

Effectiveness of treatment to agitated people in emergencies compared to community services: systematic review

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Abstract

Objective: To know the effectiveness of the treatment of people with hetero aggressive behavior in emergency departments compared with community health services. **Method:** Systematic review of studies in databases: LILACS, Psychinfo, Scopus, Web of Science, PUBMED and gray literature in Google Scholar and in the reference list. The search was conducted in June 2016. Two thousand one hundred and sixty studies were found, and six of these studies were selected for analysis after the application of exclusion criteria. **Results:** The approach to individuals with agitated, aggressive or violent behavior occurs most often in general and psychiatric emergency services with medical intervention. Medications used to control agitation and for sedation were benzodiazepine (midazolam, lorazepam), antihistamine (promethazine), typical antipsychotics (haloperidol and droperidol), and atypical antipsychotics (olanzapine, ziprasidone, risperidone and quetiapine). **Conclusion:** All evaluated drugs promote sedation, but this review shows advantages in the use of haloperidol plus promethazine combination.

Key-words: Review. Public Mental Health. Emergencies. Crisis Intervention.

Eficacia del tratamiento para las personas agitadas en situaciones de emergencia en comparación con los servicios comunitarios: revisión sistemática

Resumen

Objetivo: Conocer la eficacia del tratamiento de personas con conducta hetero agresiva en los servicios de urgencias en comparación con los servicios de salud comunitarios. **Método:** Revisión sistemática de estudios en bases de datos: LILACS, Psychinfo, Scopus, Web de Ciencia, PUBMED y literatura gris en Google Scholar y en la lista de referencias. La búsqueda se realizó en junio de 2016. Dos mil ciento sesenta estudios fueron encontrados y seis de estos estudios fueron seleccionados para su análisis después de la aplicación de los criterios de exclusión. **Resultados:** El acercamiento a individuos con comportamiento agitado, agresivo o violento ocurre con mayor frecuencia en servicios de emergencia general y psiquiátrica con intervención médica. Los medicamentos utilizados para controlar la agitación y la sedación fueron benzodiazepina (midazolam, lorazepam), antihistamínico (prometazina), antipsicóticos típicos (haloperidol y droperidol) y antipsicóticos atípicos (olanzapina, ziprasidona, risperidona y quetiapina). **Conclusión:** Todos los fármacos evaluados promueven la sedación, pero esta revisión muestra ventajas en el uso de la combinación de haloperidol más prometazina.

Palabras clave: Revisión. Salud Mental Pública. Emergencias. Intervención en Crisis.

Introduction

The work of health teams is complex and requires professional skills, both in community and hospital services. Emergency services generally receive the most complex acute situations and deal with all kinds of users' behavior, including agitated, aggressive and combative behaviors. When these people are in crisis, in other words, in extreme situations, they can cause harm to themselves and to the team receiving them, including transport and pre hospitalar services. The damage can be physical, verbal, or there can be exposure to blood and fluids. This causes concern to the professionals who assist them, especially if they are confined to closed environments

such as ambulances and emergency units.¹ Crisis or extreme situation in mental health is defined in the scientific literature as an imbalance of psychosocial functions, a manifestation of several conditions such as depression, increased anxiety or tension.²

Strategies for assisting patients experiencing crisis can make use medicines or not, and these are effective in both cases if applied at the right time. A study by Waszynski et al³ proposes non-pharmacological strategies to assist agitated patients admitted to hospitals. The authors mention that non-pharmacological strategies can be effective in reducing patients' anxiety and agitation. As non-drug strategies, they propose physical activity, social interaction with the use of ga-

mes, music and other socio-behavioral measures that promote multi-sensory stimulation, improving mood, functionality and behavior. These activities stimulate the tactile, auditory and visual systems.³

Agitated and combative psychomotor behavior frequently requires hospitalization, especially when linked to a mental disorder such as schizophrenia and bipolar disorder. Traditionally, psychiatric emergencies are the first service chosen by teams that receive the call to service. They are prepared for the rapid assessment of agitated patients, but usually the first concern of the staff working in these sectors is with clinical symptoms and not with the refinement of psychiatric diagnosis at the time of arrival in the service. The treatment strategies in these services are focused in the tolerance of the person receiving the medicine and the adaptation to the clinical management chosen by the team, rather than the protocol efficiency. In these cases, drug treatment is the most appropriate.⁴

Agitated behavior can also be identified in patients already hospitalized, including intensive care units. In such cases, the potential causes of agitation are numerous, but predictive factors can be identified, as for example, history of illicit substance use, weight gain, respiratory deficits (decreased respiratory scores), use of physical restraints. Long hospitalization periods in any hospital unit can lead to agitated, aggressive or violent behaviour. Thus, predictive factors also include history of psychiatric diagnoses, weight, decreased respiratory score, pain, and presence of genitourinary catheter. These findings are important because they allow the team working in international units to be ready to care of patients with potential agitation.

Intervention studies were included that worked with people with agitated, aggressive or violent behavior treated in emergency services or in mental health services in community.

Exclusion criteria. In a first round, the following articles were excluded from reading the abstracts: reviews, letters to

Studies information

The research was conducted using the methodology of systematic review of studies, including collection, development and analysis of data through search of full articles in the following databases: LILACS, Psychinfo, Scopus, Web of Science and PUBMED. Gray literature was also searched using Google Scholar and manual searching in the reference list of the selected articles was also carried out. There was no restriction of period or language. The search took place in June 2016.

Search strategy

For search in databases, descriptors based on *Medical Subject Headings* (MeSH) and using truncations and combinations tailored to each database were applied. All references were captured, stored and managed using the software EndNote® Web (Thomson Reuters, Philadelphia, PA).

Selection of Studies

Articles were selected in two stages. In phase one, two authors (S.S.K., G.M.M.L.) independently reviewed the titles and abstracts of all captured references. Articles that met the inclusion criteria were selected and collected. In phase two,

identifying predictive signals and preventing damage to the patient and to the medical staff.⁵

The increasing number of cases of agitation in health care services, particularly in general and psychiatric emergency services, requires professionals trained to perform care in situation of crisis and referral after stabilization. Thus, this systematic research in databases aimed to know how effective is the treatment applied to people with heteroaggressive behavior in emergency departments compared with community health services.

Methodology

Protocol and registry

This systematic review was conducted under the organizational criteria proposed by *The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)*. The review protocol was recorded in *International Prospective Register of Systematic Reviews (PROSPERO)* under number 42016041334.

Criteria for eligibility

Inclusion Criteria. This review includes intervention studies with users of health systems that have agitated, aggressive or violent behavior. The PICOS (population, intervention, comparison, outcomes, study design) were adapted to set the research question following the inclusion criteria. (Box1).

the editor and conferences summaries. In the second round, after reading articles in the full-length, were excluded: non-experimental studies, interventions based on protocols, non-randomized studies and secondary data from another studies. (Figure 1).

two authors (S.S.K., G.M.M.L.) read all texts in full length and excluded those that did not meet the inclusion criteria. The same two authors independently reviewed articles in full-length. When there was some disagreement between the first and the second author, the third author (K.C.N.) was called for reading. The expert (M.B.F) did the check up of articles considering adequation of the theme of the inclusion criteria. The research coordinator participated in the analysis of data and review of the final text.

Data collection process

One author (S.S.K.) collected the information from articles selected based on the technical characteristics of the studies (author, year, country), the population (total number, gender and age of participants), and results (main results and main conclusions). (Table 1)

Bias risk in individual studies

Authors evaluated methodologically all the selected studies to establish the risk of bias according to the Methodological Index For Non-Randomized Studies (MINORS) (Appendix). Two authors (S.S.K., G.M.M.L.) categorized the articles included as Y=Yes, N=No, U=Unclear, NA=Not applicable, according to the analysis of each study. When there was no consensus between the two authors, the third author (K.C.N.)

was called to intervene in the final decision.

Summarization of results

Studies show that there are numerous people seeking emergency services for assistance in situations of unrest, aggression or violence. Services use different strategies for dealing with the crisis, but drug therapy is the most used at first moments. Most of the studies refer mostly emergency care services. Those relating to community or prehospital activities were characterized as observational studies and are not part of the methodological scope of this review.

Ethical aspects of study

Our research involves secondary data and, consequently, does not require approval of the ethics committee, mainly because data used is already known and published in the scientific community.

Results

Selection of Studies

In phase one, 2163 articles were selected in five databases. After removing duplicates, 2160 articles from different bases remained. Subsequently, we conducted a comprehensive assessment of titles and abstracts and excluded 2103 articles, resulting in 57 articles at the end of this phase. In addition, we checked the gray literature in Google Scholar but no further articles from this source were integrated to the research. We did not identify any article from the reference lists of the studies. In the sequence, we performed the reading of 57 articles and 51 were eliminated. Thus, six articles that met the inclusion criteria were chosen for the analysis, as shown in Figure 1.

Characteristics of studies

Studies were published in English. These studies were conducted in six different countries: United States,^{9,10} India,⁶ Brazil,⁷ Australia and New Zealand,⁸ Italy.¹¹ Studies are summarized in Table 1.

Bias risk in individual studies

The qualitative evaluation showed high quality of studies. Nine areas were evaluated by the three authors who maintained consensus to examine the issues. The evaluation results that demonstrate the low risk of bias in the studies can be found on Table 2.

Individual results of studies

A study conducted in psychiatric emergencies in India, mainly involving men with severe episode of mania, compared the use of lorazepam with haloperidol + promethazine, with similar results for the two groups of drugs (96%). Tranquilization or drowsiness occurred four hours after the use of medication. There was a 40% difference in favor of antipsychotic combination with antihistamine in the first 15 minutes

increasing to 47% in 30 minutes, but decreased to 31% in 4 hours. Four people who received Lorazepam were not affected by medication and remained in a state of agitation. The evidence shows that the combination of haloperidol + promethazine was superior to lorazepam to induce sleep.⁶

Despite the superiority of antipsychotic + antihistamine in sedation, both interventions (case and control) showed differences in the proportion of people who needed restrictions, additional medication, or required new medical evaluation. The adverse events identified were respiratory difficulty, nausea and dizziness after the use of lorazepam.⁶

Baldaçara et al⁷ performed a study in Brazil about the calming effect of olanzapine, ziprasidone, haloperidol+promethazine, haloperidol+midazolam and haloperidol in agitated patients and they observed that, after the use this medicine, most of patients taking haloperidol+midazolam (70%) needed mechanical restriction within the first twelve hours, followed by ziprasidone (33%), haloperidol (20%), haloperidol+promethazine (17%), and olanzapine (3%). Besides chemical restriction, mechanical restriction was also used, plus additional doses of medication after the first dose, specifically, haloperidol+midazolam group followed by haloperidol and haloperidol+promethazine. Patients receiving olanzapine and ziprasidone required no additional medication doses. Side effects were greater with haloperidol+midazolam (50%) followed by haloperidol (38%) and haloperidol+promethazine (33%), but these differences were not statistically significant. Excessive sedation was the most commonly observed side effect (70%), occurring more frequently in the group receiving haloperidol+midazolam. Extrapyramidal effect was present in three patients who received haloperidol+midazolam, five patients who used haloperidol+promethazine and five who received only haloperidol. Hypotension was observed in one patient who received olanzapine, six patients of the ziprasidone group, five patients who received haloperidol+midazolam and five patients with promethazine.⁷

Chan et al⁸ in their study with 336 participants about time for sedation and safety in the use of droperidol or olanzapine as an adjunct to midazolam showed that combined drugs (droperidol-midazolam and olanzapine-midazolam) were more effective for the rapid and proper sedation than the isolated use of midazolam. Less time was needed and greater proportion of patients were sedated in a range between 5 to 60 minutes during hospitalization in the emergency, as well as smaller proportion of drugs was needed for further sedation or re-sedation, which are called rescue medications. The number of patients who experienced adverse events such as airway obstruction, oxygen desaturation, hypotension, arrhythmia, lower level of consciousness, was similar between groups, with 18 (15.7%), 12 (10.7%) and 9 (8.3%) cases reported in the control group, droperidol group and olanzapine group, respectively.⁸

Kinon et al⁹ determined the efficacy of an accelerated titration of oral olanzapine in combination with lorazepam to treat acute agitation in patients with schizophrenia and showed that reduced agitation was observed in both groups during the first hour of dosing, with decreased agitation score for patients using olanzapine and haloperidol. At the end of the study, olanzapine group experienced significant improvement when compared to haloperidol group for agitation score of the Positive and Negative Syndrome Scale (PANSS), as well as for

anxiety, tension and excitation. There is also an improving trend in uncooperative patients. Patients treated with olanzapine also showed significant improvement in restlessness and perseverance observed according to the Overt Agitation Severity Scale (OASS) when compared to those treated with haloperidol. As for safety, it was observed that fewer patients using olanzapine (67.3%) had adverse events compared to those who used haloperidol (85.4%). Adverse events and side effects were reported by at least 10% of the patients in each treatment group. Stand out dystonia, hypertension and increased salivation as more frequent in the haloperidol group when compared to olanzapine (8.3% and 0%, respectively). The most frequent adverse events in patients using olanzapine were somnolence (17.3%), anxiety (11.5%) and migraine (11.5%). Patients using haloperidol reported migraine (25%), somnolence (25%), nervousness (16.7%), insomnia (12.5%), pain (10.4%) and agitation (10.4%). The proportion of patients using restrictions, confinement or special nursing observations was similar between olanzapine (17.3%) and haloperidol (16.7%) use.⁹

A study verified the effectiveness of sedation using droperidol, ziprasidone and midazolam and found that most of participants who received ziprasidone (28/46) remained agitated in the first 15 min when compared with droperidol (20/50) and midazolam (15/48). In 45 minutes, agitation was more often observed in the midazolam group (14/48) when compared to droperidol (9/50) and ziprasidone (9/46) groups. An event such as respiratory depression occurred in 20 of the 50 patients who used droperidol, 26/46 who received ziprasidone and 24/48 who took midazolam. As for rescue medication or re-sedation, it is emphasized that five patients who received droperidol required six doses of rescue medication; nine patients who received ziprasidone required 11 doses; and 24 that used midazolam, 30 doses.¹⁰

Villari et al¹¹ compared the effectiveness of three second-generation drugs, namely, olanzapine, risperidone and quetiapine to haloperidol in the treatment of psychotic agitation, demonstrating that clinical improvement between the groups using second-generation drugs were not significantly different when compared the traditional group that used haloperidol. The most commonly reported side effects were: abnormal gait, dizziness, headache, hypotension, somnolence, and extrapyramidal symptoms were most common in patients treated with haloperidol when compared to other groups.¹¹

Summary of results

The approach to individuals with agitated, aggressive or violent behavior happens prevalently in general and psychiatric emergency services and with pharmacological intervention. The studies were developed in general and psychiatric emergencies. Two studies were developed in the United States;^{8,9} one was carried out in a general emergency and explored the management of acute undifferentiated agitation and the other, in a psychiatric emergency testing the adjustment of rapid doses of medications for acute agitation in schizophrenia. Other studies report the reality of India.⁶ Rapid tranquilization of agitated and violent patients was observed. The study carried out in Brazil⁷ compared the efficacy of typical and atypical antipsychotic drugs. A multicenter study conducted in Australia and New Zealand⁸ determined the efficacy and safe-

ty of olanzapine and droperidol as adjuncts to midazolam in rapid sedation, while a study developed in Italy¹¹ sought to compare three second-generation drugs in the treatment of psychotic agitation.

Studies showed that the drugs used by emergency services for agitation and sedation were benzodiazepine-based (midazolam, lorazepam) and antihistamine-based (promethazine). Atypical antipsychotic drugs (olanzapine, ziprasidone, risperidone and quetiapine) used alone showed better results and were well tolerated when compared to typical drugs. Typical drugs (haloperidol, droperidol) showed satisfactory results, but had more reports of side effects, especially when combined with midazolam.

This study demonstrated there is no concense about a singular therapeutic or drug ideal to in the crisis treatment. Therefore, the standard drug therapy that showed the best results with regard to the onset of sedation and low occurrence of adverse events or side effects was the use of haloperidol combined with promethazine.

Discussion

Studies developed on the theme show that there are different approaches to treat individuals with agitated, aggressive or violent behavior. These treatments are effective and bring good results to those involved in providing care, with harm reduction and more safety to all. Approaches can be classified as pharmacological and non-pharmacological.

Non-pharmacological strategies most frequently found in the literature include the following: continuous observation,³ use of verbal scales,¹² speaking in a lower tone of voice and at a slower speed than the person in crisis¹³ using simple verbal directions, encouraging and thanking the collaboration, let the patient know that the professional want to hear him while only one professional speak at a time, whereas this professional should be less authoritative and combative in order to create bonds,¹³ and in situations where there is risk involved in the scene, physical restriction can be used as management strategy of an agitated person.¹⁴ Although these interventions were not developed through randomized clinical trials, they have important contributions to treat individuals with agitated, aggressive or violent behavior, and they represent first-line treatment, which will point to the presence or absence of psychiatric disorder in order to define the ideal drug for treatment. However, it is noteworthy that in some cases they may be ineffective and administration of drugs may become necessary in extreme situations that require rapid control of behavior to prevent damage to person and/or to the persons involved in the care.¹⁵

The services described in the studies as the first choice for treatment were especially hospital emergencies, both general and psychiatric. The combination of complex chronic diseases, limited access to primary and mental health services and the challenges of timely coordination between the reference procedure and outpatient care are factors that result in greater demand for hospital emergencies. This consolidates emergencies as the preferred place of treatment of people with agitated behavior, especially the elderly and/or people with psychiatric disorders.¹⁶

Crisis situations that require medical management for sedation of agitated people are not often described in community

health services. Considering the complications and adverse effects caused by the use of sedatives, only the pre-hospital setting was pointed as scenario in which chemical restraint (ketamine) is employed, particularly due to the conditions of approach and transportation of the user, as well as the need for quick management. Intramuscular via is the first choice in cases requiring safety measures, as it is an easy access to the onset of action of the pharmacological agent.^{17,18}

Regarding chemical restraint, isolated and combined use of certain pharmacological agents was observed, including benzodiazepine-based and anti-histamine-based *typical* and *atypical* antipsychotics. Management using combinations of drugs is more effective than monotherapy in cases of agitation.^{8,19} However, rapid tranquilization obtained with antipsychotics and benzodiazepines can cause side effects of overdose, respiratory depression or dystonia.⁹

It is noteworthy that *typical* antipsychotics were the first to be introduced into clinical practice from the 50's. They are also called *first generation* antipsychotics and include chlorpromazine, haloperidol and fluzanazina. These drugs are associated with deficit in working memory, processing speed and motor skills. In the other hand, *atypical* or of *second generation* substances appeared in the 80's, represented by olanzapine, quetiapine, risperidone, ziprasidone and clozapine. These drugs, in general, do not impair cognitive functioning in the same way as the first-generation drugs, because they have selective action on their receptors,²⁰ justifying the best results of the use of *atypical* drugs.

Benzodiazepine-based drugs such as lorazepam and midazolam are usually used to treat agitation and were associated with higher frequency of adverse event. When used intermittently, midazolam has quick action due to its high lipid solubility. This property makes it ideal for short-term use. In contrast with midazolam, lorazepam has slower onset of action, making it less useful for use in emergencies, but it is less prone to drug interaction and has more predictable metabolism in patients with hepatic dysfunction.²¹

The pharmacological antihistaminic agent class, promethazine, was used in combination with haloperidol (first-generation antipsychotic), which has its sedative effect and antimuscarinic properties potentiated. The main side effects observed of promethazine were: gastrointestinal disorders, dry mouth, blurred vision and, less frequently, paradoxical reactions and extrapyramidal symptoms.^{7,22}

Evidence shows that there are two indicators of effectiveness in the treatment of agitation, aggression and violence.

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One refers to the sedation period after the use of medicines in monotherapy or association, and the second is related to safety standards, considering the occurrence of adverse events and side effects.

Study limitations

The main limitations of this study were those linked to studies using secondary data. We can not guarantee the total adequacy of the studies to our research objective. In several situations, data are not completely used. The studies relate to different situations, which are associated to the lack of consensus on the definition of agitated, aggressive and violent behavior, as well as the involvement of different populations and countries, which makes compatibility difficult in many cases. We also emphasize that primary studies use samples that do not guarantee the generalization of the information.

The management of people in extreme situations with agitated, aggressive or violent behavior is performed prevalently with drug intervention in general or psychiatric emergency services.

The associated use of haloperidol plus promethazine was the drug combination that showed lower incidence of adverse events and side effects with good pattern of sedation.

The present systematic review identified some shortcomings in this area of research that need to be addressed. Interventions used in the management of people in extreme situations that can lead to aggressive behavior against the individual himself or against the health team should be coded and classified by services to be used as indicators of performance and reliable quality. Standards of care in services were not identified. What is shown in the studies is a tireless movement of professionals in the health teams to handle the demands in general and psychiatric emergencies.

Statement of conflict of interests

The authors declare that there are no conflicts of interest.

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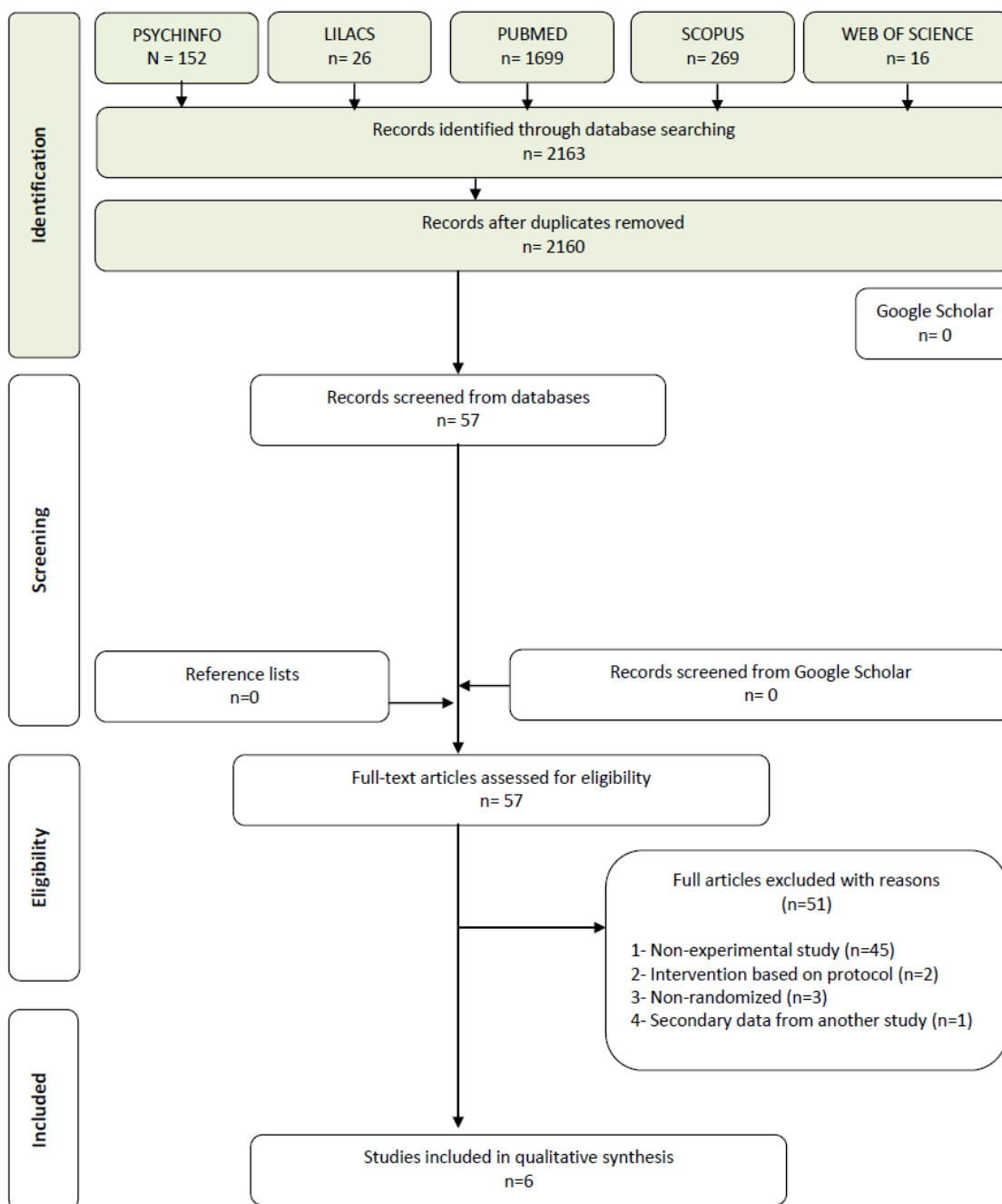
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Figuras y tablas

Box 1. PICOS description

| | |
|--|--|
| Types of participants (P) | People with agitated, aggressive or violent behavior |
| Types of interventions (I) or exposition | Treatment in emergency rooms |
| Comparison (C) | Treatment in community mental health services |
| Types of outcome measures (O) | Treatment efficacy |
| Types of studies (S) | Experimental |

Figure 1. Flow diagram of literature search and selection criteria



Note: Adapted from PRISMA

Table 1. Summary of descriptive characteristics of included articles

| Study Characteristics | | Population | | | | Intervention - Drug | | | Outcome | |
|---|---|------------|---------------|--------------------|------------------|---|--|---|--|--|
| Authors, Year, Country | Objective | N total | Year | Case (n) age | Control (n) age | Case | Control | Scale | Main Results | Main Conclusion |
| Alexander, J. et al, 2004 ⁶ , India | To compare interventions commonly used to control agitation or violence in people with serious psychiatric disorders | 200 | | 100 (32.2 years) | 100 (30.9 years) | Haloperidol (10mg) + Promethazine (25 or 50mg) | Lorazepam (4 mg) | CGI-S Clinical Impression-severity and CGI-I - Clinical Global Impression - Improvement | Haloperidol + promethazine was superior in inducing sleep as compared to lorazepam. There was a difference of 40% in favor of the combination antipsychotic + antihistamine in the first 15 min, increasing to 47% in 30 min, falling to 31% after 4h. The combination showed better clinical outcomes. | Both interventions were effective in controlling the agitated, violent behavior. If quickness is required, the combination of haloperidol + promethazine has advantages over lorazepam. |
| Baldaçara, L. et al, 2011 ⁷ , Brazil. | To compare the efficacy of olanzapine, ziprasidone, haloperidol associated with midazolam, haloperidol associated with promethazine and haloperidol alone, intramuscularly applied, as first choice in the treatment of patients with agitation and aggressivity. | 150 | 32.1 (DP 7.7) | 30x5 | 30+30+30+30+30 | Olanzapine(10mg)/ziprasidone(20mg)/haloperidol(5mg)+promethazine (50mg)/haloperidol (5mg)+midazolam(15mg)/haloperidol (5mg) | | Overt Agitation Severity Scale Total Score (OASS) and Overt Aggressive Scale (OAS) | Ziprasidone, olanzapine and haloperidol had more stable results for the control of agitation; and ziprasidone, haloperidol associated with promethazine and olanzapine to control aggressivity. | Olanzapine, ziprasidone, haloperidol associated with promethazine, haloperidol associated with midazolam and haloperidol alone were effective in controlling agitation and secondary aggressivity to mental disorders within 12 hours. All drugs had advantages and disadvantages, except for haloperidol and midazolam combination that showed the worst results in all parameters. |
| Chan, E.W. et al, 2013 ⁸ , Australia and New Zealand | To determine the efficacy and safety of intravenous application of droperidol or olanzapine as an adjunct to intravenous application of midazolam for quick sedation. | 336 | 18-65 years | 32 and 34 years | 35 years | Droperidol (droperidol5mg, placebo-olanzapine) Olanzapine (olanzapine5m, placebo-droperidol) | Placebo-droperidol, Placebo-olanzapine | ATS - Australasian Triage Scale | The characteristics were similar between groups. Patients who used droperidol and olanzapine were about 1.6-fold more sedated compared with the control group. Patients with droperidol and olanzapine needed fewer alternative drugs after initial sedation. | The main finding of this study is that combinations (droperidol-midazolam and olanzapine-midazolam) were significantly more effective than monotherapy with midazolam for rapid sedation. |
| Kinon, B.J. et al, 2003 ⁹ , U.S | To determine the efficacy of an accelerated dose titration of oral olanzapine, alone or in combination with lorazepam to treat acute agitation in patients with schizophrenia. | 100 | | 39 (SD 9.93 years) | 39.6 (SD 9.29) | Olanzapine (10mg)+lorazepam | Haldol (10mg)+lorazepam | Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI) | Reduction of agitation was observed in both groups in the first hour of dosing, and decreasing the agitation score for patients using olanzapine and haloperidol. At the end of the study, olanzapine group experienced significant improvement when compared to the haloperidol group. As for safety, it was observed that fewer patients using | Oral olanzapine in combination with lorazepam was as effective as the combination of haloperidol with lorazepam in controlling the symptoms of acute agitation in schizophrenic patients with significant improvement in the first hour of treatment. |

| | | | | | | | | | | |
|--|---|-----|----------------|--|-----------------------------|--|---|--|---|--|
| | | | | | | | | | olanzapine (67.3%) had adverse events compared to those who using haloperidol (85.4%). | |
| Martel, M. et al, 2005 ¹⁰ | To compare the effectiveness of sedation of droperidol, ziprasidone and midazolam for the treatment of undifferentiated acute agitation in patients admitted to the emergency department. | 144 | 36.9 (SD 10.9) | | | Droperidol 5mg IM (50) Ziprazidone 20mg IM (46) Midazolam 5mg IM (48) | Droperidol 5mg IM (50) Ziprazidone 20mg IM (46) Midazolam 5mg IM (48) | Altered Mental Status Scale (AMS) | Adequate sedation was achieved within 15 min among patients receiving midazolam and 30 minutes among patients receiving droperidol and ziprasidone. | Patients with acute agitation in emergency services sedated with droperidol or ziprasidone required rescue medication to achieve adequate sedation less frequently than when sedated with midazolam. The initiation of appropriate sedation was delayed with ziprasidone compared to other agents. |
| Villari, V. et al, 2007 ¹¹ Italy | To compare the effectiveness of three second-generation antipsychotics (risperidone, olanzapine and quetiapine) versus haloperidol in the treatment of psychotic agitation for 72 hours | 125 | | Risperidone 39.22 (SD 12.72) Olanzapine 41.46 (SD 12.17) Quetiapine 41.18 (SD 15.16) | Haloperidol 39.82 (SD 8.96) | Risperidone 2-6mg/day, Olanzapine 10-20mg/day Quetiapine 300-800mg/day | Haloperidol 5-15mg/day | Brief Psychiatric Rating Scale (BPRS) Modified Overt Aggression Scale (MOAS) Clinical Global Impression – severity (CGI-S) Clinical Global Impression – improvement (CGI-I) | There was an improvement in aggressive behavior in all groups with no significant difference between them. Extrapyramidal symptoms were more common in patients treated with haloperidol when compared with others. | In clinical practice of psychiatric emergency, olanzapine, risperidone and quetiapine are as effective as and better tolerated than haloperidol. |

Table 2. Risk of bias summarized assessment

| Author, Year | Risk of Bias |
|-----------------|--------------|
| Alexander 2004 | Low |
| Baldaçara, 2011 | Low |
| Chan, 2013 | Low |
| Kinon, 2004 | High |
| Martel, 2005 | High |
| Villari, 2008 | Low |

Appendix. Excluded articles

| Author, Year | Reason for exclusion |
|--|----------------------|
| ADIMANDO, A. J.; PONCIN, Y. B.; BAUM, C. R 2010 ¹ | 1 |
| BOLHOFNER, B. 1994 ² | 1 |
| BORUM, R 2000 ³ | 1 |
| BUNN, T. 2013 ⁴ | 1 |
| BURK, R. S 2014 ⁵ | 1 |
| CHERMACK, S.T et al 2014 ⁶ | 1 |
| CHOO, E. K 2013 ⁷ | 4 |
| CHOU, S. P 2012 ⁸ | 1 |
| CURRIER, G.W. et al 2006 ⁹ | 1 |
| DA SILVA, R. L 2015 ¹⁰ | 1 |
| DEITCH, K ¹¹ | 3 |
| DOWNES, M. A 2009 ¹² | 1 |
| DOWNNEY, L. V.; ZUN, L. S.; GONZALES, S. J. 2007 ¹³ | 1 |
| EPSTEIN-NGO, Q. M. et al 2014 ¹⁴ | 1 |
| ESCOBAR, R. et al. 2008 ¹⁵ | 1 |
| FERNS, T.2007 ¹⁶ | 1 |
| FULLERTON, L. 1998 ¹⁷ | 1 |
| FULTON, J. A. et al.2006 ¹⁸ | 1 |
| GILLAM, S. W.2014 ¹⁹ | 1 |
| HILLARD, J. R.; SLOWOWITZ, M.; DEDDENS, J.1988 ²⁰ | 1 |
| HUF, G. et al.2002 ²¹ | 1 |
| HUF, G.; COUTINHO, E.S.F.; ADAMS, C.E 2002 ²² | 2 |
| HOPPER, A. B. et al.2015 ²³ | 3 |
| KENNEDY, A. et al.2009 ²⁴ | 2 |
| KROPP, S. et al. 2007 ²⁵ | 1 |
| LADAVAC, A. S. et al.2007 ²⁶ | 1 |
| KOHEN, I. et al. 2005 ²⁷ | 1 |
| LATT, N. et al.2011 ²⁸ | 1 |
| LECKEY, D. K.2011 ²⁹ | 1 |
| LYNCH, D. M.; NOEL, H. C.2010 ³⁰ | 1 |
| MACDONALD, K. et al. 2010 ³¹ | 1 |
| MACDONALD, K. et al.2012 ³² | 1 |
| MARTEL, M. et al. 2005 ³³ | 1 |
| MASI, G. et al 2010 ³⁴ | 1 |
| MCGONIGLE, J. J. et al.2014 ³⁵ | 1 |
| MCNIEL, D. E.; BINDER, R. L. 2005 ³⁶ | 1 |
| MICA, L. et al.1994 ³⁷ | 1 |
| MIGON, M. N. et al. 2008 ³⁸ | 1 |
| MORITZ, F. et al. 1999 ³⁹ | 1 |
| PASCUAL, J. C. et al.2006 ⁴⁰ | 1 |
| PASCUAL, J. C. et al.2006 ⁴¹ | 3 |
| PASSAMAR, M.; TELLIER, O.; VILAMOT, B.2011 ⁴² | 1 |
| PHILLIPS, S. 2007 ⁴³ | 1 |
| REINISH, L.W.; CICCONE, J.R. 1995 ⁴⁴ | 1 |
| ROTHMAN, E. F. et al. 2011 ⁴⁵ | 1 |
| SCHPEPKE, K. A. et al. 2014 ⁴⁶ | 1 |
| SKEEM, J.; BIBEAU, L. 2008 ⁴⁷ | 1 |
| STERN, T. A. et al. 1991 ⁴⁸ | 1 |
| WASZYNSKI, C. et al.2013 ⁴⁹ | 1 |
| WEISS, S. et al 2012 ⁵⁰ | 1 |
| WITZEL, J. G. et al. 2008 ⁵¹ | 1 |

Legend: 1-Non-experimental study (n = 45); 2- Intervention based on protocol (n = 2); 3 Non-randomized (n = 3); 4 - Secondary data from another study (n = 1)

The Cochrane Collaboration's tool for assessing risk of bias

Study ID: Alexander 2004

Date: 07.11.2016

| Domain | Description | Risk of Bias | Consensus (circle) |
|--|--|---|------------------------|
| Random sequence generation | Randomisation was according to a computer-generated random numbers list in varying sized blocks of less than 10 prepared by the UK collaborator. | Was the allocation sequence adequately generated? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Allocation concealment | The team member and a pharmacist prepared consecutively numbered opaque cardboard boxes | Was allocation adequately concealed? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Blinding of participants and personnel | The team member and a pharmacist prepared consecutively numbered opaque cardboard boxes, identical in appearance and weight, on the outside of which was a form with questions to be completed by the attending doctor while 'blind' to the contents of the box. The boxes contained haloperidol (5 mg × 2 ampoules) plus promethazine (50 mg × 1 ampoules) or lorazepam (4 mg × 1 ampoule), as determined by the randomisation list, one disposable syringe and needle and study follow-up forms. All those involved clinically in the study had no indication of what medicines were in the boxes until they were opened. | Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Blinding of outcome assessment | The team member and a pharmacist prepared consecutively numbered opaque cardboard boxes, identical in appearance and weight, on the outside of which was a form with questions to be completed by the attending doctor while 'blind' to the contents of the box. The study was blind until the point of treatment assignment, which minimised selection bias. After assignment, rating for the first 2 h was not blind as the management team had to know the prescribed medications. | Was knowledge of the allocated intervention adequately prevented during the study? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Incomplete outcome data | From the existing literature, with tranquillisation of 73% of people given benzodiazepines and 57% given typical antipsychotics (Battaglia et al, 1997; Joy et al, 2003), with a power of 80% at 95% confidence intervals and an expected precision of 20%, the minimum sample size required was 90 people per arm. The remaining 200 patients were randomised. The follow-up rate for the primary outcome at 4 h was 100% for those given lorazepam and 99% for the antipsychotic-antihistamine combination. Follow-up rates for secondary outcomes and at 2 weeks were 92% for those allocated to lorazepam and 90% for people given the antipsychotic-antihistamine combination. | Were incomplete outcome data adequately addressed? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Selective outcome reporting | The results are clearly reported in separate sections of results and analysis. There was no previous protocol reported. | Are reports of the study free of suggestion of selective outcome reporting? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Other sources of bias | Clinical profile of patients includes prior diagnosis of mental disorder and patients agitated for other reasons. | Was the study apparently free of other problems that could put it at a high risk of bias? LOW / HIGH / UNCLEAR | YES NO UNCLEAR |
| Overall risk of bias | No | LOW / HIGH / UNCLEAR | HIGH LOW UNCLEAR |