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Delirium and anticholinergic burden in older patients – diagnosis, causes and treatment

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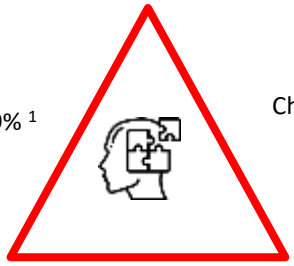
Delirium – a common adverse drug event

Hospital incidence rate 3-29% [1]

Often missed [2]



Challenge for patient, family members and hospital staff

Increased risk of frailty [3], morbidity and mortality [4]

Increased risk of institutionalization [1,4]

Longer and costlier hospitalizations [1]

=> High burden to the health care system

1. Siddiqui et al., Age and Aging 2006
2. De la Cruz et al., Supp cancer care 2015
3. Ogawa et al., PLoS ONE 2017
4. Witlox et al., JAMA, 2010

Picture: www.freepik.com

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Diagnostic Criteria of Delirium (DSM-5)

1. A disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
2. 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.
3. An additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception).
4. The disturbances in criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
5. 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 (ie, due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

Abbreviation: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

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Pervin F. et al. American Journal of Alzheimer's Disease & Other Dementias 2016, Vol. 31(1):5-17

Instruments

> 40 tools

Best validated non ICU tools [1]

- CAM
- DOSS
- DRS-R-98
- MDAS

1. Helfand et al., J Am Geriatr Soc 2021; 69(2):547-555

Confusion Assessment Method (CAM)
Short form

island health

The diagnosis of delirium by CAM requires the presence of BOTH features *A* and *B*

CAM Confusion Assessment Method

A. Acute onset and **Fluctuating course**	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: • come and go? • fluctuate during the day? • increase/decrease in severity?
B. Inattention	Does the patient: • have difficulty focusing attention? • become easily distracted? • have difficulty keeping track of what is said?
AND the presence of EITHER feature *C or D*	
C. Disorganized thinking	Is the patient's thinking: • disorganized • incoherent For example does the patient have • rambling speech/irrelevant conversation? • unpredictable switching of subjects? • unclear or illogical flow of ideas?
D. Altered level of consciousness	Overall, what is the patient's level of consciousness: • alert (normal) • vigilant (hyper-alert) • lethargic (drowsy but easily roused) • stuporous (difficult to rouse) • comatose (unrousable)

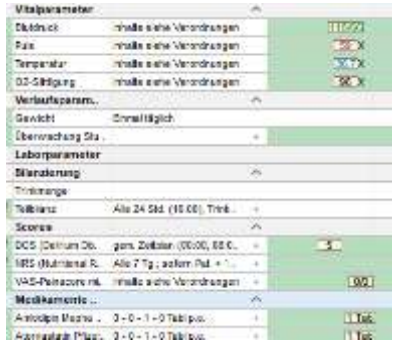
Adapted with permission from: Inouye SK, vanDyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med. 1990; 113: 941-948. Confusion Assessment Method: Training Manual and Coding Guide. Copyright © 2003, Hospital Elder Life Program, LLC.

Please see the **CAM Training Manual**, available at
http://www.hospitalelderlifeprogram.org/programs-disclaimer.php?request=01.08.00

https://www.criticalcarepractitioner.co.uk/delirium-critical-care/confusion-assessment-method-cam/

DOSS

⇒ screening instrument
⇒ brief rating with minimal training
⇒ for nurses
⇒ confirmation by experienced clinician (=> CAM)
⇒ can be implemented in the CIS:



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The DOS (Delirium Observation Screening) Scale

Please complete twice daily

Patient Details (place sticker or complete)
Name:
Hospital No:
RAE no:
DoB:

Never = The described behaviour was not observed
Sometimes = The described behaviour always was observed once, or a few times, or all the time
Unknown = The patient was asleep or did not give necessary responses OR the rater does not feel himself / herself competent to observe the absence or presence of the behaviour

	Date:						Date:					
	Timepoint 1, am Time			Timepoint 2, pm Time			Timepoint 1, am Time			Timepoint 2, pm Time		
	Never	Sometimes - always	unknown / unable	Never	Sometimes - always	unknown / unable	Never	Sometimes - always	unknown / unable	Never	Sometimes - always	unknown / unable
1 Dozes during conversation or activities	0	1	-	0	1	-	0	1	-	0	1	-
2 Is easily distracted by stimuli from the environment	0	1	-	0	1	-	0	1	-	0	1	-
3 Maintains attention in conversation or action	1	0	-	1	0	-	1	0	-	1	0	-
4 Does not finish question or answer	0	1	-	0	1	-	0	1	-	0	1	-
5 Gives answers that do not fit the question	0	1	-	0	1	-	0	1	-	0	1	-
6 Reacts slowly to instructions	0	1	-	0	1	-	0	1	-	0	1	-
7 Thinks to be somewhere else	0	1	-	0	1	-	0	1	-	0	1	-
8 Knows which part of the day it is	1	0	-	1	0	-	1	0	-	1	0	-
9 Remembers recent event	1	0	-	1	0	-	1	0	-	1	0	-
10 Is pacing, disorderly, restless	0	1	-	0	1	-	0	1	-	0	1	-
11 Pulls IV tubes, feeding tubes, catheters etc.	0	1	-	0	1	-	0	1	-	0	1	-
12 Is easily or suddenly emotional	0	1	-	0	1	-	0	1	-	0	1	-
13 Sees / hears things which are not there	0	1	-	0	1	-	0	1	-	0	1	-
Health Care Professional (HCP) to complete this section. A score of 3 or more is a delirious episode												
Total Score												
Is a delirium indicated?	YES ☐ NO ☐			YES ☐ NO ☐			YES ☐ NO ☐			YES ☐ NO ☐		
Signature of HCP												

Tools for ICUs

- CAM-ICU
- ICDSC
  (Intensiv Care Delirium Screening Checklist)

https://www.researchgate.net/publication/5355381_Delirium_in_the_intensive_care_unit/figures?lo=1

Checklist Item	Description
Altered level of consciousness*	
A	No response
B	Response to intense and repeated stimulation
C	Response to mild or moderate stimulation
D	Normal wakefulness
E	Exaggerated response to normal stimulation
Inattentiveness	Difficulty following instructions or easily distracted
Disorientation	To time, place, or person
Hallucination-delusion-psychosis	Clinical manifestation or suggestive behavior
Psychomotor agitation or retardation	Agitation requiring use of drugs or restraints, or slowing
Inappropriate speech or mood	Related to events or situation, or incoherent speech
Sleep/wake cycle disturbance	Sleeping <4 hours/day, waking at night, sleeping all day
Symptom fluctuation	Symptoms above occurring intermittently
Total score	0 to 8

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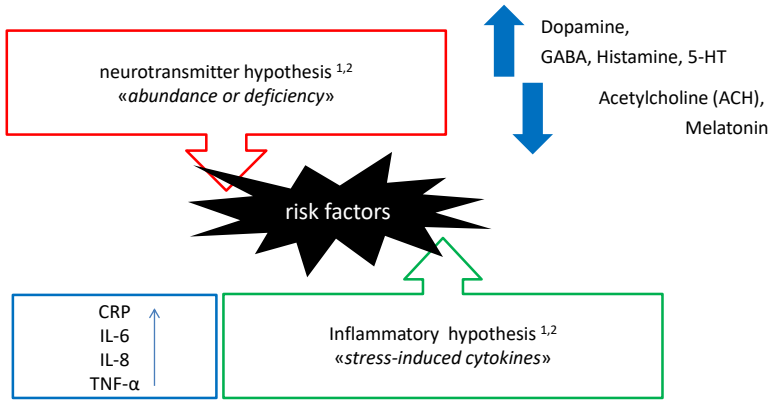
Delirium: A multifactorial syndrome



1. Savaskan / Haseman, Leitline Delir, 2007
2. Khan et al., JAGS, 2011

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Risk factors for delirium

Predisposing (non-modifiable)	Precipitating (potentially modifiable)
Demographic characteristics	
- Age > 65 years old, male sex	*Drugs*
Cognitive status	- Sedative hypnotics, anticholinergics, narcotics, benzodiazepines, drug and alcohol withdrawal
- Dementia	*Intercurrent Illness*
Functional status	- Infection, dehydration, trauma, shock, metabolic abnormalities, anemia, iatrogenic complications, malnutrition
- Immobility, history of falls	*Surgery*
Sensory impairment	- Orthopedic, cardiac, noncardiac
- Visual, hearing	*Acute neurologic diseases*
Drugs	- Stroke, meningitis, hemorrhage
- Alcohol abuse	*Environmental*
- Polypharmacy	- ICU admission, pain, physical restraints, catheters, emotional distress, sustained sleep deprivation
Comorbid conditions	
- Severe illness, stroke, neurologic disease, trauma, chronic kidney and liver disease	
Decreased oral intake	
- Dehydration, malnutrition	

Note. ICU, intensive care unit. Source: Inouye, 2006.[5]

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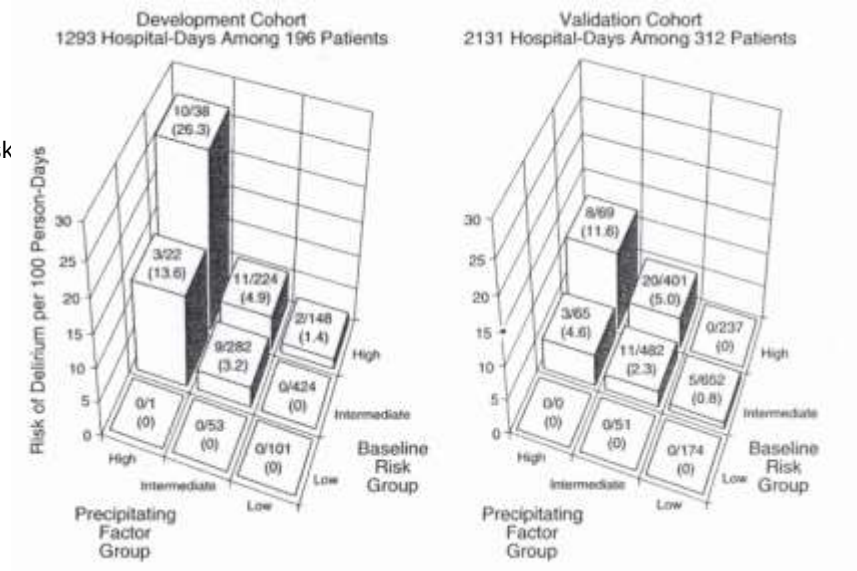
Risk



Inouye SK, Charpentier PA. JAMA. 1996 Mar 20;275(11):852-7

Risk factors for delirium

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Precipitating Factors in Delirium	Predisposing Factors in Delirium	Drug-Related Factors: Drug With High Anticholinergic Activity	Drug-Related Factors: Other Drugs
Narcotics	Older age	Antipsychotics (eg, chlorpromazine)	Antiparkinsonian agents (eg, L-DOPA)
Severe acute illness	Male sex	Antibiotics	Antidiarrheal agents (containing belladonna)
Urinary tract infection	Visual impairment presence of dementia severity of dementia depression functional dependence immobility	Codeine	Benzodiazepines
Hyponatremia Hypoxemia		Cimetidine	Chlorpheniramine
Shock		Captopril	Diphenhydramine
Anemia		Dipyridamole	Haloperidol
Pain	Hip fracture dehydration alcoholism severity of physical illness	Dyazide	Laxatives
Physical restraint		Digoxin	Narcotics
Bladder catheter use	Stroke	Furosemide	Nonsteroidal anti-inflammatory drugs
Iatrogenic event Orthopedic surgery	Metabolic abnormalities	Isosorbide dinitrate	Ranitidine
Cardiac surgery		Nifedipine	Warfarin
Noncardiac surgery		Prednisolone	
Intensive care unit admission		Theophylline	
High number of hospital procedures		Tricyclic antidepressants	

Pervin F. et al. American Journal of Alzheimer's Disease & Other Dementias 2016, Vol. 31(1):5-17

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Anticholinergic Drug Burden

How to determine the ACH burden in a patient?

- serum radioreceptor anticholinergic activity assay (SAA)
- expert-based list of medications with ACH properties

=> Anticholinergic Burden Scales

Drugs on the Anticholinergic Burden (ACB) scale
(A total ACB scale score of three or more is considered clinically relevant)

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Beclometasone dipropionate	Cyproheptadine	Chlorpheniramine
Bupropion hydrochloride	Loxapine	Chlorpromazine
Captopril	Meperidine	Clemastine
Chlorthalidone	Methotrimeprazine	Clomipramine
Cimetidine hydrochloride	Molindone	Clozapine
Clorazepate	Oxcarbazepine	Darifenacin
Codeine	Pethidine hydrochloride	Desipramine

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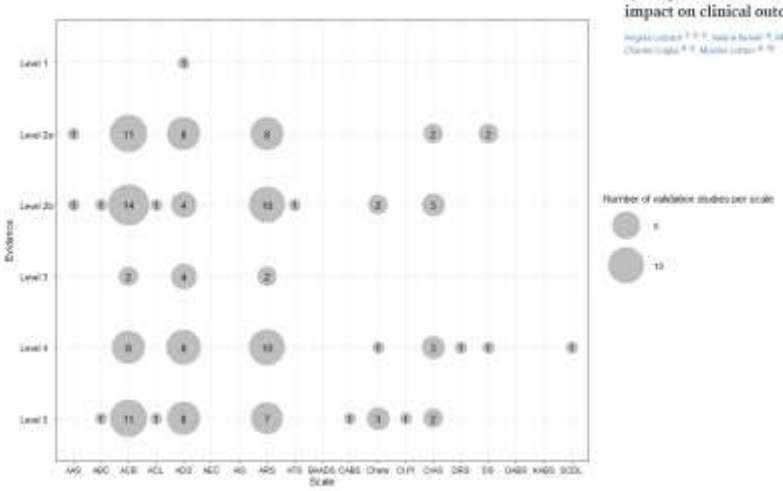
Systematic review with quality assessment

=> 19 scales

=> 147 validation studies



Quality of anticholinergic burden scales and their impact on clinical outcomes: a systematic review

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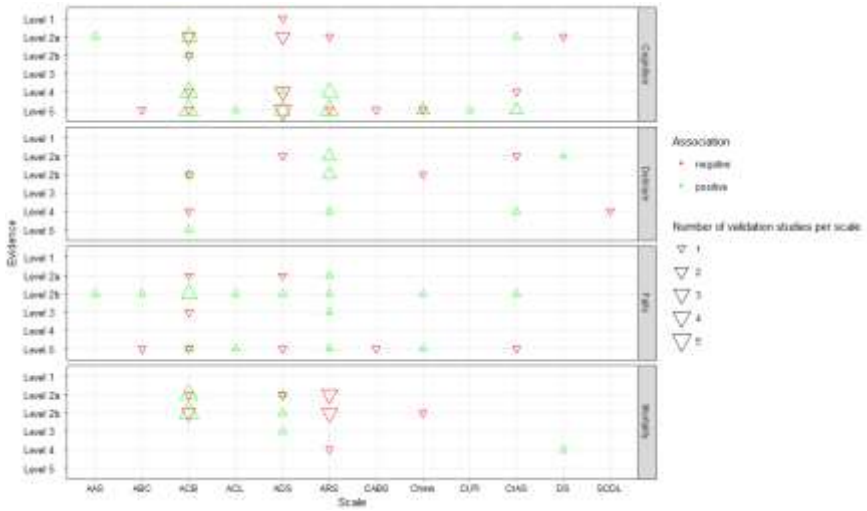
Results of validation studies



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ORIGINAL ARTICLE

Evaluation of the association of anticholinergic burden and delirium in older hospitalised patients – A cohort study comparing 19 anticholinergic burden scales

Angela Lisibach[1,2,3,4] | Giulia Gallucci[1] | Valérie Benelli[1] | Ramona Kälin[1] | Sven Schulthess[1] | Patrick E. Beeler[5] | Chantal Csajka[2,3,4] | Monika Lutters[1,6]

Inclusion criteria:

- Inpatients aged ≥ 65
- between 2015-2018
- Length of stay ≥ 48h

Exclusion criteria:

- Delirium at admission
- Having been on the ICU > 24h

Outcome Delirium:

1. Positive Confusion Assessment Method (CAM) **or** ICD-10 Code F05.0, F05.1, F05.8 or F05.9
2. CAM **or** ICD-10 **or** daily mean of 3 points or more in the Delirium Observation Scale Score (DOSS)

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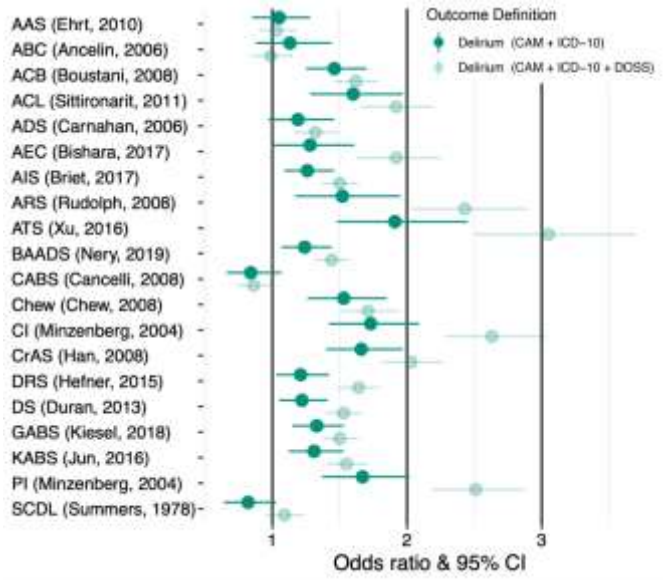
Low (< 3) vs. high anticholinergic burden

Multivariable analysis adjusted for age, sex, dementia, CRP and catheterization



Anticholinergic burden & mortality?

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TABLE 2 Multivariable regression using the binary approach for both outcomes: in-hospital mortality and length of stay (LOS)

	Mortality Multivariable regression		LOS			
Scale	OR	95% CI	Exp(B)	95% CI	Low <3 (n died (%))	High ≥3 (n died (%))
ARS[9]	1.39	1.11–1.73	1.88	1.04–3.31	15,348 (778 (5.1%))	1764 (125 (7.1%))
ADS[7]	1.49	1.17–1.87	1.80	0.96–3.03	15,512 (814 (5.2%))	1588 (99 (6.3%))
ACB[8]	1.55	1.33–1.80	1.83	1.03–3.05	22,013 (630 (2.9%))	3079 (283 (5.4%))
AIS[6]	1.58	1.37–1.82	1.87	1.06–3.09	19,345 (507 (2.6%))	7749 (486 (5.2%))
CAS[10]	1.35	1.09–1.65	1.81	1.00–3.06	24,820 (778 (3.1%))	2272 (145 (6.3%))
Chew[11]	1.37	1.12–1.66	1.22	1.09–1.35	24,234 (768 (3.1%))	2858 (145 (5.7%))
AAS[14]	1.34	1.11–1.62	1.81	0.96–3.04	24,381 (748 (3.1%))	2711 (165 (6.1%))
ARS[9]	1.92	1.50–2.42	1.81	0.97–3.05	25,021 (816 (3.2%))	1271 (97 (7.6%))
ACL[12]	1.81	1.21–1.88	1.22	1.09–1.35	24,979 (794 (3.2%))	1313 (119 (5.4%))
CyAS[13]	1.80	1.57–2.18	1.32	1.18–1.54	23,319 (679 (2.9%))	3573 (230 (6.3%))
ADS[7]	2.13	1.80–2.51	1.36	1.13–1.59	25,919 (695 (2.9%))	3173 (222 (7.0%))
SCH[15]	3.03	2.56–3.57	1.22	1.09–1.34	25,790 (677 (2.8%))	3302 (236 (7.1%))
P[16]	1.32	1.05–1.64	1.80	0.97–1.83	28,955 (791 (3.2%))	2137 (122 (5.7%))
CI[17]	1.35	1.07–1.69	0.99	0.96–1.02	25,886 (795 (3.2%))	2806 (118 (3.8%))
GAIS[18]	1.51	1.31–1.74	1.80	1.06–3.00	19,280 (467 (2.6%))	8506 (426 (5.0%))
DI[19]	1.86	1.61–2.14	1.21	1.09–1.33	19,302 (473 (2.5%))	7590 (436 (5.6%))
BAALS[20]	1.69	1.46–1.95	1.87	1.05–3.09	18,949 (473 (2.5%))	8143 (440 (5.4%))
EARS[21]	1.65	1.43–1.91	1.88	1.06–3.08	21,816 (597 (2.8%))	5676 (316 (5.6%))
ATS[14]	2.22	1.72–2.84	1.81	0.96–3.04	26,137 (821 (3.1%))	955 (92 (9.6%))
DRS[22]	1.66	1.43–1.93	1.21	1.09–1.33	21,598 (598 (2.8%))	3694 (315 (8.5%))

Note: For left column: individual ARS, two columns on the far right: absolute number of patients and percentage of prevalence of in-hospital deaths for each group. Multivariable analysis is adjusted for age, sex, dementia, delirium, congestive heart failure, hemiplegia/paraplegia, chronic obstructive pulmonary disease, rheumatoic diseases, diabetes, liver disease, cancer, renal disease, cerebrovascular disease, acute myocardial infarction, peripheral vascular disease, peptic ulcer and categorical C reactive protein. For the univariable analysis and analysis adjusted only for age and sex, see supporting information: Tables S4.1 and S8.2. For LOS, the back transformed estimate coefficient in the power of e is depicted as Exp(B) and can be interpreted as ARC Exp(B) 1.88, 8% longer hospitalization stay.

Abbreviations: AAS, Anticholinergic Activity Scale; ABC, Anticholinergic Burden Classification; ACB, Anticholinergic Cognitive Burden Scale; ACL, Anticholinergic Loading Scale; ADS, Anticholinergic Drug Scale; AEC, Anticholinergic Effect on Cognition; AIS, Anticholinergic Impregnation Scale; ARS, Anticholinergic Risk Scale; ATS, Anticholinergic Toxicity Scale; BAALS, Brazilian Anticholinergic Activity Drug Scale; CARS, Carnell's Anticholinergic Burden Scale; CI, Clinical Index; CyAS, Cyrenian-wood Anticholinergic Scale; DRS, Debrogenic Risk Scale; DI, Durso Scale; GAIS, German Anticholinergic Burden Scale; KARS, Korean Anticholinergic Burden Scale; PI, Mittenberg's Pharmacological Index; SCH., Sommer's Class of Drug List.

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Managing delirium inducing medication

⇒ Deprescribe all drugs without a clear indication

⇒ Reduce dose

⇒ Suggest possible alternatives:

Therapeutic class	Medication (examples)	Alternatives
Tricyclic antidepressants	amitryptilin clomipramine	**Depression:** SSRI, SNRI **Pain:** duloxetin, venlafaxin, pregabalin, gabapentin, patchs
First generation antihistamines	clemastine diphenhydramine doxylamine	**Allergy:** levocetirizine, fexofenadine, loratadine **Sleep:** herbs, mirtazapine, …
Spasmolytic drugs	oxybutinin, solifenacin	trospium
Analgesics	tramadol, pethidin	many alternatives
Parkinson medication	biperiden, pramipexol	none => levodopa/carbidopa

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Delirium Prevention (NICE Guidelines)

1. stable care team of healthcare professionals, avoid moving people
2. identify patients at risk for delirium within 24 hours of admission
3. give a multicomponent tailored intervention provided by a multidisciplinary trained team

- providing appropriate lighting and clear signage; a clock (consider providing a 24-hour clock in critical care) and a calendar should also be easily visible to the person at risk
- talking to the person to reorientate them by explaining where they are, who they are, and what your role is
- introducing cognitively stimulating activities (for example, reminiscence)
- facilitating regular visits from family and friends
- address risk factors like infection, pain, dehydration, nutrition, constipation
- address immobility by encouraging people to walk or do exercise
- address sensory impairment by ensuring that hearing and visual aids are available and in good working order.
- promote good sleep patterns and sleep hygiene
- **carry out a medication review for people taking multiple drugs**

Recommendations | Delirium: prevention, diagnosis and management | Guidance | NICE

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Delirium Prevention (NICE Guidelines)

1. stable care team of healthcare professionals, avoid moving people
2. identify patient at risk for delirium within 24 hours of admission

⇒ including anticholinergic burden scales

⇒ AUTOMATICALLY via CIS

3. give a multicomponent tailored intervention provided by a multidisciplinary trained team

- providing appropriate lighting and clear signage; a clock (consider providing a 24-hour clock in critical care) and a calendar should also be easily visible to the person at risk
- talking to the person to reorientate them by explaining where they are, who they are, and what your role is
- introducing cognitively stimulating activities (for example, reminiscence)
- facilitating regular visits from family and friends.
- address risk factors like infection, pain, dehydration, nutrition, constipation
- address immobility by encouraging people to walk or do exercise
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Recommendations | Delirium: prevention, diagnosis and management | Guidance | NICE

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Prediction model DELIKT

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Variable	β coefficient	SE	Odds ratio	95% CI Lower	95% CI Upper	DELIKT score
Intercept	*-1.65*	*0.04*				
Age >80 years	1.00	0.03	2.72	2.56	2.90	16
Medical Department	0.53	0.03	1.70	1.59	1.82	8
Dementia	2.31	0.06	10.03	8.98	11.23	36
Hemiplegia, Paraplegia	0.64	0.07	1.90	1.67	2.17	10
Catheterisation	0.66	0.04	1.94	1.81	2.07	10
Potassium <3.5 or 4.8< mmol/l	0.19	0.04	1.21	1.11	1.31	3
Creatinine ≥133 µmol/l	0.06	0.04	1.07	0.98	1.16	1
Polymedication >5 drugs	0.14	0.04	1.15	1.07	1.23	2
ACH burden with CrAS ≥3 points	0.76	0.04	2.14	1.97	2.34	12

Performance measures	Internal validation	External validation
AUC	0.792	0.795
Sensitivity	0.689	0.682
Specificity	0.731	0.730
	DELIKT score external validation	
AUC	0.794	
Sensitivity	0.797 (cut-off at DELIKT Score of 20 points, YI 0.42)	
Specificity	0.623 (cut-off at DELIKT Score of 20 points, YI 0.42)	
Brier score	0.083	
Odds ratio at cut-off of 20 points	5.88 (95% CI 5.17, 6.71)	

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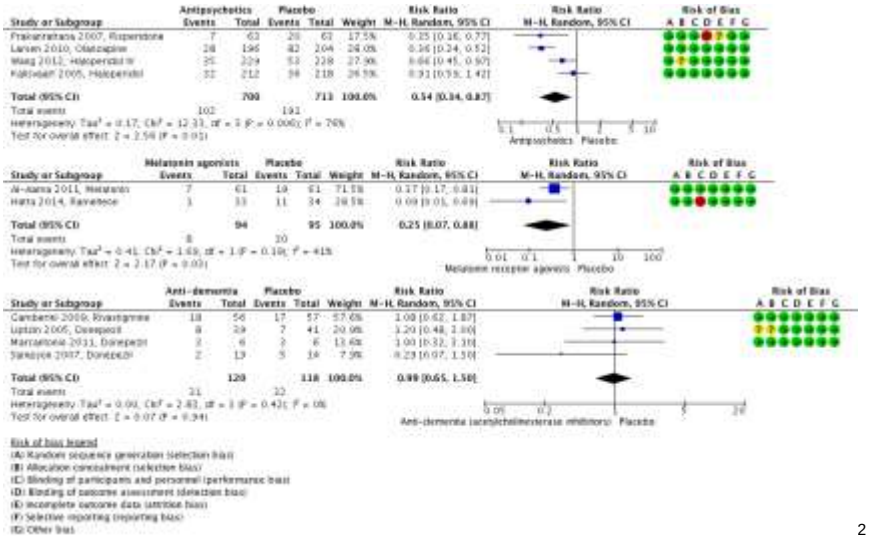
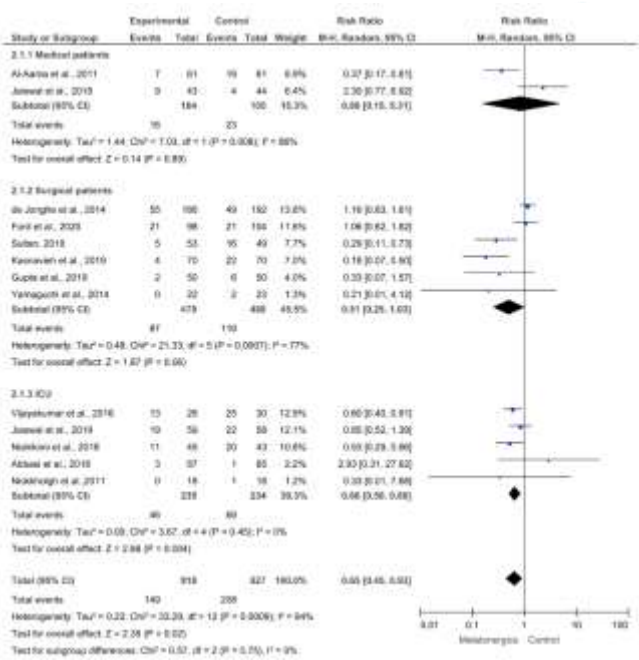
Prevention: Systematic Revue 2015



Melatonin & Ramelteon

Melatonin for delirium prevention in hospitalized patients: A systematic review and meta-analysis



Patients with sleeping disorders:
=> melatonin 2 - 6 mg
1 - 2 hours before sleeping

Treatment of Delirium

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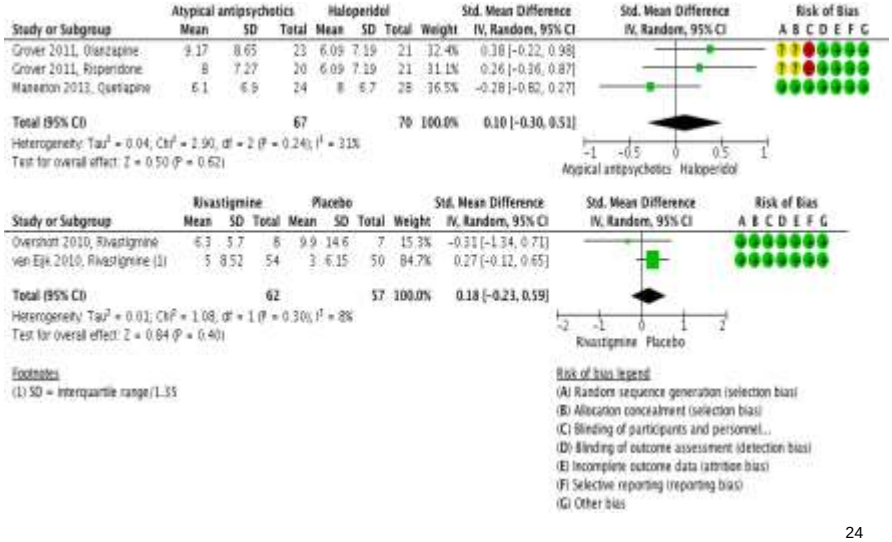

Treatment Guidelines KSBaden

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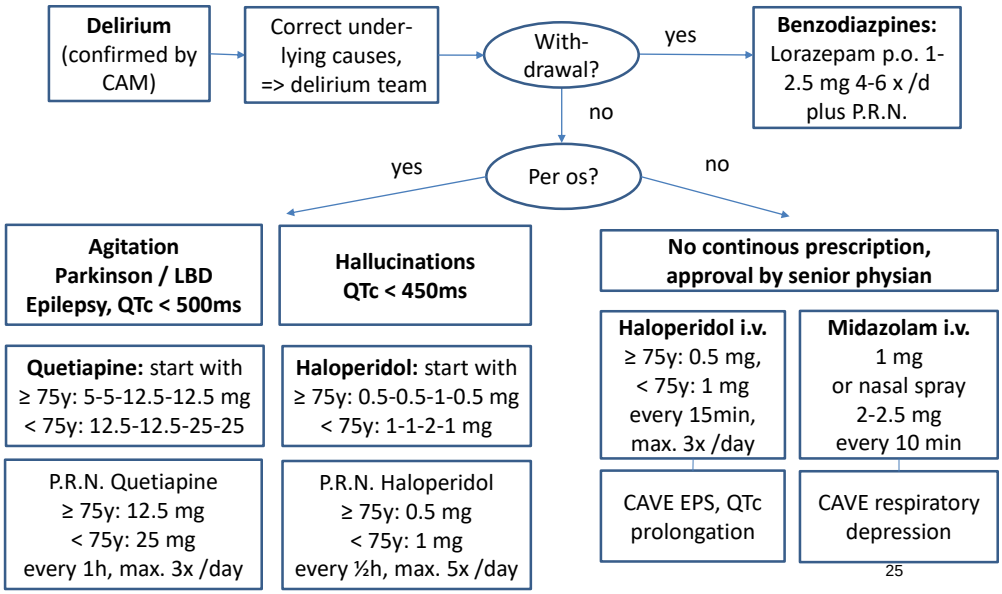

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Treatment Guidelines KSAarau

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Quetiapine 12.5 - 25 mg B.I.D. (every 12 h), max. 100 mg/d

Treatment according to symptoms:

- **Mainly agitation (+/- hallucinations), M. Parkinson, Lewy Body Dementia:** Quetiapine p.o. 12.5 - 25 mg B.I.D, max. 100 mg/d
- **Mainly aggression:** Risperidone p.o. 0.5 - 1 mg B.I.D., max. 2 mg/d
- **Sedation required:** Pipamperon p.o. 20 mg, 2-3 x /day
- **Hallucinations:** Haloperidol p.o. gtt. 0.5 -1 mg , 3-4 x /day, max. 4mg/d

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Take home messages

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- Delirium is common and represents a high burden for patients, care givers and health care systems.
- Recognizing and predicting delirium is difficult.
- Delirium is a multifactorial syndrome caused by many risk factors including anticholinergic burden.
- Anticholinergic drug burden can be assessed by scales and is associated with an increased risk of delirium, cognitive and functional decline, falls and mortality.
- Prevention is important and should include multicomponant tailored interventions provided by a multidisciplinary team.
- Treatment options are limited and often off-label.
- If needed, antipsychotics could be used at low dose and with caution.

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