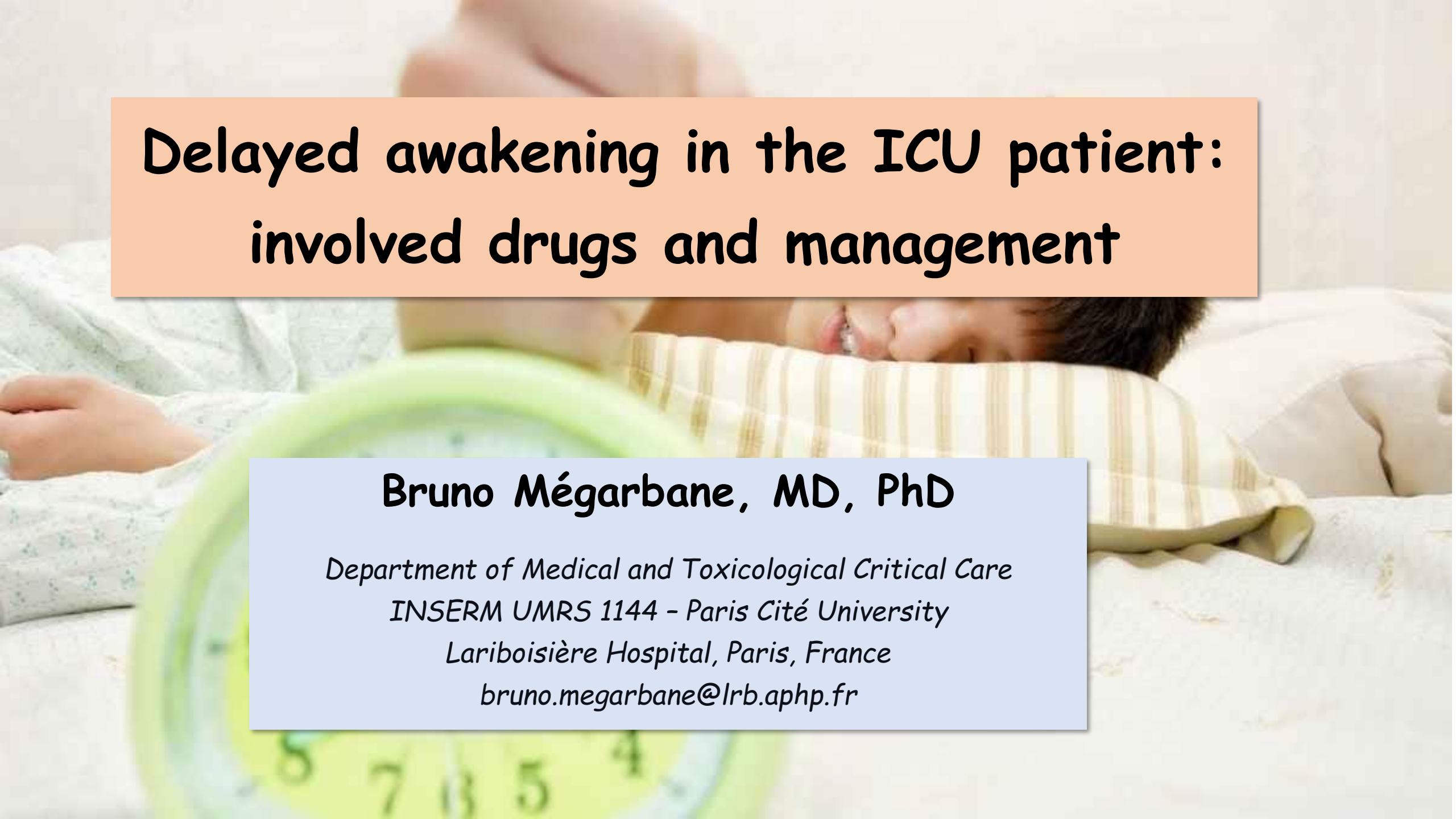
Delayed awakening in the ICU patient: involved drugs and management



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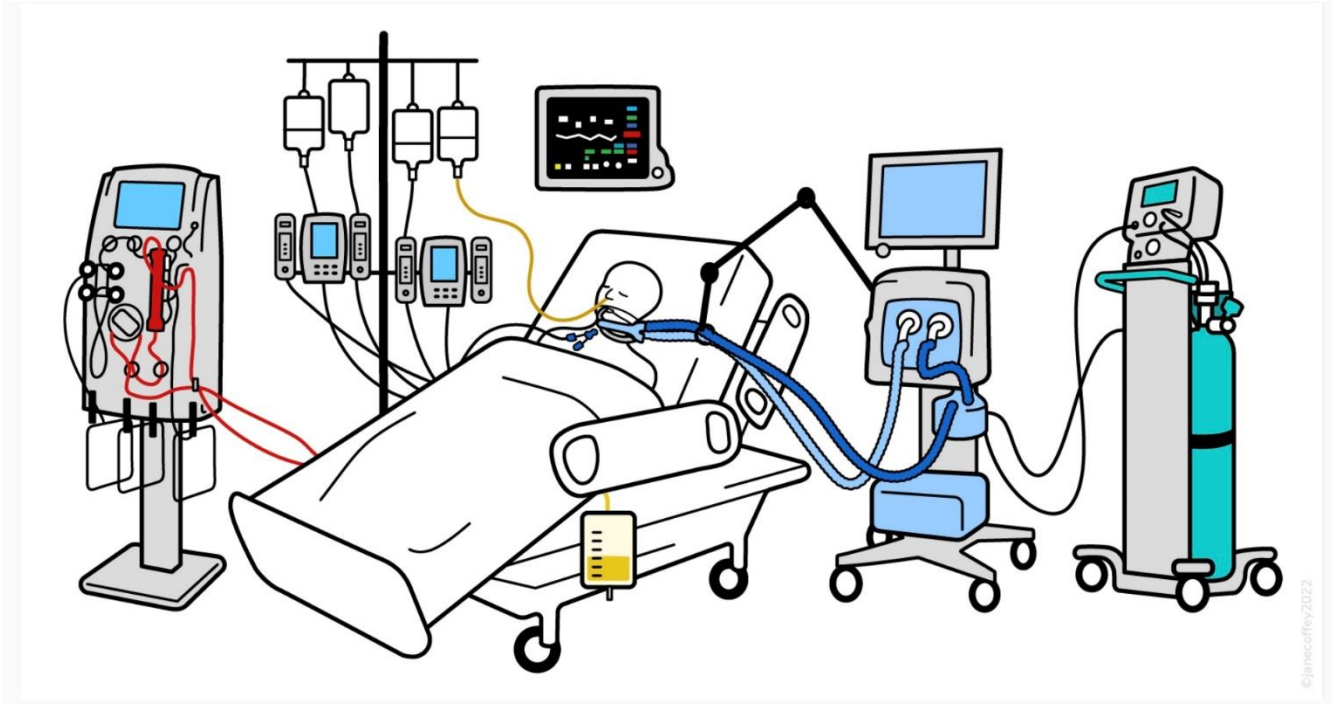
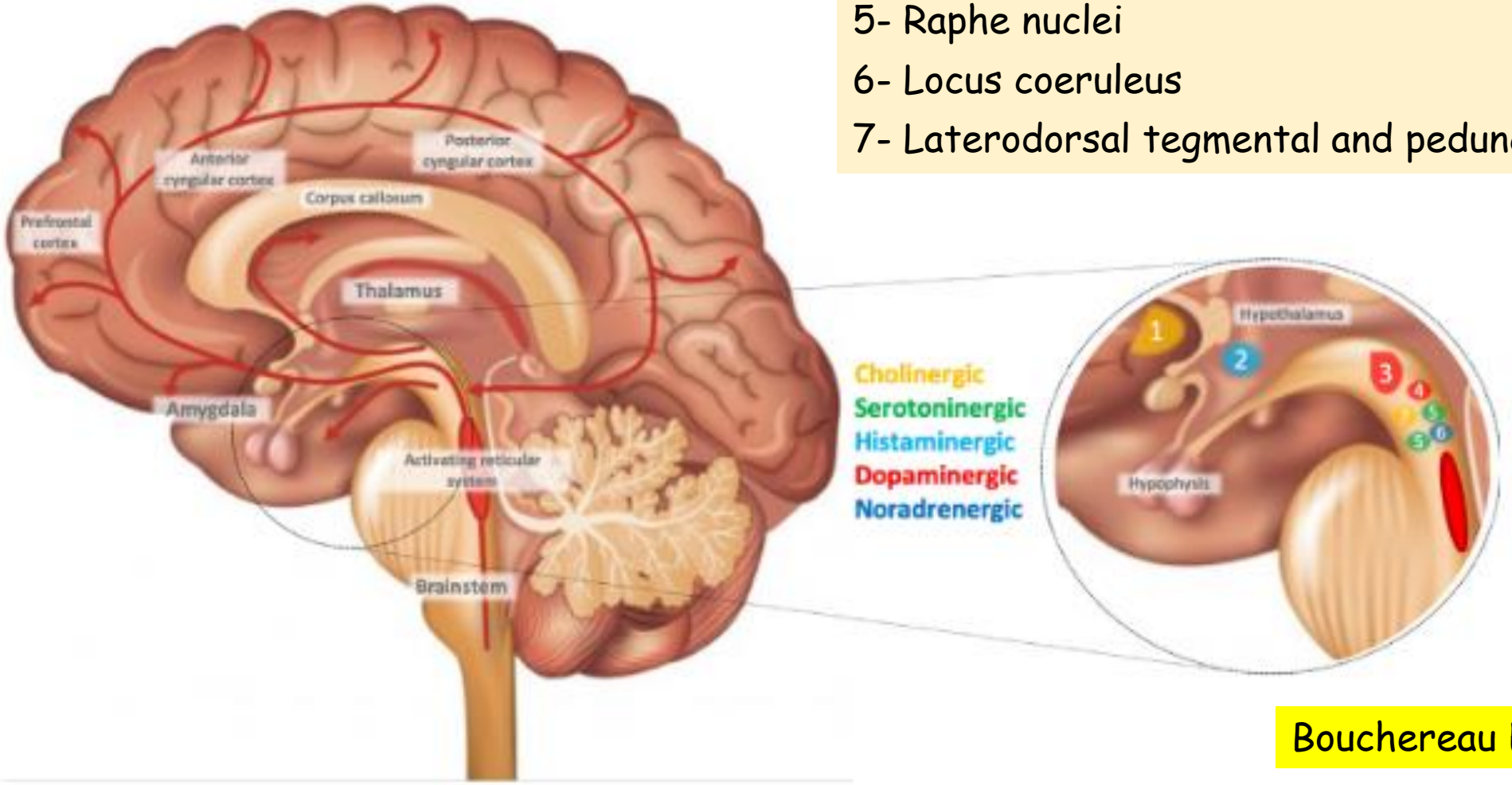


I have no conflict of interest to declare

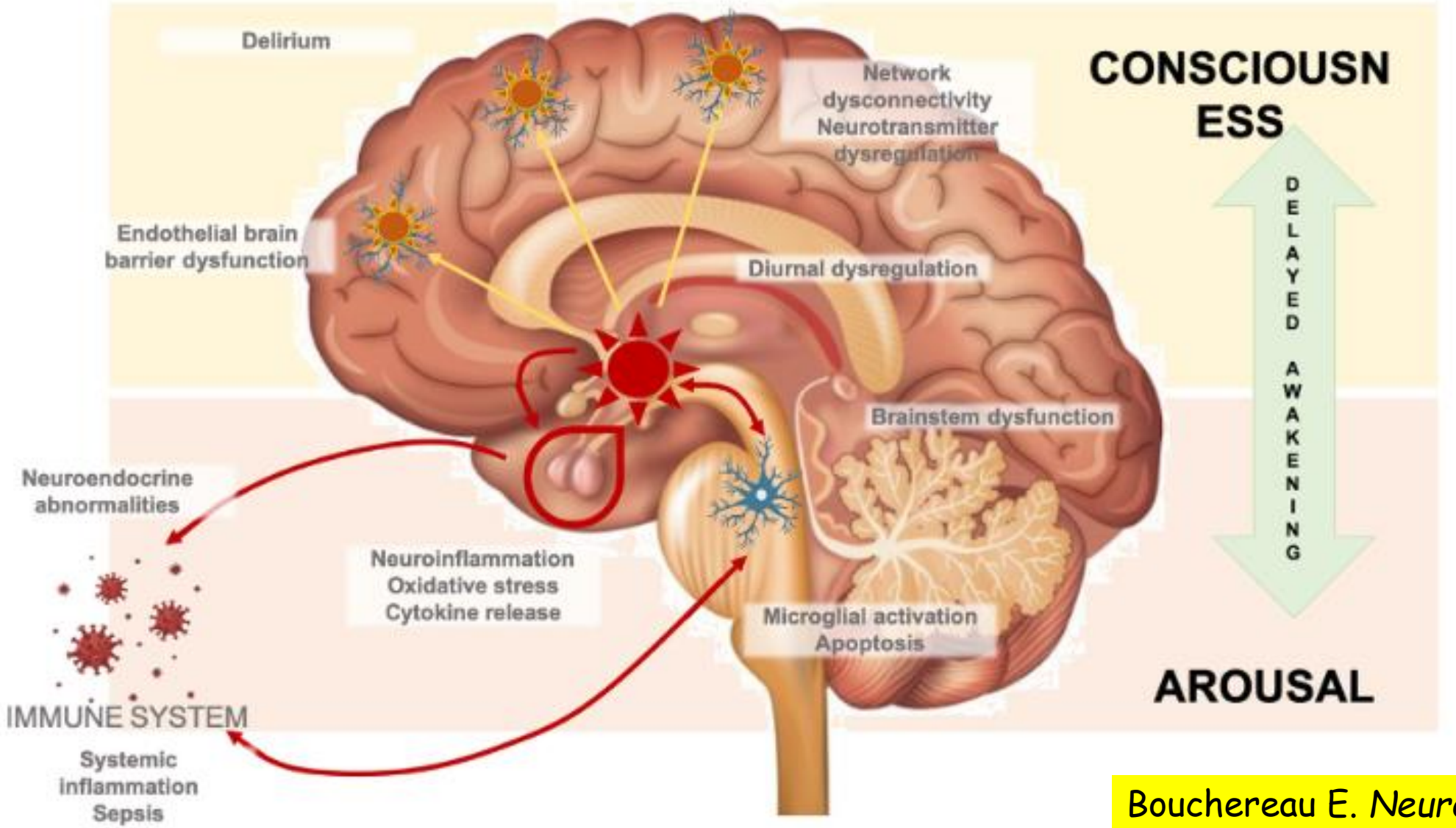
Arousal Network

1- Nucleus basalis of Meynert (basal forebrain)
2- Tuberomammillary nucleus (hypothalamus)
3- Ventral tegmental area
4- Substantia nigra
5- Raphe nuclei
6- Locus coeruleus
7- Laterodorsal tegmental and pedunculo-pontine nuclei



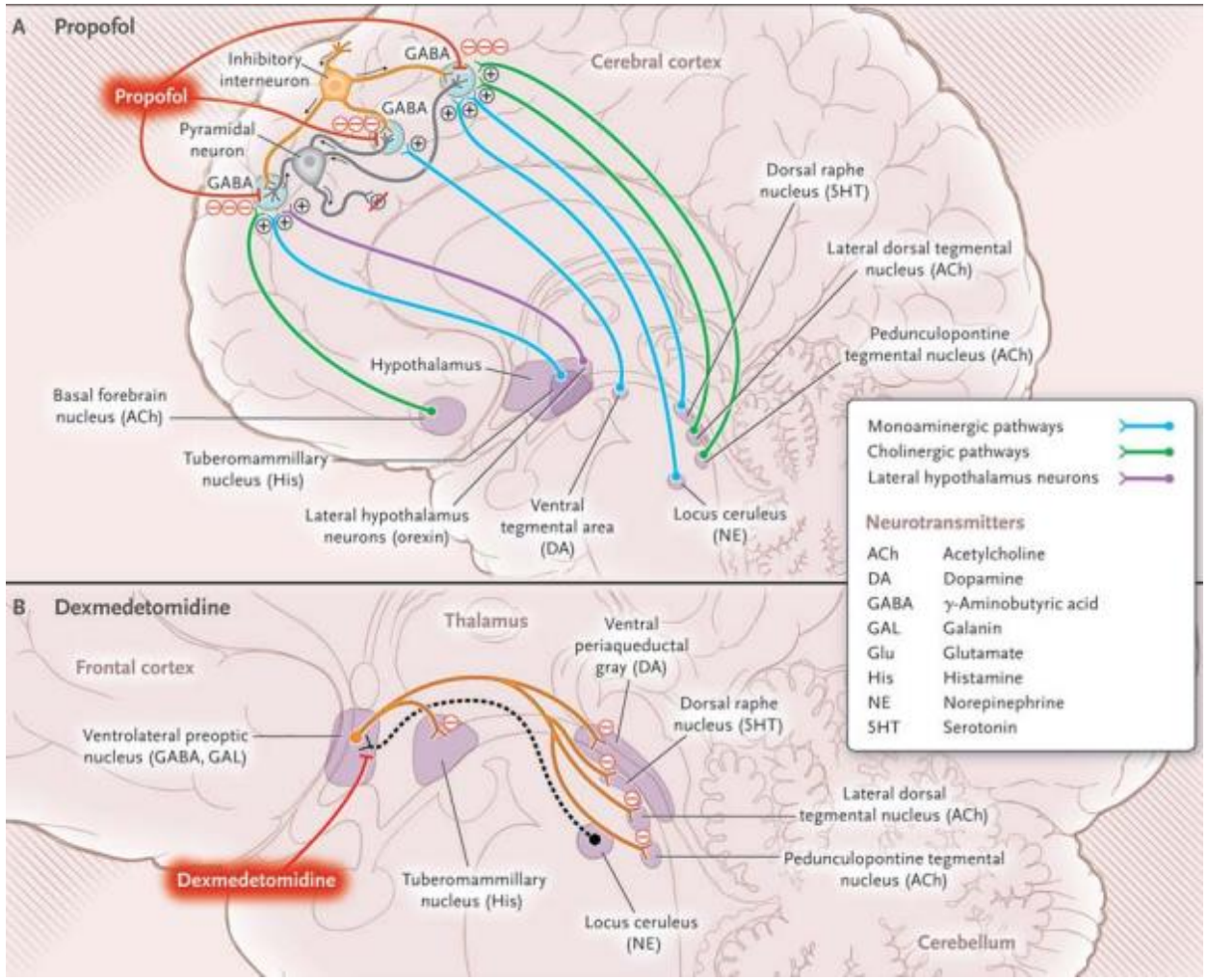
Bouchereau E. *Neurol Rev* 2021

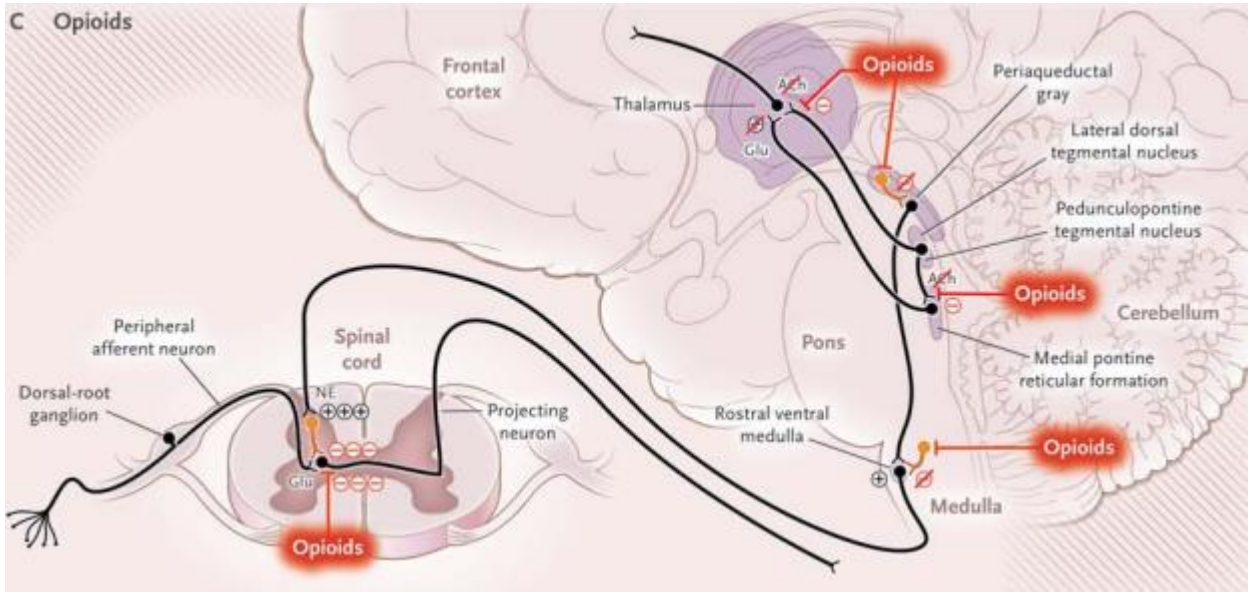
Physiopathology of delayed awakening



Bouchereau E. *Neurol Rev* 2021

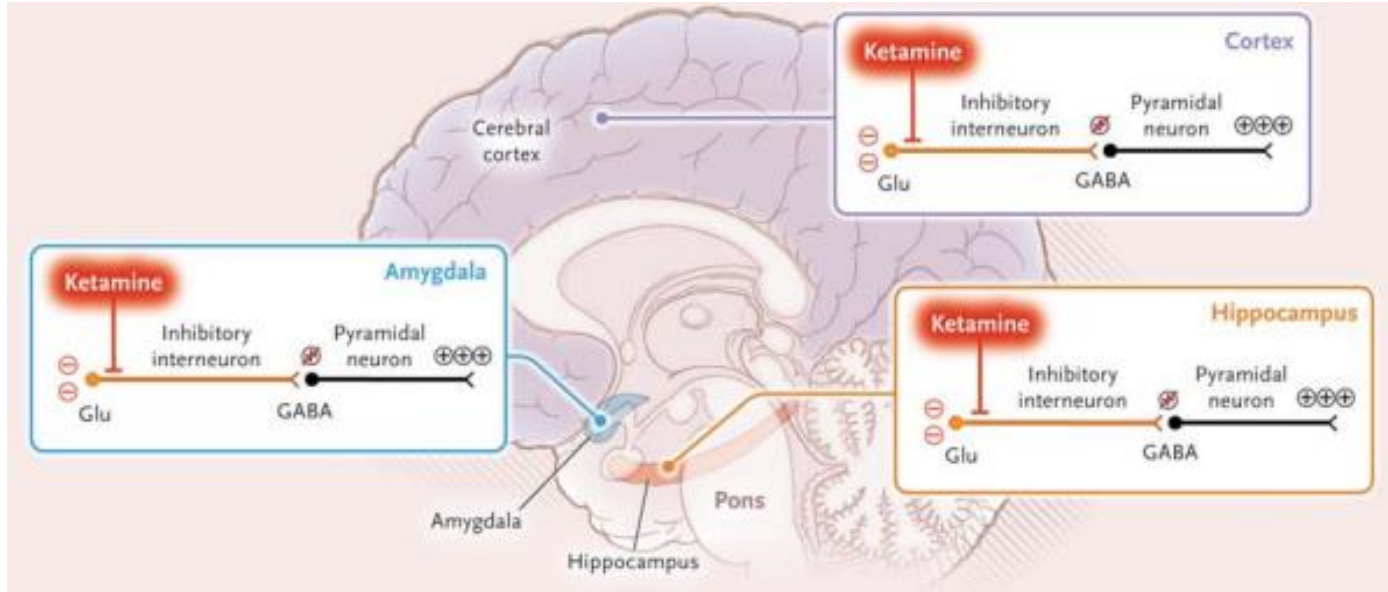
Neural-circuit mechanisms of altered arousal by anesthetic agents

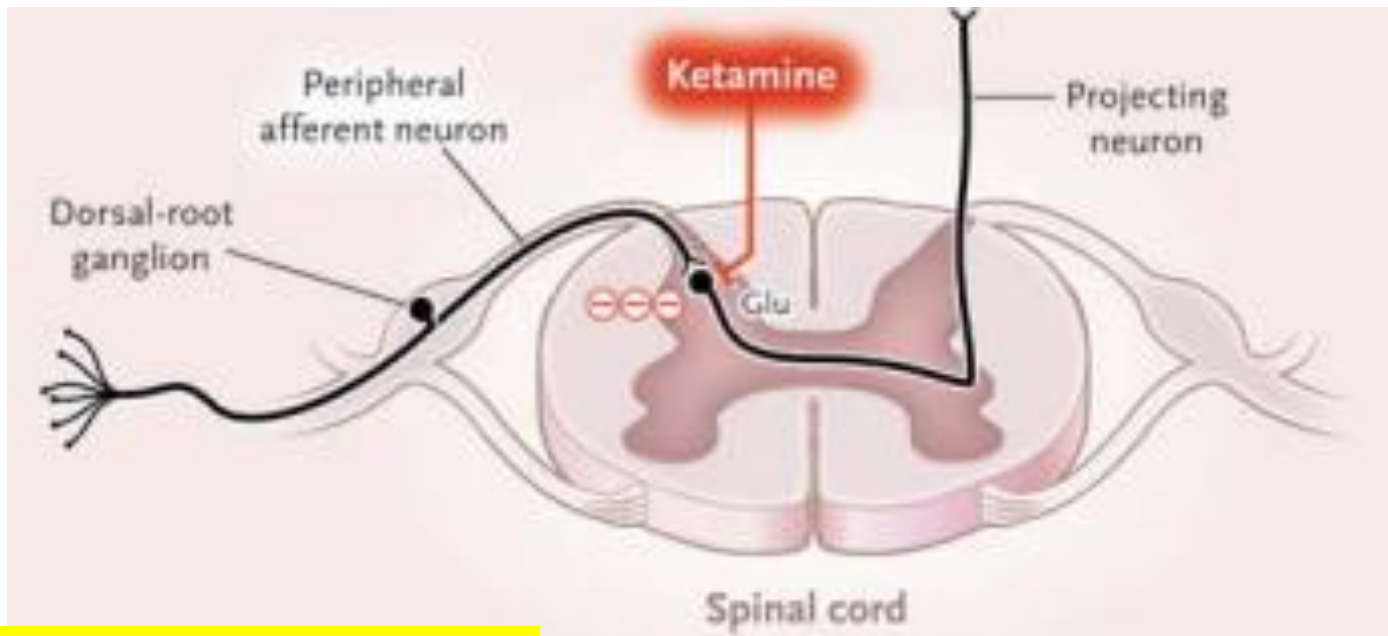




Brown EM. *NEJM* 2010

Ketamine binds preferentially to NMDA-R on inhibitory interneurons in the cortex, limbic system (amygdala), and hippocampus, promoting an uncoordinated increase in neural activity.
In the spinal cord, ketamine decreases arousal by blocking NMDA Glu mediated nociceptive signals from peripheral afferent neurons in the dorsal-root ganglion to projecting neuron





Brown EM. *NEJM* 2010

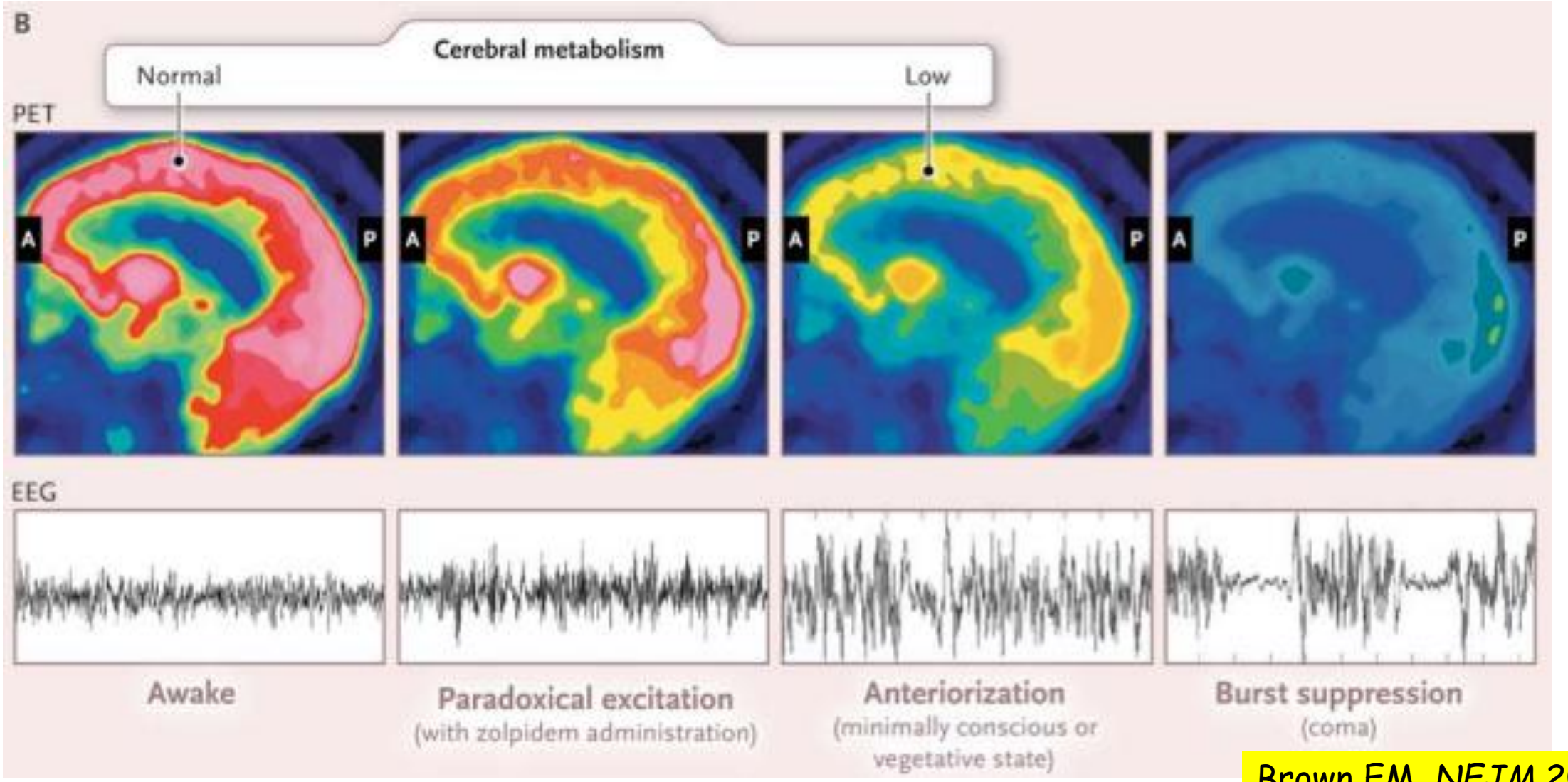
Emergence from general anesthesia & stages of recovery from coma

Emergence, phase 1
- Cessation of anesthetic drugs
- Reversal of peripheral-muscle relaxation (akinesis)
- Transition from apnea to irregular breathing to regular breathing
- Increased alpha and beta activity on EEG

Emergence, phase 2
- Increased heart rate and blood pressure
- Return of autonomic responsiveness
- Responsiveness to painful stimulation
- Salivation (7^{th} and 9^{th} cranial nerve nuclei)
- Tearing (7^{th} cranial nerve nuclei)
- Grimacing (5^{th} and 7^{th} cranial nerve nuclei)
- Swallowing, gagging, coughing (9^{th} and 10^{th} cranial nerve nuclei)
- Return of muscle tone (spinal cord, reticulospinal tract, basal ganglia, and primary motor tracts)
- Defensive posturing
- Further increase in alpha and beta activity on EEG
- Extubation possible

Emergence, phase 3
- Eye opening
- Responses to some oral commands
- Awake patterns on EEG
- Extubation possible

Cerebral metabolism, and EEG activity in stages of coma recovery



Brown EM. *NEJM* 2010

Delirium in the ICU

Relationship with delayed awakening?

Prevalence: 12 to 43%

Three subtypes according to psychomotor behavior:

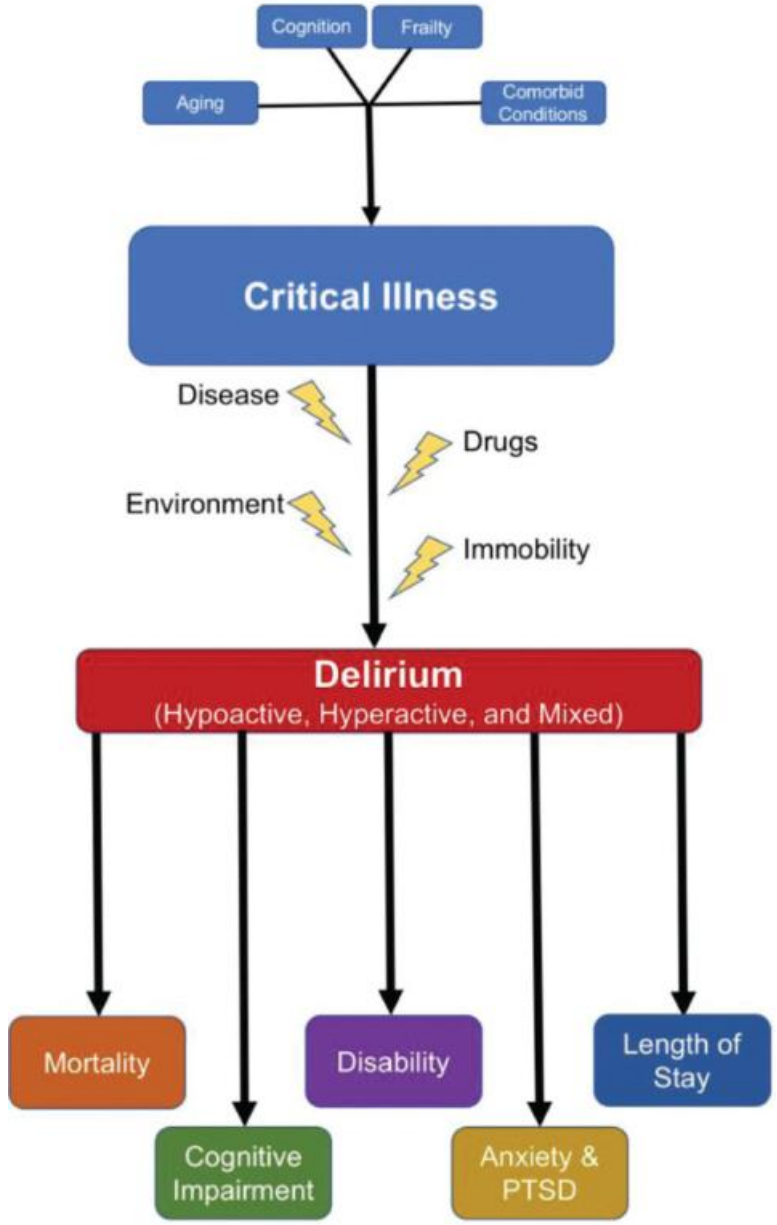
- Hypoactive delirium: 54%

decreased responsiveness, withdrawal and apathy

- Hyperactive delirium: 44%

agitation, restlessness, and emotional lability

- Mixed delirium: 2%



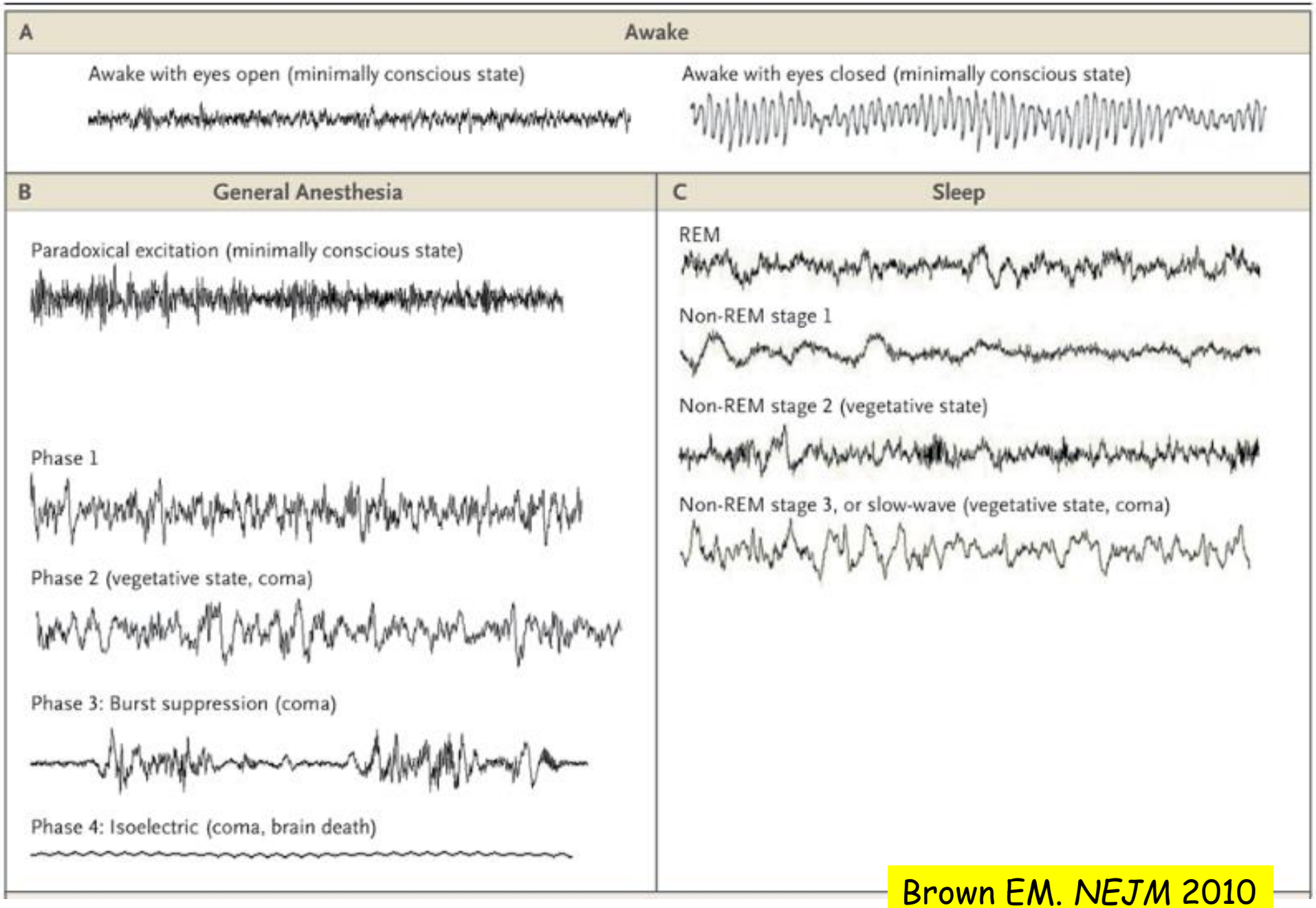
Recommended validated methods to diagnose delirium in the ICU

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
To assess acute changes in the course of mental status, inattention, disorganized thinking & altered consciousness

The Intensive Care Delirium Screening Checklist (ICDSC) 8-item screening tool based on DSM criteria
To assess disorientation in time and space, sleep disturbances, and hallucinations

Author		CAM-ICU Sensitivity	CAM-ICU Specificity	ICDSC Sensitivity	ICDSC specificity
Gusmao-Flores, 2012 [11]	Meta-analysis	0.8 (0.77 to 0.83)	0.96 (0.95 to 0.97)	0.74 (0.65 to 0.81)	0.82 (0.76 to 0.86)
Mitasova, 2012 [13]	Prospective observational study	76% (95% CI: 55–91)	98% (95% CI: 93–100)		
Bebawi, 2014 [14]	Multicenter prospective study	62% (95% CI: 44–76)	74% (95% CI: 59–85)	64% (95% CI: 49–77)	79% (95% CI: 63–89)
Reznik, 2020 [15]	Prospective observational study	41%	88%	77%	97%
Von Hofen-Hohloch, 2020 [16]	Prospective observational study	67%	93%	70%	94%

EEG patterns during the awake state, general anesthesia, and sleep



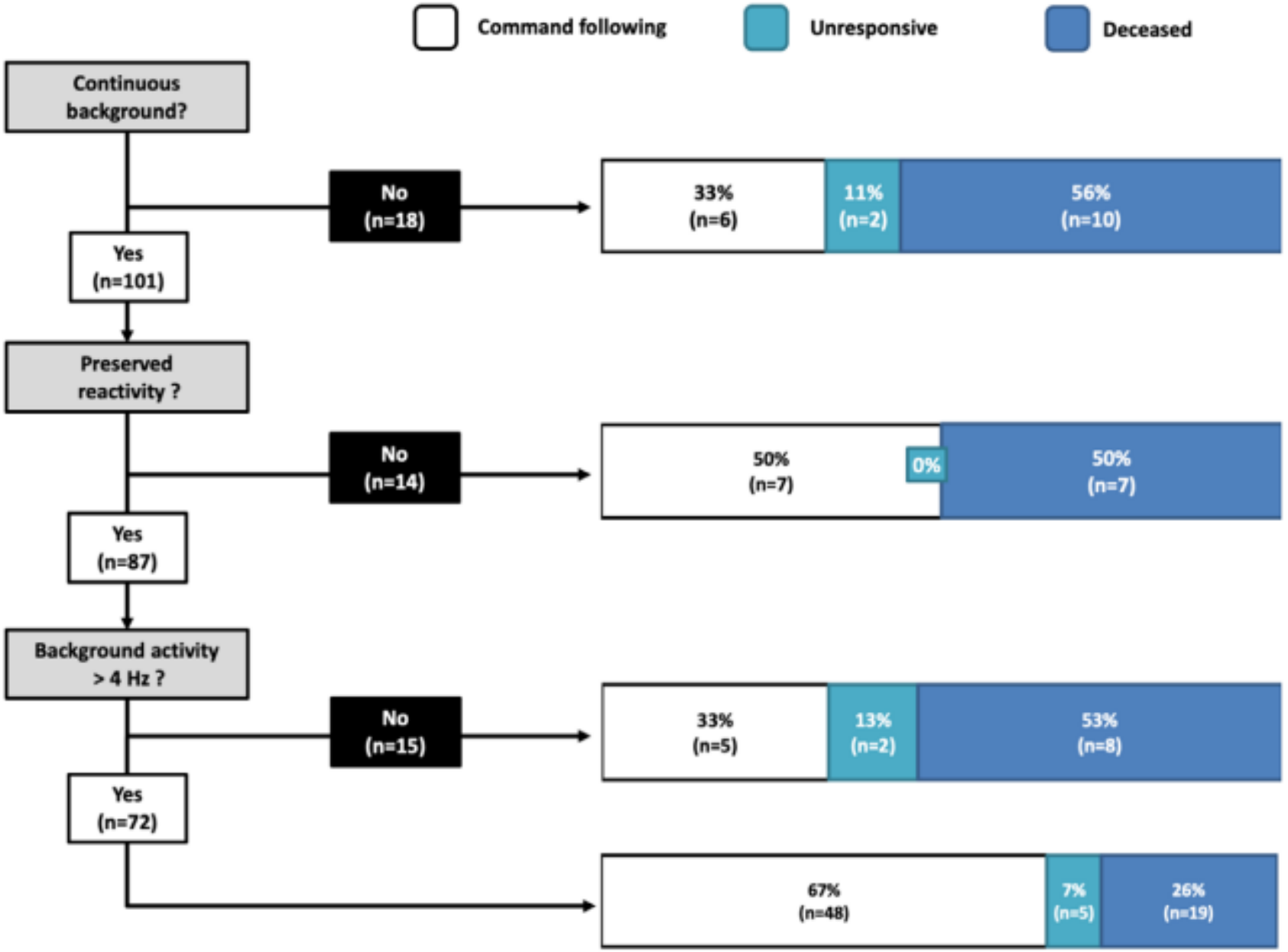
Brown EM. *NEJM* 2010

Association of EEG findings with mortality and command following in patients remaining unresponsive after sedation interruption

An EEG pattern with a background frequency ≥4 Hz was associated with decreased odds of death.

None of the EEG parameters were independently associated with command following.

Legouy C. *Crit Care Med* 2021



Risk factors of delayed awakening

PREDISPOSING FACTORS
(Present on Admission)

MODIFIABLE
Alcohol
Smoking
Hypertension

NON-MODIFIABLE
Advanced age
Pre-existing cognitive impairment
Cardiac disease
Sepsis
Frailty

DELAYED AWAKENING
DELIRIUM

MODIFIABLE
Drugs: sedatives, opiates, anticholinergics, corticosteroids
Environment: noise, sleep disruption, light, visual/ hearing deficits
Immobility
Pain
Prolonged mechanical ventilation
Metabolic disturbances

PRECIPITATING FACTORS
(Acquired In-Hospital)

NON-MODIFIABLE
Severity of illness
Onset of respiratory failure and shock
Severe anemia

Mart MF. Semin Respir Crit Care Med 2021

Causes of delayed awakening

Pharmacokinetic causes
- Impaired metabolism (liver failure, hypothyroidism)
- Impaired elimination (renal failure)
- Duration of sedation
- Drug-drug interaction

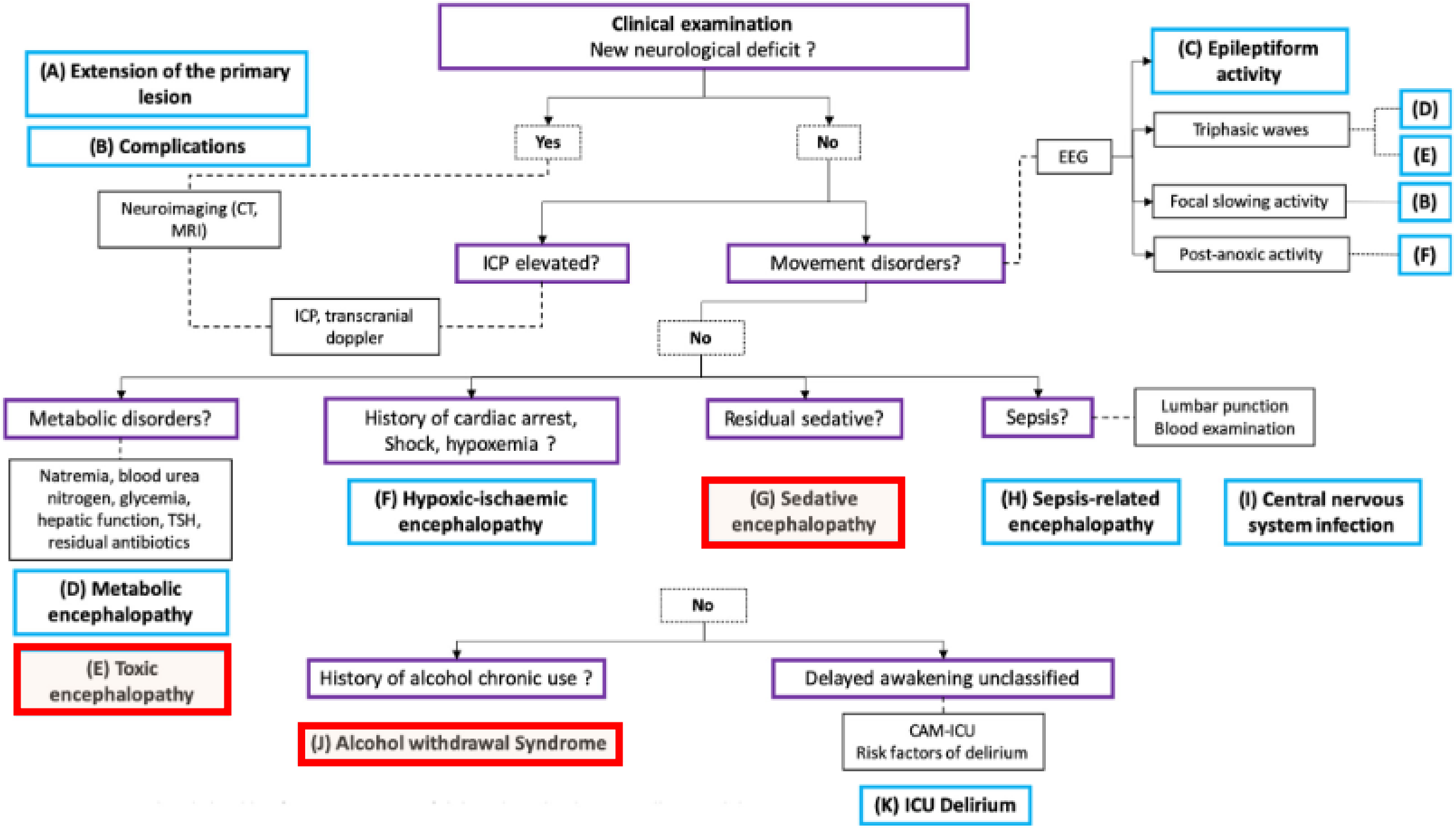
Pharmacodynamic causes
- Genetic variations
- Hypothermia
- Drug-drug interaction

Toxicity
- Antibiotics
- Alcohol (withdrawal syndrome)

Metabolic alterations
- Hypo/Hyperglycemia
- Hypo/Hypernatremia
- Acidosis
- Hyperuremia
- Hyperammoniemia

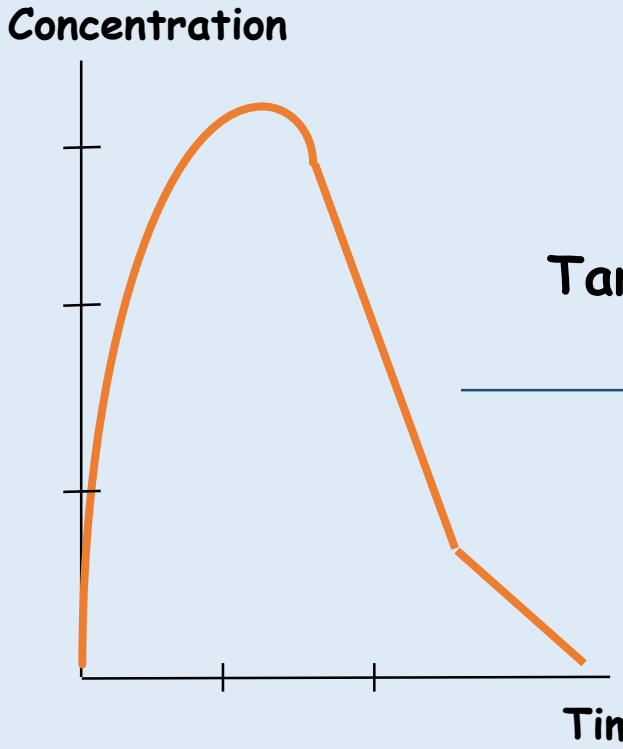
Neurological causes
- Primary lesion
- Secondary lesion (brainstem localization)
- Epilepsy
- Infection

Extra-neurological causes
- Shock
- Hypoxia
- Sepsis–systemic inflammatory


Clinical examination
New neurological deficit ?
Yes
No
(A) Extension of the primary lesion
(B) Complications
Neuroimaging (CT, MRI)
ICP elevated?
ICP, transcranial doppler
Movement disorders?
EEG
(C) Epileptiform activity
Triphasic waves
(D)
(E)
Focal slowing activity
(B)
Post-anoxic activity
(F)
No
Metabolic disorders?
Natremia, blood urea nitrogen, glycemia, hepatic function, TSH, residual antibiotics
(D) Metabolic encephalopathy
(E) Toxic encephalopathy
History of cardiac arrest, Shock, hypoxemia ?
(F) Hypoxic-ischaemic encephalopathy
Residual sedative?
(G) Sedative encephalopathy
Sepsis?
Lumbar punction
Blood examination
(H) Sepsis-related encephalopathy
(I) Central nervous system infection
No
History of alcohol chronic use ?
(J) Alcohol withdrawal Syndrome
Delayed awakening unclassified
CAM-ICU
Risk factors of delirium
(K) ICU Delirium

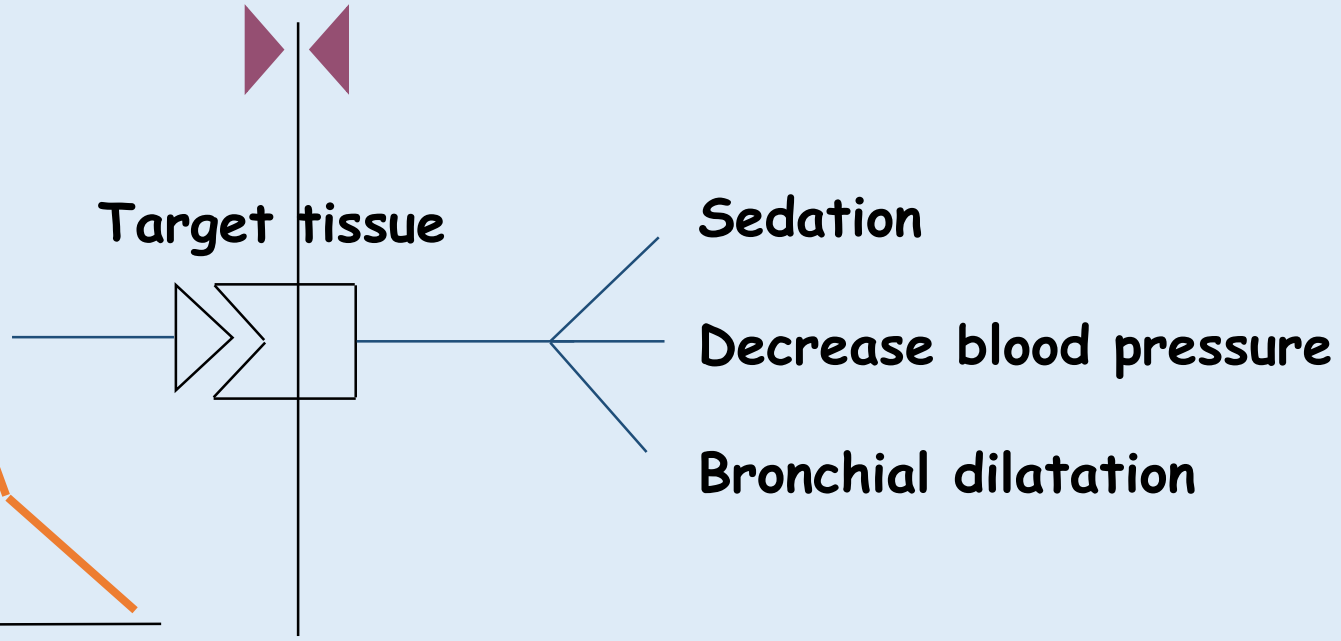
Pharmacology: a dual phenomenon

Pharmacokinetics



How the body deals with the drug

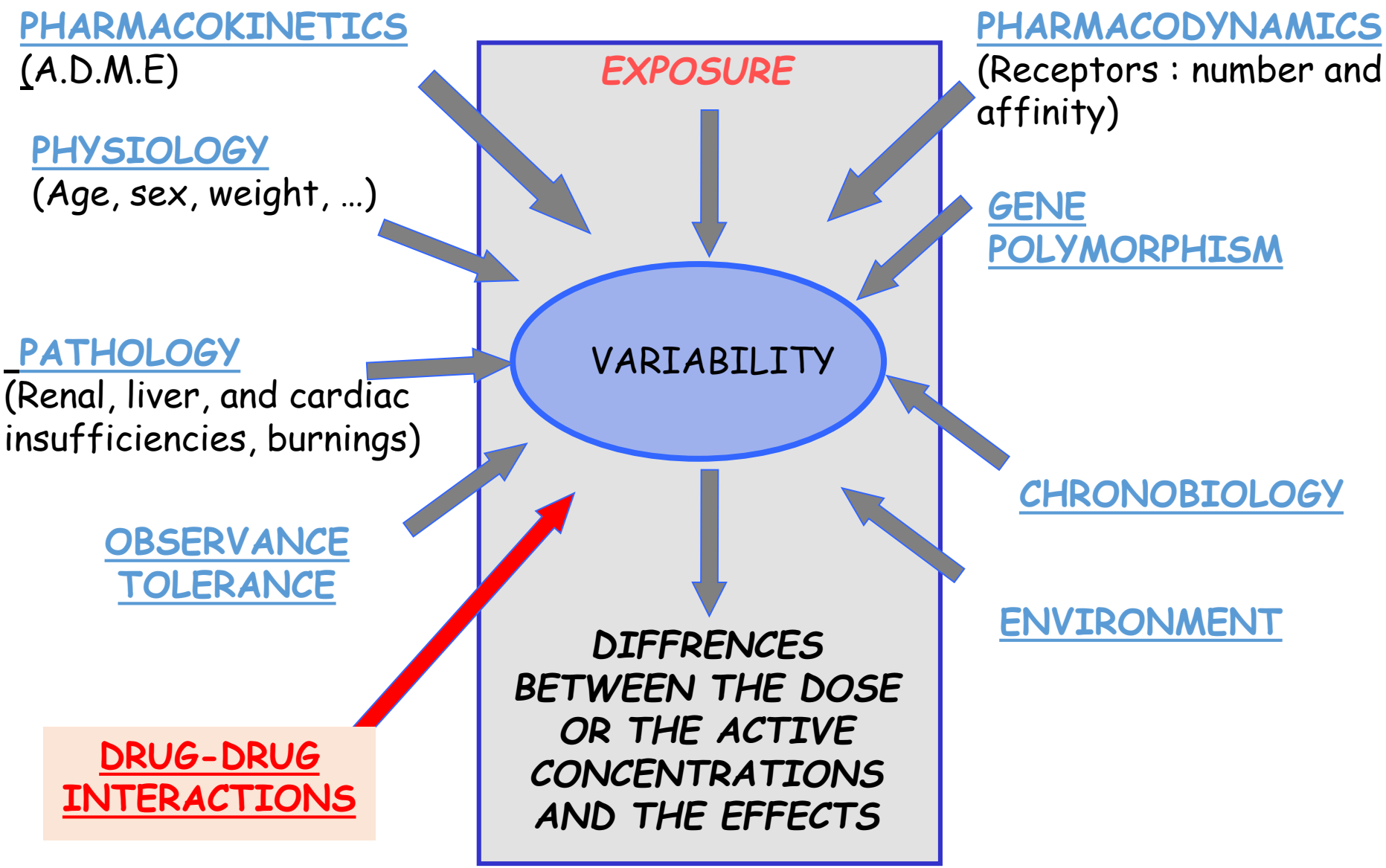
Pharmacodynamics



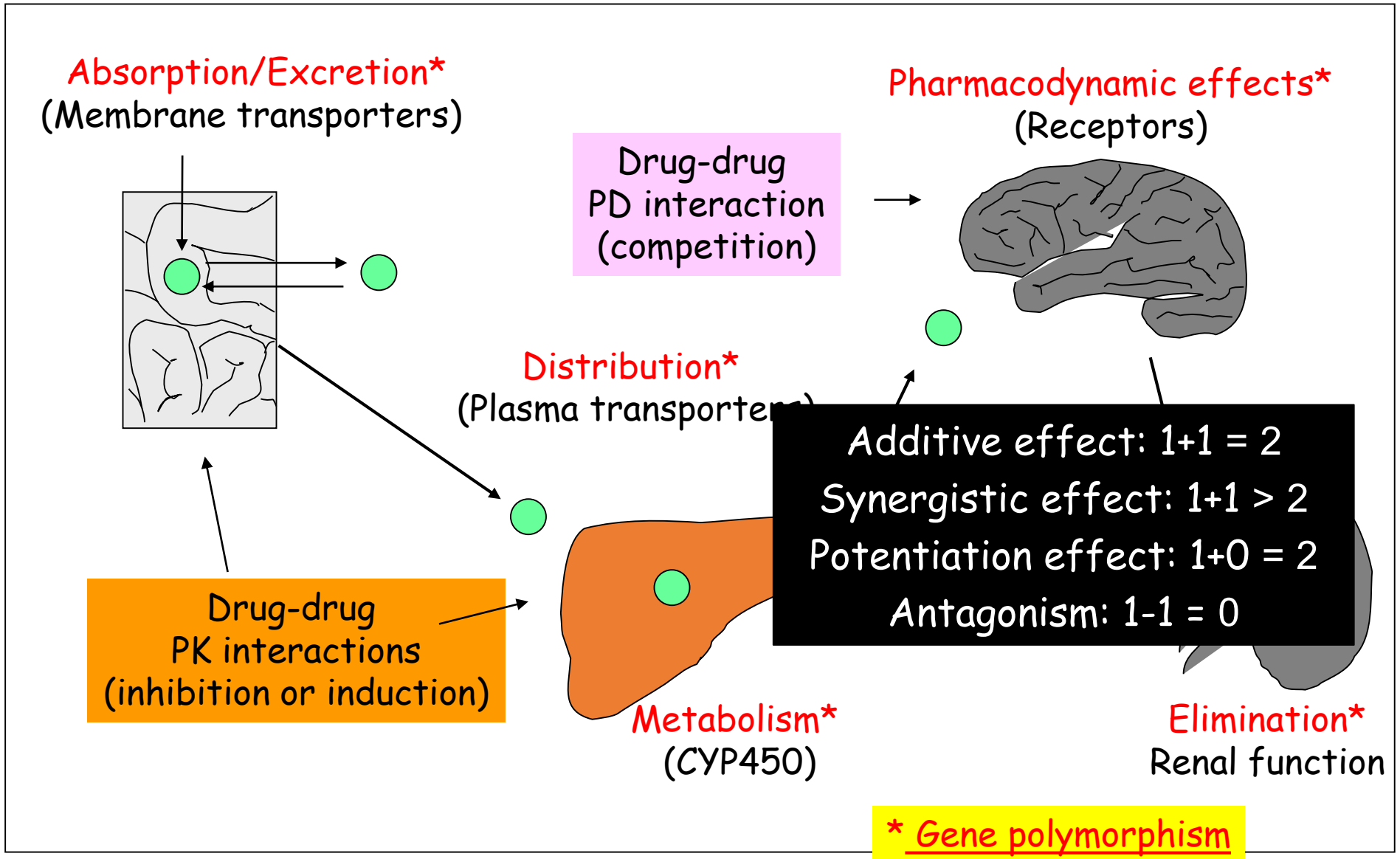
How the drug acts on the body

Mégarbane B. *Expert Opin Drug Metab Toxicol* 2008

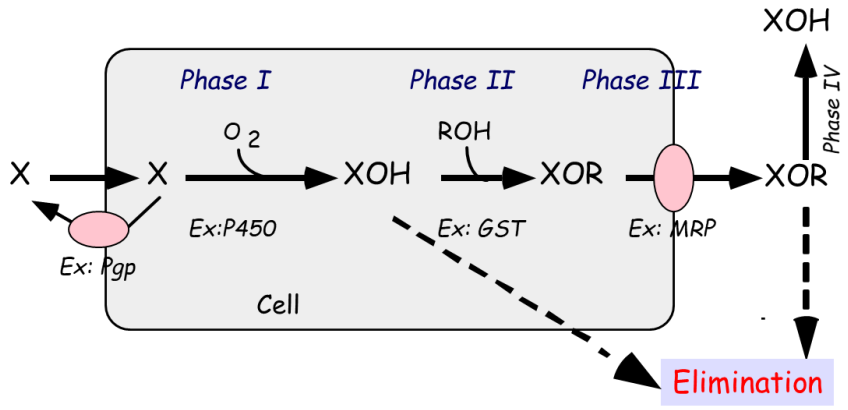
Sources of individual variability in drug response



Individual variability related to drug-drug interaction



Enzymes of drug metabolism

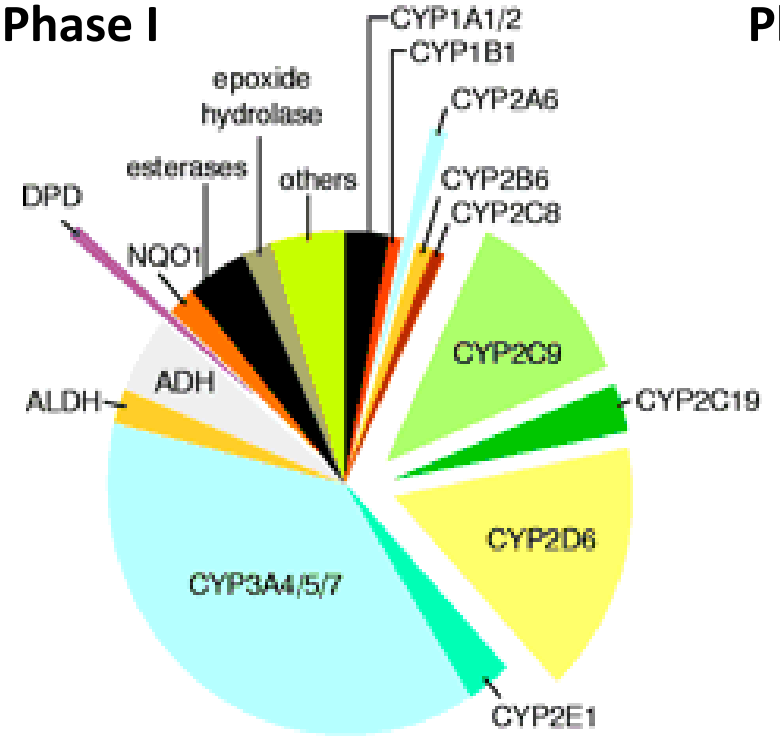


Phase I: functionalization

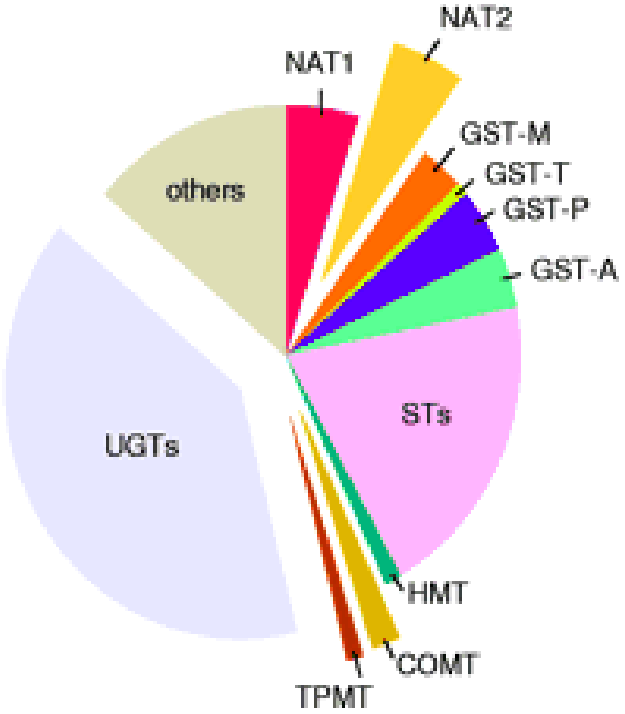
Phase II: conjugaison (+ hydrophilic)

Phase III: elimination of the conjugated or parent drug

Phase I



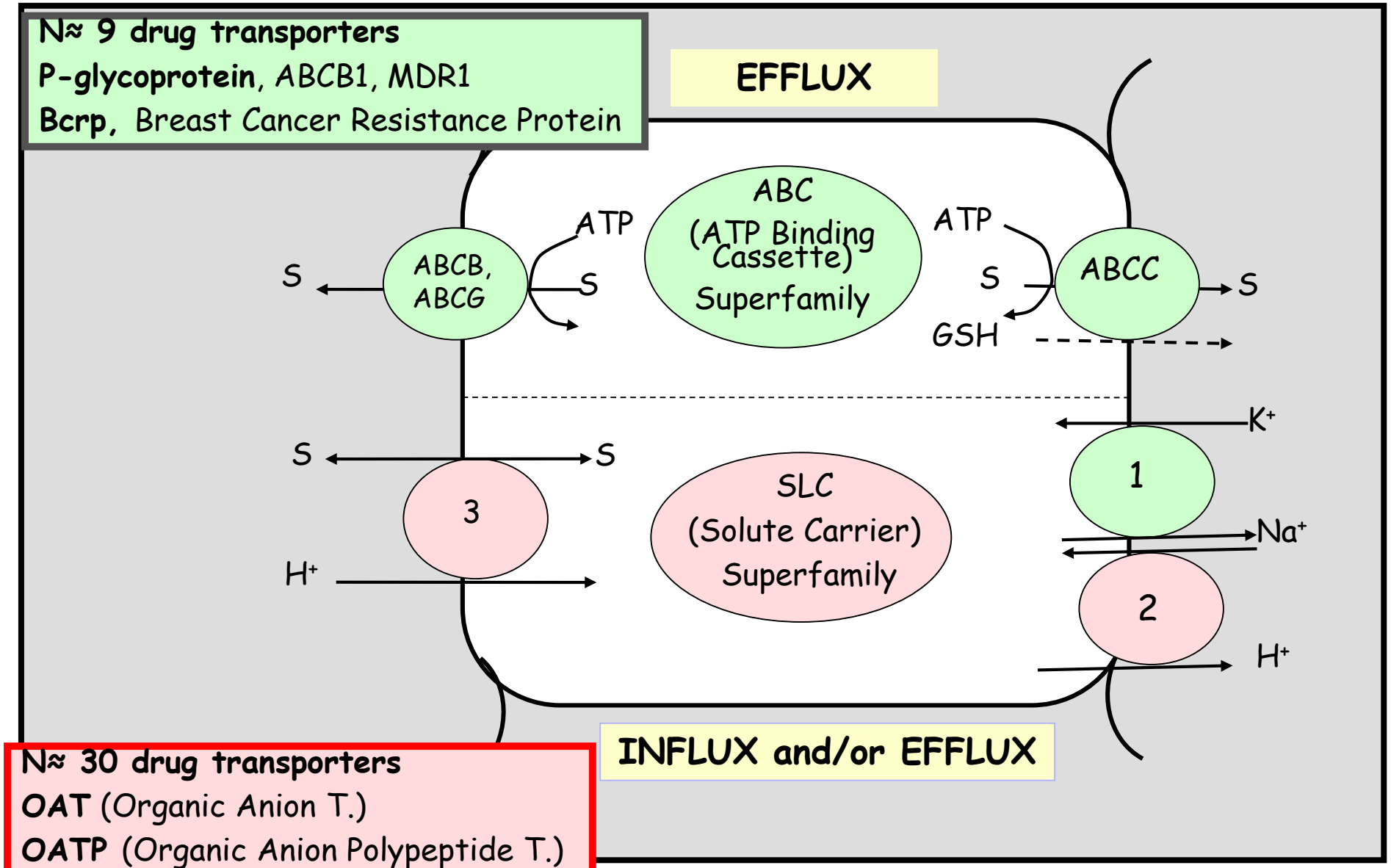
Phase II

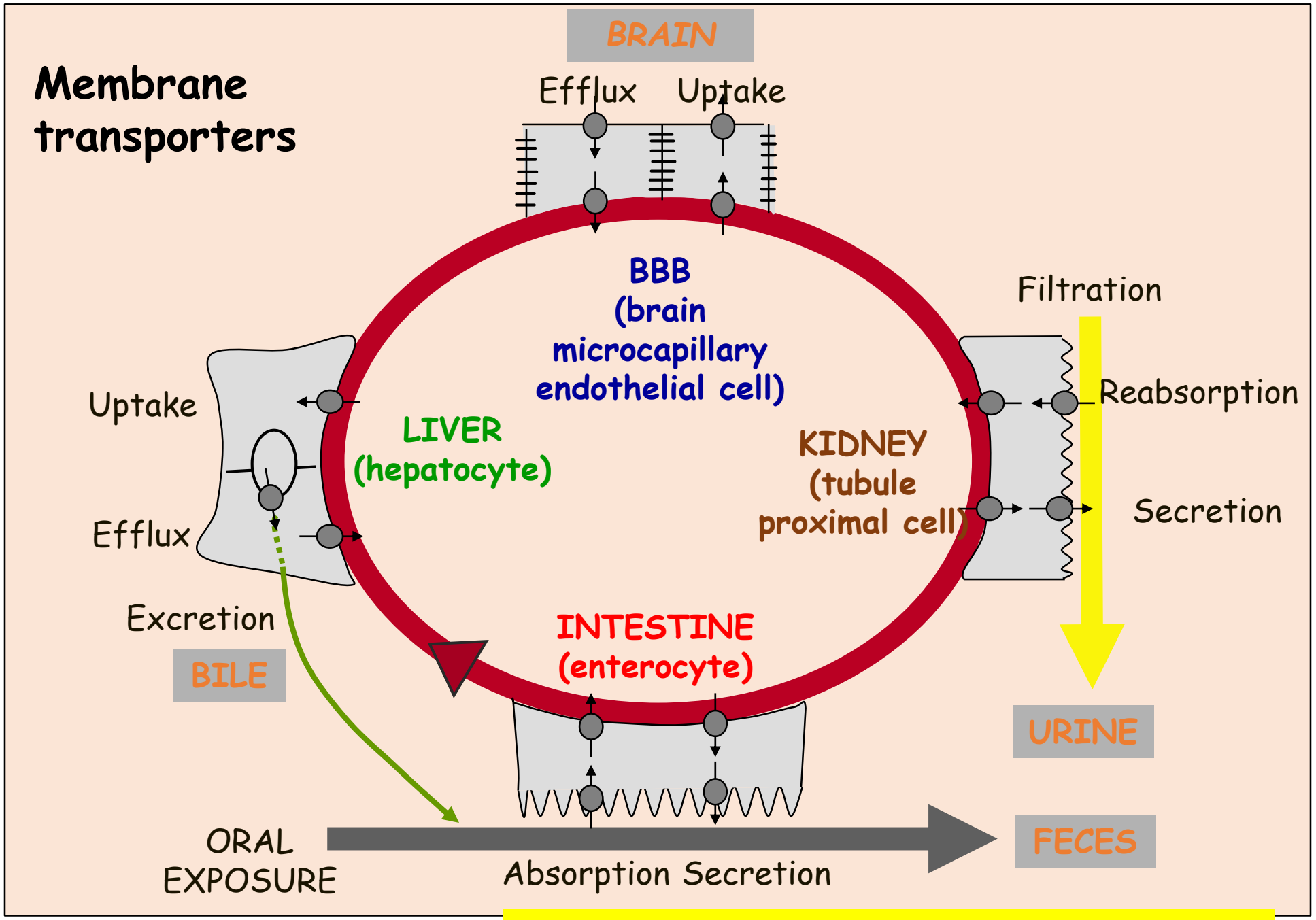


CYP drug substrates, inhibitors and inducers

Substrate	Inhibitor	Inducer
CYP1A2		
Haloperidol, theophylline	Ciprofloxacin, fluvoxamine	Carbamazepine, rifampicin, tobacco
CYP2C9		
Diclofenac, ibuprofen, naproxen, phenytoin, voriconazole, warfarin	Amiodarone, fluconazole, metronidazole, voriconazole	Carbamazepine, phenobarbital, phenytoin, rifampicin
CYP2C19		
Citalopram, diazepam, phenytoin, voriconazole	Fluoxetine, paroxetine, voriconazole	Carbamazepine, rifampicin, phenobarbital, phenytoin
CYP2D6		
Carvedilol, haloperidol, metoprolol, paroxetine, propranolol	Amiodarone, fluoxetine, paroxetine, sertraline, quinidine	
CYP3A4		
Alprazolam, amlodipine, atorvastatin, carbamazepine, cerivastatin, clarithromycin, cyclosporine, diltiazem, erythromycin, felodipine, fentanyl, hydrocortisone, midazolam, methylprednisolone, nifedipine, simvastatin, sufentanil, tacrolimus, verapamil, warfarin	Amiodarone, amlodipine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, verapamil, voriconazole	Carbamazepine, rifabutin, rifampicin, phenobarbital, phenytoin

Drug transport across the membranes





Schermann JM. Comprehensive Med Chem 2007

Major P-glycoprotein (MDR-1) substrates

Anti-cancer drugs
Doxorubicin, taxoids
Vincristin, vinblastin
Cardiovascular drugs
Digoxin
Quinidin
Antiprotease
Indinavir
Nelfinavir
Saquinavir
Anti-diarrheic drugs
Loperamid
Antibiotics
Erythromycin
Immunosuppressive drugs
Cyclosporine

Steroids
Dexamethasone
Calcium channel inhibitors
Verapamil
Adrenergic agonist drugs
Talinolol
H1- anti-histamin drugs
fexofenadine
H2- anti-histamin drugs
Cimetidine
Antidepressants
Amitriptylin
Citalopram, venlafaxine
Others
Colchicine
Phenytoine

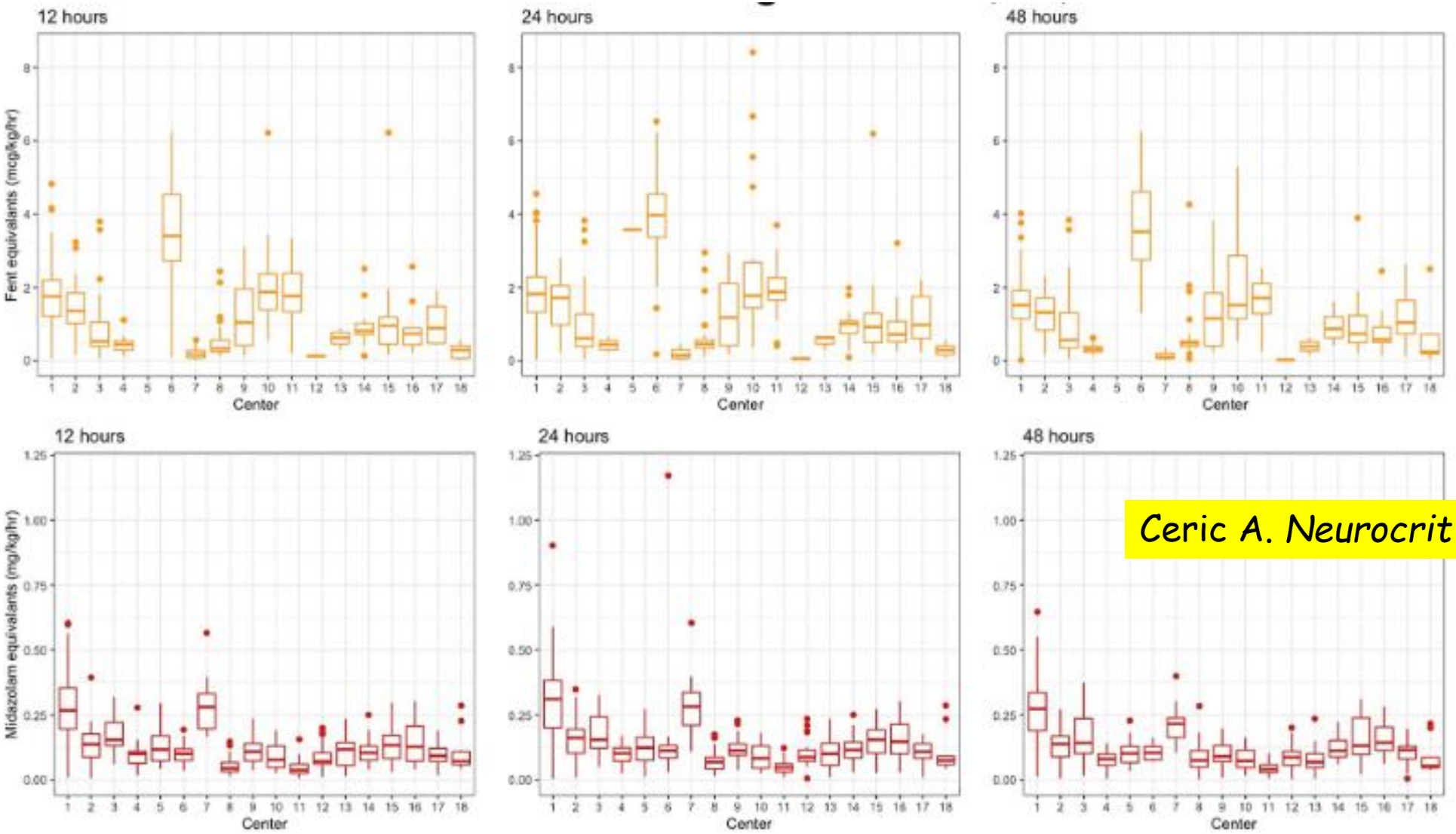
Differences in sedation and analgesia dosing during TTM

Medication	Proportion: 12 h *n* (%)	Dose: median (IQR)	Proportion: 24 h *n* (%)	Dose: median (IQR)	Proportion: 48 h *n* (%)	Dose: median (IQR)
Propofol (mg/kg/h)	421 (69)	2.3 (1.2, 3.8)	431 (70)	2.4 (1.4, 4.3)	432 (70)	2.2 (1.1, 3.7)
Midazolam (mg/kg/h)	244 (40)	0.07 (0.04, 0.13)	259 (42)	0.09 (0.05, 0.10)	258 (42)	0.06 (0.03, 0.10)
Fentanyl (mcg/kg/h)	304 (50)	1.7 (1.2, 2.3)	310 (50)	1.9 (1.3, 2.4)	311 (51)	1.6 (1.1, 2.1)
Morphine (mg/kg/h)	96 (16)	0.04 (0.02, 0.05)	101 (16)	0.04 (0.02, 0.05)	101 (16)	0.3 (0.01, 0.04)
Remifentanil (mcg/kg/h)	84 (14)	3.3 (2.0, 6.1)	87 (14)	3.5 (2.3, 6.4)	84 (14)	3.7 (2.7, 6.0)
Alfentanil (mcg/kg/min)	32 (5)	29.3 (22.5, 37.4)	31(5)	33.3 (28.3, 37.0)	15 (2)	27.8 (23.7, 33.2)
Sufentanil (mcg/kg/h)	16 (3)	0.2 (0.1, 0.3)	16 (3)	0.2 (0.2, 0.3)	18 (3)	0.2 (0.1, 0.2)

Significant differences in number of medications ($p < 0.001$), average dosages ($p < 0.001$), and titration at all time points between centers ($p < 0.001$)

Ceric A. Neurocrit Care 2023

Mean doses of sedatives and analgesics during TTM



Ceric A. Neurocrit Care 2023

Association of sedative and analgesia with CA patient outcome

Multivariable analysis with hierarchical logistic regression

Association with awakening after 5 days

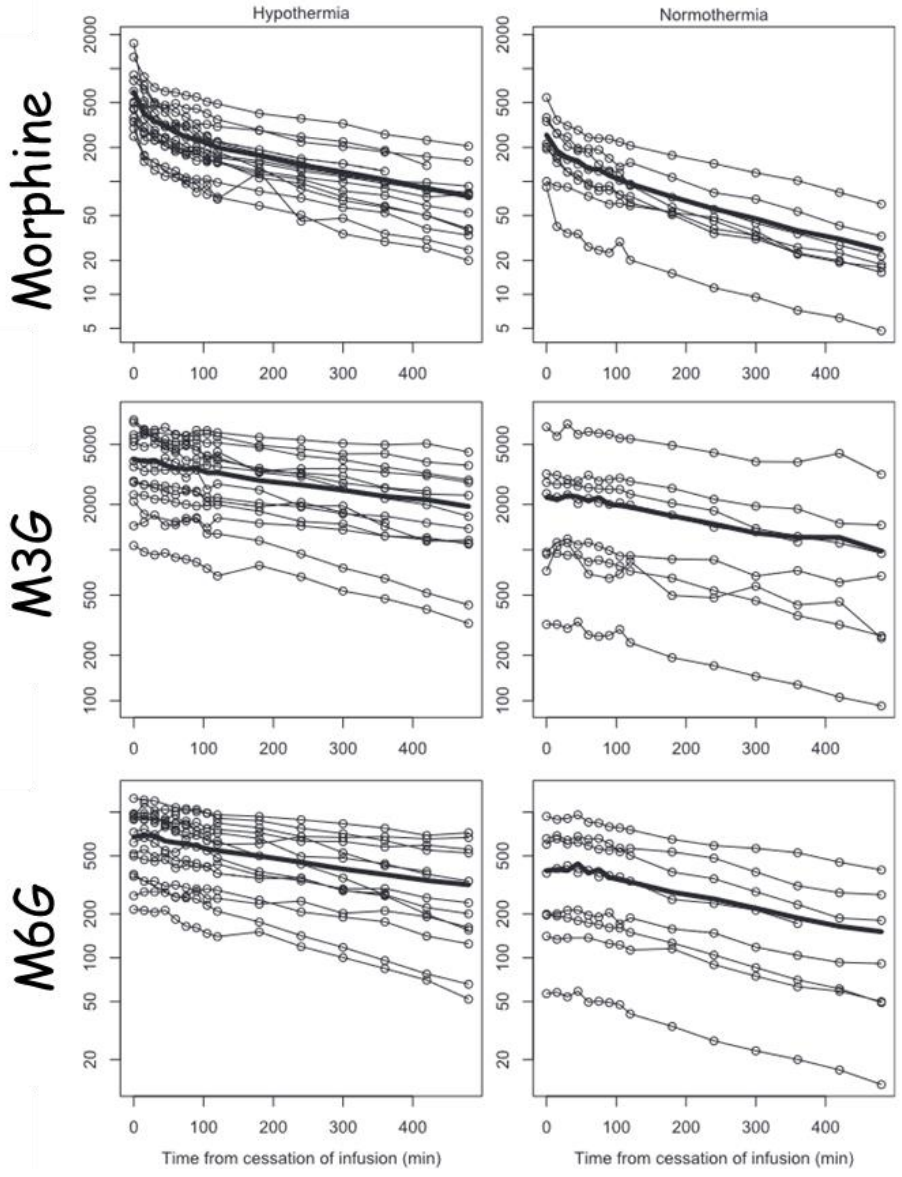
- Higher dosing at 48 h (p=0.003, OR=1.75)
- Increased titration of analgesics in 24-48 h (p=0.005, OR=4.89)
- Increased titration of sedatives in 24-48 h (p<0.001, OR>100)

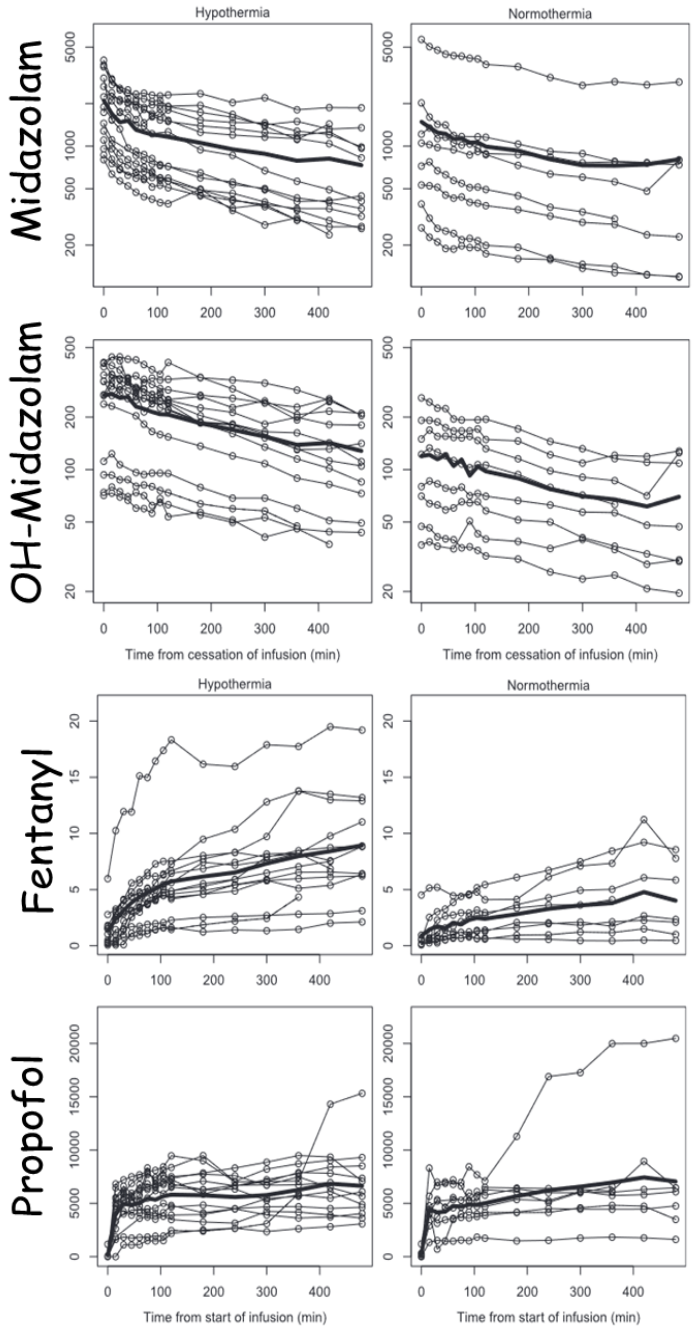
Association between ↗ incidence of clinical seizures and ↗ titration of sedatives in 24-48 h (p=0.04, OR=240)
Association between ↗ survival at 6 months and ↘ titration of analgesics (p=0.048)

However, the causal relation of these findings cannot be proven.

Ceric A. Neurocrit Care 2023

Effects of hypothermia on the disposition of morphine, midazolam, fentanyl, and propofol





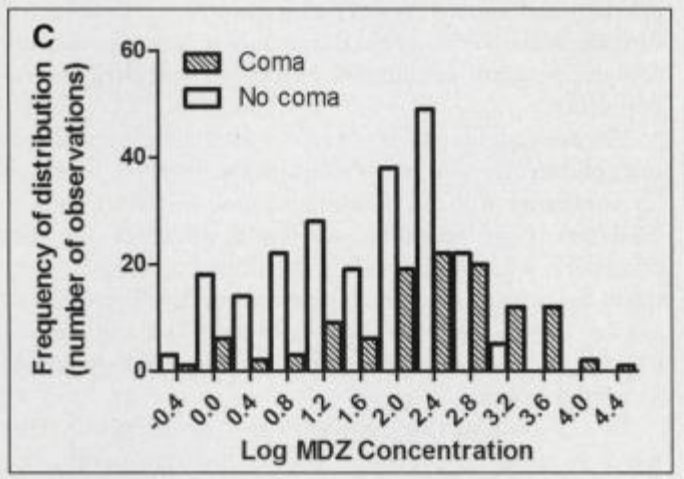
Compared with matched, normothermic patients:

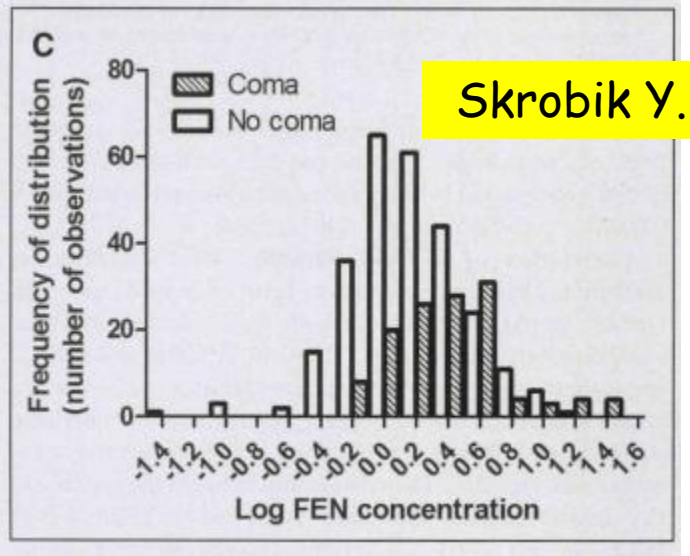
- ↗ $t_{1/2}$ morphine
- ↘ Cl_{tot} morphine, fentanyl, and propofol but not midazolam.

➔ Reducing infusion rates of morphine, fentanyl, and propofol during TTM is encouraged

Bjelland TH. *Dirug Metab Disp* 2013

Factors predisposing to coma and delirium: fentanyl and midazolam exposure; *CYP3A5*, *ABCB1*, and *ABCG2* gene polymorphisms and inflammatory factors



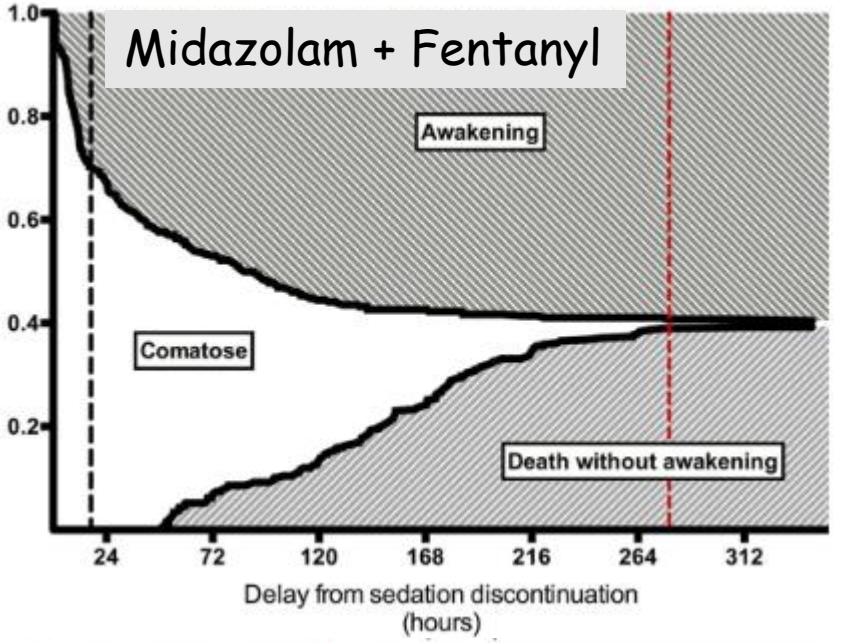


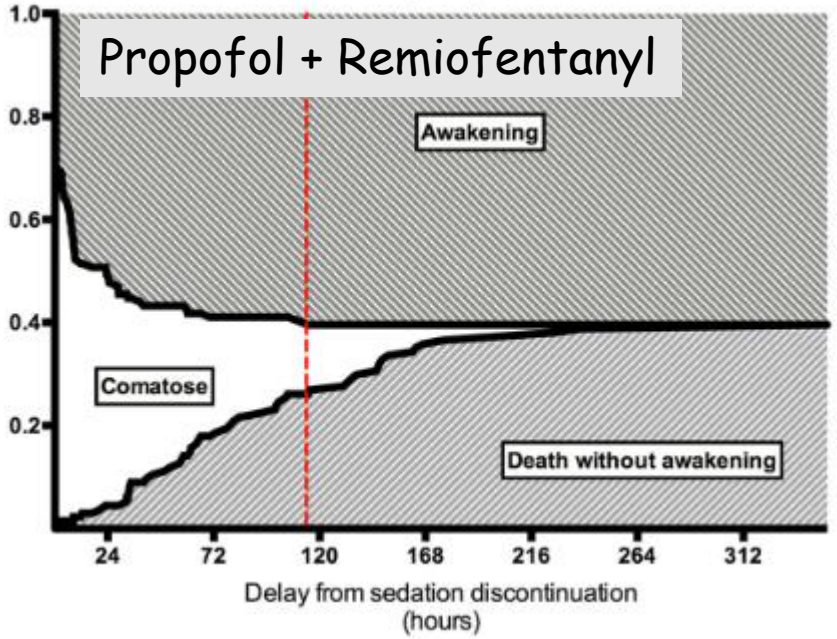
	Only Coma ($n = 15$)	Only Delirium ($n = 7$)	None ($n = 14$)	Delirium vs. Coma (p)
TNF-α	2.6 (1.7–18.7)	5.2 (3.4–23.0)	6.8 (3.4–14.4)	NS
IL-1β	1.3 (1.3–1.3)	1.3 (1.3–3.9)	1.3 (1.3–2.2)	0.07
IL-17	3.9 (3.0–3.9)	3.9 (3.9–6.8)	3.0 (2.1–3.9)	NS
IL-8	25.4 (6.3–61.3)	15.7 (10.0–65.5)	27.1 (10.0–87.0)	NS
MCP-1	199.2 (79.6–550.6)	354.3 (163.9–700.7)	205.8 (67.6–477.7)	NS
IL-1RA	2,652 (1,323–12,503)	10,427 (5,891–14,540)	6,214 (1,386–12,914)	NS
IL-10	11.6 (8.0–28.9)	11.4 (1.6–18.3)	8.0 (1.6–12.9)	NS
MIP-1β	45.0 (20.1–74.7)	62.9 (50.7–89.0)	35.3 (15.1–79.6)	NS
IL-6	35.0 (11.3–78.5)	129.3 (48.8–291.7)	48.7 (16.5–915.4)	0.05

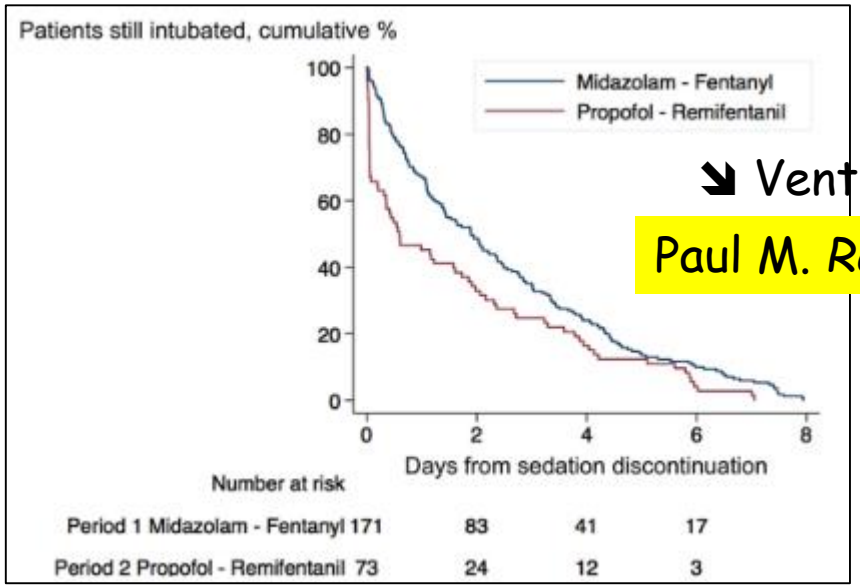
Skrobik Y. *Ctit Care Med* 2013

	Genetic Polymorphism						
	CYP3A5 *1/*3	*CYP3A5* *3/*3	*ABCB1* C/C	*ABCB1* C/T	*ABCB1* T/T	*ABCG2* C/C	*ABCG2* C/A
Coma, *n* (%)	6 (10.9)	49 (89.1)	15 (27.3)	29 (52.7)	11 (20.0)	50 (84.7)	9 (15.3)
	$p = 0.34$		$p = 0.58$			$p = 0.93$	
Delirium, *n* (%)	7 (11.7)	53 (88.3)	14 (23.3)	32 (53.3)	14 (23.3)	55 (85.9)	9 (14.1)
	$p = 0.14$		$p = 0.93$			$p = 0.72$	
No coma or delirium, *n* (%)	2 (5.1)	37 (94.9)	12 (30.8)	19 (48.7)	8 (20.5)	30 (83.3)	6 (16.7)

Comparison of two sedation regimens during TTM after cardiac arrest







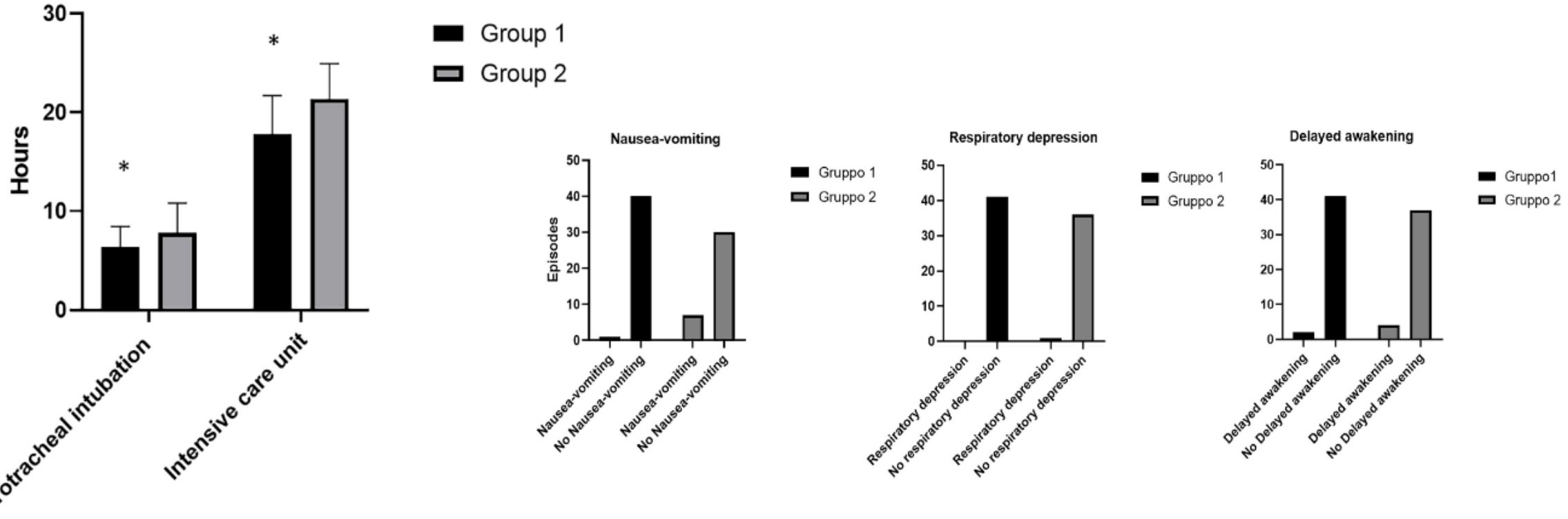
↘ Ventilator-free days

Paul M. *Ressuscitation* 2018

Factors associated with delayed awakening in multivariate analysis.

Characteristic	OR	95% IC	P
Age > 59 years	2.4	1.2–4.9	0.001
Post-resuscitation shock	2.6	1.3–5	0.004
GFR < 60 ml min $^{-1}$ at admission	2.6	1.3–5.3	0.009
Period P2 (propofol-remifentanil)	0.08	0.03–0.2	< 0.001

Reduced opioid use and ICU lengths after minimally invasive cardiac surgery- An observational retrospective study



Group 1 (N=41): ultrasound-guided pectoralis + serratus plane blocks with ropivacaine

Group 2 (N=37): IV opioids (morphine 20–25 mg/day or tramadol 200–300 mg/day)

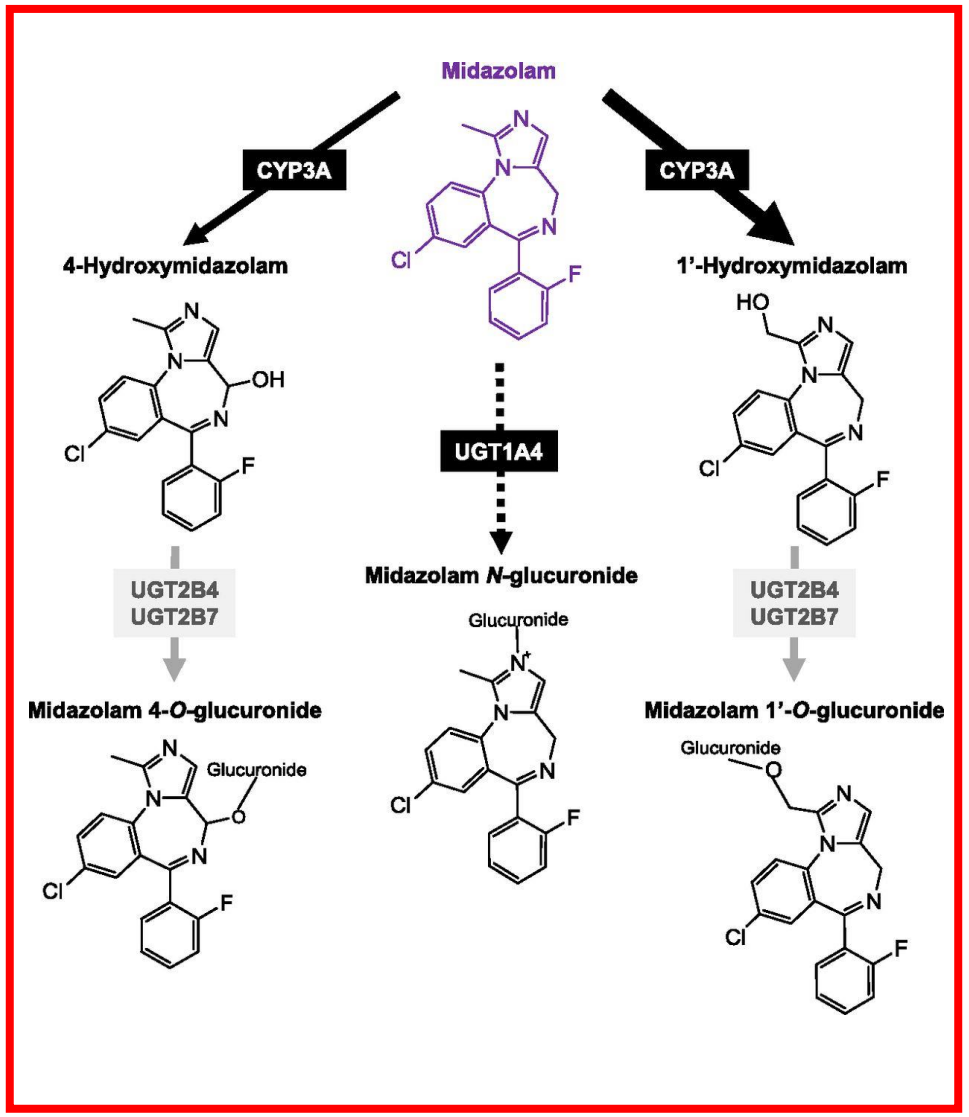
Torre DE. *Life* 2022

Clinical pharmacokinetic monitoring of midazolam

- MDZ = higher clearance and shorter half-life than other BZD
- Good correlation plasma MDZ and α1-OH MDZ / sedation
- High interpatient variability (age, renal and liver function, CYP activity/gene polymorphism)
- No simple assay to quantitate MDZ

Because plasma MDZ to achieve a constant sedation is variable, it is more prudent to monitor for sedation with a validated clinical scale than by plasma concentrations

Although not routinely recommended, MDZ monitoring is likely beneficial in patients with neurologic damage in whom sedation cannot be assessed and patients with renal failure and prolonged time to awakening



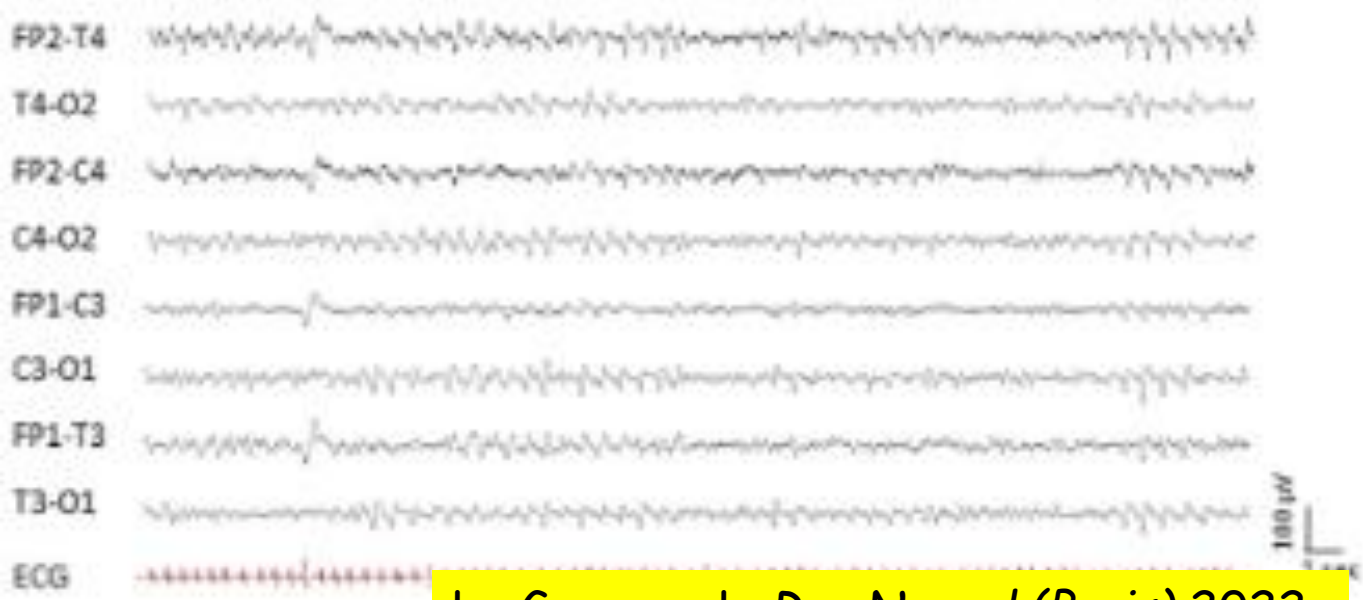
Toxic encephalopathy

Main drugs leading to toxic metabolic encephalopathy

Antiepileptics	Benzodiazepines
	Valproic acid[a]
	Barbiturates[a]
	Phenytoin
	Gabapentin
	Lacosamide
	Carbamazepine[b]
Psychiatrics	Tricyclic antidepressants
	Selective serotonin reuptake inhibitors
	Neuroleptics
	Lithium
Oncologic	Methotrexate[a]
	L-asparaginase[a]
	5-fluoro-uracil[a]
	Ifosfamide
Immunosuppressants	Calcineurin inhibitors
	Tacrolimus
Antimicrobial agents	Betalactams (including carbapenems, cefepime)
	Fluoroquinolone
	Metrodinazole
	Linezolid
	Foscavir, aciclovir
	Interferon alpha
	Fluconazole
Miscellaneous	Dopamine agonists
	Levodopa
	Opioids
	Proton pump inhibitors
	Baclofen
	Loperamide

Clinical presentation:

- Delirium
- Sleep disorders
- Myoclonus and asterixis
- Cranial nerve palsy
- Extrapyramidal signs and movement disorders



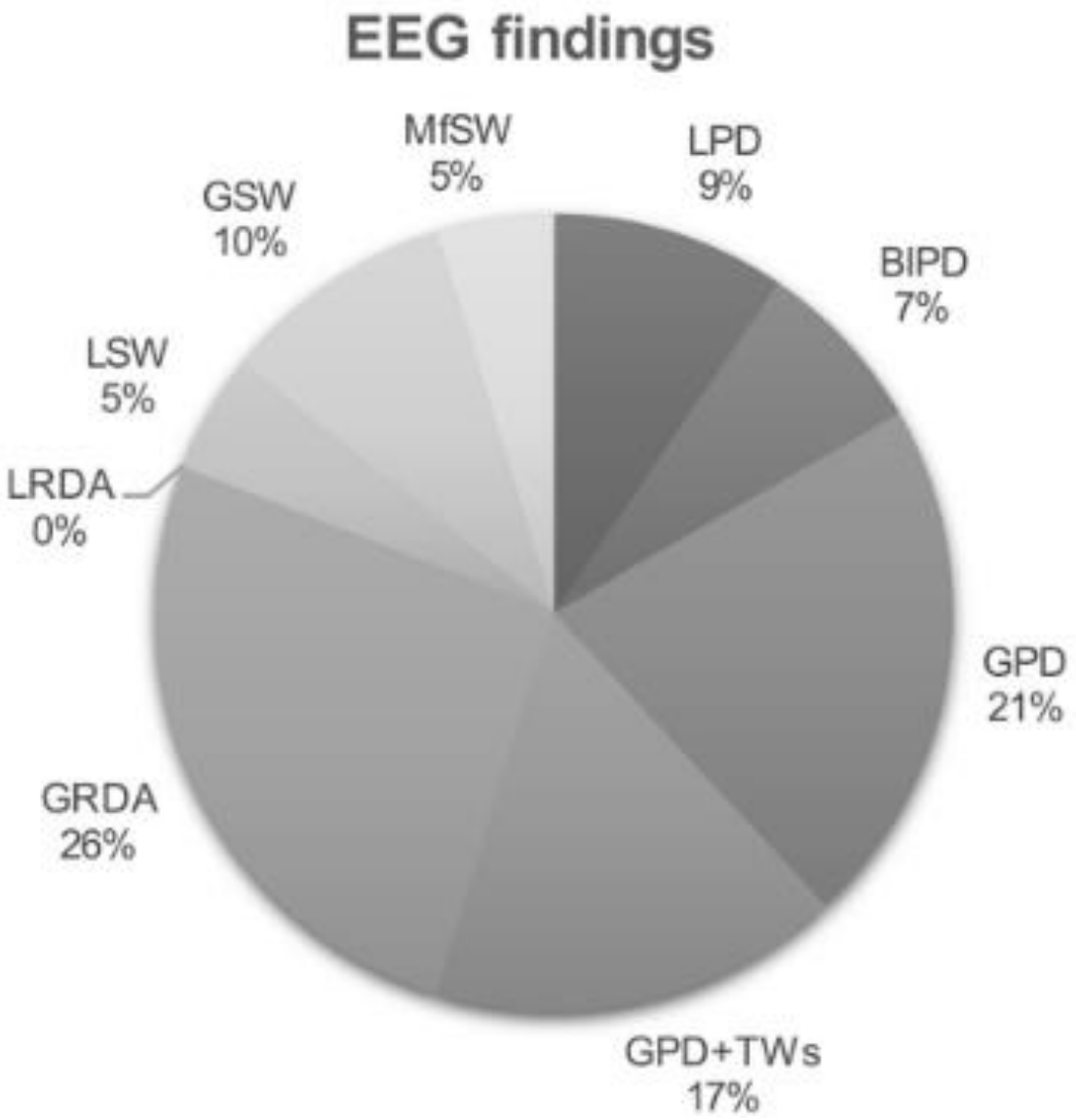
Le Guennec L. *Rev Neurol (Paris)* 2022

Cefepime-induced neurotoxicity: systematic review

	Prevalence (%)	Median (IQR)
Latency period (days)[a]	114 (95.8)[b]	4.0 (3.0–6.0)
Clinical symptoms		
Altered mental status	111 (93.3)	
Myoclonus	44 (37.0)	
Non-convulsive seizure epilepticus	33 (27.7)	
Convulsive seizure	13 (10.9)	
Aphasia	13 (10.9)	
Focal deficit	4 (3.4)	
Laboratory findings		
Blood urea nitrogen (mg/dL)	46 (38.7)	54.5 (31.1–95.2)
Creatinine (mg/dL)	68 (57.1)	2.8 (1.7–5.3)
Drug monitoring		
Serum (plasma) trough level of cefepime (mg/L)	19 (16.0)	71.3 (48.1–160.0) (range 31.0–295.0)
CSF concentration of cefepime (mg/L)	4 (3.4)	13.5 (7.8–17.0) (range 6.1–18.0)
Electroencephalography		
Positive for triphasic waves	33 (27.7)	
Treatment		
Discontinuation of cefepime	116 (97.5)	
Dose reduction of cefepime	3 (2.5)	
Anti-epileptic drugs	44 (37.0)	
Haemodialysis	25 (21.0)	
Prognosis		
Improvement of CIN symptoms	116 (97.5)[b]	
Not reported	3 (2.5)	
Time until CIN symptom resolution from cefepime discontinuation (days)	89 (74.8)[b]	3.0 (2.0–5.0)
Death	9 (7.6)[c]	

Maan G. J Antimicrob Chemother 2022

EEG features of cefepime-induced neurotoxicity



GRDA was the most frequent EEG pattern (26%), followed by GPD with or without triphasic waves.

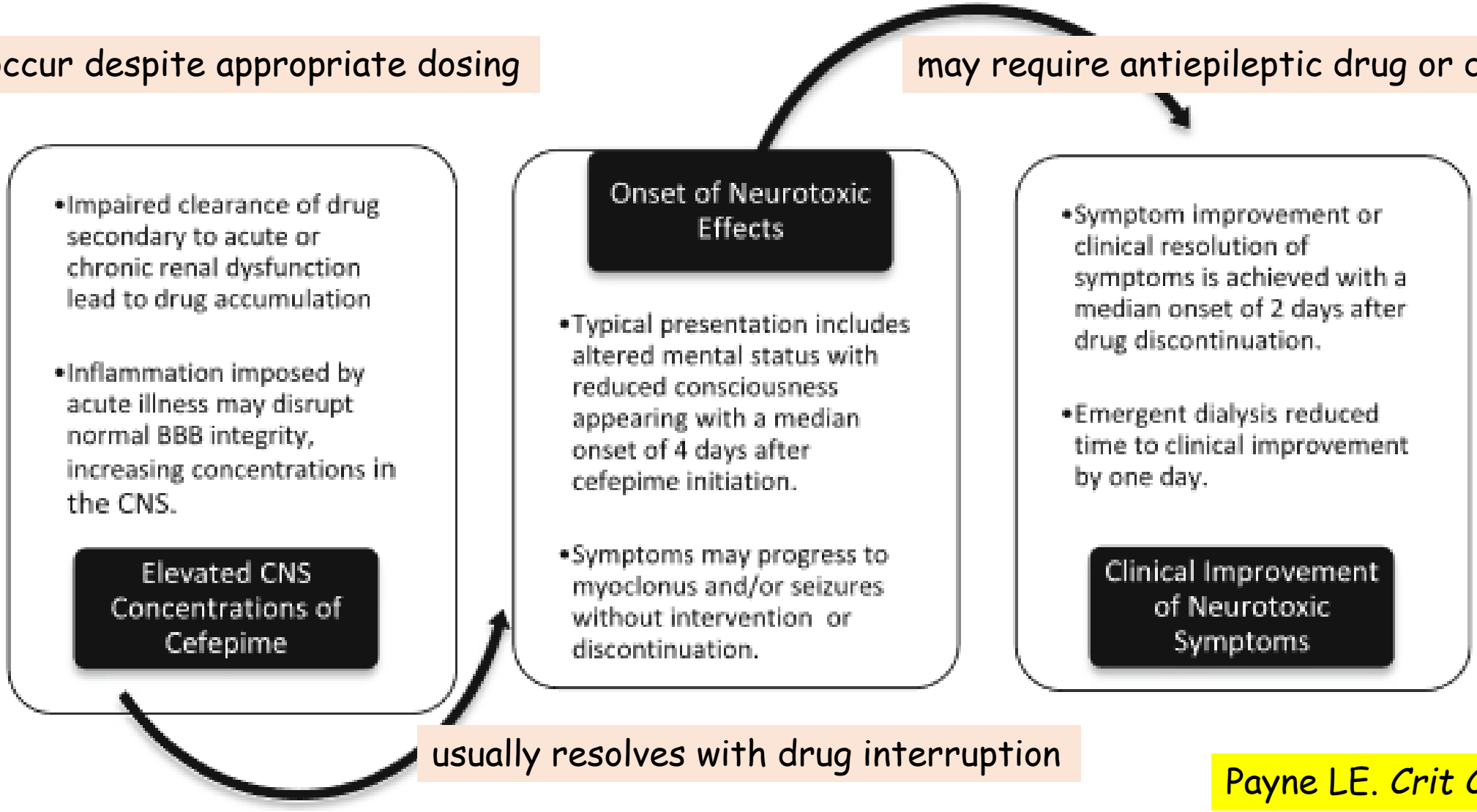
GRDA, generalized rhythmic delta activity
GPD, generalized periodic discharge
TW, triphasic waves
GSW, generalized spike-and-waves
LPD, lateralized periodic discharge
BIPD, bilateral independent periodic discharge
LSW, lateralized spike-and-waves
MfSW, multifocal spike-and-wave
LRDA, lateralized rhythmic delta activity

Li HT. *Neurocrit Care* 2019

Cefepime-induced neurotoxicity: a systematic review

can occur despite appropriate dosing

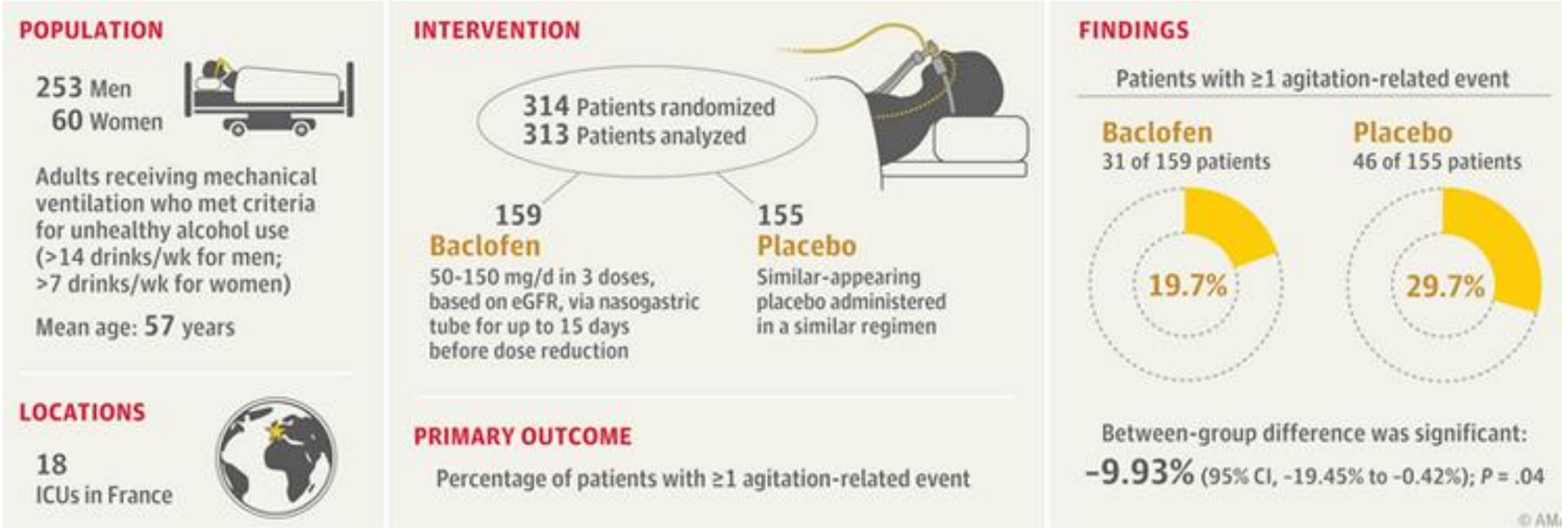
may require antiepileptic drug or dialysis



usually resolves with drug interruption

Payne LE. *Crit Care* 2017

Effect of high-dose baclofen on agitation-related events among patients with unhealthy alcohol use receiving mechanical ventilation - A RCT



Delayed awakening (no eye opening at 72h after cessation of sedative) occurred in 14 pts (8.9%) in the baclofen group vs 3 (1.9%) in the placebo group.

Vourc'h M. *JAMA* 2021

Strategies to minimize delirium incidence and avoid delayed awakening

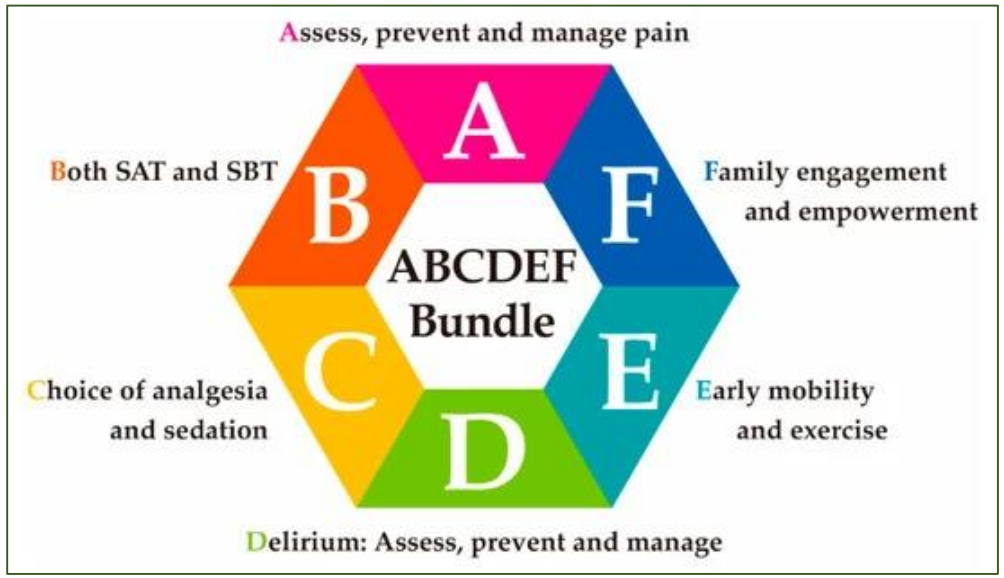
- Daily interruption of sedation
- Use of sedation algorithm to avoid over-sedation
- Analgesia prioritization-based algorithm
- Patient-centered case-based on the assessment & treatment of specific symptoms (pain, anxiety, delusion)
- Improving cognition (reorientation, cognitive stimulation, use of clocks)
- Optimizing sleep (minimizing light and noise)
- Optimizing mobility (early rehabilitation)
- Optimizing hearing (hearing aids) and vision (glasses)

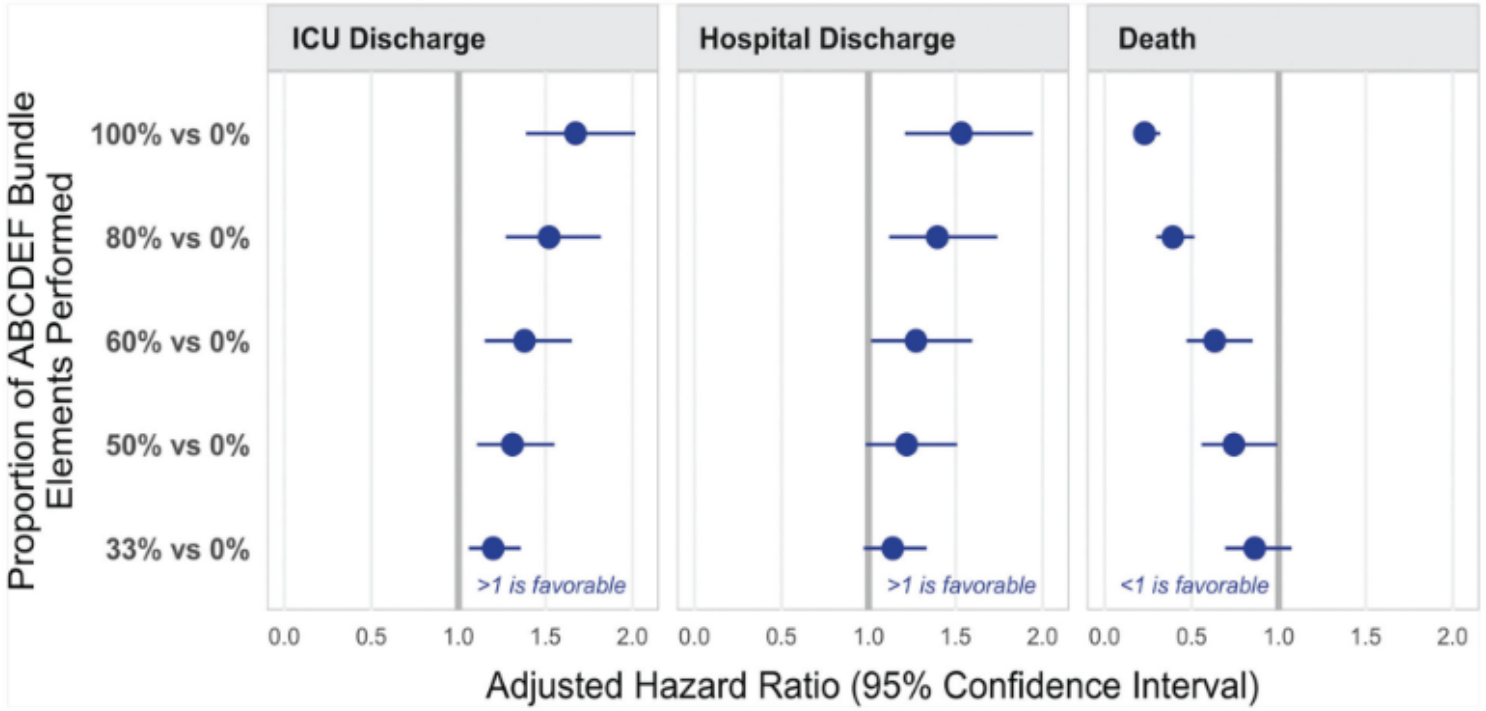
International guidelines do not recommend pharmacologic prevention of delirium, notably by haloperidol; risperidone, and dexmedetomidine

Primary delirium prevention principles
• Repeated reorientation • Provisions of cognitively stimulating activities multiple times a day • A sleep protocol • Early mobilization • Timely removal of catheters and physical restraints • Use of eye glasses, magnifying lenses, hearing aids, and earwax disimpaction • Correction of dehydration • Use of a scheduled pain management protocol • Minimization of unnecessary noise and tactile stimuli

Mnemonic	**Clinical causes and interventions**
Diseases	Evaluate the patient for new or worsening disease, such as congestive heart failure or sepsis, as well as other disease findings such as metabolic abnormalities
Drug Removal	Look for and stop deliriogenic medications including benzodiazepines, antihistamines, and inappropriate opioids
Environment	Encourage daytime mobilization and remove restraints, provide frequent reorientation as well as cues such as clocks and windows to the outside, reduce night-time interventions to promote restful sleep

Proportional performance of ABCDEF bundle and patient outcomes





Mart MF. *Semin Respir Crit Care Med 2021*

What to do when a drug-related delay in awakening is suspected ?

- Detailed neurological examination
- Critical review of sedative drug schemes
- Time-course of renal and liver function
- Investigate potential drug-drug interactions
- EEG and PD tests (naloxone, flumazenil)
- Brain imaging (including MRI)
- Measurement of plasma concentrations of sedative drugs, with at least two time-points
- CYP3A4 and UGT2B4/UGT2B7 genotyping (MDZ)
- CYP2B6/2C9 and UGTAA genotyping (propofol)

- Prolonged tight observation

Take home messages

- **Delayed awakening** is frequent in patients requiring deep sedation and associated with increased morbidity and mortality

- Management is based on a **systematic approach seeking for curable cause**

- Investigation requires
  - ➔ A cautious identification of **drug exposures and exposure times**
  - ➔ A careful examination to report **unexpected presentation**
  - ➔ Blood sampling for **drug concentration measurement**
  - ➔ If possible: time-course of concentrations, PK parameters, metabolic ratios, genotyping
  - ➔ **Mechanistic hypotheses**

- **Studies** are required to understand mechanisms, assess prognosis, and improve prevention