A comparison of etiological and phenomenological profile across motor subtypes of delirium in a multi-site international database.

A comparison of etiological and phenomenological profile across motor subtypes of delirium in a multi-site international database.

By Dr Kevin Glynn

BA MSc BMBS MRCPsych MCPsychI

A Thesis submitted for the degree of Doctor of Medicine (MD)

School of Medicine, Faculty of Education and Health Sciences, University of Limerick

Supervisor: Dr John McFarland

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Declaration of originality

I, Kevin Glynn, hereby declare that all work contained within this thesis is my own work completed in conjunction with my supervisor, Dr John McFarland. Any collaboration within this research has been appropriately acknowledged and the co-authors are aware that I am submitting this information as part of a thesis to the University of Limerick. I have not already obtained a degree in University of Limerick or elsewhere on the basis of this work. All sources used and quoted from have been duly and appropriately lists as references in this thesis.

Signed:

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Student Number:

Date:

Acknowledgements

I would like to acknowledge the help and support of Prof David Meagher, who's enthusiasm for this subject is contagious. I would also like to acknowledge all of those researchers who have been involved in collecting and adding to this database over the past twelve years as part of research undertaken at the University of Limerick and affiliated universities and hospitals. I would like to mention in particular Maeve Leonard, who was instrumental in this research and sadly passed away in 2015. Thank you also to Dr Sandeep Grover and his colleagues, who collected data for the Indian part of this study. Lastly, I would like to thank Dr John McFarland, who kindly took over as my principal supervisor for the second year of this MD.

Thesis abstract

While the concept of delirium or acute confusional state dates back for centuries, it was first formally recognised under the heading of delirium in the Diagnostic and Statistical Manual (DSM III) third edition (1980). Previously it was denoted by more than thirty different syndromes, largely based on the clinical setting in which the symptoms occurred. Perhaps predictably, the amalgamation of what were once separate syndromes under the umbrella term of delirium led to considerable heterogeneity in terms of symptomatology, etiology, treatment and prognosis of this condition.

Despite an extensive amount of research conducted in this field since this time, there remain large gaps in our knowledge as to what causes delirium and how it should be managed. In an effort to account for the heterogeneity of delirium, while continuing to view it as a unitary syndrome, recent research has focused on breaking it down into distinct motor subtypes. These comprise three broad subtypes: Hyperactive, hypoactive and mixed delirium, based on the activity levels and level of agitation of the delirious patient. The success of this subtyping method has led to the inclusion of delirium motor subtypes as other specifiers of delirium in the fifth edition of the DSM (DSM V).

A key issue with research of delirium motor subtypes is that it has tended to take place in a particular clinical setting (e.g., Intensive Care Unit, Medical unit, Palliative care etc) making the generalisability of results more difficult. Studies comprising large samples and taking place in multiple clinical settings have so far been lacking. One of the aims of the current study is to conduct a comprehensive study of the etiology and phenomenology of delirium motor subtypes across a large sample of patients from different clinical settings and to look at how dementia affects the presentation of delirium motor subtypes across these settings. This is an important area that remains poorly understood and has clinical implications in terms of patient's management and prognosis.

Thesis Aims

1) To conduct a systematic review of studies of delirium motor subtypes.

2) To compare the etiology and phenomenology of delirium motor subtypes across a multicentre international study comprising multiple clinical settings.

3) To compare etiology, phenomenology and delirium motor subtype in patients which and without an underlying dementia in a multicentre, international sample.

Thesis overview

This thesis is centred around three interlocking papers related to delirium etiology, phenomenology and motor subtype. It uses a database collated by the author from several existing data sets compiled over a twelve-year period between 2008 and 2020. Research took place at clinical sites in both Ireland and India and was conducted across three clinical settings: palliative care, old age liaison psychiatry and general adult liaison psychiatry. All data gathered was subject to ethical approval, which was received by Limerick Regional Ethics Committee and the Research Ethics Committee in Postgraduate Institute for Medical Research (PGIMER) in Chandigarh, India. References are included at the end of each chapter. Note that because this thesis is broken down into separate papers, there may be repetition of some of the key concepts and assessments throughout.

Chapter 1 comprises a systematic review of papers related to delirium motor subtyping published during the time period from a previous comprehensive review by Meagher et al (2009) to the end of 2019. Overall, 45 studies were identified for inclusion using our criterion. The review focuses on core areas of research including etiology of delirium motor subtypes and whether this differs across clinic settings. Phenomenology and treatment of delirium motor subtypes are also discussed and areas of further research are identified.

Chapter 2 comprises a completed paper that was published in the BMJ Open in March 2021. The paper studies the differences in etiology and phenomenology of delirium motor subtypes across a large international sample (n=1757) from Ireland and India across multiple clinical settings. Associations between these variables are discussed and areas for future research are outlined. To the best of the author's knowledge, this is the largest study conducted on this topic to date and lends valuable insights into this highly clinically relevant area.

Chapter 3 comprises a completed paper that has been submitted for publication to the Journal of Psychosomatic Research. The paper is based around a smaller subset (n=992) of the original database used in the previous study which focuses on patients with delirium with and without an underlying dementia. The key aim of this study is to examine whether etiology, phenomenology and delirium motor subtype differ significantly in patients with delirium with and without an underlying dementia. This paper also comprises data from multiple clinical settings in India and Ireland.

The final discussion section of this thesis gives a brief overview of the research conducted and the reasons it was necessary and relevant to do so. The key findings of the research are outlined and are discussed in the context of previous research in this area. The clinical relevance and implications of this research is also discussed and areas for future research are explored.

List of abbreviations

ADS: Agitation Distress Scale

4 AT: Assessment Test for Delirium and Cognitive Impairment

CAM: Confusion Assessment Method

CAM ICU: Confusion Assessment Method Intensive Care version

CSS: Communication Capacity Scale

CTD: Cognitive Test for Dementia

DEC: Delirium Etiology Checklist

DMSS: Delirium Motor Subtype Scale

DRS R98: Delirium Rating Scale Revised 98

DMC: Delirium Motoric Checklist

DMSS 4: Delirium Motor Subtype Scale 4

DSM III: Diagnostic and Statistical Manual of Mental Disorders Third Edition

DSM IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

DSM IV TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Test Revision

DSM V: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

ICD 10: International Classification of Diseases, Tenth Edition

ICD 9 CM: International Classification of Diseases 9th Edition Clinical Modification

LOS: Length of Stay

MDAS: Memorial Delirium Assessment Scale

MoCA: Montreal Cognitive Assessment

MMSE: Mini Mental State Exam

Nu-DESC: Nursing Delirium Screening Scale

Neecham CT: Neecham Confusion Tool

K-DMSS: Delirium Motor Subtype Scale- Korean Version

K-DRS-R98: Delirium Rating Scale Revised 98 – Korean Version

KPS: Karnofsky scale of Performance Status

RASS: Richmond Agitation Sedation Scale

RASS-PAL: Richmond Agitation-Sedation Scale, Palliative version

S CAM: Short version of Confusion Assessment Method

Delirium Motor Subtypes: A systematic review.

Glynn K, McKenna F, McFarland J and Meagher D.

Introduction

Delirium is a complex and common neuropsychiatric condition, which presents with heterogenous symptomatology and a fluctuating course[1]. While previously described as a multitude of different conditions (ICU psychosis, toxic encephalopathy etc), these conditions were brought together under the umbrella term of Delirium in the DSM III[2], signalling that they account for the same condition in different settings and comprising varying presentations. Since this time, the heterogenous and fluctuating nature of delirium has made of its recognition and management a challenge for clinicians[3].

While recognition of heterogeneity in presentation of acutely confused patients goes back to the time of Hippocrates, who described both "lethargicus" (lethargy) and "phrenus"(frenzy), Lepowski (1982)[4] was the first to provide a definition of these phenomena in modern times. He described two main subtypes of delirium, hypoactive and hyperactive, based on the observed level of agitation and activity of the patient. He later added a third distinct mixed category to account for those who displayed a mix of both subtypes. This was expanded on by Liptzin and Levkoff (1992)[5], who added an operationalised definition of subtypes.

Since this time, however, this field of research has suffered from inconsistencies in how delirium subtypes are defined and measured [6,7]. This has been due, in a large part, to the fact that criteria and tools used to differentiate delirium motor subtypes often vary in the degree they focus primarily on motor vs other neuropsychiatric symptoms (e.g. hallucinations, delusions). In recent years, focusing purely on motor symptoms has emerged as the most promising method of differentiating these subtypes. This is reflected by the fact that delirium motor subtypes are now included as other specifiers for delirium in the DSM V[1].

Understanding how we should subtype delirium is important, as previous research has shown that delirium motor subtypes can differ in terms of their prognosis, etiology, treatment and management[6,8]. Those with hypoactive delirium are more likely to be missed completely or to be mistaken for depression or dementia, whereas hyperactive delirium is more likely to be mistaken for agitated depression, hypomania, or Behavioural or Psychiatric Symptoms of Dementia (BPSD)[3]. Hypoactive delirium can also be difficult to distinguish from stupor, especially following emergence from coma[9]. Therefore, recognising delirium motor subtypes has important implications in terms of patient care.

Meagher et al (2009)[6] conducted a comprehensive review of delirium motor subtypes, identifying a number of areas where further research was needed, including greater understanding of how etiologies shape the motor profile, the relationship between motor disturbance and other symptoms of delirium, and longitudinal studies to explore the stability of subtypes over time. They also highlighted the need for studies to have greater consistency in their defining of subtypes, and to better account for comorbidities such as dementia and the role of medication in delirium.

The key conclusions of this review are outlined below:

Key findings and recommendations from Meagher et al. (2009)[6]:

- Greater consistency is needed in subtype definition.
- The use of reliable and validated methods of assessment for delirium and its subtypes is fundamental to progressing our understanding of motor subtypes.
- There is a need to clarify the clinical features best suited for use as criteria for subtyping.
- There is a need to explore the concurrent validity of tools of assessment, as well as their inter-rater reliability when used by a variety of healthcare professionals across the range of treatment settings where delirium occurs.
- Studies need to account better for the role of medications, comorbid problems (especially dementia), and underlying etiological burden in shaping motor profile in delirium.
- The relationship of motor activity profile to arousal and vigilance remains poorly studied – it is possible that motor disturbances reflect the expression of acute cognitive disturbance in the context of differing levels of arousal.
- Longitudinal studies are needed to address the stability of subtypes over time. Such work can help our understanding of whether subtypes are distinct entities.

Aims of the current review:

- Conduct a systematic review of all literature of delirium motor subtypes in the ten-year period since Meagher et al's (2009) review.
- Identify areas where progress has been made since Meagher et al's 2009 and identify areas where further research is needed.

Methods

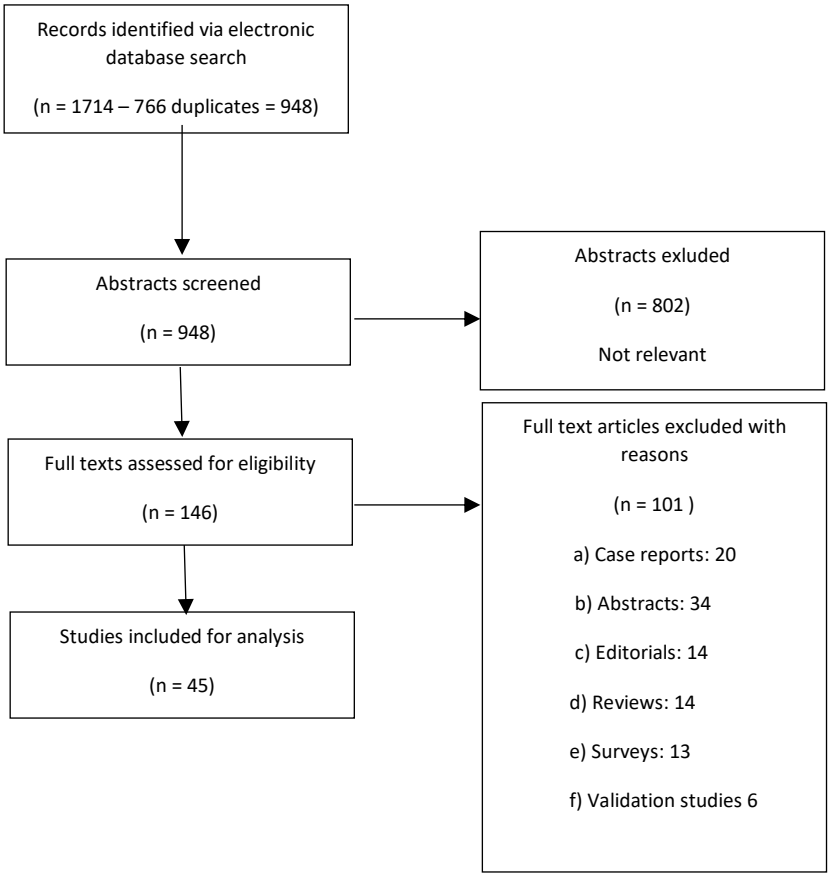
Search methodology

PRISMA guidelines for systematic review[10] were used for our literature search. The Medline, PsycINFO, EMBASE and Web of Science databases were searched in November 2019 using keywords 'delirium', 'confusion', 'disorientation', all of which were combined with 'motor subtype', 'motor subtypes', 'motoric', 'hypoactive', and 'hyperactive'. Papers were included if they were available in English and published since 2009. References of identified papers were also searched for further relevant papers.

Study Eligibility Criteria

The first author reviewed the titles and abstracts and appraised each article for inclusion before confirmation by the last author. Data collected included age demographic of sample, setting, method of delirium screening, number of participants, tools used to identify subtypes and outcomes. Discussion between authors helped to identify themes for structuring the review.

Figure 1: Flow diagram outlining study selection



Results

A total of 45 studies were included that met inclusion criteria for this review. Studies were broken down into four categories based on the clinical setting in which they took place: surgical, palliative care, medical/liaison psychiatry and Intensive Care. Table 1 outlines the population, delirium subtyping method and principal findings of the studies conducted in a surgical setting.

Table 1: Studies which took place in surgical settings.

Study	Subtyping method/pop	Principle findings
Maybrier 2019[11]	84 elderly post-surgery patients were followed up using CAM, RASS and wrist actigraphy.	Early postoperative wrist actigraphy metrics that serve as markers of sleep and wakefulness offer limited capacity as sole predictors or markers of hypoactive delirium
Bellelli 2018[12]	571 post operative hip fracture patients with 6- month follow up. Delirium diagnosed with DSM IV and subtypes using Lipowski's criteria.	Hyperactive and mixed subtypes were most common. The hypoactive and mixed group showed high mortality rates, with a significant risk of mortality associated with post operative delirium.
Hong and Park, 2018[13]	175 perioperative elderly orthopaedic patients assessed using the CAM and DSM IV TR.	39 patients were diagnosed with delirium. Hyperactive subtype was most common. Perioperative blood loss and hyponatraemia were found to be risk factors for hyperactive delirium.
Scholtens 2016[15]	76 Hip fracture patients with delirium, assessed using the DMSS and DRS R98.	Hyperactive subtype was most common initially. delirium motor subtype varied over time in 61.8% of patients.
Albrecht 2015[14]	139 Post operative hip fracture patients assessed using the CAMS and MDAS.	50% maintained subtype stability over time. Hypoactive was the most common subtype but was least likely to be documented by healthcare workers.
Slor 2013[16]	62 patients undergoing hip surgery, assessed using the CAM and DRS R98	Only 13.3% patients had a consistent motor subtype profile throughout the delirium episode. Of the patients with multiple days of delirium, hyperactive subtype was most common. Baseline characteristics and outcomes did not differ between the groups.
Osse 2008[17]	80 patients, 38 delirious and 32 control post-operative patients assessed using wrist-actigraphy as a tool. Patients were assessed using the CAM ICU.	32 controls and 38 delirious patients. Delirious patients showed lower mean activity in the first 24 hours than non-delirious controls.

CAM: Confusion Assessment Method, RASS: Richmond Agitation-Sedation Scale, MDAS: Memorial Delirium Assessment Scale, DRS-R98: Delirium Rating Scale Revised 98.

Overall, seven studies of delirium motor subtypes within a surgical setting were identified. Five of these studies were in elderly patients post hip fracture surgery[12-16], one study was conducted in patients post cardiac surgery[17] and one was of elderly patients where the type of surgery was not specified[11]. Patients were most frequently assessed using the Confusion Assessment Method (CAM), with one study using the Richmond Agitation-Sedation Scale (RASS)[11], one using the Memorial Delirium Assessment Scale (MDAS)[14] and two using the Delirium Rating Scale Revised (DRS-R98)[15,16]. Four of the studies found that hyperactive delirium was most common[12,13,15,16] and one study found that hypoactive was most common[14], where the other study did not specify this information[17]. Three of the studies showed that delirium motor subtype only stayed stable over time in 50% of less of the patients[14-16.]

Table 2: Studies which took place in palliative care settings.

Study	Subtyping method/pop	Principle findings
Okuyama et al. 2019[26]	2018 patients with advanced cancer, treated for hypoactive delirium. Delirium subtypes were assessed using the DMSS, DRS-R98, Nu-DESC, RASS-PAL CCS, ADS and assessed for adverse outcomes at T0: 0 T1: 3 and T4:7 days.	The most prevalent adverse event was sedation (9%). Delirium severity worsened after starting pharmacotherapy in 121 patients (56%) at T1. In patients whose death was expected within a few days and those with delirium caused by organ failure, symptoms of delirium were significantly more likely to deteriorate after starting pharmacotherapy.
Kim et al, 2015[20]	98 cases of delirium. Prospective cohort of terminally ill patients. Assessed using the DSM V and DRS R98.	The hypoactive and mixed subtypes of delirium were associated with shorter survival periods in terminally ill patients, and these associations interacted significantly with age
Kanbayashi et al, 2013[18]	182 consecutively admitted terminally ill cancer patients who died in a Japanese general hospital. Assessed using the DSM IV and MDAS.	Male sex, T-bilirubin, antibiotic therapy, NSAID therapy, and haematological malignancy are significant predictors for agitation severity of hyperactive delirium in terminally ill cancer patients in a general hospital setting.
Meagher 2012[19]	100 Consecutive cases of DSM-IV delirium in palliative care patients were assessed twice-weekly Assessed using the DMSS, DRS R98 and DEC.	Delirium Motor Subtypes were stable in 62% of cases. Motor subtypes occur in nearly all patients with full syndromal delirium and are often stable during an episode. Subtypes exhibited comparable levels of cognitive impairment but differed in non-cognitive symptoms
Leonard 2011[21]	100 consecutive cases of DSM IV delirium in a palliative care unit. Assessed using the DMC and DRS R98.	Hyperactive subtype was most common. The Mixed group had more severe delirium, with highest scores for DRS–R-98 sleep– wake cycle disturbance, hallucinations, delusions, and language abnormalities. Motor variants in delirium have similar cognitive profiles but differ in non-cognitive symptoms.
Meagher 2011[22]	100 Consecutive cases of DSM-IV delirium in palliative care patients were assessed twice-weekly. Assessed using the DMSS, DRS R98 and DEC.	Mean number of etiologies per case was 3.4±1.2. Hypoactive was the most common subtype. DRS-R98 Total and severity scales differed significantly across categories (highest in mixed) but only motor, sleep–wake cycle, perceptual and language disturbance items differed between subtypes.
Godfrey 2010[23]	40 palliative care patients, 30 with DSM-IV delirium measured over 24hrs with a discrete accelerometer-based activity monitor.	Clinical subtypes of delirium defined by observed motor behaviour on the ward differ in electronically measured activity levels, with hyperactive ad

	Assessed using the DMSS and DRS-R98.	mixed having the greater activity levels.
Godfrey 2010[24]	40 consecutive palliative care patients, 25 with DSM IV delirium. Assessed using 24-h accelerometer-based monitoring. Asssessed using the DMC, DRS-R98, MDAS and CTD.	Accelerometry-based measurement of a delirious cohort within a palliative setting is both a reliable and feasible method of continuous monitoring. Of the activities performed by the patients, periods of standing proved to be the most discriminatory in determining between each subtype
Godfrey 2009[25]	40 palliative care patients, 25 with DSM-IV delirium measured over 24h with a discrete accelerometer-based activity monitor. Assessed using the DRS-R98**,** MDAS and CTD.	The classification system was also implemented to successfully define other patient motoric subtypes. Motor subtypes of delirium defined by observed ward behaviour differ in electronically measured activity levels.

ADS: Agitation Distress Scale, CAM: Confusion Assessment Method, CSS: Communication Capacity Scale, CTD: Cognitive Test for Delirium, Diagnostic and Statistical Manual of Mental Disorders 4th edition, DMSS: Delirium Motor Subtype Scale, DEC: Delirium Etiology Checklist, Nu-DESC: Nursing Delirium Screening Scale RASS: Richmond Agitation-Sedation Scale, RASS-PAL: Richmond Agitation-Sedation Scale, Palliative version, MDAS: Memorial Delirium Assessment Scale, NSAID: Non-Steroidal Anti-inflammatory Drug. DRS-R98: Delirium Rating Scale Revised 98.

Nine studies were identified that took place in a palliative care setting. The Delirium Motoric Checklist (DMC)[21,24], the Delirium Motor Subtype Scale (DMSS)[19,22,23,26], the Delirium Rating Scale Revised 98 (DRS R98)[19-25] and the Memorial Delirium Assessment Scale (MDAS)[18,24,25] were the most common scales for identifying and subtyping delirium and studying its phenomenology. Hypoactive subtype was the most common subtype identified in these studies[20,22,24-26]. Longitudinal studies showed that there was a good level of stability of delirium motor subtypes over time[19,21]. Etiology and phenomenology of delirium motor subtypes were also investigated in several of these studies[18,19,21,22] (See table 2).

Table 3: Studies which took place in Medical/liaison psychiatry settings

Medical/Liaison patients		
Study	Subtyping method/pop	Principle findings
Zisper et al. 2019[48]	602 patients were managed for delirium over 20 days with the following strategies: supportive care alone or in combination with psychotropics, single, dual, or triple+ psychotropic regimens. Assessed using the DOS and S CAM.	Psychotic medications were used most commonly in mixed delirium, whereas patients on supportive treatment alone had the best outcomes.
Evensen, 2019[27]	60 patients over 75 years of age with DSM-5-delirium. Activity levels monitored over 24 hours using a wrist worn motor sensor. Assessed using the DMSS and DSM 5.	No differences in upright activity was observed between subtypes but hyperactive mixed groups had more wrist activity than the hypoactive group, indicating it may be a better way of assessing motor subtypes.
Evensen 2019[28]	311 patients over 75yrs of age admitted to acute geriatrics ward. Assessed using the DMSS and DSM 5.	93 patients had delirium. There were no significant differences in one-year mortality, length of stay or institutionalization across delirium motor subtypes in this group.
Pasinska et al 2019[29]	750 post-stroke patients, 203 diagnosed using DSM V and subtyped using DMSS 4. Patients screened on day 0-7 post admission.	Hypoactive was most common and hyperactive least common subtype. Cognitive impairment at the time of hospital admission and spatial neglect, among other factors, were identified as the best predictors for all delirium motor subtypes.
Yang et al. 2019[30]	95 delirious patients admitted to a stroke unit. DSM-5 criteria used. Patients were assessed twice weekly using K-DMSS and K-DRS-98 for 3 weeks.	Hyperactive subtype was most common. Mixed and hypoactive subtypes had longer durations and more severe symptoms of delirium Hypoactive subtype group had a significantly longer hospital stay than the other subtype groups.
Avelino-Silva 2018[31]	1409 admissions of acutely ill patients aged 60 and older Assessed using the CAMS and DI.	Hypoactive delirium was the most common subtype. Hypoactive and mixed delirium were independently associated with hospital mortality but delirium subtypes were not.
Gual 2018[32]	352 patients aged 65 and older admitted to a subacute care unit for 12 months. Assessed using the CAM and DMSS.	Worse preadmission functional status and higher comorbidity were associated with an increased risk of hypoactive delirium. Hypoactive delirium was associated with mortality compared with hyperactive delirium and mixed delirium.
Kim et al 2018[33]	224 delirium patients referred to psychiatry liaison service. Diagnosed using DSM IV TR and CAM. Assessed using the DMSS and RASS used for subtyping.	Hyperactive was most common and hypoactive least common. Hyperactive and mixed subtypes had greater mean RASS scores and greater fluctuation over a 24-hour period.

Adamis 2017[34]	119 Medicine for the elderly inpatients, 34 with delirium. Assessed using the CAMS, DRS-R98, MoCA.	Hypoactive subtype was associated with lower MoCA scores. No relationship was found between motor subtypes and mortality over a 1 year period.
Morandi 2017[35]	275 patients in a cross-sectional study. Assessed using the 4AT and DMSS.	Hypoactive the most common subtype. Atypical antipsychotics were associated with hypoactive delirium while intravenous lines were associated with mixed delirium.
Van Velthuijsen 2017[36]	407 older hospitalised patients with delirium. Assessed using the ICD 10 -clinical diagnosis. Chart reviews.	77% were hyperactive subtype. Significantly more patients with a hyperactive delirium received medication to manage their delirium than patients with a hypoactive delirium. No other significant differences between the subtypes were found.
Bellelli 2016[37]	1867 patients over 65 across 108 acute wards and 12 rehab wards. 429 patients had delirium. Cross sectional study. Assessed using the 4AT DMSS	Hypoactive was the most common subtype. Delirium was most common in neurology and geriatric settings. Several risk factors were associated with delirium diagnosis.
Park 2016[38]	210 delirious patients referred to a liaison psychiatry service. Assessed using the CAM and DRS R98.	Hyperactive was most common and associated with increased 3- month mortality. A multivariate analysis revealed that smoking cessation was an independent risk factor for hyperactive delirium
Kumar et al, 2015[39]	80 patients with delirium in medical and psychiatry wards. Diagnosed using DSM IV TR. MDAS was used for subtyping and MMSE for cognition.	Hyperactive was most common subtype and was associated with substance use disorders. The hypoactive subtype was more often found in patients with diagnoses of psychotic disorder, schizophrenia, and mood disorder; diabetes mellitus; and infection.
Boettger et al. 2014[49]	111 Patients treated for cancer were recruited. MDAS and KPS were recorded at baseline (T1), 2–3 days (T2) and 4–7 days (T3) and analyzed in respect to the subtypes of delirium and medication doses administered	In general, the response was comparable between the subtypes. However, patients with hyperactive delirium required higher doses of antipsychotics in order to achieve symptom control
Grover 2014[40]	321 patients referred to consultation liaison psychiatry service Assessed using the DRS R98 and DMSS.	Hyperactive delirium was the most common subtype. Significant differences were seen in the prevalence of perceptual disturbances, delusions, lability of affect, thought process abnormality, motor agitation and motor retardation across subtypes but no difference in cognitive symptoms.
De Crane 2012[41]	320 patients enrolled in the Delirium in Rural Long-Term Care Facilities Study, followed longitudinally for fall events for 12 months to assess no of falls. Assessed using the CAM, NEECHAM CT and MMSE.	The percentage of patients who fell was higher in all delirium subtypes than in non-cases at 12 months and was statistically significant for subsyndromal subjects.

Boettger 2011[42]	100 cancer patients with delirium. Assessed using the MDAS.	Perceptual disturbance was more common in hyperactive delirium. The prevalence of perceptual disturbances and delusions was correlated to attention and arousal but not to moderate to severe cognitive impairment.
De Crane 2011[43]	320 patients from Delirium Among the Elderly in Rural Long-Term Care Facilities Study. Assessed using the CAM, NEECHAM Scale, MMSE, (CAC-A, and Vigilance A instrument.	Risk ratios of mortality using "days of survival" did not reach statistical significance for any subgroup.
Lu et al 2011[47]	122 patients with an admission diagnosis of delirium with hyperactive symptoms and subsequently discharged from a secure unit. Assessed using the ICD 10 and RASS.	Significantly fewer patients with direct admission (n = 68) required physical restraint or chemical restraint compared with those transferred (n = 54). Patients admitted directly showed a higher discharge rate back home, shorter length of stay, shorter duration of delirium and a higher rate of recovery from delirium than transferred patients.
Han 2009[44]	303 patients presenting to ED, 25 with delirium. Assessed using the CAM ICU and RASS.	Hypoactive subtype was most common. 16 of the 25 delirious patients were not diagnosed by Emergency Department staff.
Sagawa 2009[45]	100 cancer patients referred to liaison psychiatry services with delirium. Assessed using the DSM IV TR and clinician rating.	Delirium improved in 56% of the patients after 1 week of standard treatment. The most frequent causes of delirium were opioids (29%), inflammation (27%), dehydration and/or sodium level abnormalities (15%).
Yang et al 2009[46]	441 older patients (age 65 and older) admitted with delirium in post-acute care. Assessed using the MDAS.	Among those with dementia (N=166), the hypoactive/mild class was associated with a higher risk of mortality. Among those without dementia (N=275), greater severity was associated with mortality, regardless of psychomotor features, when compared with the normal/mild class.

CAM: Confusion Assessment Method, CTD: Cognitive Test for Delirium, DOS: Delirium Observation Scale, DSM IV:, Diagnostic and Statistical Manual of Mental Disorders 4th edition, DMSS: Delirium Motor Subtype Scale, DEC: Delirium Etiology Checklist, DRS-R98: Delirium Rating Scale Revised 98. ICD 10: International Classification of Diseases 10th Edition, LOS: Length of stay, KPS: Karnofsky scale of Performance Status ,MDAS: Memorial Delirium Assessment Scale, MMSE: Mini-Mental State Exam, Neecham CT: Neecham Confusion Tool, RASS: Richmond Agitation-Sedation Scale. S CAM: Short version of Confusion Assessment Method.

Twenty-two studies were identified that took place in a medical setting. Eight of these studies used the Delirium Motor Subtype Scale (DMSS) for identifying delirium motor subtypes[27-30, 32,33,35,37,40,] , Three used the Memorial Delirium Assessment Scale (MDAS)[39.42, 46,49] The remaining studies used the Richmond Agitation Sedation Scale (RASS), Delirium Rating Scale (DRS R98) , DSM or clinical diagnosis, or other tools such as the delirium observation scale (DOS)[48]or the delirium index (DI)[31].

Table 4: Studies with took place Intensive Care Unit (ICU) settings

Study	Subtyping method/pop	Principle findings
Grover 2018[50]	66 patients ICU were screened daily for delirium using CAM ICU and diagnosed with DSM IV criteria. Assessed using the R98, MDAS and DMSS.	Hypoactive delirium was most common. Phenomenology of delirium in ICU setting is similar to that of the non-ICU settings. The factor analysis consistently demonstrated a three-factor solution, with a robust attention-arousal factor, and overlapping cognitive (core vs. non-core) motor factors.
Boettger 2017[51]	122 ICU patients with delirium. Assessed using the DMSS 4 and DRS R98.	Specificity was high across all subtypes (91.2–99.1%). The DMSS–4 yielded very sensitive ratings, particularly for hypoactive and hyperactive motor symptoms, and interrater agreement was excellent.
Lee 2017[52]	83 ICU patients. Assessed using the RASS and CAM ICU.	Hypoactive subtype was most common. Patients with pure hypoactive delirium had a similar risk of developing fast-track failure as other motor subtypes. Overall fast track failure more likely in those with delirium but no difference between subtypes.
Bui 2016[53]	1960 surgical ICU admissions screened using ICD 9 CM, CAM ICU, RASS.	ICD-9-CM codes yielded a low sensitivity for identifying patients with CAM-ICU positive delirium and were more likely to identify hyperactive/mixed delirium compared with hypoactive delirium.
Michaud 2015[54]	113 adults with documented hypoactive delirium during an ICU length of stay (LOS) of at least 72 hours. Assessed using theCAM ICU and RASS.	Treatment of hypoactive delirium with quetiapine was safe and reduced the duration of delirium compared with standard care alone.
Jayaswal et al, 2011[55]	220 ICU admissions, 88 developed delirium. Assessed using the CAM ICU and RASS.	Hypoactive delirium was the most common motor subtype and the detection rate of delirium was 12.5%.
Robinson 2011[56]	74 postoperative patients. Assessed using the CAM ICU and RASS used.	Patients with hypoactive delirium had higher 6-month mortality. Delirium-related adverse events occurred in 24.3% of patients with delirium; inadvertent tube or line removals occurred more frequently in the mixed group and sacral skin breakdown was more common in the hypoactive group.

CAM ICU: Confusion Assessment Method Intensive Care Unit, DSM IV: CTD: Cognitive Test for Delirium, DMSS: Delirium Motor Subtype Scale, DEC: Delirium Etiology Checklist, DRS-R98: Delirium Rating Scale Revised 98. ICD 9 CM: International Classification of Diseases 9th Edition Clinical Modification, MDAS: Memorial Delirium Assessment Scale, , RASS: Richmond Agitation-Sedation Scale

Seven studies of delirium motor subtypes in Intensive Care Unit (ICU) patients were identified for our review. Richmond Agitation Sedation Scale (RASS) was used for delirium motor subtyping in five of the studies[52-56], with the Delirium Motor Subtype Scale (DMSS)[50-51] used in the remaining two. Hypoactive delirium was the most common motor subtype identified in these studies (see table 4).

Discussion

Definition of delirium motor subtypes

It is clear from this review that there remains significant variation in how delirium motor subtypes are defined and diagnosed. The most frequently used scale to denote delirium motor subtypes in our review was the delirium motor subtype scale (DMSS), its precursor the delirium motoric checklist (DMC) or its abbreviated version, the DMSS-4. These scales were developed by Meagher and colleagues[3,6,7,19.] for the purpose of bringing consistency to the diagnosis of delirium motor subtypes. The scales focus mainly on core motor symptoms rather than other neuropsychiatric phenomena such as delusions and hallucinations. Several studies identified for this review[12-19,26,44.] used well established instruments for delirium detection and severity rating such as the RASS, MDAS and DRS-R98 which have not been designed or validated specifically for detecting delirium motor subtypes[7]. Because there are no set criteria for these scales, this leads to inconsistencies within the research[6].

The use of purely motor symptoms to measure delirium motor subtypes is backed up by several novel studies using motor tracking technology. Godfrey et al (2009, 2010, 2010a)[23-25] investigated delirium motor subtypes in a palliative care setting using an accelerometer-based monitor to see if the subtypes corresponded to actual levels of motor activity. They found that clinical subtypes of delirium, defined by the DMC, differ in electronically measured motor activity levels. They also concluded that accelerometry-based measurement is both a reliable and feasible method for continuous monitoring and that periods of standing proved to be the most discriminatory in determining between subtypes. Motor subtypes defined by observed ward behaviour also differed in electronically measured activity levels. In contrast, Evensen (2019)[27] found that there were no differences in upright activity between motor subtypes but mixed and hyperactive groups showed greater levels of activity on a wrist worn monitor. This may denote the fact that a patient may have hyperactive or mixed delirium even while their physical state means that they cannot stand or move around the ward. Overall, these novel studies using movement sensors suggest that measuring subtypes primarily by observing motor behaviour is an accurate and relatively straightforward way to categorise the patient's delirium.

Phenomenology of delirium motor subtypes

Phenomenology of delirium motor subtypes can be broadly broken down into two groups of symptoms : cognitive symptoms such as attention, visuospatial ability, short- and long-term memory and language and non-cognitive symptoms such as delusions and hallucinations, altered sleep-wake cycle, degree of agitation and psychomotor retardation or hyperactivity[3]. The principal scales used for measuring the phenomenology of delirium motor subtypes identified in this review were the Delirium Rating Scale Revised 98 (DRS R98) and the Memorial Delirium Assessment Scale (MDAS).

Several studies found that delirium motor subtypes did not differ significantly on cognitive items but did so on non-cognitive neuropsychiatric symptoms as described above. In their longitudinal study of delirium in palliative care patients, Meagher et al (2011, 2012)[19,22] followed up delirious patients twice per week. They found that delirium motor subtypes remain stable in 62% of cases and that delirium

motor subtypes differed on non-cognitive but not on cognitive items on the DRS R98. However, this level of stability of subtypes over time has been challenged by other studies which have showed much less concordance in other clinical populations[12]. Perhaps unsurprisingly, the mixed motor subtype was the most severe in terms of symptomatology, as it requires the criteria from both hyperactive and hypoactive subtypes to be met to be diagnosed. While scores were greater for the mixed motor subtype, there was no significant difference in symptoms such as delusions and hallucinations or altered sleep wake cycle between the hyperactive and hypoactive groups. This also concurs with a study done by Leonard et al (2011)[21] which found that the mixed motor subtype group had more severe delirium, with highest scores for DRS–R-98 sleep–wake cycle disturbance, hallucinations, delusions, and language abnormalities. Neither the total Cognitive Test for Delirium nor its five neuropsychological domains differed across Hyperactive, Mixed, and Hypoactive motor groups. These findings were supported by Grover et al (2014)[40], who also found no difference in terms of cognitive symptoms but that mixed motor subtype scored significantly greater on non-cognitive items such as delusions and hallucinations and altered sleep wake cycle. Further work by Grover and colleagues[50]found that delirium had a similar phenomenological profile when occuring in an ICU setting but did not investigate differences across delirium motor subtypes.

Boettger and Brietbart (2011)[42] used the Memorial Delirium Assessment Scale (MDAS) to measure phenomenology in one hundred cancer patients with delirium. Significant differences were found between hyperactive and hypoactive subtypes of delirium for the presence and severity of perceptual disturbances and delusions; with perceptual disturbances (e.g., hallucinations) and delusions being significantly more prevalent in hyperactive than in hypoactive delirium. There were no significant differences between hyperactive and hypoactive subtypes of delirium in respect to the severity of arousal disturbance, disorientation, short-term memory impairment, attention/concentration deficits, disorganization, and sleep–wake cycle disturbance. This reinforces the view that cognition does not differ between delirium motor subtypes but they may differ in non-cognitive neuropsychiatric symptoms such as delusions and hallucinations.

It is clear from this research that delirium motor subtypes share common cognitive symptoms in line with the unitary syndrome of delirium. It must be noted that detailed cognitive assessment is also difficult to ascertain in delirious patients who are, by definition, inattentive. Neither the DRS R98 nor the MDAS or other delirium assessment tools can be said to provide detailed cognitive assessment. The fact that delusions and hallucinations are common in hypoactive delirium, with some research showing that there is no significant different in their presence or severity compared to the hyperactive delirium subtype, is important to note from a clinical perspective, given that these patients are often not identified or misdiagnosed in a clinical setting. The fact that these patients are less agitated means that they may not come to the attention of staff to a level of those with hyperactive or mixed delirium. Several studies identified in this review also point to the fact that they have the highest mortality rates[12,19,22] of the delirium motor subtypes and it is therefore important that they are identified and managed in the optimal way to lessen their risk of morbidity or mortality.

Etiology of delirium motor subtypes

Establishing the etiology of delirium is challenging, as its causes are usually multifactorial in nature and can involve the interplay between a wide variety of predisposing and precipitating factors[9]. Studying delirium etiology is further complicated by the fact that it may differ depending on the clinical setting. It is important that we understand the etiological underpinnings of delirium, as several of these are modifiable and their treatment leads to improved morbidity and mortality.

Despite the importance of understanding the risk factors and underlying etiologies of delirium, relatively few studies have looked at whether etiologies differ between the delirium motor subtypes. Hyperactive delirium has been associated with substance abuse and withdrawal. Park et al (2016)[38] found that hyperactive delirium was most associated with smoking cessation, while Kumar et al (2015)[39] found it to be most associated with substance use disorders. Hong and Park (2018)[13] also found that perioperative blood loss and hyponatraemia were risk factors for hyperactive delirium in a surgical population.

Other studies did not find any significant difference in etiological underpinning of delirium motor subtypes. Meagher et al (2011)[22] used the Delirium Etiology Checklist in their study of 100 consecutive palliative care patients. This comprises a thirteen- item checklist of common delirium etiologies. They found that multiple etiologies (mean; 3.4, SD=1.2). were present in most cases of delirium and that drug intoxication, metabolic disturbances, systemic infection and systemic neoplasm were the most common. They did not find any significant association between etiology and delirium motor subtype. Likewise, Sagawa et al (2009)[45] found that opiods, inflammation, dehydration and/or sodium abnormalities were the most frequent causes of delirium among 100 cancer patients. They also did not find any association between motor subtype and etiology. In contrast, Kanbayashi et al (2013)[18], found that male sex, t-billirublin, antiobiotic therapy, NSAID therapy and hematological malignancy were significant predictors of agitation severity in terminally ill cancer patients.

Overall, however, this review shows that there is a lack of research on the relationship, if any, between etiology and delirium motor subtype. This is important as preventable risk factors may be identified or healthcare professsionals may be more vigilant of delirium (for example hypoactive delirium) if it is known to be associated with a particular risk factor which the patient has. The fact that different delirium motor subtypes may be more prevalent in different clinical settings suggests that etiologies may indeed differ across delirium motor subtypes and it is clear that further research, ideally encompassing a range of clinical settings and populations, is needed in this area.

Clinical significance of delirium motor subtypes

It is clear from this review that different delirium motor subtypes are more common in different clinical settings. The hypoactive delirium motor subtype is more common across medical, ICU and palliative populations, with hyperactive delirium more frequently occurring in surgical settings. This is broadly in line with previous research[3,8,9], which shows that hypoactive delirium tends to be most common but also under detected among hospital patients. This has been a significant area of concern as it is also associated with the highest risk of mortality[19,22] and has raised the question as to whether better detection would lead to improved outcomes in this group.

The largest post-surgery study was conducted by Bellelli and colleagues (2018)[12], who studied 571 post op elderly hip fracture patients daily post-surgery and at 6 months to determine 6-month mortality. They found that patients with hypoactive delirium had the highest 6-month mortality rate, followed by mixed and hyperactive subtypes. They also found that hyperactive delirium was the most common subtype overall in this population.

In studies of palliative care populations, hypoactive delirium was most common and was associated with decreased survival time compared to hyperactive and mixed motor subtypes. Meagher and colleagues (2011, 2012)[19,,22] and Leonard et al (2011)[21] found that mixed delirium carried the greatest symptoms burden in terms of DRS-R98 severity ratings on symptoms such as sleep wake cycle disturbance, hallucinations, delusions and language abnormalities. This was supported by Zisper at

al[48,] who found that the mixed motor subtype was more severe and persistent than other subtypes across a medical population.

Seven studies from this review took place in ICU settings[49-56]. They found, similar to medical and palliative populations, that the hypoactive delirium motor subtype was most common. In terms of adverse clinical outcomes, Robinson et al (2011)[56] found that delirium adverse related events such as tube and line removals occurred most frequently in the mixed delirium group, with sacral skin breakdown more common in the hypoactive group.

Overall, there remains a lack of research of delirium motor subtypes within the ICU setting, in particular as this is a patient population with a high prevalence of delirium. It is clear that more work needs to be done in exploring the clinical significance of delirium motor subtypes in different clinical settings and how these presentations and prognosis are affected by underlying etiologies such as infection, severity of illness and treatment used.

Treatment of delirium motor subtypes

Treatment of delirium generally focused on pharmacological and non-pharmacological measures. There has also been a focus in identifying risk factors and contributory etiologies such as older age, cognitive impairment, hip fracture, infection etc and on preventative measures such as adequate hydration, providing adequate lighting and a clock, talking to the person to reorientate them and regular visits from family and friends who are familiar with them. Treatment of underlying etiologies such as infection, constipation, pain and removing medication such as steroids that may be contributory remains key in the management of delirium (NICE 2019). Low dose antipsychotics such as haloperidol or quetiapine are also used, although research is mixed on how effective they are at treating symptoms or reducing the duration of delirium.

Few studies have looked at the responses of the different delirium motor subtypes to treatment. Zipser et al (2019)[48] conducted an observational cohort study of 602 hospital patients with delirium diagnosed using the Confusion Assessment Method (CAM) and the Delirium Observation Screening Scale (DOS). They were managed with either supportive care alone or in combination with psychotropics, single, dual, or triple+ psychotropic regimens and followed up for twenty days. Consistent with previous research, they found that mixed delirium more likely to receive psychotropic medication. They found that those on supportive care only benefited most from their treatment and that hyperactive delirium subtypes responded best to treatment.

Other, smaller studies, showed little evidence of a difference in response to treatment between the delirium motor subtypes. Boettger et al (2014)[49] found that, while higher doses of antipsychotics were required in patients with hyperactive delirium due to their level of agitation, they found that overall delirium resolved at similar rates among the delirium motor subtypes. They concluded that the delirium course was complicated by factors such as the severity of medical illness, level of pre-existing cognitive impairment and premorbid level of functioning. Likewise, in a small open label study of 32 patients, Boettger et al (2011)[42] concluded that risperidone and haloperidol may be equally effective in the treatment of delirium. Michaud et al (2015)[54] also found that quetiapine reduced the duration of hypoactive delirium in an ICU setting compared to standard care alone. In contrast, Okuyama et al (2019)[26] found that pharmacotherapy actually worsened symptoms of hypoactive delirium in advanced cancer patients and recommended against its use.

Overall, there appears to be limited evidence currently available to suggest that delirium motor subtypes differ in their response to treatment or should be treated differently. This is complicated by the fact that large scale trials of treatment are difficult to conduct on this population and there are a wide range of contributory factors to the patient's treatment prognosis. Patients with mixed and hyperactive delirium tend to receive antipsychotics more frequently due to their level of agitation and severity of their symptoms, whereas those with hypoactive delirium have poorer prognosis. However, it is currently unclear whether hypoactive delirium benefits from antipsychotic treatment. Further research is needed in this area.

Conclusions

This review aimed to investigate the progress in this field since the Meagher et al. (2009)[6] review ten years ago. Overall, there were forty-five studies identified for this review. Consistency of diagnosis of delirium motor subtypes has improved, with a number of studies using the same scales and their addition as other specifiers in the DSM V adding to their increasing recognition. There were also several longitudinal studies, which are beneficial as delirium is known by definition to follow a fluctuating course.

Because of the volume of research, studies were broken down into different clinical settings, with ICU, surgical, medical and palliative care identified. There were also studies identified that examined whether any treatment differences existed between the delirium motor subtypes. It was clear from our review that certain subtypes appear to be more prevalent in particular clinical settings. Patients in ICU and palliative care settings appear to be more likely to have hypoactive delirium, whereas hyperactive is more common in patients recovering from surgery. This raises the question as to whether the etiologies in these settings are having a significant impact on delirium motor subtype. For example, patients in ICU are more physically unwell, with a greater degree of comorbidities and medications than those in a general medical setting.

Studies examining the phenomenology of delirium motor subtypes suggest that they do not differ in underlying cognitive features, although detailed cognitive examination is challenging in this patient cohort. As expected, they differ in level of motor activity but results on whether psychotic symptoms differ remain mixed. Mixed delirium is rated highest in terms of symptomatology as it requires the key features of both hypoactive and hyperactive to be present and, along with the hyperactive motor subtype, are more likely to be treated with antipsychotics.

Overall, while progress has been made, it remains clear that there is a lack of consistency in how delirium motor subtypes are diagnosed. Perhaps the DSM V was a missed opportunity for a gold standard definition to add more clarity to this complex area.

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Chapter 2: How do delirium motor subtypes differ in phenomenology and contributory etiology? A cross-sectional, multi-site study of liaison psychiatry and palliative care patients.

Glynn K[1], McKenna F[1,2], Lally K[1,2], O'Donnell M[1], Grover S[3], Chakrabarti S[3], Avasthi A[3], Mattoo SK[3], , Sharma A[3], Ghosh A[3], ,Shah R[3], Hickey, D[1] ,Fitzgerald J[4], Davis, B[2], O'Regan N[2], Adamis D[2,6], Williams O[2], Awan F[2], Dunne CP[2], Cullen W[2], McInerney S[7], McFarland J[2,8], Jabbar F[10], O'Connell H[2], , Trzepacz PT[5], Leonard M[1,2], Meagher D[1,2].

1. Dept of Psychiatry, University Hospital Limerick
2. Cognitive Impairment Research Group, Graduate Entry Medical School, University of Limerick, Limerick, Ireland
3. Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
4. Department of Psychiatry, University of Cambridge School of Clinical Medicine, Cambridge Biomedical Campus, Cambridge, UK.
5. School of Medicine, Indiana University, Indianapolis, IN
6. Milford Hospice Palliative Care Centre, Limerick, Ireland
7. St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
6. Sligo Mental Health Services, Ballytivan, Sligo, Ireland
9. Department of Acute Psychiatry, Midwestern Regional Hospital, Ennis, Clare,Ireland.
10. Psychiatry for Later Life Service, University College Hospital, Galway, Ireland

Corresponding author: Kevin Glynn, email: glynnkevin@hotmail.com

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Abstract

Objectives: To investigate whether delirium motor subtypes differ in terms of phenomenology and contributory etiology.
Design: Cross sectional study
Setting: International study incorporating data from Ireland and India across palliative care, old age liaison psychiatry and general adult liaison psychiatry settings.
Participants: 1757 patients diagnosed with DSM IV delirium.
Primary and secondary outcome measures: Hyperactive, mixed and hypoactive delirium subtypes were identified using the abbreviated version of the Delirium Motor Subtype Scale (DMSS-4). Phenomenology was assessed using the Delirium Rating Scale Revised (DRS-R98). Contributory etiologies were assessed using the Delirium Etiology Checklist (DEC), with a score >2 indicating that the etiology was likely or definitely contributory.
Results: Hypoactive delirium was associated with dementia, cerebrovascular and systemic infection etiologies (P<.001) and had a lower overall burden of delirium symptoms than the other motor subtypes. Hyperactive delirium was associated with younger age, drug withdrawal and the DEC category other systemic etiologies (p<0.001). Mixed delirium showed the greatest symptom burden and was more often associated with drug intoxication and metabolic disturbance (p<0.001). All three delirium motor subtypes had similar levels of impairment in attention and visuospatial functioning but differed significantly when compared to no subtype (p<0.001).
Conclusions: This study indicates a pattern of etiology and symptomatology of delirium motor subtypes across a large international sample that had previously been lacking. It serves to improve our understanding of this complex condition and has implications in terms of early detection and management of delirium.

Strengths and Limitations of this study

- This study comprised an international database with a large sample size.
- Patients from palliative care, old age liaison psychiatry and general adult liaison psychiatry populations were included.
- Instruments used to determine delirium motor subtypes and symptomatology have been widely validated across different populations and clinical settings.
- Limitations include the fact that this study provides a broad overview in terms of contributory etiologies and further research is needed to investigate more specific etiological findings.

Introduction

Delirium is a common neuropsychiatric condition that is independently associated with significantly increased morbidity and mortality[1]. It is viewed as a unitary cognitive syndrome that is characterised by a heterogenous neuropsychiatric presentation and fluctuating course[2]. Despite its importance in terms of prognosis, it often goes undiagnosed or undetected in busy clinical settings[3]. This represents a significant issue in terms of patient care, particularly since delirium frequently represents a reversible condition and therefore its early detection and management is vital.

The different motor presentations of delirium are an important factor in complicating its diagnosis and treatment and have become the focus of efforts to improve our understanding of this complex condition. Lipowski (1982)[4] developed the concept of delirium motor subtypes in the modern era whereby he proposed two main subtypes of delirium, hypoactive and hyperactive, and later added a third distinct mixed category[5] . This was expanded on by Liptzin and Levkoff (1992)[6], who added an operationalised definition of subtypes. While issues with criteria and definitions used initially led to a lack of consistency in diagnosis between studies[7-9], focusing on purely motor rather than neuropsychiatric symptoms has emerged as the most established method of categorisation of subtypes[10-11]. This is supported by studies that have demonstrated that these subtypes can be distinguished bioelectronically by using motion analysis, can be identified as distinct categories using latent class analysis and are generally stable over time[12-14].

Studies have demonstrated that delirium motor subtypes differ in terms of their symptomatology, severity and outcomes[10-14]. Hypoactive delirium has been associated with increased risk of mortality [15-18]. However, it is unclear to what extent this is confounded by the relationship between hypoactive presentation and factors such as burden of comorbidity and medication exposure since many of these studies have taken place in a palliative care setting. In addition, patients with hypoactive presentations are typically detected later and frequently misdiagnosed as depression, with important implications for patient management and prognosis[19]. In contrast, patients with hyperactive or mixed delirium are more likely to receive antipsychotic medications and their delirium is more likely to be reversible[20]. It is therefore important that delirium motor subtypes are accurately recognised in clinical practice.

Understanding symptomatology of delirium motor subtypes can help aid in their recognition. Studies to date have generally indicated that hyperactive delirium tends to present more often with symptoms of perceptual disturbance, delusions, lability of affect and motor agitation[21] and that thought process abnormalities and motor retardation are more associated with the hypoactive subtype[22]. Some research has shown that mixed subtype is most severe in terms of having a greater burden of symptomatology with high levels of perceptual disturbance, delusions, lability of affect, and both motor agitation and motor retardation[22]. Cognitive impairment is generally similar across subtypes but findings have varied[23]. However, thus far studies have been hampered by being confined to a particular clinical setting with a paucity of large-scale research to confirm their findings.

Another key question is whether delirium motor subtypes differ in terms of their causation. Delirium reflects the interaction between a variety of predisposing factors (e.g. age, pre-existing CNS pathology) with precipitating insults (e.g. physical illness, medication exposure, medical interventions) that result in the emergence of syndromal delirium. The etiological underpinnings of delirium are thus complex and multifaceted, with typically 3-4 contributory etiologies per episode[20]. Identifying contributory etiologies to different delirium motor subtypes is important, as the primary treatment of

delirium involves treating its underlying causes. Identifying underlying causes may also help in the prevention of delirium, with a knock-on effect in terms of patient morbidity and mortality.

Despite its importance, the relationship between different contributory etiologies and delirium motor subtype remains unclear. Some evidence indicates that certain etiologies such as metabolic factors or organ failure are more common in hypoactive delirium, with substance intoxication and withdrawal more typically associated with the hyperactive subtype[24-27]. However, other studies have failed to replicate these findings[20,28] and a suitably designed study (e.g. sufficiently powered) to explore the relationship between the many different categories of etiology and delirium subtype profile has been lacking.

The aim of the current study is to compare delirium motor subtypes in terms of etiology, phenomenology and symptom severity using a large international database derived from studies conducted across a variety of different clinical populations and settings.

Methods

Patient and public involvement

No patient involvement.

Subjects and design

This study used a combined dataset of existing related databases from two countries, Ireland[20, 29-34] and India[35-43]. All research took place between 2008 and 2020 inclusive. Raters for data included in this study were trained by an expert with over twenty years' experience in the field of delirium research (DM), through training workshops in both Ireland and India using well validated assessment methods for these clinical populations as outlined below.
Research was conducted across three clinical settings: palliative care, old age liaison psychiatry and general adult liaison psychiatry.

Palliative care

This group consisted of consecutive referrals to a liaison psychiatry service in a hospice setting that were subsequently diagnosed as having delirium at the time of assessment. Research took place at Milford Hospice in Limerick, Ireland[30-33].

Old Age Community Liaison Psychiatry

This group consisted of consecutive referrals to Old Age CL Psychiatry services in two Irish Hospitals; University Hospital Limerick and University Hospital Galway, who were diagnosed with delirium at the time of assessment[20, 33-34].

General Adult CL Psychiatry

This group consisted of consecutive referrals to a General Adult CL Psychiatry service at the Postgraduate Institute for Medical Research (PGIMER) in Chandigarh, India who were diagnosed with Delirium at the time of assessment[35-43].

Assessment

Delirium diagnosis

Delirium was diagnosed by the psychiatric teams according to DSM-IV[44] criteria using all available clinical information including patient assessment and collateral information from nursing staff, family and the patient's medical records.

Dementia diagnosis

Dementia status was determined according to (i) a pre-existing diagnosis, or (ii) on the basis of detailed history and examination taking in aspects such as the patient's functional ability, neuroimaging and cognitive decline prior to assessment and was made in accordance with DSM IV. Cognitive decline prior to assessment was assessed using the Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)[45], which was administered to the patient's next of kin or main carer.

The IQCODE comprises a 16-item informant questionnaire comparing the individual's ability on day-to-day items with their performance ten years ago. Items are scored by the rater from 1 =much improved, 3 unchanged to 5=much worse. Items include aspects of daily life such as the ability to remember conversations that happened the previous day, address and telephone numbers and where things are kept. Scores are added up and divided by the total number of questions (n=16). The resultant score ranges from 1-5. All databases in this analysis that used the IQCODE score to aid in dementia diagnosis used a cut off of ≥3.5 to signify likely dementia. This was then combined with all relevant clinical information to make a diagnosis.

Delirium motor subtypes

Delirium Motor subtypes were differentiated using the abbreviated version of the Delirium Motor Subtype scale (DMSS-4)[11]. The DMSS-4 was developed from the longer, 13 item, Delirium Motor Subtype Scale (DMSS)[46] using latent class analysis to show the four symptoms that best differentiated the subtypes from the original DMSS[11]. It comprises two items denoting hyperactivity (increased activity and loss of control of activity) and two items denoting hypoactivity (decreased speed of actions and decreased amount of speech), with mixed subtype defined as the presence of both hyperactive and hypoactive criteria over the previous 24-hour period. No subtype describes a presentation in which neither the criteria for hyperactive nor hypoactive delirium are fulfilled. The DMSS-4 was developed for quick and accurate identification of delirium motor subtype in busy clinical practice and has shown a good concordance with the original DMSS and has been widely validated across a variety of populations and clinical settings [11, 29,30, 34,35].

Etiology

Contributory etiologies were identified using the Delirium Etiology Checklist (DEC)[47]. The DEC is a 13-item checklist that is designed to document the etiological underpinnings contributing to a delirium episode. Its thirteen categories are: drug intoxication, drug withdrawal, metabolic/endocrine disturbance, traumatic brain injury, seizures, infection (intracranial), infection (systemic), neoplasm (intracranial), neoplasm (systemic), cerebrovascular, organ insufficiency, other CNS and other systemic. Other CNS includes neurological conditions such as Parkinson's disease and Multiple

Sclerosis while other systemic includes conditions such as post-operative state, immunosuppression or heat stroke. These categories are present to allow the rater to list contributory etiologies that do not fit under the other 11 items.

Each etiology is rated on a scale according to its likelihood of being contributory to the delirium. This scale ranges from 0= ruled out/not present/not relevant to 4= definite cause. Raters can therefore document multiple etiologies and their level of contribution to a particular episode of delirium. For the purposes of this study, DEC items were broken down into two categories: non-contributory (score 0-2) and possibly/probably contributory (scores of 3 or 4). This also allowed for the total and mean number of likely contributory etiologies to be calculated and compared between delirium motor subtypes.

Delirium symptomatology and severity

Delirium severity and symptomatology were measured using the Delirium Rating Scale Revised-98 (DRS R98)[48]. The DRS-R98 is a 16-item clinician rated scale used to rate the severity of delirium both overall and on a broad range of neuropsychiatric and cognitive symptoms. It is made up of 13 severity items and 3 diagnostic items. Each item is rated 0 (absent/normal) to 3 (severe impairment), with descriptors attached to each severity level. The severity scale (items 1-13) range from a score or 0-39 with larger scores indicating more severe delirium. A score of over 15 points typically indicates delirium and 18 points indicates delirium when dementia is present. The DRS-R98 can be divided into non-cognitive (items 1-8) and cognitive (9-13) subscales based on construct validity. It has been validated across clinical settings and has been shown to have a high interrater reliability, sensitivity and specificity at detecting delirium. It has also been used to determine differing symptomatology and severity across delirium motor subtypes[10,12].

Ethical approval

Because of the non-invasive nature of the study, approval was given by the Limerick Regional Ethics Committee, Ireland (REC 100/12) to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical Research involving human subjects. All of the Indian studies were approved by the PGIMER Ethics Review Committee (Int/IEC/2015/659, Int/IEC/2017/690, Int/IEC/2015/229). Written consent was obtained from the primary caregivers of the patients and patients themselves wherever possible in accordance with the Helsinki Guidelines for Medical Research involving human subjects.

Statistical analysis

Patients with missing data for any of the variables being examined were excluded from our final analysis. Continuous normally distributed variables are reported as means and standard deviation, while categorical variables are reported as counts and percentages. Normally distributed data were analysed using Anova, whereas non-parametric and categorical data were compared using Kruskal Wallis and chi-square tests, respectively. Standardised adjusted residuals were used for post-hoc analysis of chi-square tests, with a level of greater than 1.96 (2.0 is used by convention) used to indicate statistical significance[49]. Dunn multiple comparison test was used for post-hoc analysis of the Kruskal Wallis test, while the Bonferroni procedure was used during post hoc analysis for ANOVA. Statistical analysis was conducted using the SPSS v25 package.

Results

Patient demographics and dementia status.

The total number of subjects after excluding missing data (n=176) was 1757. They comprised 1124 (64%) males and 633(36%) females. This included 263 patients from palliative care, 287 from old age liaison psychiatry and 1207 from general adult liaison psychiatry. Dementia status was listed in 1685 (98%) cases and marked as unknown or not listed in 72 cases. The number of patients diagnosed with comorbid dementia was 252 (15%). A breakdown of the datasets used is outlined in table 1.

Table 1: Demographic and clinical Data for overall population and subpopulations

	Total Sample (n=1757)	**Palliative care (n=263)**	**Old Age Liaison Psychiatry (n=287)**	**General Adult Liaison Psychiatry (n=1207)**	**P-Value**
Age (Mean, SD)	56.6 (20.3)	70.7 (11.3)	79.6 (8)	48.1 (17.8)	<.001
Sex (%Female)	632 (36%)	126 (48%)	139 (48%)	366 (30.3%)	<.001
Dementia (Total, %)	252 (14%)	73 (28%)	161 (56%)	18 (.01%)	<.001
Hypoactive (Total,%)	298 (17%)	74 (28%)	94 (33%)	130 (11%)	<.001
Mixed (Total, %)	426 (24%)	79 (30%)	54 (19%)	293 (24%)	<.001
Hyperactive (Total,%)	844 (48%)	70 (27%)	82 (29%)	692 (57%)	<.001
No subtype (Total, %)	189 (11%)	40 (15%)	57 (20%)	92 (8%)	<.001
DRS-R98 Total (Mean, SD)	23.8 (7.4)	20.3 (7.1)	23.4 (7)	24.7 (7.4)	<.001
DRS-R98 Severity (Mean, SD)	18.4 (6.7)	16.1 (6.5)	18.9 (6.6)	18.8 (6.6)	<.001
DRS-R98 Cog (Mean, SD)	8.6 (3.4)	8.5 (3.3)	9.3 (3)	8.4 (3.6)	<.001
DRS-R98 Non-cog (Mean, SD)	9.8 (4.2)	7.6 (4.3)	9.6 (4.8)	10.4 (3.9)	<.001
Total Etiologies (Mean, SD)	2.3 (1.1)	2.9 (1.4)	2.2 (1.2)	2.2 (1.1)	<.001

DRS R-98= Delirium Rating Scale Revised, DRS R98 Cog = Delirium Rating Scale Revised Cognition score (items 9-13), DRS R98 Non-Cog = Delirium Rating Scale Revised non-cognitive (Items 1-8), Hypoactive=Hypoactive delirium, Mixed= Mixed delirium, Hyperactive= Hyperactive delirium, No Subtype= No delirium motor subtype.

As can be seen from table 1, significant differences exist across the databases on all parameters analysed. Old Age Liaison Psychiatry were the oldest group and had the greatest proportion of patients with co-morbid dementia, while General Adult Liaison Psychiatry were youngest and had the highest overall scores on the DRS-R98. The Palliative care group had a significantly greater number of contributory etiologies than the other groups.

Table 2: Demographic information and clinical setting of delirium motor subtypes

	Hypoactive (n=298)	**Mixed (N=426)**	**Hyperactive (N=844)**	**No subtype (N=189)**	**P-value**
Age (mean, SD)	68.6 (18)	55.5 (20.7)	52.3 (19.3)	68.6 (17.7)	<.001
Dementia yes/no **Adj. residual value**	82/216 6.3/-6.3	46/341 -1..3/1.3	82/732 -5.9/5.9	42/145 3.4/-3.4	<.001
Male/female **Adj. residual value**	159/139 -4.8/4.8	260/166 -1.6/1.6	594/249 5.8/-5.8	111/78 -1.5/1.5	<.001
Palliative care **Adj. Residual value**	74 5.2	79 2.4	70 -7.5	40 2.5	<.001
Old Age Psych **Adj. Residual value**	94 7.8	54 -2.3	82 -7.2	57 5.4	<.001
General Adult Psych **Adj.Residual value**	130 -10.2	293 .0	692 11.6	92 -6.2	<.001

Hypoactive=Hypoactive delirium, Mixed=Mixed Delirium, Hyperactive=Hyperactive delirium, DF= Degrees of freedom, P-Value is significant at <0.01. SD=Standard Deviation, Adj. Residual value= Adjusted Residual Value.

Table 2 indicates that there were significant differences in mean age between the delirium motor subtypes, with hyperactive significantly younger and hypoactive significantly older. Hypoactive and no subtype were significantly associated with positive dementia status, female gender and Palliative care and Old Age Liaison Psychiatry settings. In contrast, hyperactive delirium was significantly associated with negative dementia status, male gender and had a greater proportion of cases in General Adult Liaison Psychiatry setting. Mixed delirium did not show any relationship to either gender or dementia status but was significantly associated with the Palliative Care group.

Etiology of delirium motor subtypes

Metabolic disturbance was the most common contributory etiology and was present in 782 (44%) of the total sample, followed by systemic infection in 493 (28%) and organ sufficiency which was listed 336(19%) in of cases (see table 2). The mean number of etiological factors per case was 2.11 (1.33) with more than one documented probable etiology evident in 80% of cases (n=1409). The mean and standard deviation number of etiologies in the different delirium motor subtypes were as follows: No subtype: 1.16 (1.34), Hypoactive 2.46 (1.2), Mixed 2.46 (1.2) and Hyperactive 2.3 (1.67). No subtype had significantly lower active etiologies attributed per case.

Table 3: Relationship between delirium motor subtypes and etiologies as listed on the DEC.

	Total (n=1757)*	Hypoactive (n=298)	Mixed (n=426)	Hyperactive (n=844)	No subtype (n=189)	X^2	P value
1) Drug Intoxication	84	17	31	28	8	10.4	<.001
Adj. residual value		.7	2.8	-2.7	-.4		
2) Drug withdrawal	125	9	29	77	10	15	<.001
Adj. residual value		-3.2	-.2	3.3	-1.1		
3) Met disturbance	782	120	209	391	62	22.3	<.001
Adj. residual value		-2.2	2.4	1.9	-3.7		
4) Traumatic Brain Injury	72	6	25	37	4	9.5	.02
Adj. residual value		-2.1	2.2	.7	-1.5		
5) Seizure	87	19	20	40	8	1.3	.72
Adj. residual value		1.1	-.2	-.3	-.6		
6) Intracranial infection	75	16	21	33	5	2.7	.44
Adj. residual value		.9	.8	-.6	-1.2		
7) Systemic infection	493	118	121	198	56	24.6	<.001
Adj. residual value		4.5	.3	-3.9	.3		
8) Intracranial neoplasm	65	19	19	26	1	12.3	.<.001
Adj. residual value		2.5	1	-1.2	-2.5		
9) Systemic neoplasm	173	20	37	101	15	10.3	.02
Adj. residual value		-2.2	.9	3	-1		
10)Cerebrovascular	98	31	19	39	9	14.2	<.001
Adj. residual value		3.8	-1.1	-1.6	-.6		
11) Organ insufficiency	336	54	87	161	34	1.5	.69
Adj. residual value		-.8	.9	.2	-.6		
12) CNS other	57	11	11	28	7	.7	.86
Adj. residual value		.4	.8	3	.3		
13) Systemic other	329	54	65	186	24	15.2	<.001
Adj. residual value		.6	-2.0	3.6	-2.4		

Adj. residual value: Adjusted residual value (this needs to explicitly stated somewhere-as to what does this mean), Hypoactive=Hypoactive delirium, Mixed=Mixed delirium, Hyperactive= Hyperactive delirium, X˝= Chi-squared test statistic, P-Value is significant at <0.01, *Total patients: note that several etiologies can be listed for each patient.

As seen in Table 3, hypoactive delirium was significantly associated with systemic infection, intracranial neoplasm and cerebrovascular etiologies. Mixed delirium was significantly associated with drug intoxication and metabolic disturbance and hyperactive delirium was significantly associated with drug withdrawal and other systemic etiologies. No subtype did not show any significant associations in terms of etiologies.

Symptomatology of delirium motor subtypes

Significant differences between delirium motor subtypes were found for all items on the DRS-R98 scale (See table 4). Patients with hyperactive delirium scored higher on severity of symptoms than those with hypoactive delirium and no subtype across most items, excluding motor retardation. However, severity of symptoms were not significantly different between hyperactive and mixed subtypes across several items (only statistically significant differences between pairwise comparisons are shown). Patients with mixed subtype had significantly greater total severity score than both hypoactive and hyperactive subtypes. As expected, patients with hypoactive delirium showed significantly greater severity of motor retardation (item 8) than hyperactive delirium and the opposite pattern was true for motor agitation (item 7).

Table 4: Mean (Standard deviation) DRS-R98 items for the different delirium motor subtypes (note that larger values indicate greater symptom severity).

Drs items (mean, sd)	Hypoactive I	Mixed II	Hyperactive III	No subtype IV	X^2	P	Post Hoc Significant pairs*
1. Sleep disturbance	1.72 (.8)	2.17 (.7)	2.21 (.78)	1.53 (.9)	166.5	<.001	III>I, II>I, IV<II,III
2. Perceptual Disturb.	.71 (1.1)	1.30 (1.2)	1.4 (1.2)	.7 (1.1)	135.2	<.001	III>I, II>I, IV<II,III
3. Delusions	.43 (.8)	.64 (.9)	.57 (.9)	.26 (.6)	48.3	<.001	III>I, II>I, IV<II, III
4. Lability of affect	.91 (.8)	1.26 (.9)	1.24 (.9)	.57 (.7)	125.7	<.001	III>I, II>I, IV<I,II,III
5. Language	.90 (.9)	1.22 (.9)	1.27 (1)	.71 (.8)	90.3	<.001	III>I, II>I, IV<II, III
6. Thought process	1.34 (1.8)	1.31 (.9)	1.37 (1)	1 (.83)	20.9	<.001	IV<I,II, III
7. Motor agitation	.83 (.9)	1.63 (.9)	2.1 (1.1)	.92 (1)	447.8	<.001	III>II>I, III>I, IV<II, III
8. Motor retardation	1.29 (.9)	1.27 (1)	.29 (.7)	.52 (.8)	509.4	<.001	I>III, II>III, IV<I,II,III
9. Orientation	1.53 (.9)	1.92 (.8)	2 (.8)	1.3 (1.1)	144.7	<.001	III>II>I, IV<II, III
10. Attention	1.98 (.9)	2.21(.8)	2.1 (.8)	1.7 (1)	53.5	<.001	IV<I, II, III
11. Short-term memory	1.68 (.9)	1.82 (.9)	1.85 (1)	1.5 5(1)	20.3	<.001	III>I, IV<II, III
12. Long-term memory	1.12 (1)	1.31 (1)	1.24 (1.1)	.8 (.9)	43.5	<.001	II>I, IV<I, II, III
13. Visuospatial ability	1.47 (1)	1.64 (1.1)	1.56 (1.1)	1.15 (1.1)	31.4	<.001	IV<I,II,III
14. Temporal onset	1.82 (.9)	2.1 (.7)	2.3 (1)	1.74 (1)	94	<.001	III>II>I, III>I, IV<II,III
15. Fluctuation	.97 (.6)	1.41 (.6)	1.65 (.8)	.80 (.8)	272	<.001	III>II>I, II>I, IV<II, III
16. Physical disorder	1.66 (.4)	1.82 (.4)	1.87 (.4)	1.67 (.5)	82.1	<.001	III>I, II>I, IV<II, III
Non-cognitive (i1-8)	8.12 (4.1)	10.8 (3.6)	10.4 (4.1)	6.22 (3.6)	275.8	<.001	III>I, II>I, IV<I,II,III
Cognitive(9-13)	7.76 (3.2)	8.88 (3.4)	8.44 (3.5)	6.45 (3.3)	101.7	<.001	III>I, II>I, IV<I,II,III
Severity (1-13)	15.81 (6.1)	19.67 (5.9)	19.26 (6.8)	12.62 (5.6)	38.9	<.001	III<II>I, IV<I,II, III
DRS R98 Total (1-16)	20.30 (6.9)	25 (6.4)	25.1 (7.6)	16.95 (6.7)	259.4	<.001	III>I, II>I, IV<I, II,III

DRS= Delirium Rating Scale, SD=Standard Deviation, Hypoactive=Hypoactive delirium, Mixed=Mixed delirium, Hyperactive=Hyperactive delirium, X^2=Chi-sqaured test statistic, *only significant differences at the level of P<0.01 are shown

In terms of cognition, hypoactive, mixed and hyperactive subtypes score significantly higher than no subtype on totals for cognitive scores (items 9-13). All subtypes (hypoactive, mixed, hyperactive) scored significantly greater in terms of impairment on visuospatial ability (item 13) and attention (item 10) than the no subtype group.

Discussion

This analysis of a large international sample across multiple clinical settings (palliative care, old age liaison and general adult liaison psychiatry referrals) identified that delirium motor subtypes differ in respect of etiology, neuropsychiatric symptom severity and demographic factors such as age and gender. This work emphasises the typically multifactorial nature of delirium causation, whereby there are typically 2-3 active etiological factors in any case and where single etiology delirium is the exception. These observations further enhance understanding of this complicated condition with implications for delirium recognition and management.

There was a significant difference between delirium motor subtypes in age, dementia status and gender. Patients with hypoactive delirium were more likely to be of older age, female and have comorbid dementia compared to those with hyperactive presentations. They were also more common in old age liaison psychiatry and palliative care settings. While previous research has found that hypoactive delirium tends to be more common in older patients[8,9,] this is the first time such an association has been documented in a large sample incorporating different clinical settings. This is important, as hypoactive delirium is associated with greater mortality and is often missed or misdiagnosed, particularly in older patients[19].

Despite its association with an increased risk of mortality in previous research, hypoactive delirium was rated as having a lower overall burden of delirium symptoms on the DRS-R98 than mixed or hyperactive subtypes in the current study. One possible explanation for this finding is that the those with hyperactive delirium are younger, more physically able, and are more likely to come to the attention of staff and are more florid in terms of neuropsychiatric symptoms such as delusions and hallucinations. This notion is supported by previous research, which has shown that those with hyperactive delirium were more likely to receive antipsychotic medication[22]. Mixed delirium had the greatest severity scores and burden of symptomatology which is a likely reflection of the fact that they include diagnostic criteria for both hypoactive and hyperactive subtypes. This is consistent with previous findings in the area[9].

Delirium symptoms can be divided into neuropsychiatric (involving sleep, motor behaviour and psychosis) and cognitive. Of note, the three motor subtypes differed in terms of the former but had similar levels of disturbance in respect of attention and visuospatial function which are key neuropsychological domains in delirium. This is in keeping with previous findings that suggest that delirium subtypes have a consistent cognitive profile but differ in respect of other non-cognitive symptoms, emphasising that it is a cognitive disorder with disturbances to attention and visuospatial function representing core elements. This supports the use of tests of attention and visuospatial ability for reliable and consistent detection of delirium, including all of its presentations. In addition, the majority of patients with full syndromal delirium have evidence of discernible alterations in motor behaviour such that those with no motor subtype differed in respect of overall delirium symptom severity (including less severe cognitive disturbance), suggesting that many of these patients have mild or subsyndromal illness.

While attributing etiologies to particular delirium subtypes is challenging due to the multifactorial nature of the condition, the current study aimed to give an overview of likely contributory etiologies by breaking them down into thirteen categories using the Delirium Etiology Checklist. Hypoactive delirium was significantly associated with systemic infection, intracranial neoplasm and cerebrovascular etiologies when compared to other delirium motor subtypes. This is clinically

important as delirium can be the principal presenting feature for a variety of acute medical emergencies such as sepsis and stroke[50]. This study emphasises the need to maintain a high level of vigilance regarding the multifactorial nature of delirium causation as well as the possibility of silent background etiologies.

This finding is in contrast to previous research, which has principally indicated an association between hypoactive delirium and metabolic factors and organ failure[25-28]. One possible explanation for this discrepancy is that much of this previous research has taken place in palliative care settings and therefore may lead to a disproportionate representation of particular etiologies (e.g. organ failure, neoplasm). The current study overcomes this issue by including data from multiple clinical settings with a larger sample and is therefore more likely to give more accurate and generalizable results.

Of the contributory etiologies identified, only drug withdrawal and other systemic causes were significantly associated with hyperactive subtype. Withdrawal from certain drugs, particularly alcohol, benzodiazepines and opiates are known to cause hyperactivity and agitation and our results confirm a well-established link between hyperactive delirium and drug withdrawal. The category of other systemic etiologies includes post-operative states, the effects of radiation treatment or other rarer causes such as hypothermia. Future research is needed to clarify which of these other systemic causes is most associated with the hyperactive delirium subtype.

This study has several limitations. While the study is large and incorporates data from two countries, a mix of old age and adult liaison psychiatry referrals and palliative care assessments may not be a broad enough cross section of patients to be truly generalisable. For example, delirium presentations in other setting such as ICU may differ in terms of etiology and subtype. There was also a relatively high proportion of the sample that had no delirium motor subtype, despite being diagnosed with DSM IV delirium. This raises the question as to whether this group in fact had subsyndromal delirium and requires further investigation in future research. While the Delirium Etiology Checklist has good face validity and has been used in much previous research, it has not been fully validated and it is unknown the degree to which it is affected by inter-rater reliability issue. It is also not an exhaustive list in terms of contributory etiologies and only provides a broad overview of the likely contributory factors involved in the episode of delirium (For example, metabolic disturbance and drug intoxication are broad categories that each encompasses many causes of each). The cross-sectional study design may also not be ideal when studying a condition that fluctuates considerably and a longitudinal case design may provide better insights into how complex etiological underpinnings evolve over the course of an episode of delirium.

In conclusion, the current study indicates a pattern of etiologies and symptomatology across delirium motor subtypes using a large combined international database. The association between hypoactive delirium, dementia, cerebrovascular disease and infection is an important insight for clinical practice, where these individuals may often be overlooked. Mixed delirium has the greatest symptom burden, combining both hypo- and hyperactive features and is associated with drug intoxication and metabolic etiologies. Those with hyperactive delirium are significantly younger, more likely to be male, and more likely to be suffering the effects of drug withdrawal. This is, to the best of the authors knowledge, the first time such a large international database has been used to examine differences in delirium motor subtypes and it provides useful knowledge on this complex and often misdiagnosed condition.

a. Contributorship statement
KG, FMcK , KL , M O'D, DH, combined the existing databases and KG wrote up the draft of the paper. DM was the principle investigator who oversaw the current project.
JMF, BD, NO'R, OW, FA, CPD, WC, SMcI, JMcF, FJ, H O'C, PT,ML were involved in data collection for the Irish part of the study and DA was an advisor for statistical analysis.
SC, SKM, AA, AS, AG,RS were involved in the design, data collection and analysis for the Indian part of the study while SG was the principle investigator.

b. Competing interests
None

c. Funding
Fees for publication were provided by University of Limerick, Ireland

d. Data sharing statement
No additional data available

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Chapter 3: Does the etiology, phenomenology and motor subtype of delirium differ when it occurs in patients with an underlying dementia? : A multi-site, international study.

Glynn K[1], McKenna F[1,2], Lally K[1,2], Grover S[3], Chakrabarti S[3], Mattoo SK[3], Avasthi A[3], Sharma A[3], Ghosh A[3], , Adamis D[2,4], Awan F[2], Dunne CP[2], McFarland J[2,], Jabbar F[5], O'Connell H[2], Leonard M[1,2], Meagher DJ[1,2].

1. Dept of Psychiatry, University Hospital Limerick

2. Cognitive Impairment Research Group, Graduate Entry Medical School, University of Limerick, Limerick, Ireland

3.Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

4. Sligo Mental Health Services, Ballytivan, Sligo, Ireland

5. Psychiatry for Later Life Service, University College Hospital, Galway, Ireland.

Corresponding author: Kevin Glynn. Email: glynnkevin@hotmail.com

Abstract

Background: Delirium superimposed on dementia (DSD) is a significant and potentially reversible cause of morbidity and mortality, particularly in older age groups. However, findings comparing DSD to delirium occurring without underlying dementia have shown mixed results and have been limited by small sample sizes with limited generalisability to wider clinical populations.
Methods: A combined dataset was collated from two databases of older adults (>65 years) from liaison psychiatry and palliative care populations in Ireland and India. Phenomenology and severity of delirium were analysed using the Delirium Symptom Rating Scale Revised (DRS-R98) and contributory etiologies for the delirium groups were ascertained using the Delirium Etiology Checklist (DEC). Delirium motor subtype was documented using the abbreviated version of the Delirium Motor Subtype Scale(DMSS4).
Results: A total of 992 patients were included in our analysis, comprising 474(48%) females and 518(52%) males. Groups were broken down as follows: delirium superimposed on dementia (DSD) (n=249), delirium only (n=485), dementia only (n=97), and cognitively intact controls (n=161). Delirium superimposed on dementia showed greater impairment in short term memory, long term memory and visuospatial ability than the delirium only group but showed significantly less perceptual disturbance, temporal onset and fluctuation.. Systemic infection, cerebrovascular and other Central nervous system etiology were associated with DSD while metabolic disturbance, organ insufficiency and intracranial neoplasm were associated with the delirium only group.
Conclusion: The etiology and phenomenology of delirium differs when it occurs in the patient with an underlying dementia. We discuss the implications in terms of identification and management of this complex condition.

Key words: Delirium, Dementia, Cognitive impairment, Delirium motor subtypes

Conflicts of Interest: None

Ethics approval: Ethical approval was granted by the Limerick Regional Ethics Committee, Ireland (REC 100/12) and the Post Graduate Institute of Medical Education and Research(PGIMER) Ethics Review Committee, Chandigarh, India (Int/IEC/2015/659).

Introduction

Delirium occurring in the presence of an existing dementia is known as Delirium superimposed on Dementia (DSD). It is a common and under recognised condition[1] which contributes significantly to patient and carer distress[2] , worsening of cognition[3] and risk of mortality[4].

The diagnosis of DSD can be challenging, especially in those with advanced dementia who have multiple existing cognitive deficits [4,5] and in conditions such as Lewy Body Dementia that have significant clinical overlap with delirium in terms of symptomatology[6]. Generally, the acute onset of cognitive symptoms including impaired attention, confusion and arousal in conjunction with non-cognitive symptoms such as hallucinations, delusions and altered sleep wake cycle have been shown to be good detectors of delirium in patients with existing dementia[7-10.] However, less is known as to whether DSD differs in terms of its presentation and etiology from delirium occurring in younger patients, who do not have an underlying dementia. These differences, if present, are important to understand in aiding the diagnosis and management of this condition, which comes with a high rate of mortality and morbidity[3.4.]

Despite an increased focus on this area in recent years, studies comparing DSD to delirium have shown mixed outcomes. This may be due in part to the use of a range of different tools and this research taking place in different clinical settings (e.g. palliative, ICU, surgical). Some research has shown that DSD is more severe with a greater degree of agitation, hyperactivity, perceptual disturbance and disorientation when compared to those with delirium only[11-13] while others have failed to replicate these findings.[7,10,14] Meagher et al. (2010)[7] found that measures of orientation and attention were significantly worse in those with DSD when compared to delirium alone. In contrast, Leonard et al (2016)[10] found similar cognitive profiles across all delirium (DSD and Delirium only) groups but that these groups were distinguished from controls and those with dementia in performing poorer on tests of attention and vigilance. However, thus far large-scale studies with participants from different clinical settings comparing the phenomenology of DSD to delirium in terms of cognitive and non-cognitive symptoms have been lacking.

Dementia or pre-existing cognitive impairments are known risk factors for delirium[15,16]. It has therefore been postulated that those with dementia require a lower level of physiological insult to develop delirium when compared to younger patients without cognitive impairments[13] but this has yet to be properly established. It is important to understand how etiologies trigger delirium superimposed on dementia and the nature of these etiologies as research has shown that its prevention will significantly lessen negative outcomes. However a recent review[5] has pointed to a lack of research in investigating contributory etiologies in DSD and we aim to address this issue in the current study.

The aims of the current study are twofold: 1. To compare delirium superimposed on dementia to delirium only in terms of phenomenology, etiology and motor subtype. 2. To compare the phenomenology of the delirium superimposed on dementia and delirium only group to those with dementia only and cognitively intact controls.

Methods

Subjects and design

This study used a combined dataset of existing related databases from two countries, Ireland[17, 18-20] and India[21-24]. All research took place between 2008 and 2020 inclusive. Raters for data included in this study were trained by an expert (DM), through training workshops in both Ireland and India using well validated assessment methods for these clinical populations as outlined below. Research was conducted across palliative care and liaison psychiatry settings. Only patients over the age of 65 were included in our analysis.

Palliative care

This group consisted of consecutive referrals to a liaison psychiatry service in a hospice setting that were subsequently diagnosed as having delirium, dementia, DSD or cognitively normal controls at the time of assessment. Research took place at Milford Hospice in Limerick, Ireland.

Liaison Psychiatry

This group consisted of consecutive referrals to liaison Psychiatry services for those aged >65years in two Irish Hospitals; University Hospital Limerick and University Hospital Galway and to a liaison Psychiatry service at the Postgraduate Institute for Medical Research (PGIMER) in Chandigarh, India.

Table 1: Demographic and clinical Data for overall population and sub populations

	Total Sample (n=992)	**Palliative care (n=249)**	**Liaison Psychiatry (n=743)**	**P-Value**
Age (Mean, SD)	77.2 (7.3)	75.9(6.2)	77.7(7.6)	P<.00
Sex (%Female)	474(48%)	120(48%)	354(48%)	P=.83
Dementia (Total, %)	346(35%)	87(35%)	259(35%)	P=.98
Psychotopics (%)	548(55%)	152(61%)	396(53%)	P=.30
Total medications(SD)	8.6(4.6)	9.2(3.9)	8.4(4.8)	P=.03

P value <0.05 for statistical significance, SD=Standard deviation.

Assessment

Overview of training in rating scales and assessment

Raters for data included in this study were trained by an expert (DM), through training workshops in both Ireland and India. He was involved in developing several of the tools used in this study (See below). Data between the studies was combined and harmonised as outlined below.

Delirium diagnosis

Delirium was diagnosed according to DSM-IV[25] criteria using all available clinical information including patient assessment and collateral information from nursing staff, family and the patient's medical records.

Dementia diagnosis

Dementia status was determined according to (i) a pre-existing diagnosis, or (ii) on the basis of detailed history and examination taking in aspects such as the patient's functional ability, neuroimaging and cognitive decline prior to assessment and was made in accordance with DSM IV[25] .
The Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly(Short IQCODE)[26] was also used to aid in dementia diagnosis. The Short IQCODE comprises a 16-item informant questionnaire comparing the individual's ability on day-to-day items with their performance ten years ago. Items are scored by the rater from 1 =much improved, 3 unchanged to 5=much worse. Items include aspects of daily life such as the ability to remember conversations that happened the previous day, address and telephone numbers and where things are kept. Scores are added up and divided by the total number of questions (n=16). The resultant score ranges from 1-5. All databases in this analysis that used the IQCODE score to aid in dementia diagnosis used a cut off of ≥3.5 to signify likely dementia. This was then combined with all relevant clinical information to make a diagnosis.

Delirium symptomatology and severity

Delirium severity and symptomatology were measured using the Delirium Rating Scale Revised-98 (DRS R98)[27]. The DRS-R98 is a 16-item clinician rated scale used to rate the severity of delirium both overall and on a broad range of neuropsychiatric and cognitive symptoms. It is made up of 13 severity items and 3 diagnostic items. Each item is rated 0 (absent/normal) to 3 (severe impairment), with descriptors attached to each severity level. The severity scale (items 1-13) range from a score or 0-39 with larger scores indicating more severe delirium. A score of over 15 points typically indicates delirium and 18 points indicates delirium when dementia is present. The DRS-R98 can be divided into non-cognitive (items 1-8) and cognitive (9-13) subscales based on construct validity. It has been validated across clinical settings and has been shown to have a high interrater reliability, sensitivity and specificity at detecting delirium. It has also been used to determine differing symptomatology and severity across delirium motor subtypes.

Delirium etiology

Contributory etiologies were identified using the Delirium Etiology Checklist (DEC)[28]. The Delirium Etiology Checklist is a 13-item checklist that is designed to document the etiological underpinnings contributory a delirium episode. Its thirteen categories are: drug intoxication, drug withdrawal, metabolic/endocrine disturbance, traumatic brain injury, seizures, infection (intracranial) infection (systemic), neoplasm (intracranial), neoplasm (systemic), cerebrovascular, organ insufficiency, other CNS and other systemic. Other CNS includes neurological conditions such as Parkinson's disease and Multiple Sclerosis while other systemic includes conditions such as post-operative state, immunosuppression or heat stroke. These categories are present to allow the rater to list contributory etiologies that do not fit under the other 11 items.

Each etiology is rated on a scale according to its likelihood of being contributory to the delirium. This scale ranges from 0=ruled out/not present/not relevant to 4= Definite cause. Raters can therefore document multiple etiologies and their level of contribution to a particular episode of delirium. For the purposes of this study, DEC items were broken down into two categories: present and possibly/probably contributory (scores of 3 or 4) and non-contributory (score 0-2). This also allowed for the total and mean number of likely contributory etiologies to be calculated and compared between delirium motor subtypes.

Delirium motor subtypes

Delirium motor subtypes were identified using the abbreviated version of the Delirium Motor Subtype Scale (DMSS4)[29]. The DMSS4 comprises two items taken from the original Delirium Motor Checklist (DMC)[30] and Delirium Motor Subtype Scale (DMSS)[31] denoting hyperactivity and two items denoting hypoactivity, with mixed subtype defined as the present of both hyperactive and hypoactive criteria. No subtype describes a presentation in which neither the criteria for hyperactive nor hypoactive delirium are fulfilled. It was developed for quick and accurate identification of delirium motor subtype in busy clinical practice and has shown a good concordance with the original DMC scale and the DMSS and has been widely validated across a variety of populations and clinical settings[8,10, 18-20.]

Ethical approval

Because of the non-invasive nature of the study, approval was given by the Limerick Regional Ethics Committee to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical research involving human subjects. All of the Indian studies took place at Postgraduate Institute of Medical Education and Research, Chandigarh in North India. Subjects were patients referred to an inpatient psychiatric liaison service and diagnosed with delirium as per the DSM-IV criteria . The studies were approved by the Ethics Review Committee of the Institute. Written consent was obtained from the primary caregivers of the patients and patients themselves wherever possible in accordance with the Helsinki Guidelines for Medical Research involving human subjects.

Statistical analysis

Statistical analysis was conducted using the SPSS v25 package. Continuous normally distributed variables are reported as means plus standard deviation, while categorical variables are reported as counts and percentages. Normally distributed data were analysed using Anova, whereas non-parametric data were compared using Kruskal Wallis and chi-squared tests. Adjusted residuals were used for post-hoc analysis of chi-squared tests, with a level of greater than 1.96 (2.0 is used by convention) used to indicate statistical significance. (Agresti, 2003)[32]. Dunn multiple comparison test was used for post-hoc analysis of the Kruskal Wallis test, while the Bonferroni procedure was used during post hoc analysis for ANOVA.

Results

The sample comprised 992 individuals, 518(52%) male and 474(48%) females. The mean age (standard deviation) of the sample was 77.3(7.2). Demographics of each of the four groups is outlined in table 2.

Table 2: Demographics and DRS-R98 totals for each group

	Delirium (n=485)	Dementia (n=97)	DSD (n=249)	Controls (n=161)	P Value
Age	75.1(7.3)	79.8(6.5)	79.8(6.4)	78(7.2)	P<.001
Male (no, %)	272(56%)	39(40%)	130(52.2%)	77(47.8%)	P<.001
Total Medications	6.9(4.3)	10.7(4.4)	9.4(4.4)	10.3(4.3)	P<.001
DRS R98(#1-16)	21.9(6.8)	13(5.8)	22.2(6.5)	7.5(5.1)	P<.001
DRS R98(#1-13)	16.9(6.2)	10.6(5.1)	18(6)	6(4.2)	P<.001
DRS R98Cog(#9-13)	8(3.1)	7.3(3.3)	9.7(2.9)	4.2(3.1)	P<.001
DRS R98 Non-Cog (#1-8)	8.9(4.2)	3.2(2.8)	8.4(4.3)	1.9(2.2)	P<.001

DRS-R98= Delirium Rating Scale Revised 98, No=Number, Cog=Cognitive, Non-cog= non-cognitive, DSD= Delirium superimposed on dementia.

There was a significant difference between groups in terms of age, with dementia and delirium superimposed on dementia groups being significantly older than delirium only and cognitively intact control groups. The delirium only group had the greatest percentage of males, whereas pure dementia had that greatest percentage of females. Those with dementia only had the highest mean number of medications prescribed, whereas delirium superimposed on dementia had the highest DRS-R98 total scores, severity scores and scores for cognition. This indicates a greater degree of impairment and greater symptom severity in these domains. The Delirium only group showed greater severity of non-cognitive symptoms (items 1-8), however this was not statistically significant.

Table 3: Mean and standard deviation of individual DRS-R98 items (greater scores indicate greater intensity).

	Delirium I	Dementia II	DSD III	Controls IV	Sig Post Hoc tests
1. Sleep disturbance	1.9(.9)	.7(.7)	1.7(.9)	.6(.7)	I > II, IV, III > II, III > IV
2. Perceptual disturbance	1.1(1.2)	.3(.8)	.8(1.2)	.2(.5)	I >II, III, IV, III > II, IV
3. Delusions	.5(.9)	.2(.6)	.5(.9)	.1(.4)	I > II, IV, III > II, IV
4. Liability	.9(.9)	.3(.6)	1(.9)	.2(.9)	I >II, IV, III > II, IV
5. Language	1(.9)	.3(.6)	1(1)	.1(.5)	I >II, IV, III> II, IV
6. Thought process	1.3(1.7)	.7(.8)	1.4(1)	.4(.7)	I > II, II > IV, III >II, IV
7. Motor Agitation	1.4(1)	.3(.7)	1.1(1)	.1(.4)	I >II, III, IV, III > II, IV
8. Motor retardation	.8(.9)	.4(.6)	.9(1)	.3(.5)	I >II, IV, III>II, IV
9. Orientation	1.7(.9)	.9(.7)	1.5(.8)	.2(.6)	I > II >I V, III > II, IV
10. Attention	2.1(.9)	1.6(1)	2.2(.8)	.7(.9)	I > II >IV, III > II, IV
11. Short-term memory	1.7(.9)	1.8(1.1)	2.2(.9)	1.3(1)	I > IV, II > IV, III > I,II, IV
12. Long-term memory	1(.9)	1.4(1)	1.7(1)	.7(.9)	I, II > IV, III > I, IV
13. Visuospatial	1.4(1)	1.8(1.1)	2(1.1)	1.1(1)	I > II >IV, III > I, IV
14. Temporal onset	2(1.1)	.6(.8)	1.6(.8)	.3(.6)	I >II, III, IV, III> II, IV
15. Fluctuation	1.2(.6)	.4(.6)	.9(.7)	.1(.3)	I > II, III, IV, II > IV, III > II, IV
16. Physical disorder	1.8(.5)	1.4(.6)	1.7(.5)	1(.5)	I > II > IV, II > IV, III >II, IV

DSD=Delirium superimposed on Dementia

DSD and Delirium

DSD showed greater impairment on short term memory, long term memory and visuospatial ability than the delirium only group. The delirium only group showed significantly greater severity in perceptual disturbance, motor agitation, temporal onset and fluctuation than DSD. In contrast, As expected, both delirium and delirium superimposed on dementia scored significantly higher than dementia only and control groups on most DRS-R98 items.

DSD and Dementia

DSD differed from dementia across a wide range of cognitive (#1-8) and non-cognitive items (#9-13) on the DRS-R98. In terms of cognition, DSD showed significantly greater impairment in orientation, attention, and short-term memory but there were no significant differences in measures of long-term memory and visuospatial ability. DSD showed significantly greater severity than dementia on all non-cognitive items (#1-8).

Table 3: Etiology of delirium with and without dementia

Total (%)	Delirium (n=485)	DSD (n=249)	X^2	P Value
1. Drug Intoxication	49(10%)	26(10%)	0.3	.57
Adj, residual value	-.6	.6		
2. Drug withdrawal	28(6%)	14(6%)	0.4	.84
Adj, residual value	-.2	.2		
3. Metabolic Disturbance	292(60%)	97(40%)	22.4	.00
Adj, residual value	4.7	-4.7		
4. Traumatic Brain injury	9(2%)	9(4%)	2.8	.09
Adj, residual value	-1.7	1.7		
5. Seizure	23(5%)	18(7%)	2.9	.09
Adj, residual value	-1.7	1.7		
6. Intracranial infection	9(2%)	6(2%)	.45	.5
Adj, residual value	-.7	.7		
7. Systemic infection	210(43%)	142(57%)	17.4	.00
Adj, residual value	-4.2	4.2		
8. Intracranial neoplasm	36(7%)	5(2%)	7.6	.00
Adj, residual value	2.8	-2.8		
9. Systemic neoplasm	112(23%)	61(24%)	1.3	.26
Adj, residual value	-1.1	1.1		
10. Cerebrovascular	59(12%)	59(24%)	20.4	.00
Adj, residual value	-4.5	4.5		
11. Organ insufficiency	160(33%)	55(22%)	5.6	.02
Adj, residual value	2.4	-2.4		
12. CNS other	34(7%)	46(18%)	27.9	.02
Adj, residual value	-5.3	5.3		
13. Other systemic	116(24%)	50(20%)	.35	.55
Adj, residual value	.6	-.6		
Antipsychotics prescribed	195(40%)	193(77%)	37.5	.00
Adj, residual value	-6.1	6.1		
Benzodiazepines prescribed	129(26%)	57(23%)	.15	.74
Adj, residual value	-.4	.4		

Adj. residual value= Adjusted residual value, DSD= Delirium superimposed on Dementia.

Only those who had delirium present (n=734) were included in the group assessed with the DEC. This group was made up of 402 males and 332 females, with a mean age of 76.7 (7.3). More than one contributory etiology was listed in 561 (76%) number of cases. In terms of listed etiologies, delirium superimposed on dementia was significantly associated with systemic infection (57% of cases), Cerebrovascular (24% of cases) and other CNS etiologies (18% of cases) when compared to the delirum only group. The delirium only group was significantly associated with metabolic disturbance (60% of cases), intracranial neoplasm (7% of cases) and organ insufficiency (33% of cases). A significantly greater proportion of the delirium superimposed on dementia group had antipsychotics prescribed but there was no difference in benzodiazepines between the groups. The mean number of etiologies was 2.4 (1.2), there was no significant difference in the mean number of etiologies between groups, with delirium having a mean 2.3 and DSD 2.4.

Delirium motor subtypes were documented in 707 patients (missing values =27). Chi- squared test showed a significant association between delirium motor subtype and dementia status (X^2= 8.1, df =3, P<.05) and adjusted residual values showed that there is a significant association between DSD and hypoactive motor subtype (see table 5).

Table 5: A comparison of delirium motor subtypes in DSD and Delirium groups

	No subtype (n=124)	**Hypoactive (n=188)**	**Mixed (n=156)**	**Hyperactive (n=239)**	**Total**
DSD	43	78	47	70	469
Adj residual	.3	2.7	-1.1	-1.8	
Delirium	81	110	109	169	238
Adj. residual	-.3	-2.7	1.1	1.8	

DSD=Delirium Superimposed on Dementia, Hypoactive= Hypoactive delirium, Mixed= Mixed Delirium, Hyperactive= Hyperactive Delirium.

Discussion

This study aimed to compare delirium superimposed on dementia to delirium only in terms of phenomenology, etiology and motor subtype and to compare the phenomenology of the delirium superimposed on dementia and delirium only group to those with dementia only and cognitively intact controls.

Our findings demonstrate that delirium superimposed on dementia (DSD) differs from delirium without underlying dementia in terms of phenomenology, etiology and delirium motor subtype. In terms of non-cognitive symptoms, delirium occurring without an underlying dementia showed significantly greater levels of perceptual disturbance , motor agitation and fluctuation than those with DSD. This is contrary to some previous research that has shown the opposite pattern or that there was no difference in non-cognitive neuropsychiatric symptoms between the groups[10-13]. However, a greater proportion of the DSD had at least one antipsychotic medication prescribed at the time of our study and this may partially explain the fewer perceptual disturbances and agitation when compared to the delirium only group at the time of assessment. DSD was also significantly associated with hypoactive delirium subtype and therefore more subtle perceptual disturbance may have been more difficult to detect in this group.

In terms of cognition, both delirium groups (Delirium and DSD) did not differ in terms of attention but DSD scored significantly worse in short term memory, long term memory and visuospatial functioning than the delirium only group. Impairment in attention is a key diagnostic criteria[25] for delirium and therefore it is expected that this would be present to a high degree in both groups. Memory impairment is generally more associated with dementia and this may be reflected in the worse scores of the DSD group. Therefore, the pre-existing cognitive impairments in those with dementia would be expected to worsen the scores of those with DSD in comparison to delirium but the two groups did not differ in terms of the core cognitive features of delirium such as attentional difficulties. This supports the view that delirium is not fundamentally different in terms of its cognitive profile when it occurs with and without an underlying dementia.

This study supports the view that delirium is most often multifactorial, with an average of 2.4 etiologies listed per delirium case. There were no significant differences in the number of contributory

etiologies in patients with DSD vs those with delirium. This does not therefore support the hypothesis that those with dementia are more vulnerable to delirium and therefore require a lower level of physiological insult to become delirious. Systemic infection and cerebrovascular etiologies were more common in those with DSD, pointing to the importance of a thorough investigation for an infective cause when a patient with dementia starts to exhibit signs of delirium. Cerebrovascular etiologies such as transcient ischaemic attacks may also be cause of delirium in this group and it is important that risk factors for these conditions are managed in order to reduce the likelihood of delirium.

In keeping with previous research[10], we found that Delirium Superimposed on Dementia was distinguishable from dementia only on a range of non-cognitive neuropsychiatric (e.g. sleep wake cycle disturbance, perceptual abnormalities) and cognitive items when assessed with a detailed and well validated scale (DRS-R98) administered by trained raters. Three related cognitive domains: attention, orientation and short-term memory were significantly worse is the DSD group, but there was no difference between groups in visuospatial ability and long-term memory. This shows that DSD should be readily detectable in those with dementia but there is a need to develop reliable rapid tests that require minimal time and training for use in this group. There is also a need for research into delirium in different types of dementia and at different stages of dementia as these are factors likely to present particular challenges in the diagnosis is DSD.

It is important to note that our study has several limitations. Although the DRS-R98 is rated on the patient's presentation over the previous 24 hours, a longitudinal study may be preferable to our cross-sectional design when assessing a fluctuating condition such as delirium. We were unable to include type of dementia, which is important as some types of dementia such as Lewy Body Dementia differ significantly to others such as Alzheimer's disease in terms of symptomatology. The Delirium Etiology Checklist has good face validity but has yet to be fully validated across populations and is only gives a broad overview of contributory etiologies (e.g. systemic infection, metabolic disturbance) and more detailed assessment may have been valuable in this regard.

Overall, this study found that delirium superimposed on dementia differed from delirium occurring without an underlying dementia in phenomenology, etiology and motor subtype. To the best of the authors knowledge, this is the largest study to compare these groups to date and took place across two countries including patients from palliative care and liaison psychiatry settings. We found that delirium superimposed on dementia was more likely to present with worse memory and visuospatial ability, be the hypoactive motor subtype and be prescribed antipsychotic medication than the delirium only group, who were more likely to show greater perceptual disturbances and be the hyperactive motor subtype. Delirium superimposed on dementia was also easily differentiated from dementia only by a wide range of symptoms including non-cognitive and cognitive neuropsychiatric items. Our study also supports the notion that delirium is multifactorial and describes a pattern of the most frequent etiologies between those with DSD and delirium. It is important to understand the differences in delirium when it occurs in the context of an underlying dementia, as it can be difficult to detect and treat in a clinical setting. We believe that this study contributes to our knowledge of this complex area. Further research may focus on detecting DSD in more challenging cases of advanced dementia and lewy body dementia, where a strong degree of overlap in symptomatology exist. This can have a beneficial effect in terms of identifying this condition and lessening the morbidity and mortality with which it associated.

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Final Discussion

The aims of the current study were threefold: 1) To conduct a systematic review of research relating to delirium motor subtypes over the past ten years 2)To compare the etiology and phenomenology of delirium motor subtypes across a multicentre international study comprising multiple clinical settings. 3) To compare etiology, phenomenology and delirium motor subtype in patients which and without an underlying dementia in multicentre, international sample.

An initial systematic review of 45 studies relating to delirium motor subtypes consolidated and analysed the work done in this area over the past ten years. It found that there is still an issue in terms of consistency in differentiating delirium motor subtypes and that scales that have not been validated for this purpose continue to be used regularly in research. This was particularly the case in the ICU setting, where the Confusion Assessment Method for the ICU and the Richmond Agitation Sedation Scale were the most frequently used instruments.

Scales developed by Meagher et al for the specific purpose of differentiating delirium motor subtypes (e.g. DMC, DMSS, DMSS4) were used more commonly in medical and palliative care populations. These scales focus on motor symptoms and activity levels as a primary means of differentiation of delirium motor subtypes and this method is backed up by several studies using motion trackers to measure activity levels in delirious patients. These studies confirm that motor subtype corresponds to levels of physical activity in these patients.

Studies included in the systematic review suggest that delirium motor subtypes do not differ in terms of cognitive scores but do differ in non-cognitive symptoms such as altered sleep-wake cycle and the presence of delusions and hallucinations. This is in line with the view that delirium is a unitary syndrome with characteristic cognitive deficits as one of its key features.

This conclusion was backed up in the study outlined in chapter 2 of this thesis. This study incorporated a large sample of patients taken from multiple clinic settings (Palliative Care, Liaison Psychiatry and Old Age Liaison Psychiatry) in India and Ireland. It showed that delirium motor subtypes did not differ significantly in cognitive items on a well validated test, DRS R-98, but that hyperactive and mixed subtypes scored significantly higher than hypoactive delirium on non-cognitive items such as sleep disturbance, perceptual disturbance, delusions and lability of affect. There was no significant difference between hyperactive and mixed motor subtypes on scores for these items. All delirium motor subtypes scored higher on deficits of attention and visuospatial ability than the non-subtype group, supporting the idea that these cognitive deficits are core features of delirium and do not differ significantly across delirium motor subtype. This is also in keeping with previous research in this area but had not been definitively shown across such a large population until now.

Another key finding from the systematic review was that etiologies contributing to delirium remain poorly understood. There were also few studies identified that examined specifically whether etiologies differed across delirium motor subtypes. This is in part due to the complexity of most delirium cases, with each case generally comprising multiple potential etiologies. The study outlined in chapter two of this thesis aimed to address this paucity of research. It showed that there are differences in the etiology and phenomenology of delirium motor subtypes across a large, international sample, comprising multiple clinical settings. Hypoactive delirium was found to be more common in older female patients and in those with comorbid dementia, whereas the hyperactive subtype was associated with younger patients. Delirium was found to be multifactorial in nature, with a mean of 2-3 etiologies listed per case. In term of contributory etiologies, hypoactive delirium was associated with systemic infection, cerebrovascular disease and intracranial neoplasm whereas the

hyperactive subtype was associated with drug withdrawal and other systemic causes. This is the first time that such a pattern has been found across such a large sample that incorporated multiple clinical settings and is important, as previous research has shown that hypoactive delirium is more likely to go undetected and carries a greater risk of mortality.

None of the studies in the initial systematic review examined whether the etiology and phenomenology of delirium differs when it occurs in the context of an underlying dementia. This was therefore identified as an important area for our current study and is examined in the third paper of this thesis (See Chapter 3).

The second study used a subset of patients, aged 65 and over, from the initial database and broke them down in to patients with delirium superimposed on dementia (DSD), patients with delirium only, patients with dementia only and cognitively intact controls. It found that delirium superimposed on dementia does differ in etiology, phenomenology and motor subtype when compared to a delirium occurring in patients without an underlying dementia. DSD is significantly associated with the hypoactive motor subtype and scores less on neuropsychiatric symptoms such as perceptual disturbance, motor agitation and symptom fluctuation than the delirium only group. Patients with DSD were also more likely to be prescribed one or more antipsychotic. Perhaps unsurprisingly, the DSD group showed a greater degree of cognitive impairment than those with delirium only. Different etiologies were associated with the two groups, with systemic infection, cerebrovascular and other central nervous system etiologies associated with DSD, while metabolic disturbance, organ insufficiency and intracranial neoplasm were associated with the delirium only group.

Overall, this thesis has shown different patterns of etiology and phenomenology across delirium motor subtypes and in patients with delirium occurring with and without an underlying dementia. A strength of the study is the fact that it incorporated such a large sample and took place across multiple clinical settings and across two countries. These aspects were lacking in previous research, and it is, to the best of the authors knowledge, the largest study of its kind to date. It also used well validated tools for differentiating delirium motor subtypes and a tool with good face validity, the Delirium Etiology Checklist, for identifying contributory etiology. Limitations include the fact that cognitive testing is very challenging in this group of patients and floor effects on testing may exist for patients with delirium. While the Delirium Etiology Checklist comprises key etiologies likely to be contributary to a delirium episode, it is not exhaustive and identifying contributory etiologies can be clinically challenging, especially in settings such a palliative care or the intensive care unit, where a multitude of predisposing and perpetuating factors may be contributing to the episode of delirium.

While the inclusion of delirium motor subtypes under 'other specifiers' of delirium in the DSM V marks a step forward in this area and is a reflection of the important research done to date, there remains no clear gold standard for diagnosis. As was identified in the initial systematic review, this continues to lead to a lack of consistency in defining delirium motor subtypes. Research needs to continue to examine whether the definition of motor subtypes should focus primarily on activity levels and other 'pure' motor symptoms as opposed to neuropsychological symptoms such as delusions and hallucinations etc. This may have an effect on the detection and management of delirium, in particular hypoactive delirium which is typically under-detected and carries a worse prognosis if left untreated.

Further large-scale studies, across multiple clinic settings, are needed to examine whether the findings outlined in this thesis can be repeated. A more detailed examination of the etiology of delirium motor subtypes, which could perhaps include predisposing, precipitating and likely perpetuating factors would be clinically valuable and would further our knowledge of this complex area. The role of medication in terms of an etiology was also not examined thoroughly in our research and may be a

significant factor in determining delirium motor subtype, especially where multiple medications which can have a sedating effect are used such as in the ICU or palliative care setting.

The fact that delirium superimposed on dementia is associated with hypoactive delirium in this study is highly clinically relevant as the hypoactive subtype is more difficult to detect in a clinical setting and is associated with a greater risk of mortality. This is a key area for future research as early detection and management is likely to improve patient outcomes. Large scale studies with an aim of improving detection of delirium in this group are therefore imperative. The etiologies identified in our study such as systemic infection and cerebrovascular etiology and also generally preventable and treatable and this should be taken into account in a patient that is identified as having hypoactive delirium.

Overall, I believe that our current study has made a valuable contribution to the area of delirium research. It is my hope that this will serve as a catalyst for future research in this important and complex clinical field.

Appendix 1

Richmond Agitation Sedation Scale (RASS) *

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* **(≥10 seconds)**	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* **(<10 seconds)**	Verbal Stimulation
-3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**	Verbal Stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	Physical Stimulation

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. **(score 0 to +4)**
2. If not alert, state patient's name and *say* to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. **(score –1)**
   c. Patient awakens with eye opening and eye contact, but not sustained. **(score –2)**
   d. Patient has any movement in response to voice but no eye contact. **(score –3)**
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. **(score –4)**
   f. Patient has no response to any stimulation. **(score –5)**

* Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Keane KA et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166:1338-1344.

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

Appendix I

Memorial Delirium Assessment Scale (MDAS)©1996

INSTRUCTIONS: Rate the severity of the following symptoms of delirium based on current interaction with subject or assessment of his/her behavior or experience over past several hours (as indicated in each time.)

ITEM 1–REDUCED LEVEL OF CONSCIOUSNESS (AWARENESS): Rate the patient's current awareness of and interaction with the environment (interviewer, other people/objects in the room; for example, ask patients to describe their surroundings).

☐ 0: none (patient spontaneously fully aware of environment and interacts appropriately)
☐ 1: mild (patient is unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded strongly; interview is prolonged but not seriously disrupted)
☐ 2: moderate (patient is unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; interview is prolonged but not seriously disrupted)
☐ 3: severe (patient is unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult-to-impossible, even with maximal prodding

ITEM 2–DISORIENTATION: Rate current state by asking the following 10 orientation items: date, month, day, year, season, floor, name of hospital, city state, and country.

☐ 0: none (patient knows 9–10 items)
☐ 1: mild (patient knows 7–8 items)
☐ 2: moderate (patient knows 5–6 items)
☐ 3: severe (patient knows no more than 4 items)

ITEM 3–SHORT-TERM MEMORY IMPAIRMENT: Rate current state by using repetition and delayed recall of 3 words [patient must immediately repeat and recall words 5 min later after an intervening task. Use alternate sets of 3 words for successive evaluations (for example, apple, table, tomorrow; sky, cigar, justice)].

☐ 0: none (all 3 words repeated and recalled)
☐ 1: mild (all 3 repeated, patient fails to recall 1)
☐ 2: moderate (all 3 repeated, patient fails to recall 23)
☐ 3: severe (patient fails to repeat 1 or more words)

ITEM 4–IMPAIRED DIGIT SPAN: Rate current performance by asking subjects to repeat first 3, 4, then 5 digits forward and then 3, then 4 backwards; continue to the next step only if patient succeeds at the previous one.

☐ 0: none (patient can do at least 5 numbers forward and 4 backward)
☐ 1: mild (patient can do at least 5 numbers forward, 3 backward)
☐ 2: moderate (patient can do 4–5 numbers forward, cannot do 3 backward)
☐ 3: severe (patient can do no more than 3 numbers forward)

ITEM 5–REDUCED ABILITY TO MAINTAIN AND SHIFT ATTENTION: As indicated during the interview by questions needing to be rephrased and/or repeated because patient's attention wanders, patient loses track, patient is distracted by outside stimuli or over-absorbed in a task.

☐ 0: none (none of the above; patient maintains and shifts attention normally)
☐ 1: mild (above attentional problems occur once or twice without prolonging the interview)
☐ 2: moderate (above attentional problems occur often, prolonging the interview without seriously disrupting it)
☐ 3: severe (above attentional problems occur constantly, disrupting and making the interview difficult-to-impossible)

ITEM 6–DISORGANIZED THINKING: As indicated during the interview by rambling, irrelevant, or incoherent speech, or by tangential, circumstantial, or faulty reasoning. Ask patient a somewhat complex question (for example, "Describe your current medical condition.").

☐ 0: none (patient's speech is coherent and goal-directed)
☐ 1: mild (patient's speech is slightly difficult to follow; responses to questions are slightly off target but not so much as to prolong the interview)
☐ 2: moderate (disorganized thoughts or speech are clearly present, such that interview is prolonged but not disrupted)
☐ 3: severe (examination is very difficult or impossible due to disorganized thinking or speech)

ITEM 7–PERCEPTUAL DISTURBANCE: Misperceptions, illusions, hallucinations inferred from inappropriate behavior during the interview or admitted by subject, as well as those elicited from nurse/family/chart accounts of the past several hours or of the time since last examination:

☐ 0: none (no misperceptions, illusions, or hallucinations)
☐ 1: mild (misperceptions or illusions related to sleep, fleeting hallucinations on 1–2 occasions without inappropriate behavior)
☐ 2: moderate (hallucinations or frequent illusions on several occasions with minimal inappropriate behavior that does not disrupt the interview)
☐ 3: severe (frequent or intense illusions or hallucinations with persistent inappropriate behavior that disrupts the interview or interferes with medical care)

ITEM 8–DELUSIONS: Rate delusions inferred from inappropriate behavior during the interview or admitted by the patient, as well as delusions elicited from nurse/family/chart accounts of the past several hours or of the time since the previous examination.

☐ 0: none (no evidence of misinterpretations or delusions)
☐ 1: mild (misinterpretations or suspiciousness without clear delusional ideas or inappropriate behavior)
☐ 2: moderate (delusions admitted by the patient or evidenced by his/her behavior that do not or only marginally disrupt the interview or interfere with medical care)
☐ 3: severe (persistent and/or intense delusions resulting in inappropriate behavior, disrupting the interview or seriously interfering with medical care)

ITEM 9–DECREASED OR INCREASED PSYCHOMOTOR ACTIVITY: Rate activity over past several hours, as well as activity during interview, by circling (a) hypoactive, (b) hyperactive, or (c) elements of both present.

☐ 0: none (normal psychomotor activity)
☐ a b c 1: mild (Hypoactivity is barely noticeable, expressed as slightly slowing of movement. Hyperactivity is barely noticeable or appears as simple restlessness.)
☐ a b c 2: moderate (Hypoactivity is undeniable, with marked reduction in the number of movements or marked slowness of movement; subject rarely spontaneously moves or speaks. Hyperactivity is undeniable, subject moves almost constantly; in both cases, exam is prolonged as a consequence.)
☐ a b c 3: severe (Hypoactivity is severe; patient does not move or speak without prodding or is catatonic. Hyperactivity is severe; patient is constantly moving, overreacts to stimuli, requires surveillance and/or restraint; getting through the exam is difficult or impossible.)

ITEM 10–SLEEP–WAKE CYCLE DISTURBANCE (DISORDER OF AROUSAL): Rate patient's ability to either sleep or stay awake at the appropriate times. Utilize direct observation during the interview, as well as reports from nurses, family, patient, or charts describing sleep–wake cycle disturbance over the past several hours or since last examination. Use observations of the previous night for morning evaluations only.

☐ 0: none (at night, sleeps well; during the day, has no trouble staying awake)
☐ 1: mild (mild deviation from appropriate sleepfulness and wakefulness states: at night, difficulty falling asleep or transient night awakenings, needs medication to sleep well; during the day, reports periods of drowsiness or, during the interview, is drowsy but can easily fully awaken him/herself)
☐ 2: moderate (moderate deviations from appropriate sleepfulness and wakefulness states: at night, repeated and prolonged night awakening; during the day, reports of frequent and prolonged napping or, during the interview, can only be roused to complete wakefulness by strong stimuli)
☐ 3: severe (severe deviations from appropriate sleepfulness and wakefulness states: at night, sleeplessness; during the day, patient spends most of the time sleeping or, during the interview, cannot be roused to full wakefulness by any stimuli)

Delirium Motor Subtype Scale 4

(a) Hyperacve subtype defined by the presence of either (i) or (ii)

(i) Increased acvity levels evidenced by a posive response to *either*:

Is (s)he more acve than before?

Does (s)he seem overacve?

(ii) Loss of control of acvity evidenced by a posive response to either:

Are his/her movements unproducve or lacking in purpose?

Has (s)he lost a sense of control over their acons?

(b) Hypoacve subtype defined by the presence of either (iii) or (iv)

(iii) Decreased speed of acons evidenced by a posive response to either:

Is (s)he moving more slowly than before?

Does it take longer than previously to perform simple tasks?

(iv) Decreased amount of speech evidenced by a posive response to either:

Does (s)he speak less than before?

Is (s)he lacking in spontaneous speech? E.g. only speaks when spoken to.

(c) Mixed subtype defined by the presence of both hyperacve and hypoacve criteria as outlined in (a) and (b) above.

(d) No subtype if neither hyperacve nor hypoacve criteria as outlined in (a) and (b) above.

DELIRIUM RATING SCALE-R-98 (DRS-R-98)

This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 SEVERITY SCALE

1. Sleep-wake cycle disturbance

Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present
1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations

Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and ''complex" if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present
1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2. Illusions present
3. Hallucinations present

3. Delusions

Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present
1. Mildly suspicious, hypervigilant, or preoccupied
2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3. Delusional

4. Lability of affect

Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present
1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language

Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assessfluency,grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language
1. Mild impairment including word-finding difficulty or problems with naming or fluency
2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities

Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes
1. Tangential or circumstantial
2. Associations loosely connected occasionally, but largely comprehensible
3. Associations loosely connected most of the time

7. Motor agitation

Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation
1. Mild restlessness of gross motor movements or mild fidgetiness
2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation

Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements
1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
3. Severe motor retardation with few spontaneous movements.

9. Orientation

Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time
1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both
2. Disoriented to time and place
3. Disoriented to person

10. Attention

Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive
1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses
2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task
3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory

Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact
1. Recalls 2/3 items; may be able to recall third item after category cueing
2. Recalls 1/3 items; may be able to recall other items after category cueing 3. Recalls 0/3 items

DRS-R-98 SCORESHEET Date: / / Time: _____

Name of patient: _____

Name of Rater: _____ [ ]

SEVERITY SCORE: [ ] **TOTAL SCORE:**

Severity Item	Item Score				Optional Information
Sleep-wake cycle	0	1	2	3	Naps Nocturnal disturbance only Day-night reversal
Perceptual disturbances	0	1	2	3	Sensory type of illusion or hallucination: olfactory tactile auditory visual Format of illusion or hallucination: simple complex
Delusions	0	1	2	3	Type of delusion: persecutory Nature: poorly formed systematized
Lability of affect	0	1	2	3	Type: angry anxious elated irritable dysphoric
Language	0	1	2	3	Check here if intubated, mute, etc.
Thought process	0	1	2	3	Check here if intubated, mute, etc.
Motor agitation	0	1	2	3	Check here if restrained *Type of restraints:*
Motor retardation	0	1	2	3	Check here if restrained *Type of restraints:*
Orientation	0	1	2	3	Date: Place: Person:
Attention	0	1	2	3	
Short-term memory	0	1	2	3	Record # of trials for registration of items: Check here if category cueing helped
Long-term memory	0	1	2	3	Check here if category cueing helped
Visuospatial ability	0	1	2	3	Check here if unable to use hands
Diagnostic Item	**Item Score**				**Optional Information**

Temporal onset of symptoms	0	1	2	3	Check here if symptoms appeared on a background of other psychopathology
Fluctuation of symptom severity	0	1	2		Check here if symptoms only appear during the night

Confusion Assessment Method (CAM)

(Adapted from Inouye et al., 1990)

Patient's Name: _____ Date: _____

Instructions: Assess the following factors.

Acute Onset

1. Is there evidence of an acute change in mental status from the patient's baseline?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Inattention

(*The questions listed under this topic are repeated for each topic where applicable.*)

2A. Did the patient have difficulty focusing attention (for example, being easily distractible or having difficulty keeping track of what was being said)?

_____ Not present at any time during interview

_____ Present at some time during interview, but in mild form

_____ Present at some time during interview, in marked form

_____ Uncertain

2B. (*If present or abnormal*) Did this behavior fluctuate during the interview (that is, tend to come and go or increase and decrease in severity)?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

2C. (*If present or abnormal*) Please describe this behavior.

_____

_____

Disorganized Thinking

3. Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable, switching from subject to subject?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Altered Level of Consciousness

4. Overall, how would you rate this patient's level of consciousness?

_____ Alert (*normal*)

_____ Vigilant (*hyperalert, overly sensitive to environmental stimuli, startled very easily*)

_____ Lethargic (*drowsy, easily aroused*)

_____ Stupor (*difficult to arouse*)

_____ Coma (*unarousable*)

_____ Uncertain

Disorientation

5. Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Memory Impairment

6. Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Perceptual Disturbances

7. Did the patient have any evidence of perceptual disturbances, such as hallucinations, illusions, or misinterpretations (for example, thinking something was moving when it was not)?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Agitation

8A. At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent, sudden changes in position?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Psychomotor Retardation

8B. At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space, staying in one position for a long time, or moving very slowly?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Altered Sleep-Wake Cycle

9. Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?

___ YES ___ NO ___ UNCERTAIN ___ NOT APPLICABLE

Scoring:

For a diagnosis of delirium by CAM, the patient must display:

1. Presence of acute onset and fluctuating discourse

AND

2. Inattention

AND EITHER

3. Disorganized thinking

OR

4. Altered level of consciousness

Source:

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948.

Confusion Assessment Method (CAM) Diagnostic Algorithm

Feature 1: Acute Onset and Fluctuating Course

This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day; that is, did it tend to come and go, or increase and decrease in severity?

Feature 2: Inattention

This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention; for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3: Disorganized Thinking

This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: Altered Level of Consciousness

This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

Source:

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948.

Table 1. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

FEATURES AND DESCRIPTIONS	ABSENT	PRESENT
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to three or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor or coma? ALERT: spontaneously fully aware of environment and interacts appropriately VIGILANT: hyperalert LETHARGIC: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally STUPOR: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state COMA: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4):	**Yes____**	**No____**

* The scores included in the 10-point RASS range from a high of 4 (combative) to a low of –5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores –1 to –5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: -1 for more than 10 seconds, -2 for less than 10 seconds, and –3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scores as either –4 for eye opening or movement with physical or painful stimulation or –5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.

† In completing the visual ASE, the patients were shown 5 simple pictures (previously published) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to nod "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter A during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: S, A, H, E, V, A, A, R, A, T. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

Ely, E.W., Inouye, S.K., Bernard, G.R., Gordon, S., Francis, J., May, L., Truman, B., Speroff, T., Gautam, S., Margolin, R., Hart, R.P., & Dittus, R. (2001). Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA, 286(21), 2703-2710.* Table 1, p. 2705.

The Hartford Institute for Geriatric Nursing would like to acknowledge the original author of this *Try This:*® Mary Elizabeth Happ, PhD, RN, FGSA, FAAN, for her contribution to this work.

DELIRIUM ETIOLOGY RATING CHECKLIST

This checklist accounts for the multifactorial etiologies in causing delirium by allowing a weighted approach for documenting the range of potential inputs in any single case. Therefore, raters may indicate multiple categories as contributing toward reaching the threshold for delirium. The relative importance of history, examination, and tests in supporting the significance of any particular causative factor will vary among cases so that the certainty of causation will depend on the judgement of the clinician involved based on all available information. Specific disorders assigned to categories are noted on the reverse side of this page.

Please "X" a box for each row as appropriate.

	[1]Definite Cause	[2]Likely Cause	[3]Present and Possible Contributory	[4]Present but Apparently not Contributory	[5]Ruled Out/Not Present/Not Relevant
Drug Intoxication					
Drug Withdrawal					
Metabolic/Endocrine Disturbance					
Traumatic Brain Injury					
Seizures					
Infection (intracranial)					
Infection (systemic)					
Neoplasm (intracranial)					
Neoplasm (systemic)					

Cerebrovascular					
Organ Insufficiency					
Other CNS					
Other					

See either side for a more detailed list of conditions grouped under each of the above categories and please check each one you considered as a contributory (definite, likely, or possible) factor.

Instrument	Delirium Index NOTE: This card is populated with information from the instrument's original validation study only.
Acronym	DI, DIDX
Primary use	Delirium Severity
Area assessed (Number of questions)	7 areas assessed: disorders of attention, thought, consciousness, orientation, memory, perception, psychomotor activity; 7 items total
Description	Observational delirium severity scale that does not require additional information from family members, clinical staff, or medical records; meant to be used in conjunction with the Mini-Mental State Examination (MMSE) and requires use of at least the first five questions of MMSE (can be substituted with similar questions from another cognitive screening tool). DI can be rated one or more times daily.
Versions	1
Scoring information	Each area scored on a scale from 0 (absent) to 3 (present and severe) using operational criteria for each score; total scores range from 0-21 with higher scores indicating higher severity. DI items are scored in conjunction with MMSE (or equivalent cognitive testing questions).
Cognitive testing	DI requires use of the MMSE or another cognitive screening tool to provide a basis for observation; at least the first five questions of MMSE constitute the basis of ratings.
Estimated time to rate	10 mins (estimate)
Require trained rater	Yes – clinician or trained lay rater
Administer to	Patient, in-person
Special resources required	MMSE instrument – copyright restrictions apply, see below for details to obtain. MMSE can be substituted with a similar cognitive screening tool.
How to obtain	Available for download at http://dx.doi.org/10.1111/j.1532-5415.2004.52471.x (Note: article may be located behind paywall). MMSE available at https://www.parinc.com/products/pkey/237
Licensing Fee*	None for instrument; MMSE has licensing fee for use (see link above).
Languages available	English, French
Highest COSMIN** rating	5.5/6†
Test Performance Characteristics	**McCusker 2004** •Reliability (internal consistency, Cronbach's alpha 0.74; inter-rater, intraclass correlation efficient 0.98) •Convergent validity (Compared to MMSE, Spearman correlation coefficients [delirium and dementia patients -0.83; delirium patients only -0.79; dementia patients only -0.78; neither delirium nor dementia -0.66) •Responsiveness (Standardized response mean in delirious patients with dementia/delirious patients without dementia [8-week follow up, -0.64/-0.64; 6 months -0.45/-0.81; 12 months -0.34/-0.51])

* Fees and licensing information is effective as of 2018, but is subject to change over time

Reference:

McCusker, J., Cole, M.G., Dendukuri, N., Belzile, E. (2004). The Delirium Index, a Measure of the Severity of Delirium: New Findings on Reliability, Validity, and Responsiveness. *Journal of the American Geriatrics Society*, 52:1744-9. doi:10.1111/j.1532-5415.2004.52471.x

Instrument	Cognitive Test for Delirium NOTE: This card is populated with information from the instrument's original validation study only.
Acronym	CTD
Primary use	Delirium Screening
Area assessed (Number of questions)	5 areas assessed: orientation (1 item); attention span (2 items); memory (2 items); comprehension (2 items); vigilance (2 items) 9 items total
Description	Assessment to identify delirium in the intensive care unti (ICU) that focuses on cognitive function. Designed to be brief and easy to administer to patients who are intubated or otherwise functionally restricted. Since cognitive testing is embedded in CTD and patients' scores may improve over time, this instrument is not ideal for daily rating.
Versions	1
Scoring information	Each area assessed has a formula to calculate a subtest score (0-6); the sum of these five subtest scores is the total score (0-30).
Cognitive testing	Assessment requires use of the Wechsler Memory Scale and Boston Diagnostic Aphasia Examination [these are copyrighted instruments; details on how to access listed below]
Estimated time to rate	10-15 minutes to administer and rate
Require trained rater	Yes – trained lay rater or clinician
Administer to	Patients in the ICU setting, including intubated or functionally restricted patients
Special resources required	Pictures for memory test and conversion formulas are included with test
How to obtain	Test available for download at http://dx.doi.org/10.1016/S0033-3182(96)71517-7 Wechsler Memory Scale: https://www.pearsonclinical.com/psychology/products/100000281/wechsler-memory-scale--fourth-edition-wms-iv.html Boston Diagnostic Aphasia Examination: http://www.linguisystems.com/products/product/display?itemid=10301
Licensing Fee*	None for instrument; Wechsler Memory Scale and Boston Diagnostic Aphasia Examination have licensing fees for use (see links above).
Languages available	English
Highest COSMIN** rating	In progress
Test Performance Characteristics	**Hart 1996** •Inter-rater Reliability: coefficient alpha=0.87 •Concurrent Validity: Correlation with Mini-Mental State Examination [MMSE] in patients with: delirium=0.82; dementia=0.81; depression=0.51; schizophrenia=0.48 •Sensitivity compared to MMSE=100% •Specificity compared to MMSE=95.1%

* Fees and licensing information is effective as of 2018, but is subject to change over time

** COSMIN is used to rate a study's evaluation of a survey or test's measurement properties. COSMIN does NOT rate the instrument itself, but helps readers understand if they can have confidence in the results of studies evaluating measurement properties of surveys and tests. For example, a rigorous study evaluating a test with poor measurement properties will receive a "good" COSMIN rating, while a poorly-conducted study evaluating a test with good measurement properties will receive a "poor" COSMIN rating. Small sample size can impact all COSMIN ratings. You must consider both the COSMIN rating and the results of studies provided when forming your opinion about that test. *COSMIN ratings shown are based solely on the instrument's original validation study.*

Reference:

Hart, R.P., Levenson, J.L., Sessler, C.N., Best, A.M., Schwartz, S.M., Rutherford, L.E. (1996). Validation of a Cognitive Test for Delirium in Medical ICU Patients. *Psychosomatics*, 37:533-546. doi:10.1016/S0033-3182(96)71517-7

The *Nursing Delirium Screening Scale*.

Features and descriptions	Symptom Rating (0-2)		
Symptom	Midnight-8am	8AM-4PM	4 PM - Midnight
I. Disorientation Verbal or behavioral manifestation of not being oriented to time or place or misperceiving persons in the environment			
II. Inappropriate behavior Behavior inappropriate to place and/or for the person; e.g. pulling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like.			
III. Inappropriate communication Communication inappropriate to place and/or for the person; e.g., incoherence, noncommunicativeness, nonsensical or unintelligible speech.			
IV. Illusions/Hallucinations Seeing or hearing things that are not there; distortions of visual objects.			
V. Psychomotor retardation Delayed responsiveness, few or no spontaneous actions/words; e.g., when the patient is prodded, reaction is deferred and/or the patient is unarousable.			
Total score			

Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. J Pain Symptom Manage. 2005;29(4):368-75.