



BMH Med. J. 2018;5(2):51-56 **Brief Review**

Drug-Induced Delirium: A Mini Review

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Abstract

Delirium is a neuropsychiatric disorder that has detrimental futuristic complications, ranging from long-term cognitive impairment to death within several months, especially in the elderly and critically ill patients. One of the key elements in delirium management is to assess, identify and control any associated risk factors. Elevated risk and incidence of delirium have been reported with the use of a number of drugs from various pharmacological classes. Different medical agents indicated for cardiovascular conditions, central nervous system (CNS) disorders, anesthesia, cancer chemotherapy, and other medical conditions, have been reported to precipitate delirium episodes. Therefore, cautious assessment and continuous monitoring of patients' medical profiles may significantly reduce the risk of delirium. This mini review aims to explore the recently published scientific evidence on drug-induced delirium; in addition, attempting to find reasonable relations between the drugs' mode of action and delirium pathogenesis. Ultimately, providing medical experts with an update and a brief overview for the uprising scientists in the field.

Keywords: Delirium, Drug-induced delirium, Delirium risk factors, Delirium drug interactions.

Introduction

Delirium is a neuropsychiatric disorder, which can be defined as an acute transient state of confusion that alters the individuals' baseline/normal cognitive functions [1]. Delirium diagnosis depends mainly on the presence of a set of defined signs and symptoms that indicates delirium occurrence. The symptoms may include; illusions, sleep disturbances, hyper or hypoactivity, inability to focus, perceptual defects and other cognitive impairments [2]. Nevertheless, there is a high probability of delirium misdiagnosis, as delirium symptoms might be confused with other mental disorders [3]. Therefore, it is well recommended to undertake delirium diagnosis carefully in order to intervene rapidly and prevent any further complications. Delirium is found to be prevalent in elderly, dementia, and hospitalized patients, especially in individuals who have recently undergone major surgeries or required mechanical ventilation [4]. Despite the fact that, delirium mechanism is not fully understood, a number of hypotheses were introduced in order to explain the pathophysiology behind delirium. The most accepted theory is the neurotransmitters disturbance hypothesis, which insinuates the involvement of a number of CNS neurotransmitters in precipitating delirium [5]. Disrupted levels of acetylcholine, dopamine, norepinephrine, serotonin, glutamate, and gamma-

aminobutyric acid (GABA), are all suggested to play a role in delirium pathogenesis [6]. Other pathophysiological hypotheses include; the inflammatory theory and structural defects theory [7]. Furthermore, the futuristic complications of delirium; for instance, long-term cognitive impairment, increased hospitalization period and elevated mortality rates, are well observed [8]. Serious handling and assessment of the patient’s case are vital in identifying and limiting potential risk factors that would subsequently aid in enhancing the outcomes of delirium management. Delirium has a wide range of associated risk factors, multiple of which may coexist in a single patient; thus, adding more complexity to the treatment protocol. Risk factors can be categorized into three major groups; baseline (i.e. predisposing), hospitalization-associated, and underlying acute illness factors [9]. Drug-induced delirium can be listed under the risk factors title; as when a particular medical agent is administered to the patient, it is suggested to be responsible for inducing or at least increasing the risk of delirium incidence. Therefore, full review of the patient’s medications list, especially in polypharmacy cases, is an essential step to avoid any potential risk of developing delirium.

Cardiovascular Medical Agents

A number of medical agents used to treat cardiac conditions are suggested to elevate the risk of delirium. The antiarrhythmic drug disopyramide is suggested to induce delirium; in addition to, a number of other psychotic symptoms [10]. Disopyramide mechanism in delirium is proposed to be mediated via its relative anticholinergic activity, which is believed to promote delirium development [11]. Digoxin is observed to induce delirium; nevertheless, its mechanism involved in precipitating delirium is not clear [12]. Furthermore, beta-blockers; propranolol, atenolol, metoprolol, and carvedilol, are all reported to induce acute delirium, in accordance with their relative ability to cross the blood brain barrier that might possibly be responsible for the development of organic brain syndrome [13]. Moreover, electrolyte imbalance associated with the use of diuretics might be the reason behind their elevated delirium risk [14]. Centrally acting antihypertensive agents; clonidine and methyldopa, are also claimed to increase delirium occurrence [15].

CNS Drugs

This group has the advantage of being able to efficiently cross the blood brain barrier into the CNS; therefore, have stronger chances in altering brain homeostasis, which make it more in peril to delirium development compared to other drug groups. The use of some anticonvulsants, such as levetiracetam and valproic acid, has been found to exhibit higher delirium incidence that may require patient hospitalization and critical care [16-17]. Other anticonvulsants; carbamazepine, phenobarbital, and phenytoin, have a wide variety of drug interactions that may participate in the induction of delirium and other cognitive impairments; however, a sudden stop of these treatments may also contribute to a rebound seizure [18]. In contrast, benzodiazepines, which are strongly suggested to induce delirium as well, and other anticonvulsants have shown to be beneficial in the management of delirium cases associated with alcohol withdrawal [19]. Tricyclic antidepressants; doxepin and amitriptyline, are known to exert anticholinergic activity, which may trigger a delirium episode [20]. The anti-Parkinsonian medical agents; levodopa and amantadine, alter the levels of dopamine and norepinephrine. According to the neurotransmitters disturbance theory, they would lead to a reduction in acetylcholine levels; thus, explaining the elevated delirium risk [21]. Moreover, a number of case reports have concluded that delirium could be a result of using these agents [22]. Lastly, the use of opioids was found to be strongly associated with the transition to delirium development in critically ill patients and recommended to be listed as a vital modifiable risk factor for delirium in such cases [23].

Anesthetics

Hospital-related risk factors of delirium may include; sleep disturbances, physical restraint, type of medical intervention (i.e. medical vs. surgical), and any other factors related to the hospital environment. The use of anesthetics prior to surgeries has been linked to an increased risk of post-

surgical delirium. Nevertheless, a number of factors, such as the anesthetic dose, stress during surgery, and monitoring anesthesia depth, may influence the post-operative outcomes including delirium development [24]. Furthermore, the type of anesthesia (i.e. inhaled vs. intravenous anesthetics) used may differ in the outcomes, as observed by a study which compared between intravenous propofol and inhaled sevoflurane. The study findings have shown a significant difference between the two groups, in which postoperative delirium incidence was (26.7%) with sevoflurane compared to only (6.9%) with propofol [25]. Another example is ketamine, which has also been linked to a high post-operative delirium incidence. Although, some argued that ketamine may have a potential in reducing the risk of delirium; however, it failed to show any notable success [26]. At last, the exact mechanism by which anesthetics induce delirium is complex and not fully understood.

Chemotherapeutic Agents

Even though chemotherapeutic agents are less likely to enter the CNS, small lipophilic antineoplastic drugs are able to cross the blood brain barrier and have been observed to trigger delirium in cancer patients [27]. The mechanism by which they induce delirium and cognitive defects is suggested to be via their cytotoxic activity, cellular stress, and activation of pro-inflammatory cytokines pathways [28]. Examples include; bleomycin, carmustine, cisplatin, ifosfamide, methotrexate, vincristine, and vinblastine [29].

Miscellaneous Therapeutic Agents

This group includes a number of selected medical agents from their major pharmacological groups. Drugs under this heading have some evidence to support the claims about their role in the induction of delirium. These agents can be summarized as the following:

- Anticholinergics: atropine, scopolamine [30].
- Antibiotics: quinolones [31].
- Anti-emetics: dronabinol, phenothiazine, metoclopramide [32].
- Oral hypoglycemic agents: sulfonylureas (e.g. chlorpropamide, glyburide, glipizide, glimepiride) [33].
- Non-Steroidal Anti-Inflammatory (NSAIDs): indomethacin, celecoxib, rofecoxib [34].
- H₂ - blockers: cimetidine, ranitidine [35].
- First generation antihistamines: diphenhydramine, chlorpheniramine [36].

Discussion

Up to date, delirium is still a clinical challenge due to the massive number of variables that may participate in the disease pathogenesis. Despite the fact that few medical guidelines have recommended the use of certain drugs for the treatment of delirium; for instance, antipsychotics (i.e. both typical & atypical), no single medical agent has been approved yet by the Food and Drug Administration (FDA) for the treatment of delirium [37]. On the other hand, huge efforts are aiming towards minimizing or possibly preventing delirium in the first place. Nevertheless, in order to achieve this goal, a number of clinical concerns should be addressed carefully. These concerns are mainly based on identifying any potential factors that could elevate the risk of delirium. First, identifying vulnerable individuals who are known to frequently develop delirium, such as elderly, critically ill patients (i.e. ICU patients) and patients undergoing major surgeries. Next, carefully assessing each case individually in order to find any potential risk factors associated with delirium. In this step, patients' medications should be reviewed carefully to avoid any possible drug-interactions or drug-induced complications, especially in polypharmacy cases or patients with

impaired liver or kidney functions. However, according to the National Institute for Health and Care Excellence (NICE) guidelines, if delirium did happen, the initial procedure is to treat the underlying cause; in other words, managing the acute condition responsible for patient admission into critical care, such as strokes, invasive infections, drug toxicities, etc.[38] Then, re-screening for other risk factors; for instance, if the patient is administered a drug suggested to induce delirium, then it should be stopped immediately during the delirium episode. Other pharmacological treatments and non-pharmacological techniques (e.g. maintaining a good sleep rhythm) might also be used to ease delirium severity, duration, and future negative outcomes. Eventually, early detection and diagnosis of delirium are vital, especially in the hypoactive subtype, in which a patient might not display obvious signs and symptoms of delirium. Therefore, the use of Confusion Assessment Method (CAM-ICU) and Richmond Agitation-Sedation Scale (RASS) is advised to confirm delirium diagnosis [39]. Nonetheless, various aspects including; delirium definitive diagnosis, risk stratification, pathophysiology, medical management, are yet to be absolutely validated and are still debatable points in the scientific community that require further clinical investigations.

Conclusion

Patients may enter the ICU for an acute condition and be discharged with long-term debilitating cognitive impairments and a high risk of mortality within several months, because of a delirium episode. Many factors attached to delirium are considered modifiable and avoidable that may rescue lives if handled carefully. Drug-induced delirium is a major concern in patients at risk. This paper has mentioned several common medical agents suggested to induce delirium with the latest evidence that supports claims about their involvement, and the relation between their mechanism of action and delirium pathogenesis. However, due to delirium complexity, further clinical investigations should be undertaken to confirm the current recommended practices and guidelines in delirium management.

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