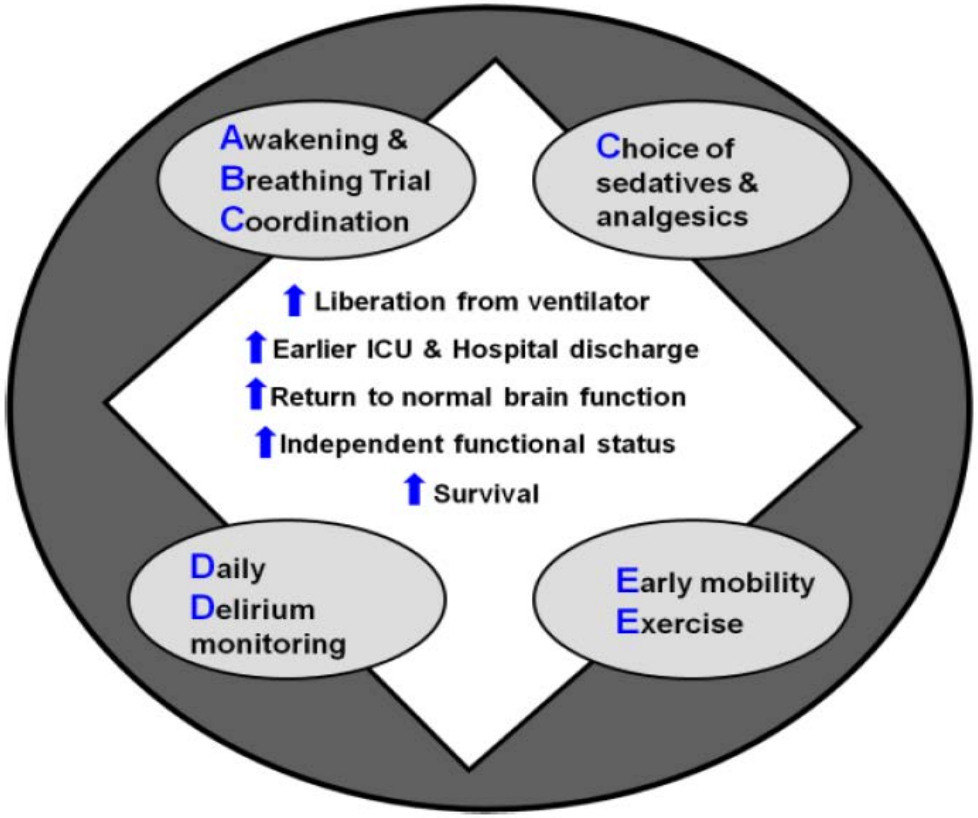
"Try to get some rest. I'll be in every few minutes to make sure you don't."

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Nonpharmacological Treatment

- **ABCDEF Protocol for delirium in ICUs**

F- stands for Family Involvement



Pharmacological Treatment

- Antipsychotics
- Benzodiazepine (only for alcohol withdrawal)
- Acetyl cholinesterase inhibitors (rivastigmine)
- Alpha-2 adrenergic receptor agonist (dexmedetomidine)
- Melatonin
- Combinations of the above

Pharmacological Treatment

Pharmacological management

- Antipsychotics are the main stay of treatment
- Haloperidol -most commonly recommended drug
- Recent evidence: olanzapine, risperidone, quetiapine, lurasidone, ziprasidone are equally efficacious
- Lower doses of antipsychotics may be sufficient
- Start low and titrate

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Pharmacological Treatment

Pharmacological management

- Weigh the benefits and risks of using antipsychotics
- Antipsychotics must be started in liaison with the family/caregivers and members of the primary treating team
- Before starting antipsychotics- baseline ECG must be done to evaluate the QTc interval
- Clearly document the indications for starting antipsychotics
- Use lowest effective dose
- Start with lower doses and gradually titrate upwards
- Monitor the symptoms of delirium
- Monitor for side effects: over-sedation, extrapyramidal side effects
- In general, antipsychotics are not recommended for management of patients with hypoactive delirium

[Grover S, Avasthi A. Clinical Practice Guidelines for management of Delirium in Elderly. Indian J Psychiatry,2018;60: 329-340]

Pharmacological Treatment

TABLE 2

ANTIPSYCHOTIC MEDICATIONS IN THE TREATMENT OF DELIRIUM[1]

Medication	Dose Range	Routes of Administration	Side Effects	Comments
Typical Antipsychotics				
Chlorpromazine	12.5–50 mg every 4–6 hours	PO, IV, IM, SC, PR	Monitor for hypotension and anticholinergic side effects	May be preferred in agitated patients due to its sedative effect
Haloperidol	0.5–2 mg every 2–12 hours	PO, IV, IM, SC	Extrapyramidal side effects are more likely at doses >4.5 mg/day. Monitor QT interval on EKG	Remains the gold-standard therapy for delirium
Atypical Antipsychotics				
Aripiprazole	5–30 mg every 24 hours	PO*, IM	Monitor for akathisia	Evidence is limited to case reports and case series
Olanzapine	2.5–5 mg every 12–24 hours	PO*, IM	Sedation is the main dose-limiting adverse effect	Older age, pre-existing dementia, and hypoactive delirium have been associated with poor response
Quetiapine	12.5–100 mg every 12–24 hours	PO	Sedation, orthostatic hypotension	Sedating effects may be helpful in patients with insomnia
Risperidone	0.25–1 mg every 12–24 hours	PO*	Extrapyramidal adverse effects are more likely seen at doses >6 mg/day. Orthostatic hypotension	May be more effective in hypoactive delirium given lower risk of sedation
Ziprasidone	10–40 mg every 12–24 hours	PO, IM	Monitor QT interval on EKG	Evidence is limited to case reports

* Risperidone, olanzapine, and aripiprazole are available in the form of orally disintegrating tablets.

PO=by mouth; IV=intravenous; IM=intramuscular; SC=without food; PR=per rectum; EKG=electrocardiogram.

Alici Y, Breitbart W. *Primary Psychiatry.* Vol 16, 5. 2009.

Pharmacological Treatment

Agents for Delirium

Antipsychotic Agent	Dosage Form	Metabolism	Metabolizing Enzyme	Equiv. Dosages (approx) (mg)	Max Dose (mg/day)	Adverse Effects				
						QTc Prolongation Potential Dose Related Effect[a]	Sedation	Dopaminergic$_2$ Receptor Affinity/ Extrapyramidal Symptoms[b]	Anticholinergic Effects	Orthostatic Hypotension
Black Box Warning: Increased mortality seen when used in elderly patients with dementia-related psychosis due to cardiovascular or infectious complications. The use of these agents for delirium in ICU patients has not been tested in large, randomized, placebo-controlled trials.										
Haloperidol (Haldol)	Tab, IV injection	$T_{½}$: 21 hrs Hepatic	CYP3A4, 2D6	2	35*	Low	Low	High	Low	Low[b]
** Use heightened caution and be aware that there is a dose related QT interval prolongation and torsades de pointes (TdP) risk when using in excess of >20 mg per day.*										
QUEtiapine[c] (SEROquel)	Tab	$T_{½}$: 6 hrs Hepatic	CYP3A4	125	400	Moderate	Moderate	Low	Moderate	High
Risperidone (Risperdal)	Tab, ODT tab, solution (1 mg/ml)	$T_{½}$: 3 hrs Hepatic	CYP2D6, 3A4	1	4	Moderate	Low	High	Low	Moderate
Aripiprazole (Abilify)	Tab, solution (5mg/ml), IM injection	$T_{½}$: 75 hrs Hepatic	CYP2D6, 3A4	5	30	Low	Low	Low	Low	Low
The following agents are NOT recommended for ICU use.										
Ziprasidone[d] (Geodon)	Capsule	$T_{½}$: 7 hrs Hepatic	CYP3A4, 1A2	40	160	High	Low	High	Low	Moderate
OLANZapine[e] (ZyPREXA)	Tab, ODT tab, IM injection	$T_{½}$: 30 hrs Hepatic	CYP1A2	5	20	Low	Moderate	Low	Moderate	Low

a Low: 3-10 msec, Medium: 10-15 msec, High: > 15 msec

[b] Increased with IV formulation

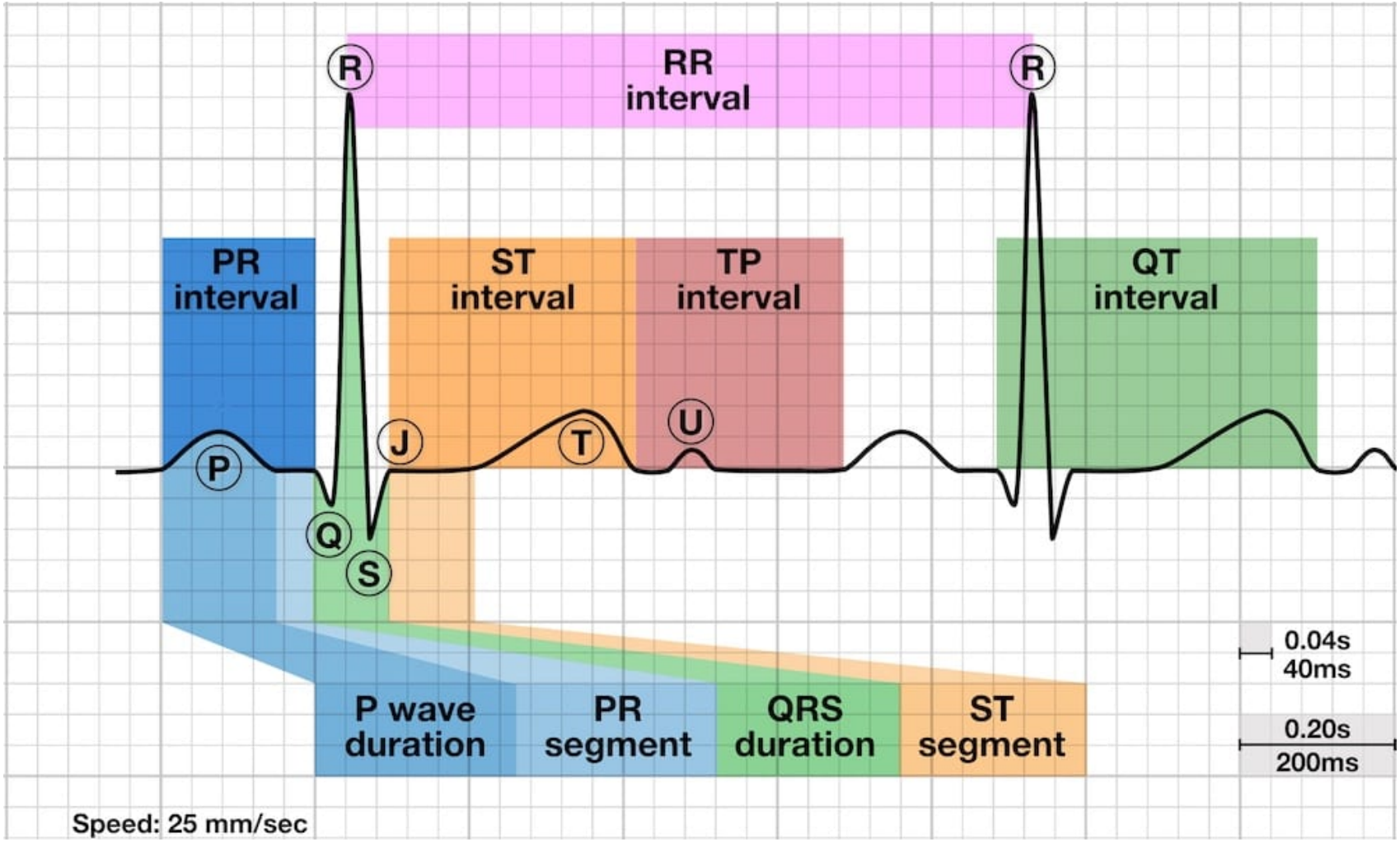
[c] Caution: Bone marrow suppression; blood dyscrasias

[d] Secondary to high risk for QT prolongation

[e] Secondary to high risk for metabolic syndrome

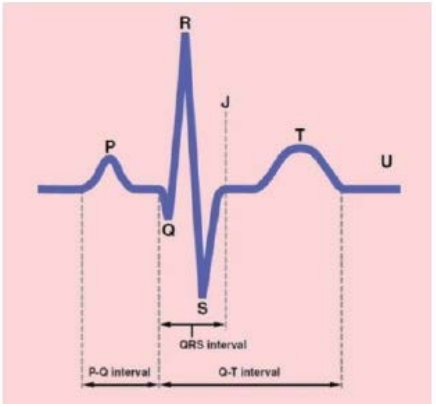
Pharmacological Treatment

Measurement of QTc interval



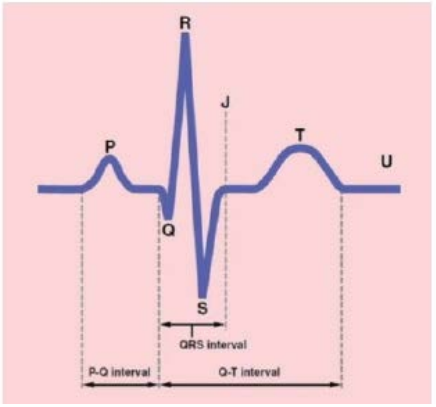
Pharmacological Treatment

Measurement of QTc interval



- Find the beginning of Q wave (and QRS complex at the same time)
- Localize the end of T wave
- Measure the distance between these two points on X-axis, You can use a ruler or a caliper
- Transform the length of QT interval from millimeters or boxes to milliseconds. With a paper speed of 25 mm/s one small box (1 mm) lasts 0.04 s, one big box (5 mm) – 0.2 s.

Pharmacological Treatment



Measurement of QTc interval

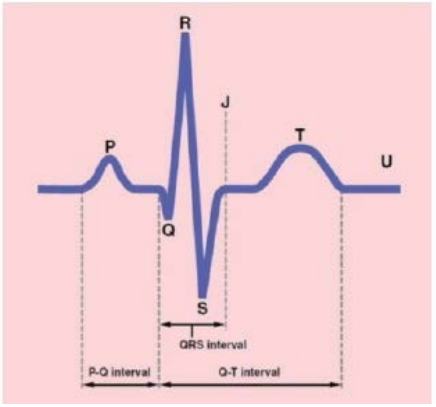
What is QTc ?

- It is corrected QT interval, takes, the heart rate into account

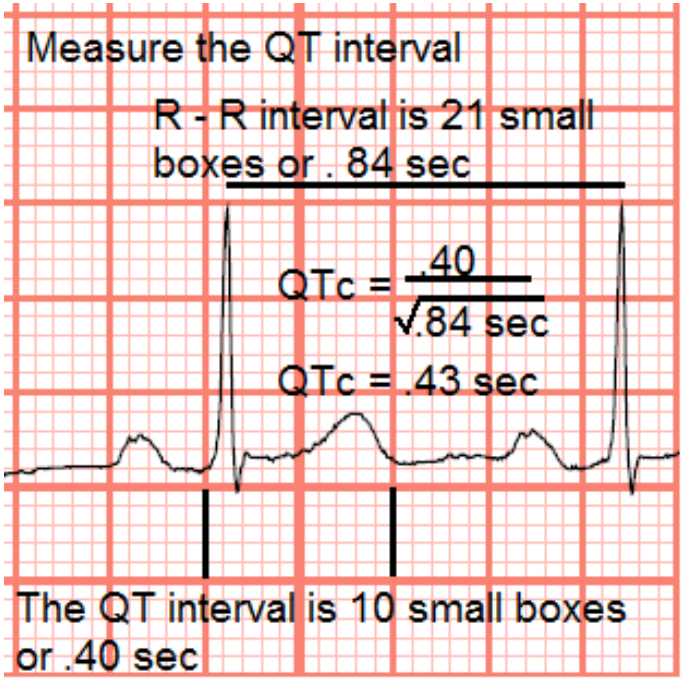
$$QTc = \frac{QT}{\sqrt{RR}}$$

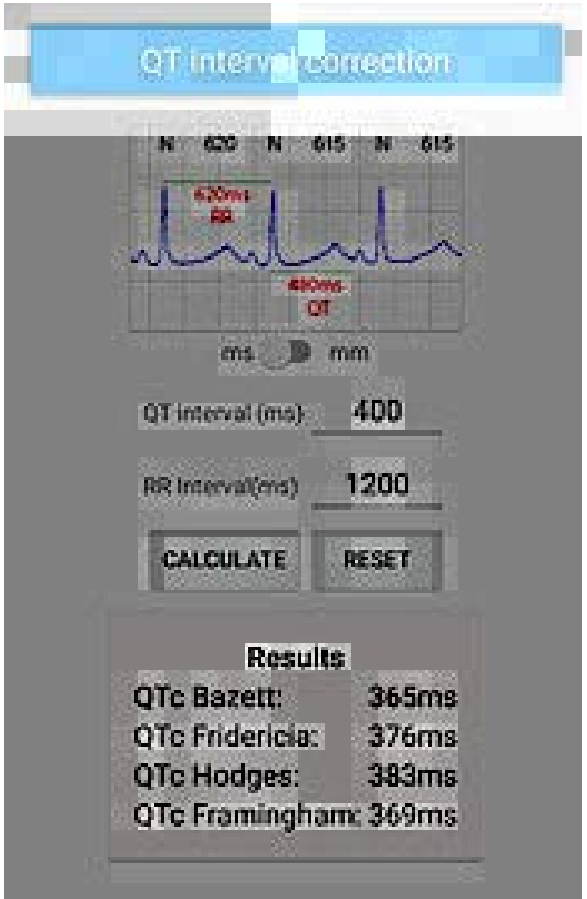
Pharmacological Treatment

Measurement of QTc interval

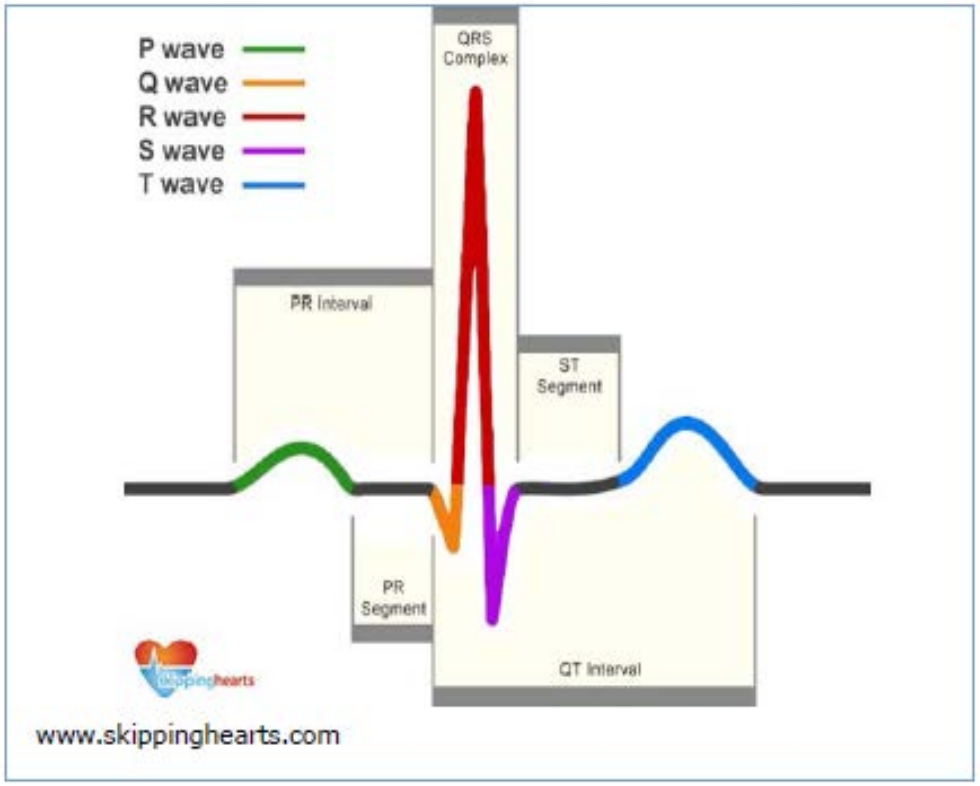


What is QTc ?





Pharmacological Treatment



QTc > 420-460 msec is generally considered prolonged, monitoring – Baseline QTc monitoring is recommended for patients receiving

Pharmacological Treatment

QTc Prolongation and Torsades de Pointes (TdP)

Table 2

Drugs Associated with QT Prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

Source: References 1, 3, 4, 8, 9, 14.

Pharmacological Treatment

QTc Prolongation and Torsades de Pointes (TdP)

Table 2. Psychiatric Drugs With a Higher Risk of QTc Prolongation at Therapeutic Doses

Drug Class	Drug Name
Typical antipsychotics	Thioridazine, haloperidol, chlorpromazine, pimozide
Atypical antipsychotics	Ziprasidone, iloperidone, quetiapine
SSRIs	Citalopram, escitalopram
TCAs and TeCAs	Amitriptyline, imipramine, maprotiline, nortriptyline, desipramine, clomipramine, trimipramine
SNRIs	Venlafaxine
Other antidepressants	Mirtazapine

QTc: corrected QT; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant.
Source: References 2-12, 14-18, 24.

Pharmacological Treatment

QTc Prolongation and Torsades de Pointes (TdP)

Risk Factors

- Age
- Female gender
- Bradycardia
- Left ventricular failure
- Recent cardioversion
- Congenital long QT syndrome
- Electrolyte abnormalities
  - Hypomagnesemia
  - Hypokalemia
  - Hypocalcemia
- Hepatic dysfunction

Pharmacological Treatment

How to determine the medication doses

- **What is to be achieved ??**

Pharmacological Treatment

Riker Sedation-Agitation Scale (SAS)

Riker Sedation-Agitation Scale (SAS)		
Score	**Term**	**Descriptor**
SAS Target Sedation = 3 to 4		
7	Dangerous Agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and Cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Jacobi J, Fraser GL, Coursin DB, et al. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. Vol. 30, No. 1

Pharmacological Treatment

Guidelines for SAS Assessment

1. Agitated patients are scored by their most severe degree of agitation, as described.
2. If patient is awake or awakens easily to voice ("awaken" means responds with voice or head shaking to a question or follows commands), that is a SAS 4 (same as calm and appropriate – might even be napping).
3. If more stimuli such as shaking is required but patient eventually does awaken, that is a SAS 3.
4. If patient arouses to stronger physical stimuli (may be noxious) but never awakens to the point of responding yes/no or following commands, that is a SAS 2.
5. Little or no response to noxious physical stimuli is a SAS 1.

This helps separate sedated patients into those you can eventually awaken (SAS 3), those you cannot awaken, but can arouse (SAS 2), and those you cannot arouse (SAS 1).

Pharmacological Treatment

Pharmacological treatment: Choline esterase inhibitors

- **Donepezil, Physostigmine, rivastigmine**

Donepezil: **Useful in delirium**

Physostigmine: **No different that placebo**

Rivastigmine:

- **May help reduce the frequency and shorten the duration of delirium**
- **Addition of rivastigmine to antipsychotics led to recovery from chronic delirium in 71.4 % of cases**

Melatonin/Ramelteon

[Goff et al, 1985; Schuster et al, 1977; Stern et al, 1973; Kaufer et al, 1998; Hori et al, 2003; Moretti et al, 2004; Dautzenberg et al, 2004; Gamberini et al, 2009; Van Ejik et al, 2010]

Pharmacological Treatment

Pharmacological treatment:

- **Melatonin**
- **Ramelteon**

Pharmacological Treatment

TABLE 6 Physiological effects of melatonin and deliriolytic effects

Melatonin play important roles in multiple bodily functions, which may have potential implications regarding the development of delirium in the medically ill
○ Chronobiotic effect (affecting aspects of biological time structure)
○ Sleep-wake cycle regulatory effects
○ Helps reset circadian rhythm disturbances
○ Effective free radical scavenger with extensive antioxidant activity (with a particular role in the protection of nuclear and mitochondrial DNA) with strong antiapoptotic signaling function
○ Extensive anti-inflammatory activity
○ Melatonin scavenges hydroxyl, carbonate, and various organic radicals as well as a number of reactive nitrogen species
○ Melatonin also enhances the antioxidant potential of cells by stimulating the synthesis of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and glutathione reductase and by augmenting glutathione levels
○ Melatonin preserves mitochondrial homeostasis, reduces free radical generation and protects mitochondrial adenosine triphosphate synthesis by stimulating complexes I and IV activities
○ Antinociceptive and analgesic effects
○ Melatonin receptors appear to be important in mechanisms of learning and memory
○ Inhibits the aggregation of the amyloid beta protein into neurotoxic microaggregates responsible for the neurofibrillary tangles characteristics of Alzheimer's disease and it prevents the hyperphosphorylation of the tau protein; protect against the neurotoxicity of Abeta and glutamate.
○ Reduces the affinity of glucocorticoid (GC) receptors, prevents GC inhibition of cell proliferation, and reduces the GC-induced neurotoxicity and apoptosis

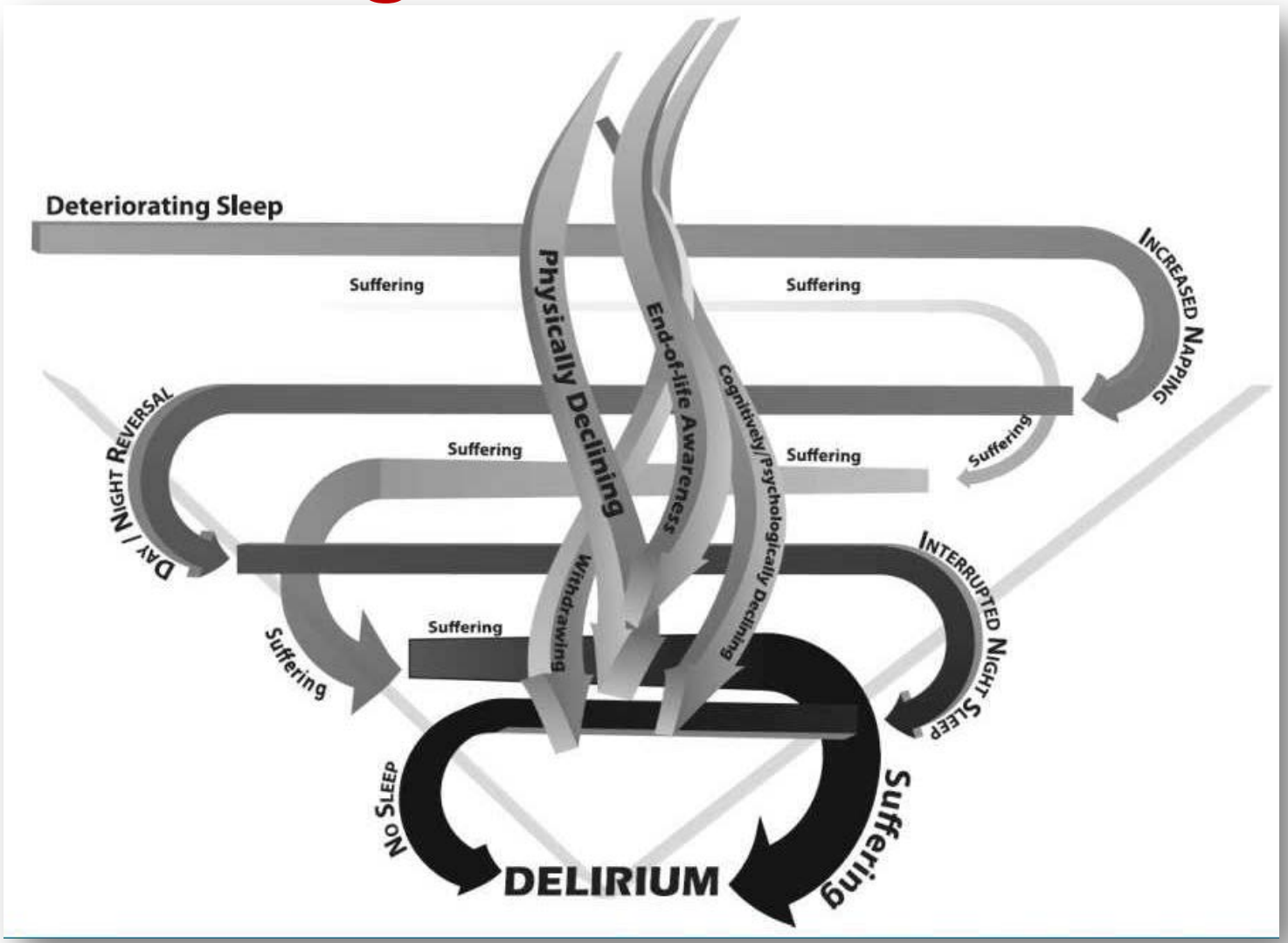
*[*Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry. 2017 Dec 26. doi: 10.1002/gps.4823. [Epub ahead of print*]*

Pharmacological Treatment

- **Sleep deprivation can lead to delirium**
- **Patients with delirium have low melatonin levels**
- **Prophylactic use of melatonin – associated with reduced incidence of delirium**

[Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013 Dec;21(12):1190-222]

Pharmacological Treatment



[Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013 Dec;21(12):1190-222]

Pharmacological Treatment

- **Medical illnesses/hospitalization- sleep deprivation**
- **Aging leads to decreased level of melatonin**

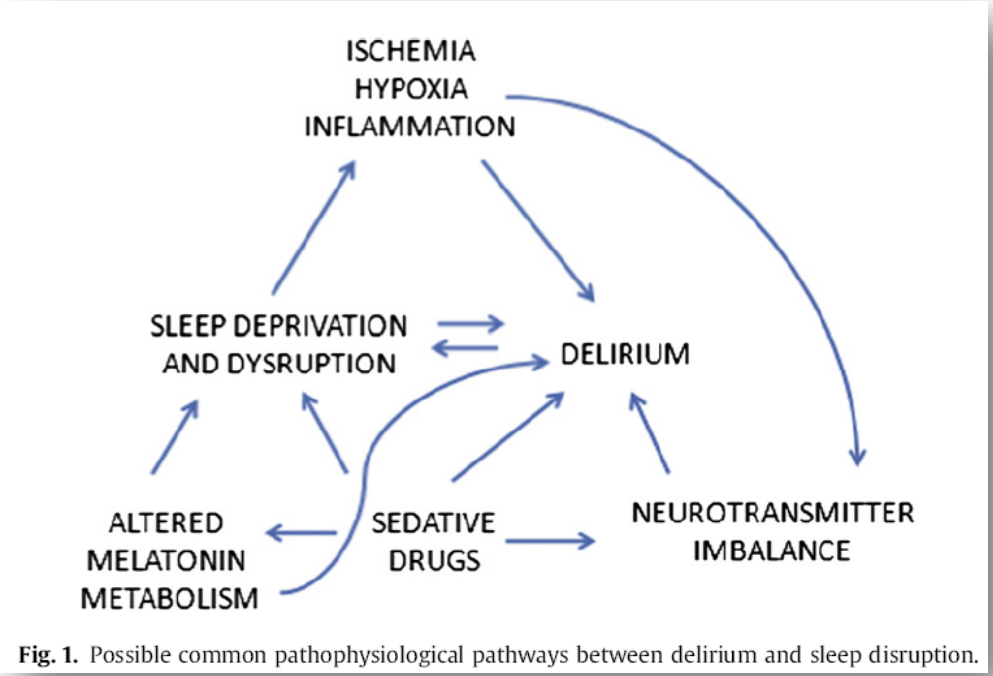
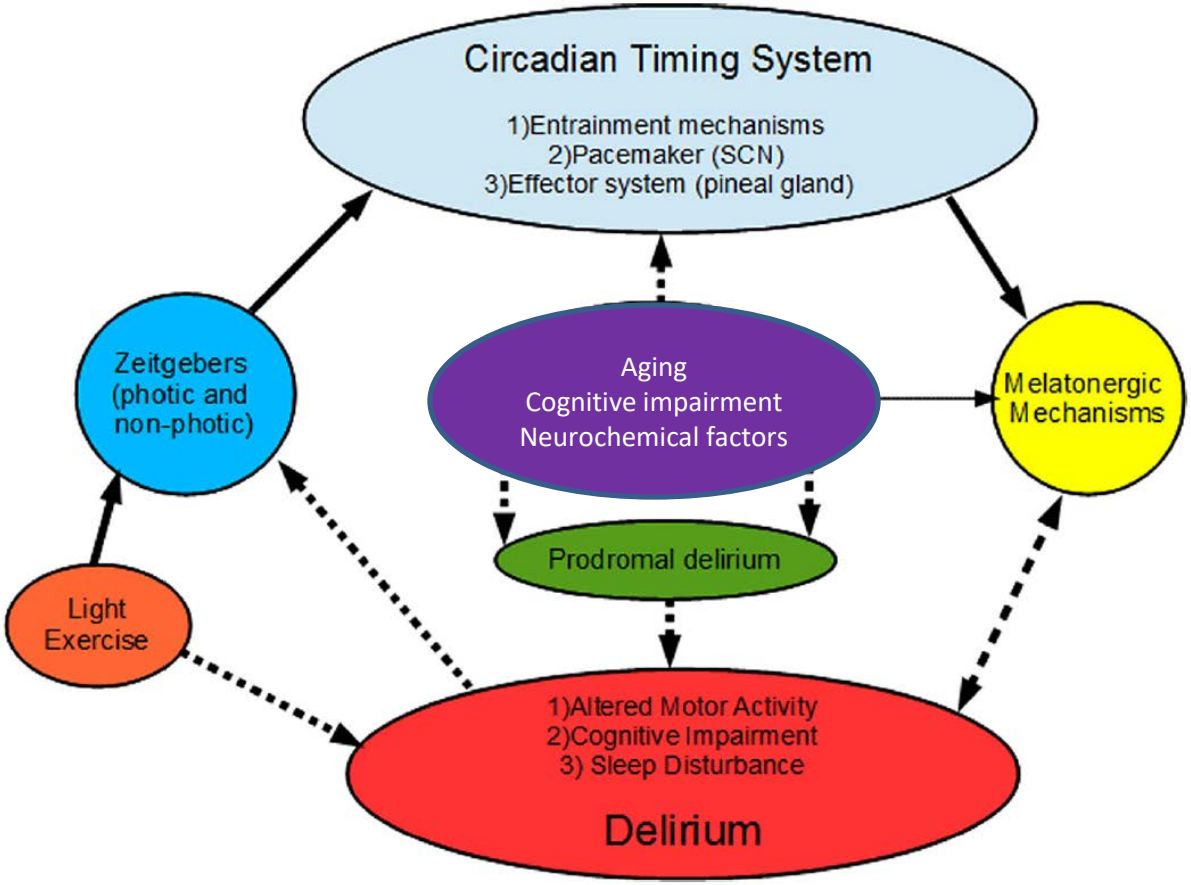


Fig. 1. Possible common pathophysiological pathways between delirium and sleep disruption.

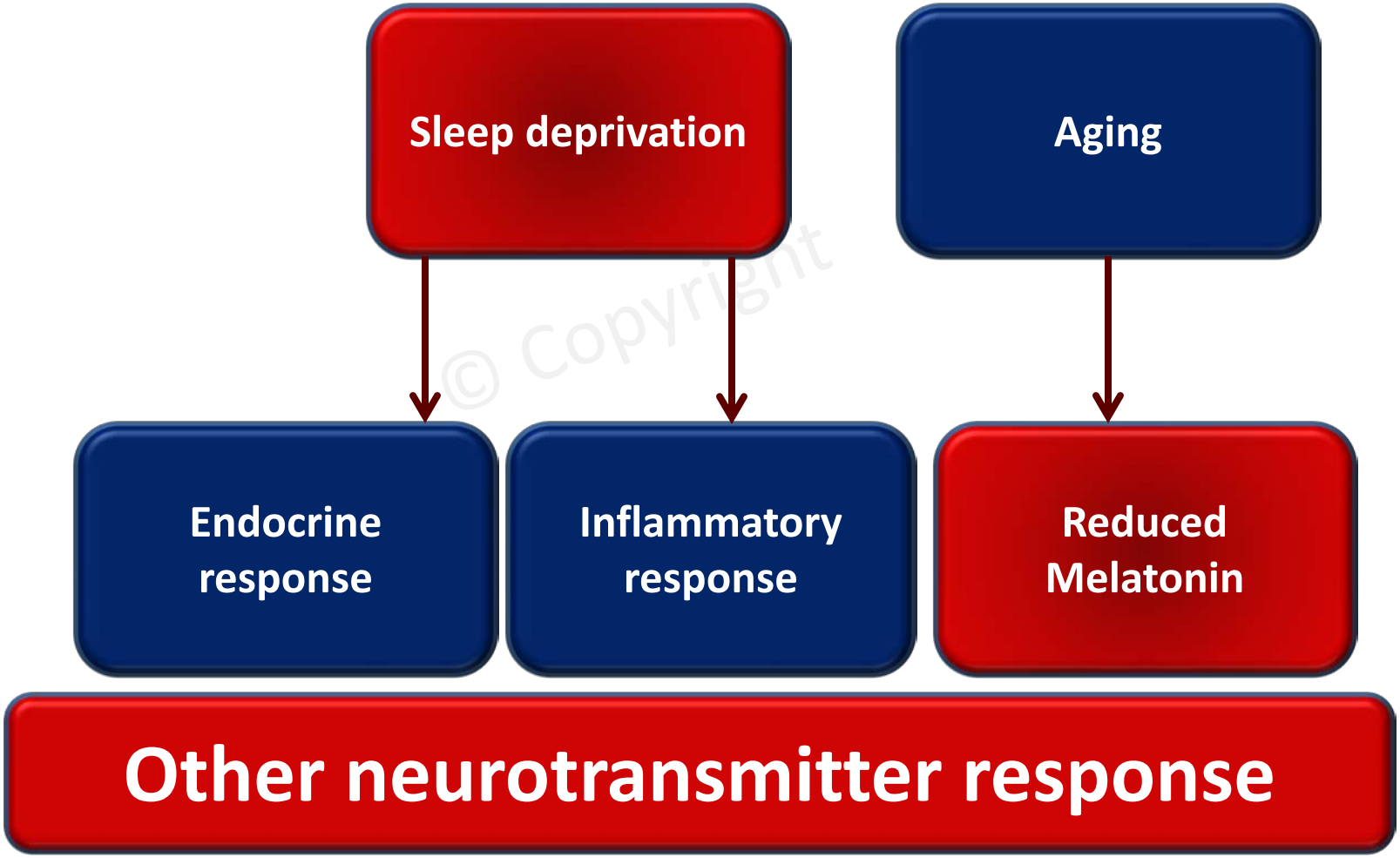
[Watson PL, Ceriana P, Fanfulla F. Delirium: is sleep important? Best Pract Res Clin Anaesthesiol. 2012 Sep;26(3):355-66]

Pharmacological Treatment



[Fitzgerald JM et al. Delirium: a disturbance of circadian integrity? Med Hypotheses. 2013 Oct;81(4):568-76]

Pharmacological Treatment



Pharmacological Treatment

- Role of melatonin in prevention of delirium has been evaluated in some of the randomized controlled trials and there is lack of consensus with respect to its role in prevention of delirium
- Data on role of melatonin in management of delirium is limited to case reports and case series and there is lack of prospective randomized controlled trials

Pharmacological Treatment

- A metanalysis, which included data for 669 elderly patients from 4 RCTs of use of melatonin in prevention of delirium, concluded that compared to the control group, use of melatonin was associated with a **trend towards reduction in the incidence of delirium** (relative risk: 0.41; confidence interval- 0.15-1.13; p value 0.08).

Chen S, Shi L, Liang F, Xu L, Desislava D, Wu Q, et al. Exogenous Melatonin for Delirium Prevention: a meta-analysis of randomized controlled trials. Mol Neurobiol. 2016; 53(6):4046-53

Steps in Assessment & Management of Delirium

- Communicate the colleague about the possibility
- Communicate with other treating team members
- Discuss about reversible etiological agent & implicating medications
- Communicate with the family members

Prevention of Delirium

- Evaluate the cognitive functions at the baseline
- Identify/evaluate for the risk factors for delirium
- Monitor cognitive functions on regular basis by using MMSE, MoCA, HMSE; In case there is a fall in 2 points on various cognitive function assessment instruments, screen the patient for delirium
- Minimize sensory deprivation (restoration of eyeglasses and hearing aids), Ensure proper sleep
- Stop unnecessary medications
- Minimize exposure to medications which have a high propensity to cause delirium (anticholinergic) and use alternative agents if possible
- Weigh the risk and benefit of use of medications with high anticholinergics properties, opioids and sedatives, especially among vulnerable elderly patients

[Grover S, Avasthi A. Indian Psychiatric Society Clinical Practice Guidelines for Management of Delirium in Elderly., Draft Document]

Prevention of Delirium

- Avoid use of high doses of medications, especially while using polypharmacy
- Maintain adequate lighting of the area
- Take measures so that patient gets adequate sleep and encourage normalization of sleep–wake cycles
- Change of rooms must be kept to the minimum
- Frequent reorientation, Appropriate cognitive stimulation
- Adequate pain management
- Reduce immobility
- Avoid use of physical restraints
- Quite environment: minimize or remove the unexpected & irritating noises (e.g., alarms)
- Minimise the use of indwelling urinary catheters

[Grover S, Avasthi A. Indian Psychiatric Society Clinical Practice Guidelines for Management of Delirium in Elderly., Draft Document]


THANK
YOU

Delirium: Top Tips

1. LOOK CAREFULLY FOR DELIRIUM

PINCHME
Pain
Infection
Constipation
Hydration
Medication
Environment

Then use the 4AT to help diagnose delirium
www.the4at.com

SLEEP DEPRIVATION
makes delirium worse:
Encourage good sleep hygiene

ASK ABOUT ALCOHOL

GLASSES? Put them on!

HEARING AIDS? Put them in (& check batteries!)

2. HARNESS THE POWER OF THE FAMILY

LISTEN to family/ friends/carers who tell you the patient is confused

ALLOW open visiting & family photos at bedside. MINIMISE ward transfers (and document all this!)

3. FIND/STOP CULPRIT MEDS

- Amitriptyline
- Combo analgesics
- Anticholinergics
- Benzodiazepines

… can all cause or worsen delirium. Can you deprescribe anything?

4. ORIENTATE YOUR PATIENT

Clocks & calendars

IF YOU REALLY HAVE NO OPTION BUT TO PRESCRIBE MEDICATION TO RELIEVE SEVERE AGITATION OR DISTRESS
then use haloperidol or olanzepine at lowest possible dose, and consider benzodiazepines if antipyschotics are CI.

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This is a #FOAMed production: please share it far & wide!