Tools to Detect Delirium Superimposed on Dementia: A Systematic Review

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OBJECTIVES: To identify valid tools to diagnose delirium superimposed on dementia.

DESIGN: Systematic review of studies of delirium tools that explicitly included individuals with dementia.

SETTING: Hospital.

PARTICIPANTS: Studies were included if delirium assessment tools were validated against standard criteria, and the presence of dementia was assessed according to standard criteria that used validated instruments.

MEASUREMENTS: PubMed, Embase, and Web of Science databases were searched for articles in English published between January 1960 and January 2012.

RESULTS: Nine studies fulfilled the selection criteria. Of 1,569 participants, 401 had dementia, and 50 had delirium superimposed on dementia. Six delirium tools were evaluated. One study using the Confusion Assessment Method (CAM) with 85% of participants with dementia had high specificity (96–100%) and moderate sensitivity (77%). Two intensive care unit studies that used the CAM for the Intensive Care Unit (CAM-ICU) reported 100% sensitivity and specificity for delirium in 23 individuals with dementia. One study using electroencephalography reported sensitivity of 67% and specificity of 91% in a population with a 100% prevalence of dementia. No studies examined potential effects of dementia severity or subtype on diagnostic accuracy.

CONCLUSIONS: The evidence base on tools for detection of delirium superimposed on dementia is limited, although some existing tools show promise. Further studies of existing or refined tools with larger samples and more-detailed characterization of dementia are required to address the identification of delirium superimposed on dementia. **J Am Geriatr Soc 60:2005–2013, 2012.**

Key words: delirium; dementia; delirium superimposed on dementia; delirium tools

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DOI: 10.1111/j.1532-5415.2012.04199.x

Delirium is a common geriatric syndrome characterized by acute and fluctuating disturbance of consciousness, inattention, and deficits in arousal and cognition. Delirium that occurs in individuals with dementia is referred to as delirium superimposed on dementia (DSD). The prevalence of DSD in community and hospital setting ranges from 22% to 89%[1] and is greater than found in individuals without dementia. By 2050, the number of individuals aged 65 and older in the United States with Alzheimer's disease, the most common form of dementia, is projected to be between 11 million and 16 million.[2] By extrapolation based on the expected proportion of individuals with dementia, up to 14 million individuals will potentially experience DSD, representing a massive healthcare challenge.[3]

DSD is associated with adverse outcomes that include accelerated cognitive and functional decline, rehospitalization, institutionalization, and mortality.[4] Delirium has

0002-8614/12/$15.00

been proposed as an additional vital sign,[5] and its presence is often the first sign of a change in clinical condition, especially in older persons and those with dementia. For instance DSD might be the harbinger of an undiscovered infection or a recent change of a medication with psychoactive effects. Recognition of DSD should prompt an urgent and thorough clinical evaluation of the individual and subsequent therapeutic actions.

The diagnosis of DSD is often challenging because signs of delirium might be mistaken for the fluctuation of cognitive function or psychological symptoms of individuals with dementia. Aside from low levels of delirium detection in general,[6–8] practitioners may not assess for DSD because of the perception that it cannot be readily distinguished from dementia. There may also be a belief that current delirium detection instruments lack adequate measurement properties in the context of dementia.

Although multiple tools have been developed and validated to diagnose delirium, it is currently unclear which tools, if any, can be used in individuals with dementia and how accurately such tools perform in this growing population. This is surprising, given that a substantial number of individuals with delirium also have dementia. A recent systematic review of instruments to detect delirium[9] reported detection instrument characteristics in hospitalized noncritically ill individuals but did not comment specifically on the performance of these tools in individuals with dementia.

The purpose of this systematic review is to summarize the available literature on the performance characteristics of delirium screening instruments in samples explicitly containing individuals with dementia.

METHODS

Literature Search Strategy

This systematic review was registered on the Prospero systematic review website (PROSPERO 2011: CRD42011001271). Searches of PubMed, EMBASE, and Web of Science were conducted for articles published between January 1960 and January 22, 2012. The search terms were delirium tools, delirium assessments combined with delirium, confusion, acute confusional state, acute brain failure, acute confusion, dementia, cognitive impairment, and Alzheimer's disease. A complete search strategy can be found in Appendix S1, available in the online version.

Study Selection and Data Extraction

Validation studies were included that had evaluated delirium with tools using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)[10] or DSM-III[11] criteria as a criterion standard and included individuals (diagnosed using a neuropsychological battery consisting of the DSM-III; DSM-III, Revised (DSM-III-R); DSM-IV; DSM-IV, Text Revision (DSM-IV-TR);[10–12] National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA);[13] Blessed Dementia Rating Scale (BDRS);[14] Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE);[15] Clinical Dementia Rating Scale (CDR))[16] with dementia (BDRS $\geq$ 4; CDR $\geq$ 1) or severe dementia (BDRS score $\geq$ 12, CDR = 3). Admissible study designs were randomized controlled trials or observational studies with longitudinal or cross-sectional designs.

Studies that assessed solely alcohol-related delirium, had a study population with age younger than 18, did not apply DSM-IV or DSM-III criteria as a criterion standard delirium assessment, and did not assess dementia with validated measures, as described above, were excluded. Review articles, case series, duplicates, studies in which the same individual administered the index and reference tests, and studies in which the index and reference tests were administered on different days were also excluded.

Two reviewers (AM and JM, EV and DF, GB and JCJ) independently reviewed each abstract to identify publications that met inclusion and exclusion criteria, and studies included and excluded were reported using the PRISMA systematic review protocol.[17] During the screening process, full texts were retrieved when information in the abstract was not available or insufficient. In cases of disagreement between the two reviewers, inclusion decisions were resolved by discussion and consensus with a third reviewer. This procedure was required for five articles (5%) of the 100 selected.

The reviewers independently extracted data using the Standards for Reporting of Diagnostic Accuracy (STARD)[18] and the Assessment of Methodological Quality (QUADAS).[19] Data on sensitivity, specificity, and likelihood ratios of the tools that included individuals with dementia; sensitivity; specificity; number of individuals with dementia; number of individuals with delirium and DSD; presence of confounding psychiatric illnesses (e.g., depression); time interval between assessment for delirium; definition of dementia; and rater for delirium and dementia were extracted if available.

Assessment of Quality and Biases

Outcome reporting bias was evaluated by comparing the methods section of each article with the results. Unreported outcomes were those mentioned in the Methods section of the study but not in the Results section. Publication bias was evaluated by reviewing reference lists in each included study for abstracts that had not been formally published in full manuscript format. Quality of data reporting was evaluated using the Assessment of Quality of Reporting (STARD criteria: score range 1–25, higher = better).[18] Quality of study methodology was assessed using the Assessment of Methodological Quality (QUADAS tool: score range 1–14, higher = better).[19]

RESULTS

Search Results

Ten thousand two hundred seventy-three citations were identified in the original literature search (Figure 1). An additional 10 articles were identified through hand searching, and 12 duplicates were removed, resulting in

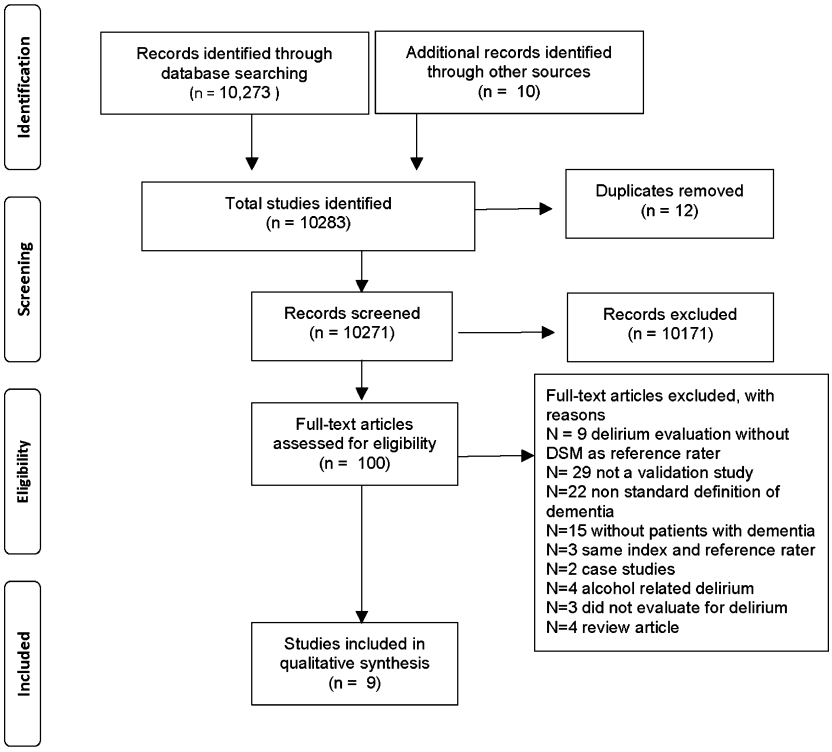

Figure 1. PRISMA flow diagram.

10,271 records that were screened for inclusion; 10,171 abstracts met initial exclusion criteria, and 100 full-text articles were assessed for inclusion eligibility; 91 of those were excluded, with nine included in the final review (Table 1).

Participant Characteristics

The age range of the study populations was 34 to 84 (mean 75.8 ± 11.5). Participants were tested mainly in three clinical settings: inpatient geriatric and medical units, stroke units, and intensive care units (ICUs). Six studies were conducted in the United States and one each in Germany, Finland, and the Czech Republic.[20–27] Overall sample sizes ranged from 35 to 791 (mean 174 ± 243). Of the included studies, only one[28] specifically evaluated delirium in individuals with dementia, whereas the others included participants with dementia as a subgroup of participants in the validation. The prevalence of dementia in individual studies ranged from 12% to 100%. The number of participants with identified DSD in individual studies ranged from seven to 12; the total number of participants with DSD from the whole population studied was 50. None reported severity or subtype of dementia.

Delirium Screening Instruments

Six tools (Confusion Assessment Method (CAM), CAM for the Intensive Care Unit (CAM-ICU), Cognitive Test for Delirium (CTD), Delirium Rating Scale (DRS), electroencephalography (EEG), and Short-Portable Mental Status Questionnaire (SPMSQ)) were used to assess DSD.[20–27]

Reporting Quality

Eighty-nine percent of the studies reviewed achieved a high-quality methodology rating (QUADAS score $\geq$ 10), and 67% had a high-quality data reporting rating (STARD score $\geq$ 20) (Table 2). Forty-four percent of the studies did not report the time interval between the delirium assessment of the DSM rater and the index tool rater (Table 2). Two studies[20,21] allowed a maximum time of 4 hours or less, one study of 3 hours or less,[25] one study of 2 hours or less,[27] and one up to a maximum of 6 hours.[24] The DSM raters for delirium were neurologists, geriatricians, geriatric psychiatrists, or experienced neuropsychologists, providing a high standard of evaluation. Similarly, expert clinicians diagnosed probable dementia or dementia (neurologists, psychiatrists, or geriatric psychiatrists) (Table 1).

Screening for Delirium Superimposed on Dementia Test Characteristics

The CAM was assessed in two studies including participants with dementia.[24,25] It was originally[24] developed and validated in a population of elderly adults admitted to a medical-geriatric ward (N = 56); 12 of these (21%) had dementia, nine of whom had DSD. Presence of dementia was defined according to DSM-III-R criteria after an evaluation by a geriatric psychiatrist. The sensitivity of the delirium tool in the entire sample ranged from 94% (95% confidence interval (CI) = 68–100) to 100% (95% CI = 54–100) and the specificity from 90% (95% CI = 54–100) to 95% (95% CI = 73–100), but specific measures for those with dementia were not reported. A subsequent validation

Table 1. Characteristics of Included Studies

Tool (Author, Year)	Age, Mean ± Standard Deviation	Setting	Sample, N	With Delirium	Without Delirium or Dementia	With Dementia	With Delirium Superimposed on Dementia	With Depression	Sensitivity of Tool in Entire Sample	Specificity of Tool in Entire Sample
				n (%)					%	
Short Portable Mental Status Questionnaire (Erkinjuntti, 1987)[22]	75.2 ± 7.2	Geriatrics	282	58 (20.5)	197 (70)	34 (12)	7 (2)	NA	7.3–98	82–100
CAM (Inouye, 1990)[24]	77–81 ± 5.4–7.9	Internal medicine service	56	26 (46)	27 (48)	12 (21)	9 (16)	9	94–100	90–95
Delirium Rating Scale (Rosen, 1994)[26]	72.6 ± 9.4	Geriatrics	791	70 (9)	524 (66)	197 (27)	NA	NA	94	82
Cognitive Test for Delirium (Hart, 1996)[23]	34.4–64.9 ± 12.3–14.6	ICU	103	22 (21)	55 (53)	26 (25)	NA	224 (28), major depression	100	95
CAM-ICU (Ely, 2001)[20]	55.3 ± 17.4	ICU	96	80 (83)	15 (16)	12 (15)	11(11)	30 (29)	93–100	98–100
CAM-ICU (Ely, 2001)[21]	60 ± 19	ICU	38	33 (89)	5 (13)	11 (29)	NA	NA	95–100	89–93
CAM-ICU (Mitasova, 2011)[27]	71.2 ± 11.5	Stroke unit	129	55 (47)	88 (68)	41 (31.8)	21 (38)	NA	76	98
Electroencephalography (Thomas, 2007)[28]	84.1 ± 3.9	Geriatrics	35	23 (65)	0 (0)	35 (100)	12 (34)	NA	67	91
CAM (Hestermann, 2009)[25]	82.6 ± 6.7	Geriatrics	39	13 (33)	26 (67)	33 (85)	11 (28)	NA	77	96–100

CAM = Confusion Assessment Method; ICU = intensive care unit; NA = not available.

Table 2. Characteristics of Included Studies: Delirium Raters and Quality of Methodology and Reporting

Tools (Author, Year)	Definition of Dementia and Dementia Rater	Delirium Rater DSM Criteria	Delirium Rater Delirium Tool	Time Between Assessment for Delirium and DSM Rater	Quality of Methods[a]	Quality of Data Report[b]
Short Portable Mental Status Questionnaire (Erkinjuntti, 1987)[22]	DSM (neurologist)	Neurologist	Psychologist	Not reported	10	11
CAM (Inouye, 1990)[24]	DSM-III-R (psychiatrist)	Geriatric psychiatrist	Geriatrician	Maximum 6 hours	13	25
Delirium Rating Scale (Rosen, 1994)[26]	DSM-III-R (geriatric psychiatrists)	Geriatric psychiatrist	Research clinician	Not reported	11	20
Cognitive Test for Delirium (Hart, 1996)[23]	DSM-III-R, Mattis Dementia Rating Scale (neuropsychologist)	Psychiatrist	Research nurses	Not reported	9	19
CAM-ICU (Ely, 2001)[20]	DSM-IV; BDRS (geriatrician, geriatric psychiatrist; nurses)	Geriatrician, geriatric psychiatrist neuropsychologist	Research nurses	$\leq$4 hours	13	24
CAM-ICU (Ely, 2001)[21]	DSM-IV; BDRS (geriatrician, geriatric psychiatrist; nurses)	Geriatrician, geriatric psychiatrist	Research nurses, intensivists	$\leq$4 hours	13	24
CAM-ICU (Mitasova, 2011)[27]	BDRS (neuropsychologist)	Neurologist, neuropsychologist, psychiatrist, speech therapist	Neurology-resident	<2 hours	13	23
Electroencephalography (Thomas, 2007)[28]	IQCODE, DSM-IV, neuropsychological tests (geriatrician, geriatric psychiatrist, gerontologist, neurologist)	Geriatrician, geriatric psychiatrist, gerontologist, neurologist	Neurophysiologist	Not reported	10	21
CAM (Hestermann, 2009)[25]	IQCODE; DSM-IV (psychologist, gerontologist; geriatric psychiatrist)	Geriatric psychiatrist, geriatrician	Psychologist, gerontologist	$\leq$3 hours	13	19

BDRS = Blessed dementia rating scale score; CAM = Confusion Assessment Method; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; CTD = Cognitive Test for Delirium; ICU = intensive care unit; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; NA = not available.

[a] Quality of study methodology was assessed using the Assessment of Methodological Quality tool, range 1–14 (higher = better).[19]

[b] Quality of data reporting was assessed using the Assessment of Quality of Reporting tool (Standards for Reporting of Diagnostic Accuracy criteria), range 1–25 (higher = better).[18]

study of a German translation of the CAM[25] included a high percentage (85%) of participants with dementia (n = 33). In the entire group (N = 39) of elderly adults admitted to an acute geriatric unit, the CAM had high specificity (96–100%) and moderate sensitivity (77%) in delirium detection, with a likelihood ratio for a positive test of 19.2. Eleven participants had DSD (28% of the total sample, 33% of those with dementia), but the test characteristics of this subgroup were not reported. Diagnosis of dementia was made according to a consensus between a geriatric neuropsychiatrist and a geriatrician blinded to the diagnosis of delirium and obtained through the CAM evaluation. The psychiatrist conducted a structured interview with the family following the DSM-IV criteria. The final diagnosis of dementia was obtained by combining this information with the IQCODE, a surrogate interview administered to a close relative of each participant by a psychologist. No information was provided as

to whether the raters of the SPMSQ and reference standard were blinded to the results of the other test.

Two validation studies of the CAM-ICU included a small number of participants with dementia among the 134 total participants[20,21] admitted to an ICU. Sensitivity was 98% to 100% in the entire sample and 100% (95% CI = 63–100%) for the diagnosis of DSD, and specificity was 93% in the entire sample and 100% (95% CI = 3–100%) for the diagnosis of DSD. The presence of dementia was defined according to a combination of a geriatrician or geriatric psychiatrist evaluation and the DSM-IV criteria or to the BDRS performed by study nurses. According to these methods, 23 participants were classed as having dementia. The age range was 55 to 66. Individuals with suspected severe dementia were excluded. Although these studies specifically report the sensitivity and specificity of the CAM-ICU in the subgroup of participants with dementia, the prevalence of DSD could not be determined in one of the two validation studies. The CAM-ICU was also applied[27] in 129 individuals admitted to a stroke unit (mean age 71.2 ± 11.5), of whom 31.8% had probable dementia defined according to the BDRS performed by a neuropsychologist and 21 (38%) had DSD. As in the other two CAM-ICU studies, individuals with severe dementia were excluded. In the entire sample, sensitivity (76%) was moderate and specificity (98%) was high.

The quantitative EEG[28] had high specificity (96–100%) and moderate sensitivity (77%) for the diagnosis of DSD in 35 individuals with dementia admitted to an acute geriatric ward. An expert panel (geriatric specialist, neurologist, geriatric psychiatrist, psychologist, and gerontologist) diagnosed dementia according to the DSM-IV criteria using complete medical history, chart information, caregiver questionnaires, and neuropsychological testing, although it is unclear how neuropsychological testing was used in the context of delirium. Individuals with severe dementia were excluded. An expert neurophysiologist who was blinded to the clinical diagnosis of delirium performed the EEG. The time between the clinical delirium assessment and the EEG evaluation was not reported. The authors used two EEG techniques: resting EEG (rEEG) and quantitative EEG (qEEG) with eyes open. With the rEEG, pathological results were frequent but were not different between individuals with DSD and individuals with dementia alone. The rEEG provided sensitivity of 42% and specificity of 86% in detecting DSD. The qEEG, with the presence of greater delta and lower alpha2 activity during activation, had greater sensitivity (67%) and specificity (91%) in detection of DSD.

The SPMSQ was evaluated[22] in 282 elderly adults with a mean age of 75 ± 7.2; 34 of these (12%) had dementia previously documented, and 7 (2%) experienced DSD. The sensitivity of the tool in the entire population ranged from 7.3% to 98% and the specificity from 82% to 100%. The wide variation in the sensitivity is related to the numbers of errors detected with the SPMSQ, which could be used as different cutoffs for the diagnosis of delirium. The diagnosis of dementia was ascertained through a neurologist interview according to DSM criteria. The quality of the data reporting was lower than in the other studies (STARD score 11). In particular, the time between the SPMSQ evaluation and the reference standard rater was not reported, creating potential bias in the diagnosis of delirium given the fluctuation of this syndrome, and no information was provided as to whether the readers of the index tests and reference standard were blinded to the results of the other test.

The CTD[23] was tested in 103 individuals in the ICU (mean age 34.4–64.9) with a 25% prevalence of dementia. The overall tool sensitivity (100%) and specificity (95%) were high. A neuropsychologist assessed the presence of dementia according to the DSM-III criteria and the MDRS. The CTD was found to have lower-quality methodology than the other tools (QUADAS score 9). In particular, two features were found to be unclear: whether the reference standard for delirium was independent of the index test and whether the individuals received the same reference standard regardless of the index result. As in the previous study, the interval between the CTD evaluation and the DSM rater evaluation was not reported.

The DRS[26] was evaluated in 791 elderly adults admitted to an acute care psychogeriatric unit (mean age 72.6) with a prevalence of dementia of 27% (N = 197). The number of individuals with DSD was not reported, but the overall prevalence of delirium in the entire population was 9% (n = 70). The sensitivity of the tool (DRS score $\geq$ 10) in the entire population was 94% and specificity 82%. As in other studies,[22,23] time between the DRS evaluation and the DSM rater evaluation was not reported. The diagnosis of dementia was obtained through a consensus conference attended by three to six geriatric psychiatrists according to the DSM-III criteria.

Documentation of Depression

Information on the presence of depression was reported in only three studies.[23,24,26] The proportion of participants with depression ranged from 16% to 29%.[23,24] One study[24] reported a prevalence of major depression of 28%. No specific subgroup analyses were reported showing how the tools would perform differently in diagnosing delirium in the presence of depression.

Overall, the evidence of marked heterogeneity of the studies as reflected by the differing populations and tests for delirium made a meta-analysis of this data not feasible.

DISCUSSION

This is the first systematic review of the literature on the performance of existing tools for delirium detection in individuals with dementia. It found that the CAM and the CAM-ICU had preliminary data supporting their use in the general ward and ICU settings, respectively. Nonetheless, the overall evidence base is small. Only nine studies were of sufficient quality to meet the final inclusion criteria. Although 1,569 individuals were assessed in the included studies, only 50 had DSD as measured according to validated methods. The prevalence of DSD ranged from 2% to 38%. None of the studies reported any effects of dementia severity or subtype. An expanded evidence base is required to draw firmer conclusions about the performance characteristics of delirium measurement tools in the growing and diverse populations of individuals with dementia.

On the basis of the available evidence, the CAM and the CAM-ICU have the most support for use in the diagnosis of DSD. Both CAM studies included individuals with dementia, although neither specifically targeted a dementia subgroup. One study[25] provided a potential indication of the use of the CAM in individuals with dementia given the high prevalence of dementia (85%). In that study, the CAM had high specificity for delirium but lower sensitivity. The probability of missing the diagnosis was almost 30%, a level that is somewhat lower than that of delirium instruments used in a general population for routine clinical use. In the CAM-ICU validation study,[20,21] individuals with severe dementia were excluded, and no information was reported on the number of individuals with probable mild and moderate dementia, although the overall sensitivity and specificity of the tools in individuals with dementia were high. Serial EEGs have been proposed as a useful method in the diagnosis of delirium.[29] One study[28] had mixed results; specificity of EEG was high, but sensitivity in the population with dementia was only 67%. In addition, the exclusion of individuals with severe dementia limited the studies' generalizability. Thus, EEG might have a place in detecting DSD in research studies, although further replication in larger groups that include a greater variation in degrees of cognitive impairments is needed.

This review has shown that the current evidence base is small and preliminary. Some questions that future work might address will now be discussed.

The differences between delirium and dementia provide an obvious focus for the development of scales with better ability to discriminate these conditions. One important such area is how to most effectively capture information from caregivers in making the diagnosis of DSD. Caregiver information is essential to ascertain whether there has been an acute decline (characteristic of delirium) but also to determine whether there has also been a much longer decline (characteristic of dementia). Caregivers can also clarify whether fluctuations in the level of alertness or of cognitive functions are different from baseline fluctuations. It may be that a simple question asking about change is sufficient, but a more-detailed dimension-based checklist might have additional value. Another valuable discriminating feature is level of consciousness. Alterations in level of consciousness are not always present in delirium, but when present, they are highly specific to this diagnosis.[30] It may be that this feature is particularly valuable in situations in which cognitive testing is hard to interpret because of significant underlying impairments or in which such testing or even interviews are impossible because of altered level of consciousness. Moreover, other noncognitive domains might be exploited in this way. For example, the Trunk Control Test—a measure of the ability of a individual to control trunk position—was reported as a possible tool to distinguish DSD from dementia.[31] Better descriptions of motor disturbance may also be useful, because individuals with DSD may have greater perturbation in motor agitation and retardation than those with dementia.[32]

Cognitive differences between delirium and dementia could also be examined in more depth. Inattention is a core feature of delirium, and thus differences in the severity and types of attentional deficits that occur between delirium and dementia may be useful in future diagnostic tools. For example, sustained visual attention as assessed using an objective computerized instrument (Edinburgh Delirium Test Box) was reported to be highly impaired in delirium but intact in Alzheimer's disease. In addition, visual perception is impaired in delirium but relatively preserved in most types of dementia.[33,34] By contrast, tests of memory are generally impaired in delirium and Alzheimer's disease. Thus, objective evaluation of specific deficits in sustained attention may be useful in differentiating delirium-related inattention from typical dementia symptoms. The use of eye tracking technology[35] might represent a further novel approach to assess visual attention. Eye tracking might be used to test visuospatial and perceptual attention, working memory, motor agitation, or retardation.[35] These tests should be then compared with existing delirium tools to identify which tools perform better in dementia and in different stages of dementia. These types of tasks appear to have good or excellent ability to discriminate between delirium and dementia, although it is unknown how these tasks perform in different stages and types of dementia.

Another important knowledge gap is in understanding the effects of the severity and subtype of dementia. This matters because severe dementia is associated with neuropsychological deficits, including in attentional functioning. Therefore, some attentional tests might discriminate between mild or moderate dementia and delirium but not severe dementia. Subtypes of dementia differ with respect to neuropsychological profile, fluctuations, and psychotic features. Therefore, research taking account of these parameters of the individuals with dementia would be informative. For instance, visual and visuospatial dysfunction, which has been studied in the context of delirium, is a prominent feature of dementia with Lewy bodies, but it is relatively rare in Alzheimer's disease.[36] By contrast, individuals with frontotemporal dementia have better preserved visuospatial abilities.[37]

The variation in dementia diagnostic procedures may add interpretational biases and lead to populations with varying degrees of severity of dementia. A formal definition of dementia obtained using neuropsychological testing, neuroimaging, and biomarkers would be ideal for improving comparisons between studies. As often happens in studies of acute hospitalized inpatients, it is cumbersome and often not practical to obtain a complete prehospital evaluation. Although the included studies each used accepted methods to define the presence of dementia, future studies should strive to apply similar methods of diagnosis to enable better comparability of the research findings.

Finally, the overlap of delirium and depression might interfere with the screening and diagnosis of delirium and needs to be further elucidated in future work. How clinicians and researchers are limited in the diagnosis of delirium because of difficulties in differentiating delirium from emotional alterations such as depression has been previously highlighted.[38] The current delirium tools do not include measures of mood and affect, although anxiety and depressed mood are features of delirium.[39] This gap might lead to delirium and depression misclassification.

One study found that 46% of individuals referred to a psychiatric liaison consultation were misdiagnosed, and in 31% of the individuals, depressive disorder was the most common incorrect diagnosis.[40] An overlap of delirium, depression, and dementia would create additional challenges to the diagnosis of delirium. Of the tools identified in this current systematic review as promising, only one study[24] included a measure of depression, but given the small number of individuals with depression, a formal analysis of the tool characteristics in individuals with dementia and depression was not performed. Future studies are also warranted to provide further insights into the role of the overlap between delirium, depression, and dementia for the diagnosis and screening of delirium.

Limitations of this systematic review include the small number of identified studies, the small numbers of participants with dementia and DSD included in the studies the lack of any studies conducted specifically to examine test performance in individuals with dementia or evaluate performance in different dementia severity subgroups, that only studies published in English were included, and that studies evaluating solely alcohol-related delirium were excluded. The majority of these limitations are a result of the small number of studies of delirium diagnosis in individuals with dementia with a formal diagnosis. Although these limitations may decrease the generalizability and strength of the overall findings, they provide guidance on the future directions that research in this domain should move to improve the ability to diagnose DSD.

Recent underlined research priorities in individuals with advanced dementia include the need to develop "new advanced dementia-specific instruments for outcomes currently lacking valid measures."[41] This systematic review provides the most up-to-date and comprehensive information on test characteristics of existing tools for diagnosis of DSD and highlights the gaps in the literature. There are three tools with preliminary evidence in support of their use in DSD: the CAM, the CAM-ICU, and the EEG, the last of which lacks widespread clinical applicability. Further work is now needed to assess how these tools perform in the different stages and types of dementia, and studies with more participants with DSD are required. Additional tests such as objective assessments of attention and examination of the discriminatory value of level of consciousness are promising areas for future study.

ACKNOWLEDGMENTS

We thank Professor Melissa McPheeters for her advice on the study design.

Conflict of Interest: Professor MacLullich holds patents on instruments for assessment of attentional deficits in delirium. The other authors report no financial conflict of interest.

Dr. Vasilevskis is supported by the National Institutes of Health (NIH) (K23AG040157), the Veterans Affairs Clinical Research Center of Excellence, and the Geriatric Research, Education and Clinical Center. Dr. Bellelli has received honoraria from Novartis, Pfizer, Lilly, and Lundbeck. Dr. Ely is supported by the Veterans Affairs Clinical Science Research and Development Service (VA Merit Review Award), and NIH (AG027472). Dr. Ely has received honoraria from GSK, Pfizer, Lilly, Hospira, and Aspect. Dr. Fick acknowledges partial support for this work from Award R01 NR011042 from the National Institute of Nursing Research (NINR). Professor MacLullich is supported by grants from the UK Medical Research Council. Professor MacLullich has received honoraria from Lundbeck, Novartis, and Shire. Dr. Shenkin and Professor MacLullich are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative. Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and Medical Research Council is gratefully acknowledged. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINR or NIH.

Author Contributions: Study conception and design: all authors. Acquisition of data: Morandi, McCurley, Vasilevskis, Fick, Bellelli, Jackson, Lee. Interpretation of results: all authors. Drafted manuscript: Morandi. Critically revised the manuscript: all authors. Final approval of manuscript: all authors.

Sponsor Role: None. The authors' funding sources did not participate in the planning, collection, analysis or interpretation of data or in the decision to submit for publication. The investigators had full access to the data and were responsible for the study protocol, progress of the study, analysis, reporting of the study and the decision to publish.

REFERENCES

1. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: A systematic review. J Am Geriatr Soc 2002;50:1723–1732.
2. Hebert LE, Scherr PA, Bienias JL et al. Alzheimer disease in the US population: Prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–1122.
3. Rudolph JL, Boustani M, Kamholz B et al. Delirium: A strategic plan to bring an ancient disease into the 21st century. J Am Geriatr Soc 2011;59 (Suppl 2):S237–S240.
4. Witlox J, Eurelings LS, de Jonghe JF et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. JAMA 2010;304:443–451.
5. Flaherty JH, Rudolph J, Shay K et al. Delirium is a serious and underrecognized problem: Why assessment of mental status should be the sixth vital sign. J Am Med Dir Assoc 2007;8:273–275.
6. Inouye SK, Foreman MD, Mion LC et al. Nurses' recognition of delirium and its symptoms: Comparison of nurse and researcher ratings. Arch Intern Med 2001;161:2467–2473.
7. Morandi A, Solberg LM, Habermann R et al. Documentation and management of words associated with delirium among elderly patients in postacute care: A pilot investigation. J Am Med Dir Assoc 2009;10:330–334.
8. Spronk PE, Riekerk B, Hofhuis J et al. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive Care Med 2009;35:1276–1280.
9. Wong CL, Holroyd-Leduc J, Simel DL et al. Does this patient have delirium? Value of bedside instruments. JAMA 2010;304:779–786.
10. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision. Washington, DC: American Psychiatric Association, 2000.
11. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Washington, DC: American Psychiatric Association, 1980.
12. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 1994.
13. McKhann G, Drachman D, Folstein M et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.

14. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797–811.
15. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. Psychol Med 1994;24:145–153.
16. Hughes CP, Berg L, Danziger WL et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
17. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 2009;151:264–269, W64.
18. Bossuyt PM, Reitsma JB, Bruns DE et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. Ann Intern Med 2003;138:40–44.
19. Fontela PS, Pant PN, Schiller I et al. Quality and reporting of diagnostic accuracy studies in TB, HIV and malaria: Evaluation using QUADAS and STARD standards. PLoS One 2009;4:e7753.
20. Ely EW, Margolin R, Francis J et al. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370–1379.
21. Ely EW, Inouye SK, Bernard GR et al. Delirium in mechanically ventilated patients: Validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA 2001;286:2703–2710.
22. Erkinjuntti T, Sulkava R, Wikstrom J et al. Short Portable Mental Status Questionnaire as a screening test for dementia and delirium among the elderly. J Am Geriatr Soc 1987;35:412–416.
23. Hart RP, Levenson JL, Sessler CN et al. Validation of a cognitive test for delirium in medical ICU patients. Psychosomatics 1996;37:533–546.
24. Inouye SK, van Dyck CH, Alessi CA et al. Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med 1990;113:941–948.
25. Hestermann U, Backenstrass M, Gekle I et al. Validation of a German version of the Confusion Assessment Method for delirium detection in a sample of acute geriatric patients with a high prevalence of dementia. Psychopathology 2009;42:270–276.
26. Rosen J, Sweet RA, Mulsant BH et al. The Delirium Rating Scale in a psychogeriatric inpatient setting. J Neuropsychiatry Clin Neurosci 1994;6:30–35.
27. Mitasova A, Kostalova M, Bednarik J et al. Poststroke delirium incidence and outcomes: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2012;40:484–490.
28. Thomas C, Hestermann U, Walther S et al. Prolonged activation EEG differentiates dementia with and without delirium in frail elderly patients. J Neurol Neurosurg Psychiatry 2008;79:119–125.
29. Jacobson S, Jerrier H. EEG in delirium. Semin Clin Neuropsychiatry 2000;5:86–92.
30. Chester JG, Grande LJ, Milberg WP et al. Cognitive screening in community-dwelling elders: Performance on the clock-in-the-box. Am J Med 2011;124:662–669.
31. Bellelli G, Speciale S, Morghen S et al. Are fluctuations in motor performance a diagnostic sign of delirium? J Am Med Dir Assoc 2011;12:578–583.
32. Meagher DJ, Leonard M, Donnelly S et al. A comparison of neuropsychiatric and cognitive profiles in delirium, dementia, comorbid delirium-dementia and cognitively intact controls. J Neurol Neurosurg Psychiatry 2010;81:876–881.
33. Perry RJ, Watson P, Hodges JR. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: Relationship to episodic and semantic memory impairment. Neuropsychologia 2000;38:252–271.
34. Brown LJ, Fordyce C, Zaghdani H et al. Detecting deficits of sustained visual attention in delirium. J Neurol Neurosurg Psychiatry 2011;82:1334–1340.
35. Exton C, Leonard M. Eye tracking technology: A fresh approach in delirium assessment? Int Rev Psychiatry 2009;21:8–14.
36. Johnson DK, Morris JC, Galvin JE. Verbal and visuospatial deficits in dementia with Lewy bodies. Neurology 2005;65:1232–1238.
37. Blair M, Kertesz A, McMonagle P et al. Quantitative and qualitative analyses of clock drawing in frontotemporal dementia and Alzheimer's disease. J Int Neuropsychol Soc 2006;12:159–165.
38. Leonard M, Spiller J, Keen J et al. Symptoms of depression and delirium assessed serially in palliative-care inpatients. Psychosomatics 2009;50:506–514.
39. Matsushima E, Nakajima K, Moriya H et al. A psychophysiological study of the development of delirium in coronary care units. Biol Psychiatry 1997;41:1211–1217.
40. Armstrong SC, Cozza KL, Watanabe KS. The misdiagnosis of delirium. Psychosomatics 1997;38:433–439.
41. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. N Engl J Med 2009;361:1529–1538.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Delirium Systematic Review Methodology.

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