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Delirium induzido por medicamento: desafios na prática clínica

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Declaração de conflito de interesse

Declaro não apresentar conflitos de interesse que possam ser relacionados à esta apresentação.

Agenda

- ✓Contextualização.
- ✓Diagnóstico e triagem.
- ✓Fisiopatologia.
- ✓Fatores de risco.
- ✓Prevenção e manejo.
- ✓Perspectivas.

Contextualização

✓Delirium é considerado um grave problema de saúde pública.

Inouye et al. The Lancet 2014; 383: 911-922.

✓Está associado com angústia e sofrimento considerável para pacientes e cuidadores.

Williams, et al. Eur. Geriatr. Med. 2020; 11: 63–70.

✓Frequentemente não é diagnosticado ou reconhecido por profissionais da saúde.

Inouye et al. The Lancet 2014; 383: 911-922.

✓Pode ser evitado em 30–40% dos casos.

Inouye et al. N Engl J Med 1999; 340: 669–76.

✓ É um indicador da qualidade da assistência à saúde, sobretudo para idosos.

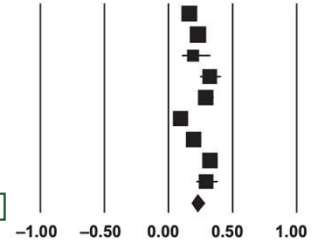
Wachter RM. Understanding patient safety, 2nd edn. New York: McGraw-Hill Medical, 2012.

Epidemiologia

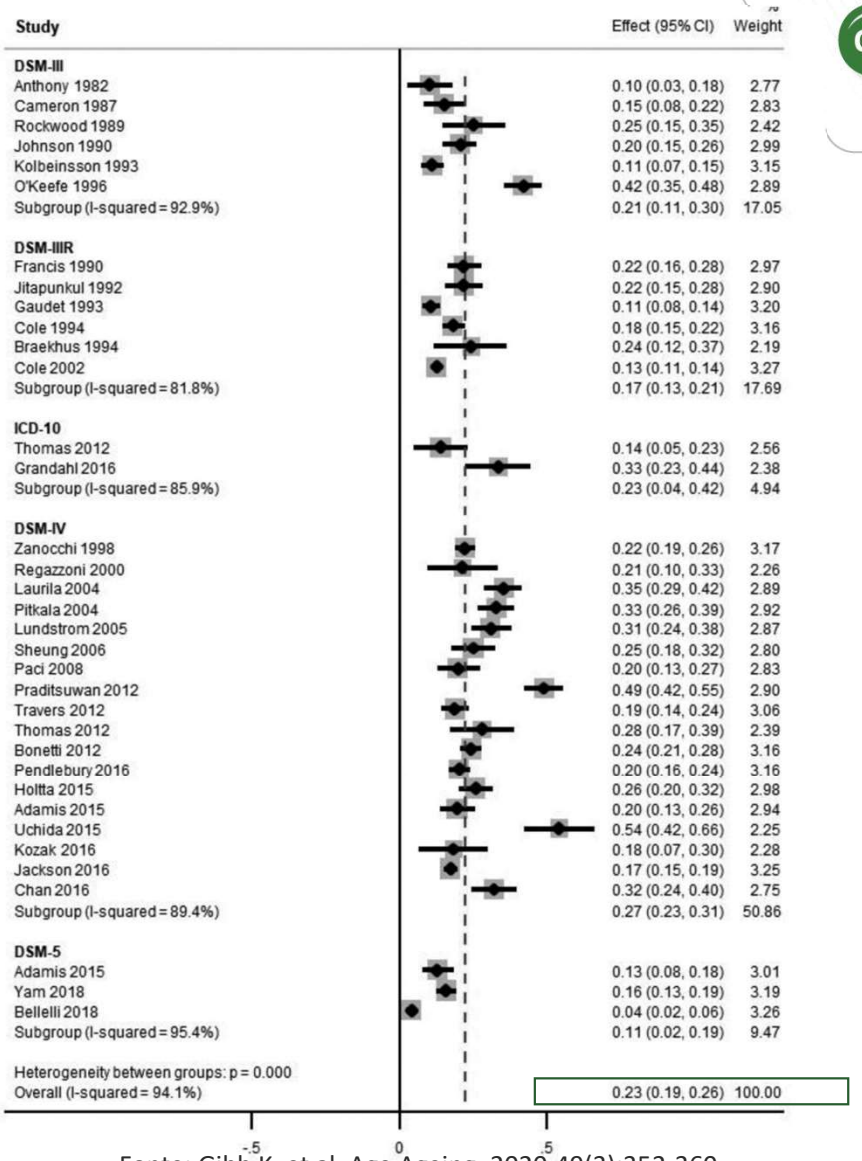
TABLE 3 Meta-analysis results on delirium point prevalence

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Casey et al., 2019	0.163	0.134	0.196	−14.294	0.000
Bellelli et al., 2016	0.230	0.211	0.249	−21.987	0.000
Hosie et al., 2016	0.191	0.103	0.329	−3.885	0.000
Norbaek & Glipstrup, 2016	0.322	0.244	0.411	−3.779	0.000
Giraud & Vuylsteke, 2014	0.290	0.234	0.354	−5.977	0.000
Elliott et al., 2013	0.093	0.069	0.125	−13.682	0.000
Ryan et al., 2013	0.196	0.154	0.247	−9.366	0.000
Salluh et al., 2010	0.323	0.266	0.386	−5.263	0.000
Spiller & Keen, 2006	0.294	0.216	0.386	−4.175	0.000
	0.223	0.178	0.277	−8.498	0.000

Statistics for each study — Event rate and 95% CI



Fonte: Koirala B, et al. J Clin Nurs. 2020;29(13-14):2083-2092.

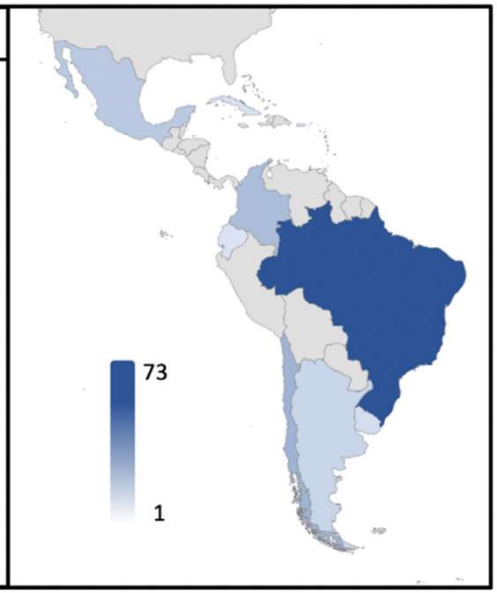


Fonte: Gibb K, et al. Age Ageing. 2020;49(3):352-360.

Epidemiologia

FIGURE 2 Countries of origin of the population included in each study (total 149 articles).

Country	Number of articles
Argentina	8
Brazil	73
Chile	25
Colombia	20
Ecuador	1
México	14
Uruguay	4
Puerto Rico	3
Cuba	1



Fonte: Maximiliano B, et al. Acta Psychiatr Scand. 2022. Epub ahead of print.

TABLE 1 Characteristics of the included studies

	Countries (number of studies)	Age years (min–max)	Occurrence % (min–max)
General ward ($n = 59$)	Brazil (20) Mexico (10) Colombia (12) Chile (12) Argentina (4) Uruguay 1	18–104	2.1–60.4
Post-operative ($n = 30$)	Brazil (18) Mexico (1) Colombia (1) Chile (7) Uruguay (2) Cuba (1)	42–102	5.45–52.3
ICU ($n = 55$)	Brazil (32) Mexico (1) Colombia (7) Chile (6) Argentina (4) Uruguay (1) Ecuador (1) Puerto Rica (3)	18–92	9.6–94.8
ER ($n = 5$)	Brazil (3) Mexico (2)	19–93	10.68–62

Fonte: Maximiliano B, et al. Acta Psychiatr Scand. 2022. Epub ahead of print.

Epidemiologia

Table 2
Prevalence of delirium in elderly in-patients across different services over one year.

	N = 10,261	Period prevalence (%)	p_*	OR	95%-CI
4º	Medical pooled	34.23	< 0.001	1.18	1.09–1.29
	Angiology	16.91	< 0.001	0.42	0.32–0.56
	Cardiology	26.68	< 0.001	0.75	0.65–0.87
	Endocrinology	7.14	0.046	0.16	0.02–1.25
	Gastroenterology	26.21	0.032	0.75	0.57–0.98
	Geriatrics	28.57	0.696	0.85	0.37–1.93
	Haematology	38.39	0.146	1.33	0.91–1.95
	Infectiology	37.04	0.575	1.25	0.57–2.73
	Internal medicine	48.49	< 0.001	2.13	1.84–2.47
→	Nephrology	50.00	< 0.001	2.15	1.52–3.03
	Neurology (in-patient)	30.43	0.552	0.93	0.72–1.19
	Oncology	43.82	< 0.001	1.69	1.36–2.10
	Pneumology	26.71	0.146	0.77	0.54–1.10
	Rheumatology	8.72	< 0.001	0.20	0.12–0.32
3º	Surgical pooled	28.74	< 0.001	0.72	0.67–0.79
→	Cardiac surgery	56.30	< 0.001	3.00	2.58–3.48
	Craniofacial surgery	21.86	0.003	0.59	0.41–0.84
	Dermatology	18.63	< 0.001	0.47	0.38–0.58
	Gynecology	18.77	< 0.001	0.48	0.37–0.62
	Neurosurgery (in-patient)	41.41	0.001	1.52	1.18–1.95
	Ophthalmology	8.98	< 0.001	0.20	0.14–0.28
	Otorhinolaryngology	13.37	< 0.001	0.31	0.24–0.41
	Plastic surgery	19.51	< 0.001	0.51	0.36–0.72
	Thoracic surgery	28.85	0.275	0.86	0.65–1.13
	Trauma (in-patient)	27.19	0.028	0.79	0.63–0.97
	Urology	16.15	< 0.001	0.39	0.32–0.47
	Visceral surgery	36.68	0.029	1.24	1.02–1.51
2º	Intermediate care (IMC) pooled	39.81	0.002	1.42	1.13–1.78
	Abdominal IMC	61.11	0.008	3.34	1.30–8.64
	Cardiothoracic IMC	38.56	0.013	1.35	1.06–1.70
1º	ICU pooled	83.25	< 0.001	12.34	9.95–15.31
	Burn/plastic ICU	88.00	< 0.001	15.67	4.69–52.40
→	Cardiovascular ICU	91.23	< 0.001	22.42	8.95–56.19
	Medical ICU	79.43	< 0.001	8.52	5.89–12.32
	Neurological stroke unit	52.01	< 0.001	2.39	1.97–2.91
	Neurosurgical ICU	82.89	< 0.001	10.66	6.98–16.30
	Thoracic-transplant ICU	83.91	< 0.001	11.30	6.37–20.05
	Trauma ICU	84.00	< 0.001	11.48	7.11–18.56

Fonte: Fuchs et al. General Hospital Psychiatry 2020; 67: 19–25.

Diagnóstico

✓Delirium:

- Síndrome complexa de início agudo, caracterizada por distúrbios flutuantes:
  a) Na atenção (habilidade em focar, manter ou desviá-la);
  b) Na consciência (por exemplo, menor orientação para o ambiente) ;
  c) Na cognição (déficit de memória, desorientação, linguagem, capacidade visuoespacial ou percepção);
- que não são explicados por por outro transtorno neurocognitivo preexistente, estabelecido ou em desenvolvimento e não ocorrem no contexto de um nível gravemente diminuído de estimulação, como no coma (critério D).

American Psychiatric Association. Manual Diagnóstico e Estatístico de Transtornos Mentais - DSM-5. 5a. ed. Porto Alegre : Artmed, 2014.

Diagnóstico

Table 2
Assessment of suspected delirium

Assessment	Actions
History	Check baseline cognitive function and recent (within past 2 weeks) changes in mental status (eg, family, staff) Recent changes in disorder, new diagnoses, complete review of systems Review all current drugs (including over-the-counter and herbal preparations); pay special attention to new drugs and drug interactions Review alcohol and sedative use Assess for pain and discomfort (eg, urinary retention, constipation, thirst)
Vital signs	Measure temperature, oxygen saturation, fingerstick glucose concentration Take postural vital signs as needed
Physical and neurological examination	Search for signs of occult infection, dehydration, acute abdominal pain, deep vein thrombosis, other acute illness; assess for sensory impairments Search for focal neurological changes and meningeal signs
Targeted laboratory assessment (selected tests based on clues from history and physical)[a]	Consider full blood count; urinalysis; measurement of concentrations of electrolyres, calcium, and glucose; measurement of renal, liver, and thyroid function; taking cultures of urine, blood, sputum; measurement of drug concentrations; measurement of concentrations of ammonia, vitamin B12, and cortisol Measure arterial blood gas Do electrocardiography Chest radiography Lumbar puncture should be reserved for assessment of fever with headache and meningeal signs or suspicion of encephalitis
Targeted neuroimaging (selected patients)	Assess focal neurological changes (stroke can present as delirium) Test for suspected encephalitis (for temporal lobe changes) Assess patients with histories or signs of head trauma
Electroencephalography (selected patients)	Assess for occult seizures Differentiate psychiatric disorder from delirium

Fonte: Hshieh TH, et al. Clin Geriatr Med 2020; 36(2):183-19.

Diagnóstico- subtipos (critério E)

Table 1 ICD-10 codes proposed by the DSM-5 applied to screening potential delirium. Source: American Psychiatric Association (2013)[17]

ICD-10 codes for delirium					
Related to medicines or substances				Clinical or mixed	Unspecified
Substance	Withdrawal	Intoxication	Medication-induced		
Opioids	F11.23	F11.121; F11.221	F11.921	F05	R41.0
Sedative, hypnotic, or anxiolytic	F13.231	F13.121; F13.221	F13.921		R45.0
Amphetamine (or other stimulant)	–	F15.121; F15.221	F15.921		
Other classes	F19.231	F19.121; F19.221	F19.921		

Fonte: Raso J, et al. International Journal of Clinical Pharmacy (2022) 44:548–556.

Diagnóstico- Especificadores

✓ **Curso:**
- Agudo
- Persistente

✓ **Atividade motora:**
- Hiperativo
- Hipoativo
- Misto

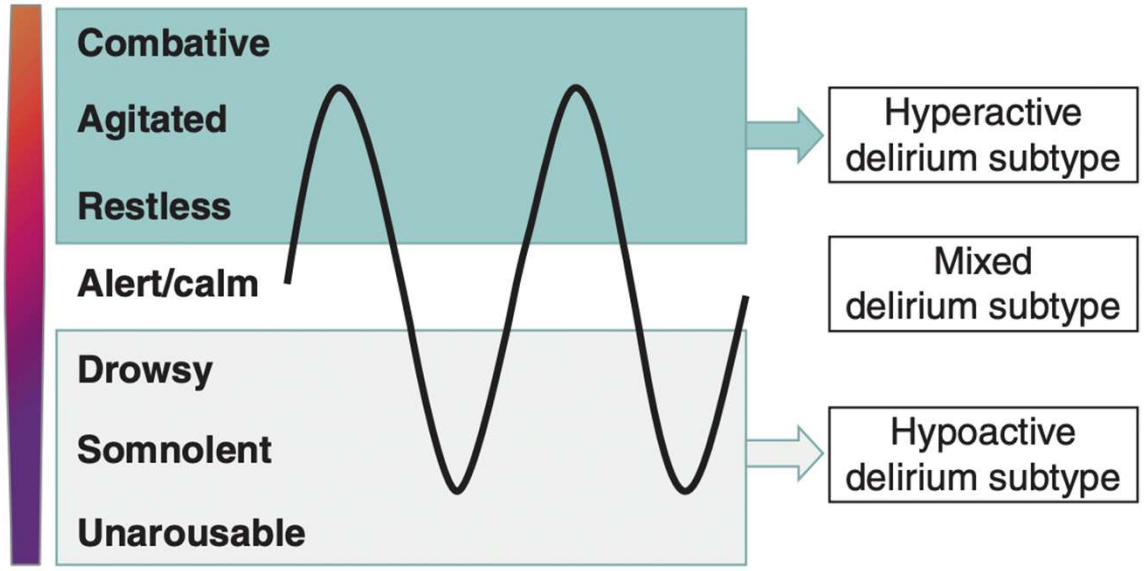
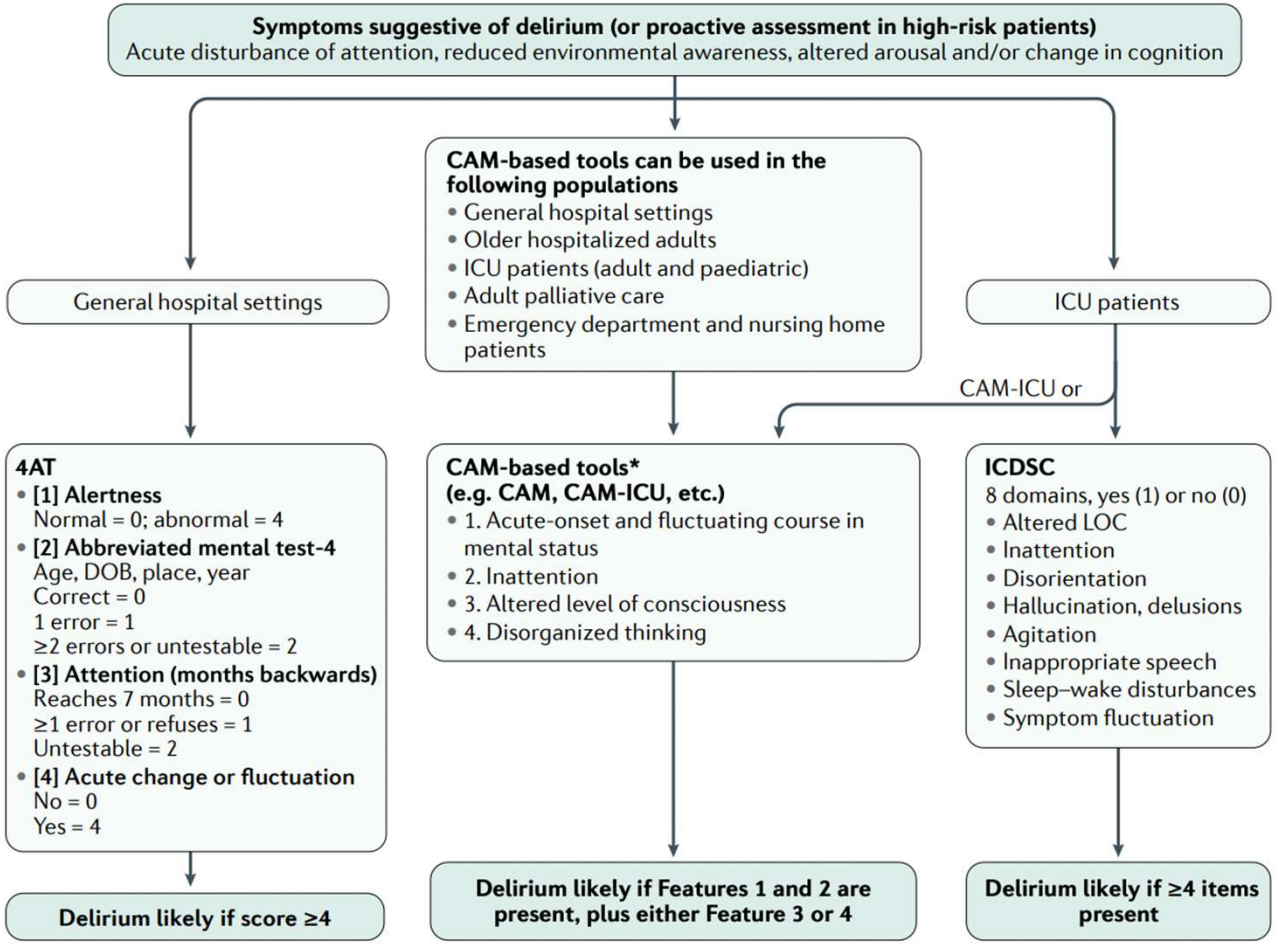


Fig. 2.2 The motor subtypes of delirium. The motor subtypes of delirium include hyperactive (pure overactive state represented in *blue*), hypoactive (pure underactive state represented in *gray*), and mixed (fluctuation between over- and underactive represented by *black line*)

Fonte: Robinson TN. Delirium. In. Lee AG, et al., (eds). Geriatrics for specialists. Springer Nature Switzerland AG, 202.1

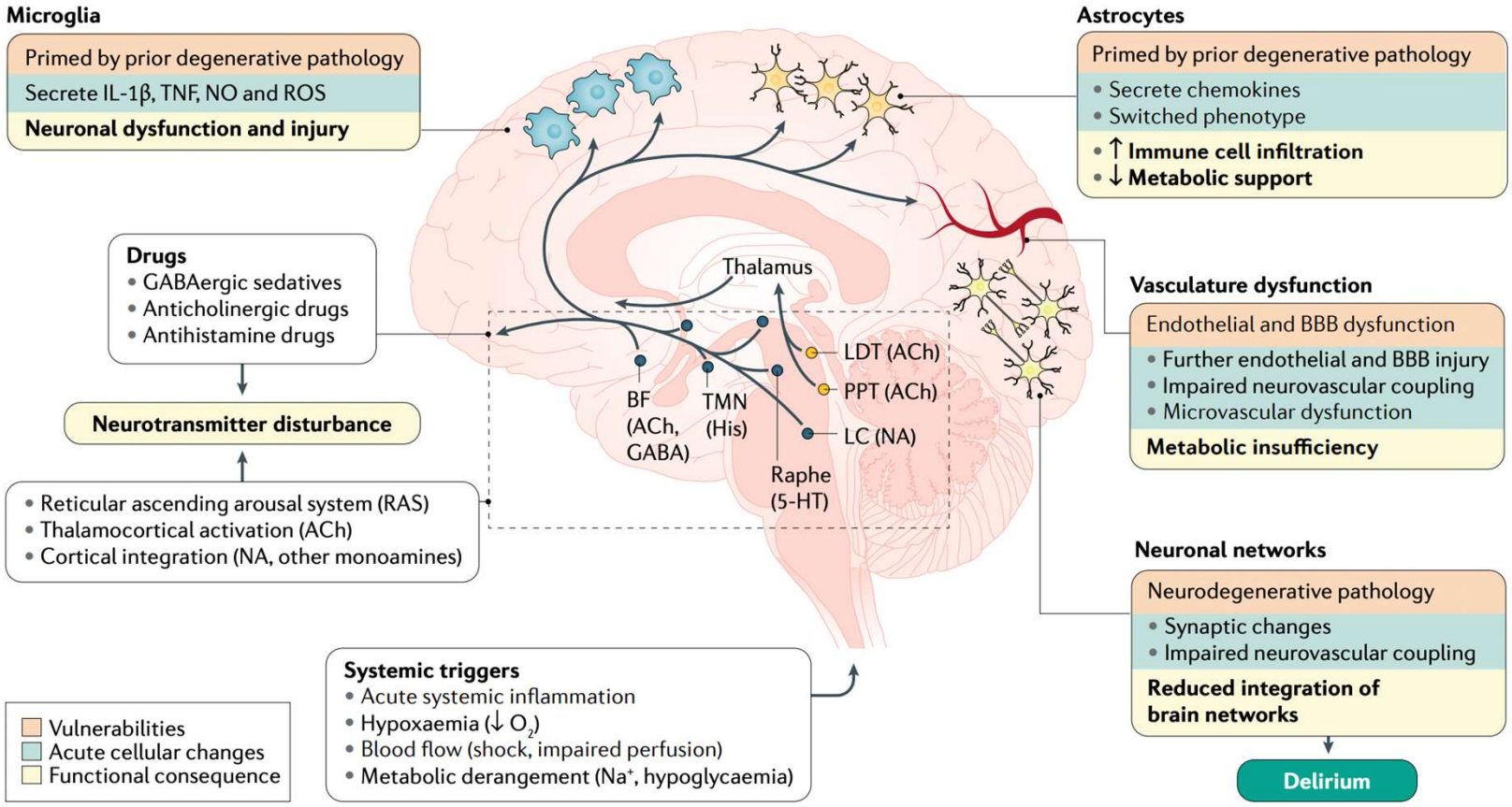
American Psychiatric Association. Manual Diagnóstico e Estatístico de Transtornos Mentais - DSM-5. 5a. ed. Porto Alegre : Artmed, 2014.

Triagem



Fonte: Wilson JE, et al. Nat Rev Dis Primers. 2020; 6(1):94.

Fisiopatologia



Fonte: Wilson JE, et al. Nat Rev Dis Primers. 2020; 6(1):94.

Fisiopatologia

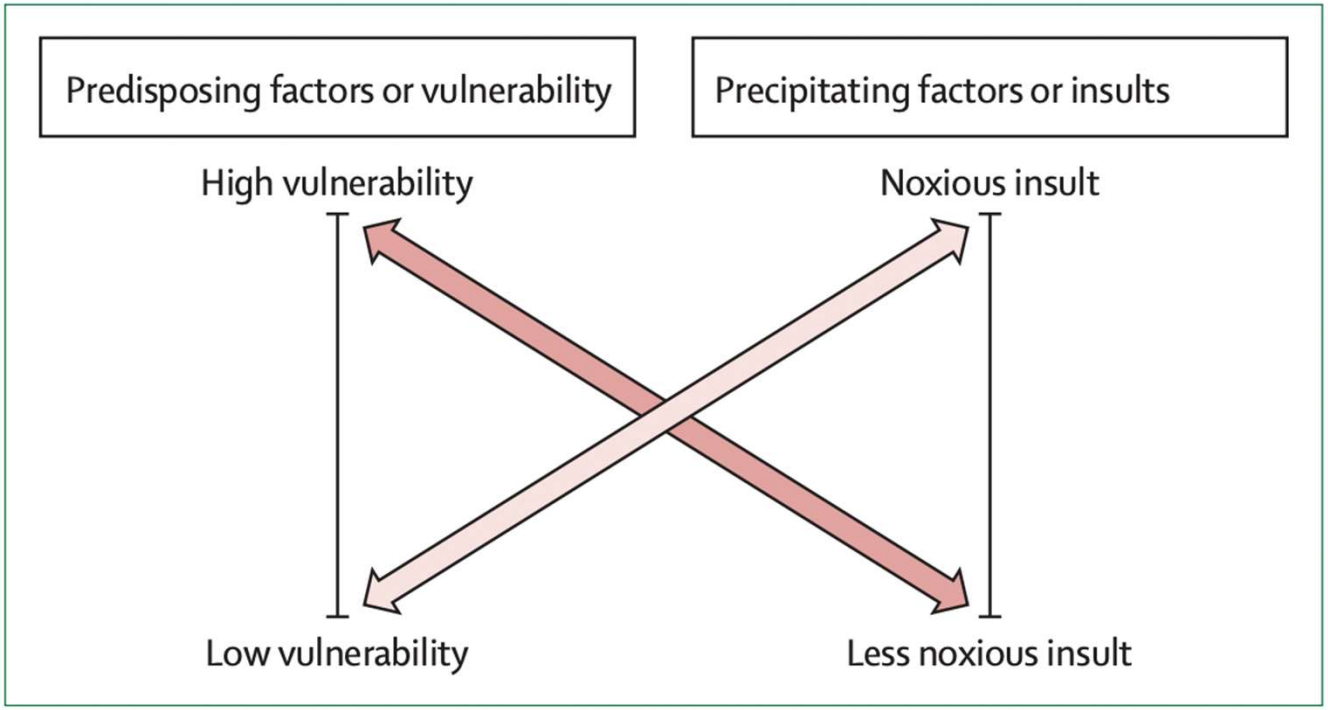


***Figure*: Multifactorial model of delirium in older people**
Onset of delirium is dependent on a complex interaction between the patient's baseline vulnerability (predisposing factors) at admission and precipitating factors or noxious insults occurring during hospital admission. Adapted from Inouye and Charpentier,[31] by permission of the *Journal of the American Medical Association*.

Fonte: Inouye et al. The Lancet 2014; 383: 911-922.

Fatores de risco

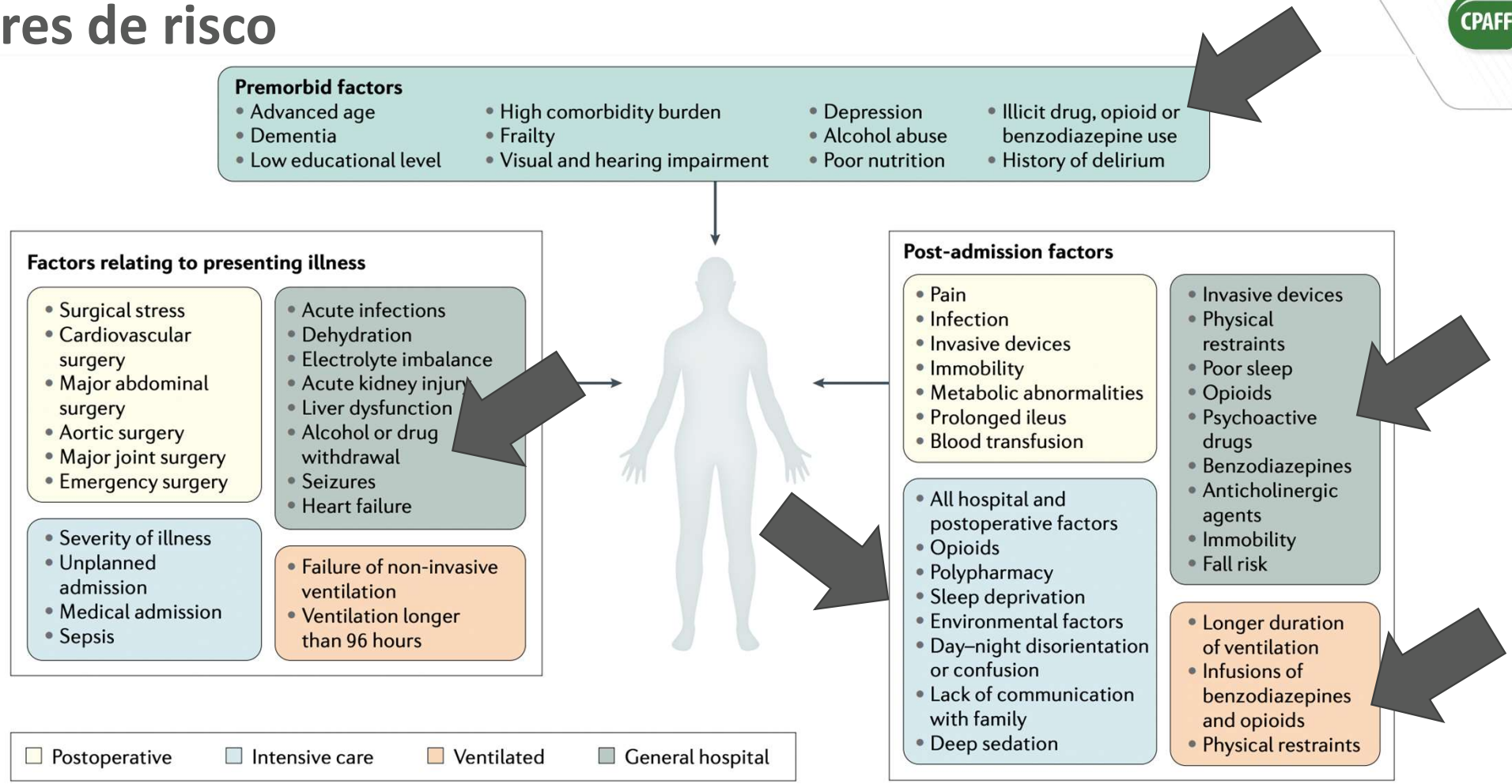


Fig. 1 | **Risk factors for delirium.** Risk factors for delirium relate to premorbid or predisposing factors (that is, a patient's characteristics) and to precipitating factors, which are factors relating to the presenting illness or that occur after hospital or intensive care unit admission.

Fonte: Wilson JE, et al. Nat Rev Dis Primers. 2020; 6(1):94.

Delirium induzido por medicamento

✓Cerca de 10 a 30% dos casos de delirium em idosos é induzido por medicamentos.

Carter GL, et al. Drug Saf. 1996;15(4):291-301. Ahmed S, et al. Age Ageing. 2014; 43(3):326-33 Catic AG. Drugs Aging. 2011;28(9):737-48.

✓É a quinta reação adversa a medicamento mais prevalente em idosos hospitalizados.

Jennings ELM, et al. Age Ageing. 2020; 23;49(6):948-958.

- Polifarmácia Ahmed S, et al. Age Ageing. 2014; 43(3):326-33
- Carga deliriogênica Nguyen et al., International Psychogeriatrics (2018), 30:4, 503–510.
- Carga anticolinérgica Vondeling AM, et al. Eur J Intern Med. 2020; 78:121-126.
- Exposição à psicofármacos Burry LD, et al. J Crit Care. 2017; 42:268-274.
- Exposição à corticosteroides Yamada C, et al. Crit Care Nurs. 2018; 47:15-22.
- Uso de medicamentos inapropriados para a faixa etária.

Raso J, et al. International Journal of Clinical Pharmacy 2022; 44:548–556.

Heterogeneidade e ausência de padronização

✓Problema relacionado à farmacoterapia de necessidade.

- Dor não tratada. Daoust R, et al. Acad Emerg Med. 2020;27(8):708–16.

Delirium induzido por medicamento

Table II. Drugs associated with cognitive impairment

Drug Class	Examples	Risk	Comment
Anticholinergics	Atropine Scopolamine	High	Glycopyrronium bromide is a safer agent for anaesthetic premedication
Benzodiazepines	Nitrazepam Flurazepam	High	Cognitive impairment is more common with long-acting agents. Withdrawal delirium also occurs
	Diazepam Temazepam	Medium	
Opioid analgesics	Pethidine (meperidine)	High	Risk may be highest with pethidine
Antipsychotics	Thioridazine Chlorpromazine	Medium	Although often used in the treatment of delirium, antipsychotics with significant anticholinergic activity can worsen confusion
	Risperidone	Low	
Antiparkinsonian drugs	Trihexyphenidyl	High	Risk is highest in drugs with anticholinergic activity
	Benzatropine Bromocriptine Levodopa Selegiline (deprenyl)	Medium	
Antidepressants	Amitriptyline Imipramine	High	Risk is highest in drugs with anticholinergic activity
	Nortriptyline Desipramine	Medium	
	SSRIs	Low	
Anticonvulsants	Primidone	Medium	Risk may be lowest with valproic acid and newer anticonvulsants
	Phenytoin	Low	
H_2 Antagonists[a]	Cimetidine Ranitidine	Low	Proton pump inhibitors may be less likely to cause delirium
H_1 Antagonists[a]	Chlorphenamine	Low	Antihistamines are available in many over-the-counter preparations
Cardiovascular drugs	Quinidine Digoxin Methydopa β-Blockers	Medium	Digoxin toxicity is dose-related, but in elderly people confusion may occur with normal serum concentrations
	Diuretics ACE inhibitors	Low	
Corticosteroids	Prednisolone	Medium	Risk is dose-related
NSAIDs	Indomethacin	Medium	Paracetamol is a safer alternative for short term use
	Ibuprofen	Low	
Antibiotics	Cephalosporins Penicillin Quinolones	Low	Although delirium has been reported with many antibiotics, this may be more related to the effect of the underlying infection

a Histamine receptor antagonist.
SSRI = selective serotonin reuptake inhibitor.

Fonte: Moore AR, et al. Drugs & Aging 1999; 15 (1): 15-28

Table 2. Evidence hierarchy table summarising the risk of delirium with different medication classes and different agents within a class of medications

Medication class	Study	Setting	Agent	Type of analysis	Result OR/RR (95% CI)	Evidence quality
Neuroleptic	Kalisvaart *et al.* [21]	Orthopaedic (hip surgery)	Haloperidol	RCT	RR 0.9 (0.6–1.3)	High
	Schor *et al.* [29]	Mixed medicine/surgery	All neuroleptics	Multivariate	OR 4.5 (1.8–10.5)	Moderate
Opioid	Schor *et al.* [29]	Mixed medicine/surgery	All opioids	Multivariate	OR 2.5 (1.2–5.2)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	All opioids	Matched	OR 1.4 (0.5–4.3)	Moderate
	Pandharipande *et al.* [26]	ICU	Fentanyl	Multivariate	OR 1.2 (1.0–1.5)	Moderate
	Pandharipande *et al.* [26]	ICU	Morphine	Multivariate	OR 1.1 (0.9–1.2)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	Meperidine (pethidine)	Matched	OR 2.7 (1.3–5.5)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	Morphine	Matched	OR 1.2 (0.6–2.4)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	Fentanyl	Matched	OR 1.5 (0.6–4.2)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	Oxycodone	Matched	OR 0.7 (0.3–1.6)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	Codeine	Matched	OR 1.1 (0.4–3.6)	Moderate
Benzodiazepine	Marcantonio *et al.* [24]	Mixed surgical	All benzodiazepines	Matched	OR 3.0 (1.3–6.8)	Moderate
	Pandharipande *et al.* [26]	ICU	Lorazepam	Multivariate	OR 1.2 (1.1–1.4)	Moderate
	Pandharipande *et al.* [26]	ICU	Midazolam	Multivariate	OR 1.7 (0.9–3.2)	Moderate
Antihistamine (H_1)	Marcantonio *et al.* [24]	Mixed surgical	Diphenhydramine	Matched	OR 1.8 (0.7–4.5)	Moderate
Dihydropyridine	van der Mast *et al.* [30]	Cardiac surgery	Nifedipine	Multivariate	OR 2.4 (1.0–5.8)	Low
H_2 Antagonist	Schor *et al.* [29]	Mixed medicine/surgery	All H_2 antagonists	Univariate	OR 1.4 (0.8–2.5)	Low
Cardiac glycoside	Schor *et al.* [29]	Mixed medicine/surgery	Digoxin	Univariate	OR 0.5 (0.3–0.9)	Low
Steroid	Schor *et al.* [29]	Mixed medicine/surgery	All steroids	Univariate	OR 0.5 (0.2–1.7)	Low
NSAIDs	Schor *et al.* [29]	Mixed medicine/surgery	All NSAIDs	Univariate	OR 0.4 (0.1–1.5)	Low
Tricyclic antidepressant	Gustafson *et al.* [20]	Orthopaedic (hip fracture)	All tricyclic antidepressants	Univariate	RR 1.7 (1.4–2.1)	Very low
Antiparkinson	Gustafson *et al.* [20]	Orthopaedic (hip fracture)	Antiparkinson	Univariate	RR 1.3 (0.9–1.7)	Very low

Following a sensitivity analysis, only higher quality evidence has been included for each class of medication where possible.

H1, histamine 1 receptor; H2, histamine 2 receptor; NSAID, non-steroidal anti-imflammatory drug; TCA, tricyclic antidepressant; ICU, intensive care unit; RR, risk ratio; OR, odds ratio; CI, confidence interval.

Fonte: Clegg A, et al. Age Ageing. 2011;40(1):23-9.

Table 3. Summary of results presenting risk of delirium for medications split by dose and duration of action

Medication class	Study	Setting	Agent	Dose	Study quality	Type of analysis	Result OR/RR (95% CI)	Evidence quality
Opioids	Morrison *et al.* [25]	Orthopaedics (Hip fracture)	All opioids	Morphine dose equivalent 10–30 mg	Moderate	Multivariate	RR 4.4 (0.3–68.6)	Moderate
	Morrison *et al.* [25]	Orthopaedics (Hip fracture)	All opioids	Morphine dose equivalent <10 mg	Moderate	Multivariate	RR 25.2 (1.3–493.3)	Moderate
Benzodiazepines	Marcantonio *et al.* [24]	Mixed surgical	All benzodiazepines	High dose (>5 mg diazepam or dose equivalent in 24 h)	Moderate	Matched	OR 3.3 (1.0–11.0)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	All benzodiazepines	Low dose (≤5 mg diazepam or dose equivalent in 24 h	Moderate	Matched	OR 2.6 (0.8–9.1)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	All benzodiazepines	Long acting[a]	Moderate	Matched	OR 5.4 (1.0–29.2)	Moderate
	Marcantonio *et al.* [24]	Mixed surgical	All benzodiazepines	Short acting[b]	Moderate	Matched	OR 2.6 (1.1–8.5)	Moderate
Antihistamine H_1	Marcantonio *et al.* [24]	Mixed surgical	Diphenhydramine	High dose (>25 mg in 24 h)	Moderate	Matched	OR 1.5 (0.3–6.9)	Moderate
	Marcantonio *et al.* [24]	MIxed surgical	Diphenhydramine	Low dose (≤25 mg in 24 h)	Moderate	Matched	OR 1.5 (0.5–4.1)	Moderate

H1, histamine H1 receptor; RR, risk ratio; OR, odds ratio.

[a]Long-acting benzodiazepines defined as chlordiazepoxide, diazepam and flurazepam.

[b]Sort-acting benzodiazepines defined as oxazepam, lorazepam, triazolam, midazolam and temazepam.

Fonte: Clegg A, et al. Age Ageing. 2011;40(1):23-9.

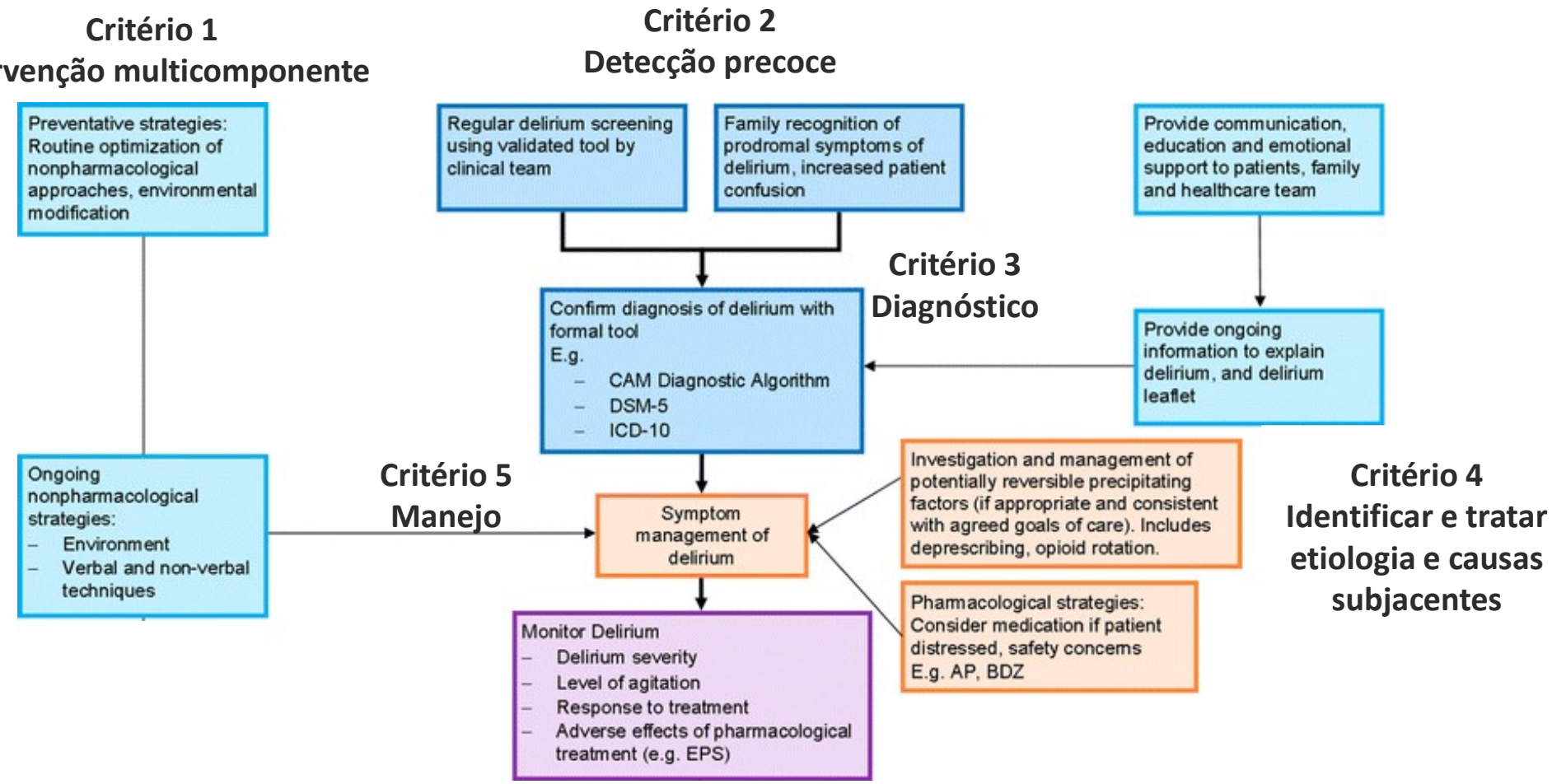
Análise de causalidade

✓Dificuldades:

TEMPORALIDADE	Dificuldade em caracterizar o início da síndrome.
DECHALLENGE POSITIVO	E quando todos os medicamentos suspeitos são descontinuados ao mesmo tempo?
RECHALLENGE POSITIVO	É uma opção no contexto clínico?

Moore AR, et al. Drugs & Aging 1999; 15 (1): 15-28

Prevenção e Manejo



Fonte: Bush SH, et al. Drugs. 2017;77(15):1623-1643.

Perspectivas

✓ Treinamento da equipe multiprofissional:

- Triagem e Diagnóstico. Bush SH, et al. Drugs. 2017;77(15):1623-1643.
- Documentação em prontuário. Zalon ML,et al . J Gerontol Nurs. 2017;43(3):32-40.
- Melhorar quanti e qualitativamente as notificações de delirium como evento adverso a medicamento.

  Varallo, F. R. , et al. New Insights into the Future of Pharmacoepidemiology and Drug Safety [Internet]. London: IntechOpen; 2021 [cited 2022 Sep 12].

✓ Desenhos epidemiológicos de melhor qualidade para esclarecer: Cascella M, et al. World J Crit Care Med 2019; 8(3): 18-27

- Caracterização da farmacoterapia como fator de risco modificável.
  - Descrição do esquema terapêutico, janela de exposição, análise de causalidade.
- Identificar medidas profiláticas e curativas seguras e efetivas (resolução, duração e gravidade do delirium).
- Desenvolvimento e validação de ferramentas para a triagem.

✓ Inteligência artificial para desenvolvimento de modelos preditivos para detecção precoce de pacientes com maior vulnerabilidade. McMaster C, et al. Drug Saf. 2019;42(6):721-725.

Muito obrigada pela atenção

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