Review Article

A Scoping Review to Map Empirical Evidence Regarding Key Domains and Questions in the Clinical Pathway of Delirium in Palliative Care

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Abstract

Context. Based on the clinical care pathway of delirium in palliative care (PC), a published analytic framework (AF) formulated research questions in key domains and recommended a scoping review to identify evidence gaps.

Objectives. To produce a literature map for key domains of the published AF: screening, prognosis and diagnosis, management, and the health-related outcomes.

Methods. A standard scoping review framework was used by an interdisciplinary study team of nurse- and physician-delirium researchers, an information specialist, and review methodologists to conduct the review. Knowledge user engagement provided context in refining 19 AF questions. A peer-reviewed search strategy identified citations in Medline, PsycINFO, Embase, and CINAHL databases between 1980 and 2018. Two reviewers independently screened records for inclusion using explicit study eligibility criteria for the population, design, delirium diagnosis, and investigational intent.

Results. Of 104 studies reporting empirical data and meeting eligibility criteria, most were conducted in patients with cancer (73.1%) and in inpatient PC units (52%). The most frequent study design was a one or more group, nonrandomized trial or cohort (67.3%). Evidence gaps were identified: delirium risk prediction; comparative effectiveness and harms of prevention, variability in delirium management across PC settings, advanced directive and substitute decision-maker input, and transition of care location; and estimating delirium reversibility. Future rigorous primary studies are required to address these gaps and preliminary concerns regarding the quality of extant literature.

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Conclusion. Substantial evidence gaps exist, providing opportunities for future research regarding the assessment, prognosis, and management of delirium in PC settings. J Pain Symptom Manage 2019;57:661−681.

Key Words
Delirium, palliative care, assessment, prognosis, management, analytic framework

Introduction

Delirium is a complex neurocognitive and behavioral manifestation of an underlying medical abnormality. Its frequent occurrence is therefore not unexpected in the context of patients with advanced life-threatening illness in palliative care (PC) settings. Although the terms PC and hospice care are often used interchangeably, PC is considered applicable anywhere in a person's life-threatening illness trajectory, whereas hospice care has a more traditional association with the terminal phase of end-of-life care.[1] Both specialists and generalists deliver PC across a variety of settings: inpatient PC units in acute care settings and stand-alone inpatient hospices; hospital PC consult teams; and community PC services.[1] Although delirium is acknowledged as a frequent clinical problem in the context of PC,[2] its poor recognition and documentation in clinical practice is a substantive concern.[3,4] Across all health care settings, delirium is associated with high levels of mortality and morbidity, and poorer outcomes in general[5,6]; it is thus a major contributor to health care costs.[7]

Standardized clinical criteria, such as those of the International Classification of Diseases, 10th and recently released 11th edition (ICD-10 and ICD-11), and the Diagnostic Statistical Manual of Mental Disorders, fifth edition (DSM-5), exist to aid clinicians in diagnosing delirium.[8−10] The Confusion Assessment Method (CAM) is a briefly administered assessment tool that is widely used to screen for delirium.[11] Although it was validated in relation to the earlier DSM-III-R criteria,[12] it broadly operationalizes the current DSM-5 delirium criteria.[13] The DSM-5 delirium features include the following: a disturbance of attention and awareness; short onset (hours to days) and fluctuation over the course of the day; an additional cognitive disturbance, such as disorientation, memory, or language deficits, or perceptual abnormalities; the disturbances are not better explained by an evolving or existing dementia, or that they occur in a coma; and there is clinical evidence through history, examination or investigations that the disturbance is related to another general medical condition, substance intoxication (e.g., a medication) or withdrawal, or multiple etiologic factors.[13] On the basis of the type of psychomotor disturbance observed, delirium is classified as no motor subtype (normal psychomotor activity), hypoactive or hyperactive, or a mixed subtype with both hypoactive and hyperactive features.[14,15] The hypoactive subtype is common in PC settings and is the most prone to go undetected.[16] Misdiagnosis of delirium most commonly occurs as dementia and depression.[17−19] Regular screening for delirium in PC settings has been advocated,[20,21] particularly in view of its characteristic fluctuations, the frequency of the hypoactive subtype, and the risk of misdiagnosis, but there has been very limited evaluation of the effectiveness of screening in this context.[22]

Although advanced age, preexisting or evolving dementia, and frailty may confer a baseline vulnerability or risk toward delirium in older persons in general,[2] delirium occurring in the PC context is particularly precipitated by one or more acute medical events, such as organ failure, infection, and medication or metabolic effects.[23] Although baseline and precipitant risk factors for delirium have been identified in other care settings, there has been relatively limited evaluation of these in PC settings. Furthermore, findings from studies that evaluate either delirium risk or therapeutic interventions in settings such as postoperative or critical care may have limited generalizability to PC settings. Delirium generates high levels of distress for patients, their families, and their professional caregivers in PC settings by impeding potentially precious communication and generating behavioral disturbances.[24] The standard PC approach to delirium management involves symptomatic management and treatment of reversible precipitating factors (if consistent with the goals of care) in addition to patient and family support.[22,23,25] Symptomatic management may involve varying degrees of nonpharmacological and pharmacological interventions.[22,26]

Most patients in PC settings experience an irreversible delirium in the last hours or days of life.[27] Part or full reversal of delirium may occur before the terminal phase but depends on the presence of modifiable etiologic factors, their investigation, and treatment. The patient's goals of care are typically more focused on comfort in many PC settings, particularly in hospice care. This may limit the investigation and treatment

of delirium precipitants, thus perhaps increasing the use of antipsychotic and other sedating medications to symptomatically treat delirium. If the goals of care are unclear and clinical uncertainty exists regarding the reversibility of an episode of delirium, there is a potential risk of adopting the extremes of either undue fatalism (missing potentially reversible delirium precipitants and premature use of deep pharmacological sedation to control the symptoms of delirium) or, alternatively, taking an overly medicalized (inappropriately burdensome and non−cost-effective intervention) approach to delirium management.[23]

The association of delirium with older age, dementia and comorbidity burden,[2,28] and the projected population increase in the proportion of elderly person[29] together signal a pressing need for knowledge synthesis to guide all practitioners in palliative and end-of-life care to conduct effective, evidence-based interventions at all points along the clinical care pathway of delirium. Recognizing this need, our group organized an international interdisciplinary research planning meeting with a broad spectrum of leading delirium researchers and knowledge-users in 2012 as part of an overarching program of research, entitled Studies to UNderstand Delirium In Palliative Care Settings (SUNDIPS).[30] We identified key areas of potential uncertainty, controversy, or clinical equipoise in the clinical care pathway of delirium in PC: the benefit/burden ratio for therapeutic decisions; the outcomes and impact of delirium; the goals of care; the use of deep pharmacological sedation to control the symptoms of delirium; cost-effectiveness issues; patient-reported outcomes, experiential impact of delirium, and its treatment on family and caregivers; and limited access to certain therapeutic interventions and the potential need to transition to a new place of care, such as home to hospice or hospice to acute care. We subsequently constructed and published an analytic framework (AF) with pivotal research questions, based on the delirium care pathway in PC.[31]

As a preliminary step, a comprehensive map of the scope and nature of the knowledge in the scientific literature and its gaps is a prerequisite to proceeding with systematic reviews and further clinical research studies.[31] We conducted a scoping review of delirium in PC settings with specific aims: 1) to map the literature for the key domains and pivotal questions in the clinical care pathway of delirium in PC settings, as previously identified in our AF: screening, prognosis, and diagnosis; management (including pharmacological and nonpharmacological therapeutic interventions) in the context of the goals of care; and outcomes and impact, including clinical, experiential (patient, family, and professional caregivers), and economic; 2) to identify the knowledge gaps and research priorities regarding delirium in PC settings, thus providing the potential to refine the existing research questions in our AF, and determine where systematic reviews are feasible and warranted before planning future clinical research studies; and 3) to consolidate our integrated knowledge user, consultative and collaborative process, as initiated in our SUNDIPS meeting, so as to address the specific contextual decision-making issues regarding delirium in PC and establish research priorities.

Methods

Study Team Composition

The core study team consisted of two PC physicians based in an inpatient care setting, a critical care physician, two postdoctoral PC nursing delirium researchers, a critical care pharmacoepidemiologist, an information specialist, a systematic review methodologist, an epidemiologist, and two research assistants. Collaborative author input was received from a psychiatrist who conducted many delirium studies in a hospice setting and PC physicians from across a variety of settings, including a community consult service, a hospital consult service, and a university academic department.

Scoping Review Framework

A scoping review has been defined as "a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge."[32] Scoping reviews thus represent a novel approach to mapping the landscape of published literature. Following previous recommendations regarding scoping review methodology,[32,33] we adopted a standard six-phase framework approach to the conduct of the review: 1) developing a rationale and identifying the research questions; 2) identifying relevant studies; 3) study selection; 4) charting the data; 5) collating, summarizing, and reporting the results; and 6) collaborative consultation, which partly preceded but was also an integral part of Phase 1 and Phase 5 of this framework.

Developing a Rationale and Identifying the Research Questions

The background and rationale for this scoping review have been described in relation to the inaugural SUNDIPS meeting.[30,31] Many of the knowledge-users, methods experts, and independent researchers who attended this meeting collaborated on many of its related publications.[21,27,31,34−36] Although a broader

consultative meeting is not a formal requirement in scoping reviews,[33] we considered the initial and sustained engagement of knowledge-users (administrators, senior nursing personnel, and policy developers) as an important aspect of the review. We therefore scheduled an initial two-hour meeting of knowledge-users and core study team members to review the research questions from the AF. Through this meeting and both subsequent consultation and iterative input, the 18 initially identified AF questions were refined and a question in relation to transition of care was added. An updated version of the AF is depicted in Figure 1, and the refined research questions now totaling 19 are outlined in Table 1. We did not publish or register the protocol because of the absence of such formal arrangements for scoping reviews but signaled the basis of the scoping review in our published AF paper.[31]

Consistent with standard recommendations that the primary research question of a scoping review be broad, we asked the question: What is the scope and nature of the scientific literature addressing the assessment, management, outcomes, and impact of delirium in PC settings? This broad question encompasses the specific AF research questions, as initially identified in the SUNDIPS meeting and further refined through subsequent consultation.

Identifying Relevant Studies

A search strategy was developed by an experienced information specialist (L. S.) and externally peer reviewed by another information specialist. The search was conducted across Medline (via Ovid), Embase (via Ovid), CINAHL (via EBSCOhost), and PsycINFO (via Ovid) databases. Pilot screening of a sample of retrieved records was used to further refine the search concept and strategy and help finalize key data extraction items. The search strategy included a combination of various terms in relation to "palliative care" and "delirium." (Appendix 1, Supplementary Table 1). The strategy was modified as appropriate in accordance with the specific database searched. Secondary searching of the included studies was also used to identify and map studies in relation to the pivotal areas in the AF. The literature search was initially limited to the time period of 1980 to July 2, 2015; further updated searches were conducted on December 31, 2016, and May 16, 2018. The rationale

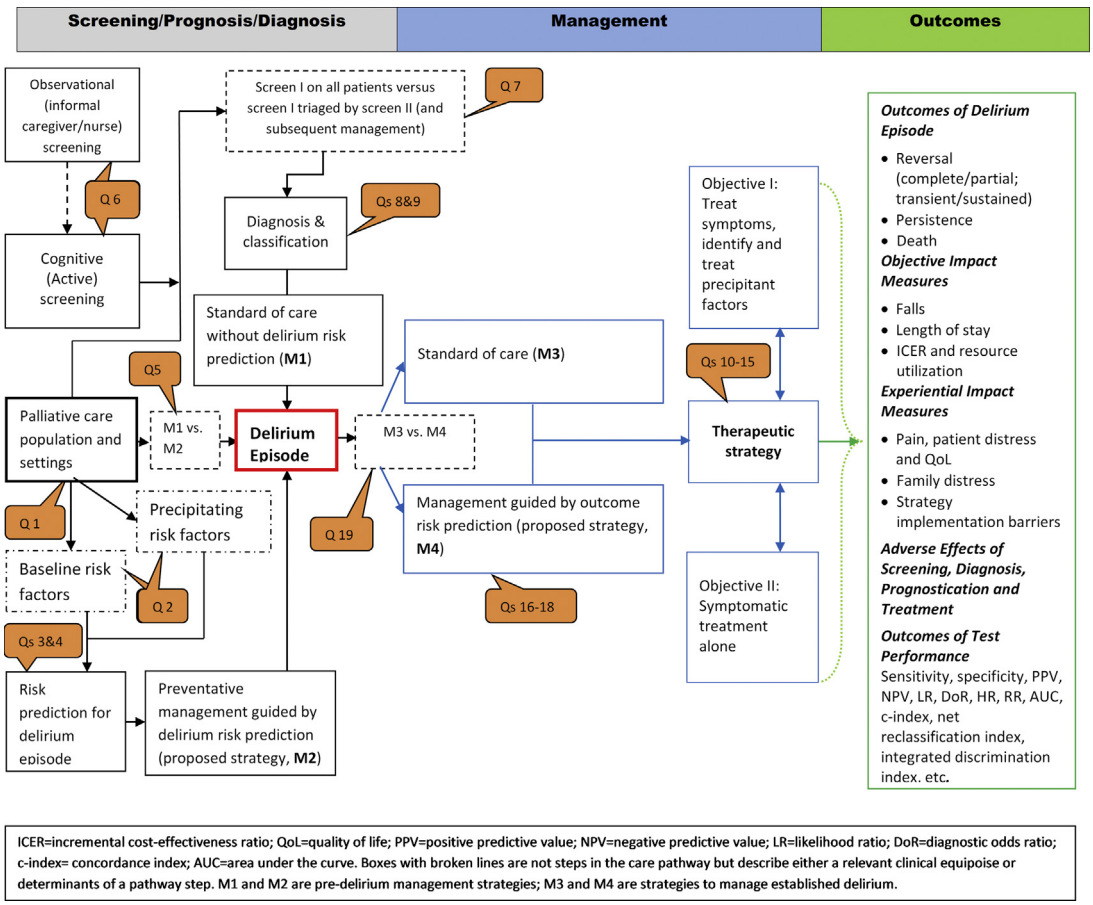

Fig. 1. Analytic framework based on clinical pathway of delirium with key domains and related research questions (Q).

Table 1
Research Domains and Questions Related to Analytic Framework in *Figure 1*

Epidemiological burden of delirium
1. What are the incidence and prevalence rates of delirium in the various palliative care settings (acute care, inpatient hospice and hospital care, and community palliative services)?

Delirium prediction and prevention
2. What are the baseline and precipitating risk factors for onset of delirium?
3. What is the performance of the various delirium risk prediction models under current standards of care and how do they compare with each other?
4. Does the model have transportability or external validity?
5. What are the comparative effectiveness and harms of the various delirium-preventative management strategies (including but not limited to management guided by delirium risk prediction) among themselves or between them and a no delirium-preventative management option?

Screening for delirium in PC settings
6. What is the test performance of the various delirium screening tests (e.g., cognitive active screening, informal caregiver observational passive screening, etc.) and how do they compare with each other?
7. What are the comparative effectiveness and harms of the various delirium screening tests/strategies among themselves or between them and a no screening option (e.g., cognitive active screening of all patients vs. cognitive active screening triaged by nurse/informal caregiver observational passive screening for important delirium-associated outcomes)?

Diagnosis and classification of delirium
8. What is the diagnostic performance of the various validated delirium diagnostic and classification tools (in current use) and how do they compare with each other?
9. What are the comparative effectiveness and harms of the various validated delirium diagnostic and classification tools/strategies (in current use) among themselves or between them and a no diagnostic testing option or no classification option, respectively?

Management of delirium
10. What is the extent of variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services)?
11. Is the variability in management of delirium across the various care settings (acute care, inpatient hospice and hospital care, and community palliative services) associated with important differences in outcomes of benefits and harms?
12. What are the comparative effectiveness and harms of delirium management strategies that incorporate advanced directives and/or substitute decision-maker input versus those that do not?
13. What are the comparative effectiveness and harms of the various pharmacologic symptom-directed interventions among themselves, against nonpharmacologic therapies or a no therapy option?
14. What are the comparative effectiveness and harms of the various nonpharmacologic symptom-directed interventions among themselves, against pharmacologic therapies or a no therapy option?
15. For patients in community settings (private home, nursing home, long-term care facility) who develop delirium in the context of predominantly palliative goals of care, what is the comparative effectiveness (e.g., higher probability of reversal of delirium; quality of life gain; reduction of family caregiver burden) and harms (undue invasive procedures, break in continuity of care, burdensome transition; potential separation from family) of transfer to hospital care settings (emergency or inpatient care) or inpatient hospice care for subsequent management versus continued care in their community settings? What patient or environmental factors might explain any observed heterogeneity in outcomes across studies?

Prediction of response to management and treatment of delirium
16. In patients with established delirium, what are the risk factors that predict its nonreversibility or its complete or partial reversibility and sustainability of response?
17. What is the performance of the various risk prediction models that predict complete or partial reversibility of delirium under current standards of care and how do they compare with each other?
18. Does the model have transportability or external validity?
19. What are the comparative effectiveness and harms of patient management guided by models predicting delirium reversibility among themselves or between them and a no delirium prediction-based management option?

PC = palliative care.

for the 1980 limit was based on the absence of DSM diagnostic criteria for delirium before 1980.

Study Selection

The titles and abstracts of those studies identified in the literature search were uploaded into DistillerSR,[37] a software program designed to support the conduct of systematic reviews. Explicit a priori eligibility criteria (Table 2) were applied at Level 1 (title and abstract) and Level 2 (full text) screening. The principal inclusion criterion was for the study (including systematic reviews) to address one or more of the 19 questions in the AF. Furthermore, from a feasibility perspective, we reserved the option of modifying the scoping review and limiting it to a subset of questions if either the volume of retrieved records or included studies became unmanageable.

In addition to including relevant studies that were clearly documented as having been conducted in palliative settings and involving participants with a clearly defined principal palliative indicator diagnosis, we also included relevant studies whose study populations had cancer or adult immune deficiency syndrome (AIDS) as a progressive life-threatening illness and were unequivocally eligible for PC referral but had study assessments conducted by oncology, psychiatry, psycho-oncology, or a designated supportive care service. We excluded publications such as editorials, commentaries, narrative reviews, and letters that did not report primary empirical data. Studies were excluded

Table 2
Eligibility Criteria for Delirium Scoping Review

1. Inclusion criteria: a record was included if it provided an answer to at least one of the 19 questions (see *Table 1*) in the analytic framework (see *Fig. 1*) and meets none of the exclusion criteria.
2. Exclusion criteria: a record was excluded if it met one or more of the criteria (a–i); reviewers selected a single best response.

a) Availability: insufficient information to ascertain relevance beyond title (neither abstract nor full text are available)
b) Language: abstract and/or full text of record is in a language other than English
c) Sample size: less than 20 participants
d) Population: not adult (exclusively or as an analytic subgroup) or does not meet the contextual criterion of patients in palliative care settings (admitted to an inpatient palliative care or hospice unit; followed by a hospital consult palliative care team; having cancer or AIDS as a progressive life-threatening illness and unequivocally eligible for palliative care referral but assessed by an oncology, psychiatry, psycho-oncology, or supportive care service; or under the care of a community hospice or palliative care program)
e) Diagnosis of delirium: is not clearly defined according to standard criteria such as one or more of the following: Diagnostic and Statistical Manual (DSM) of Mental Disorders criteria for delirium, International Classification of Diseases (ICD) diagnostic criteria, a diagnostic cutoff score on a validated assessment (diagnostic or screening) tool such as the Confusion Assessment Method (CAM), or standard psychiatric assessment
f) Design: it is not a systematic review, randomized controlled trial, or analytic observational study (cohort, case-cohort, nested case-control, case-control, or time series)
g) Investigational intent (primary or secondary): does not aim to empirically investigate any of the following:

- incidence or prevalence estimates of delirium or its level of reversal (complete, partial, or nonreversal)
- risk factors for delirium onset or its reversal (complete, partial, or nonreversal)
- accuracy, performance, effectiveness or harms of medical tests for screening, diagnosis, or classification of delirium
- development, performance, validation, effectiveness or harms of risk prediction models for delirium onset or its reversal (complete, partial, or nonreversal)
- comparative effectiveness or harms of delirium-preventative management strategies
- variability in management of delirium across palliative care settings
- comparative effectiveness or harms of delirium management or treatment, transfer to hospital care settings (emergency or inpatient care), or inpatient hospice care for subsequent management
- cost-effectiveness of delirium screening, diagnosis, classification, prognosis, or management/treatment

h) Insufficient information: investigational intent, study design, population, or sample size remains unclear due to insufficient information in full-text or abstract-only records
i) Other reason(s): as documented by reviewers

if the diagnosis of delirium was not clearly defined according to standard criteria such as DSM or ICD diagnostic criteria, or a diagnostic cutoff score on a validated assessment (diagnostic or screening) tool such as the CAM, or standard psychiatric assessment. The scoping methodology supported an inclusive approach, which involved the inclusion of conference abstracts and systematic reviews, based on their meeting eligibility criteria and their potential to address at least one of the 19 AF questions.

Full texts of included studies were examined to confirm inclusion, extract relevant data, and map them to specific research questions. In the absence of a full-text publication, an abstract-only article was included if it otherwise met the eligibility criteria. Dual screening at Levels 1 and 2 was conducted independently by two senior researchers (P. G. L. and S. H. B.), and all conflicting selections were discussed and resolved, if necessary, through the input of a third reviewer (M. T. A.). The single best reason for exclusion at Level 2 was also recorded. The data extraction process was undertaken by a single reviewer (P. G. L.) with a two-reviewer (P. G. L. and S. H. B.) consensus reserved for unclear records. As a quality check to verify the accuracy of data extraction, a random 10% of the data were independently verified by a third reviewer (N. A. R.).

Charting the Data

Data extraction included the following items: study design, country of origin, study population, sample size, delirium diagnostic criteria used or validated tool used for diagnosis, and key outcome domains. Study records were tagged by the research question(s) that they addressed. In keeping with the standards for scoping reviews, included studies were not formally appraised for risk of bias.[33,38] We adopted an inclusive approach to comparative effectiveness and harms evaluation: in addition to therapeutic interventions, we also included screening and diagnostic and prognostic tool evaluations if they reported some comparative effectiveness or harms outcomes.

Collating, Summarizing, and Reporting the Results

Cognizant of the potential overlap between some primary studies and included systematic reviews, relevant findings were reported separately or discretely (e.g., using the term "multiple" in relation to systematic review characteristics) where possible to avoid exaggerating the available evidence in relation to our research questions. We used the broad qualitative characteristics and the numerical distribution of mapped evidence addressing each of the

a priori research questions to formulate our recommendations for future research: a subsequent systematic review, a survey of patient experience or experience of those who care for patients at risk of or in delirium in a PC setting, or a primary experimental/observational study to fill the knowledge gaps identified.

Toward the end of the project, once the data were summarized, the knowledge-users were again consulted and their opinions noted in relation to future research priorities from among the research questions, the identified knowledge gaps, and the potential for knowledge synthesis, as generated through the scoping review. The main outcome of our scoping review was to answer the broad primary research question and thus advance the SUNDIPS program of research by setting the foundation for future studies.

Results

Study Screening and Inclusion

The literature search, including updates, identified 6800 citation records. The flow of information in identifying, screening, and selecting studies is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[39] flow diagram in Figure 2. Screening at title and abstract level identified 390 citation records as eligible to proceed to full-text review level. Of the 287 references reviewed and excluded at full-text review level, the three most frequent single reasons for exclusion were the investigational intent of the study ($n = 90$), the study design ($n = 63$), and the lack of valid diagnostic criteria used for delirium diagnosis ($n = 56$), together accounting for 209 (73%) of the single reasons for exclusion. A total of 104 studies therefore met the eligibility criteria

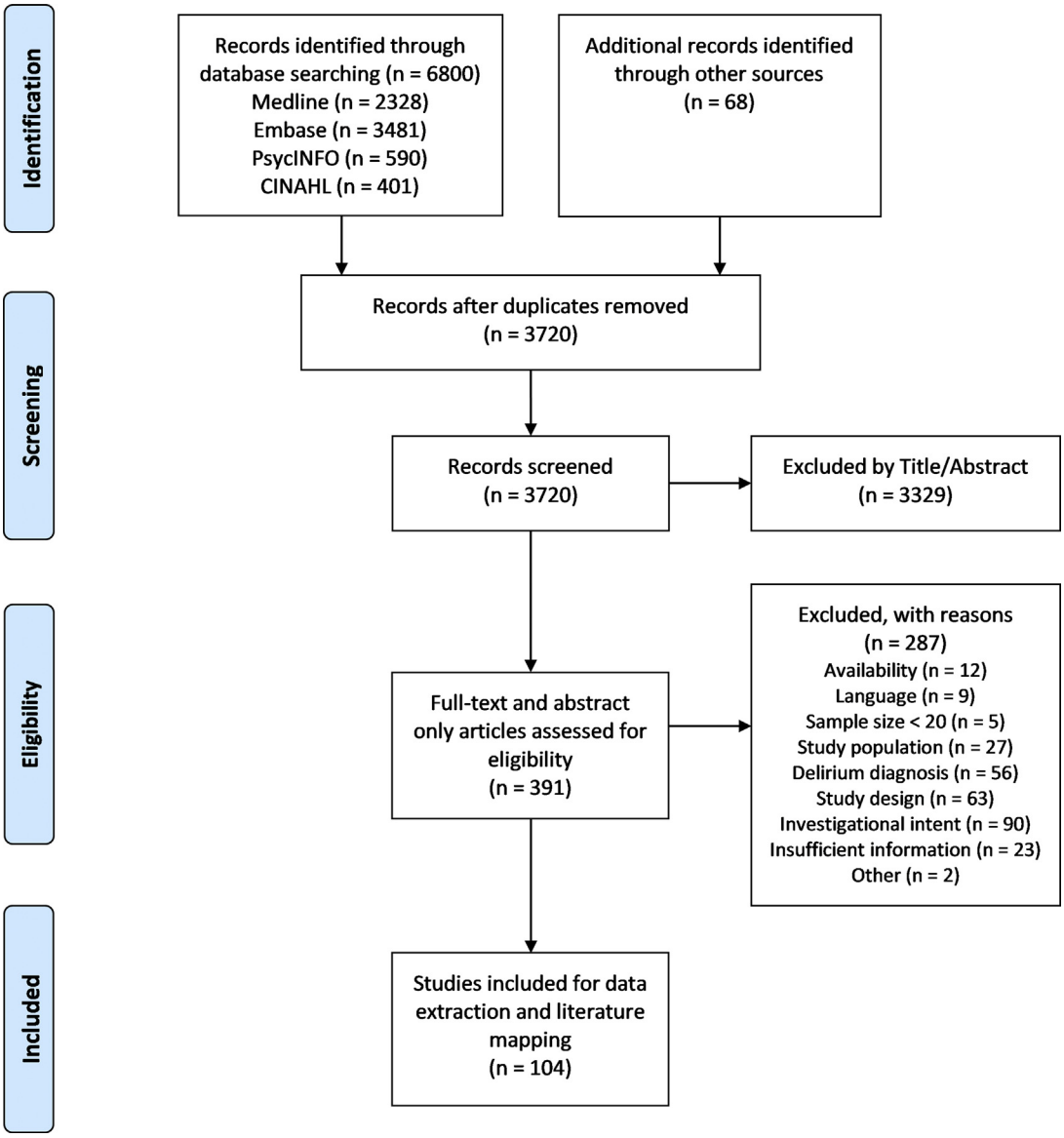

Fig. 2. PRISMA flow diagram for delirium scoping review.

for final inclusion.[40–143] These included a published PhD thesis[50] and also a prospective study with 19 patients[106] that, despite the arbitrary eligibility cutoff of 20 for sample size, was deemed by consensus to warrant inclusion because of the very few studies that prospectively evaluated terminal delirium. Eleven of the included studies were conference abstracts with no available full text but were included because their abstracts met the review's eligibility criteria.[40,58,74,79,89,99,104,114–116,143]

General Study Characteristics

The general study characteristics of the included studies are summarized individually in Appendix 2, Supplementary Table 2, and an aggregate summary of their characteristics with citations is presented in Table 3. Thirty-seven studies (35.6%) originated from the U.S.; 14 (13.5%) from Japan; 10 (9.6%) from Canada; 6 (5.8%) from two or more countries; 6 (5.8%) from Australia; 5 (4.8%) from U.K.; 4 (3.8%) from each of Ireland, Spain, and Portugal; 2 (1.9%) from each of the Netherlands, Germany, Italy, and Taiwan; and 1 (1%) from each of Hong Kong, South Korea, Belgium, Norway, Turkey, and Mexico.

Seventy-six (73.1%) study samples were individually comprised mostly (≥79%) of subjects with a cancer diagnosis. Eight (7.7%) studies had sample subjects with a heterogeneous mix of life-threatening diagnoses. In 3 (2.9%) studies,[54,75,141] all or ≥90% of the sample had a diagnosis of AIDS. One (1%) study was conducted exclusively in patients with hepatic failure[139] and 1 (1%) exclusively in patients with dementia.[121] In 12 (11.5%) studies, the palliative indicator diagnosis was unclear or not reported. The baseline dementia status was unclear or unreported in 55 (52.9%) of the included studies. Patients with dementia were excluded in 15 (14.4%) studies, and 33 (31.7%) studies included or reported a mix of patients with and without dementia. In 1 (1%) study,[121] all patients had dementia. Three studies reported a subgroup analysis on the basis of dementia status.[47,56,111] One included study (1%) reported the baseline Parkinson's disease status of the study sample.[94]

Forty-eight (46.2%) studies were conducted exclusively in single-center inpatient PC units. The other PC-specific settings of study samples consisted of a mix across hospital and community settings. Seventeen (16.3%) studies were conducted through a psychiatry service in an eligible population for study inclusion in our review. A further 15 (14.4%) studies were conducted in hospitalized oncology patients who met our population eligibility criteria, but PC service involvement was not reported, and similarly, 1 (1%) study of patients with cancer attending a cancer center emergency department was also included.

Of the included studies, 60 (57.7%) were uncontrolled, nonrandomized trials or single-group cohort studies, 10 (9.6%) involved two or multiple groups in a nonrandomized trial or cohort study (comparative studies of two or more interventions, tests, risk factors, or other exposures). Forty-two (40.4%) of the included studies had either a prospective cohort design or a prospective cohort component, and a further 12 (11.5%) were reported as secondary analyses of prospectively collected data; the remainder ($n = 15$) of the cohort studies were retrospective. The second most frequent design was cross-sectional, occurring in 18 (17.3%) studies. There were both 5 (4.8%) formal systematic reviews and randomized controlled trials among the included studies. Based on reviewer consensus, two additional reviews were included[124,131]: both involved systematic literature searches and addressed some of the AF questions but lacked a quality appraisal of their included studies, and by definition were not formal systematic reviews. Apart from these reviews, the remaining 97 included primary studies were conducted in a total of 25,690 subjects. Most (79.8%, $n = 83$) of the study samples had a mix of adult age groups and were not age selected. Similarly, most (71.2%, $n = 74$) of the study samples comprised a heterogeneous mix of male and female subjects. Age and sex status were either unclear or unreported in 15 (14.4%) and 25 (24%) studies, respectively.

The diagnostic criteria and/or validated assessment tools used to make the diagnosis of delirium are summarized in Appendix 3 and Supplementary Table 3.[8,9,12,55,67,82,144–156] The most common criteria used among the included studies were those of the DSM: the DSM-IV[146] or DSM-IV-TR[147] was used in 45 (43.3%) studies, and the DSM-III-R,[145] in 9 (8.7%) studies. Of validated tools, the CAM,[12] Delirium Rating Scale (DRS) or its revised form (DRS-98-R),[148,149] and MDAS[55] were used in 32 (30.8%), 17 (16.3%), and 27 (26%) studies, respectively. A classification of delirium based on psychomotor status was reported in 36 (35%) studies; one of these also reported a syndromal and subsyndromal classification.[127]

Studies of Epidemiological Burden, Prediction, and Prevention of Delirium

Studies investigating the epidemiological burden (prevalence or incidence), prediction, and prevention of delirium are summarized in Table 4 in relation to related questions (Q1–Q5) from the AF. A total of 48 (46.2%) and 31 (29.8%) studies investigated prevalence and incidence, respectively. Thirty-eight studies (36.5%) investigated risk factors for the onset of delirium; these included 9 (8.7%) studies that reported some form of risk prediction model. There

Table 3
Aggregate Summary of Study Characteristics of Included Studies ($N = 104$)

Study Characteristics	Studies $N = 104$ (%)
Geographic origin	
U.S.[45–57,60,63–66,69–71,73–75,94,104,106,120–122,128,133,134,136,139,141,142]	37 (35.6)
Japan[42,97,107,108,112–115,117,118,130,137,138,140]	14 (13.5)
Canada[76–83,100,101]	10 (9.6)
Multiple countries[62,91,93,95,109,110]	6 (5.8)
Australia[40,41,92,105,127,132]	6 (5.8)
U.K.[44,59,89,126,135]	5 (4.8)
Other[43,58,61,67,68,72,84–88,90,96,98,99,102,103,111,116,119,123–125,129,131,143]	26 (25)
Palliative indicator diagnosis[a]	
Cancer in all or ≥90%[40,42,43,45–53,55–57,60,61,63–66,68–73,77–81,83,85–88,90–94,96–108,111–118,122,125,127,129–133,135–138,140]	74 (71.2)
Heterogeneous mix of life-threatening illnesses[41,44,62,76,119,120,128,134]	8 (7.7)
AIDS[54,75,141]	3 (2.9)
AIDS or cancer (systematic reviews, each included reference #[54])[59,95,124]	3 (2.9)
Hepatic failure[139]	1 (1)
Dementia[121]	1 (1)
Unclear or unreported[58,67,74,82,84,89,109,110,123,126,142,143]	12 (11.5)
Care setting or service	
Single inpatient palliative care unit (PCU)	48 (46.2)
Hospital based[44,58,67,69,74,88,92,96,98–101,103,108,111,112,114,115,117,118,125,136,143]	23 (22.1)
Hospice based[57,72,78,79,84,102,107,109,110,121,123,126–129,135]	16 (15.4)
Cancer center based[65,66,85–87,93,94,133]	8 (7.7)
Institutional base unclear[141]	1 (1)
Inpatient PCU combined with either one or more other inpatient PCU or a non-inpatient PC setting	6 (5.8)
Inpatient PCUs[40,41,43,61,77]	5 (4.8)
Inpatient PCU with community PC setting[120]	1 (1)
Other specific PC settings	11 (10.6)
Hospital PC consult service[63,71,89,113,116,138,142]	7 (6.7)
Community PC settings[64,76,134]	3 (2.9)
Hospital PC outpatient setting[104]	1 (1)
Multiple PC settings in formal systematic reviews and systematic literature reviews[62,90,91,95,124,131]	6 (5.8)
Psychiatry service referrals in eligible population[42,45–48,53–56,59,60,75,97,106,122,130,139]	17 (16.3)
Hospitalized oncology patients[49–52,68,73,80–83,105,119,132,137,140]	15 (14.4)
Cancer center emergency department[70]	1 (1)
Study design	
Formal systematic review[59,62,90,91,95]	5 (4.8)
Randomized controlled trial[41,54,57,94,103]	5 (4.8)
Uncontrolled nonrandomized trial or cohort with one or more groups	70 (67.3)
Prospective[40,56,61,67–69,72,73,75,77,78,81–88,93,96–98,100,102,105–107,112,116–118,121,123,125,126,128–130,140,143]	41 (39.4)
Mixed prospective cohort and cross-sectional parts[135]	1 (1)
Secondary analysis of prospective data[45–53,66,80,134]	12 (11.5)
Retrospective[42,58,63,64,71,74,104,108,115,119,122,133,137,138,141]	15 (14.4)
Unclear or unreported[111]	1 (1)
Cross-sectional study[43,55,60,65,70,76,79,92,99,101,109,113,114,120,127,132,136,139]	18 (17.3)
Case-control study[110,142]	2 (1.9)
Uncontrolled before-after study[44,89]	2 (1.9)
Nonformal systematic review study with systematic literature review[b,124,131]	2 (1.9)
Demographics of study sample subjects	
Age	
Age mixed/not age selected[41,42,45–49,53–64,66–73,75–88,91–94,96–103,105–113,117–120,122,123,125,127–130,132–138,141–143]	83 (79.8)
Age ≥ 65[50–52,74,140]	5 (4.8)
Age < 59[139]	1 (1)
Unclear or unreported[40,43,44,65,89,90,95,104,114–116,121,124,126,131]	15 (14.4)
Sex	
Mixed/not sex selected[41,42,45,46,48–57,59,61–64,66,68–73,76–78,81,83–88,91–94,96–101,103,105–113,117,118,120,122,123,125–130,132,133,135–138,140]	74 (71.2)
Male only selected[75,134,141,142]	4 (3.8)
Female only selected[60]	1 (1)
Unclear or reported[40,43,44,47,58,65,67,74,79,80,82,89,90,95,102,104,114–116,119,121,124,131,139,143]	25 (24)

[a]In two additional studies,[102,136] cancer was the principal palliative indicator diagnosis in 87.2% and 79% of subjects, respectively.
[b]Both of these reviews involved systematic literature searches and addressed some of the AF questions but lacked a quality appraisal of their included studies and by definition were not formal systematic reviews.

were 2 (1.9%) studies that reported the comparative effectiveness/harms of delirium prevention strategies,[57,77] one involved hydration as a preventive intervention,[57] and no study examined delirium-preventative management strategies guided by risk prediction.

Studies of Screening, Diagnosis, and Classification of Delirium

Studies investigating the screening, diagnosis, and classification of delirium are summarized in Table 5 in relation to related questions (Q6–Q9) from the AF. A total of 18 (17.3%) studies investigated delirium screening;

Table 4
Studies That Addressed the Epidemiological Burden, Prediction, and Prevention of Delirium

Research Domains and Related Questions (Q)[a]		Study Reference Number	Studies $N = 104$ (%)
Epidemiological burden of delirium			
Q1	Prevalence investigated	42,44,50,52,58,60,63–65,70–72,75,76,78–83, 87–93,96,98–100,104–107,111–114,116, 120,126,135,136,139–141,143	48 (46.2)
	Incidence investigated	50,52,58,60,66–68,73,75,77–82,88,91,98,100, 105,106,114–116,119,125–127,134,137,142	31 (29.8)
Prediction and prevention			
Q2	Investigates risk factor(s) for onset of delirium (risk association study)	40,48,50,52,53,58,61,66,68,73,75,81,83,84,88, 98–100,104–108,114,115,118,119,122,125, 126,130,134,135,137,139–142	38 (36.5)
Q3	Involved development of delirium risk prediction model (or score)	73,81,83,105,114,119,134,141,142	9 (8.7)
Q4	Investigates transportability or external validity of risk prediction model		0 (0)
Q5	Investigates effectiveness and/or harms of delirium-preventative management strategies guided by risk prediction		0 (0)
	Compares effectiveness and harms of other delirium-preventative management strategies with each other or routine care?	57,77	2 (1.9)

[a]Domains and questions (Q1–Q5) from the analytic framework as presented in Table 1 and Figure 1.

these included 7 (6.7%) and 5 (4.8%) studies that investigated the diagnostic performance of a screening test against a reference standard, and the diagnostic performance of two or more screening tests against a reference standard, respectively. Nine (8.7%) studies reported the comparative effectiveness or harms of screening tests.

A total of 9 (8.7%) studies investigated the diagnosis of delirium; these included 6 (5.8%) and 2 (1.9%)

Table 5
Studies That Addressed Screening, Diagnosis, and Classification of Delirium

Research Domains and Related Questions (Q)[a]		Study Reference Numbers	Studies $N = 104$ (%)
Screening			
Q6	Investigates screening to detect subsyndromal and/or full syndromal delirium	44,62,64,67,72,78,80,82,89,90,121,126–129,132,136,139	18 (17.3)
	Investigates the diagnostic performance of a delirium screening test versus a reference standard	62,64,67,78,90,129,136	7 (6.7)
	Investigates the comparative diagnostic performance of delirium screening tests (Test A vs. reference standard; Test B vs same reference standard)	62,80,82,132,139	5 (4.8)
Q7	Investigates comparative effectiveness and/or harms of screening tests among themselves or between them and routine patient care	44,62,72,80,89,121,126–128	9 (8.7)
Diagnosis and classification			
Q8	Investigates the establishment of delirium diagnosis	43,55,82,89,90,101,110,113,123	9 (8.7)
	Investigates the diagnostic performance of a delirium diagnostic test versus a reference standard	43,55,90,101,110,123	6 (5.8)
	Investigates the comparative diagnostic performance of delirium diagnostic tests (Test A vs. reference standard; Test B vs. same reference standard)	82,110	2 (1.9)
Q9	Investigates comparative effectiveness and/or harms of diagnostic tests among themselves or between them and routine patient care	89,101,113	3 (2.9)
Q8	Investigates diagnostic performance of one or more psychomotor classification test(s) of delirium	84,109,131	3 (2.9)
Q9	Investigates comparative effectiveness/harms of one or more psychomotor classification test(s) of delirium		0 (0)

[a]Domains and questions (Q6–Q9) from the analytic framework as presented in Table 1 and Figure 1.

studies that evaluated the test performance of a diagnostic test against a reference standard, and the test performance of two or more diagnostic tests against a reference standard, respectively. Three (2.9%) studies reported on the comparative effectiveness or harms of diagnostic tests.

A total of 3 (2.9%) studies investigated the psychomotor classification of delirium; these included 2 (1.9%) and 1 (1%) studies that investigated the diagnostic performance of a psychomotor classification test against a reference standard, and the diagnostic performance of two or more psychomotor classification tests against a reference standard, respectively. None of these studies reported on the comparative effectiveness or harms of psychomotor classification tests.

Studies of the Management of Delirium and Prediction of Response

Studies investigating the management of delirium and the prediction of response to management are summarized in Table 6 in relation to related questions (Q10–Q19) from the AF. A total of 24 (23.1%) studies investigated the comparative effectiveness or harms of one or more pharmacological management approach (Q13), whereas 2 (1.9%) studies, including a systematic review, investigated the comparative effectiveness or harms of nonpharmacological management approaches (Q14). A total of 13 (12.5%) studies investigated risk factors for the prediction of response (reversibility) to the management of delirium (Q16); these included 4 (3.8%) studies of predictive models for reversibility (Q17). None of the included studies investigated variability in delirium management across PC settings (Q10, Q11), delirium management strategies incorporating advanced directives (Q12), or the impact of transition of care setting for delirium management (Q15).

Reported Comparative Effectiveness or Harms Outcomes

A total of 37 (35.9%) of the included studies reported comparative effectiveness or harms outcomes; three of these studies involved the use of additional assessment tools that were not previously referenced in the review: the Richmond Agitation-Sedation Scale (RASS)[157], the Chinese version of the DRS (DRS-Chinese)[158], and Mini–Mental State Examination[159]. (Appendix 4, Supplementary Table 4). Thirteen (12.5%) of these studies involved a direct comparison of two or more active study interventions[46–48,54,59,62,74,80,86,94,95,103,124]. Among these, there were two formal systematic reviews, one of screening tools[62,95,119], and one of pharmacological intervention[95] that overlapped with a primary study;[54] one systematic literature review study of pharmacological interventions[124], overlapping with two primary studies[47,54]; one study of screening[80]; the remaining 10 studies involved pharmacological comparisons with most having delirium severity change and adverse events related to therapy as study outcomes. A further 13 (12.5%) studies included two formal systematic reviews, one of screening tools[62] and one of assisted hydration and delirium severity[95]; a systematic literature review study that reported on effectiveness and harms of pharmacological interventions and exercise[131], overlapping with one primary study in relation to exercise[138]; primary studies comparing one or more active study interventions against placebo[41,57] or no active intervention[122,138] or current standard management,[72,77,113,121,127] or reference standard in the context of an assessment tool[101]. A total of 14 (13.5%) studies reported comparative effectiveness or harms using a before and after analysis; these included one systematic literature review study[124], overlapping with a primary study on olanzapine[56]; four studies of assessment tools[44,89,126,128], and the remaining nine studies involved pharmacological intervention[45,53,56,69,75,85,107,117,133]. Although a wide

Table 6
Studies That Addressed the Management of Delirium and Prediction of Response

Research Domains and Related Questions (Q)[a]		Study Reference Numbers	Studies $N = 104$ (%)
Management approach			
Q13	Investigates comparative effectiveness and/or harms of one or more pharmacological management approaches to delirium	41,45–48,53,54,56,57,59,69,74,75,85,86,94,95,97,103,107,117,122,124,133	24 (23.1)
Q14	Investigates comparative effectiveness and/or harms of one or more nonpharmacological management approaches to delirium	131,138	2 (1.9)
Prediction of response to management			
Q16	Prediction of response (reversibility) to management of delirium	49,51,53,56,68,98,100,102,111,118,122,124,130	13 (12.5)
Q17	Investigates model development for predictors of delirium reversibility	98,100,102,111	4 (3.8)

[a]Domains and questions (Q10–Q19) from the analytic framework as presented in Table 1 and Figure 1: none of the included studies mapped onto the following questions: Q10–12, Q15, Q18, and Q19.

variety of outcomes were reported in association with comparative effectiveness and harms analyses, neither falls nor economic cost were among these outcomes. Objective outcomes were most commonly reported, for example, delirium severity measure changes and adverse events related to treatment were reported in 21 (20.3%) and 18 (17.3%) of studies, respectively, whereas experiential outcomes were infrequently reported.

Evidence Gaps and Potential Opportunities for Further Studies

Based on identified gaps, the study group's recommendations regarding future primary studies and related outcomes, endorsed by knowledge user consultation, are summarized along with systematic review opportunities in Table 7. Among the studies investigating the epidemiological burden (prevalence or incidence), prediction of and prevention of delirium (Q1-5 in AF), there were substantive study numbers to address Q1-3, with most of the risk factor studies reporting crude, unadjusted risk association. However, none of the studies with risk prediction models reported external validation (Q4) and there were only two studies addressing Q5, the prevention of delirium in PC settings. Overall, these data suggest that there are enough studies to consider systematic reviews for Q1-3 and that further primary studies are needed for Q4-5. Among the studies investigating delirium screening (Q6-7), diagnosis (Q8-9), psychomotor classification (Q8 only), and management (Q13−14 and Q16−17 only) there appears to be sufficient numbers of studies to support the conduct of a systematic review in relation to each of these questions. Remarkably, none of the primary studies that were included in this scoping review addressed the questions regarding variability of practice across different PC settings (Q10−12), nor did any address the comparative effectiveness or harms of care location transition in relation to delirium (Q15), the external validation of any of the predictive models for delirium reversibility (Q18) or their comparative effectiveness or harms (Q19), indicating the need for primary studies in relation to Q10−12, Q15 and Q18−19.

Discussion

Using recommended scoping review methods, 104 published studies with empirical data were mapped onto research domains and key questions from a prespecified AF. In addition to the contribution of recognized delirium researchers, the generation of key questions and their subsequent refinement and expansion was based on the initial and ongoing engagement of a broad spectrum of decision-makers and knowledge-users from clinical, administrative,

Table 7
Future Research Recommendations Regarding Delirium in Palliative Care Settings

Research Strategy	AF Domain/Questions (Qs)	Relevant Focus or Recommendation
Systematic review (SR)	Epidemiological burden (Q1)	• Incidence and prevalence; pooled estimates
	Prognosis (Q2−3)	• Predictive model and risk association studies
	Screening (Q6)	• Screening test performance and CEH
	Diagnosis (Q8−9)	• Diagnostic test performance and CEH
	Classification (Q8)	• Sufficient studies for test performance only
	Management (Q13−14) and reversibility (Q16−17)	• CEH; current formal SRs require updating • Predictive model and risk association studies
Primary studies	Risk factor identification and prevention strategies (Q2−5)	• Predictive models for delirium occurrence; predictive score to determine risk; CEH of such models/scores • RCTs of preventive strategies, particularly nonpharmacological interventions to prevent delirium
	Screening, diagnosis, and classification (Q6−9)	• Diagnostic performance studies of assessment tools in these domains • CEH studies of screening, diagnosis, and psychomotor classification
	Management issues (Q10−19)	• Variability across PC settings and related outcomes • Advanced directives and goals of care designation • Community studies and impact of transition of care setting for delirium management • Pharmacological and particularly nonpharmacological intervention; both RCTs and PTs • Externally validated predictive models for reversibility
	Outcomes needing further evaluation (related to Q2−19 in AF)	• CEH in general, including assessment and management interventions • Experiential (patient/family/professional caregiver) • Economic cost

AF = analytic framework; CEH = comparative effectiveness or harms; RCT = randomized controlled trial; PC = palliative care; PT = pragmatic trial.

and policy sectors in palliative and hospice care. These collective perspectives informed commentary on core aspects of the review: general appraisal of the literature; the strengths, challenges and limitations of the review; methodological and other considerations regarding future research. The emerging methodological concerns, as identified in the scoping review, along with related recommendations are summarized in Table 8.

General Appraisal of the Literature

Of the 278 excluded studies at full-text-level review, 56 (19.5%) were excluded because of failure to report clear or valid delirium diagnostic criteria, which highlights the importance of using standardized diagnostic criteria in future studies. Most (73.1%) of the included studies in the review were conducted in patients with cancer. This raises concerns for the generalizability for some research findings to the broader current and projected PC population, which will not only include a substantive proportion of patients with cancer but increasingly is likely to be comprised of a heterogeneous mix of palliative indicator diagnoses, comorbid chronic illness and multimorbidity, including dementia and various organ failure diagnoses.[160,161] Moreover, dementia is one of the strongest risk factors for delirium in the elderly, yet its baseline status was either not reported or unclear in 52.9% of the studies included in the review. Similarly, the baseline Parkinson's disease status was only documented in one study; this is a concern, particularly in studies of antipsychotics in delirium management and the need to determine extrapyramidal effects due to these medications. Of the included studies, approximately half were conducted in inpatient PC units, whereas only 6.7% and 2% were conducted in hospital PC consult service settings and community PC settings, respectively. The generalizability of any study findings across these different study settings could be problematic. There were few systematic reviews and randomized controlled trials (RCTs); the lack of RCTs may reflect ethical, symptom burden, and attritional challenges of conducting such studies in frail PC populations.[36,162] Taken together, the underrepresentation of certain palliative indicator diagnoses in study samples, the low number of hospital consultation and community-based PC service studies, the deficits in baseline documentation, and the relative paucity of RCTs and systematic reviews highlight gaps and raise both generalizability and quality concerns in the current literature, with the caveat that a full quality and risk of bias appraisal is beyond the remit of a scoping review.

Strengths, Challenges, and Limitations of the Review

This review has many strengths: a rigorous peer-reviewed search strategy; an updated search of the most relevant databases; engagement of knowledge-users; interprofessional study team input with high-level clinical and methodological expertise; refined and expanded key questions derived from an AF that was based on the clinical pathway of delirium in PC; independent dual screening of records; and conduct of the review in accordance with recommended standards. The restriction of studies selected to those of English language is a limitation. We also encountered many challenges in conducting the review, some of which might also be acknowledged as limitations.

One of the challenges encountered was semantic ambiguity in relation to delirium terminology. The literature on delirium is replete with multiple terms

Table 8
Additional Methodological Considerations Regarding Future Research

Methodological Issue	Recommendation
Defining a palliative care population	• Reality is that the PC population is becoming increasingly heterogeneous; some studies (e.g., risk factor evaluation) may benefit from selecting a more homogeneous sample regarding palliative indicator diagnosis; alternatively, consider stratification or subgroup analysis
Delirium diagnosis	• Use ICD/DSM standard criteria or standard cutoff score on a tool validated against ICD/DSM criteria • Diagnostic algorithm for chart diagnosis/coding in database studies
Baseline documentation of dementia status	• Document due to potential impact on outcomes and their evaluation; consider stratification or subgroup analysis on the basis of dementia status
Baseline documentation of Parkinson's disease status	• Document particularly in studies of antipsychotics; potential to cause extrapyramidal side effects
Outcomes: definition; evaluation of additional outcomes	• Definition of core outcomes • Experiential outcomes for patients, families, and professional caregivers; mixed-methods approach will likely be required for some aspects
Collaboration	• Consider multicenter collaboration to facilitate recruitment for RCTs and PTs • Consider interdisciplinary and knowledge user collaboration

PC = palliative care; ICD = International Classification of Disease[9,10]; DSM = Diagnostic Statistical Manual of Mental Disorders[8]; RCT = randomized controlled trial; PT = pragmatic trial.

for delirium[28], such as encephalopathy and acute confusional state, to name just two. We addressed this issue in part by setting clear eligibility criteria for study inclusion: for the diagnosis of delirium, included studies were required to have met DSM or ICD diagnostic criteria or have used a diagnostic score on an assessment tool that had been either directly or indirectly validated against the DSM or ICD diagnostic criteria. Despite this, there were many studies of hepatic encephalopathy, for example, in which we strongly suspect that the subjects had delirium. However, although the criteria used specifically for hepatic encephalopathy were clearly met in these studies, they were not directly congruent with DSM or ICD criteria. This mismatch in taxonomy between the disciplines of hepatology and psychiatry meant that many of the hepatic encephalopathy studies were excluded at Level 1 or 2 screening phases.

We encountered somewhat similar issues in relation to defining the PC population for the purposes of the review. The World Health Organization definition of PC is inclusive of those with "life-threatening illness."[163] This broad definition includes many patients who are admitted to critical care units, although such units might not be conventionally viewed as "palliative care settings" per se. There has been a huge surge in studies of delirium in critical care over the past decade, and although this has contributed greatly to our understanding of delirium, the focus and intensity of medical management may differ quite a bit between an inpatient hospice and critical care setting. Consequently, studies of patients admitted to critical or intensive care were excluded in our review: the consensus was that ultimately the inclusion of critical care studies of delirium, although desirable, might limit the generalizability of the scoping review findings. We acknowledge this as a limitation that was arguably unavoidable. We also encountered some uncertainty regarding studies of patients with cancer or AIDS as a progressive life-threatening illness and were not necessarily seen by a PC service in consultation yet were unequivocally eligible for PC referral but assessed by oncology, psychiatry, psycho-oncology, or supportive care services; such studies were included in our review if they otherwise met the eligibility criteria.

Although the AF key questions encompassed many of the pertinent decision-making questions in the clinical care pathway of delirium, we acknowledge that the review's calibration toward addressing these clinical and epidemiological questions with empirical data and the consequent exclusion of gray literature and qualitative studies could mean that important components of care such as family education and support may have fallen outside the scope of the review. Similarly, by limiting the scope of screening and diagnostic assessment tools to the PC context, perhaps the search did not capture studies addressing the use of delirium assessment tools in other populations or contexts that might have potential applicability in the PC setting. Moreover, the outcomes reported in the included studies were largely clinical and limited in relation to patient, family, and professional caregiver experience. Although we adopted a standardized approach to capturing data in relation to knowledge user input through the SUNDIPS meeting, funding restrictions meant that subsequent knowledge user input was recorded in a less formal, standardized, and therefore transparent manner. Furthermore, lack of a more formal engagement of knowledge-users at the end of the study can be viewed as a missed opportunity in terms of knowledge translation.

Methodological and Other Considerations Regarding Future Research

Based on absence of data, primary studies are required in relation to many issues in the care pathway of delirium in PC settings: external validation of delirium risk prediction models; comparative effectiveness and harms of prevention strategies and psychomotor classification of delirium; variability in delirium management and related outcomes across the various PC settings and in relation to advanced directive and substitute decision-maker input; the experiential impact of transition of care location in relation to delirium management; and external validation of predictive models in estimating delirium reversibility. In addition to these primary study requirements, other primary studies and methodological issues warrant consideration.

Our group is currently conducting systematic reviews of delirium in the PC context with regard to its epidemiological burden, assessment, and reversibility. Although systematic reviews appear feasible in relation to some of our research questions, our preliminary concerns, based on a broad and admittedly not an in-depth appraisal of quality and risk of bias of the selected extant literature, also indicate a need for more rigorous primary studies in relation to the domains or questions for which data already exist. This is particularly relevant to the evidence base for delirium management in PC, especially the pharmacological approach to the symptomatic management of delirium in PC settings, for which four RCTs were identified in the review.[41,54,94,103] One of these RCTs included a placebo arm and demonstrated better symptom distress scores in the placebo-treated group compared to the antipsychotic-treated (haloperidol or risperidone) groups.[41] This result has generated vigorous debate and calls for more studies regarding this issue.[164] A recent survey of medical specialists in Palliative Medicine highlighted the marked variability

in pharmacological management of delirious symptoms and the perceived need for more rigorous studies.[165] Although RCTs contribute the highest level of evidence, depending on the intervention, pragmatic clinical trials, despite their challenges,[166] may provide useful data regarding effectiveness, and in the PC setting may offer a more feasible alternative.

Risk prediction models or scores for the onset and reversibility of delirium could potentially provide key information for optimal management decision-making by categorizing and triaging patients into specific risk categories and accordingly tailoring patient management.[167,168] Use of this approach has the potential to reduce unnecessary testing and treatment, thus minimizing related harms and costs. Evidence for risk prediction is ideally developed sequentially, involving development, validation, and impact assessment phases.[169] Studies of risk factors inform the development of high performing risk prediction models, which are subsequently externally validated in various relevant population subgroups and settings. Finally, evidence of their effectiveness and impact establishes them in routine clinical practice. This scoping review highlights important gaps in evidence in this regard. No studies exist that have established the effectiveness of an externally validated risk prediction model, while few extant risk prediction model development studies for delirium occurrence and reversibility were identified. Future research agenda filling this research gap could use existing administrative databases to develop and validate rigorous risk prediction models; their clinical effectiveness could be established in subsequent studies. The degree to which existing databases can be examined might be compromised due to uncertainty regarding the validity of the coding for the diagnosis of delirium; validating the relevant diagnostic codes might therefore be a prerequisite step.[170]

In terms of the various study outcomes associated with delirium management, and the recognized economic cost associated with delirium in other settings, we were unable to find any studies that reported an economic cost associated with delirium and its management in PC settings. Although delirium has a reported reversibility of 50% for episodes in an acute PC unit[100], and vigorous pursuit of reversal is often appropriate, it is also the case in clinical practice that delirium reversal is often inappropriately pursued with potentially burdensome and expensive investigations in the absence of externally validated predictive models or risk scores to guide the most appropriate level of therapeutic intervention. There is therefore a need to link an economic evaluation of delirium management with the intensity of the therapeutic attempts at delirium reversal. Some researchers have already begun to work toward developing a common core set of predefined delirium outcomes, albeit that some outcomes will be setting specific.[171] Future primary studies will require broad collaborative input with substantive interdisciplinary involvement, and for larger adequately powered trials, multicenter collaboration is essential. Furthermore, mixed-methods approaches that capture the experiences of patients and families and engage knowledge-users to inform and define the most meaningful outcomes in rigorously designed controlled trials and other studies would be well suited to address the complexity of delirium and its management in the PC setting.[172]

Conclusion

In examining the scope and nature of the published scientific literature that addresses the assessment, management, outcomes, and impact of delirium in PC settings, primary studies are required to address many existing gaps: lack of external validation of delirium risk prediction models; lack of reports on the comparative effectiveness and harms of prevention strategies and psychomotor classification of delirium; no data on the degree of variability in delirium management and related outcomes across the various types of PC settings, advanced directive and substitute decision-maker input, the experiential impact of transition of care location in relation to delirium management; and lack of external validation of predictive models in estimating delirium reversibility. Based on the number of studies, it appears feasible to conduct systematic reviews in relation to some aspects: the epidemiological burden (incidence and prevalence) of delirium, the risk factors for and diagnosis of delirium, the test performance of delirium psychomotor classification strategies, the pharmacological and nonpharmacological management of delirium, and the prediction of delirium reversibility. The scoping review's broad appraisal of study quality and limited external validity of some studies, based on population selection, together raised some preliminary concerns that warrant a more in-depth analysis and also reflect the importance of rigor in future studies. In addition, future studies will require broad collaboration from a multicenter, interdisciplinary, and administrative knowledge user perspective. Mixed-methods approaches incorporating experiential outcomes for patient, family, and professional caregivers will be required to address some of the more complex aspects of delirium.

This scoping review's findings will hopefully guide researchers and assist us toward the long-term goal of studies in the SUNDIPS research program: to generate knowledge synthesis and translation, inform guidelines and policy for delirium management and thus improve the experience of patients (and their

families) with or at risk of delirium in PC settings and across the spectrum of end-of-life care.

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Supplementary Data

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References

1. Kelley AS, Morrison RS. Palliative care for the Seriously ill. N Engl J Med 2015;373:747–755.

2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–922.

3. Irwin SA, Rao S, Bower KA, et al. Psychiatric issues in palliative care: recognition of delirium in patients enrolled in hospice care. Palliat Support Care 2008;6:159–164.

4. Smith J, Adcock L. The recognition of delirium in hospice inpatient units. Palliat Med 2012;26:283–285.

5. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.

6. 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.

7. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. J Am Geriatr Soc 2011;59(Suppl 2): S241–S243.

8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.

9. World Health Organisation. International Statistical Classification of Diseases and Related Health Problems 10th Revision: World Health Organisation 2010. Available from: http://apps.who.int/classifications/icd10/browse/2016/en. Accessed July 1 2018.

10. World Health Organisation. International Classification of Diseases 11th Revision: World Health Organisation 2018. Available from: https://icd.who.int/browse11/l-m/en. Accessed July 1st 2018.

11. Wei LA, Fearing MA, Sternberg EJ, et al. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 2008;56:823–830.

12. 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.

13. Adamis D, Rooney S, Meagher D, et al. A comparison of delirium diagnosis in elderly medical inpatients using the CAM, DRS-R98, DSM-IV and DSM-5 criteria. Int Psychogeriatr 2015;27:883–889.

14. Meagher D. Motor subtypes of delirium: past, present and future. Int Rev Psychiatry 2009;21:59–73.

15. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. J Psychosom Res 2012;72:236–241.

16. Hosker C, Ward D. Hypoactive delirium. BMJ 2017;357: j2047.

17. Downing LJ, Caprio TV, Lyness JM. Geriatric psychiatry review: differential diagnosis and treatment of the 3 D's - delirium, dementia, and depression. Curr Psychiatry Rep 2013;15:365.

18. Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. Arch Intern Med 1995;155:2459–2464.

19. Oh ES, Fong TG, Hshieh TT, et al. Delirium in older persons: Advances in diagnosis and treatment. JAMA 2017; 318:1161–1174.

20. Lawlor PG, Bush SH. Delirium diagnosis, screening and management. Curr Opin Support Palliat Care 2014;8: 286–295.

21. Leonard MM, Nekolaichuk C, Meagher DJ, et al. Practical assessment of delirium in palliative care. J Pain Symptom Manage 2014;48:176–190.

22. Bush SH, Lawlor PG KR, et al. Delirium in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol 2018;29.

23. Lawlor PG, Bush SH. Delirium in patients with cancer: assessment, impact, mechanisms and management. Nat Rev Clin Oncol 2015;12:77–92.

24. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43:183–194.

25. Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. J Clin Oncol 2012;30: 1206–1214.

26. Bush SH, Tierney S, Lawlor PG. Clinical Assessment and Management of Delirium in the Palliative Care Setting. Drugs 2017;77:1623–1643.

27. Bush SH, Leonard MM, Agar M, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. J Pain Symptom Manage 2014;48:215–230.

28. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med 2017;377:1456–1466.

29. United Nations DoEaSA, Population Division. World Population Ageing 2015:1–149. New York.

30. Lawlor PG. Foreword. The SUNDIPS meeting and papers. J Pain Symptom Manage 2014;48:157–158.

31. Lawlor PG, Davis DHJ, Ansari M, et al. An analytical framework for delirium research in palliative care settings: integrated epidemiologic, clinician-researcher, and knowledge user perspectives. J Pain Symptom Manage 2014;48:159–175.

32. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. J Clin Epidemiol 2014;67:1291–1294.

33. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Social Res Methodol Theor Pract 2005;8:14.

34. Bush SH, Kanji S, Pereira JL, et al. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manage 2014;48:231–248.

35. Leonard MM, Agar M, Spiller JA, et al. Delirium diagnostic and classification challenges in palliative care: subsyndromal delirium, comorbid delirium-dementia, and psychomotor subtypes. J Pain Symptom Manage 2014;48:199–214.

36. Sweet L, Adamis D, Meagher DJ, et al. Ethical challenges and solutions regarding delirium studies in palliative care. J Pain Symptom Manage 2014;48:259–271.

37. Evidence Partners. DistillerSR. Systematic Review and Literature Review Software. Ottawa, Canada: Evidence Partners, 2018.

38. O'Brien KK, Colquhoun H, Levac D, et al. Advancing scoping study methodology: a web-based survey and consultation of perceptions on terminology, definition and methodological steps. BMC Health Serv Res 2016;16:305.

39. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–1012.

40. Agar M, Currow D, Draper B, et al. Anticholinergic levels and risk of delirium in advanced cancer (Abstract). Support Care Cancer 2012;20:S202.

41. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. JAMA Intern Med 2017;177:34–42.

42. Akechi T, Nakano T, Okamura H, et al. Psychiatric disorders in cancer patients: descriptive analysis of 1721 psychiatric referrals at two Japanese cancer center hospitals. Jpn J Clin Oncol 2001;31:188–194.

43. Barahona E, Pinhao R, Galindo V, et al. The diagnostic Sensitivity of the memorial delirium assessment scale-Spanish version. J Pain Symptom Manage 2018;55:968–972.

44. Barnes J, Kite S, Kumar M. The recognition and documentation of delirium in hospital palliative care inpatients. Palliat Support Care 2010;8:133–136.

45. Boettger S, Breitbart W. An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. Palliat Support Care 2011;9:351–357.

46. Boettger S, Breitbart W, Passik S. Haloperidol and risperidone in the treatment of delirium and its subtypes. The Eur J Psychiatry 2011;25:59–67.

47. Boettger S, Friedlander M, Breitbart W, et al. Aripiprazole and haloperidol in the treatment of delirium. Aust New Zealand J Psychiatry 2011;45:477–482.

48. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. Palliat Support Care 2015;13:1079–1085.

49. Boettger S, Jenewein J, Breitbart W. Delirium in advanced age and dementia: a prolonged refractory course of delirium and lower functional status. Palliat Support Care 2015;13:1113–1121.

50. Bond SM. Trajectories and patterns of delirium and vulnerability in older cancer patients in the hospital and at home near the end of life. University of North Carolina at Chapel Hill, 2006.

51. Bond SM, Neelon VJ. Delirium resolution in hospitalized older patients with cancer. Cancer Nurs 2008;31:444–451.

52. Bond SM, Neelon VJ, Belyea MJ. Delirium in hospitalized older patients with cancer. Oncol Nurs Forum 2006;33:1075–1083.

53. Breitbart W, Jenewein J, Boettger S. Delirium and functionality: the impact of delirium on the level of functioning. Eur J Psychiatry 2014;28:86–95.

54. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996;153:231–237.

55. Breitbart W, Rosenfeld B, Roth A, et al. The memorial delirium assessment scale. J Pain Symptom Manage 1997;13:128–137.

56. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002;43:175–182.

57. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. J Clin Oncol 2013;31:111–118.

58. Calvo C, Galanena B, Ruiz De Gaona E. Survival after delirium in patients with advanced cancer in a palliative care unit (Abstract). Palliat Med 2014;28:819.

59. Candy B, Jackson KC, Jones L, et al. Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev 2012;11:Cd004770.

60. Cerfolio N. Psychiatric liaison to gynecological oncology. Psycho-Oncology 1995;4:143–147.

61. Chung YH, Kim JA, Song BC, et al. Impact of delirium on the short term prognosis of advanced cancer patients. Cancer 2000;89:1145–1149.

62. De J, Wand APF. Delirium screening: a systematic review of delirium screening tools in hospitalized patients. Gerontologist 2015;55:1079–1099.

63. De la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. Support Care Cancer 2015;23:2427–2433.

64. De la Cruz M, Noguera A, San Miguel-Arregui MT, et al. Delirium, agitation, and symptom distress within the final seven days of life among cancer patients receiving hospice care. Palliat Support Care 2015;13(2):211–216.

65. De la Cruz M, Ransing V, Yennu S, et al. The frequency, characteristics, and outcomes among cancer patients with delirium admitted to an acute palliative care Unit. Oncologist 2015;20:1425–1431.

66. De la Cruz M, Yennu S, Liu D, et al. Increased symptom Expression among patients with delirium admitted to an acute palliative care Unit. J Palliat Med 2017;20:638–641.

67. Detroyer E, Clement PM, Baeten N, et al. Detection of delirium in palliative care unit patients: a prospective descriptive study of the Delirium Observation Screening Scale administered by bedside nurses. Palliat Med 2014;28: 79–86.

68. Doriath V, Paesmans M, Catteau G, et al. Acute confusion in patients with systemic cancer. J Neurooncol 2007;83: 285–289.

69. Elsayem A, Bush SH, Munsell MF, et al. Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. J Pain Symptom Manage 2010;40:774–782.

70. Elsayem AF, Bruera E, Valentine AD, et al. Delirium frequency among advanced cancer patients presenting to an emergency department: a prospective, randomized, observational study. Cancer 2016;122:2918–2924.

71. Fadul NA, Osta BE, Dalal S, et al. Comparison of symptom burden among patients referred to palliative care with hematologic malignancies versus those with solid tumors. J Palliat Med 2008;11:422–427.

72. Fang CK, Chen HW, Liu SI, et al. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. Jpn J Clin Oncol 2008;38:56–63.

73. Fann JR, Hubbard RA, Alfano CM, et al. Pre- and post-transplantation risk factors for delirium onset and severity in patients undergoing hematopoietic stem-cell transplantation. J Clin Oncol 2011;29:895–901.

74. Felton M, Jarrett J, Hoffmaster R, et al. Haloperidol versus non-haloperidol antipsychotics for the management of delirium in an inpatient geriatric palliative care population (Abstract). Pharmacotherapy 2016;36:e234.

75. Fernandez F, Levy JK, Mansell PWA. Management of delirium in terminally ill AIDS patients. Int J Psychiatry Med 1989;19:165–172.

76. Freeman S, Hirdes JP, Stolee P, et al. Care planning needs of palliative home care clients: development of the interRAI palliative care assessment clinical assessment protocols (CAPs). BMC Palliat Care 2014;13:58.

77. Gagnon P, Allard P, Gagnon B, et al. Delirium prevention in terminal cancer: assessment of a multicomponent intervention. Psycho-Oncology 2012;21:187–194.

78. Gagnon P, Allard P, Masse B. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis and continuous monitoring. J Pain Symptom Manage 2000; 19:412–426.

79. Gagnon P, Tardif F, LeMoignan Moreau J, et al. Psychiatric disorders and psychotropics in 200 terminal cancer patients (Abstract). Psycho-Oncology 2014;23:366–367.

80. Gaudreau JD, Gagnon P, Harel F, et al. Impact on delirium detection of using a sensitive instrument integrated into clinical practice. Gen Hosp Psychiatry 2005;27:194–199.

81. Gaudreau JD, Gagnon P, Harel F, et al. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712–6718.

82. Gaudreau JD, Gagnon P, Harel F, et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage 2005;29:368–375.

83. Gaudreau JD, Gagnon P, Roy MA, et al. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. Cancer 2007;109:2365–2373.

84. Godfrey A, Conway R, Leonard M, et al. A classification system for delirium subtyping with the use of a commercial mobility monitor. Gait Posture 2009;30:245–252.

85. Gonçalves F, Almeida A, Pereira S. A protocol for the control of agitation in palliative care. Am J Hosp Palliat Med 2016;33:948–951.

86. Gonçalves J, Almeida A, Costa I, et al. Comparison of haloperidol alone and in combination with midazolam for the treatment of acute agitation in an inpatient palliative care service. J Pain Palliat Care Pharmacother 2016;30: 284–288.

87. Gonçalves J, Alvarenga M, Silva A. The last Forty-eight hours of life in a Portuguese palliative care Unit: Does it differ from Elsewhere? J Palliat Med 2003;6:895–900.

88. Gulcin S, Nese U, Gonca O, et al. Delirium frequency and risk factors among patients with cancer in palliative care unit. Am J Hosp Palliat Med 2017;34:282–286.

89. Hey J, Speechley H, Hosker C, et al. Delirium detection and management in a hospital specialist palliative care team; impact of an education session and introduction of the confusion assessment method (Abstract). Psycho-Oncology 2013;22:18.

90. Hjermstad M, Loge JH, Kaasa S. Methods for assessment of cognitive failure and delirium in palliative care patients: implications for practice and research. Palliat Med 2004;18:494–506.

91. Hosie A, Davidson PM, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. Palliat Med 2013;27:486–498.

92. Hosie A, Lobb E, Agar M, et al. Measuring delirium point-prevalence in two Australian palliative care inpatient units. Int J Palliat Nurs 2016;22:13–21.

93. Hui D, Dos Santos R, Reddy S, et al. Acute symptomatic complications among patients with advanced cancer admitted to acute palliative care units: a prospective observational study. Palliat Med 2015;29:826–833.

94. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial. JAMA 2017;318: 1047–1056.

95. Keeley PW. Delirium at the end of life. Clin Evid (online) 2009.

96. Kim S-Y, Kim S-W, Kim J-M, et al. Differential associations between delirium and mortality according to delirium subtype and age: a prospective cohort study. Psychosom Med 2015;77:903–910.

97. Kishi Y, Kato M, Okuyama T, et al. Treatment of delirium with risperidone in cancer patients. Psychiatry Clin neurosciences 2012;66:411–417.

98. Lam PT, Tse CY, Lee CH. Delirium in a palliative care unit. Prog Palliat Care 2003;11:126–133.

99. Landa Teran CP, Farriols Danes C, Ruiz Ripoll AI, et al. Prevalence of delirium in patients with advanced cancer disease admitted to a palliative care unit. Observational study during a 6-year period (Abstract). Palliat Med 2014;28:660.

100. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 2000;160: 786–794.

101. Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: assessing delirium in advanced cancer. Cancer 2000;88: 2859–2867.

102. Leonard M, Raju B, Conroy M, et al. Reversibility of delirium in terminally ill patients and predictors of mortality. Palliat Med 2008;22:848–854.

103. Lin CJ, Sun FJ, Fang CK, et al. An open trial comparing haloperidol with olanzapine for the treatment of delirium in palliative and hospice center cancer patients. J Intern Med Taiwan 2008;19:346–354.

104. Livermore SD, Xavier MF. Delirium rate and risk factors in palliative oncology outpatients and associated caregiver coping (Abstract). J Clin Oncol 2014;32.

105. Ljubisavljevic V, Kelly B. Risk factors for development of delirium among oncology patients. Gen Hosp Psychiatry 2003;25:345–352.

106. Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. Am J Psychiatry 1983;140:1048–1050.

107. Matsuo N, Morita T, Matsuda Y, et al. Predictors of delirium in Corticosteroid-treated patients with advanced cancer: an exploratory, multicenter, prospective, observational study. J Palliat Med 2017;20:352–359.

108. Matsuoka H, Yoshiuchi K, Koyama A, et al. Chemotherapeutic drugs that penetrate the blood-brain barrier affect the development of hyperactive delirium in cancer patients. Palliat Support Care 2015;13:859–864.

109. Meagher D, Adamis D, Leonard M, et al. Development of an abbreviated version of the delirium motor subtyping scale (DMSS-4). Int Psychogeriatr 2014;26:693–702.

110. Meagher DJ, Morandi A, Inouye SK, et al. Concordance between DSM-IV and DSM-5 criteria for delirium diagnosis in a pooled database of 768 prospectively evaluated patients using the delirium rating scale-revised-98. BMC Med 2014; 12:164.

111. Metitieri T, Bianchetti A, Trabucchi M. Delirium as a predictor of survival in older patients with advanced cancer. Arch Intern Med 2000;160:2866–2868.

112. Minagawa H, Uchitomi Y, Yamawaki S, et al. Psychiatric morbidity in terminally ill cancer patients. A prospective study. Cancer 1996;78:1131–1137.

113. Miyajima K, Fujisawa D, Hashiguchi S, et al. Symptoms overlooked in hospitalized cancer patients: impact of concurrent symptoms on oversight [corrected] by nurses. [Erratum appears in Palliat Support Care. 2014 Apr;12(2): 171]. Palliat Support Care 2014;12:95–100.

114. Mizukami N, Yamauchi M, Watanabe A, et al. Relationships between incidence of delirium and initiating factors of delirium in cancer patients receiving palliative medicine (Abstract). Eur J Anaesthesiology 2012;29:7.

115. Mizukami N, Yamauchi M, Watanabe A, et al. Multivariate analysis of correlations between incidence of delirium and delirium-initiating factors in advanced cancer patients in a palliative care unit (Abstract). Support Care Cancer 2013;21:S129.

116. Moreira C, Goncalves E, Couto G, et al. Delirium: dimension of the problem in a palliative care service (Abstract). Palliat Med 2012;26:465.

117. Morita T, Takigawa C, Onishi H, et al. Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial. J Pain Symptom Manage 2005;30:96–103.

118. Morita T, Tei Y, Tsunoda J, et al. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 2001; 22:997–1006.

119. Neefjes ECW, van der Vorst M, Verdegaal B, et al. Identification of patients with cancer with a high risk to develop delirium. Cancer Med 2017;6:1861–1870.

120. Nowels DE, Bublitz C, Kassner CT, et al. Estimation of confusion prevalence in hospice patients. J Palliat Med 2002; 5:687–695.

121. Oligario G, Buch C, Piscotty R. Nurses' assessment of delirium with underlying dementia in end-of-life care. J Hosp Palliat Nurs 2015;17:16–23.

122. Olofsson SM, Weitzner MA, Valentine AD, et al. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. Support Care Cancer 1996;4:351–357.

123. O'Sullivan R, Meagher D, Leonard M, et al. A comparison of the revised delirium rating scale (DRS-R98) and the memorial delirium assessment scale (MDAS) in a palliative care cohort with DSM-IV delirium. Palliat Support Care 2015;13:937–944.

124. Perrar KM, Golla H, Voltz R. Pharmacological treatment of delirium in palliative care patients. A systematic literature review. Schmerz 2013;27:190–198.

125. Plaschke K, Petersen KA, Frankenhauser S, et al. The impact of Plasma Cholinergic Enzyme activity and other risk factors for the development of delirium in patients receiving palliative care. J Pain Symptom Manage 2016;52: 525–532.

126. Porteous A, Dewhurst F, Gray W, et al. Screening for delirium in specialist palliative care inpatient units: perceptions and outcomes. Int J Palliat Nurs 2016;22:444–447.

127. Rainsford S, Rosenberg J, Bullen T. Delirium in advanced cancer: screening for the incidence on admission to an inpatient hospice unit. J Palliat Med 2014;17: 1045–1048.

128. Rao S, Ferris FD, Irwin SA. Ease of screening for depression and delirium in patients enrolled in inpatient hospice care. J Palliat Med 2011;14:275–279.

129. Ryan K, Leonard M, Guerin S, et al. Validation of the confusion assessment method in the palliative care setting. Palliat Med 2009;23:40–45.

130. Sagawa R, Akechi T, Okuyama T, et al. Etiologies of delirium and their relationship to reversibility and motor

subtype in cancer patients. Jpn J Clin Oncol 2009;39:175–182.

131. Sanchez-Roman S, Beltran Zavala C, Lara Solares A, et al. Delirium in adult patients receiving palliative care: a systematic review of the literature. Rev Psiquitr Salud Ment 2014;7:48–58.

132. Sands MB, Dantoc BP, Hartshorn A, et al. Single question in delirium (SQiD): testing its efficacy against psychiatrist interview, the confusion assessment method and the memorial delirium assessment scale. Palliat Med 2010;24:561–565.

133. Shin SH, Hui D, Chisholm G, et al. Frequency and outcome of Neuroleptic rotation in the management of delirium in patients with advanced cancer. Cancer Res Treat 2015;47:399–405.

134. Slatore CG, Goy ER, O'Hearn DJ, et al. Sleep quality and its association with delirium among veterans enrolled in hospice. Am J Geriatr Psychiatry 2012;20:317–326.

135. Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. Palliat Med 2006;20:17–23.

136. Stillman MJ, Rybicki LA. The bedside confusion scale: development of a portable bedside test for confusion and its application to the palliative medicine population. J Palliat Med 2000;3:449–456.

137. Tanaka R, Ishikawa H, Sato T, et al. Incidence of delirium among patients having cancer injected with different opioids for the first time. Am J Hosp Palliat Med 2017;34:572–576.

138. Tatematsu N, Hayashi A, Narita K, et al. The effects of exercise therapy on delirium in cancer patients: a retrospective study. Support Care Cancer 2011;19:765–770.

139. Trzepacz PT, Maue FR, Coffman G, et al. Neuropsychiatric assessment of liver transplantation candidates: delirium and other psychiatric disorders. Int J Psychiatry Med 1986;16:101–111.

140. Uchida M, Okuyama T, Ito Y, et al. Prevalence, course and factors associated with delirium in elderly patients with advanced cancer: a longitudinal observational study. Jpn J Clin Oncol 2015;45:934–940.

141. Uldall KK, Berghuis JP. Delirium in AIDS patients: recognition and medication factors. AIDS Patient Care STDS 1997;11:435–441.

142. Zimmerman KM, Salow M, Skarf LM, et al. Increasing anticholinergic burden and delirium in palliative care inpatients. Palliat Med 2014;28:335–341.

143. Zuriarrain Reyna Y, Bravo Perez MC, Gonzalez Garza M, et al. Pilot study of Delirium in two inpatients palliative care units (Abstract). Palliat Med 2014;28:829–830.

144. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 3rd ed. (DSM-III). Washington, DC: American Psychiatric Association, 1980.

145. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 3rd ed., revised (DSM-III-R). Washington, DC: American Psychiatric Association, 1987.

146. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th ed. Washington, DC: American Psychiatric Association, 1994.

147. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), 4th ed. Washington, DC: American Psychiatric Association, 2000. Text Revision ed.

148. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;23:89–97.

149. Trzepacz PT, Mittal D, Torres R, et al. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001;13:229–242.

150. Neelon VJ, Champagne MT, Carlson JR, et al. The NEECHAM Confusion Scale: construction, validation, and clinical testing. Nurs Res 1996;45:324–330.

151. Steel K, Ljunggren G, Topinkova E, et al. The RAI-PC: an assessment instrument for palliative care in all settings. Am J Hosp Palliat Care 2003;20:211–219.

152. Williams MA, Ward SE, Campbell EB. Confusion: testing versus observation. J Gerontol Nurs 1988;14:25–30.

153. Steis MR, Evans L, Hirschman KB, et al. Screening for delirium using family caregivers: convergent validity of the family confusion assessment method and interviewer-rated confusion assessment method. J Am Geriatr Soc 2012;60:2121–2126.

154. Hart RP, Levenson JL, Sessler CN, et al. Validation of a cognitive test for delirium in medical ICU patients. Psychosomatics 1996;37:533–546.

155. Katzman R, Brown T, Fuld P, et al. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983;140:734–739.

156. Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859–864.

157. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983–2991.

158. Huang MC, Lee CH, Lai YC, et al. Chinese version of the Delirium Rating Scale-Revised-98: reliability and validity. Compr Psychiatry 2009;50:81–85.

159. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

160. Etkind SN, Bone AE, Gomes B, et al. How many people will need palliative care in 2040? Past trends, future projections and implications for services. BMC Med 2017;15:102.

161. Kane PM, Daveson BA, Ryan K, et al. The need for palliative care in Ireland: a population-based estimate of palliative care using routine mortality data, inclusive of nonmalignant conditions. J Pain Symptom Manage 2015;49:726–733.e1.

162. Hui D, Glitza I, Chisholm G, et al. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 2013;119:1098–1105.

163. Organisation WH. WHO Definition of Palliative Care. Available from: http://www.who.int/cancer/palliative/definition/en/#. Accessed 22 October 2017.

164. Meagher D, Agar MR, Teodorczuk A. Debate article: antipsychotic medications are clinically useful for the treatment of delirium. Int J Geriatr Psychiatry 2018;33:1420–1427.

165. Boland J, Kabir M, Bush SH, et al. Delirium management by specialists in palliative medicine: an association for palliative medicine (APM) of Great Britain and Ireland survey. Presentated at the APM's Annual supportive & palliative care conference, March 15-16, 2018: Bournemouth, UK. (Abstract). BMJ Support Palliat Care 2018;8.

166. Heim N, van Stel HF, Ettema RG, et al. HELP! Problems in executing a pragmatic, randomized, stepped wedge trial on the Hospital Elder Life Program to prevent delirium in older patients. Trials 2017;18:220.

167. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ 2012;344:e420.

168. Pendlebury ST, Lovett NG, Smith SC, et al. Delirium risk stratification in consecutive unselected admissions to acute medicine: validation of a susceptibility score based on factors identified externally in pooled data for use at entry to the acute care pathway. Age Ageing 2017;46: 226–231.

169. Moons KG, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: what, why, and how? BMJ 2009;338: b375.

170. Kim DH, Lee J, Kim CA, et al. Evaluation of algorithms to identify delirium in administrative claims and drug utilization database. Pharmacoepidemiol Drug Saf 2017;26: 945–953.

171. Rose L, Agar M, Burry LD, et al. Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): study protocol. BMJ open 2017;7:e016371.

172. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655.

Appendix

Supplementary Table 1
Database Search Strategies

Database	Initial Search[a]	First Updated Search[b]	Second Updated Search[c]	Total
Medline	1904	259	165	2328
Embase	2624	518	339	3481
PsycINFO	494	63	33	590
CINAHL	126	152	123	401
Total	5148	992	660	6800

[a]July 2, 2015.
[b]December 31, 2016.
[c]May 16, 2018.

Total duplicates = 3148.
Total identified through database searching (with duplicates removed) = 3652.
Additional references identified through reference lists on included papers = 68.
Total references identified for eligibility screening = 3720.

Medline

1. Delirium/
2. deliri*.tw.
3. (acute adj1 confusion*).tw.
4. (acute adj1 brain adj1 syndrome).tw.
5. (metabolic adj1 encephalopath*).tw.
6. (acute adj1 organic adj1 psychosyndrome).tw.
7. (acute adj1 psycho-organic adj1 syndrome).tw.
8. (clouded adj1 state).tw.
9. (clouding adj3 consciousness).tw.
10. (exogenous adj1 psychos*).tw.
11. (toxic adj1 confusion).tw.
12. (toxic adj1 psychos*).tw.
13. Confusion/
14. (acute adj1 confusional adj1 state).tw.
15. (acute adj1 brain adj1 failure).tw.
16. (terminal* adj1 restless*).tw.
17. (terminal adj1 agitation).tw.
18. (psychomotor adj1 agitation).tw.
19. (cognitive adj1 failure).tw.
20. disorientation.tw.
21. (terminal adj2 delir*).tw.
22. encephalopath*.tw.
23. (organic adj3 psychos*).tw.
24. or/1−23
25. Palliative Care/
26. (end* adj3 life).tw.
27. (last year of life or LYOL).tw.
28. palliat*.tw.
29. Terminally Ill/
30. hospice*.tw.
31. (terminal* adj3 (car* or ill* or diseas*)).tw.
32. (terminal-stage* or terminal stage* or dying or (close adj4 death)).tw.

33. exp Terminal Care/
34. Hospice Care/
35. (dying adj3 care).tw.
36. ((end-stage* or end stage* or incurable or advanced) adj5 (disease* or ill* or care or cancer* or malignan*)).tw.
37. or/25-36
38. 24 and 37

Embase

1. *delirium/
2. deliri*.tw.
3. (acute adj1 confusion*).tw.
4. (acute adj1 brain adj1 syndrome).tw.
5. (metabolic adj1 encephalopath*).tw.
6. (acute adj1 organic adj1 psychosyndrome).tw.
7. (acute adj1 psycho-organic adj1 syndrome).tw.
8. (clouded adj1 state).tw.
9. (clouding adj3 consciousness).tw.
10. (exogenous adj1 psychos*).tw.
11. (toxic adj1 confusion).tw.
12. (toxic adj1 psychos*).tw.
13. *confusion/
14. (acute adj1 confusional adj1 state).tw.
15. (acute adj1 brain adj1 failure).tw.
16. (terminal* adj1 restless*).tw.
17. (terminal adj1 agitation).tw.
18. (psychomotor adj1 agitation).tw.
19. (cognitive adj1 failure).tw.
20. disorientation.tw.
21. (terminal adj2 delir*).tw.
22. encephalopath*.tw.
23. (organic adj3 psychos*).tw.
24. or/1-23
25. exp palliative therapy/
26. (end* adj3 life).tw.
27. (last year of life or LYOL).tw.
28. palliat*.tw.
29. exp terminally ill patient/
30. hospice*.tw.
31. (terminal* adj3 (car* or ill* or diseas*)).tw.
32. (terminal-stage* or terminal stage* or dying or (close adj4 death)).tw.
33. terminal care/
34. hospice care/
35. (dying adj3 care).tw.
36. ((end-stage* or end stage* or incurable or advanced) adj5 (disease* or ill* or care or cancer* or malignan*)).tw.
37. or/25-36
38. 24 and 37
39. limit 38 to human

PsycINFO

1. delirium/
2. deliri*.tw.
3. (acute adj1 confusion*).tw.
4. (acute adj1 brain adj1 syndrome).tw.
5. (metabolic adj1 encephalopath*).tw.
6. (acute adj1 organic adj1 psychosyndrome).tw.
7. (acute adj1 psycho-organic adj1 syndrome).tw.
8. (clouded adj1 state).tw.
9. (clouding adj3 consciousness).tw.
10. (exogenous adj1 psychos*).tw.
11. (toxic adj1 confusion).tw.
12. (toxic adj1 psychos*).tw.
13. mental confusion/
14. (acute adj1 confusional adj1 state).tw.
15. (acute adj1 brain adj1 failure).tw.
16. (terminal* adj1 restless*).tw.
17. (terminal adj1 agitation).tw.
18. (psychomotor adj1 agitation).tw.
19. (cognitive adj1 failure).tw.
20. disorientation.tw.
21. (terminal adj2 delir*).tw.
22. encephalopath*.tw.
23. (organic adj3 psychos*).tw.
24. or/1-23
25. palliative care/
26. (end* adj3 life).tw.
27. (last year of life or LYOL).tw.
28. palliat*.tw.
29. terminally ill patients/
30. hospice*.tw.
31. (terminal* adj3 (car* or ill* or diseas*)).tw.
32. (terminal-stage* or terminal stage* or dying or (close adj4 death)).tw.
33. hospice/
34. (dying adj3 care).tw.
35. ((end-stage* or end stage* or incurable or advanced) adj5 (disease* or ill* or care or cancer* or malignan*)).tw.
36. or/25-35
37. 24 and 36

CINAHL

S35	S23 AND S34
S34	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S33	((end-stage* or end stage* or incurable or advanced) N5 (disease* or ill* or care or cancer* or malignan*))
S32	(dying N3 care)
S31	(terminal-stage* or terminal stage* or dying or (close N4 death))
S30	(terminal* N3 (car* or ill* or diseas*))
S29	(last year of life or LYOL)
S28	(end* N3 life)
S27	(MH "Terminally Ill Patients+")
S26	(MH "Terminal Care")
S25	(MH "Hospice Care")
S24	(MH "Palliative Care")
S23	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S22	(organic N3 psychos*)
S21	encephalopath*
S20	(terminal N2 delir*)
S19	disorientation
S18	(cognitive N1 failure)
S17	(psychomotor N1 agitation)
S16	(terminal N1 agitation)
S15	(terminal* N1 restless*)
S14	(acute N1 brain N1 failure)
S13	(acute N1 confusional N1 state)
S12	(toxic N1 psychos*)
S11	(toxic N1 confusion)
S10	(exogenous N1 psychos*)
S9	(clouding N3 consciousness)
S8	(clouded N1 state)
S7	(acute N1 psycho-organic N1 syndrome)
S6	(acute N1 organic N1 psychosyndrome)
S5	(metabolic N1 encephalopath*)
S4	(acute N1 brain N1 syndrome)
S3	(acute N1 confusion*)
S2	deliri*
S1	(MH "Confusion+")

Supplementary Table 2

General Characteristics of Individual Included Studies ($N = 140$)

Author	Country	Palliative Indicator Diagnosis	Care Setting	Sample Size	Study Design Characteristics
Agar et al.[40]	Australia	All or ≥90% with cancer diagnosis	Inpatient PCUs	126	One group NRT or cohort[a] [P]
Agar et al.[41]	Australia	Mix of life-threatening diagnoses	Mix of 11 inpatient hospice and hospital units	247	RCT
Akechi et al.[42]	Japan	All or ≥90% with cancer diagnosis	Referrals to a psychiatry service in a cancer center	1721	One group NRT or cohort [R]
Barahona et al.[43]	Spain	All or ≥90% with cancer diagnosis	Hospice ($n = 40$) and hospital ($n = 27$)	67	Cross-sectional[a] [P]
Barnes et al.[44]	U.K.	Mix of life-threatening diagnoses	Inpatient PCU in a hospital	120	Before-after study [M]
Boettger et al.[45]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service in a cancer center	21	One group NRT or cohort [SA]
Boettger et al.[46]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service in a cancer center	64	Two or multiple groups in NRT or cohort [SA]
Boettger et al.[47]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service in a cancer center	42	Two or multiple groups in NRT or cohort [SA]
Boettger et al.[48]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service in a cancer center	84	Multiple groups in NRT [SA]
Boettger et al.[49]	U.S.	All or ≥90% with cancer diagnosis	Inpatients in a cancer center	111	Two or multiple groups in NRT or cohort [SA]
Bond[50]	U.S.	All or ≥90% with cancer diagnosis	Hospitalized older patients with a cancer diagnosis	76	One group NRT or cohort [SA]
Bond and Neelon[51]	U.S.	All or ≥90% with cancer diagnosis	Hospitalized older adults with a cancer diagnosis	43	One group NRT or cohort [SA]
Bond et al.[52]	U.S.	All or ≥90% with cancer diagnosis	Hospitalized older patients with a cancer diagnosis	76	One group NRT or cohort [SA]
Breitbart et al.[53]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service referrals in a cancer center	111	One group NRT or cohort [SA]
Breitbart et al.[54]	U.S.	All or ≥90% with AIDS	Referrals to a hospital psychiatry service	244	RCT
Breitbart et al.[55]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry inpatient referrals in a cancer center	33–51	Cross-sectional [P]
Breitbart et al.[56]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry service in a cancer center	79	One group NRT or cohort [P]
Bruera et al.[57]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	129	RCT
Calvo et al.[58]	Spain	Unclear or not reported	Inpatient PCU in a hospital	192	One group NRT or cohort[a] [R]
Candy et al.[59]	U.S.	All or ≥90% with AIDS	Hospital psychiatry consultation service	30	Systematic review
Cerfolio[60]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry referrals from gynecologic oncology	82	Cross-sectional [P]
Chung et al.[61]	Italy	All or ≥90% with cancer diagnosis	Inpatient PCUs	393	One group NRT or cohort [P]
De and Wand[62]	Multiple	Mix of life-threatening diagnoses	Hospital inpatients	19–906	Systematic review
de la Cruz et al.[63]	U.S.	All or ≥90% with cancer diagnosis	Hospital inpatient PC consult team	771	One group NRT or cohort [R]
de la Cruz et al.[64]	U.S.	All or ≥90% with cancer diagnosis	Community PC service	78	One group NRT or cohort [R]
de la Cruz et al.[65]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	556	Cross-sectional [R]
de la Cruz et al.[66]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	329	Two or multiple groups in NRT or cohort [SA]
Detroyer et al.[67]	Netherlands	Unclear or not reported	Inpatient PCU in a hospital	48	One group NRT or cohort [P]
Doriath et al.[68]	Belgium	All or ≥90% with cancer diagnosis	Inpatient unit in a cancer center	100	One group NRT or cohort [P]
Elsayem et al.[69]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	25	One group NRT or cohort [P]
Elsayem et al.[70]	U.S.	All or ≥90% with cancer diagnosis	Emergency department in a cancer center	243	Cross-sectional [P]
Fadul et al.[71]	U.S.	Solid tumors; hematological malignancies	Hospital inpatient PC consult team	250	Two or multiple groups in NRT or cohort [R]
Fang et al.[72]	Taiwan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	228	One group NRT or cohort [P]
Fann et al.[73]	U.S.	All or ≥90% with cancer diagnosis	Pre- and post-hematopoietic stem cell transplant	90	One group NRT or cohort [P]

Felton et al.[74]	U.S.	Unclear or not reported	Inpatient PCU in a hospital	319	Two or multiple groups in NRT or cohort[a] [R]
Fernandez et al.[75]	U.S.	All or ≥90% with AIDS	Referrals to a psychiatry consultation service	206	One group NRT or cohort [P]
Freeman et al.[76]	Canada	Mix of life-threatening diagnoses	Community PC service	6769	Cross-sectional [R]
Gagnon et al.[77]	Canada	All or ≥90% with cancer diagnosis	Hospice and PCU in hospital	1516	Two or multiple groups in NRT or cohort [P]
Gagnon et al.[78]	Canada	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	89	One group NRT or cohort [P]
Gagnon et al.[79]	Canada	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	200	Cross-sectional[a] [R]
Gaudreau et al.[80]	Canada	All or ≥90% with cancer diagnosis	Hospital oncology/internal medicine unit	134	One group NRT or cohort [SA]
Gaudreau et al.[81]	Canada	All or ≥90% with cancer diagnosis	Hospital hemato-oncology internal medicine unit	261	One group NRT or cohort [P]
Gaudreau et al.[82]	Canada	Unclear or not reported	Hospital hemato-oncology internal medicine unit	146	One group NRT or cohort [P]
Gaudreau et al.[83]	Canada	All or ≥90% with cancer diagnosis	Hospital hemato-oncology internal medicine unit	114	One group NRT or cohort [P]
Godfrey et al.[84]	Ireland	Unclear or not reported	Inpatient PCU in a hospice	40	One group NRT or cohort [P]
Gonçalves et al.[85]	Portugal	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	135	One group NRT or cohort [P]
Gonçalves et al.[86]	Portugal	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	79	Two or multiple groups in NRT or cohort [P]
Gonçalves et al.[87]	Portugal	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	300	One group NRT or cohort [P]
Gulcin et al.[88]	Turkey	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	213	One group NRT or cohort [P]
Hey et al.[89]	U.K.	Unclear or not reported	Hospital inpatient PC consult team	292	Before-after study[a] [M]
Hjermstad et al.[90]	Norway	All or ≥90% with cancer diagnosis	Multiple palliative care settings; 22 in total	20–393	Systematic review
Hosie et al.[91]	Multiple	All or ≥90% with cancer diagnosis	Inpatient PCUs in hospice and hospital settings	1079	Systematic review
Hosie et al.[92]	Australia	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	47	Cross-sectional [P]
Hui et al.[93]	U.S. and Brazil	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	352	One group NRT or cohort [P]
Hui et al.[94]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	90	RCT
Keeley[95]	Multiple	Mix of life-threatening diagnoses	Systematic review (multiple settings)	30–42	Systematic review
Kim et al.[96]	South Korea	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	322	One group NRT or cohort [P]
Kishi et al.[97]	Japan	All or ≥90% with cancer diagnosis	Psychiatry service referrals in an acute care hospital	29	One group NRT or cohort [P]
Lam et al.[98]	Hong Kong	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	28	One group NRT or cohort [P]
Landa Teran et al.[99]	Spain	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	1826	Cross-sectional[a] [U]
Lawlor et al.[100]	Canada	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	104	One group NRT or cohort [P]
Lawlor et al.[101]	Canada	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	104	Cross-sectional [P]
Leonard et al.[102]	Ireland	87.2% had a cancer diagnosis	Inpatient PCU in a hospice	121	One group NRT or cohort [P]
Lin et al.[103]	Taiwan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	30	RCT
Livermore and Xavier[104]	U.S.	All or ≥90% with cancer diagnosis	Outpatient PC clinic	52	One group NRT or cohort[a] [R]
Ljubisavljevic and Kelly[105]	Australia	All or ≥90% with cancer diagnosis	Inpatient oncology ward	113	One group NRT or cohort [P]
Massie et al.[106]	U.S.	All or ≥90% with cancer diagnosis	Psychiatric assessment in hospital oncology unit	19	One group NRT or cohort [P]
Matsuo et al.[107]	Japan	All or ≥90% with cancer diagnosis	Multiple: mix of inpatient hospice and hospital inpatient PC team referrals	207	One group NRT or cohort [P]
Matsuoka et al.[108]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	166	One group NRT or cohort [R]
Meagher et al.[109]	Multiple	Unclear or not reported	Subgroup of hospice inpatients ($n = 249$)	487	Cross-sectional [R]
Meagher et al.[110]	Multiple	Unclear or not reported	Inpatient PCU in a hospice	269	Case control [R]
Metitieri et al.[111]	Italy	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	60	One group NRT or cohort [U]
Minagawa et al.[112]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	93	One group NRT or cohort [P]

(*Continued*)

Supplementary Table 2
Continued

Author	Country	Palliative Indicator Diagnosis	Care Setting	Sample Size	Study Design Characteristics
Miyajima et al.[113]	Japan	All or ≥90% with cancer diagnosis	Hospital inpatient PC consult team	255	Cross-sectional [P]
Mizukami et al.[114]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	56	Cross-sectional[a] [P]
Mizukami et al.[115]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	76	One group NRT or cohort[a] [R]
Moreira et al.[116]	Portugal	All or ≥90% with cancer diagnosis	Hospital inpatient PC consult team	119	One group NRT or cohort[a] [P]
Morita et al.[117]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	21	One group NRT or cohort [P]
Morita et al.[118]	Japan	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	237	One group NRT or cohort [P]
Neefjes et al.[119]	Netherlands	Mix of life-threatening diagnoses	Medical oncology unit in a hospital	574	One group NRT or cohort[a] [R]
Nowels et al.[120]	U.S.	Mix of life-threatening diagnoses	Hospice research network (inpatient and community)	299	Cross-sectional [P]
Oligario et al.[121]	U.S.	Dementia	Inpatient PCU in a hospice	50	One group NRT or cohort [P]
Olofsson et al.[122]	U.S.	All or ≥90% with cancer diagnosis	Psychiatry consult service in a cancer center	90	One group NRT or cohort [R]
O'Sullivan et al.[123]	Ireland	Unclear or not reported	Inpatient PCU in a hospice	77	One group NRT or cohort [P]
Perrar et al.[124]	Germany	Mix of life-threatening diagnoses	Three studies included; AIDS ($n = 1$) and cancer ($n = 2$)	30–121	Systematic review
Plaschke et al.[125]	Germany	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospital	100	One group NRT or cohort [P]
Porteous et al.[126]	U.K.	Unclear or not reported	Inpatient PCU in a hospice	298	One group NRT or cohort [P]
Rainsford et al.[127]	Australia	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	51	Cross-sectional [P]
Rao et al.[128]	U.S.	Mix of life-threatening diagnoses	Inpatient PCU in a hospice	22	One group NRT or cohort [P]
Ryan et al.[129]	Ireland	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	85	One group NRT or cohort [P]
Sagawa et al.[130]	Japan	All or ≥90% with cancer diagnosis	Referrals to a hospital psychiatry service	100	One group NRT or cohort [P]
Sanchez-Roman et al.[131]	Mexico	All or ≥90% with cancer diagnosis	Multiple settings based on search word, "palliative."	34–1516	Systematic review
Sands et al.[132]	Australia	All or ≥90% with cancer diagnosis	Inpatient PC referrals in an oncology center	21	Cross-sectional [P]
Shin et al.[133]	U.S.	All or ≥90% with cancer diagnosis	Inpatient PCU in a cancer center	167	One group NRT or cohort [P]
Slatore et al.[134]	U.S.	Mix of life-threatening diagnoses	Community PC service	105	One group NRT or cohort [SA]
Spiller and Keen[135]	U.K.	All or ≥90% with cancer diagnosis	Inpatient PCU in a hospice	100	Mixed cross-sectional and one group NRT or cohort [P]
Stillman and Rybicki[136]	U.S.	79% had a cancer diagnosis	Inpatient PCU in a hospital	31	Cross-sectional [P]
Tanaka et al.[137]	Japan	All or ≥90% with cancer diagnosis	Cancer center	114	Two or multiple groups in NRT or cohort [R]
Tatematsu et al.[138]	Japan	All or ≥90% with cancer diagnosis	Hospital inpatient PC consult team	48	One group NRT or cohort [R]
Trzepacz et al.[139]	U.S.	Hepatic failure	Hospital psychiatry referrals from a medical service	40	Cross-sectional [P]
Uchida et al.[140]	Japan	All or ≥90% with cancer diagnosis	General medical ward (hospital)	61	One group NRT or cohort [P]
Uldall and Berghuis[141]	U.S.	All or ≥90% with AIDS	Hospice type setting for AIDS patients	137	One group NRT or cohort [R]
Zimmerman et al.[142]	U.S.	Unclear or not reported	Hospital inpatient PC consult team	217	Case control [R]
Zuriarrain Reyna et al.[143]	Spain	Unclear or not reported	Inpatient PCU in a hospital	55	One group NRT or cohort[a] [P]

PC = palliative care; PCU = palliative care unit; NRT = nonrandomized trial; RCT = randomized controlled trial.
[a]Conference abstract only; [P] = prospective; [R] = retrospective; [M] = mixed prospective and retrospective; [SA] = secondary analysis of prospective study data; [U] = unclear as to whether prospective or retrospective.

Supplementary Table 3

Delirium Diagnostic Criteria and Validated Assessment Tools Used in Included Studies[a]

Reference Number	ICD-10[9]	DSM-III[144]	DSM-IIIR[145]	DSM-IV[146] or DSM-IV-TR[147]	DSM-5[8]	CAM[12]	DRS[148] or DRS-98-R[149]	MDAS[55]	Other	Comment
40								X		
41				X				X		
42				X						
43						X				
44						X				
45				X				X		
46				X				X		
47				X				X		
48				X				X		
49				X						
50									X	NEECHAM[150]
51									X	NEECHAM
52									X	NEECHAM
53				X				X		
54			X				X			
55			X	X						
56				X				X		
57								X		
58				X						
59			X				X			SR
60			X							
61						X				
62	X	X	X	X			X		X	Psychiatrist interview; SR
63				X				X		
64								X		
65				X				X		
66				X				X		
67						X			X	DOS[67]
68				X						
69				X						
70						X		X		
71				X						
72				X						
73							X	X		
74	X									
75			X							
76									X	InterRAI-PC[151]
77									X	CRS[152]
78						X				
79									X	NuDESC[82]
80						X				
81									X	Nu-DESC > 2
82				X		X		X		
83									X	Nu-DESC > 1
84				X			X	X		
85						X				
86						X				
87						X				

(*Continued*)

Supplementary Table 3
Continued

Reference Number	ICD-10[9]	DSM-III[144]	DSM-IIIR[145]	DSM-IV[146] or DSM-IV-TR[147]	DSM-5[8]	CAM[12]	DRS[148] or DRS-98-R[149]	MDAS[55]	Other	Comment
88				X			X			
89						X				
90			X	X		X	X	X		SR
91	X		X	X		X	X	X	X	Psychiatrist interview; SR
92					X			X	X	Nu-DESC
93								X		
94				X						
95							X		X	Psychiatrist interview; SR
96				X		X	X			
97				X			X			
98				X						
99				X						
100				X						
101				X				X		
102				X		X	X			
103				X						
104									X	FAM-CAM[153]
105						X				
106		X								
107						X				
108				X						
109				X		X	X			
110				X						
111				X						
112			X							
113				X						
114						X				
115						X				
116						X				
117				X						
118				X						
119									X	DOS
120				X						
121						X				
122									X	Psychiatrist interview
123				X						
124							X	X	X	Nu-DESC; SR
125										
126						X				
127						X	X			
128						X				
129				X		X	X	X	X	CTD[154], SOMCT[155]
130				X						
131									X	Standard criteria or validated instruments; SR
132				X		X		X		
133								X		
134						X				

135					X			
136					X			
137							X	ICDSC[156]
138					X			
139	X							
140		X		X				
141					X			
142							X	Validated chart audit tool
143						X		

ICD-10 = International Classification of Disease, 10th edition;[9] DSM-III = Diagnostic Statistical Manual of Mental Disorders, third edition[144]; DSM-III-R = Diagnostic Statistical Manual of Mental Disorders, third edition revised[145]; DSM-IV = Diagnostic Statistical Manual of Mental Disorders, fourth edition[146]; DSM-IV-TR = Diagnostic Statistical Manual of Mental Disorders, fourth edition, text revised[147]; DSM-5 = Diagnostic Statistical Manual of Mental Disorders, fifth edition[8]; CAM = Confusion Assessment Method[12]; DRS = Delirium Rating Scale[148]; DRS-98-R = Delirium Rating Scale (Revised-98 version)[149]; MDAS = Memorial Delirium Assessment Scale[55]; NEECHAM = NEECHAM Confusion Scale[150]; SR = multiple diagnostic tools as part of either formal systematic reviews[59,62,90,91,95] or systematic literature review studies[124,131]; InterRAI-PC = Residential Assessment Instrument—Palliative Care version[151]; CRS = Confusion Rating Scale[152]; Nu-DESC = Nursing Delirium Screening Scale[82]; FAM-CAM = Confusion Assessment Method (Family Version)[153]; DOS = Delirium Observation Scale[67]; CTD = Cognitive Test of Delirium[154]; SOMCT = Short Orientation Memory Concentration Test[155]; ICDSC = Intensive Care Delirium Screening Checklist.[156]

[a]Guide to initials used (in order of appearance in table).

Supplementary Table 4
Studies of Comparative Effectiveness or Harms Outcomes

Comparative Approach	Study Reference Number	Specific Comparison[a]	Study Outcomes[b]
Direct comparison of two or more active study interventions	46	Haloperidol versus risperidone	C, M
	47	Aripiprazole versus haloperidol	C, M
	48	Haloperidol, aripiprazole, olanzapine, risperidone	C, M
	54	Haloperidol, chlorpromazine, and lorazepam	C, M
	59	Haloperidol versus chlorpromazine versus lorazepam; overlaps with primary study[54]	C, M
	62	Systematic review comparing multiple screening tools for delirium	O [most effective screening tool for population/settings]
	74	Haloperidol versus nonhaloperidol antipsychotics (olanzapine, risperidone, quetiapine)	M, O [length of stay; sedation level; QTc prolongation]
	80	Nu-DESC versus CRS	O [delirium detection; cost-effectiveness description]
	86	Haloperidol alone versus haloperidol and midazolam	O [agitation; consciousness]
	94	Haloperidol + lorazepam versus haloperidol + placebo	C, D, F, I, M, O [change on agitation-sedation scale; communication capacity; discharged alive]
	95	Systematic review with one included study comparing haloperidol versus chlorpromazine vs lorazepam, overlaps with primary study[54]	C, M
	103	Haloperidol versus olanzapine	C, M
	124	Systematic literature review study: haloperidol versus aripiprazole; chlorpromazine versus haloperidol versus lorazepam	C, M
Comparison of one or more active study interventions (test or treatment) versus placebo/no intervention/ reference standard	41	Risperidone versus haloperidol versus placebo	C, D, M
	57	Normal saline 1 L per day versus placebo using MDAS and Nu-DESC as measures of delirium severity and RASS as a measure of agitation-sedation	C, D, J, O [change in delirium severity scores; change in agitation-sedation using RASS]
	62	Systematic review comparing multiple screening tools for delirium	O [most effective screening tool for population/settings]
	72	DRS-Chinese version versus routine care	O [detection of delirium]
	77	Multicomponent prevention strategies versus routine care	A, C, L, O [adherence to or completion of screening; patient-days in delirium; duration of delirium episode; time to onset of incident delirium]
	95	Systematic review included a study of hydration with hypodermoclysis versus standard care	C, M
	101	MDAS versus MMSE versus DSM-IV criteria	H
	113	Psychiatrist assessment versus nurse assessment	O [delirium recognition]
	121	Subjective nurse ratings versus objective researcher ratings using the CAM	O [recognition of delirium occurring in patients with dementia]
	122	Haloperidol versus no antipsychotic	M
	127	Screening versus routine clinical assessment	A, O [comparative rates of recognition of delirium or subsyndromal delirium]
	131	Systematic literature review study of delirium in adult patients receiving palliative care; included exercise study[138]	A, C, K, O [multiple outcomes of included studies as part of systematic review]
	138	Exercise therapy versus nonexercise therapy	O [antipsychotic doses used as a severity index of delirium]
Single-arm, pre- and post-intervention comparison	44	CAM versus routine care	H, O [delirium documentation (as an index of recognition); acceptability of screening to health care staff; delirium prevalence]
	45	Aripiprazole	C, M
	53	Antipsychotic use (haloperidol, risperidone, olanzapine, aripiprazole)	B, C, O [functional status change]
	56	Olanzapine	C, M
	69	Olanzapine in patients who already were on haloperidol	C, M

(*Continued*)

Supplementary Table 4
Continued

Comparative Approach	Study Reference Number	Specific Comparison[a]	Study Outcomes[b]
	75	Haloperidol and lorazepam	B, C, D, M
	85	Haloperidol and midazolam combination	M, O [time to control of agitation]
	89	CAM screening	O [prevalence of documented delirium]
	97	Risperidone	B, C, M
	107	Initiation of corticosteroid treatment	A, O [severity of psychomotor disturbance]
	117	Opioid switch to fentanyl	B, C, I, O [functional status change]
	124	Systematic literature review study that included a study of olanzapine[56]	C
	126	CAM	H, O [acceptability and utility of screening procedure]
	128	CAM screening	H, O [burden of regular screening for staff and patients]
	133	Response to haloperidol	C, D, M, O [need to switch to a different antipsychotic]

Nu-DESC = Nursing Delirium Screening Scale[82]; CRS = Confusion Rating Scale[152]; MDAS = Memorial Delirium Assessment Scale[55]; RASS = Richmond Agitation-Sedation Scale[157]; DRS-Chinese version = Chinese version of the Delirium Rating Scale[158]; MMSE = Mini–Mental State Examination[159]; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition[146]; CAM = Confusion Assessment Method.[12]

[a]Guide to initials used in third column (specific comparison) in order of appearance.

[b]Coded study outcomes: A, new onset delirium; B, delirium reversal or nonreversal; C, delirium severity change other than reversal or nonreversal; D, death/survival; E, falls; F, length of inpatient stay; G, cost or incremental cost-effectiveness ratio; H, inconvenience/burden as defined by authors; I, proxy caregiver ratings of patient distress due to other symptoms; J, quality of life; K, family distress (as defined by authors); L, adverse events related to screening, diagnostic testing, risk prediction; M, adverse events related to therapy; N, palliative sedation required to control delirium; O, other outcomes.