Chapter 5

Management of Delirium

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Additional information is available at the end of the chapter

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1. Introduction

Delirium is categorized in the cognitive disorders, characterized by acute onset, global impairment in cognitive, emotional, mental, and behavioral functioning, fluctuating level of consciousness, attention impairment, decreased or increased psychomotor activity and the disturbance of sleep-wake cycle. Emotional and behavioral abnormalities are common presented with some neurological manifestations, e.g., tremor, asterixis, nystagmus, incoordination, urinary incontinence.

Delirium is a behavioral disturbance and serious complication commonly found in consultation-liaison psychiatry. Its prevalence and incidence rates are varied, possibly depend on severity of illness, patient population, the method of assessment and the diagnostic criteria. Prevalence of delirium ranges from 10% to 30% and its incidence is between 3% and 29% for patients admitted in general hospitals (Siddiqi et al., 2006, Maneeton et al., 2007a, Praditsuwan et al., 2012). High prevalence and incidence are noted in elderly and severely ill patients. For instance, the prevalence of delirium in elderly and ICU patients are up to 40% and 80%, respectively (Bledowski and Trutia, 2012, Praditsuwan et al., 2012).

An occurrence of delirium is associated with miserable clinical outcomes. It often increases morbidity, mortality, length of hospitalization, institutionalization, and poor functional outcome (Siddiqi et al., 2006, Cole et al., 2009, Fong et al., 2012). The mortality rate is higher in patients with hypoactive subtype of delirium (Yang et al., 2009).

Delirium is often under recognized by health professionals. There are many faces for the clinical presentation of delirium. It can be caused by a variety of etiology. To prevent and minimize the consequences of delirium, physician should prompt intervenes for this condition (Attard et al., 2008).

This chapter aims to summarize current strategies for managing and preventing delirium caused by a variety of etiology, except substance withdrawal delirium. In addition, etiologies, clinical manifestations and risk factors are also addressed.

2. Definition

According to the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (DSM-IV-TR), delirium due to a general medical condition is defined by four criteria: a. disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention; b. a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia; c. the disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day; d. there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition(American Psychiatric Association, 2005).

For the ICD-10, delirium not induced by alcohol and other psychoactive substances is defined as an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep-wake schedule. The duration is variable, and the degree of severity ranges from mild to very severe (World Health Organization, 1993).

3. Clinical manifestation

The hallmark of delirium is rapid and fluctuated disturbance of consciousness, orientation and global cognitive functioning.

3.1. Prodromal phase

Prodromal symptoms may be observed for hours to a few days in some patients. These symptoms include restlessness, anxiety, irritability, hypervigilance, drowsiness, transient hallucination, nightmare and etc. Because these symptoms are not specific for delirium, they may be overlooked by health care providers.

3.2. Fluctuating course

Most patients have rapidly changes of emotion and cognition. The diurnal fluctuation is common. Because the patient’s condition is usually worse at night time, this clinical feature may be called "sundowner's syndrome". During thi speriod of time, delusion, hallucination, depression, irritability and anxiety are frequently prominent.

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3.3. Disorientation

Most patients are disoriented to time, place and/or person.

3.4. Sleep-wake cycle abnormality

Sleep-wake disturbance is usually noted in delirium. The patients may be sleepy during the day and stay awake at night. The sleep pattern is characterized by brief and fragmented periods of sleeping time.

3.5. Psychomotor disturbance

Arousal disturbance is common and usually related to the abnormality of reticular activating system. Currently, psychomotor behavior of delirium is categorized into four subtypes, including normal, hypoactive, hyperactive, and mixed (Yang et al., 2009). Hyperactive delirium is characterized by agitation, restlessness and hypervigilance. Lethargy, somnolence, apathy, depression, catatonia and quiet confusion are common for hypoactive delirium. For the mixed subtype, it manifests both psychomotor hypoactivity and hyperactivity.

3.6. Perceptual disturbance

Because most delirious patients cannot discriminate and integrate the sensory stimuli around them, illusions and hallucinations are common in this population. The patients are easily frustrated or distracted when they encounter new information.

3.7. Dysfunction of higher cortical function

Although the DSM IV-TR does not include language difficulties, most patients have speech abnormality, such as rambling, irrelevancy and incoherent. Impairment of memory, especially the short-termone, can be found in most patients. The impaired short-term memory may be explained by the loss of concentration, perceptual disturbance, and/or malfunction of the hippocampus. Since delirium is a global cerebral dysfunction, higher cortical dysfunction such as dysphasia, dyspraxia, dysgraphia, is also common. In addition, the patients may have other neurological signs, e.g., tremor, asterixis, incoordination and urinary incontinence.

4. Predisposing and risk factors

Individuals are differently susceptible to delirium. Despite the exposing to the same causative factor, individuals are not equally prone to develop delirium. Predisposing and risk factors appear to play a role in the susceptibility to delirium. There have been numerous studies on predisposing and risk factors of delirium. For instance, Inouye and Charpentier (1996) demonstrated the five independent precipitating factors for delirium, including use of physical restraints, malnutrition, more than three medications taken, use of bladder catheter

and any iatrogenic event. Recently, risk factors for delirium have been established in four domains, including patient characteristics, chronic pathology, acute illness, and environmental factors (Van Rompaey et al., 2009). Another study in elderly patients receiving hip surgery found that early symptoms of memory impairments, incoherence, disorientation and underlying somatic illness were predictors of delirium (de Jonghe et al., 2007).

In general, the common predisposing and risk factors for delirium that have been recognized are age of 60 years or over, brain damage (e.g., stroke, brain injury), chronic organic brain syndrome (e.g., dementia of Alzheimer type), postoperative patients, history of delirium, diabetes, malignancy, sensory impairment (e.g., blindness, deafness) and HIV infection.

5. Etiology

Common causes of delirium include central nervous system (CNS) diseases, systemic diseases, intoxication or withdrawal from substance and toxic agent. Most delirious patients often encounter with multiple causes.

5.1. Medications

The use of medication is one of the most common causes of delirium. Medications that have been identified are antibiotics, antidepressants, antihistamines, anticholinergic agents, antiparkinson agents, antipsychotic medications, antineoplastics, anticonvulsants, antituberculosis agents, cardiac drugs, diuretics, non-steroidal anti-inflammatory drugs, L-dopa, lithium, opiates, sedative-hypnotics, steroids, sympathomimetic agents. It has been found that the administration of three medications or more is a risk factor for delirium. Because elderly patients tend to take multiple medications, they are a population at particular risk for delirium (Inouye, 2004, Clegg and Young, 2011, Catic, 2011).

5.2. Neurological causes

Delirium is a state of global cerebral dysfunction. Therefore, any pathology in the CNS may cause this syndrome. Common neurological contributors for delirium consist of head injury, stroke, hypertensive encephalopathy, intracranial neoplasm and epilepsy (Ramirez-Bermudez et al., 2006, Martin, 2012).

5.3. Infection

Infection, in particular sepsis, can be a cause of delirium (Rahkonen et al., 2000, Srinonprasert et al., 2011, Zampieri et al., 2011). Other infectious diseases commonly found, including CNS infection (Ramirez-Bermudez et al., 2006); meningitis, encephalitis, brain abscess, neurosyphilis, HIV encephalopathy and other systemic infection (Warshaw and Tanzer, 1993, Eriksson et al., 2011, van Gool et al., 2010).

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5.4. Metabolic disorders

Metabolic disturbances are frequently associated with delirium (Khurana et al., 2011, Grover et al., 2012). Common metabolic abnormalities consist of hepatic encephalopathy, hypo- or hyperglycemia, hypoxia, hypo- or hypernatremia, hypo- orhypercalcemia, hypo- orhypermagnesemia, acidosis, uremia and metabolic acidosis (Aldemir et al., 2001, Khurana et al., 2011).

5.5. Vitamin deficiency

Vitamin deficiency, such as thiamine, B12, nicotinic acid, folic acid, is a common factor contributing to the development of delirium (Kane et al., 1993, O'Keeffe et al., 1994, Harrington et al., 2011).

5.6. Endocrine abnormalities

Several lines of evidence suggest that endocrine disturbances may be a cause of delirium (Olsson, 1999, Grover et al., 2012). Common abnormalities include hypo- or hyperthyroidism, hypo- or hyperparathyroidism, Cushing's syndrome, Addison's disease, pheochromocytoma and hypopituitary diseases (Olsson, 1999, Maldonado, 2008a).

5.7. Withdrawal syndrome

The withdrawal of some drugs or substances could precipitate the phenomena of delirium. Those possible causative agents are alcohol, benzodiazepines, barbiturates, other sedatives and hypnotics (Saitz, 1998, Trevisan et al., 1998, Maldonado, 2008a, Yu et al., 2012).

5.8. Substance abuse

Numerous substances, for instance methamphetamine, cocaine, hallucinogens, inhalants, opioids and bath salts may be a cause of delirium (Nakatani and Hara, 1998, Maldonado, 2008a, Fadel and Serra, 2009, Kasick et al., 2012 Burapakajornpong et al., 2012).

5.9. Toxin exposure

Toxin exposure is also a significant contributor in the development of delirium. Example toxic agents are heavy metals and toxins (Maldonado, 2008a).

6. Pathophysiology

Since there have been only a few studies on the mechanism of delirium, its pathophysiology are still poorly understood. However, some recent findings suggest several mechanisms possibly related to the development of delirium, including abnormality in neurotransmitters, inflammatory response, the blood-brain barrier permeability, cerebral oxidative metabolism and the hypothalamic-pituitary adrenal axis (Flacker and Lipsitz, 1999, van der Mast,

1998, Gunther et al., 2008, Marcantonio et al., 2006). However, the heterogeneity of the delirium syndrome and the populations are the major challenges. The mechanism may differ in the various clinical settings and individual risk factors (Chaput and Bryson, 2012).

6.1. Neurotransmitter abnormalities

According to the neurotransmitter hypothesis, delirium is a result of complex interacting neurotransmitter systems that modulate the control of cognition, behavior, and emotion and pathologic processes. The decreased oxidative metabolism of the brain causes cerebral dysfunction due to abnormalities of many neurotransmitter systems. Various symptoms and clinical manifestations of delirium may be associated with numerous neurotransmitter activities (van der Mast, 1998). More specifically, the pathogenesis of delirium may include the decreased cholinergic activity; both decreased and increased serotonergic and gamma-aminobutyric acid activities and excessive release of dopamine, norepinephrine and/or glutamate (Flacker and Lipsitz, 1999).

6.2. Reduction of cerebral oxidative metabolism

Impaired oxidative metabolism is related to the development of delirium (Seaman et al., 2006). Its dysfunction is often associated with a decrease of oxygen supply to the brain, which leads to the widespread of cerebral dysfunction. Therefore, patients with oxygen exchange dysfunction, such as cardiac diseases, intraoperative hypotension, perioperative factors, intrinsic lung diseases and anemia may be important causes of delirium (Maldonado, 2008b, Ali et al., 2011).

6.3. Inflammatory response

Delirium is high prevalence in patients with systemic inflammatory diseases, including infection, malignancy, and the postoperative state (Marcantonio et al., 2006). Recent findings suggest the association between cytokines and the development of delirium. Cytokine dysregulation can cause neuronal injury by means of (1) abnormal neurotransmission, (2) apoptosis and (3) activation of microglia and astrocytes producing free radicals, complement factors, glutamate, and nitric oxide (Wilson et al., 2002, Simone and Tan, 2011).The cytokines considered as proinflammatory factors (e.g., interleukin-1, interleukin-6 and interleukin-8, tumor necrosis factor-alpha, interferon gamma and C-reactive protein) and anti-inflammatory factors (e.g., interleukin receptor antagonist and insulin-like growth factor -1) have been hypothesized as factors related to the pathogenesis of delirium (Gunther et al., 2008, van den Boogaard et al., 2011).

6.4. Increased activity of the hypothalamic-pituitary adrenal axis

The disturbance of hypothalamic-pituitary-adrenal (HPA) axis is another hypothesis relevant to the pathogenesis of delirium. It has been known that excessive cortisol or glucocorticoid affect memory and mood in delirium (Maldonado, 2008b). The association between delirium and disturbance of dexamethasone suppression (DST) has been noted (Robertsson

et al., 2001). In addition, the elevation of cerebrospinal fluid (CSF) and plasma cortisol levels observed in hip fracture patients with delirium also support the hypothesis that high brain cortisol levels are related to delirium development (Pearson et al., 2011).

7. Management

Once delirium is diagnosed, prompt and appropriated interventions should be implemented. Other than the DSM IV-TR criteria for delirium, several measures are helpful to confirm the diagnosis and determine the progress of illness course. Since common causes of delirium are medical/surgical conditions and medications, priority should be given to specific treatment for the removal of these causes. Frequently, delirium is associated with multi-factorial etiology, all possible causes, therefore, should be investigated and corrected. Because behavioral and other psychiatric disturbances are also common, psychopharmacological and psychosocial interventions are also needed in most patients. Those include the control of behavioral disturbances, preventing complications (e.g., accident, falling) and supporting functional needs (Burns et al., 2004).

7.1. Assessment

Physicians should review all possible contributed factors for the development of delirium, including histories of medical/psychiatric illness, prescribed or over-the-counter medications and substance uses. Physical examination should address in all systems, especially the one possibly causing or contributing to the development of delirium. Mental status examination should focus on cognitive function, such as orientation, memory, concentration, attention, language ability, mood/affect and psychotic symptoms.

The use of screening tests or tools prior to the occurrence of delirium or in patients suspected of having delirium is very helpful for the early detection of delirium. In addition, some measures can be used to determine the progress of delirium. Bedside cognitive screening tests, such as the three-item registration, the three-item delayed recall test, the clock drawing test, the problem-solving task and the ability of abstraction, can determine the cognitive impairment (de Wet et al., 2007). Example measures of delirium are the Mini-Mental State Examination (MMSE), the original and revised versions of Delirium Rating Scale (DRS and DRS-98), the Memorial Delirium Assessment Scale (MDAS) and the Confusion Assessment Method (CAM) recommended (Breitbart et al., 1997, Trzepacz et al., 2001, Salawu et al., 2009, Wongpakaran et al., 2011, Inouye et al., 1990).

To identify the causes of delirium, laboratory studies are essential. Generally, basic investigation for delirium includes a routine blood test, including complete blood count, electrolytes, glucose levels, liver function test, thyroid function test, renal function test, blood alcohol, blood ammonia, calcium/magnesium/phosphate levels, pulse oximetry, urinalysis, urine drug screen, electrocardiogram (ECG), CSF study, radiological studies (e.g., chest x-ray and computed tomography (CT) the head) (Salawu et al., 2009, Lorenzl et al., 2012). However, further studies to verify infection, hypoxia and etc are also important for some pa-

tients. In equivocal case, electroencephalography (EEG) can be helpful. While the EEG pattern of alcohol or sedative withdrawal delirium usually presents with the prominence of beta activity, diffuse bilateral slowing records are typical for delirium due to a general medical condition. This later pattern of the EEG is also helpful for being used as a confirm test for the delirious state (Jacobson and Jerrier, 2000, Salawu et al., 2009, Sidhu et al., 2009).

7.2. Specific and supportive treatment

The specific treatment for delirium is the removal of all possible causes. Therefore, the precipitating factors must be promptly addressed and corrected (Burns et al., 2004). However, the etiology may not be identifiable when the patient is diagnosed, sometimes cannot be identified until the patient is recovery, and, for rare cases, cannot be identified at all. Consequently, the initially supportive and symptomatic treatments are, therefore, essential in all patients with delirium.

7.3. Psychopharmacological treatment

7.3.1. Antipsychotics

7.3.1.1. Typical antipsychotics

To our knowledge, only two RCTs of typical antipsychotics, including haloperidol and chlorpromazine, have been carried out.

7.3.1.1.1. Haloperidol

Haloperidol, a dopamine antagonist, has been used in various neuropsychiatric conditions. It is considered as a first-line medication for the symptom control of delirium (American Psychiatric Association, 1999). The advantages of this medication are that it can be administered through several routes. In addition, it has fewer active metabolites, less anticholinergic effect and fewer sedative or hypotensive effects compared with other antipsychotics (Attard et al., 2008).

Breitbart et al. (1996) conducted an RCT to compare the efficacy and safety among haloperidol, chlorpromazine and lorazepam in adult AIDS patients with delirium. Thirty patients met the DSM-III-R criteria for delirium and scored 13 or more on the DRS. The measures used included the DRS, the Mini-Mental State and the extrapyramidal symptoms (EPS). The sample size was relatively small (n's for haloperidol = 11,chlorpromazine = 13 and lorazepam = 6). Based on the DRS scores, haloperidol (2.8±2.4 mg)and chlorpromazine (50±23.1 mg) were significantly superior to lorazepam for controlling the symptoms of delirium in the first 24 hours, usually before the underlying medical causes of delirium could be identified. The improvement of delirious symptoms was continued until the study end. The doses of haloperidol from day 2 to the study end were decreased for an average of 1.4±1.2 mg/day. While cognitive improvement, as measured by the Mini-Mental State, was observed as soon as day 2 of haloperidol or chlorpromazine treatment, no cognitive improvement was found

in the lorazepam group. At the study end, cognitive function of the haloperidol group was significantly improved. No patient developed extrapyramidal symptoms.

Several RCTs have been conducted in comparing the efficacy and tolerability between haloperidol and atypical antipsychotic medications. An RCT compared the efficacy and safety of haloperidol and olanzapine for the treatment of delirium in the medical and surgical intensive care unit. A total of 80 delirious patients were randomized to receive either haloperidol or olanzapine, administered orally. Measured by Delirium Index, the findings indicated that haloperidol (a mean dose of 6.5 mg/day, range: 1–28 mg), was as effective as olanzapine (a mean dose of 4.54 mg/day, range: 2.5–13.5 mg) in the treatment of delirium. However, the EPS measured by Ross-Chouinard and Angus-Simpson scales was significantly more severe in the haloperidol group (Skrobik et al., 2004).

There was a double-blind trial comparing haloperidol and risperidone for the treatment of delirium. A total of 28 patients with delirium were enrolled and randomly assigned to receive either a flexible-dose regimen of haloperidol or risperidone for 7 days. The measure in efficacy is the reduction of the MDAS scores. Significant reduction of delirious symptoms was observed in both haloperidol and risperidone groups. The average resolution times, measured by the MDAS score of 13 or lower, were 4.22±2.48 days in the haloperidol group and 4.17±2.14 days in the risperidone group. At the study end, the mean daily doses of the haloperidol and the risperidone groups were 1.71±0.84 and 1.02±0.41mg, respectively. No patient reported clinically significant side effects, except one patient in the haloperidol group experienced mild akathisia (Han and Kim, 2004).

Grover et al. (2011) conducted an RCT to compare the efficacy and safety of haloperidol, olanzapine and risperidone in medical and surgical in patients with delirium. A total of 64 patients (20 in the haloperidol group, 21 in the risperidone group and 23 in the olanzapine group) participated in the study. The patients were randomly assigned to receive the flexible dose regimens, including 0.25 to 10 mg of haloperidol, 0.25 to 4 mg of risperidone and 1.25 to 20 mg of olanzapine. The efficacy measures were the DRS-R 98 and MMSE. The mean doses of haloperidol, olanzapine and risperidone were 0.88±0.98 mg (range: 0.25–5 mg), 3.05±1.44 mg (range: 1.25–10 mg) and 0.95±0.28 mg (range: 0.5-2 mg), respectively. According to DRS-R98 and MMSE scores, haloperidol was significantly superior for the reduction of delirious symptoms on day 6. However, the efficacy of all three regimens was not significantly different from other days. Four patients in a haloperidol group had some side effects.

Maneeton and colleagues conducted an RCT comparing the efficacy and tolerability between quetiapine and haloperidol in delirious inpatients. All participants, aged 18-75 years, were delirious patients who were consulted to a psychiatric department. The diagnoses of all patients with DSM-IV delirium were confirmed by using the CAM. The primary efficacy outcome was the DRS-R-98. The other efficacy measures were the Clinical Global Impression (CGI) and hours of night sleep. The EPS was assessed by using the Modified (9-item) Simpson-Angus Scale (MSAS). All measures were applied daily. Thirty-eight patients were randomly to receive either a flexible dose regimen of quetiapine and haloperidol. Mean (SD) doses of the quetiapine and haloperidol groups were 34.0±12.8 and 0.9±0.5 mg/day, respectively. Based on the DRS-R-98 and CGI scores, both haloperidol and quetiapine significantly

reduced the symptoms of delirium from baseline to day 7. The mean hours of night-time sleep in haloperidol and quetiapine group were 6.9±3.5 and 7.8±1.8 hours (not significantly different). In the respect of EPS, the MSAS scores were not significantly different between groups (Maneeton et al., 2011).

Intravenous (IV) haloperidol should be used only if the oral administration is unlikely accessible, or a rapid resolution is needed. Although some previous findings suggest the use of IV haloperidol in these patients, most studies have low methodological quality. Two prospective studies with small sample sizes demonstrated the efficacy of intravenous haloperidol in disturbed behavioral control. The patients experienced a low risk of EPS (Menza et al., 1987, Moulaert, 1989). Another prospective, controlled study of EPS in delirious patients found that the combination of IV haloperidol and IV benzodiazepine reduced a risk of EPS compared with IV haloperidol mono therapy (Menza et al., 1988).

Although IV haloperidol appears to be effective for delirium, it should be used with great caution. Its incidence of QT prolongation (QTP) and torsades de pointes (TdP) has been increasing reported.

Meyer-Massetti et al. (2010) summarized 54 and 42 cases with intravenous haloperidol-related TdP and QTP, respectively. A cumulative dose in TdP cases ranged from 5 to 645 mg, while a that in patients with QTP alone was 2 to 1540 mg. this serious adverse event frequently occurred in the patients with concomitant risk factors. These findings suggest that a total cumulative dose of IV haloperidol less than 2 mg appears to be safely administered. At this cumulative dose range (<2 mg), ECG monitoring may not be needed for delirious patients who have no concomitant risk factors.

The administration of IV haloperidol may not be possible in severe delirious and aggressive patients. Therefore, intramuscular injection (IM) may be an alternative route for this condition. In addition, several settings cannot routinely monitor ECG in these cases. Based on some pharmacokinetic studies, IM haloperidol also had more rapid onset of action than that of oral administration (Schaffer et al., 1982, Froemming et al., 1989, Wang et al., 2012).

So far, there has been promising evidence that haloperidol is effective and safe for the management of delirium. However, a few patients may experience EPS. In the respect of efficacy, haloperidol is comparable to atypical antipsychotic medications (e.g., risperidone, olanzapine and quetiapine) but superior to lorazepam. Parenteral route for haloperidol is widely used for the management of acute delirium. Although the IV haloperidol may rapidly control disruptive behavior of delirious patients, it also increases the incidence of TdP and QTP. ECG monitoring may be needed for patients with concomitant risk factors or received a total cumulative dose of 2 mg or more for IV haloperidol. Alternatively, the administration of IM haloperidol is effective and safe for the treatment of severe delirium. Although it has been widely used, there has been no RCT comparing haloperidol and placebo in delirious patients. Further randomized, placebo-controlled trials are useful to confirm its efficacy and tolerability.

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7.3.1.1.2. Chlorpromazine

Chlorpromazine is the first antipsychotic drug widely used in various psychotic disorders. The only one RCT demonstrated that it is effective for controlling delirious symptoms. Breitbart et al. (1996) suggested that the low doses of chlorpromazine (50±23.1 mg) may rapidly reduce the delirious symptoms in AIDS patients in the first 24 hours and continuously improved the symptoms until the study end. This efficacy was comparable to haloperidol but significantly superior to lorazepam. After the first 24 hours of treatment, the average dose of chlorpromazine from day 2 to the study end was decreased for 36±18.4 mg/day. Although the cognitive improvement could be observed in the first two days of chlorpromazine treatment, it is slightly declined from day 2 until the treatment end. This phenomenon may be caused by the high anticholinergic property of chlorpromazine. No patient developed clinically significant extrapyramidal symptoms.

These findings show that chlorpromazine is effective and tolerable for treating delirium. However, due to its anticholinergic effects, cognitive function and other anticholinergic side effects should be monitored.

7.3.1.2. Atypical antipsychotics

Although typical antipsychotic medications are the mainstay for managing behavioral disturbance in delirium, its side effects, in particular EPS and anticholinergic effects are an issue of concern. The use of atypical antipsychotic medications with less propensity to induce EPS or cause anticholinergic effects is, therefore, an alternative. Several studies have demonstrated the efficacy and tolerability of atypical antipsychotic agents for controlling delirious symptoms.

7.3.1.2.1. Risperidone

Risperidone is probable the first atypical antipsychotic agent used for controlling delirious symptoms. An RCT comparing risperidone with haloperidol demonstrated that risperidone is as effective as haloperidol in reducing delirious symptoms. No patient receiving risperidone developed significant side effects (Han and Kim, 2004).

In a 7-day, RCT comparing the efficacy of risperidone and olanzapine in the treatment of delirium. The outcomes included the DRS-R-98, reported adverse events and EPS. Patients with dementia, serious hepatic problems, or bone marrow suppression, as well as those already taking antipsychotics for behavioral problems, were excluded. Thirty-two patients, aged 36-82 (median = 72) years, were included and randomly assigned to receive either risperidone (n = 17) or olanzapine (n = 15). Twenty-three patients had malignant cancer, and the rest had femur fracture, head trauma, or pneumonia. The mean initial doses of risperidone and olanzapine were 0.6±0.2 and 1.8±0.6 mg/day, respectively. However, the mean doses of risperidone and olanzapine at the last observation were 0.9±0.6 and 2.4±1.7 mg/day, orderly. With respected to the decreased DRS-R-98 scores, risperidone as well as olanzapine were significantly superior in reducing delirious symptoms over the 7 days of study. However, the response rates were not significantly different between groups (risperidone group:

64.7%, olanzapine group: 73.3%). The response to risperidone was poorer in the older age group. The median times to the recovery of delirium in the risperidone and olanzapine groups were 5 and 3 days, respectively. Risperidone, like olanzapine, was well tolerated. Although a few patients developed extrapyramidal symptoms, they were tolerable (Kim et al., 2010).

Another RCT conducted by Grover et al.(2011) compared the efficacy and safety of olanzapine, risperidone and haloperidol in medical and surgical inpatients with delirium. The findings indicated that risperidone, like olanzapine, was as effective as haloperidol.

Several findings support that low doses of risperidone are effective and tolerable for delirious patients. Its efficacy is comparable to other typical and atypical antipsychotic medications. To our knowledge, there has not been a randomized, placebo-controlled trial of risperidone in delirious patients.

7.3.1.2.2. Quetiapine

Quetiapine is an atypical antipsychotic agent approved for the treatment of schizophrenia, bipolar disorder and major depressive disorder. However, its evidence in controlling delirious symptoms has been increased. There have had several RCTs conducted to determine the efficacy and safety of quetiapine in the management of delirium.

There was a randomized, double-blind, placebo-controlled trial of quetiapine in critically ill patients with delirium. A total of 36 delirious adult patients admitted in intensive care units were enrolled. All patients had a score of 4 or more on the Care Delirium Screening Checklist, were tolerable to enteral nutrition and had no neurologic condition. The patients were randomly assigned to receive either quetiapine 50 mg every 12 hours (n = 18) or placebo (n = 18). The doses of quetiapine were increased every 24 hours for up to 200 mg/day. The results showed that quetiapine was superior to placebo in the respects of time to resolution of delirium, [1.0 (0.5-3.0) vs. 4.5 days (2.0-7.0), p =0.001], duration of delirium [36 (12-87) vs. 120 hours (60-195, p =0.006], and duration of agitation [6 hours (0-38) vs. 36 hours (11-66), p =0.02)]. However, the length of hospitalization was similar in both groups (16 days vs. 16 days). The incidence of QTc prolongation and EPS were not significant different between groups. However, somnolence was more common in the quetiapine groups (22% vs. 11%, p =.66). In addition, the rate of discharge to home or rehabilitation was greater in the quetiapine group (89% vs. 56%, p =0.06) (Devlin et al., 2010).

Tahir et al. (2010) conducted an RCT to investigate the efficacy and acceptability of quetiapine for the control of delirious symptoms. Forty-two patients (21 in each group) were randomly received either quetiapine or placebo. The DRS-R-98 was used as the primary outcome. The results demonstrated that improvement for quetiapine, as measured by DRS-R-98 severity score, was faster than that of placebo. Based on DRS-R-98 severity score, the quetiapine group recovered faster than the placebo group (P=0.026). In addition, the non-cognitive items of the DRS-R-98, including restlessness, agitation, thought disorder and perceptual impairment in the quetiapine group were significantly improved faster than that of placebo group (p=0.048).

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Lee et al. (2005) conducted an open, randomized, prospective trial to investigate the effectiveness and tolerability of quetiapine and amisulpride in delirious patients. Forty patients with delirium were randomly assigned to receive a flexible dose of amisulpride or quetiapine. Outcome measures included the DRS-R-98 and CGI-Severity (CGI-S), the total sleep time and the quality of sleep. The mean doses of quetiapine and amisulpride were 113 mg/day and 156.4 mg/day, respectively. The DRS-R-98 scores of both groups decreased over time. Time to recovery for the quetiapine group was 7.4±4.1 days. The quality of sleep and the total sleep time were not significantly different between groups. Both quetiapine and amisulpride were well tolerated.

After the reveal of promising benefits of quetiapine for delirium in an open-label study (Maneeton et al., 2007b), Maneeton and colleagues conducted an RCT to compare the efficacy and tolerability of quetiapine and haloperidol in the management of delirium. Based on the DRS-R-98 and CGI scores, quetiapine was as effective as haloperidol in the treatment of delirium. The mean of night time sleep was 7.8±1.8 hours for the quetiapine group. Quetiapine and haloperidol were well tolerated. In addition, the incidence rates of extrapyramidal side effects were very low in both groups (Maneeton et al., 2011).

The above mentioned findings suggest that low doses of quetiapine are effective and safe in the treatment of delirium. Its efficacy is, at least, comparable to typical and other atypical antipsychotic agents. Compared with other antipsychotic agents, only quetiapine has been shown its superiority to placebo in the management of delirium. It also causes only few adverse events, including EPS and QTc prolongation, which may be comparable to placebo.

7.3.1.2.3. Olanzapine

Olanzapine is, also, an atypical antipsychotic medication approved in the treatment of schizophrenia and bipolar disorder. There have been a few RCTs of this agent in patients with delirium.The RCT carried out by Skrobik et al. (2004) compared the safety and efficacy of olanzapine and haloperidol in delirious patients admitted in a critical care unit. The results indicated that olanzapine was as effective as haloperidol in controlling delirious symptoms. Olanzapine was a safe alternative agent, especially for delirious patients contraindicated to haloperidol.

The study of Kim and colleagues demonstrated that olanzapine was effective for delirium. This agent also had low incidence of adverse events, especially EPS. Its efficacy is equal to the effects of risperidone (Kim et al., 2010).

Elsayem et al. (2010) conducted a prospective, open-label study to investigate the safety, tolerability and efficacy of subcutaneous (SC) olanzapine for hyperactive or mixed delirium in the cancer patients. The subjects had the MMSE scores of 24 or higher and agitation with Richmond Agitation Sedation Scale (RASS) score of 1 or more. In addition, they were those who had not responded to 10 mg or more of parenteral haloperidol over 24 hours. All subjects received olanzapine 5mg SC every eight hours for three days and continued haloperidol for controlling agitation. Twenty-four patients, aged 49 to 79, were evaluated. The

findings indicated that the patients tolerated well with the SC olanzapine. In the respect of agitation, only 37.5% of the subjects were rated as responders.

There was an RCT comparing the efficacy of olanzapine, risperidone and haloperidol in delirious patients. The findings suggested that olanzapine was comparable to risperidone and haloperidol (Grover et al., 2011).

Olanzapine appears to be an effective and tolerable antipsychotic medication in the control of delirious behavior. It can be administered in several routes, such as oral, intramuscular and subcutaneous administration. Further well-defined studies should be conducted to confirm these findings.

7.3.1.2.4. Aripriprazole

Aripiprazole is a dopamine partial agonist approved in the treatment of schizophrenia and bipolar disorder. Similar to other antipsychotic medications, it is widely used for controlling the behavioral disturbances and psychotic symptoms in patients with dementia and delirium. As an agent with little sedative and anticholinergic effects, it may have a few adverse effects on attention, concentration and sleep-wake cycle. In addition, it may be beneficial for hypoactive delirium (Straker et al., 2006). However, only a few studies of this agent have been carried out in delirious patients.

The study of Boettger et al. (2011) compared the efficacy and tolerability between aripiprazole and haloperidol for the reduction of delirious symptoms. The subjects were 21 delirious patients treated with aripiprazole and 21 case-matched, delirious patients treated with haloperidol. The measures consisted of the MDAS, the Karnofsky Performance Scale (KPS) and the abbreviated Udvalg Kliniske Undersogelser Side Effect Rating Scale (UKU). With respect to the MDAS, both groups improved significantly from baseline to day 7. The resolution rates of delirium were 76.2% for both groups. Both hypoactive and hyperactive deliriums significant improved. For those with hypoactive delirium, the rates of delirium resolution in the aripiprazole and haloperidol groups were 100 and 77.8%, respectively. For those with hyperactive delirium, such rates were 58.3% and 75%, respectively. However, the haloperidol group had more side effects.

Boettger and Breitbart (2011) conducted an open-label study to determine the efficacy and safety of aripiprazole for controlling delirious symptoms in hospitalized cancer patients. Twenty-one patients were treated with aripiprazole. Based on the changed MDAS scores, the aripiprazole group improved significantly. The mean dose of aripiprazole was 18.3 (range 5-30) mg/day at the end of study. The rates of delirium resolution were 100% for hypoactive delirium and 58.3% for hyperactive delirium. The patients with pre-morbid cognitive deficits and the hyperactive subtype of delirium did not respond well to aripiprazole treatment. The clinically significant adverse events were not found.

The case series of Straker et al. (2006) also demonstrated the efficacy of aripiprazole in the treatment of delirium. Fourteen patients, aged 18 to 85 and met DSM-IV-TR criteria for a diagnosis of delirium, were included. The results found that 12 patients had ≥ 50 % reduction in DSR-R-98, and 13 patients showed improvement on the CGI scores. The mean dose of ari-

piprazole was 8.9±3.5 mg/day. The adverse events were rare.The finding suggested that aripiprazole appeared to be effective and safe in the treatment of hypoactive delirium.

The above-mentioned findings demonstrate that aripiprazole is safe and effective for delirium. As a non sedating antipsychotic agent, it may be suitable for hypoactive delirium. However, its evidence in delirious patients is still limited.

7.3.1.2.5. Amisulpride

Amisulpride is an atypical antipsychotic agent used for the treatment of psychoses and manic episode. Its low doses may be effective for the treatment of depression. However, some studies have been carried out to examine its efficacy for controlling delirious symptoms.

There was an RCT comparing the efficacy, tolerability and sleep quality of amisulpride and quetiapine in controlling delirious symptoms. The findings showed that, similar to quetiapine, amisulpride was safe and effective for delirious patients. The mean time to stabilization in the amisulpride group was 6.3±4.4 days (Lee et al., 2005). The finding suggested that amisulpride, like quetiapine, appear to be effective and tolerable for the management of delirium. However, further studies are still needed to confirm its efficacy and safety.

Drug	Treatment route	Resolution or response time (days)	Level of evidence*	Comments
Haloperidol	Oral, IM, IV	4	Ib	IV administration increases risk of the QT prolongation and torsades de pointes
Chlorpromazine	Oral	-	Ib	worsen the cognitive impairment
Risperidone	Oral	4-5	Ib	as effective as haloperidol
Olanzapine	Oral, SC	3	Ib	limited efficacy in agitated delirium for SC administration
Quetiapine	Oral	1-7	Ib	effective with low risk of EPS
Amisulpride	Oral	6	Ic	
Aripriprazole	Oral	-	IIIb	effective in hypoactive delirium

* Gray and Taylor (2010), IM: intramuscular injection; IV: intravenous injection; SC; subcutaneous injection

Table 1. Summary of evidence on antipsychotic agents for managing delirium

7.3.2. Benzodiazepine

Lorazepam is primary used as hypnotics and anxiolytics. It has rapid onset and shorter duration of action, a low risk of accumulation and no major active metabolites. Its bioavailabili-

ty is predictable when it is administered either orally or intramuscularly (Attard et al., 2008). Due to these preferable pharmacokinetic profiles, it is alternatively administered for controlling disruptive behavior in several clinical settings.

There was a prospective study suggested that intravenously administration of benzodiazepine added haloperidol can reduce the risk of EPS (Menza et al., 1988). An RCT of lorazepam monotherapy (3.0±3.6 mg for first 24 hours and 4.6±4.7 mg/day after day 2) did not show its efficacy in controlling delirious symptoms in AIDS patients. In addition, it continuously decreased cognitive function, as measured by the MMSE. Due to these preliminary results, this study was prematurely stopped (Breitbart et al., 1996).

Based on the results of a systematic review, there has been no adequate RCT to support the use of benzodiazepines in the management of non-alcohol withdrawal related delirium in patients admitted in the hospital (Lonergan et al., 2009). Although benzodiazepines are the first-line treatment for alcoholic withdrawal delirium, their evidence in the treatment of non-alcoholic delirium is very limited.

7.3.3. Cholinesterase inhibitors

Presumably, cholinergic deficiency (Mussi et al., 1999, Trzepacz, 2000) is postulated as neurochemical correlates of delirium. In addition, anticholinergic medications are correlated to drug-induced delirium (Han et al., 2001), and cholinergic medications can reduce symptoms of delirium in dementia (Wengel et al., 1998). It has been hypothesized that cholinesterase inhibitors may be beneficial for treating cholinergic deficiency in delirium.

Overshott et al. (2010) conducted a double-blind, placebo-controlled randomized trial of rivastigmine in the management of delirious patients hospitalized in medical settings. Patients (age≥ 65 years) were diagnosed as delirium by using the CAM. After entry, the patients in each group were assessed by using the CAM daily. Patients with delirium were randomly assigned to receive either rivastigmine 1.5 mg once a day and increased to 1.5 mg twice a day after seven days or an identical placebo (two tablets after seven days). A total of 15 patients were included in the study. Eight patients received rivastigmine, and seven patients received placebo. With regarded to the CAM scores, all patients in the rivastigmine group and 3 patients in the placebo group had a resolution of delirium when they exited the trial. However, there was no significant difference between groups on the duration of delirium (rivastigmine group 6.3 days versus placebo group 9.9 days).

There was an RCT comparing the efficacy and tolerability of donepezil and placebo. A total of 80 patients were randomly assigned to orally administered donepezil 5 mg once a day or a placebo capsule once a day, commenced 14 days before the surgery and continued taking for 14 days following the surgery. The delirium was identified with the Delirium Symptom Interview, the CAM, daily medical record, nurse-observation reviews, and the DSM-IV diagnostic criteria for delirium. With respect to DSM-IV criteria, patients diagnosed as delirium were suggested to receive a double dose of donepezil or placebo treatments. No measure outcome was used to assess in severity of delirium. The mean duration of postop-

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erative delirium for the donepezil and placebo groups were 1.0 and 1.3 days, respectively (Liptzin et al., 2005, Overshott et al., 2008).

Marcantonio et al. (2011) conducted an RCT comparing the efficacy and safety of donepezil and placebo in reduction of the prevalence and severity of delirium in older adults undergoing hip fracture repair. Seventeen patients aged 70 or more were randomized to receive a daily donepezil 5 mg or placebo, initiated on the day before surgery or unless possible, administered within 24 hours after surgery. The treatment was continued for 30 days, unless side effects occurred. The presence and severity of delirium were measured by using the CAM and MDAS. Patients in the donepezil group had significantly more adverse events. With regard to delirium presence over time or the CAM scores over time, there were no significant differences between the donepezil and placebo groups in terms of delirium incidence or severity.

A pilot study of Oldenbeuving et al. (2008) investigated the efficacy and tolerability of rivastigmine in the treatment of delirium after stroke. Seventeen patients with delirium (DRS≥12) were treated with oral rivastigmine within the dose range of 3-12 mg a day. Based on the DRS scores, 16 of 17 patients had a decrease in severity of delirium after rivastigmine treatment. The mean duration of the delirium for 16 patients was 6.7 (2-17) days. No significant adverse event was observed.

Based on the findings, there has been no strong evidence supporting the use of cholinesterase inhibitors in the treatment of delirium. Conversely, these agents may cause a greater risk of adverse events in this population. Further studies should be carried out.

Delirious symptoms are likely to be improved by themselves after the recovery of underlining diseases. Judgment on the severity of these behavioral symptoms is easily biased by raters. In addition, placebo effects are noted in all area of therapeutic approach (Kradin, 2011). The percentage of placebo effect on psychiatric illness, such as anxiety and depression is often high (Raz et al., 2011). According to the nature of this medical condition, a randomized, placebo-controlled trial of a medication for controlling delirious symptoms is desperately needed to assess the efficacy and safety of a particular agent.

Among the medications mentioned above, only quetiapine has been examined in a placebo-controlled study. The superiority of quetiapine to placebo may suggest that the agents may be considered as first-line treatment for controlling the disruptive behavior of delirium. Low dose of other typical and atypical antipsychotics may be also effective. The evidence so far also suggests that haloperidol may be associated with EPS, and chlorpromazine has a risk for anticholinergic side effects. Other atypical antipsychotics that appear to be effective and tolerable in the management of delirium are risperidone, olanzapine, amisulpride and aripiprazole. Only aripiprazole may be effective for hypoactive delirium. Although benzodiazepine, especially lorazepam, is widely used in delirium, there is no evidence supporting its efficacy for the treatment of non-withdrawal delirium. Therefore, the use of benzodiazepine should be limited to alcohol or benzodiazepine withdrawal delirium only. Similarly, there has not been evidenced to demonstrate the efficacy of cholinesterase inhibitors, including donepezil and rivastigmine, in the treatment of delirium.

7.4. Environmental intervention

The reticular formation and its connections, the main sites of arousal and attention, are involved in delirium. Dysfunction of this system may affect the perception and interpretation of environmental stimuli in delirious patients. The reduction or over activity of the environmental factors may exacerbate the symptoms of delirium. Several studies, especially multicomponent programs, have supported that an environmental intervention is also effective in the management of delirium.

Cole et al. (1994) conducted an RCT to determine a systematic intervention in elderly inpatients with DSM-IV delirium. Eighty-eight patients, aged 75 years or more, were enrolled in the study. The patients were randomized to either the treatment group (n=42) or the control group (n=46). Each treatment patient received a consultation by a geriatric internist or psychiatrist and followed up by a liaison nurse. Regular medical care was provided in the control group. The environmental intervention, used in this study, was the nursing intervention protocol, including the interventions for (1) environment: appropriate sensory input, only one stimulus or task background stimulation at a time, and medication not interrupting sleep, (2) orientation: environmental cues, such as clock, calendar and etc., verbal reminders of time, place and person, and needs of eye glasses or hearing aids, (3) familiarity: familiar possession from home, family members to stay with the patients, and the same staff to care for them (4) communication: clear, slow paced, simple and repetitive instructions and explanations, use of face-to-face contact, a warmth attitude and kind firmness, identification by name and information, acknowledgement of their emotions and encouragement of verbal expression, (5) activities: avoidance in physical restraint, free movement, provision of safety, encouragement of self-care and other personal activities. Two weeks after hospitalization, as measured by the Short Portable Mental Status Questionnaire (SPMSQ), the improvement was observed in the intervention group, while deterioration was observed in the control group. However, the difference was not reported by the end of 8-week period. There were statistically significant differences between the groups in terms of the use of restraints, length of hospital stay, discharges to a setting providing more care than needed before admission or mortality rate.

Milisen et al. (2001) developed and investigated the effectiveness of a nurse-led interdisciplinary intervention program for delirium. A total 120 participants (60 for intervention cohort, 60 for a usual care/non-intervention cohort) were included. The intervention protocol consisted of education for the nursing staff; systematic cognitive screening; consultative services by a delirium resource nurse, a geriatric nurse specialist, or a psychogeriatrician; use of a scheduled pain protocol. The findings showed that the intervention cohort group had shorter duration of delirium (p=0.3), less severity of delirium (p=0.049) and less memory impairment (p=0.046) than those of the control group. The length of hospital stay tended to be decreased in the intervention cohort compared with the control (p=0.09). The study suggested that this intervention was beneficial for older hip-fracture patients with delirium.

Cole et al. (2002) conducted an RCT to investigate the effectiveness of systematic detection and multidisciplinary care of delirium in reducing time to improvement of cognitive status in older patients admitted to general medical settings. Two hundred twenty-seven patients

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with high prevalent or incident delirium participated in the study. Significant differences between groups were not observed within the eight weeks after enrolment in terms of time to and rate of improvement of the Delirium Index, the Barthel Index, length of stay, rate of discharge into the community, living arrangements after discharge or survival. Based on the findings, systematic detection and multidisciplinary care of delirium did nots how a benefit over usual care for elderly patients in medical settings.

A prospective intervention study conducted by Lundstrom et al. (2005) determine an education program and a reorganization of nursing and medical care for improving the symptoms of delirium in elderly patients. A total of 400 patients, aged 70 or older, were consecutively admitted to either an intervention or a control ward. The intervention program composed of staff education emphasizing on the assessment, prevention, and treatment of delirium, as well as caregiver-patient interaction. The Organic Brain Syndrome Scale and the MMSE were used as outcome measures. Fewer patients in the intervention ward had delirious symptoms on day 7 compared with the control group (30.2% vs 59.7%, p=0.001). The mean length of hospitalization was significantly shorter in the intervention patients as compared with the control ones (9.4±8.2 vs 13.4±12.3 days, P< 0.001), especially for the delirious patients (10.8±8.3 vs 20.5±17.2 days, P< 0.001).

Inouye et al. (2006) conducted a cross-sectional survey of the Hospital Elder Life Program (HELP) dissemination in 17 study sites. The trained interdisciplinary teams assessed and intervened on six delirium risk factors, including orientation, therapeutic activities, early mobilization, vision/hearing optimization, oral volume repletion and sleep enhancement. The finding that the HELP improved hospital outcomes in delirium was promising in this population.

There was a prospective analysis to determine the pattern and frequency of implementation of environmental intervention in managing delirious patients admitted in an acute hospital service. Forty-six patients meeting the ICD-10 criteria for delirium were studied. The patients were categorized into hyperactive, hypoactive or mixed subtypes of delirium. The environmental strategies were the eight basic nursing strategies for delirium, including (1) frequent observation; (2) efforts by staff to re-orientate the patient to the surroundings; (3) effort made to avoid excessive staff changes; (4) nurse in single room; (5) uncluttered nursing environment; (6) use of an individual night light; (7) specific effort to minimize noise levels and (8) relatives or friends specifically requested to visit regularly in an effort to enhance re-orientation. The study found that these environmental strategies were more beneficial in the management of behavioral difficulties, such as overall severity of delirium, agitation, mood lability and sleep-wake cycle disturbance, than the core features of delirium, such as severity of disorientation, disturbed perception/thinking (Meagher et al., 1996).

The above-mentioned studies suggest the benefits ofthe environmental interventions for delirium, and, therefore, should be recommended in all patients with delirium. Those interventions aim to correct or reduce the sensory impairment, and to improve the patient's perception, by using eyeglasses and hearing aids. Optimal sensory stimulation is helpful to decrease the behavioral disturbance of delirium. While sensory deprivation may exacerbatethe behavioral disturbance, over stimulation, such as loud noise, should be also avoided.

Providing environmental cues, such as calendar, clock, family pictures, windows, should be encouraged to facilitate orientation. In addition, supportive interventions, including re-orientation, reassurance and explanation about delirium, could reduce fear and anxiety.

8. Prevention

Once a patient with high risks of delirium is hospitalized, all risks should be addressed, followed by the employment of effective preventive strategies (Salawu et al., 2009). Some studies have shown the benefits of some preventive interventions for delirium. In general, those strategies usually include the multidisciplinary and psychopharmacological interventions.

8.1. Non-pharmacological interventions

Multi-factors, including patient vulnerabilities, predisposing factors at admission and precipitating factors during hospitalization can interactively cause syndrome of delirium.

Inouye (2000) conducted a controlled clinical trial in 852 subjects to prevent delirium in elderly inpatients. Significant predisposing factors for delirium included vision impairment, severe illness, cognitive impairment and dehydration. Precipitating factors were physical restraint use, malnutrition, adding more than three drugs, bladder catheter use, and any iatrogenic event. The findings showed that the incidence of delirium was significantly reduced in the intervention group compared with usual care (9.9% vs. 15.0%, 95% CI: 0.39-0.92). The total number of days and episodes of delirium were also significantly smaller in the intervention group. These findings suggested that delirium prevention is useful and could reduce the morbidity and mortality associated with delirium in elderly patients.

Colombo et al. (2012) conducted a two-stage prospective observational study to determine the epidemiology, risk factors and predictors of delirium. The subjects were all patients admitted to the ICU settings over a year. The first phase was the observational stage, while the second one was the interventional phase. Delirium assessment was performed by using of the CAM twice daily after the sedation interruption. For the second phase, the patients were received both a re-orientation and environmental manipulations (e.g., acoustic and visual stimulation). The patients in phase 1 and 2 were 170 and 144, respectively. The incidence rate of delirium was significantly lower in the interventional group (phase-I vs. phase-II: 22% vs. 35.5%, p = 0.020). Based on the Cox's Proportional Hazard model, the use of re-orientation strategy was the strongest protective factor of delirium: (HR 0.504, 95% C.I. 0.313-0.890, p=0.034), while age (HR 1.034, 95% CI: 1.013-1.056, p=0.001) and sedation with midazolam plus opiate (HR 2.145, 95% CI: 2.247-4.032, p=0.018) were negative predictors.

Milisen et al. (2001) conducted a systemic review to investigate the characteristics and efficacy of various multicomponent programs for managing older patients with delirium admitted in hospitals. Three RCTs, three controlled trials and one before-after study were included in the review. The multicomponent strategies for preventing delirium appear to be

the most efficacious in reducing the incidence, both in surgical and medical patients. In addition, some additional effects of preventive intervention were observed in the duration and severity of delirium, as well as functional status. The review suggested that multicomponent strategies are effective for preventing delirium.

Yang et al. (2008) conducted a prospective cohort study to investigate the mediating role of activity participation between educational attainment and risk of delirium. The contributions of participation in specific activities for the development of delirium were also determined. Seven hundred seventy-nine newly admitted patients without dementia, aged 70 or older, were studied. The findings showed that activity participation before hospitalization mediated the relationship between education and risk for delirium in elderly persons without dementia. It also suggested that participation in regular exercise was a significantly protective factor of delirium.

Another study examined the efficacy of multicomponent intervention for preventing delirium. Inpatients with an intermediate or high risk for delirium were randomly assigned to receive either a non-pharmacological intervention delivered by family members (144 patients) or standard management (143 patients). The outcome measure was the occurrence of delirium during hospitalization. The incidence rates of delirium in the intervention group and the control group were 5.6% and 13.3% (relative risk:0.41; 95% CI: 0.19–0.92; P = 0.027), respectively. The findings suggested that the non-pharmacological prevention of delirium given by family members, as compared with standard management, could reduce the patients' risk of delirium (Martinez et al., 2012).

These findings suggest that non-pharmacological interventions can reduce the incidence of delirium. Effective interventions, including multicomponent approach frequently focuses on predisposing factors in an individual patient. However, environmental prevention, such as re-orientation and environmental stimulation, are also effective for preventing delirium. A strong protective factor against delirium is the routinely participation in exercise. The use of multicomponent interventions by family members can also reduce the risk of delirium.

8.2. Psychopharmacological interventions

There have been several studies examining the effectiveness of antipsychotic medications for preventing delirium. Kalisvaart et al. (2005) conducted an RCT comparing haloperidol and placebo for preventing postoperative delirium in elderly hip-surgery patients, who were at risk for delirium. A number of 430 hip-surgery patients, aged 70 and older, at risk for postoperative delirium were randomly assigned to receive haloperidol 1.5 mg/d or placebo, started before surgery and continued for up to 3 days after surgery. The incidence rates of postoperative delirium in both groups were not significantly different (haloperidol vs placebo, 15.1% vs. 16.5%). The means of delirium duration in haloperidol and placebo treatment groups were 5.4 vs 11.8 days, orderly (mean difference 4.0, 95% CI=2.0-5.8, P<.001), and the means of hospital stay were 17.1±11.1 and 22.6±16.7 days, respectively (mean difference 5.5 days, 95% CI=1.4-2.3; P<.001). The adverse events were not significantly different between groups. These results suggested that low doses of haloperidol might not be able to prevent postoperative delirium. However, it is safe

and can decrease the severity, duration, and the length of hospitalization for these patients.

Wang et al. (2012) conducted an RCT to determine the efficacy and safety of intravenous haloperidol for preventing delirium in critically ill elderly patients who had undergone non-cardiac surgery. A total of 457 patients, aged 65 years older, who were admitted to the intensive care unit after non cardiac surgery, were included and randomized to receive either haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hours; n = 229) or placebo (n = 228). The incidence rates of delirium were significantly lower in the haloperidol group(15.3% vs 23.2%, p = 0.031) during the first seven day after surgery. No drug related adverse event was noted. A short-term, low-dose intravenous haloperidol prophylaxis appeared to reduce the incidence rate of postoperative delirium.

Prakanrattana and Prapaitrakool (2007) conducted an RCT to determine the effects of risperidone in preventing postoperative delirium after cardiac surgery with cardiopulmonary bypass. A total of 126 adult patients underwent elective surgery were randomized to receive risperidone 1 mg or placebo after regained consciousness. With regard to the using of CAM, the incidence of postoperative delirium in the risperidone group was significantly lower than that in the placebo group (11.1% vs. 31.7% respectively, P=0.009, relative risk: 0.35, 95% CI: 0.16-0.77).

Larsen et al. (2010) conducted an RCT comparing the efficacy of olanzapine and placebo in preventing postoperative delirium in elderly patients after joint-replacement surgery. A total of 400 elderly patients, aged 65 years or more, who had undergone elective knee- or hip-replacement surgery, were randomly assigned to receive either 5 mg of orally-disintegrating olanzapine or placebo before and after surgery. The findings showed that the olanzapine group had a significantly lower incidence of delirium.

There have been a few studies of cholinesterase inhibitors for preventing delirium. Liptzin et al. (2005) conducted an RCT comparing donepezil and placebo for the prophylaxis of postoperative delirium in elderly patients, who had undergone elective total joint-replacement surgery. Eighty patients without dementia were randomly assigned to receive either donepezil or placebo for 14 days before surgery and 14 days afterward. The findings did not show any benefit of donepezil in preventiong delirium in this population.

Gamberini et al. (2009) conducted an RCT to compare rivastigmine and placebo for preventing delirium in elderly patients during the first six days after elective cardiac surgery. A total of 120 patients, aged 65 or older, underwent the surgery with cardiopulmonary bypass were randomized to receive either placebo or rivastigmine. The incidence rates of delirium were not significantly between groups (30% vs 32%, p = 0.8). The findings did not support a short-term oral administered rivastigmine for delirium prophylaxis in this population.

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Drug	Route administration	Dose	Level of evidence*	Comment
Haloperidol	IV	0.1 mg/hr	1b	0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs
Risperidone	Oral	1 mg/day	1b	
Olanzapine	Oral	5 mg/day	1b	
Melatonin	Oral	0.5 mg/day	1b	Administer at night

* Gray and Taylor (2010)

Table 2. Summary of evidences relevant to the pharmacological prophylaxis of delirium

There was a randomized, double-blinded, placebo-controlled trial of low dose exogenous melatonin in preventing delirium. A total of 145 patients, aged 65 years or older, hospitalized in a medical unit were randomly assigned to receive either 0.5 mg of melatonin or placebo every night for 14 days or until discharge. Based on the CAM, the incidence rate of delirium in the melatonin group was significant lower than that in the placebo group (12% vs 31%, p=0.014). The findings suggested that exogenous low dose melatonin may be of benefit in preventing delirium in this population (Al-Aama et al., 2012).

The above-mentioned findings demonstrate the benefits low-dose risperidone and olanzapine in preventing delirium. While they can reduce the incidence rate of delirium, their adverse events, in particular EPS, appear to be comparable to placebo. Similarly, exogenous low-dose melatonin administered at night time may be able to prevent delirium. Although haloperidol can reduce severity, duration and length of hospital stay in postoperative delirium, it might not be able to prevent the occurrence of this condition. However, cholinesterase inhibitors, including donepezil and rivastigmine may have no efficacy in this regard. Therefore, at low doses, high-potency antipsychotic agents, atypical antipsychotic medications or exogenous melatonin may be beneficial for the prevention of delirium in patients at high risk or subsydrome of delirium.

9. Further studies

Several lines of evidence indicate that pharmacological and environmental interventions are effective in the management and prophylaxis of delirium. However, those studies still have some limitations, including methodological weakness, small sample sizes, lack of placebo control in several studies and the specific patients. Further randomized, placebo-controlled trials and systemic reviews with well-defined methodology, large sample sizes, consistent outcomes and various clinical settings may be helpful in clarifying the benefits of these interventions.

10. Conclusion

Delirium is a condition in medical emergency, common in medical or surgical settings and highly incident in intensive care units. Several causative factors for the development of delirium have been identified. Specific treatment for curing or removing the causes is an effective approach. Initially, the precipitating factors are often overlooked or unidentified. Therefore, supportive and symptomatic managements are beneficial. For hyperactive type of delirium, all antipsychotic medications may help relief the behavioral disturbance, including psychotic symptoms. Although haloperidol is considered as the first-line treatment, it may increase the risk of adverse events, especially EPS. Alternatively, atypical antipsychotic agents, which have low propensity to induce EPS, may be useful in this condition. Intravenous haloperidol may be associated with QT prolongation and torsades de pointes. To avoid these serious adverse events, only low doses of IV haloperidol (a total cumulative dose < 2 mg) should be administered in delirious patients without concomitant risk factors. Based on its pharmacokinetic profile, IM haloperidol can be an alternative for the behavioral control of acute or severe delirium. For hypoactive delirium, only aripriprazole, a non sedative antipsychotic agent, is evidently beneficial. In addition to psychopharmacological interventions, environmental manipulation is also necessary in the management of delirium and should be used in all delirious patients. Preventing delirium is challenging. A number of studies demonstrate the efficacy of some interventions in preventing delirium. The multicomponent strategy, systemically focusing on predisposing factors in individual patients is one of the highly effective approaches. Pharmacological prophylaxis is another strategy in preventing delirium. The evidence so far suggests that risperidone, olanzapine and melatonin may be effective in preventing delirium.

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References

[1] Al-Aama, T., Brymer, C., Gutmanis, I., Woolmore-Goodwin, S. M., Esbaugh, J. & Dasgupta, M. (2012). Melatonin decreases delirium in elderly patients: a randomized,

placebo-controlled trial. *International journal of geriatric psychiatry,* Vol. 26, No. 7, pp. 687-694, ISSN1099-1166

[2] Aldemir, M., Ozen, S., Kara, I. H., Sir, A. & Bac, B. (2001). Predisposing factors for delirium in the surgical intensive care unit. *Critical care,* Vol. 5, No. 5, pp. 265-270, ISSN1364-8535

[3] Ali, S., Patel, M., Jabeen, S., Bailey, R. K., Patel, T., Shahid, M., Riley, W. J. & Arain, A. (2011). Insight into delirium. *Innovations in clinical neuroscience,* Vol. 8, No. 10, pp. 25-34, ISSN 2158-8341

[4] American Psychiatric Association. (1999). American Psychiatric Association Practice guideline for the treatment of patients with delirium. *The American journal of psychiatry,* Vol. 156, No. supplement 5, pp. 1-20, ISSN 0002-953X

[5] American Psychiatric Association. (2005) *Diagnostic and statistical manual of mental disorders,* American Psychiatric Association, ISBN 0-89042-061-0, Washington, USA

[6] Attard, A., Ranjith, G. & Taylor, D. (2008). Delirium and its treatment. *CNS drugs,* Vol. 22, No. 8, pp. 631-644, ISSN 1172-7047

[7] Bledowski, J. & Trutia, A. (2012) A review of pharmacologic management and prevention strategies for delirium in the intensive care unit. *Psychosomatics,* Vol. 53, No. 3, pp. 203-211,ISSN 1545-7206

[8] Boettger, S. & Breitbart, W. (2011). An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. *Palliative & supportive care,* Vol. 9, No. 4, pp. 351-357, ISSN 1478-9523

[9] Boettger, S., Friedlander, M., Breitbart, W. & Passik, S. (2011). Aripiprazole and haloperidol in the treatment of delirium. *The Australian and New Zealand journal of psychiatry,* Vol. 45, No. 6, pp. 477-482, ISSN 1440-1614

[10] Breitbart, W., Marotta, R., Platt, M. M., Weisman, H., Derevenco, M., Grau, C., Corbera, K., Raymond, S., Lund, S. & Jacobson, P. (1996). A double-blind trial of haloperidol,chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *The American journal of psychiatry,* Vol. 153, No. 2, pp. 231-237,ISSN 0002-953X

[11] Breitbart, W., Rosenfeld, B., Roth, A., Smith, M. J., Cohen, K. & Passik, S. (1997). The Memorial Delirium Assessment Scale. *Journal of pain and symptom management,* Vol. 13, No. 3, pp. 128-137, ISSN 0885-3924

[12] Burapakajornpong N., Maneeton, B. & Srisurapanont M. (2012) Pattern and risk factors of alcohol withdrawal delirium. *Journal of the Medical Association of Thailand,* Vol. 94, No. 8, pp. 991-997, ISSN 0125-2208

[13] Burns, A., Gallagley, A. & Byrne, J. (2004). Delirium. *Journal of neurology, neurosurgery, and psychiatry,* Vol. 75, No. 3, pp. 362-367, ISSN 0022-3050

[14] Catic, A. G. (2011). Identification and management of in-hospital drug-induced delirium in older patients. *Drugs & aging,* Vol. 28, No. 9, pp. 737-748, ISSN 1170-229X

[15] Chaput, A. J. & Bryson, G. L. (2012). Postoperative delirium: risk factors and management: continuing professional development. *Canadian journal of anaesthesia,* Vol. 59, No. 3, pp. 304-320, ISSN 1496-8975

[16] Clegg, A. & Young, J. B. (2011). Which medications to avoid in people at risk of delirium: a systematic review. *Age and ageing,* Vol. 40, No. 1, pp. 23-29, ISSN 1468-2834

[17] Cole, M. G., Ciampi, A., Belzile, E. & Zhong, L. (2009). Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age and ageing,* Vol. 38, No. 1, pp. 19-26, ISSN 1468-2834

[18] Cole, M. G., Mccusker, J., Bellavance, F., Primeau, F. J., Bailey, R. F., Bonnycastle, M. J. & Laplante, J. (2002). Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. *Canadian Medical Association journal,* Vol. 167, No. 7, pp. 753-759, ISSN 0820-3946

[19] Cole, M. G., Primeau, F. J., Bailey, R. F., Bonnycastle, M. J., Masciarelli, F., Engelsmann, F., Pepin, M. J. & Ducic, D. (1994). Systematic intervention for elderly inpatients with delirium: a randomized trial. *Canadian Medical Association journal,* Vol. 151, No. 7, pp. 965-970, ISSN 0820-3946

[20] Colombo, R., Corona, A., Praga, F., Minari, C., Giannotti, C., Castelli, A. & Raimondi, F. (2012). A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. *Minerva anestesiologica,*(July 6), ISSN 1827-1596,[Epub ahead of print]

[21] De Jonghe, J. F., Kalisvaart, K. J., Dijkstra, M., Van Dis, H., Vreeswijk, R., Kat, M. G., Eikelenboom, P., Van Der Ploeg, T. & Van Gool, W. A. (2007). Early symptoms in the prodromal phase of delirium: a prospective cohort study in elderly patients undergoing hip surgery. *The American journal of geriatric psychiatry,* Vol. 15, No. 2, pp. 112-121, ISSN 1064-7481

[22] De Wet, H., Levitt, N. & Tipping, B. (2007). Executive cognitive impairment detected by simple bedside testing is associated with poor glycaemic control in type 2 diabetes. *South African medical journal,* Vol. 97, No. 11, pp. 1074-1076, ISSN 0256-9574

[23] Devlin, J. W., Roberts, R. J., Fong, J. J., Skrobik, Y., Riker, R. R., Hill, N. S., Robbins, T. & Garpestad, E. (2010). Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Critical care medicine,* Vol. 38, No. 2, pp. 419-427, ISSN 1530-0293

[24] Elsayem, A., Bush, S. H., Munsell, M. F., Curry, E., 3rd, Calderon, B. B., Paraskevopoulos, T., Fadul, N. & Bruera, E. (2010). Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. J*ournal of pain and symptom management,* Vol. 40, No. 5, pp. 774-782, ISSN 1873-6513

[25] Eriksson, I., Gustafson, Y., Fagerstrom, L. & Olofsson, B. (2011). Urinary tract infection in very old women is associated with delirium. *International psychogeriatrics,* Vol. 23, No. 3, pp. 496-502, ISSN 1741-203X

[26] Fadel, D. & Serra, H. A. (2009). Cocaine-induced agitated delirium, a different consequence of cocaine addiction. *Vertex,* Vol. 20, No. 84, pp. 85-92, ISSN 0327-6139

[27] Flacker, J. M. & Lipsitz, L. A. (1999). Neural mechanisms of delirium: current hypotheses and evolving concepts. *The journals of gerontology. Series A, Biological sciences and medical sciences,* Vol. 54, No. 6, pp. B239-246, ISNN 1079-5006

[28] Fong, T. G., Jones, R. N., Marcantonio, E. R., Tommet, D., Gross, A. L., Habtemariam, D., Schmitt, E., Yap, L. & Inouye, S. K. (2012). Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. *Annals of internal medicine,* Vol. 156, No. 12, pp. 848-856, ISSN 1539-3704

[29] Froemming, J. S., Lam, Y. W., Jann, M. W. & Davis, C. M. (1989). Pharmacokinetics of haloperidol. *Clinical pharmacokinetics,* Vol. 17,No. 6, pp. 396-423, ISSN 0312-5963

[30] Gamberini, M., Bolliger, D., LuratiBuse, G. A., Burkhart, C. S., Grapow, M., Gagneux, A., Filipovic, M., Seeberger, M. D., Pargger, H., Siegemund, M., Carrel, T., Seiler, W. O., Berres, M., Strebel, S. P., Monsch, A. U. & Steiner, L. A. (2009). Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery-a randomized controlled trial. *Crit Care Med,* Vol. 37, No. 5, pp. 1762-1768, ISSN 1530-0293

[31] Gray, G. E. & Taylor, C. B. (2010). Searching for answers, In: *How to practice evidence-based psychiatry: basic principles and case studies*, C. B. Taylor, (Ed.), 21-34, American Psychiatric Publisher, Inc., ISBN 978-1-58562-365-5, Arlington, USA

[32] Grover, S., Kate, N., Agarwal, M., Mattoo, S. K., Avasthi, A., Malhotra, S., Kulhara, P., Chakrabarti, S. & Basu, D. (2012). Delirium in elderly people: a study of a psychiatric liaison service in north India. *International psychogeriatrics,* Vol. 24, No. 1, pp. 117-127, ISSN 1741-203X

[33] Grover, S., Kumar, V. & Chakrabarti, S. (2011). Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. *Journal of psychosomatic research,* Vol. 71, No. 4, pp. 277-281, ISSN 1879-1360

[34] Gunther, M. L., Morandi, A. & Ely, E. W. (2008). Pathophysiology of delirium in the intensive care unit. *Critical care clinics,* Vol. 24, No. 1, pp. 45-65, viii, ISSN 0749-0704

[35] Han, C. S. & Kim, Y. K. (2004). A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics,* Vol. 45, No. 4, pp. 297-301, ISSN 0033-3182

[36] Han, L., Mccusker, J., Cole, M., Abrahamowicz, M., Primeau, F. & Elie, M. (2001). Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Archives of internal medicine,* Vol. 161, No. 8, pp. 1099-1105, ISSN 0003-9926

[37] Harrington, A. L., Dixon, T. M. & Ho, C. H. (2011). Vitamin B(12) deficiency as a cause of delirium in a patient with spinal cord injury. *Archives of physical medicine and rehabilitation,* Vol. 92, No. 11, pp. 1917-1920,ISSN 1532-821X

[38] Inouye, S. K. (2000). Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. *Annals of medicine,* Vol. 32, No. 4, pp. 257-263, ISSN 0785-3890

[39] Inouye, S. K. (2004). A practical program for preventing delirium in hospitalized elderly patients. *Cleveland Clinic journal of medicine,* Vol. 71, No. 11, pp. 890-896, ISSN 0891-1150

[40] Inouye, S. K., Baker, D. I., Fugal, P. & Bradley, E. H. (2006). Dissemination of the hospital elder life program: implementation, adaptation, and successes. J*ournal of the American Geriatrics Society,* Vol. 54, No. 10, pp. 1492-1499, ISSN 0002-8614

[41] Inouye, S. K. & Charpentier, P. A. (1996). Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA,* Vol. 275, No. 11, pp. 852-857, ISSN 0098-7484

[42] Inouye, S. K., Van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P. & Horwitz, R. I. (1990). Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine,* Vol. 113, No. 12, pp. 941-948, ISSN 0003-4819

[43] Jacobson, S. & Jerrier, H. (2000). EEG in delirium. *Seminars in clinical neuropsychiatry,* Vol. 5, No. 2, pp. 86-92, ISSN 1084-3612

[44] Kalisvaart, K. J., De Jonghe, J. F., Bogaards, M. J., Vreeswijk, R., Egberts, T. C., Burger, B. J., Eikelenboom, P. & Van Gool, W. A. (2005). Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *Journal ofthe American Geriatrics Society,* Vol. 53, No. 10, pp. 1658-1666, ISSN 0002-8614

[45] Kane, F. J., JR., Remmel, R. & Moody, S. (1993). Recognizing and treating delirium in patients admitted to general hospitals. *Southern medical journal,* Vol. 86, No. 9, pp. 985-988, ISSN 0038-4348

[46] Kasick, D. P., Mcknight, C. A. & Klisovic, E. (2012). "Bath salt" ingestion leading to severe intoxication delirium: two cases and a brief review of the emergence of mephedrone use. *The American journal of drug and alcohol abuse,* Vol. 38, No. 2, pp. 176-180, ISSN 1097-9891

[47] Khurana, V., Gambhir, I. S. & Kishore, D. (2011). Evaluation of delirium in elderly: a hospital-based study. *Geriatrics & gerontology international,* Vol. 11, No. 4, pp. 467-473, ISSN 1447-05941447-0594

[48] Kim, S. W., Yoo, J. A., Lee, S. Y., Kim, S. Y., Bae, K. Y., Yang, S. J., Kim, J. M., Shin, I. S. & Yoon, J. S. (2010). Risperidone versus olanzapine for the treatment of delirium. *Human psychopharmacology,* Vol. 25, No. 4, pp. 298-302, ISSN 1099-1077

[49] Kradin, R. L. (2011). Placebo response: a consideration of its role in therapeutics. *Current psychiatry reports,* Vol. 13, No. 1, pp. 37-42, ISSN 1535-1645

[50] Larsen, K. A., Kelly, S. E., Stern, T. A., Bode, R. H., JR., Price, L. L., Hunter, D. J., Gulczynski, D., Bierbaum, B. E., Sweeney, G. A., Hoikala, K. A., Cotter, J. J. & Potter, A. W. (2010). Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics,* Vol. 51, No. 5, pp. 409-418, ISSN 1545-7206

[51] Lee, K. U., Won, W. Y., Lee, H. K., Kweon, Y. S., Lee, C. T., Pae, C. U. & Bahk, W. M. (2005). Amisulpride versus quetiapine for the treatment of delirium: a randomized, open prospective study. *International clinical psychopharmacology,* Vol. 20, No. 6, pp. 311-314, ISSN 0268-1315

[52] Liptzin, B., Laki, A., Garb, J. L., Fingeroth, R. & Krushell, R. (2005). Donepezil in the prevention and treatment of post-surgical delirium. *The American journal of geriatric psychiatry,* Vol. 13, No. 12, pp. 1100-1106, ISSN 1064-7481

[53] Lonergan, E., Luxenberg, J. & AreosaSastre, A. (2009). Benzodiazepines for delirium. *Cochrane database of systematic reviews (Online),* No. 4, pp. CD006379, ISSN 1469-493X

[54] Lorenzl, S., Fusgen, I. & Noachtar, S. (2012). Acute confusional States in the elderly-diagnosis and treatment. *DeutschesArzteblatt international,* Vol. 109, No. 21, pp. 391-400, ISSN 1866-0452 1866-0452

[55] Lundstrom, M., Edlund, A., Karlsson, S., Brannstrom, B., Bucht, G. & Gustafson, Y. (2005). A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. Journal of the American Geriatrics Society, Vol. 53, No. 4, pp. 622-628, ISSN 0002-8614

[56] Maldonado, J. R. (2008a). Delirium in the acute care setting: characteristics, diagnosis and treatment. *Critical care clinics,* Vol. 24, No. 4, pp. 657-722, vii, ISSN 0749-0704

[57] Maldonadoaldonado, J. R. (2008b). Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Critical care clinics,* Vol. 24, No. 4, pp. 789-856, ix, ISSN 0749-0704

[58] Maneeton, B., Khemawichanurat, W. & Maneeton, N. (2007a). Consultation-liaison psychiatry in MaharajNakorn Chiang Mai Hospital. *ASEAN Journal of Psychiatry,* Vol. 8, No. 2, pp. 124-130, ISSN 2231-7805

[59] Maneeton, B., Maneeton, N. & Srisurapanont, M. (2007b). An open-label study of quetiapine for delirium. *Journal of the Medical Association of Thailand,* Vol. 90, No. 10, pp. 2158-2163, ISSN 0125-2208

[60] Maneeton, B., Maneeton, N. & Srisurapanont, M. (2011). A double-blind, randomised, controlled trial of quetiapine versus haloperidol for the treatment of delirium: a preliminary report. *European Neuropsychopharmacology,* Vol. 21, pp. s557

[61] Marcantonio, E. R., Palihnich, K., Appleton, P. & Davis, R. B. (2011). Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. *Journal of the American Geriatrics Society,* Vol. 59 Suppl 2, pp. S282-8, ISSN 1532-5415

[62] Marcantonio, E. R., Rudolph, J. L., Culley, D., Crosby, G., Alsop, D. & Inouye, S. K. (2006). Serum biomarkers for delirium. *The journals of gerontology. Series A, Biological sciences and medical sciences,* Vol. 61, No. 12, pp. 1281-1286, ISSN 1079-5006

[63] Martin, J. J. (2012). Confusion, agitation and delirium. *Frontiers of neurology and neuroscience,* Vol. 30, pp. 46-49, ISSN 1662-2804

[64] Martinez, F. T., Tobar, C., Beddings, C. I., Vallejo, G. & Fuentes, P. (2012). Preventing delirium in an acute hospital using a non-pharmacological intervention. *Age and ageing*, Vol. 41, No. 5, pp. 629-634, ISSN 1468-2834

[65] Meagher, D. J., O'Hanlon, D., O'Mahony, E. & Casey, P. R. (1996). The use of environmental strategies and psychotropic medication in the management of delirium. *The British journal of psychiatry,* Vol. 168, No. 4, pp. 512-515, ISSN 0007-1250

[66] Menza, M. A., Murray, G. B., Holmes, V. F. & Rafuls, W. A. (1987). Decreased extrapyramidal symptoms with intravenous haloperidol. *The Journal of clinical psychiatry,* Vol. 48, No. 7, pp. 278-280, ISSN 0160-6689

[67] Menza, M. A., Murray, G. B., Holmes, V. F. & Rafuls, W. A. (1988). Controlled study of extrapyramidal reactions in the management of delirious, medically ill patients: intravenous haloperidol versus intravenous haloperidol plus benzodiazepines. *Heart Lung,* Vol. 17, No. 3, pp. 238-241, ISSN 0147-9563

[68] Meyer-Massetti, C., Cheng, C. M., Sharpe, B. A., Meier, C. R. & Guglielmo, B. J. (2010). The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *Journal of hospital medicine,* Vol. 5, No. 4, pp. E8-16, ISSN 1553-5606

[69] Milisen, K., Foreman, M. D., Abraham, I. L., De Geest, S., Godderis, J., Vandermeulen, E., Fischler, B., Delooz, H. H., Spiessens, B. & Broos, P. L. (2001). A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *Journal of the American Geriatrics Society,* Vol. 49, No. 5, pp. 523-532, ISSN 0002-8614

[70] Moulaert, P. (1989). Treatment of acute nonspecific delirium with i. v. haloperidol in surgical intensive care patients. *ActaanaesthesiologicaBelgica,* Vol. 40, No. 3, pp. 183-186, ISSN 0001-5164

[71] Mussi, C., Ferrari, R., Ascari, S. & Salvioli, G. (1999). Importance of serum anticholinergic activity in the assessment of elderly patients with delirium. *Journal of geriatric psychiatry and neurology,* Vol. 12, No. 2, pp. 82-86, ISSN 0891-9887

[72] Nakatani, Y. & Hara, T. (1998). Disturbance of consciousness due to methamphetamine abuse. A study of 2 patients. *Psychopathology,* Vol. 31, No. 3, pp. 131-137, ISSN 0254-4962

[73] O'Keeffe, S. T., Tormey, W. P., Glasgow, R. & Lavan, J. N. (1994). Thiamine deficiency in hospitalized elderly patients. *Gerontology,* Vol. 40, No. 1, pp. 18-24, ISSN 0304-324X

[74] Oldenbeuving, A. W., De Kort, P. L., Jansen, B. P., Kappelle, L. J. & Roks, G. (2008). A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative. *BMC neurology,* Vol. 8, pp. 34, ISSN 1471-2377

[75] Olsson, T. (1999). Activity in the hypothalamic-pituitary-adrenal axis and delirium. *Dementia and geriatric cognitive disorders,* Vol. 10, No. 5, pp. 345-349, ISSN 1420-8008

[76] Overshott, R., Karim, S. & Burns, A. (2008). Cholinesterase inhibitors for delirium. Cochrane database of systematic reviews (Online),No. 1, pp. CD005317, ISSN 1469-493X

[77] Overshott, R., Vernon, M., Morris, J. & Burns, A. (2010). Rivastigmine in the treatment of delirium in older people: a pilot study. *International psychogeriatrics,* Vol. 22, No. 5, pp. 812-818, ISSN 1741-203X

[78] Pearson, A., De Vries, A., Middleton, S. D., Gillies, F., White, T. O., Armstrong, I. R., Andrew, R., Seckl, J. R. & Maclullich, A. M. (2011). Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. *BMC research notes,* Vol. 3, pp. 33, ISSN 1756-0500

[79] Praditsuwan, R., Limmathuroskul, D., Assanasen, J., Pakdeewongse, S., Eiamjinnasuwat, W., Sirisuwat, A. & Srinonprasert, V. (2012). Prevalence and incidence of delirium in Thai older patients: a study at general medical wards in Siriraj Hospital. *Journal of the Medical Association of Thailand,* Vol. 95 Suppl 2, pp. S245-250, ISSN 0125-2208

[80] Prakanrattana, U. & Prapaitrakool, S. (2007). Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesthesia and intensive care,* Vol. 35, No. 5, pp. 714-719, ISSN 0310-057X

[81] Rahkonen, T., Makela, H., Paanila, S., Halonen, P., Sivenius, J. & Sulkava, R. (2000). Delirium in elderly people without severe predisposing disorders: etiology and 1-year prognosis after discharge. *International psychogeriatrics,* Vol. 12, No. 4, pp. 473-481, ISSN 1041-6102

[82] Ramirez-Bermudez, J., Lopez-Gomez, M., Sosa Ana, L., Aceves, S., Nader-Kawachi, J. & Nicolini, H. (2006). Frequency of delirium in a neurological emergency room. *The Journal of neuropsychiatry and clinical neurosciences,* Vol. 18, No. 1, pp. 108-112, ISSN 0895-0172

[83] Raz, A., Campbell, N., Guindi, D., Holcroft, C., Dery, C. & Cukier, O. (2011). Placebos in clinical practice: comparing attitudes, beliefs, and patterns of use between academic psychiatrists and nonpsychiatrists. *Canadian journal of psychiatry,* Vol. 56, No. 4, pp. 198-208, ISSN 1497-0015

[84] Robertsson, B., Blennow, K., Brane, G., Edman, A., Karlsson, I., Wallin, A. & Gottfries, C. G. (2001). Hyperactivity in the hypothalamic-pituitary-adrenal axis in de-

mented patients with delirium. *International clinical psychopharmacology,* Vol. 16, No. 1, pp. 39-47, ISSN 0268-1315

[85] Saitz, R. (1998). Introduction to alcohol withdrawal. *Alcohol health and research world,* Vol. 22, No. 1, pp. 5-12, ISSN 0090-838X

[86] Salawu, F. K., Danburam, A. & Ogualili, P. (2009). Delirium: issues in diagnosis and management. *Annals of African medicine,* Vol. 8, No. 3, pp. 139-146, ISSN 0975-5764

[87] Schaffer, C. B., Shahid, A., Javaid, J. I., Dysken, M. W. & Davis, J. M. (1982). Bioavailability of intramuscular versus oral haloperidol in schizophrenic patients. *Journal of clinical psychopharmacology,* Vol. 2, No. 4, pp. 274-277, ISSN 0271-0749

[88] Seaman, J. S., Schillerstrom, J., Carroll, D. & Brown, T. M. (2006). Impaired oxidative metabolism precipitates delirium: a study of 101 ICU patients. *Psychosomatics,* Vol. 47, No. 1, pp. 56-61, ISSN 0033-3182

[89] Siddiqi, N., House, A. O. & Holmes, J. D. (2006). Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and ageing,* Vol. 35, No. 4, pp. 350-364, ISSN 0002-0729

[90] Sidhu, K. S., Balon, R., Ajluni, V. & Boutros, N. N. (2009). Standard EEG and the difficult-to-assess mental status. *Annals of clinical psychiatry,* Vol. 21, No. 2, pp. 103-108, ISSN 1547-3325

[91] Simone, M. J. & Tan, Z. S. (2011). The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. *CNS neuroscience & therapeutics,* Vol. 17, No. 5, pp. 506-513, ISSN 1755-5949

[92] Skrobik, Y. K., Bergeron, N., Dumont, M. & Gottfried, S. B. (2004). Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive care medicine,* Vol. 30, No. 3, pp. 444-449, ISSN 0342-4642

[93] Srinonprasert, V., Pakdeewongse, S., Assanasen, J., Eiamjinnasuwat, W., Sirisuwat, A., Limmathuroskul, D. & Praditsuwan, R. (2011). Risk factors for developing delirium in older patients admitted to general medical wards. *Journal of the Medical Association of Thailand,* Vol. 94 Suppl 1, pp. S99-104, ISSN 0125-2208

[94] Straker, D. A., Shapiro, P. A. & Muskin, P. R. (2006). Aripiprazole in the treatment of delirium. *Psychosomatics,* Vol. 47, No. 5, pp. 385-391, ISSN 0033-3182

[95] Tahir, T. A., Eeles, E., Karapareddy, V., Muthuvelu, P., Chapple, S., Phillips, B., Adyemo, T., Farewell, D. & Bisson, J. I. (2010). A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. *Journal of psychosomatic research,* Vol. 69, No. 5, pp. 485-90, ISSN 1879-1360

[96] Trevisan, L. A., Boutros, N., Petrakis, I. L. & Krystal, J. H. (1998). Complications of alcohol withdrawal: pathophysiological insights. *Alcohol health and research world,* Vol. 22, No. 1, pp. 61-66, ISSN 0090-838X

[97] Trzepacz, P. T. (2000). Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Seminars in clinical neuropsychiatry,* Vol. 5, No. 2, pp. 132-148, ISSN 1084-3612

[98] Trzepacz, P. T., Mittal, D., Torres, R., Kanary, K., Norton, J. & Jimerson, N. (2001). Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *The Journal of neuropsychiatry and clinical neurosciences,* Vol. 13, No. 2, pp. 229-242, ISSN 0895-0172

[99] Van Den Boogaard, M., Kox, M., Quinn, K. L., Van Achterberg, T., Van Der Hoeven, J. G., Schoonhove, L. & Pickkers, P. (2011). Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Critical care,* Vol. 15, No. 6, pp. R297, ISSN 1466-609X

[100] Van Der Mast, R. C. (1998). Pathophysiology of delirium. *Journal of geriatric psychiatry and neurology,* Vol. 11, No. 3, pp 138-45; discussion 157-158, ISSN 0891-9887

[101] Van Gool, W. A., Van De Beek, D. & Eikelenboom, P. (2010). Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet,* Vol. 375, No. 9716, pp. 773-775, ISSN 1474-547X

[102] Van Rompaey, B., Elseviers, M. M., Schuurmans, M. J., Shortridge-Baggett, L. M., Truijen, S. & Bossaert, L. (2009). Risk factors for delirium in intensive care patients: a prospective cohort study. *Critical care,* Vol. 13, No. 3, pp. R77, ISSN 1466-609X

[103] Wang , W., Li, H. L., Wang, D. X., Zhu, X., Li, S. L., Yao, G. Q., Chen, K. S., Gu, X. E. & Zhu, S. N. (2012). Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. *Critical care medicine,* Vol. 40, No. 3, 731-739, ISSN 1530-0293

[104] Warshaw, G. & Tanzer, F. (1993). The effectiveness of lumbar puncture in the evaluation of delirium and fever in the hospitalized elderly. *Archives of family medicine,* Vol. 2, No. 3, pp. 293-297, ISSN 1063-3987

[105] Wengel, S. P., Roccaforte, W. H. & Burke, W. J. (1998). Donepezil improves symptoms of delirium in dementia: implications for future research. *Journal of geriatric psychiatry and neurology,* Vol. 11, No. 3, pp. 159-161, ISSN 0891-9887

[106] Wilson, C. J., Finch, C. E. & Cohen, H. J. (2002). Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *Journal of the American Geriatrics Society,* Vol. 50, No. 12, pp. 2041-2056, ISSN 0002-8614

[107] Wongpakaran, N., Wongpakaran, T., Bookamana, P., Pinyopornpanish, M., Maneeton, B., Lerttrakarnnon, P., Uttawichai, K. & Jiraniramai, S. (2011). Diagnosing delirium in elderly Thai patients: utilization of the CAM algorithm. *BMC family practice,* Vol. 12, pp. 65, ISSN 1471-2296

[108] World Health Organization. (1993). *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research,* World Health Organization, ISBN 92-4-154422-8, Geneva, Switzerland

[109] Yang, F. M., Inouye, S. K., Fearing, M. A., Kiely, D. K., Marcantonio, E. R. & Jones, R. N. (2008). Participation in activity and risk for incident delirium. *Journal of the American Geriatrics Society*, Vol. 56, No. 8, pp. 1479-1484, ISSN 1532-5415

[110] Yang, F. M., Marcantonio, E. R., Inouye, S. K., Kiely, D. K., Rudolph, J. L., Fearing, M. A. & Jones, R. N. (2009). Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. *Psychosomatics,* Vol. 50, No. 3, pp. 248-254, ISSN 1545-7206

[111] Yu, Y. H., Chen, A. C., Hu, C. C., Hsieh, P. H., Ueng, S. W. & Lee, M. S. (2012). Acute Delirium and Poor Compliance in Total Hip Arthroplasty Patients With Substance Abuse Disorders. *The Journal of arthroplasty*, Vol. 27, No. 8, pp. 1526-1529, ISSN 1532-8406

[112] Zampieri, F. G., Park, M., Machado, F. S. & Azevedo, L. C. (2011). Sepsis-associated encephalopathy: not just delirium. *Clinics (Sao Paulo, Brazil),* Vol. 66, No. 10, pp. 1825-1831, ISSN 1980-5322