REVIEW ARTICLE

Benzodiazepinics and the treatment of delirium: a literature review

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SUMMARY

OBJECTIVE: *To discuss the role of the benzodiazepine class in delirium patient management.*

METHODS: *Using the PubMed database, articles were reviewed after the year 2000 containing in their title the words 'delirium' and 'benzodiazepines'.*

DISCUSSION: *Delirium is an acute confusional state that leads to altered attention, awareness, and cognition. It presents with some well-established risk factors, especially older individuals with cognitive decline. There is currently no definite consensus regarding its pathophysiology, nor regarding pharmacological measures, especially concerning the benzodiazepine class.*

CONCLUSION: *Evidence suggests that there may be a role for the use of pharmacological class in the treatment of this condition, indicating a change in the previously paradigmatic pattern of treatment.*

KEYWORDS: *Delirium. Benzodiazepines. Review.*

INTRODUCTION

Delirium is an acute confusional state observed mainly in patients with specific characteristics and in contexts of greater vulnerability, such as lower cognitive reserve and prolonged hospital admissions, that evolves with a significant increase in morbidity and mortality of patients affected[1,2]. In studies conducted in the general population, the prevalence of the condition was 1% in individuals from the age of 55 years, demonstrating, also, to be the cause of 5% to 10% of elderly care in the emergency services[3]. According to the DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, the criteria of delirium focus on symptoms developed over a short period, such as change of attention, consciousness, and cognition. It can present in three forms: hyperactive, hypoactive, and mixed level of activity; its physiopathology

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remains not entirely understood and involves a complex interaction between precipitating and predisposing factors[4]. The risk factors include individuals above 65 years of age, cognitive decline, infection, iatrogenic factors - such as immobilization and sleep deprivation[5] - in addition to its association with the use of medications, particularly those that act in the dopaminergic, cholinergic, or gamma-aminobutyric receptors. Pharmacological treatments that involve the class of benzodiazepines are commonly remembered as a potential risk for the development of delirium; however, recent trials and meta-analyzes have had results that question such a risk, which motivated this article.

Currently, the focus of the treatment is on the cause of the delirium; drugs are resources for situations in which patients present psychomotor agitation, psychotic symptoms, or insomnia, and in scenarios that are refractory to the initial non-pharmacological approaches. Benzodiazepines, well-established drugs for the treatment of delirium associated with alcohol abstinence are also often used as sedatives in other presentations of the condition, despite its association, by several studies, with the onset or perpetuation of the condition.

METHODS

We used the PubMed database as a source for this study; we accessed it in August 2019. The articles were screened based on their titles, abstracts, and year of publication. We retrieved a total of 19 publications with the keywords "delirium and benzodiazepines", used as inclusion criterion the English or Portuguese language; the exclusion criteria included date prior to 2000 (two papers excluded), articles specifically on delirium tremens (two papers excluded), and republished articles (two papers excluded). In total, 14 articles were selected and reviewed, including a meta-analysis published in 2019[6] to discuss the pharmacological approach of delirium.

RESULTS AND DISCUSSION

Randomized clinical trials that establishing a causal relationship between drugs, particularly benzodiazepines, and delirium, are old. Many of them are based on inconclusive findings[7] or were interrupted due to severe adverse effects, such as severe sedation. Other studies have shown evidence that suggests an increased risk of developing a confusional state associated with the use of benzodiazepines[1,2,4,5,8].

Lonergan et al.[2] published a literature review on the use of benzodiazepines and delirium, selecting only randomized, double-blind clinical trials. A single study conducted by Pandharipande in 2007 demonstrated the superiority of dexmedetomidine in minimizing delirium, when used sedating patients under mechanical ventilation, in comparison with lorazepam. Patients treated with the first drug had more days without coma or delirium; however, its use in a highly select group - those in mechanical ventilation - prevents the extrapolation of the results to the population with delirium as a whole. In addition, the absence of control groups makes it impossible to compare the effects of lorazepam on the scenario in question[2]. We found no controlled studies to support the use of benzodiazepines in the treatment of delirium unrelated to alcohol abstinence, denoting the need for new research with this purpose[2].

A review aiming to relate drugs potentially associated with delirium found a nested case-control study that associates benzodiazepines to an increased risk of delirium (RR 3.0; CI 95% 1.3-6.8)[8].

A prospective cohort study conducted by Smith et al.[5] in 300 pediatric patients from 6 months to 5 years of age, from March 2013 to October 2014, with the goal of determining risk factors associated with delirium, found that exposure to benzodiazepines was the only independent predictor for the development of delirium on the day following the exposure in comparison with the normal mental state (RR 2.47; 95% CI 1.36 to 4.49; p=0.005).

In 2015, in another retrospective observational study conducted in a pediatric population that had been screened prospectively for delirium, with six-month duration, also found that benzodiazepines were strongly and independently associated with the transition from a normal mental state to delirium, more than quadrupling the rates (OR, 4.4; 95% CI, 1.7-11.1; p=0.002), when compared to children with a normal cognitive state who did not receive sedatives. A univariate model also evaluated the dose-response relationship, showing that, for each logarithmic increase in the dose of benzodiazepines, there was an increase of 43% in the risk of transition to delirium in the following day[4]. Regarding the different types of delirium, the most common was hypoactive, found in 52% of cases, followed by the mixed and hyperactive presentations[4].

The iatrogenic damage from the use of benzodiazepines in adults has been consistently shown to include greater development and duration of delirium, greater duration of mechanical ventilation, and a longer stay in the ICU and hospital[5]. In addition, patients with high exposure to benzodiazepines were significantly more likely to develop delirium on the day following the exposure, when compared to those with minimal or no exposure[5]. A set of evidence focused on modifiable risk factors showed clear associations between exposure to benzodiazepines and the development of delirium in surgical and ICU patients (Pandharipande, 2006).

In 2018, a review by Hui[9] was published aiming to evaluate the role of benzodiazepines in the management of hyperactive delirium in palliative care; it included three randomized controlled trials and concluded that the literature based its application on terminal delirium and delirium tremens. Midazolam and lorazepam are among the drugs of choice, depending on the time of short half-life and parenteral availability. The association between lorazepam and haloperidol was also assessed and proved to be superior to haloperidol alone to manage the resistance of hyperactive delirium and promote more comfort for terminally ill patients[9].

A meta-analysis conducted by Wu et al.[6] and published in February 2019 confronted the use of benzodiazepines in the management of delirium. It assessed 58 articles: 20 related drug therapy with delirium, both in an interventional and preventive way, with the participation of 1,435 patients, and 38 articles focused on the prevention of the condition, with the participation of 8,168 individuals. Interventional therapeutic actions demonstrated the statistical superiority of the association of haloperidol and lorazepam (OR 28.13; CI 95% 2.38-333.08) or haloperidol alone (OR 2.37; 95% CI 1.04-5.43) in comparison to a placebo/control. However, it is important to emphasize that none of the other drugs studied obtained results lower than the placebo/control (rivastigmine tartrate, chlorpromazine hydrochloride, lorazepam, quetiapine, amisulpride, ziprasidone hydrochloride, haloperidol, and rivastigmine tartrate, risperidone, ondansetron)[6].

Currently, the management of delirium is mostly focused on treating the underlying cause while providing physical, sensory, and environmental support. Drug therapy is usually used in patients who manifest psychosis or insomnia. The drug of choice is haloperidol, orally, twice a day (⅔ administered before sleep). However, due to its effects on the heart, such as the prolongation of the QT interval, an electrocardiogram should be performed initially and then monitored. The use of benzodiazepines is more indicated for the management of insomnia, and those with a short or intermediary half-life are the most widely used. In addition, it is recommended to avoid its use alone in the treatment of delirium unrelated to alcohol abstinence[3].

CONCLUSION

With this review, we noticed that currently there is no consensus regarding drug therapy. Health services usually try to identify the underlying causes, establish a non-pharmacological treatment and, as a last resort, if necessary, make use of drugs, particularly antipsychotics, to try to stabilize patients in the best possible way. Many variables limit the creation of a guideline on the management of these patients, including the patient's age, presence of comorbidities, type, and duration of delirium. With this review, it is possible to observe that the articles that focused on the deleterious association between the use of benzodiazepines and delirium failed to reach a consensus on that association[7,8]. The meta-analysis published in 2019 by Wu et al.[6] demonstrated benefits from the association between lorazepam and haloperidol, which may suggest a change in the previously paradigmatic pattern of treatment for acute confusional state[6,9].

RESUMO

OBJETIVO: *Discutir o papel da classe de benzodiazepínicos no manejo do paciente em delirium.*

MÉTODOS: *Utilizando base de dados PubMed, foram revisados artigos posteriores ao ano 2000 contendo em seu título as palavras "delirium" e "benzodiazepines".*

DISCUSSÃO: *O delirium é um estado confusional agudo, que cursa com alteração da atenção, consciência e cognição. Apresenta-se com alguns fatores de risco bem estabelecidos, sobretudo em indivíduos de maior idade e com declínio cognitivo. Não há, atualmente, um consenso definido quanto a sua fisiopatologia, tampouco referente às medidas farmacológicas, principalmente acerca da classe dos benzodiazepínicos.*

CONCLUSÃO: *Evidências sugerem que pode haver um papel do uso da classe farmacológica no tratamento do quadro em questão, indicando uma mudança no padrão anteriormente paradigmático do tratamento.*

PALAVRAS-CHAVE: *Delírio. Benzodiazepinas. Revisão.*

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