REVIEW

Delirium in the ICU – A structured review of promising diagnostic and therapeutic approaches: Next steps in ICU delirium

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Abstract

Background: The purpose of this review is to provide a structured overview of emerging diagnostic and therapeutic modalities for delirium in critically ill patients.

Methods: Literature searches were carried out to identify relevant articles for both diagnostic and therapeutic approaches other than those included in the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU guidelines, including prospective and retrospective studies.

Results: Regarding diagnostic approaches seven articles were included. The Neelon and Champagne (NEECHAM) Confusion Scale, Stanford Proxy Test for Delirium (S-PTD), and DelApp-ICU yielded excellent diagnostic performances. We included seven articles studying different therapies. Some therapies showed potential to decrease the burden of delirium, using different pathophysiological pathways than antipsychotics.

Conclusion: Alternative screening tools may help in ICU delirium detection, either as replacement or combined with the Confusion Assessment Method for ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC), and other therapies than antipsychotics may reduce delirium burden, but further studies are required.

Introduction

Delirium is a common form of acute cerebral dysfunction, occurring in 11% to 80% of critically ill patients.[1,2] It is characterised by an abrupt disturbance of attention, consciousness and either perception or cognition, and has been associated with deleterious long-term outcomes, among which increased mortality rates and cognitive impairment.[3-7] The reference standard for diagnosing delirium is the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria as assessed by delirium experts.[8,9] However, due to sedation and mechanical ventilation the detection of delirium in the ICU is challenging. Routine delirium screening in the ICU with a valid screening tool, such as the Confusion Assessment Method for ICU (CAM-ICU)[1] or Intensive Care Delirium Screening Checklist (ICDSC),[10] is strongly recommended by the 2018 ICU Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) guidelines in order to improve the identification of delirium and delirium management.[11] The accuracy of these two tools, however, varies in different ICU populations.[12] Also, in 2013 the Diagnostic and Statistical Manual fourth edition (DSM-IV) was revised into DSM-5, along with a change in criteria for delirium diagnosis.[13] Consequently, we should explore methods for diagnosing delirium in the ICU which are more accurate and easier to administer. Furthermore, evidence on effective therapies for delirium is very scarce.[11] Small studies have been conducted on the efficacy of therapeutic approaches not discussed in the 2018 PADIS guidelines. In this structured review, we aim to provide an overview of potentially new diagnostic and therapeutic approaches for delirium in the ICU.

Methods

This is a structured review aiming to describe alternative diagnostic and therapeutic approaches to ICU delirium, compared with those described in the 2013 Pain, Agitation and Delirium (PAD) and 2018 PADIS guidelines.[11, 14] To that end, two separate literature searches (one aimed at diagnostic approaches and another one at therapeutic approaches) were carried out by a biomedical information specialist of the Erasmus Medical Center library in the electronic databases Embase, Medline (Ovid), Web of Science, Cochrane and Google Scholar until 29 April 2019. The selection of articles was done by one of the authors (LS).

Article search

Titles and abstracts of the articles were screened for eligibility. Subsequently we screened the full text of articles meeting our inclusion criteria. For both searches, we included English full text articles involving adult ICU patients. Both prospective and retrospective studies were considered for this review. We excluded review articles, meta-analyses, case reports, letters to

the editor, and abstracts that did not result in original papers. We collected information on the authors, journal, year of publication, study design, inclusion period, number of patients, numbers of observations, and patient population.

Diagnostic approaches: Search terms included DSM-5, CAM-ICU, ICDSC, delirium, ICU and associated free terms *(see appendix 1 for details)*. We included articles comparing any diagnostic tool for ICU delirium with DSM-5 as the reference, published after 2013 (publication of the DSM-5 [9]), and articles assessing diagnostic tools with CAM-ICU or ICDSC as the reference standard, published after 2001 (the publication validation studies of both CAM-ICU and ICDSC[1, 10]). Articles not mentioning any quantitative data, such as sensitivity, specificity, positive predictive value, area under the curve or receiver operating characteristic curve, were excluded. We specifically extracted total number of patients diagnosed with delirium, APACHE score and sensitivity and specificity of the diagnostic tools, when available.

Therapeutic approaches: Search terms included among others delirium, ICU, delirium and coma-free days, therapy and associated free terms *(see appendix 2 for details)*. We selected original articles assessing therapeutic approaches for ICU delirium, which had not been discussed in the 2018 PADIS guidelines (i.e. we excluded articles on antipsychotics, HMG-CoA reductase inhibitors, dexmedetomidine, bright light therapy, and multicomponent intervention bundles). We excluded prophylactic or prevention intervention trials, and studies related to alcohol or substance withdrawal. We specifically extracted patient population, delirium and coma-free days, and APACHE score.

Assessment of risk of bias in included studies
We used the validated Cochrane Risk of Bias Tool to assess the risk of bias for included randomised controlled trials,[15] and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for included diagnostic studies.[16] For observational studies the Newcastle-Ottawa Quality Assessment Form was used.[17] We classified the type of research according to the algorithm published by Grimes & Schulz.[18]

Statistics
Due to the narrative character of this review, statistical analysis was not appropriate for the summary of study data. Meta-analysis was therefore not attempted or possible, also given the fact that we focused on articles that did not comply with the evidence level aimed at in the PADIS guidelines.

Results
Diagnostic approaches for delirium in the ICU: search results
Our literature search into new diagnostic approaches identified seven articles meeting inclusion criteria *(appendix 3)*. The characteristics of the included studies can be found in *table 1*.

Bedside screening tools
The Neelon and Champagne (NEECHAM) Confusion Scale has good diagnostic accuracy for delirium in non-intubated older surgical ICU and mixed ICU patients, with a reported sensitivity of 99.2% and 87%, respectively, and a specificity of 95% for both ICU populations, as compared with the CAM-ICU. It assesses information processing, behaviour and physiological condition, leading to a numeric score and the ability to classify patients as 'delirious' (score below 20), 'at risk', 'mild confusion' and 'normal'. The NEECHAM Confusion Scale may be an easy to use scale for bedside nurses, taking less than 10 minutes to complete.[20] Advantages are that the categories 'at risk' and 'mild confusion' give opportunities for preventive measures as compared with CAM-ICU, which is a binary scale. Caution however is warranted for cardiac surgery patients, as its sensitivity is reported to be 67%.[19] Another limitation is that its use in ventilated patients is not validated.[19] The Stanford Proxy Test for Delirium (S-PTD) on the other hand may be a fitting tool for intubated patients.[21] Twelve items are assessed, including various cognitive processes, awareness and alertness, perceptions, visuospatial abilities and sleep pattern. The S-PTD yielded an excellent sensitivity (82.7%) and specificity (95.3%) for ICU delirium diagnosis as compared with DSM-5 based neuropsychiatric examination.[21] Advantages are that this test takes one minute to administer by an ICU nurse and that no patient interaction is required.

Computerised and smartphone-based tests
The Edinburgh Delirium Test Box (EDTB) for the ICU may be able to discriminate between delirious and non-delirious ICU patients.[22] The EDTB-ICU is a custom-built computerised device which measures arousal and sustained visual attention. The DelApp-ICU is a smartphone-based test developed to administer the EDTB-ICU.[23] With this application, a behavioural assessment is performed initially in order to examine arousal (maximum score of 3) and a visual task to identify visual changes. After successful completion, the sustained attention test is performed. During nine trials patients have to indicate the amount of circles shown on the smartphone, leading to a total score from 0 to 9. Hence, the total score obtained during the attention task ranges between 0 and 12. With the graded measure of attention, it might provide physicians with a degree of delirium severity. A DelApp-ICU score of ≤6 has a delirium detection sensitivity of 100% and a specificity of 96%. The DelApp-ICU requires little training, can be used in non-ventilated as well as ventilated patients, and is easy to use, taking 3-8 minutes to administer. Despite its promising diagnostic potential, this was an initial exploratory study with a small sample size, and further evaluation and validation is necessary. Limitations of this application and other smartphone-based tests include concerns about infection control, discouragement of using phones on an ICU, and limited application in case of visual impairment.

Table 1. Main characteristics of the studies evaluating new diagnostic tools

Study	Study design	Inclusion period	Tool studied	N	No. of observations	Patient population	Delirious patients (%)	Mean APACHE II score	Sensitivity	Specificity	Risk of bias?*
Bedside screening tools											
Alosaimi et al. 2018 [21]	Cross-sectional study	June 2016-Oct 2017	S-PTD by nurse vs. DSM-5 by psychiatrist	135 ICU patients (out of 288 total)	-	ICU and 3 general medical wards	DSM-5: 44/135 (32.6%) S-PTD: 37/135 (27.4%)	-	S-PTD≥2: 86.4%; S-PTD≥3: 79.6%	S-PTD≥2: 91.2%; S-PTD≥3: 97.8%	Yes
Matarese et al. 2013 [19]	Cross-sectional study	1 Oct 2008-30 Apr 2009	NCS vs. CAM-ICU	41	164	Surgical ICU	27.3%	-	Cut-off 25: 99.19%	Cut-off 25: 95%	Yes
Van Rompaey et al. 2008 [20]	Cross-sectional study	July-Aug 2006 & Feb-Mar 2007	NCS vs. CAM-ICU	172	559	Mixed ICU, non-intubated	CAM-ICU: 19.8%; NEECHAM scale: 20.3%	21	Cut-off 20: 87%	Cut-off 20: 95%	Yes
Computerised and smartphone-based tests											
Tang et al. 2018 [23]	Case-control study	-	DelApp-ICU vs. CAM-ICU	46	89	General ICU	21 (46%)	14	DelApp-ICU score 6: 100%	DelApp-ICU score 6: 96%	Yes
Green et al. 2017, [22]	Case-control study	-	EDTB-ICU vs. CAM-ICU	30	79	General ICU	38%	18 (median); delirious: 22; non-delirious: 14	EDTB-ICU score ≤ 5: 100%	EDTB-ICU score ≤ 5: 92%	Yes
Continuous electroencephalography (EEG)											
Plaschke et al. 2010 [24]	Case-control study	-	Bilateral BIS vs. CAM-ICU	114	-	After cardiac surgery	32 (28%)	Delirious: 28.5; non-delirious: 26.5	27%	96%	Yes
Chart-based methods											
Pisani et al. 2006 [25]	Cohort study	3 Sept 2002-30 Sept 2003	Validated chart-based delirium method vs. CAM-ICU	178	1457 patient days	Medical ICU, patients ≥60 years	143 (80%) patients; 929/1457 (64%) patient-days	23.4	64%	85%	Yes

BIS = Bispectral index; CAM-ICU = Confusion Assessment Method for the ICU; EEG = electroencephalography; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EDTB-ICU = Edinburgh Delirium Test Box-ICU; NCS = Neelon and Champagne (NEECHAM) Confusion Scale; S-PTD = Stanford Proxy Test for Delirium.
* Risk of bias is assessed with the QUADAS-2 tool. Its more extensive assessments may be found in table 4.

Electroencephalography
Electroencephalography (EEG) might be promising considering the limitations of intermittent assessment of bedside screening tools and the fact that healthcare personnel may find the bedside tools cumbersome. However, continuous EEG is relatively expensive, needs time-consuming 16-channel cortical function monitoring, and requires training for interpreting the obtained data. Bilateral Bispectral Index (BIS) EEG measurements require a four-channel frontotemporal EEG system and hence may be more practical. In cardiac surgery patients, the BIS EEG data were different for patients who experienced postoperative delirium as opposed to non-delirious patients, with a lower mean BIS index, relative alpha slowing and increased relative theta activity.[24] Bilateral BIS index as a screening tool for postoperative ICU delirium was found to have a sensitivity of 27% and specificity of 96%.[24]

Assessment methods based on the patients' medical record
Pisani et al. described a research algorithm in which delirium is assessed daily with the CAM-ICU combined with a validated chart review method, in which the patient's medical record is examined for symptoms of acute confusion.[25] The chart-based method had a sensitivity of 64% and a specificity of 85% as compared with the CAM-ICU. However, this method is time-consuming with 15 to 30 minutes spent per patient. Additionally, while the chart-based method may be effective for research settings, the CAM-ICU may still be preferred for application in clinical use due to its better diagnostic performance.

New treatments for ICU delirium: search results
Our literature search yielded 6326 articles, of which seven were included in this review *(appendix 4)*. Characteristics of the included articles may be found in *table 2*.

Pharmacological management of delirium
Other medications than antipsychotics which are already in use in ICUs might be beneficial for treating ICU delirium. Opioids are frequently used as analgesic agents in the ICU, but have

Table 2. Main characteristics of the studies evaluating new therapeutic approaches

Study	Study design	Intervention	Inclusion period	N	No. of observations	Patient population	Delirium related outcomes	APACHE II score	Risk of bias*	Remarks
Pharmacological management of delirium										
Bakri et al. 2015 [28]	Randomised controlled trial	i.v. 1 µg/kg 2dd dexmedetomidine or 4mg 2dd ondansetron vs. 5mg 2dd haloperidol during 3 consecutive days	23-month period	96	-	Postoperative delirium in trauma patients	No significant difference in mean daily ICDSC scores and remaining number of delirious patients at last day of study	-	Low	Significantly more patients in ondansetron group used rescue haloperidol in higher dose
Bayindir et al. 2000 [27]	Descriptive study	Single dose ondansetron 8mg i.v.	-	35	-	Coronary artery bypass graft surgery	Significant decrease of delirium score 10 minutes after gift	-	High	No valid delirium screening tool used
Gagnon et al. 2017 [29]	Descriptive study	Valproate; 42% with loading dose; maintenance dose 1500mg/d (23 mg/kg/d) in 1-4 doses	Dec 2012-Feb 2015	53	522 patient-days	Mixed ICU	Incidence of delirium decreased from valproate day 1 to day 3: 68% vs 49%, p=0.012	Median APACHE III: 59	High	Significant reduction in agitation and daily amount of administered fentanyl and lorazepam equivalents
Atalan et al. 2013 [26]	Randomised controlled trial	5mg Morphine i.m. vs. 5mg Haldol i.m.	Jan 2010-July 2012	53	-	Postoperative hyperactive delirium in cardiac surgical patients	Delirium hours: morphine 31.56, haldol 33.9 (p=0.607)	5.69±1.93 (haldol) vs. 6.33±1.79 (morphine), p=0.218	High	Morphine group: less additive sedative drug (8 vs 1 patient, p=0.011), less reintubation (23.1% Haldol vs 3.7%, p=0.050)
Thom et al. 2018, [31]	Cohort study	Ramelteon	1 Oct 2015-31 May 2016	322	-	Medical ICU	DCFH: No ramelteon: 0 (IQR 0-196), ramelteon: 46 (IQR 0-168), p=0.105	24.5±7.5 (ramelteon) vs. 23.9±8.4 (no ramelteon), p=0.600	Low	Ramelteon was not associated with changes in extubation or mortality. Ramelteon more median ventilator-free hours (156 vs. 4.5, p=0.005), but most likely due to administration of ramelteon postextubation
Daniels et al. 2018 [30]	Cohort study	No pharmacological treatment, melatonin only, antipsychotics only, both melatonin and antipsychotics	1 July 2015-30 June 2016	449	-	Medical ICU	No reduction of delirium duration	Median APACHE III: Total 75. Neither: 73.0; Melatonin: 78; Antipsychotic: 79; Both: 79; p=0.04	Low	Melatonin or antipsychotics did not reduce ICU/hospital LOS or 28-day mortality. Antipsychotic use only associated with longer hospital LOS
Non-pharmacological treatment options										
Mailhot et al. 2017 [32]	Randomised controlled trial	Nursing intervention involving families in delirium management vs usual care	2 June 2013-6 June 2015	30	-	Post cardiac surgery ICU	Mean delirium days: Intervention: 1.94; control: 4.14. (no p value available)	-	High	No difference in delirium severity. Significant differences favouring intervention for patients' psycho-functional recovery

APACHE = Acute Physiology and Chronic Health Evaluation; DCFD = delirium and coma-free days; DCFH = delirium and coma-free hours; DSI = delirium severity index; ICDSC = intensive care delirium screening checklist; i.m. = intramuscularly; i.v. = intravenously; LOS = length of stay
*Risk of bias is assessed with either the Cochran Risk of Bias Tool or the Newcastle-Ottawa Quality Assessment Form. Its more extensive assessments may be found in table 3 and table 5.

anxiolytic properties if used in higher dosages.[26] Atalan et al. studied the efficacy of morphine for postoperative hyperactive delirium in cardiac surgical patients as compared with haloperidol in dosages of 5 mg intramuscularly.[26] They found no differences between the two groups with regard to delirium duration, but did report a lower reintubation rate, less sedative use and more patients with target Richmond Agitation-Sedation Scale (RASS) scores in the morphine group. Ondansetron, a selective 5-hydroxytryptamine 3 receptor antagonist involved in the serotonergic system with anxiolytic properties, has also been studied for the treatment of ICU delirium. A prospective study in postcardiotomy patients described a decrease in agitation and delirium shortly after a single dose of 8 mg intravenous ondansetron was administered.[27] However, this study was performed without a valid delirium screening tool and lacked a control group. The efficacy of ondansetron for postoperative delirium in a trauma ICU has been studied in a randomised controlled trial, comparing dexmedetomidine and ondansetron with haloperidol in 96 patients.[28] No differences were found between the study groups. However, in the ondansetron group more rescue haloperidol was needed to obtain the same anti-delirium effects. For dexmedetomidine as well as ondansetron no QTc interval prolongation or serious adverse events were reported, suggesting their safety in an ICU setting. Furthermore, another agent with potential anti-delirium effects is the antiepileptic drug valproate. In a recent descriptive study valproate (1500 mg in 1-4 divided daily doses) was associated with significantly reduced incidence of delirium from 68% to 49% within 48 hours of initiation. [29] Additionally, it was associated with reduced incidence of agitation and administration of opioids, dexmedetomidine and quetiapine. However, 19% developed hyperammonaemia and 13% thrombocytopenia, which might limit the safety of this drug. Lastly, melatonin has been studied as a potential delirium treatment. A recent retrospective cohort study found no effect of melatonin as sole treatment or in combination with antipsychotics on ICU delirium duration as compared with no treatment.[30] No other beneficial effects on relevant patient outcomes were found, such as ICU and hospital length of stay and mortality. Similarly, another recent retrospective study found no effect of ramelteon, a melatonin receptor agonist, on median delirium-and-coma free hours, nor was administration of ramelteon associated with length of mechanical ventilation or mortality rates.[31]

Non-pharmacological treatment options
Recently the importance of involving family members in routine patient care gained more attention. Mailhot et al. conducted a pilot randomised controlled trial studying the feasibility of a nursing intervention involving family caregivers in delirium management.[32] They found a significant difference in psycho-functional recovery in patients who received delirium management interventions by family caregivers. Differences in other outcomes favoured the intervention group, among which delirium duration, hospital length of stay, and anxiety and self-efficacy experienced by the caregivers. These results, however, did not reach statistical significance as this was a pilot study with a small sample size.

Risk of bias of included studies
All included studies evaluating new diagnostic tools have been found to be at risk of bias with the QUADAS-2 tool, as shown in *table 3*.[16] As depicted in *table 4* and *table 5*, most of the studies assessing new treatments for ICU delirium have been judged as having a high risk of bias. The studies by Bakri et al., Daniels et al. and Thom et al., respectively, investigating the effect of ondansetron, melatonin and ramelteon, had a low risk of bias.[28, 30, 31]

Discussion
This structured review identified and discussed several potential alternatives regarding the diagnostic tools and treatments for ICU delirium which, after further study, may become useful additions to the current diagnostic and

Table 3. Risk of bias assessments for included diagnostic studies using the QUADAS-2 tool

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Alosaimi et al. 2018 [21]	-	-	+	-	-	-	-
Matarese et al. 2013 [19]	-	-	-	+	-	-	-
Van Rompaey et al. 2008 [20]	+	-	-	+	-	-	-
Tang et al. 2018 [23]	-	-	-	-	-	-	-
Green et al. 2017 [22]	-	-	-	+	-	-	-
Plaschke et al. 2010 [24]	+	-	-	+	-	-	-
Pisani et al. 2006 [25]	+	-	-	+	-	-	-

+ = low risk of bias; - = high risk of bias.

Table 4. Risk of bias assessments for included randomised controlled trials using the Cochrane Risk of Bias Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bakri et al. 2015 [28]	-	-	+	-	-	-	-
Atalan et al. 2013 [26]	-	-	-	+	-	-	-
Mailhot et al. 2017 [32]	+	-	-	+	-	-	-

+ = low risk of bias; - = high risk of bias.

therapeutic armamentarium. Diagnostic alternatives with good diagnostic performance include two bedside screening tools – NEECHAM Confusion Scale and S-PTD – and the DelApp-ICU smartphone-based test, with reported sensitivities between 82.6% and 100%, and specificities between 95% and 96%. With regards to treatment options that were not discussed in the PADIS guidelines, we found that valproate and ondansetron may constitute potentially beneficial treatments for the burden of delirium, if future research provides more high-quality evidence.

The 2018 PADIS guidelines recommend routine delirium screening in critically ill patients with either the CAM-ICU or ICDSC.[33] Recently these tools have been shown to be less accurate, possibly due to a trend of less sedation as recommended by the 2013 PADIS guidelines.[8,14] This is disconcerting, as false-positive results may lead to unnecessary and unproven treatments, while false-negative results may result in persisting unrecognised delirium, with associated undesirable patient outcomes.

In the studies included in this review, we identified heterogeneous diagnostic modalities. The most used delirium bedside screening tools are the CAM-ICU and ICDSC.[12, 34] Our results add to current literature that NEECHAM Confusion Scale and S-PTD are promising delirium assessment tools with good diagnostic performance as compared with recent DSM-5 criteria, CAM-ICU or ICDSC. These have not been discussed in previous recent systematic reviews involving delirium assessment tools.[12, 34, 35] However, NEECHAM Confusion Scale is not suitable for ventilated patients. Additionally, BIS EEG showed good specificity, but a sensitivity of 27%, in one study involving cardiac surgery patients. The authors of this study did

not account for sedation effects. After adjusting for arousal, BIS may have less diagnostic utility in diagnosing ICU delirium.[36] Furthermore, compared with previously published reviews, we did not examine biomarkers as a potential diagnostic tool for ICU delirium.[37] Our literature search yielded articles studying biomarkers, but these were excluded as the articles did not mention diagnostic data, such as sensitivity and specificity, yet showed results as biomarkers associated with risk of developing delirium. Similarly, EEG has been hypothesised to be a promising diagnostic modality.[38] However, due to the lack of data in the identified articles, we have not discussed the potential of EEG in our review.

Despite the increasing amount of research on ICU delirium, there is no robust evidence for the efficacy of pharmacological or non-pharmacological treatment options. Previous reviews on pharmacological treatment options have mainly focused on antipsychotics and dexmedetomidine.[34, 39, 40] Our results add to the current literature that melatonin or melatonergic agonists, opioids, ondansetron and valproate may require further evaluation in prospective trials.

Current evidence supporting non-pharmacological interventions to treat ICU delirium is also lacking.[41] Our results regarding non-pharmacological treatment options are in line with previous research. Based on one identified pilot study, involving family in ICU care seems promising, as the intervention seems to be easy to implement with gain in patient as well as family outcomes. A recent systematic review also found benefits of a protocolised family support intervention, including shorter ICU and hospital length of stay.[42] Future research is warranted to study the effect and optimal frequency of family involvement in delirium management.

Limitations of this review include: few eligible articles, especially few randomised controlled trials, restricted search to English articles, and the included studies mostly had small sample sizes, and used inconsistent methodologies, primary outcomes and study designs, among which varying study populations and lack of comparison groups, with most studies having a high risk of bias. This limits generalisability and comparability of these diagnostic and therapeutic approaches. Another limitation intrinsic to this study is that the diagnostic and therapeutic approaches discussed were not included in the 2018 PADIS guidelines. Therefore, the level of evidence, or quality, of studies

Table 5. Risk of bias assessments for included observational studies using the Newcastle-Ottawa Quality Assessment Form

Study	Selection	Comparability	Outcome/exposure	Overall quality
Bayindir et al. 2000 [27]	1 point	0 points	1 point	Poor
Gagnon et al. 2017 [29]	3 points	0 points	2 points	Poor
Thom et al. 2018 [31]	4 points	2 points	2 points	Good
Daniels et al. 2018 [30]	4 points	2 points	3 points	Good

included are necessarily lower than in the PADIS guidelines. Hence, we would like to emphasise that this structured review is meant to be an overview of new possibilities to diagnose or treat ICU delirium, for which further research is required, and that recommendations for their use in clinical practice are not yet appropriate. Furthermore, as mentioned before, the accuracy of the CAM-ICU and ICDSC has decreased in recent studies. This might imply that the articles presented in this review which compared diagnostic tools with the CAM-ICU or ICDSC instead of the DSM-5 may not be as accurate as well. Even though the CAM-ICU and ICDSC are the most used delirium bedside screening tools in the ICU, these tools are generally not considered to be the reference standard for the diagnosis of delirium. The potential diagnostic modalities, which were compared with the CAM-ICU or ICDSC as the reference, may therefore only be considered to be validated diagnostic tools if future studies compare them with the DSM-5. On the other hand, it can be argued that most studies done with CAM-ICU or ICDSC show strong associations of delirium diagnosed with these instruments with mortality (indicating their clinical relevance), whereas for the DSM diagnosis this association is less well established. In other words, whether DSM diagnosis or well validated and widely implemented screening tools are more justified to diagnose delirium may be amenable to discussion in our view. Additionally, for some intervention studies assessing efficacy of drugs, the optimal dose for treatment of ICU delirium is uncertain. Strengths of this review are its structured design and comprehensive search with a highly experienced medical information specialist.

We recommend future research to report on the association of the diagnostic tool used and the clinical outcomes of the ICU patients. Indeed, aside from the accuracy of the diagnostic tools, it might be of interest to pay attention to the patient outcomes, such as mortality and length of stay, associated with delirium as diagnosed with these different tools. Which new therapeutic approach is suited for which specific ICU population should also be further elucidated. Valproate may be a potential therapy, but a large randomised controlled trial to study its efficacy on delirium duration is recommended. However, considering the multifactorial pathway of delirium, it is unlikely that treatment of ICU delirium can be pinned down to one specific pharmacological agent.

Alternative bedside screening tools or smartphone based tests may become aids for the ICU physician and nurse in diagnosing delirium in critically ill patients by either using these tools as a replacement of or combined with the CAM-ICU and ICDSC.

Conclusion

Due to the adverse patient outcomes associated with delirium in critically ill patients, it is important to use a reliable and valid delirium screening tool and safe and effective treatments. This structured review has provided an overview of currently available and promising alternative diagnostic and therapeutic approaches for delirium in critically ill patients, as an addition and future perspective to the current state of the art diagnostic and therapeutic practices as summarised in the recent 2018 PADIS guidelines. However, it is clear that additional studies are needed to establish whether these new diagnostic and therapeutic approaches should be implemented for the management of ICU delirium.

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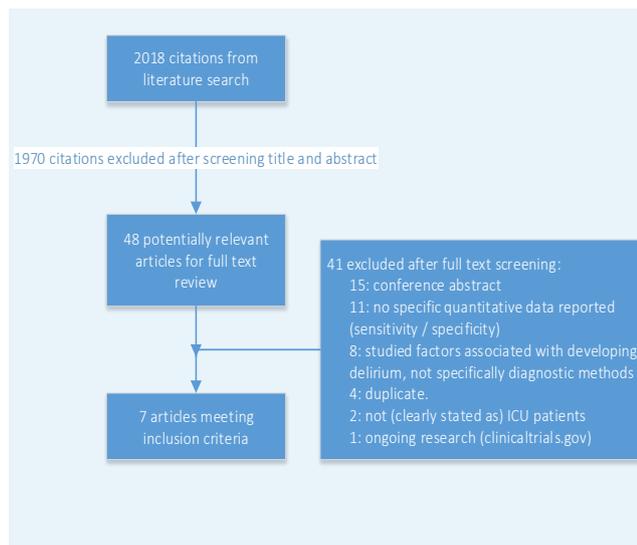
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Appendix 1 en 2. Literature and search details

https://njcc.nl/sites/nvic.nl/files/hd%2019-84%20Smit%20Appendix%201%20en%202%20QR.pdf

Appendix 3. Flowchart literature search: diagnostic approaches

2018 citations from literature search

1970 citations excluded after screening title and abstract

48 potentially relevant articles for full text review

41 excluded after full text screening:
15: conference abstract
11: no specific quantitative data reported (sensitivity / specificity)
8: studied factors associated with developing delirium, not specifically diagnostic methods
4: duplicate.
2: not (clearly stated as) ICU patients
1: ongoing research (clinicaltrials.gov)

7 articles meeting inclusion criteria

Appendix 4. Literature search details: therapeutic approaches

6326 citations from literature search

6292 citations excluded after screening title and abstract

34 potentially relevant articles for full text review

27 excluded after full text screening:
2: prevention trial
14: conference abstract
3: terminated research (clinicaltrials.gov / Clinicaltrialsregister.eu)
1: ongoing research (clinicaltrials.gov)
2: recruitment completed but no results reported yet (IRCT + ISRCTN)
1: duplicate (clinical trials registration of finished research)
2: no full text available
1: atypical antipsychotic
1: no delirium data available

7 articles meeting inclusion criteria