Australasian Journal of Neuroscience Volume 29 ● Number 1 ● May 2019

Considering Causes for Hypoactive Delirium

Malissa A Mulkey[1], Sonya R Hardin[2], DaiWai M Olson[3], Cindy L Munro[4], Erik Everhart [5]

[1]Duke University Hospital, Durham, NC; [2]University of Louisville, Louisville, KY; [3]University of Texas Southwest, Dallas, TX, [4]Miami University, Coral Gables, FL ; [5]East Carolina University, Greenville, North Carolina.

Abstract

Delirium is defined as a mental disorder characterized by an abnormal state of cognition and awareness. Delirium is associated with an annual cost of $350 billion between the United States and Europe. Approximately 80% of delirium cases are either not identified or misdiagnosed. Older adults have the highest incidence due to the consequences of aging. Hypoactive delirium or "quite delirium" is the most common delirium subtype experienced by older adults.

Hypoactive delirium, is difficult to recognize and has worse outcomes than other subtypes. If detected, symptoms of hypoactive delirium are frequently dismissed as depression or dementia. Therefore, nurses need heightened vigilance in assessment and identification of hypoactive delirium. This article seeks to assist nurses in identifying hypoactive delirium by outlining factors that increase an individual's potential for developing hypoactive delirium.

Key Words

Delirium, Hypoactive, Pathophysiology, Nursing Care, Subtype.

Introduction

Delirium was defined by the American Psychiatric Association as a mental disorder characterized by an abnormal state of cognition and awareness (American Psychiatric Association, 1987). Additional delirium features include disorientation, inattention, misperception and hallucinations (American Psychiatric Association, 1987). Delirium subtypes (hypoactive, hyperactive and mixed) were identified in 1983, by Lipowski (Lipowski, 1983). The hypoactive subtype is frequently called "pure lethargy" or "quiet delirium." See Table 1. It manifests itself as decreased psychomotor activity, lethargy, inattention, slow responses to questions, and looks similar to depression and sedation (Bui, Pham, Shirkey, & Swan, 2017; Bush et al., 2017; Han et al., 2009; Wan, Kasliwal, McKenzie, & Barrett, 2011). As a result, it is often overlooked without a standardized delirium assessment (Han et al., 2009; Robinson, Raeburn, Tran, Brenner, & Moss, 2011; Zhang et al., 2016).

Like all delirium subtypes, hypoactive delirium can occur in a variety of individuals and settings. However, hypoactive delirium receives the least attention and is more difficult to recognize (American Psychiatric Association, 2013; Bush et al., 2017). Individuals with hyperactive or mixed delirium are 50% more likely to be identified than those with the hypoactive subtype (Bush, Marchington et al. 2017). Bui et al. (2017) compared delirium presence to International Classifications of Diseases (ICD) coding finding that only 3% of individuals who were delirium positive had a diagnosis of delirium due to lack of recognition or misdiagnosis (Bui et al., 2017).

Delirium triples mortality risk, however, rates are considerably higher in the setting of hypoactive delirium (Bui et al., 2017). Further complicating hypoactive delirium, survivors frequently have greater risk for long term cognitive impairment (Bush et al., 2017; Lipowski, 1983; van den Boogaard, Schoonhoven, van der Hoeven, van Achterberg, & Pickkers, 2012). A study by Avelino-Silva (2018) found 38% of hospitalized patients will die within 12 months of hospitalization. Of the 38% who died, delirium occurred in 47% of hospital admissions (Avelina-Silva, 2018). When comparing delirium subtype, hypoactive delirium was associated with 33% of the

Questions or comments about this article should be directed to Malissa Mulkey
Email address: Malissa.mulkey@icloud.com

DOI: 10.21307/ajon-2017-015

Table 1. Delirium Subtypes

Delirium Subtype	Definition /Defining Characteristics
Delirium	An acute fluctuating disturbance in attention, cognition, and level of consciousness
Hyperactive	Agitation Aggressiveness. Fidgety or restless Speaks quickly and loudly Vigilant Readily distracted Verbal and physical agitation Effective communication is difficult Hallucinations and delusions
Hypoactive	Motor retardation, Apathy Slowing of speech, Appears to be sedated Lethargic and quiet. Unusually listless Appears depressed Lack of motivation Withdrawn Almost mute Extreme stupor
Mixed	Combination of hyperactive and hypoactive delirium

cases and a hazard ratio of 2.43 (95%-1.64-3.59). The high mortality rates are likely because only 12% of nurses can definitively identify its core features resulting in delayed or missed identification (Bui et al., 2017; Bush et al., 2017).

While the underlying etiology is not completely clear, proposed mechanisms include metabolic derangements, inflammation, and neurotransmitter imbalances (van den Boogaard, Schoonhoven, Evers, et al., 2012). It is likely a combination of the three mechanisms that explain the evolution of hypoactive delirium. For example, as individuals adapt to overwhelming physiological stressors, inflammation ensues and alterations in neurotransmitters (mainly dopamine and acetylcholine) lead to behavioral symptoms (Mulkey, Hardin, Olson, & Munro, 2018). Predisposing factors particularly associated with the hypoactive subtype include advanced age, prior cognitive impairment, and medications (especially sedatives). As many as 80% of older adults experience delirium during hospitalization (Mulkey, Hardin, et al., 2018). Of those experiencing delirium, the hypoactive subtype accounts for 65% (Inouye, Westendorp, & Saczynski, 2014; van Velthuijsen, Zwakhalen, Mulder, Verhey, & Kempen, 2017) When combined predisposing factors with risk factors such as higher severity of illness, organ failure, metabolic abnormalities, hypoxia and/or anoxia, hypoactive delirium evolves (Hosker & Ward, 2017). One study found causes associated with delirium were infections at 38%, surgery at 24%, 5% were associated with medication use and 3% were related to falls. The remaining 30% had no established direct cause (van Velthuijsen et al., 2017). Another study looking at the frequency of delirium in older adults with dementia found as many as 89% of individuals with dementia develop delirium in the hospital (van Velthuijsen et al., 2017). This article seeks to assist nurses in identifying hypoactive delirium by outlining factors that increase an individual's potential for developing hypoactive delirium.

Advanced Age

Because of normal physiological changes, older adults are more likely to develop hypoactive delirium OR 3.3 (1.9-5.9) (Peterson et al., 2006). The aging process leads to declines in functional reserve, especially for those over 70 years of age. As a result, risk for hypoactive delirium triples (Bilotta, Lauretta, Borozdina, Mizikov, & Ro-

sa, 2013). For example, an age associated reduction in acetylcholine reduces the brain's ability to respond to stress (Mulkey, Hardin, et al., 2018).

Older adults often have a reduction in pulmonary vital capacity as high as 40% (Lowery, Brubaker, Kuhlmann, & Kovacs, 2013). As physiologic stress increases, cerebral oxygen delivery is diminished; further reducing the brain's ability to compensate. Therefore, even mild hypoxia can lead to decreased cognitive function (Maldonado, 2008). A multivariate analysis revealed that individuals with the hypoactive and mixed subtypes of delirium survived for shorter periods compared to individuals without delirium (hazard ratio [HR] =1.65 [95% confidence interval (CI) = 1.05–2.59, p = .029] and HR = 2.30 [95% CI = 1.44–3.69, p = .001], respectively in a cohort of palliative care patients (Kim, Kim, Bae, Park, & Kim, 2015). Therefore, nurses should have a heightened suspicion for delirium in older adults with an acute or critical illness, especially in the presence of co-morbid condition.

Prior Cognitive Impairmen

Prior cognitive impairment, such as dementia, is a significant risk factor for hypoactive delirium (Avelino-Silva, Campora, Curiati, & Jacob-Filho, 2017; Davis et al., 2015; Peritogiannis, Bolosi, Lixouriotis, & Rizos, 2015). Susceptibility to acute insults increases with underlying cognitive or neurodegenerative pathology (Davis et al., 2015). Synaptic loss related to dementia is a strong correlate of cognitive decline and neuronal pathology occurring years before signs of impairment (Avelino-Silva et al., 2017). The progressive degeneration represents significant brain disconnectivity and quantifiable loss of "brain reserve," or ability to compensate (Avelino-Silva et al., 2017; Numan et al., 2017; Rowe et al., 2015).

Although synaptic disconnection is a major contributor to delirium, other aspects of dementia, such as activation of the immune system and cholinergic dysfunction, are also likely contributors (Avelino-Silva et al., 2017; Davis et al., 2015; Numan et al., 2017). These factors contribute to the overall brain function frailty and simply reveal the degenerating brain's inability to compensate during times of overwhelming acute stress, such as critical illness (Avelino-Silva et al., 2017; Davis et al., 2015). Therefore, while not the cause, delirium may unmask an underlying neurodegenerative process such as dementia. These underlying neurodegenerative processes in turn, increase the susceptibility to delirium. Because prior cognitive impairment increases the brain's vulnerability, nurses should closely monitor any patient admitted with a history of dementia, brain injury or other cerebral conditions.

Medications

Factors associated with medication related hypoactive delirium include the number of medications or polypharmacy (generally > 3), the drug's anticholinergic potential, and the use of psychoactive medications (Kruskal-Wallis test: 17.39, p<0.005) (Horacek, Krnacova, Prasko, & Latalova, 2016). The number of agents is associated with the pharmacokinetic and pharmacodynamic effects of combining agents (e.g., drug-drug interactions, metabolic inhibitions, and additive negative effects) (Mulkey, Hardin, et al., 2018). Therefore, nurses should suspect the development delirium in patients with more than three medications such as those with multiple co-morbidities or advanced age.

Medications with psychoactive activity (i.e., opiates, benzodiazepines and anticholinergics) contribute to as much as 75% of hypoactive delirium (Horacek et al., 2016; Numan et al., 2017). Sedative agents contribute through several mechanisms. Sedatives decrease the amount of acetylcholine causing an acetylcholine deficiency. This deficiency results in a disruption of the blood-brain barrier's (BBB) ability to act as a filter, meaning the ability to restrict what crosses over from central circulation into cerebral circulation is impaired, therefore, neuronal damage is enhanced. Anticholinergics are also associated with a subsequent increase in symptom severity (Maldonado, 2008). Even after adjusting for physical impairment and admission diagnosis, anticholinergic drugs can double the risk for hypoactive delirium in acutely ill older adults.

Among sedatives, GABAergic medications (i.e. lorazepam and propofol) are the most significant and frequent culprits causing hypoactive delirium. Propofol has a higher incidence because it significantly reduces the brain's information integration capacity (Bilotta et al., 2013). Additionally, lorazepam increases the daily risk for delirium transition (Maldonado, 2008). Meagher (2011) found 15/35 or 42% of transitions into the hypoactive subtype were preceded by increased benzodiazepine dosing. In turn, benzodiazepine antagonists have been shown to reverse coma and improve hypoactive delirium, particularly in hepatic encephalopathy. Delirium has been found to increase length of time requiring mechanical ventilation [OR 7.0 (4.7-10.5)] more frequently than sedative use alone [OR 2.9 (1.8-4.6)]. These alterations

result in sensory overload and a disruption of the circadian rhythm, thereby, interfering with physiologic sleep patterns (Numan et al., 2017). Therefore, polypharmacy, anticholinergics and/or use of psychoactive drugs are one of the primary risk factors that quadruple the risk for developing hypoactive delirium (Rowe et al., 2015). Nurses need to be aware of the increased risk for developing delirium in patients with receiving sedatives, psychoactives or any anticholinergic medications.

Critical Illness

Illness, trauma, and surgical procedures offer several triggering factors: anesthetic use, extensive tissue trauma, blood loss and anemia, blood transfusions, hypoxia, and initiating the inflammatory process (Horacek et al., 2016). van den Boogaard (2012) found hypoactive delirium increased ICU length of stay (LOS) from 1-5 days to 2-9 days and hospital LOS from 1-5 days to 8-32 days. The severity of the initial injury or underlying medical condition, mechanical ventilation and high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) scores are significantly directly correlated with hypoactive delirium (Adamis, Meagher, Rooney, Mulligan, & McCarthy, 2017).

In a recent meta-analysis, mortality rates were significantly higher in individuals with reduced levels of consciousness admitted with respiratory conditions (38%). Respiratory conditions were found to increase the odds of developing delirium (OR 3.35 [2.59, 4.33] higher than cardiac at 5.4% (OR 10.00 [3.6, 27.76], endocrine at 2.5% (OR 25.6 [4.05, 161.73]) or gastrointestinal at 5.9% with odds ratios of 11.26 [4.34, 29.25] conditions (Todd et al., 2017). The more intense the insult, the more pronounced the response.

The combination of an intense insult such as an acute infection or trauma, and the associated systemic inflammatory response result in high levels of stress capable of altering BBB permeability. This leads to the initiation of a cerebral inflammatory response and release of cerebral cytokines (Kozak et al., 2017). As a result, there are shifts in extravascular fluid with potential to develop perivascular edema. With the formation of edema, there is a significant risk for diffuse microcirculatory impairment along with decreased perfusion and longer oxygen diffusion distances (Kozak et al., 2017).

Cerebral and systemic leukocyte activation (immune response) result in release of free oxygen radicals and enzymes exacerbating the systemic inflammatory response and further contributing to the evolution of hypoactive delirium (Bergeron, Dubois, Dumont, Dial, & Skrobik, 2001; Nguyen et al., 2014; van den Boogaard, Schoonhoven, Evers, et al., 2012). Therefore, delirium may represent a central nervous system manifestation of a systemic disease state that has crossed the BBB. Because critical illness increases physiologic stress on the brain, patients in critical care units are particularly vulnerable and should be routinely monitored for an appropriate standardized delirium screening tool (Mulkey, Roberson, Everhart, & Hardin, 2018).

Organ Failure and Metabolic Abnormalities

Abnormal laboratory values can significantly increase the risk of hypoactive delirium in all populations OR 3.4 (1.3-8.7) (Bilotta et al., 2013; Horacek et al., 2016; Inouye et al., 2014). Alterations in sodium (sodium <130 or >150 mEq/L) and potassium (<3.0 or >6.0 mEq/L) levels (Pearson's r=0.2189, P< 0.05), as well as other electrolyte, can lead to the mental status changes associated with delirium. While not clearly understood, sodium imbalances lead to cellular swelling, thereby impairing oxygen delivery (Maldonado, 2008). In the elderly, electrolyte abnormalities, especially hyponatremia, often caused by renal disease and chronic diuretic therapy should be promptly corrected (Bilotta et al., 2013). Patients with an increased risk electrolyte abnormalities such as those with renal impairment, diabetes, cirrhosis or the presence of electrolyte imbalances should be closely observed for signs and symptoms of delirium.

Dehydration, fluid deficits, prolonged fasting time (> 6 hours), and low serum albumin concentrations contribute because of hypoperfusion, both cerebral and renal (Horacek et al., 2016). This is thought to be due to increased drug and metabolite concentrations and decreased renal elimination of drugs, metabolites, and toxic by-products. Failure to correct hypoglycemia (<60 mg/dL), hyperglycemia (>300 mg/dL), and anemia (Hb <120g/L) are risk factors due to the effects on brain metabolism and oxygen transport. For example, Horace (2016) found low Hb levels (<120g/L) increased delirium duration by 11 hours. These alterations induce drug and hormone binding activity along with antioxidant and oxygen radical trapping and are correlated with cognitive impairment. Because of the associated impairment in cognitive performance these abnormalities are considered precipitating factors (Horacek et al., 2016).

Therefore, nurses should be suspicious for delirium in patients who have an increased

risk for dehydration or anemia such as post-operative patients and those with acute bleeding.

Hypoxia and Anoxia

Hypoxia and global mild ischemic illness injury often co-exist with critical illness, increasing oxidative failure. This correlates with a 17% increased risk for developing hypoactive as well as delirium progression (Bilotta et al., 2013; Maldonado, 2008; Stransky et al., 2011). Low hemoglobin, hematocrit, and pulse oximetry occur approximately 48 hours before the onset of oxidative stress with alterations being more severe in individuals experiencing hypoactive delirium (Maldonado, 2008; Stransky et al., 2011). Severe illness, combined with decreased oxygen supply and/or increased oxygen demand leads to decreased cerebral oxygen availability (Maldonado, 2008). Inadequate oxygenation leads to abnormal neurotransmitter function, ineffective elimination of neurotoxic by-products, and alterations in electrolytes (Numan et al., 2017).

Rapid depletion of energy stores from cerebral ischemia result in cell death. These changes then result in reconfiguration of neuronal networks. For example, sepsis causes an oxygen supply and demand imbalance due to lower hemoglobin level, cerebral blood flow, and cerebral oxygen delivery (Nedergaard, Jensen, Stylsvig, Lauridsen, & Toft, 2016). In critically ill delirious patients, reduced cerebral blood flow and the associated imbalances increase the chronic hypoxic injury. Patients admitted with an acute respiratory distress or failure and those with a history of respiratory conditions such as asthma and COPD are at increased risk.

Identification and Assessment

Using a standardized assessment tool for sedation and agitation can assist with identifying patients who may be developing hypoactive and hyperactive delirium symptoms (Mulkey, Roberson, et al., 2018). Likewise, use of these assessment screening tools can differentiate delirium subtypes in patients identified. The Richmond Agitation Sedation Scale (RASS) is a component of the Confusion Assessment Method- Intensive Care Unit (CAM-ICU). Scoring is based on the individual's activity with -5 being nonresponsive to +4 being agitated and combative. Individuals with a RASS of -2 to +4 are considered appropriate for delirium assessment with the CAM-ICU. If the CAM-ICU is positive for delirium, the RASS score can also be used to indicate a delirium subtype. Individuals with a lower score (0 to -3) are considered hypoactive while a higher score (+1 to +4) indicates hyperactive delirium (Michaud, Bullard, Harris, & Thomas, 2015; Peterson et al., 2006).

Table 2. Implications for Practice

Hypoactive delirium is difficult to detect
Understanding clinical features and risk factors is critical for detection
Standardized assessment tools appropriate for the population should be used
Frequent assessments are needed because delirium fluctuates
Prevention and intervention strategies should be implemented early
Regularly assess medication for delirium risk and response
Strongly consider continuation of home medications,
Promote adequate pain management and reduction of sedation to the minimum dose required
Early mobility, limiting restraint, adequate hydration and nutrition are key to prevention and treatment
Timing of care should promote periods of uninterrupted rest and sleep (i.e. giving up middle of the night bathing, timing of medication administration and routine lab/x-rays)
Establishing day and night routines will reduce risk and help resolve delirium

Nursing Implications

Nurses are the cornerstone to prevention and identification of hypoactive delirium and preventing the associated negative sequela. Because hypoactive delirium is more difficult to detect, nurses need to ensure they understand the clinical features and risk factors. For early accurate detection nurses should frequently assess individuals using an appropriate standardized tool. Maintaining consistency and accuracy of assessments has been identified as a significant challenge to obtaining ongoing accurate assessments. (See Table 2) Understanding factors that increase an individual's risk for developing delirium will assist with identification, and selection of prevention and intervention strategies specific to the individual. Because medications can have a significant impact on delirium risk, medications and patient response should be reviewed on an ongoing basis. Serious consideration should be directed toward continuation of home medications, adequate pain management and reducing sedation to the minimum dose required.

Early mobility, limiting use of restraints, adequate hydration, and limiting interruptions to maintaining adequate nutrition are key to prevention and treatment of delirium. Finally, timing of care is also extremely important. Promoting quiet time consistent with circadian rhythms (2-4 am & 2-4 pm), uninterrupted sleep, establishing day and night routines and timing of care (i.e. giving up middle of the night bathing, timing of medication administration and routine lab/x-rays) will reduce risk and help resolve delirium. To assist in remembering key components of nursing care vital to delirium management, the following acronym Q-U-I-E-T has been provided. (See Table 3)

Conclusion

Often unrecognized and underappreciated, hypoactive delirium or "quiet delirium" is more difficult to detect, therefore, frequently associated with delays in delirium treatment and increased mortality (up to 58%) (Todd et al., 2017). Advanced age and prior cognitive impairment are predisposing factors due to a reduced ability to compensate for neurochemical changes. Medications with anticholinergic or sedative effects and severe illness result in higher levels of stress. While there are many causes for hypoactive delirium, combining risk factors, as seen in critical illness, magnifies these risks. Understanding the risk factors will allow nurses to identify the presence of hypoactive delirium. Identification through ongoing assessment for delirium is of the utmost importance (Peritogiannis et al., 2015).

Reflective Questions

How is hypoactive delirium different from other delirium subtypes, and why is it important?

Of the individuals I care for, who is at greatest risk for developing hypoactive delirium?

What interventions might be appropriate for the prevention of hypoactive delirium?

Do I currently provide care that promotes the prevention of delirium?

Acknowledgements

Beverly Murphy, MLS, AHIP, FMLA, Medical Librarian for assistance with the literature review.

References

Adamis, D., Meagher, D., Rooney, S., Mulligan, O., & McCarthy, G. (2017). A comparison of outcomes according to different diagnostic systems for delirium (DSM-5, DSM-IV, CAM, and DRS-R98). International Psychogeriatrics, 1-6. doi:10.1017s1041610217001697

American Psychiatric Association. (1987). Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R (3rd, rev. ed.). Wash-

Table 3. Nursing Delirium Prevention Strategies

Q- Quick and Accurate Assessment with a validated tool

U- Understand Risk Factor

I- Initiate Discussion of Home Medications, Adequate Pain Control and Minimizing Sedation

E- Encourage Early Mobility, Nutrition, Hydration, and Restraint Release

T- Timing of Care to Promote Sleep

ington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (Fifth ed.). Arlington, VA: American Psychiatric Association.

Avelino-Silva, T. J., Campora, F., Curiati, J. A., & Jacob-Filho, W. (2017). Association between delirium superimposed on dementia and mortality in hospitalized older adults: A prospective cohort study. PLoS Medicine, 14 (3), e1002264. doi:10.1371/journal.pmed.1002264

Bergeron, N., Dubois, M. J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Medicine, 27(5), 859-864.

Bilotta, F., Lauretta, M. P., Borozdina, A., Mizikov, V. M., & Rosa, G. (2013). Postoperative delirium: Risk factors, diagnosis and perioperative care. Minerva Anestesiologica, 79(9), 1066-1076.

Bui, L. N., Pham, V. P., Shirkey, B. A., & Swan, J. T. (2017). Effect of delirium motoric subtypes on administrative documentation of delirium in the surgical intensive care unit. Journal of Clinical Monitoring and Computing, 31(3), 631-640. doi:10.1007/s10877-016-9873-1

Bush, S. H., Marchington, K. L., Agar, M., Davis, D. H., Sikora, L., & Tsang, T. W. (2017). Quality of clinical practice guidelines in delirium: a systematic appraisal. BMJ Open, 7(3), e013809. doi:10.1136/bmjopen-2016-013809

Davis, D. H., Skelly, D. T., Murray, C., Hennessy, E., Bowen, J., Norton, S., . . . Cunningham, C. (2015). Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium. American Journal of Geriatric Psychiatry, 23 (4), 403-415. doi:10.1016/j.jagp.2014.08.005

Han, J. H., Morandi, A., Ely, E. W., Callison, C., Zhou, C., Storrow, A. B., . . . Schnelle, J. (2009). Delirium in the nursing home patients seen in the emergency department. Journal of the American Geriatrics Society, 57(5), 889-894. doi:10.1111/j.1532-5415.2009.02219.x

Horacek, R., Krnacova, B., Prasko, J., & Latalova, K. (2016). Delirium as a complication of the surgical intensive care. Neuropsychiatric Disease and Treatment, 12, 2425-2434. doi:10.2147/NDT.S115800
Hosker, C., & Ward, D. (2017). Hypoactive delirium. BMJ : British Medical Journal (Online), 357. doi:http://dx.doi.org/10.1136/bmj.j2047

Inouye, S. K., Westendorp, R. G., & Saczynski, J. S. (2014). Delirium in elderly people. Lancet, 383(9920), 911-922. doi:10.1016/s0140-6736(13)60688-1

Kim, D. W., Kim, H. K., Bae, E. K., Park, S. H., & Kim, K. K. (2015). Clinical predictors for delirium tremens in patients with alcohol withdrawal seizures. American Journal of Emergency Medicine, 33(5), 701-704. doi:10.1016/j.ajem.2015.02.030

Kozak, H. H., Uguz, F., Kilinc, I., Uca, A. U., Serhat Tokgoz, O., Akpinar, Z., & Ozer, N. (2017). Delirium in patients with acute ischemic stroke admitted to the non-intensive stroke unit: Incidence and association between clinical features and inflammatory markers. Neurologia i Neurochirurgia Polska, 51(1), 38-44. doi:10.1016/j.pjnns.2016.10.004

Lipowski, Z. J. (1983). Transient cognitive disorders (delirium, acute confusional states) in the elderly. American Journal of Psychiatry, 140(11), 1426-1436. doi:10.1176/ajp.140.11.1426

Lowery, E. M., Brubaker, A. L., Kuhlmann, E., & Kovacs, E. J. (2013). The aging lung. Clinical Interventions in Aging, 8, 1489-1496. doi:10.2147/CIA.S51152

Maldonado, J. (2008). Pathoetiological model of delirium: A comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. Critical Care Clinics, 24(4), 789-856, ix. doi:10.1016/j.ccc.2008.06.004

Michaud, C. J., Bullard, H. M., Harris, S. A., & Thomas, W. L. (2015). Impact of Quetiapine Treatment on Duration of Hypoactive Delirium in Critically Ill Adults: A Retrospective Analysis. Pharmacotherapy, 35(8), 731-739. doi:10.1002/phar.1619

Mulkey, M. A., Hardin, S. R., Olson, D. M., & Munro, C. L. (2018). Pathophysiology review: Seven neurotransmitters associated with delirium. Clinical Nurse Specialist, 32(4), 195-211. doi:10.1097/nur.0000000000000384

Mulkey, M. A., Roberson, D. W., Everhart, D. E., & Hardin, S. R. (2018). Choosing the

Right Delirium Assessment Tool. Journal of Neuroscience Nursing, 50(6), 343-348. doi:10.1097/jnn.0000000000000403

Nedergaard, H. K., Jensen, H. I., Stylsvig, M., Lauridsen, J. T., & Toft, P. (2016). Non-sedation versus sedation with a daily wake-up trial in critically ill patients recieving mechanical ventilation - effects on long-term cognitive function: Study protocol for a randomized controlled trial, a substudy of the NONSEDA trial. Trials, 17(1), 269. doi:10.1186/s13063-016-1390-5

Nguyen, D. N., Huyghens, L., Zhang, H., Schiettecatte, J., Smitz, J., & Vincent, J. L. (2014). Cortisol is an associated-risk factor of brain dysfunction in patients with severe sepsis and septic shock. Biomed Research International, 2014, 712742. doi:10.1155/2014/712742

Numan, T., Slooter, A., van der Kooi, A. W., Hoekman, A. M. L., Suyker, W. J. L., Stam, C. J., & van Dellen, E. (2017). Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clinical Neurophysiology, 128(6), 914-924. doi:10.1016/j.clinph.2017.02.022

Peritogiannis, V., Bolosi, M., Lixouriotis, C., & Rizos, D. V. (2015). Recent Insights on Prevalence and Corelations of Hypoactive Delirium. Behavioural Neurology, 2015, 416792. doi:10.1155/2015/416792

Peterson, J. F., Pun, B. T., Dittus, R. S., Thomason, J. W., Jackson, J. C., Shintani, A. K., & Ely, E. W. (2006). Delirium and its motoric subtypes: A study of 614 critically ill patients. Journal of the American Geriatrics Society, 54(3), 479-484. doi:10.1111/j.1532-5415.2005.00621.x

Robinson, T. N., Raeburn, C. D., Tran, Z. V., Brenner, L. A., & Moss, M. (2011). Motor subtypes of postoperative delirium in older adults. Archives of Surgery, 146(3), 295-300. doi:10.1001/archsurg.2011.14

Rowe, A. S., Hamilton, L. A., Curtis, R. A., Davis, C. R., Smith, L. N., Peek, G. K., & Reynolds, V. W. (2015). Risk factors for discharge on a new antipsychotic medication after admission to an intensive care unit. Journal of Critical Care, 30(6), 1283-1286. doi:10.1016/j.jcrc.2015.08.009

Stransky, M., Schmidt, C., Ganslmeier, P., Grossmann, E., Haneya, A., Moritz, S., . . . Trabold, B. (2011). Hypoactive delirium after cardiac surgery as an independent risk factor for prolonged mechanical ventilation. Journal of Cardiothoracic and Vascular Anesthesia, 25(6), 968-974. doi:10.1053/j.jvca.2011.05.004

Todd, A., Blackley, S., Burton, J. K., Stott, D. J., Ely, E. W., Tieges, Z., . . . Shenkin, S. D. (2017). Reduced level of arousal and increased mortality in adult acute medical admissions: a systematic review and meta-analysis. BMC Geriatrics, 17(1), 283. doi:10.1186/s12877-017-0661-7

van den Boogaard, M., Schoonhoven, L., Evers, A. W., van der Hoeven, J. G., van Achterberg, T., & Pickkers, P. (2012). Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Critical Care Medicine, 40(1), 112-118. doi:10.1097/CCM.0b013e31822e9fc9

van den Boogaard, M., Schoonhoven, L., van der Hoeven, J. G., van Achterberg, T., & Pickkers, P. (2012). Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. International Journal of Nursing Studies, 49(7), 775-783. doi:10.1016/j.ijnurstu.2011.11.016

van Velthuijsen, E. L., Zwakhalen, S. M., Mulder, W. J., Verhey, F. R., & Kempen, G. I. (2017). Detection and management of hyperactive and hypoactive delirium in older patients during hospitalization: A retrospective cohort study evaluating daily practice. International Journal of Geriatric Psychiatry. doi:10.1002/gps.4690

Wan, R. Y., Kasliwal, M., McKenzie, C. A., & Barrett, N. A. (2011). Quetiapine in refractory hyperactive and mixed intensive care delirium: a case series. Critical Care (London, England), 15(3), R159. doi:10.1186/cc10294

Zhang, W., Hu, W., Shen, M., Ye, X., Huang, Y., & Sun, Y. (2016). Profiles of delirium and the clinical outcomes of patients who underwent coronary artery bypass grafting: a prospective study from China. Journal of Clinical Nursing, 25(5-6), 631-641. doi:10.1111/jocn.13089