Delirium Treatment

Subjects: Pathology
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The presentation of common acute diseases in older age is often referred to as "atypical". Frequently, the symptom is neither single nor tissue- related. In most cases, the onset of symptoms and diseases is the expression of diminished reserve with failure of body-system, and imbalance of brain function. Delirium is one of the main devastating and prevalent atypical symptoms and could be considered as a geriatric syndrome. It is encompassing an array of neuropsychiatric symptoms and represents a disarrangement of the cerebral function in response to one or more stressors. The most recent definition, reported in the DSM-V, depicts delirium as a clear disturbance in attention and awareness. The deficit is to be developed in a relatively short time-period time (usually hours or days). The attention disorder must be associated with another cognitive impairment in memory, orientation, language, visual-spatial or perception abilities.

For the treatment it is imperative remove potential causes of delirium, before prescribing drugs. Even a non-pharmacological approach to reduce precipitating causes should be identified and treated. When we are forced to approach the pharmacological treatment of hyperkinetic delirium in older persons, we should select highly cost-effective drugs. High attention should be devoted to the correct balance between improvement of psychiatric symptoms and occurrence of side-effects. Clinicians should be guided in the correct choice of drugs following cluster symptoms presentation, excluding drugs that potentially could produce complications rather than advantages. In this brief point-of-view, we propose a novel pharmacological flow-chart of treatment in relation to the basic clusters of diseases of the older patient admitted acutely to the hospital and in particular we emphasized “how should we do not do!”, with the intention of avoiding possible side effects of drugs used.

Keywords: delirium ; drugs, side-effects, older persons

1. Introduction

It is now widely accepted that the approach to identifying delirium should be realized by a multidisciplinary team, able to realize a comprehensive geriatric assessment and offer holistic care to multimorbid patients developing delirium [1][2]. The evaluation of medications, the intake of alcoholic beverages, and a detailed history of the patient are key points for understanding the causes of delirium. A history of a similar incidents and the presence of a pre-existing cognitive impairments should be particularly investigated. Particular attention should be devoted to masked signs of delirium such as falls or sudden incontinence. Even a rapid change in behavior should be considered delirium until proven guilty.

Primary prevention with non-pharmacological multicomponent approaches is widely accepted as the most effective strategy for delirium. The most famous approach is the Hospital Elder Life Program (HELP) [3], a multicomponent intervention strategy including reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilization, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations. The program, which has been shown to be effective in different settings, should be implemented by a skilled interdisciplinary team assisted by either nursing staff or trained volunteers.

Then, neuro-geriatric approaches should ensure an adequate oxygenation, hydration, nutrition, and normal levels of metabolites of the patient and remove drugs that could produce negative effects on the brain. Physical restraints should be avoided, as they can increase agitation and risk of injury. In order to avoid the use of restraints, some patients may require constant supervision, especially from their family members or caregivers.

2. Treatment of Delirium Based on Toxicity, Side-Effects of Drugs

Recently, the Scottish Intercollegiate Guidelines Network (SIGN) developed evidence-based clinical practice guidelines for the National Health Service (NHS) in Scotland [4] (www.sign.ac.uk › sign-157-delirium), emphasizing advice for risk reduction and the non-pharmacological treatment of delirium. In detail, they pointed out, as an imperative rule, the

necessity of avoiding and treating numerous causes that interact in any one person to cause delirium. Non-pharmacological treatment is emphasized as well as multidisciplinary assessment and care of patients with high risk for delirium. Point by point, the list of activities that should be planned for identifying predisposing and precipitating causes, according to the current guidelines [4] (www.sign.ac.uk › sign-157-delirium), includes a package of care for patients at risk of developing delirium: orientation and ensuring patients have their glasses and hearing aids; promoting sleep hygiene; early mobilization; pain control; prevention, early identification, and treatment of postoperative complications; maintaining optimal hydration and nutrition; regulation of bladder and bowel function; and provision of supplementary oxygen, if appropriate. Then, pathways of good care should be realized to manage patients with delirium with special attention to acute, life-threatening causes of delirium including low oxygen level, low blood pressure, low glucose level, and drug intoxication or withdrawal. The systematic identification and treatment of potential causes (medications, acute illness, etc.) is highly recommended. The personnel are also encouraged to optimize physiology, manage concurrent conditions, environment (reduce noise), medications, and natural sleep to promote brain recovery. Specific attention should be also devoted to detecting and assessing the causes of and treat agitation and/or distress using non-pharmacological means only if possible. Communicate the diagnosis to patients and caregivers, encourage involvement of caregivers, and provide ongoing engagement and support. Aim to prevent complications of delirium, such as immobility, falls, pressure sores, dehydration, malnourishment, and isolation. Monitor for recovery and consider a specialist referral if not recovering. Consider frequent follow-ups and clinical re-evaluations of the entire situation including revision of prescribed drugs.

Regarding pharmacological treatment, in the present review, we focus especially on hyperactive delirium. Even though the hypoactive phenotype shows a higher prevalence if compared to the hyperactive form, the latter requires higher care and attention for decision makers, due to the fact of inappropriate or unsafe behavior of patients with severe agitation that poses safety risks. We performed a non-structured bibliographic search and selected the most relevant studies available in the peer-reviewed literature dealing with this specific topic. According to the evidence-based pyramid, each study selected received a score ranging from one to five stars (*), depending on the design of the study. Animal and in vitro studies received *, narrative review **, observational studies (cohort and case-control) ***, randomized-controlled studies ****, meta-analysis and systematic reviews *****. By searching most relevant studies available in the peer-reviewed literature, it emerged that many clinical trials failed to reduce significantly the duration of delirium in different settings [5], for example, the ICU [6], or critically ill adults [7], etc., and it is accepted worldwide that, if necessary, antipsychotics should be used at the lowest dosage, for the minimal necessary time, and, especially, antipsychotics with lower anticholinergic effect should be preferred, such as haloperidol [8].

In some cases, pharmacological treatment is necessary and should not be avoided, especially for the hyperactive delirium and agitated persons with aggressiveness. According to these studies, clinicians could follow the suggestions and automatically choose the best pharmacological treatment based on the cluster symptoms presentation of the patients [9][10][11]. For example, if the patient has hyperactive delirium but had an anamnestic cardiac disease, such as atrial fibrillation or sever heart failure without evidence of respiratory insufficiency, the utilization of benzodiazepines (BDZs) [12] orally or intramuscularly according to the severity of delirium, should be chosen, especially if hyperactive delirium is associated with alcohol withdrawal (Table 1); on the contrary, atypical or typical antipsychotics should be avoided. The second line of treatment could be olanzapine intramuscularly, given its lower cardiac effects than the oral formulation [13].

Table 1. Warning for the utilization of psychoactive drugs in agitated delirium due to the fact of their toxicity or side effects.

Hyperactive Delirium	Warning According to Toxicity and/or Side Effects of Drugs	Reference and Quality's Score
1. No extrapyramidal signs but respiratory and severe hepatic failure	**High toxicity: Benzodiazepines Moderate toxicity: Risperidone; Trazodone Light toxicity: Gabapentin**	**[14] *****, [12] ***, [15] **, [16] ** [10] **, [17] **, [18] **, [19] ** [18] **, [20] **
2. Extrapyramidal signs with respiratory and severe hepatic failure	**High toxicity: Benzodiazepines Moderate toxicity: Haloperidol; Trazodone Light toxicity: Risperidone; Gabapentin**	**[14] *****, [15] **, [16] **, [18] ** [15] **, [18] ** [17] **, [18] **, [19] **
3. No extrapyramidal signs with respiratory and severe renal failure	**High toxicity: Benzodiazepines Moderate toxicity: Olanzapine Light toxicity: Haloperidol; Trazodone**	**[14] *****, [12] ***, [15] **, [16] ** [8] **, [13] ***, [17] **, [19] ** [7] *****, [21] ***

Hyperactive Delirium	Warning According to Toxicity and/or Side Effects of Drugs	Reference and Quality's Score
4. Extrapyramidal signs with respiratory and severe renal failure	**High toxicity: Benzodiazepines Moderate toxicity: Quetiapine; Gabapentin Light toxicity: Trazodone**	**[14] *****, [12] ***, [15] **, [16] ** [10] **, [15] **, [17] **, [19] ** [21] ***
5. Extrapyramidal signs with cardiac disease and pathological corrected QT interval (QTc) and severe hepatic failure	**High toxicity: Haloperidol; Atypical antipsychotics Moderate toxicity: Trazodone Light toxicity: Gabapentin; Lorazepam**	**[5] *****, [7] *****, [17] **, [22] *** [21] *** [22] ***, [16] **, [20] **
6. Extrapyramidal signs with cardiac disease and pathological QTc and severe hepatic failure	**High toxicity: Haloperidol; Atypical antipsychotics Moderate toxicity: Trazodone Light toxicity: Gabapentin; Lorazepam**	**[5] *****, [7] *****, [17] **, [22] *** [21] *** [22] ***, [18] **, [16] **, [20] **
7. Agitated delirium without extrapyramidal signs with cardiac disease and pathological QTc and severe renal insufficiency	**High toxicity: Haloperidol; Atypical antipsychotics Moderate toxicity: Trazodone; Gabapentin Light toxicity: Lorazepam**	**[17] **, [22] *** [21] ***, [20] ** [10] **, [22] ***, [19] **, [16] **

Footnotes: Quality's score of studies selected ranging from * (lower quality) to ***** (higher quality). * animal and in vitro studies; ** narrative review; *** observational studies (cohort and case-control); **** randomized-controlled studies; ***** meta-analysis and systematic reviews.

Another example is represented by a patient with respiratory failure and hyperactive delirium. In this case, use of typical or atypical antipsychotics could be chosen, with trazodone as adjuvant (Table 1). On the contrary, BDZs should be avoided, given their effect on respiratory depression.

The selection of the drug to be used firstly should take into account patient's neurological co-morbidity. In particular, a patient with dementia and superimposed hyperactive delirium without active cardiac diseases and with parkinsonism could be treated with quetiapine or clozapine, for minimizing extrapyramidal signs and dysphagia (Table 1) [15]. Differently, a patient with hyperactive delirium superimposed on dementia and epilepsy could be treated with antiepileptic drugs.

The selection of the drug deserves particular attention in the hyperactive delirium superimposed on dementia and parkinsonism. In this case, the reduction of the general mobility or walking ability of the patient should be considered and suggested (Table 1). Moreover, drugs that produce a strong blockade of D2 receptors, such as risperidone or typical antipsychotics, should be avoided [17]. In this recent review [17] on this topic, the authors proposed a continuum spectrum of "atypia" that begins with risperidone (the least atypical) to clozapine (the most atypical), presenting all the other antipsychotics within the extremes of this spectrum. Clozapine is still considered the gold standard in refractory schizophrenia and in psychoses and hallucination present in Parkinson's disease, though it has been associated with adverse effects like agranulocytosis (at least 1.0% of users) and weight gain. It becomes interesting searching for new drugs as effective as clozapine for avoiding its side effects. In detail, the success of clozapine and other antipsychotics introduced a new concept in relation to the mechanism of action. For instance, those drugs with a low affinity for the dopamine D2 receptor could be an effective antipsychotic through the involvement of other receptors such as 5-HT2A serotonin receptors. The involvement of serotonin (5-HT) receptors was an important step forward to understand the mechanism of actions of antipsychotics, and, moreover, the affinity ratio 5-HT2A/D2 was considered a hallmark for antipsychotics. Other mechanisms, such as G protein-coupled receptors (GPCRs), including muscarinic, noradrenergic, glutamatergic, and histamine receptors, have been proposed to explain the characteristics of atypical antipsychotics.

In addition, new concepts related to GPCR function, such as biased agonism and receptor dimerization have recently been suggested which have added further complexity and intrigue over the mechanism of action of atypical antipsychotics. In fact, several studies have demonstrated how the activation of specific functions of the 5-HT2A receptor can be responsible to distinguish clozapine and other antipsychotics [17][23].

The D2 receptors are mostly expressed in the basal ganglia nuclei and are responsible for the appearance of extrapyramidal symptoms. In particular, extrapyramidal symptoms (EPS) may occur when more than 80% of D2 receptors are blocked. This type of block is relevant especially for risperidone and eventually for olanzapine, given that they have

high affinity for the D2 receptor and, at certain dosages, can have a receptor occupancy of 80% or above. On the contrary, clozapine and quetiapine never show a D2 receptor occupancy above 80% at their therapeutic concentrations which could explain why they never cause parkinsonism [17].

Antipsychotics, both typical and atypical, have pro-arrhythmogenic effects and should be avoided in patients with a prolongation of corrected QT interval of the electrocardiogram (ECG). Their uncontrolled use can lead to polymorphic ventricular tachycardia and sudden cardiac death (SCD) [22]. In this case, benzodiazepines could be safely used if the patient had no history of respiratory diseases and respiratory failure and in the case of alcohol withdrawal (Table 1).

On the other hand, when the patient has respiratory but not cardiac diseases, antipsychotics are drugs with the lowest risk of side effects. However, the choice of the antipsychotic should be oriented by the presence of extrapyramidal signs of the patients because atypical less than typical and quetiapine less than olanzapine or risperidone produce a worsening of these signs.

In the presence of liver or kidney severe insufficiency haloperidol could be used [18] without adjustment of the dosages (Table 1). Even atypical antipsychotics could be safely used in the presence of severe renal or liver dysfunction [19]. Only the utilization of chlorpromazine is contraindicated in the case of liver insufficiency [18]. Then, when BDZs are the most appropriate choice, lorazepam seems the correct drug, because it undergoes direct glucuronidation without prior cytochrome p450 metabolism. Because of this characteristic, lorazepam can be used in patients with hepatic or renal dysfunction with only minor interaction on pharmacokinetics of other drugs [16].

When patients also take antidepressants, mirtazapine, venlafaxine, bupropion, and duloxetine, the correct dosage of medication should be adopted in relation to the severity of renal insufficiency [19].

The most used antiepileptic drugs in psychiatry are valproate, carbamazepine, topiramate, lamotrigine, and gabapentin [19]. Of these drugs, valproate is associated with the greatest risk of potential liver toxicity. Gabapentin and pregabalin are the safest, but contraindicated if severe renal insufficiency is present. In detail, gabapentin is a structural analogue of GABA, and it has been approved for adjunctive treatment of patients (12 years or older) with partial seizures and mixed seizure disorders and refractory partial seizures especially in children. Its use is also suggested in ameliorating different types of neuropathic pain in preclinical as well as in clinical settings [21]. Its effect could be useful when a patient shows pain, history of seizures, insomnia associated with anxiety, and light agitated delirium. Obviously, these hypotheses should be formally tested in a future placebo-controlled clinical trial.

Finally, although additional evidence is required, especially for hyperactive delirium, trazodone can be considered a candidate first-line drug for delirium [20]. Some evidence supports the effectiveness of low doses of trazodone (50–300 mg/day) in contrasting aggressiveness and behavioral disorders in patients with depression, insomnia, and dementia suffering from agitation [24][25]. The supposed mechanisms of action include the low anticholinergic activity, the fact that it is less active as an inhibitor of noradrenaline and serotonin re-uptake than other drugs, and that decreases gamma-aminobutyric acid (GABA) release [26]. However, some authors emphasize a complex interaction between the GABAergic and serotoninergic systems for explaining the sedation and anxiolytic properties that accompany the antidepressant activity of trazodone [27]. The potential safety of low doses of trazodone as treatment for delirium is supported by its little effect on cardiac conduction, being better tolerated and more effective in major depressives simultaneously debilitated by significant cardiovascular disease [26][28]. However, further placebo-controlled clinical trials are needed to support its safety in treatment of delirium.

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