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TRANQUILIZAÇÃO RÁPIDA EM PACIENTES COM AGITAÇÃO PSICOMOTORA DE NATUREZA PSIQUIÁTRICA

Sorocaba/SP
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Dissertação apresentada à Banca Examinadora do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Mestre em Ciências Farmacêuticas.

Orientador: Dra. Cristiane de Cássia Bergamaschi

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Graça e paz vos sejam multiplicadas, pelo conhecimento de Deus, e de Jesus nosso Senhor; 2 Pedro 1:2

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RESUMO

A tranquilização rápida é um método utilizado em situações que exijam o controle rápido da agitação, agressão ou excitação do paciente com problemas mentais e comportamentais graves. As revisões sistemáticas avaliaram diversos medicamentos e grupos farmacológicos utilizados para este fim, e no presente estudo reuniu-se a evidência disponível a respeito desta intervenção. O objetivo deste estudo foi sintetizar a evidência disponível a respeito da eficácia e segurança dos medicamentos usados para a tranquilização rápida em pacientes com agitação psicomotora de natureza psiquiátrica. Trata-se um estudo de *overview* de revisões sistemáticas e metanálises de ensaios clínicos controlados randomizados (*ECCR*) cujos estudos foram identificados nas bases de dados MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library (CDSR - *Cochrane Database of Systematic Reviews*) e LILACS até abril de 2015, utilizando os descritores "agitação psicomotora", "agentes tranquilizantes" e "transtornos mentais" sem restrição de idioma e ano de publicação. Foi utilizada a ferramenta AMSTAR (*Assessing the Methodological Quality of Systemathic Reviews*) para avaliar a qualidade metodológica dos estudos incluídos. Foram coletados os desfechos: tempo para tranquilizar e/ou dormir; nenhuma resposta clínica importante; necessidade do uso de medicamento adicional; alterações do comportamento, do estado mental e estado geral do paciente; abandono precoce do tratamento e evento adverso aos medicamentos. Uma equipe de revisores, aos pares e de forma independente selecionaram os estudos elegíveis e avaliaram a qualidade metodológica deles. Quatro estudos foram selecionados e tiveram seus dados extraídos. Foram identificados 61 ECCR e um total de 8.021 participantes. A síntese dos achados demonstrou que haloperidol associado à prometazina foi eficaz em promover tranquilização dos pacientes e apresentou melhor perfil de segurança comparado a midazolam, lorazepam e haloperidol. Olanzapina administrada de maneira isolada demonstrou benefício para a tranquilização e bom perfil de segurança, mas necessitou de maior administração de medicamento adicional devido a sua curta ação. Não se observou benefício do uso de haloperidol sozinho ou associado a outro psicotrópico ou a benzodiazepínico para a maioria dos desfechos de eficácia e segurança. Também não foi observado benefício do uso de benzodiazepínicos sozinhos ou associados à antipsicóticos em relação ao uso de antipsicóticos, embora, tenham apresentado melhor perfil de segurança. Concluiu-se que haloperidol associado à prometazina demonstrou desejável perfil de eficácia e segurança; no entanto, para a maioria das intervenções encontradas na literatura, a evidência disponível foi considerada de baixa qualidade, demonstrando a necessidade de mais estudos para afirmar os achados de eficácia e segurança das intervenções investigadas.

Palavras-chave: Agitação psicomotora. Agentes tranquilizantes. Transtornos mentais.

ABSTRACT

Rapid tranquilization is a method used in situations that require quick control of agitation, aggression or excitement in patients with severe mental and behavioral issues. Systematic reviews evaluated several drugs and pharmacological groups aiming at this control, and in the present study, the available evidence regarding this intervention was gathered. The aim of this study was to synthesize the available evidence regarding efficacy and safety of drugs used for rapid tranquilization in patients with psychomotor agitation of a psychiatric nature. It is an overview study of systematic reviews and meta-analysis of randomized clinical trials (RCT) whose studies were identified in the database of MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library (CDSR - Cochrane Database of Systematic Reviews) and LILACS up to April 2015, using the keywords “psychomotor agitation”, tranquilizing agents” and “mental disorders” without language restriction and year of publication. The tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) was used in order to assess the methodological quality of the studies included. The following outcomes were collected: period of time to tranquilize and/or sleep; no important clinical response; need of additional drugs; alterations in patient’s behavior, mental and general conditions; early dropout and drug adverse event. A team of reviewers, in pairs and independently selected the eligible studies and evaluated their methodological quality. Four studies were selected and had their data extracted. Sixty-one RCT were identified and a total of 8,021 participants. A summary of the findings demonstrated that haloperidol associated to promethazine was effective to promote tranquilization in patients and presented a better safety profile compared to midazolam, lorazepam and haloperidol. Olanzapine administered in isolation demonstrated benefit towards tranquilization and a good safety profile, but there was a need for a higher administration of additional drugs due to its short period of action. No benefit in the use of haloperidol alone or associated to another psychotropic neither to benzodiazepines was observed for the most outcomes of efficacy and safety profile. No benefit in the use of benzodiazepines alone or associated to antipsychotics regarding the use of antipsychotics was also observed, even though they presented a better safety profile. In conclusion, haloperidol associated the promethazine demonstrated a desirable profile of efficacy and safety, however, for the most interventions found in literature, the available evidence was considered of low quality, showing the need for further studies in order to establish its efficacy and safety findings.

Keywords: Psychomotor agitation. Tranquilizing agents. Mental disorders.

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AP	Agitação Psicomotora
AT	Antipsicóticos Atípicos
ATC	*Anatomical Therapeutic Chemical*
BZD	Benzodiazepínicos
DM	Diferenças entre as Médias
ECG	Eletrocardiograma
ECCR	Ensaio Clínico Controlado Randomizado
EV	Endovenosa
H	Haloperidol
IC	Intervalo de Confiança
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
IM	Intramuscular
MA	Metanálise
MeSH	*Medical Subject Headings*
O	Olanzapina
PZ	Prometazina
TR	Tranquilização Rápida
RAM	Reação Adversa ao Medicamento
RR	Risco Relativo
RS	Revisão Sistemática
VO	Via Oral

SUMÁRIO

1 INTRODUÇÃO

Os serviços de saúde mental no mundo estão sendo revistos e redesenhados. Essas mudanças refletem, em parte, a crescente evidência do custo-benefício do cuidar do paciente psiquiátrico e é também um reconhecimento das falhas dos sistemas de cuidados das instituições psiquiátricas (BARROS; TUNG; MARI, 2010; BOSI et al., 2012; LUCENA; BEZERRA, 2012). Sendo assim, é cada vez mais evidente a demanda de serviços de emergências psiquiátricas em hospitais, tornando necessário seu bom funcionamento (CARDOSO; GALERA, 2011; DEL-BEN; TENG, 2010).

Constantemente os profissionais de saúde, principalmente os que atuam na área de urgência e emergência, se deparam com pacientes agitados ou agressivos, que compreendem cerca de 10% de todo o atendimento psiquiátrico de emergência (BALDAÇARA et al., 2011; MANTOVANI et al., 2010). Mais de 1,7 milhões de visitas médicas anuais nos Estados Unidos ocorrem nos departamentos de emergência e dentre eles, encontram-se aproximadamente de 10 á 20% dos pacientes estão agitados devido distúrbios psiquiátricos (ZELLER; RHOADES, 2010). No Brasil, devido às políticas de desinstitucionalização do doente mental, houve um aumento do atendimento em serviços de emergência psiquiátrica em torno de 3% (DEL-BEN; TENG, 2010). No entanto, dados epidemiológicos mais recentes não foram encontrados.

A agitação é caracterizada pelo excesso de atividade motora ou atividade verbal, irritabilidade, falta de cooperação e por gestos ameaçadores. As principais características presentes em pacientes com agitação psicomotora incluem inquietação com atividade motora excessiva, irritabilidade, capacidade aumentada de resposta a estímulos internos e externos e condição clínica instável. Agressão não é uma característica fundamental de agitação, e a frequência com que está associada com a agitação não é claramente estabelecida (ZELLER; RHOADES, 2010; CITROME, 2012).

A tranquilização rápida é um método utilizado em situações que exijam o controle rápido da agitação, agressão ou excitação do paciente com problemas mentais e comportamentais graves, incluindo agressão associada à esquizofrenia, mania e outras psicoses (MANTOVANI et al., 2010, NATIONAL INSTITUTE FOR

HEALTH AND CLINICAL EXCELLENCE, 2005, RAVEENDRAN; THARYAN; ALEXNDRE, 2007).

Os medicamentos utilizados para este fim, de modo geral, devem assegurar a tranquilização de maneira rápida e segura e proporcionar um estado de calma com o usuário permanecendo consciente sempre que possível (BALDAÇARA et al., 2011; MANTOVANI et al., 2010). No entanto, alguns estudos disponíveis sobre o tema (AHMED; JONES; ADAMS, 2012; BELGAMWAR; FENTON, 2005; GILLIES et al., 2013; HUF et al., 2009a; JONES; AHMED; ADAMS, 2010; PACCIARDI; MAURI; CARGIOLI, 2013; POWNEY; ADAMS; JONES, 2013) avaliaram diferentes grupos farmacológicos, bem como, diferentes medicamentos ou suas associações, o que dificulta a tomada de decisão quanto à escolha da melhor intervenção farmacológica para o paciente que necessite da tranquilização rápida.

Apesar dos progressos realizados em opções de tratamento para a tranquilização rápida, ainda existem resultados de tratamentos farmacológicos insatisfatórios (DOLD; LEUCHT, 2014). Associado a isso, as revisões sistemáticas e metanálises de ensaios clínicos controlados randomizados sobre o tema identificaram inúmeras intervenções medicamentosas disponíveis na literatura (BELGAMWAR; FENTON, 2005; GILLIES et al., 2013; HUF et al., 2009a; POWNEY; ADAMS; JONES, 2013).

A revisão sistemática é um desenho de estudo que avalia de maneira crítica e cuidadosa as informações da literatura (SHEA et al., 2007), limitando o viés dos estudos e buscando confiabilidade dos achados para a tomada de decisão (MULROW, 1994). *Overview* é um desenho de estudo que integra e sintetiza as informações existentes das revisões sistemáticas, sobre uma determinada situação clínica, considerando as intervenções disponíveis para tratamento ou prevenção de uma situação clínica ou a compreensão de forma mais abrangente de um problema de saúde, podendo estar relacionado ou não às politicas em saúde (SILVA; MUCENECK, 2010; WHITTEMORE; KNAFL, 2005).

Diante dos achados da literatura, o presente estudo sintetizou, por meio de um estudo de *overview,* a evidência disponível em revisões sistemáticas e metanálises a respeito da eficácia e segurança dos medicamentos usados para tranquilização rápida de pacientes com agitação psicomotora de natureza psiquiátrica, procurando contribuir para a tomada de decisão quanto à escolha destes medicamentos.

2 REFERENCIAL TEÓRICO

2.1 Agitação psicomotora de natureza psiquiátrica

Distúrbios de natureza psiquiátrica ou psicoses podem ocorrer devido a hiperatividade dopaminérgica em várias vias cerebrais onde a dopamina exerce papel central, em equilíbrio com a ação de outros neurotransmissores. Regiões como o córtex frontal, giro anterior do cíngulo, estruturas do sistema límbico e as conexões dessas regiões com os núcleos da base são áreas cerebrais também frequentemente implicadas em distúrbios neuropsiquiátricos, como os episódios de alucinações e delírios (GOLDSTEIN; VOLKWOU, 2002; SILVA; MUCENECK, 2010).

O comportamento agitado constitui até 10% das intervenções de emergência psiquiátrica (PACCIARDI; MAURI; CARGIOLI, 2013). Agitação psicomotora compreende componentes verbais e físicos, agressivos e não agressivos, sendo suas principais características: inquietação motora, responsividade aumentada a estímulos internos e externos, irritabilidade, atividade verbal ou motora inadequada ou sem propósito (LINDENMAYER, 2000).

A agitação psicomotora pode causar uma interrupção temporária da colaboração médico-paciente que interfere na avaliação e tratamento do paciente e requer intervenção imediata (ALLEN, 2000). O estudo da agitação em doença mental é de difícil compreensão por uma série de definições, muitas vezes imprecisas ou conflitantes, referentes ao diagnóstico da doença (MINTZER, 2006), sendo que ocorre a maioria dos incidentes em ambientes psiquiátricos devido a doenças graves como esquizofrenia, bipolaridade ou abuso de substâncias lícitas ou ilícitas (HUF; COUTINHO; ADAMS, 2002).

A agitação pode estar associada a problemas psiquiátricos, incluindo esquizofrenia, desordem bipolar, desordem de personalidade, transtorno de ansiedade generalizada, transtorno do pânico e depressão maior, mas também pode ter origem em outras doenças do sistema nervoso central, incluindo doença de Parkinson, doença de Alzheimer e outros tipos de demência (ZELLER; RHOADES, 2010).

Dalgalarrondo (2000) refere a agitação como uma condição de curso flutuante, podendo modificar-se rapidamente ao longo do tempo e a classifica em nove subtipos, descritos a seguir:

- Agitação maníaca: secundária a um intenso taquipsiquismo. O indivíduo se apresenta inquieto, com ideias de grandeza e desinibição social.
- Agitação paranoide: secundária ao delírio paranoide e alucinações. O paciente se mostra desconfiado, hipervigilante, potencialmente agressivo e hostil, pronto para defender-se das possíveis ameaças que supostamente o cercam.
- Agitação catatônica: agitação impulsiva e intensa com movimentos repentinos e explosões agressivas.
- Agitação no delírio: com origem orgânica. Além da agitação e irritabilidade, o paciente se encontra obnubilado, desorientado no tempo e espaço e com fluxo confuso de pensamento.
- Agitação nas demências: secundária ao quadro demencial, podendo estar associada a episódios paranoides, obnubilação e piora das capacidades cognitivas.
- Agitação oligofrênica: devido à dificuldade em compreender o ambiente, o paciente com deficiência mental se constrange e desespera-se, entrando em estado de agitação podendo ficar hetero ou auto-agressivo.
- Agitação explosiva: associada a transtornos de personalidade do tipo explosivo, *borderline* e sociopático. Os pacientes, quando minimamente frustrados, reagem de maneira agressiva e explosiva, voltando a calma quando atendidas suas necessidades.
- Agitação histérica: agitação mais teatral e escandalosa, com sentido comunicativo.
- Agitação ansiosa: secundária a ansiedade e angústia extrema; o paciente se mostra irritado, tenso, andando rapidamente de um lado para o outro. Neste caso, o risco de suicídio deve ser sempre considerado e as medidas de segurança rapidamente tomadas.

Sendo assim, tranquilização rápida é uma intervenção inicial de diferentes doenças, mais focada em sintomas agudos do que no diagnóstico específico do paciente com agitação psicomotora (DE-FRUYT; DEMYTTENAERE, 2004).

2.2 Tranquilização rápida como intervenção farmacológica da agitação psicomotora

Diante do quadro de agitação e agressividade do paciente, várias intervenções são possíveis e incluem: ambiente com reduzido estímulo, contenção física, intervenção verbal e abordagem farmacológica. O paciente agitado que não perdeu o controle pode responder favoravelmente a uma intervenção verbal. Entretanto, um paciente agitado, com distúrbio psicótico, pode necessitar do uso de contenção física e/ou intervenção farmacológica (BERNIK; GOUVEA; LOPES, 2010).

Tranquilização rápida é uma abordagem que consiste no uso de medicamentos para acalmar de maneira rápida e severa o paciente que se encontra em processo de agitação, com objetivo de diminuir comportamento agressivo e permitir o tratamento da doença subjacente (KARAGIANIS et al., 2001; MANTOVANI et al., 2010).

Os medicamentos utilizados para a tranquilização rápida devem assegurar que a pessoa se tranquilize de maneira efetiva, segura e rápida. Inquéritos sobre a preferência e a prática dos clínicos quanto ao tratamento farmacológico revelam algumas variações, embora as classes mais usadas sejam os antipsicóticos de primeira geração e/ou benzodiazepínicos (BALDAÇARA et al., 2011).

Estudo observacional realizado no Brasil verificou uma variedade de medicamentos (haloperidol, prometazina, clorpromazina, diazepam e midazolam) e de doses prescritas para tratamento da agitação psicomotora. Os autores sugerem uma tendência da prescrição de prometazina e haloperidol (80% das prescrições) entre os psiquiatras brasileiros e evidenciaram que tal prática se dá pela experiência do médico prescritor, com poucas evidências científicas (HUF; COUTINHO; ADAMS, 2002).

A escolha deve ser guiada, quando possível, pela doença psiquiátrica subjacente quando esta for conhecida, sendo que a agitação em um paciente psicótico deve ser tratada com antipsicótico; enquanto a agitação em um paciente ansioso deve ser tratada, preferencialmente, com benzodiazepínico. Caso o diagnóstico não seja conhecido, o tratamento deve ser realizado através do quadro de sinais e sintomas que o paciente apresente (BERNIK; GOUVEA; LOPES, 2010;

CURRIER; MEDORI, 2006; HUF et al., 2009a; NOBAY; SIMON; LEVITT, 2004; POWNEY; ADAMS; JONES, 2013).

A escolha da via de administração deve estar atrelada à colaboração do paciente. A via intramuscular pode ser utilizada quando o paciente não apresenta condições de receber medicamentos por via oral. A via de administração intravenosa não é recomendada, embora apresente resposta rápida para tranquilização (ALLEN, 2000). A administração de antipsicóticos pela via intravenosa pode expor o paciente à alteração no eletrocardiograma (prolongamento das ondas QT), assim como, a administração de benzodiazepínico por esta via, pode predispor a risco maior de o paciente apresentar depressão respiratória (ALLEN; CURRIER; HUNGHES, 2001; GARZA; HOLLISTER; OVERRALL, 1989; PACCIARDI; MAURI; CARGIOLI, 2013; HASAN; BELLI; URAL, 2012; NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE, 2015).

Historicamente, os antipsicóticos de primeira geração são frequentemente utilizados como primeira linha para tratamento da forma aguda de agitação, em parte devido à disponibilidade de preparações parenterais. No entanto, devido a recente introdução de formas parenterais de antipsicóticos de segunda geração, como olanzapina e ziprasidona, estes medicamentos ganharam popularidade como opções de primeira linha de tratamento devido aos perfis de efeitos colaterais mais favoráveis (PACCIARDI; MAURI; CARGIOLI, 2013; BATTAGLIA et al., 2003).

Haloperidol, antipsicóticos de primeira geração, pode promover níveis adequados de tranquilização quando administrado por via intramuscular, mas pode causar como efeitos adversos agudos: acatisia, distonia e síndrome neuroléptica maligna. Apesar de estes efeitos poderem ocorrer mesmo em dose única, tem sido o tratamento preferencial em situações de emergência (PACCIARDI; MAURI; CARGIOLI, 2013). Clorpromazina, levomepromazina e zuclopentixol são outros medicamentos deste grupo que podem ser prescritos em quadros psiquiátricos agudos e também no controle de psicoses de longa evolução (POWNEY; ADAMS; JONES, 2013)

Haloperidol é um dos fármacos mais antigo e amplamente utilizado para o controle de pacientes em estado de agitação, incluindo aqueles devido à demência ou psicoses que apresentem quadro de alucinações ou delírios. No entanto, o fato de apresentar efeitos colaterais significativos pode ser um problema com o uso

deste medicamento (FRUENSGAARD; KORSGAARD; JORGENSEN, 1977; LONERGAN et al., 2001).

Antipsicóticos de segunda geração incluem: aripiprazol, olanzapina, quetiapina, risperidona, sertindol, ziprasidona, droperidol, perfenazina, tiotixeno e magnésio de valproato. Belgamwar e Fenton (2005) compararam a eficácia e segurança da olanzapina em relação às demais intervenções encontradas nos ensaios clínicos por eles selecionados, sendo este, o medicamento deste grupo mais estudado para a tranquilização rápida. É indicado para o tratamento agudo e de manutenção da esquizofrenia e outras psicoses nas quais sintomas positivos (delírios, alucinações, alterações de pensamento, hostilidade e desconfiança) e/ou negativos (afeto diminuído, isolamento emocional e social, pobreza de linguagem) são proeminentes (POWNEY; ADAMS; JONES, 2013; BREIER et al., 2001).

Os benzodiazepínicos (diazepam, lorazepam, midazolam, clonazepam e flunitrazepam) são também utilizados para este fim e foram avaliados quanto à eficácia e segurança na revisão sistemática de Gillies et al. (2013). Estes medicamentos causam sedação e podem promover efeitos adversos como deficiências psicomotoras, amnésia e depressão respiratória (CURRAN; BIRCH 1991; SALZAM; SOLOMON; MIYAWAKI, 1991).

Além dos psicotrópicos citados, a literatura mostra estudos que avaliaram o uso de prometazina (HUF et al., 2009a; GILLES et al., 2013). A combinação de haloperidol e prometazina administrada por via intramuscular é consistentemente usada no Brasil e na Índia (BALDAÇARA et al., 2011; GROUP, 2003; HUF; COUTINHO; ADAMS, 2007). Esta associação é considerada de baixo custo e além disso, os fármacos pertencem a lista de medicamentos essenciais da Organização Mundial da Saúde (OMS) (HUF; COTINHO; ADAMS, 2009b).

O britânico “Instituto Nacional de Saúde e Excelência Clínica” em sua diretriz “Clinical Guideline 28” refere que a combinação de prometazina e haloperidol parece ser eficaz e relativamente segura para uso em alguns países, no entanto, não há provas suficientes de sua segurança na prática clínica do Reino Unido, pois neste País, utilizam-se ações primordialmente psicossociais para conter o paciente (NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE, 2014).

Prometazina reduz o risco de convulsão e apresenta bons efeitos sedativos e anticolinérgicos (HUF; COUTINHO; ADAMS, 2002). É um anti-histamínico (bloqueador de receptor H_1) originando como principal efeito adverso, a sedação.

Além disso, pode causar sonolência e redução das funções cognitivas, da memória e do desempenho psicomotor, contribuindo para a tranquilização (PASTORINO, 2010). Devido a sua ação anticolinérgica (bloqueador de receptores muscarínicos), o uso de prometazina associada a antipsicótico pode diminuir substancialmente a incidência de sintomas extrapiramidais (HUF et al., 2009a), agudos (ocorrem horas após a administração do medicamento) ou tardios (ocorrem semanas após o início do tratamento) (JESIC; FELIPOVIC, 2012).

Acredita-se que o antagonismo de receptores D2 da dopamina pelos antipsicóticos seja também a causa de efeitos extrapiramidais, sendo os mais comuns, distonia, acatisia e discinesia. Distonia são contrações musculares sustentadas, torção e movimentos posturais anormais de forma repetitiva, podendo aparecer de forma aguda ou tardia, sendo sua incidência entre 2-3% nos pacientes tratados com antipsicóticos de segunda geração e 50% entre os pacientes tratados com antipsicóticos de primeira geração. Acatisia tem como principal característica a inquietação psicomotora e a incapacidade de permanecer imóvel, sendo provavelmente resultado do bloqueio de receptores dopaminérgicos, com prevalência de 5 a 50% das pessoas em uso de antipsicóticos. A discinesia tardia é classificada como movimentos musculares repetitivos involuntários que se manifestam como efeito colateral em longo prazo ou com o uso de altas doses de antipsicóticos (JESIC; FELIPOVIC, 2012).

Os sinais de parkinsonismo também podem ser classificados como um efeito extrapiramidal do uso de antipsicóticos e que regride entre 4 a 16 semanas após a descontinuação do uso de antipsicóticos (JESIC; FELIPOVIC, 2012).

3 OBJETIVOS

3.1 Primário

Sintetizar a evidência disponível a respeito da eficácia e segurança dos medicamentos usados para tranquilização rápida de pacientes com agitação psicomotora de natureza psiquiátrica.

3.2 Secundários

- Identificar os principais medicamentos utilizados para tranquilização rápida
- Avaliar a qualidade metodológica das revisões incluídas.
- Comparar os desfechos de eficácia e segurança das intervenções medicamentosas usadas para tranquilização rápida de pacientes psiquiátricos por meio de *overview* de revisão sistemática de ECCR.

4 RESULTADOS

Esta dissertação é apresentada no formato de artigo científico, elaborado conforme as recomendações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (Anexo B).

Title: Rapid tranquilization for psychiatric patients with psychomotor agitation: What is known about it?

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Abstract

Rapid tranquilization is an intervention used in situations requiring quick control of agitation, aggression or excitement in patients with severe mental and behavioral issues. The aim of this study was to synthesize the available evidence regarding efficacy and safety of drugs used for rapid tranquilization in psychiatric patients with psychomotor agitation. It is an overview study of systematic reviews and meta-analysis of randomized controlled trials (RCT) whose studies were identified in the database of MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library and LILACS until April 2015. A team of reviewers, in pairs and independently, identified eligible studies and assessed methodological quality using AMSTAR. Data were extracted from four studies, a total of 61 RCT and 8,021 participants. The association of haloperidol with promethazine was effective to promote tranquilization in patients and presented better safety profile, with moderate quality evidence. Olanzapine demonstrated benefit towards tranquilization and good safety profile, but needed additional administration of the drug in order to keep tranquilization. There was no benefit in the use of haloperidol alone or associated to another psychotropic, neither to benzodiazepines to most outcomes evaluated. The use of benzodiazepines alone or associated to antipsychotics did not present higher efficacy than the antipsychotics. The evidence was of low quality to most of the interventions. Haloperidol associated to promethazine was considered a good option for rapid tranquilization, however, more RCT are necessary to confirm the efficacy and safety of the available interventions.

Keywords: Psychomotor agitation; Tranquilizing Agents; Mental Disorders

1. Introduction

Health professionals, mainly the ones working in emergency and urgency areas, often face agitated or aggressive patients who comprise about 10% of all emergency psychiatric care [6]. Mental health services throughout the world are going through review and redesign, and these changes are partly, due to the increasingly evidence of the cost benefit of the psychiatric patient care and the acknowledgment of failures in the mental health systems [8,16,63].

Agitation is characterized by excessive motor or verbal activity, irritability, lack of cooperation and threatening behavior. The main characteristics present in patients with psychomotor agitation include restless, behavior with excessive motor activity, irritability, increased capacity of response to internal and external stimulation and unstable clinical condition. Aggression is not a fundamental characteristic of agitation, and the frequency that agitation is associated to aggression is not clearly established [96,85].

Rapid tranquilization is a pharmacological approach used in conditions that require fast control of agitation, aggression or excitement in patients suffering from mental disorders and severe behavioral issues, including aggression associated to schizophrenia, mania and other psychosis, [63] aiming to reduce the aggressive behavior and allow the treatment of the subjacent disease [53,28].

The drugs used to that end, in general must assure fast and safe tranquilization and provide a state of calmness while the patient remains conscious as often as possible [6,63]. Inquiries about preference and practice of the clinicians regarding pharmacological treatment reveal some variations, even though the most used classes are the first generation antipsychotics and/or benzodiazepines [6]. An observational study conducted in Brazil verified a tendency of prescribing haloperidol with promethazine among psychiatrists; such practice is done due to the prescriber's experience [49].

In spite of the progress made concerning the pharmacological treatment options for rapid tranquilization, it was observed that the results obtained are still unsatisfactory [31]. Some available studies about the subject [1,13,38,45,52,74,77] assessed different pharmacological groups, drugs and/or their associations, which makes the decision making for the best choice of pharmacological intervention for patients in need of rapid tranquilization even harder.

Given the findings in the literature, the aim of this study was to synthesize, through an overview study, the evidence available in systematic reviews and meta-analyzes regarding the efficacy and safety of the drugs used in rapid tranquilization for patients with psychomotor agitation of a psychiatric nature, and then, contribute to the decision making concerning the choice of pharmacological interventions with better evidence.

2. Methods

2.1 Study Design

Overview of systematic reviews and meta-analyzes of randomized clinical trials (RCT).

2.2 Eligibility criteria

The inclusion criteria defined for the selection of reviews were:

Patients and intervention: patients regardless of age with psychomotor agitation or aggression due to psychiatric disturbances and that need of rapid tranquilization;

Type of study: RCT systematic review with or without meta-analyzes;

Language and publishing date: no restrictions for language or date of publication;

All reviews that include study design other than RCT were excluded as well as those in which clinical trials were included in systematic review published in more recent date.

2.3 Research method for identification of studies

2.3.1 Database searched

The following electronic database were searched: MEDLINE, EMBASE and CINAHL (via OVID); Web of Science; Cochrane Library (CDSR - Cochrane Database of Systematic) and LILACS until April 2015.

2.3.2 *Other search methods*

For each potentially eligible study and mainly for review articles, one of the reviewers analyzed the reference list or citations in the text in order to verify other potentially eligible studies for this review. A search was also conducted at *http//:www.opengrey.eu*.

2.4 Search strategy

The terms MeSH (Medical Subject Headings) and its synonyms were used, and the combinations of MeSH terms made with the use of the boolean operator “AND” and the similar terms by the operator “OR” (Chart 1).

Chart 1 - MeSH terms and its synonyms used for the search strategy in databases

Psychomotor Agitation	**AND- Tranquilizing Agents**	**AND Mental Disorders**	**AND Review, Systematic**
OR- Psychomotor Hyperactivity OR- Hyperactivity, Psychomotor OR- Agitation, Psychomotor OR- Restlessness OR- Excitement, Psychomotor OR- Psychomotor Excitement OR- Psychomotor Restlessness OR- Restlessness, Psychomotor OR- Akathisia	OR- Agents, Tranquilizing OR- Tranquilizing Drugs OR- Drugs, Tranquilizing OR- Tranquillizing Drugs OR- Drugs, Tranquillizing OR- Ataractics OR- Tranquillizing Agents OR- Agents, Tranquillizing OR- Tranquilizing Effect OR- Effect, Tranquilizing OR- Tranquilizing Effects OR- Effects, Tranquilizing	OR Disorder, Mental OR Disorders, Mental OR Mental Disorder, OR Diagnosis, Psychiatric OR Psychiatric Diagnosis OR Behavior Disorders OR Disorders, Behavior	

2.5 Determination of eligibility

The identified studies were inputted into EndNote®. The selection of the studies was made in two phases and by two reviewers (CCB and CGA) independently. Initially, the selection of the studies was made based on title and abstract. The second phase, which consisted on the reading of the abstract and/or full text, identified which studies fulfilled the eligibility criteria. The differences were solved through consensus in both phases.

2.6 Methodological quality

The methodological quality of the systematic reviews was evaluated by the tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) made of 11 questions that allowed to assess and determine the methodological quality of this type of study [66,87]. The methodological quality was ranked as low (AMSTAR ≤ 4), moderate (AMSTAR 5 to 8) and high (AMSTAR 9 to 11). The studies classified as having moderate or high quality were included [66]. The quality of the studies was too evaluated by two reviewers (CCB and CGA), independently.

2.7 Data collection and data presentation

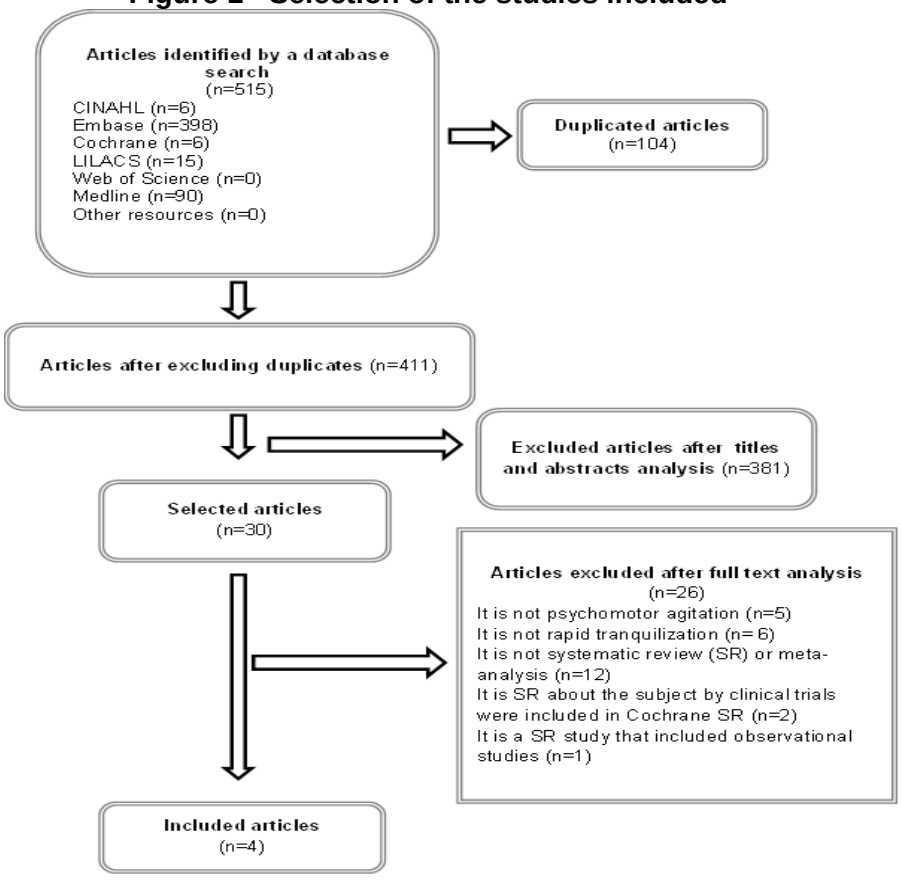
The data extracted from each systematic review were organized in an Excel® sheet. The choice of the outcomes took into account the ones with higher relevance for clinical practice and the ones that were shown in a higher number of studies, including the reviews. It was verified whether the evidence sustained a benefit, harm/risk of the intervention or not enough evidence for recommendation.

Primary outcomes were identified as: time to tranquilize and/or sleep; need for additional tranquilization; behavioral changes, patient's mental and general conditions and presence of adverse drug reaction. Secondary outcomes were: no important clinical response, early dropout in treatment and need for physical contention after tranquilization. The outcomes were descriptively presented in tables according to efficacy and safety.

3. Results

Five hundred and fifteen articles were identified and 104 among them were duplicates. After title and abstract analyses, 381 articles were excluded for not having the eligibility criteria. From the 30 articles selected, 26 were excluded (Figure 1).

Figure 1 - Selection of the studies included



The four studies included were systematic reviews with meta-analysis published on the journal “Cochrane Database of Systematic Reviews”: [13,38,45,77] (all with AMSTAR=9). Huf et al [45] compared the association of haloperidol plus promethazine with benzodiazepines, haloperidol and olanzapine for the control of agitation and/or aggression of patients with unspecific psychosis. They concluded that the evidence seems to favor the use of haloperidol with promethazine. Powney et al [77] compared the use of haloperidol with placebo, antipsychotics and benzodiazepines. Haloperidol presented the best results for tranquilization time, but evidence is weak and this drug caused more collateral effects. There was also no good evidence of benefit for the use of other antipsychotics or for the association of benzodiazepines with haloperidol. Better evidence is observed when haloperidol is associated to promethazine. Belgamwar and Fenton [13] compared olanzapine with placebo, lorazepam and haloperidol in patients with severe mental diseases. Olanzapine seems to benefit the contention of aggression or agitation and causes less adverse drug reactions than haloperidol. Gillies et al [38] estimated the effects of benzodiazepines (alone or combined with antipsychotics) compared to placebo, antipsychotics, benzodiazepines and antihistamines. They observed that the use of benzodiazepine alone shows low quality evidence and that adding benzodiazepine to other drugs do not seem to present advantages and may present undesirable adverse drug reactions (Table 1).

Table 1 - Description of the systematic reviews included

Author (year)	Title	Aims	Conclusions
Huf et al [45] n=4, N=1,117	Haloperidol plus promethazine (H+P) for psychosis-induced aggression	To evaluate the administration of H+P intramuscularly for control of agitation and/or aggression.	All drugs evaluated are effective in adults with specific psychosis, but H+P seem to be more effective and safe. Benzodiazepines work well (midazolam faster than H+P), but may cause respiratory depression (midazolam in higher degree).
Powney et al [77] n=32, N=3,877	Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation)	To investigate whether haloperidol alone is effective treatment for psychosis-induced agitation or aggression.	The evidence for haloperidol alone and other antipsychotic is weak. The association of benzodiazepines with haloperidol does not present strong evidence of benefits and exposes the patient to additional risk. Further clinical trials are necessary.
Belgamwar and Fenton [13] n=4, N=1,059	Olanzapine IM or Velotab® for acutely disturbed/agitated individuals with suspected serious mental illnesses	To evaluate the effects of intramuscular, oral-velotab, or standard oral olanzapine compared with other treatments for controlling aggressive behavior or agitation thought to be due to severe mental illness.	Olanzapine had some value in reducing aggression or agitation in patients with mixed or manic bipolar disorder and dementia and caused less extrapyramidal alterations than haloperidol, but more than lorazepam. Studies did not report important outcomes for clinical practice and further clinical trials must be conducted.
Gillies et al [38] n=21, N=1,968	Benzodiazepines for psychosis-induced aggression or agitation.	To evaluate the effects of benzodiazepines, alone or in combination with antipsychotics, to treat aggression, agitation or psychosis.	The evidence from trials for the use of benzodiazepines alone is not good and further clinical trials are necessary in this area. Adding a benzodiazepine to other drugs does not seem to present advantage and may present undesirable adverse drug reactions.

RCT: Randomized Clinical Trial

Huf et al [45] included 4 RCT (n=1,117 participants) comparing haloperidol with promethazine to: midazolam, lorazepam, haloperidol and olanzapine. Haloperidol with promethazine demonstrated efficacy for tranquilization outcome and even though midazolam had a faster onset, it was considered less safe due to respiratory depression. Lorazepam alone did not present a good safety profile either. The association of haloperidol plus promethazine or use of olanzapine was considered safe, but olanzapine needed additional administration.

Powney et al [77] included 32 RCTs (n=3,877 participants) comparing haloperidol with 18 interventions (placebo, antipsychotics, benzodiazepines and its associations). Haloperidol tranquilized more patients when compared to placebo and lorazepam, but it was not more effective than the other treatments. For the reduction of agitation and for the majority of the other efficacy outcomes, haloperidol did not demonstrate benefit when used alone or associated to benzodiazepines or other

antipsychotics. In general, haloperidol was not different from the other treatments regarding safety profile; or presented more adverse drug reactions (insomnia, dizziness, tachycardia, dyspepsia, diarrhea, nausea, vomit, dystonia, extrapyramidal symptoms, leucopenia, anticholinergic effects, excitement, and cardiovascular effects, among others). No patient died. The authors verified that the evidence is weak due to the low number of studies and participants for most interventions (Table 2).

Belgamwar and Fenton [13] study included 4 RCTs (n=1,059 participants) comparing olanzapine with haloperidol or placebo (n=1), lorazepam (n=1) and placebo (n=1). All drugs were effective or did not present any differences among them for the majority of the assessed outcomes, but olanzapine required more additional drug administration (the drug itself) due to the short period of action. The most found adverse drug reactions were from the administration of haloperidol, thus, olanzapine presented a higher safety profile compared to haloperidol but lower than lorazepam’s. No death report was observed in the clinical trials included (Table 3).

Table 2 - Efficacy and safety of studies which evaluated the use of haloperidol and haloperidol and promethazine compared to placebo, antipsychotic and benzodiazepines

Interventions	Efficacy outcomes	Safety outcomes
HALOPERIDOL + PROMETHAZINE versus MIDAZOLAM (n=1, N=301) [45]	Haloperidol (up to 10mg) + promethazine (up 50 mg) "tranquilized 2/3 of patients in 30 minutes", but midazolam (up to 15 mg) was faster (RR=2.9 CI95%=1.75- 4.80).	One individual from "midazolam group" presented respiratory depression in the first 30 minutes of administration and one individual (with a history of epilepsy) that used the combination had a seizure.
HALOPERIDOL + PROMETHAZINE versus LORAZEPAM (n=1, N=200) [2]	More individuals were "tranquilized in 30 minutes" with the combination (70% compared to 54% in haloperidol group (RR=0.26 CI95%=0.10-0.68).	There was one case of respiratory depression with the use of lorazepam
HALOPERIDOL + PROMETHAZINE versus HALOPERIDOL (n=1, N=316) [73]	More individuals were "tranquilized in 20 minutes" with the combination (RR=0.65 CI95%=0.49-0.87). In the outcome "sleep after 2 hours of treatment", there was no difference between the groups (RR=1.01 CI95%=0.77-1.31).	The highest incidence of adverse drug reactions and severe adverse drug reactions in haloperidol group ($p<0.05$). In the H+P group, one patient presented malnutrition.
HALOPERIDOL + PROMETHAZINE versus OLANZAPINE (n=1, N=300) [73]	The "tranquilization in 15 minutes" with olanzapine (up to 10 mg) was as fast as the combination (RR=0.74 CI95%=0.38-1.41), but the duration of the effect was shorter.	In olanzapine group, two individuals presented akathisia and another an episode of nausea
HALOPERIDOL versus PLACEBO (n=5, N=700) [9,16,17,18,81]	In the outcome "sleep in 2 hours", more patients that used haloperidol were sleeping (RR=0.88 CI95% 0.82-0.95), and also more effective in reducing agitation (RR=1.62 CI95%=1.28-2.07). Placebo group needed more additional drug (RR=0.51 CI95%=0.42-0.62) and did not present improvement in their "general conditions" (RR=0.61 CI95%=0.44-0.84), while the use of haloperidol improved patient's "mental conditions" (MD=-1.04 CI95%=-0.54-1.54). There were no differences between the groups regarding dropout.	Insomnia, headaches, nausea and vomit were reported in both groups ($p<0.05$). Haloperidol was less safe, due to the fact that patients had tachycardia and dizziness and needed anti-Parkinson drugs due to extrapyramidal effects (RR=5.57 CI95%= 1.37-22.65). No death was observed.
HALOPERIDOL versus ARIPIPRAZOLE (n=2, N=599) [17, 18]	Patients from haloperidol group presented less need to repeat the drug for tranquilization (RR=0.78 CI95%=0.62 0.99). Control of "agitation in two hours" was favorable for the use of aripiprazole (RR=1.07 CI95%=0.92-1.26). There was no difference between the groups regarding: need of additional benzodiazepine administration (RR=1.26 CI95%=0.74-2.16), "improvement of mental conditions" (MD=-0.23 CI96%=-1.28-0.82) and early dropout (RR=2.07 CI95%=0.86-4.98). The administration of anti-Parkinson drugs was necessary to reduce extrapyramidal symptoms.	No differences were found between the group concerning adverse drug reactions in 24 hours (RR=1.18 CI95%=0.95-1.46). More individuals in the haloperidol group had adverse drug reaction after administration of second injection (RR=1.34 CI95%=1.03-1.74) and after 72 hours of drug administration (RR=1.33 CI95%=1.04-1.70). No patient died, but both groups presented severe adverse drug reactions. More individuals from haloperidol group complained about insomnia, dizziness, tachycardia, dyspepsia, diarrhea, nausea, vomit, dystonia and extrapyramidal symptoms.

HALOPERIDOL versus CHLORPROMAZINE (n=1, N=39) [62]	Individuals using chlorpromazine presented a better result for the outcome “Tranquil or sleeping after two hours of drug administration” (RR=1.93 CI95%=1.04-3.60). Both groups needed repeated tranquilization (RR=1.50 CI95%=0.53 4.26) and there was no difference between the global conditions (RR=0.79 CI95%=0.61-1.02) and the study’s dropout rate (RR=0.21 CI95%=0.07-0.71).	One individual using chlorpromazine had an epileptic episode (RR=0.33 CI95%=0.01-7.58) and two had hypotension (RR=0.51 CI95%=0.10-2.60). Adverse drug reactions were reported; an individual from the chlorpromazine group had high levels of GPT (Glutamic Pyruvic Transaminase) (RR=0.33 CI95%=0.01-7.81) and a patient from the haloperidol group developed mild leucopenia (RR=3.00 CI95%=0.13-70.30).
HALOPERIDOL versus DROPERIDOL (n=1, N=27) [81]	Only two outcomes were evaluated in the study. More individuals that used haloperidol presented the need of additional drug (RR 2.23 CI95%=0.99-5.06).	Only one individual from the haloperidol group presented dystonia as an effect (RR= 2.12 CI95%=0.9-47.68).
HALOPERIDOL versus LOXAPINE (n=3, N=119) [36,76, 92]	For the outcome “sedated or sleeping in 12 hours”, loxapine seemed to sedate more than haloperidol (RR=4.31 CI95%=0.54-34.48). No differences were observed between the groups for agitation (RR=1.17 CI95%=0.51-2.66) and aggression (RR=1.10 CI95%=0.69-1.76) levels; “improvement in general conditions” in: 48 hours (RR=0.93 CI95%=0.14-6.15) and 4 weeks (RR=0.40 CI95%=0.12-1.32) and improvement in mental conditions (MD=6.10 CI95%=4.48-7.72). However, more individuals from loxapine group were sedated in up to 120 minutes (RR=7.00 CI95%=0.98- 50.16). No differences were found between the group regarding dropout (RR=1.18 CI95%=0.67-2.07).	No difference was found regarding the reported adverse drug reactions (anticholinergic effects, excitement, cardiovascular effects and movement disturbances) (RR=0.80 CI95%=0.44-1.45). One individual from loxapine group abandoned the study because it was toxic (RR=2.84 CI95%=0.12-65.34).
HALOPERIDOL versus OLANZAPINE (n=4, N=631) [9,16, 33, 54]	More individuals using olanzapine were “sleeping for two hours” (RR=1.16 CI95%=1.02-1.32). No difference between the groups regarding the need of additional drug for tranquilization (RR=1.06 CI95%=0.75-1.51) neither the use of additional benzodiazepine in 24 hours (RR=1.05 CI95%=0.63-1.74). Olanzapine group presented less treatment dropout (RR=1.66 CI95%=1.04-2.65).	The use of haloperidol was less safe (RR=1.26 CI95%=1.01-1.59), but there was no severe adverse drug reaction in both groups. Haloperidol group tended to present more movement disturbances (RR=7.65 CI95%=1.78-32.98). Both groups presented anticholinergic effects (increase in salivation, gastric problems and nasal bleeding).
HALOPERDIOL versus PERPHENAZINE (n=1, N=44) [34]	In assessing the global effect “no improvement in treatment” one individual from haloperidol group and two from perphenazine group did not present any improvement (RR=0.46 CI95%=0.04-4.68). There were no differences between the groups regarding early dropout.	No difference was found between the groups for adverse drug reactions (RR=1.30 CI95%=0.61-2.80). Six individuals from haloperidol group and two from perphenazine group needed anti-Parkinson drugs (RR=2.74 CI95%=0.62-12.12). One individual from perphenazine group presented hypotension (RR=0.31 CI95%=0.01-7.12). Extrapyramidal effects were presented in both groups (RR=1.83 CI95%=0.18-18.70). One individual from haloperidol group abandoned the study due to somnolence/tension and no therapeutic effect.

HALOPERIDOL versus RISPIRIDONE (n=2, N=286) [25, 26]	Haloperidol was more effective than risperidone for the outcome "not tranquil or sleeping for up to 2 hours" (RR=0.84 CI95%=0.74-0.95). Around 80% of the participants (in both groups) had at least 50% reduction in agitation index (RR=0.96 CI95%=0.79-1.16). Patients using lorazepam needed additional benzodiazepine. A patient from risperidone group was taken out of the study due to no control of agitation (RR= 0.33 CI95%=0.01-8.03). There were no differences between the groups regarding dropout.	There was no difference between the groups in the evaluation of adverse drug reactions during 24 hours (RR=1.01 CI95%=0.84 -1.23). Haloperidol group presented a higher level of excitement (RR-1.90 CI95%=1.39-2.59).
HALOPERIDOL versus THIOTHIXENE (n=2, N=74) [53, 89]	No differences between haloperidol and thiothixene were found for the outcomes: need of additional drug (RR=1.07 CI95%=0.89-1.28), alteration in the behavior "agitation" (RR=0.28 CI95%=0.01-6.52), evaluation of global result (RR=2.50 CI95%=0.57-11.05). No dropout was reported.	No differences between haloperidol and thiothixene were found regarding the presence of adverse drug reactions (RR=1.47 CI95%=0.97-2.22). No extrapyramidal effects were reported
HALOPERIDOL versus ZIPRASIDONE (n=3, N=739) [19, 57, 88]	No difference was found between the groups for the outcomes: "agitation in a period of 2 hours" (MD=0.06 CI95%=-1.13-1.25) "agitation up to 72 hours" (MD=0.62 CI95%=-0.45-1.69), need of anxiolytic (RR=1.11 CI95%=0.84-1.48) and "mental conditions" (MD=1.11 CI95%=-0.45-2.67). No difference between the groups regarding early dropout in 72 hours (RR=1.77 CI95%=0.53-5.94).	Patients using haloperidol presented more adverse drug reactions in 72 hours after administration (RR=1.77 CI95%=1.49-2.11), but in 7 days, there were no differences between the groups (RR=1.31 CI95%=0.93-1.83). The group using ziprasidone presented a larger number of movement disturbances, acute dystonia, ECG alterations and tachycardia. In general, more individuals from haloperidol group presented extrapyramidal and anticholinergic effects (blurred vision and dry mouth) ($p<0.05$).
HALOPERIDOL versus ZUCLOPENTHIXOL ACETATE (n=1, N= 70) [91]	Haloperidol patients needed extra three additional injections for tranquilization (RR=02.54 CI95%=1.19-5.46). No early dropout in both groups.	There was no difference between the groups regarding adverse drug reactions, but one local reaction was observed in one participant from haloperidol group. Seven individuals from haloperidol group and two from zuclopenthixol acetate developed tremors ($p>0.05$).
HALOPERIDOL versus FLUNITRAZEPAM (n=1, N= 28) [31]	No differences between the groups were observed for "reduction of aggression in 90 minutes" after drug administration (RR=1.15 CI95%=0.86-1.55)	No participants from both groups (haloperidol and flunitrazepam) presented extrapyramidal effects.
HALOPERIDOL versus LORAZEPAM (n=3, N=205) [37, 35, 12]	For the outcome "sedated or sleeping after one hour of drug use" there was advantage in the use of haloperidol (RR=1.05 CI 0.76-1.44), however, after three hours, the result was favorable to lorazepam (RR=1.93 CI95%=01.14– 03.27). There was no difference between the groups for the following outcomes: need of additional drug (RR=1.14 CI95%=0.91-1.43 e RR=1.11 CI95%=0.50-2.45), improvement in global conditions in one hour (RR=1.64 CI95%=0.54–05.03) and improvement in mental conditions (MD=3.26 CI95%=-4.13-10.65). Early dropout results were not presented.	One-third of the participants from both groups presented some drug adverse drug reaction; however, they did not report severe adverse drug reactions. There were no differences between the groups concerning adverse drug reactions: dry mouth, movement disturbance, dystonia, speech disturbances, tremor and need of anti-Parkinson drugs. The participants from haloperidol group presented more extrapyramidal effects (RR=15.00 CI95%=2.11-106.49).

HALOPERIDOL versus MIDAZOLAM (n=1, N=84) [75]	Midazolam group presented better results for the outcome “sedated or sleeping” (RR=1.33 CI95%=0.48-3.65). There were no differences between the groups regarding need of additional drug (RR=1.14 CI95%=0.46-2.87). Early dropout results were not presented.	Two individuals from haloperidol group presented adverse drug reactions; one had hypotension (RR=3.00 CI95%=0.13-71.61) and the other apnea (RR= 3.00 CI95%=0.13-71.61).
HALOPERIDOL versus LEVOMEPROMAZINE (n=1, N=19) [44]	Only the outcome “no improvement in global conditions” was evaluated. The author reports no clear difference between the groups, impossible to identify improvement in the participants involved in the study (RR=8.18 CI95%=0.50-133.66).	No safety outcome was evaluated.
HALOPERIDOL versus HALOPERIDOL + LORAZEPAM (n=2, N=113) [12, 37]	The association presented better result in the outcome “sleeping for a three-hour period” (RR=1.83 CI95%=1.11-3.02) and fewer individuals needed additional drug administration for tranquilization (RR=1.5 CI95%=0.87-1.27). In 60 minutes, both groups presented “improvement in general conditions” (p>0.05). Early dropout results were not presented.	There were no differences between the groups regarding general adverse drug reactions (RR=1.16 CI95%=0.62-2.18). Specific adverse drug reactions were more present with the use of haloperidol: dystonia, anticholinergic effects (dry mouth), cardiovascular effects (high blood pressure) (RR=0.91 CI95%=0.06-14.02) and dizziness (RR= 1.37 CI95%=0.24-7.69).
HALOPERIDOL versus HALOPERIDOL + PROMETHAZINE (n=1, N=316) [48]	H+P was more effective for “tranquilization or sleeping” in 20 minutes (RR=1.60 CI95%=1.18- 2.16) and 40 minutes (RR=1.26 CI95%=0.83-1.91). The use of additional drug for tranquilization (RR=1.67 CI95%= 0.71-3.91), alteration in behavior (aggression within 24 hours after drug administration) (RR=1.06 CI95%=0.68-1.65) and need for physical contention 120 minutes after drug administration (RR=1.21 CI95%=0.84-1.76) occurred mostly in haloperidol group, but without statistical difference. There was no difference in dropout rate (RR=3.1 CI95%=0.06-16.25).	The use of haloperidol caused individuals to need extra doctor appointment (RR=1.50 CI95%=1.05-2.14) and presented more adverse drug reactions (RR=11.28 CI95%=1.47-86.35). Nine individuals from haloperidol group presented acute dystonia (RR=19.48 CI95%=1.14-31.92). Two individuals from haloperidol group and one from H+P group had seizure (RR=5.2 CI95%=0.19-22.39).
HALOPERIDOL versus QUETIAPINE +MAGNESIUM VALPROATE (n=1, N=60) [41]	The results did not show any differences between the groups regarding agitation control (RR=1.17 CI95%=0.44-3.06)	No results were presented.

n= number of studies. N= number of participants, RR= relative risk, CI95%=confidence interval 95%, MD=mean difference.

Table 3 - Efficacy and safety of the studies which evaluated olanzapine comparing to placebo, lorazepam and haloperidol

Interventions	Efficacy outcomes	Safety outcomes
OLANZAPINE versus PLACEBO (n=4, N=222) [17, 65, 67, 94]	All four studies compared olanzapine to placebo and observed a fewer number of individuals using olanpazine that experienced no important clinical response (RR=0.49 CI95%=0.42-0.59). The groups did not present differences regarding dropout rates (RR=0.31 CI95%=0.06-1.55). The need for additional drug took place in the placebo group (RR=0.48 CI95%=0.40-0.58), including additional injection of benzodiazepines (RR=0.32 CI95%=0.21-0.47).	No difference between the groups concerning adverse drug reactions (n=150) (RR=1.35 CI95%= 0.78=2.32) in the first 24 hours. Patients from placebo group presented a higher level of anxiety (RR=0.04 CI95%=0.00-0.75). Severe adverse drug reaction was presented in olanzapine group (ECG alteration and anemia) (RR=0.74 CI95%=0.03-17.92). The studies did not present information about patients that committed suicide, self-mutilation or harm to third parties.
OLANZAPINE versus HALOPERIDOL (n=1, N=482) [94]	Olanzapine and haloperidol did not differ regarding global effects (RR=1.00 CI95%=0.73-1.38). There were also no differences between the groups concerning dropout rates (RR=0.87 CI95%=0.36-2.06), need of additional injection after 24 hours of drug administration (RR=0.95 CI95%=0.57-1.60) and need of additional administration of benzodiazepines (RR=0.99 CI95%= 0.71-1.38).	More individuals presented akathisia with the use of haloperidol after five days of drug use (RR=0.51 CI95%=0.32-0.80). Dystonia was not observed in participants using haloperidol in the first 24 hours, however, eleven patients using haloperidol presented episodes of anguish (RR=0.05 CI95%= 0.01-0.44). Individuals using olanzapine presented less Parkinson symptoms (RR=0.59 CI95%=0.41-0.87). One patient presented a severe adverse drug reaction with the use of olanzapine (ECG alteration and anemia) (RR=0.66 CI95%=0.03-15.94). There was no difference between the groups concerning anxiety, headache and insomnia during the five-day treatment. The studies did not present information about patients that committed suicide, self-mutilation or harm to third parties.
OLANZAPINE versus LORAZEPAM (n=2, N=355) [64, 65]	Olanzapine did not present difference in global effects (RR=92 CI95%=0.66-1.30) and dropout rates comparing to lorazepam (RR=0.50 CI95%=0.21-1.16). A higher number of individuals that used olanzapine needed additional injections for 24 hours different from patients that used lorazepam (RR=0.68 CI95%=0.49-0.95).	Individuals that received olanzapine were less inclined to present adverse drug reaction compared to the use of lorazepam in 24 hours (RR=0.62 CI95%=0.43-0.89). Individuals using olanzapine presented fewer episodes of nausea (RR=0.15 CI95%=0.03-0.68) and vomit (RR=0.09 CI95%=0.01-0.69). Accidental lesions in the elderly, dizziness, ECG alteration, headache, and somnolence were observed in both groups. No differences were found between the drugs as for the need of anticholinergic agents (RR=1.16 CI95%=0.38-3.58).

n= number of studies. N= number of participants. RR= relative risk, CI95%= confidence interval, MD=mean difference.

Gilles et al [38] identified 21 eligible studies regarding interventions for the treatment of adults with agitation and aggression induced by psychosis comparing benzodiazepines to: placebo or antipsychotics or its associations (benzodiazepines + antipsychotics compared to lorazepam or antipsychotics). Lorazepam demonstrated little benefit compared to placebo and was not different, in most outcomes assessed, when used it alone or combined with haloperidol or olanzapine. No benefits from benzodiazepines in relation to antipsychotics were observed in the studies that compared diazepam, lorazepam or clonazepam with olanzapine, droperidol or haloperidol. The combination of lorazepam or midazolam with haloperidol and of clonazepam with risperidone did not present benefits for the majority of the outcomes assessed, however, the patients that received benzodiazepine associated with haloperidol were more sedated compared to haloperidol. Benefits were observed in the combination of haloperidol plus promethazine compared to lorazepam or midazolam. Although better safety profile, the use of benzodiazepines alone or associated to antipsychotics did not demonstrates benefits in relation to the use of antipsychotics (Table 4).

Table 4 - Efficacy and safety of the studies which evaluated the use of benzodiazepines (alone or associated) compared to placebo, benzodiazepines and antipsychotics

Interventions	Efficacy outcomes	Safety outcomes
LORAZEPAM versus PLACEBO (N=1, N=102) [10]	In the evaluation of the outcome "no important clinical response" there was no difference between lorazepam (2.5mg) and placebo in relation to the number of individuals that had important clinical response in a short period (RR= 0.89 CI95%=0.69-1.16). More individuals that used placebo needed additional drug (RR=1.00 CI95%=0.69-1.44) or additional sedation (RR=1.67 CI95%=0.42-6.61). There was some improvement in patients behavior in the ones using lorazepam (MD=3.61 CI95%=5.92 -1.30) and there was no difference between the groups in the improvement of mental condition (MD=-2.57 CI95%=-6.23-1.09).	There were no differences between the groups for the adverse drug reactions found (dizziness, nausea and vomit) (RR=0.33 CI95%=0.04-3.10) and in relation to dropout for any reason (RR=0.60 CI95%=0.15-2.38).
BENZODIAZEPINE versus ANTIPSYCHOTIC (n=10, N=224) [22, 79, 57, 32, 28, 84, 12, 36, 9, 56]	In the outcome "global impression", a larger number of individuals using clonazepam or diazepam did not present improvement in medium-term (30 hours) (RR=1.84 CI95%=3.18-1.06) compared to olanzapine, but the result did not differ when compared to haloperidol (RR=0.88, CI95%=0.66-1.17). Patients using droperidol (RR=1.87 CI95%=0.83-4.19) or haloperidol (RR= 0.87 CI95%=0.70-1.09) were more inclined to receive additional drug when compared to the use of benzodiazepines. There were no differences regarding sedation (in medium-term) among benzodiazepines and haloperidol or olanzapine. However, individuals using benzodiazepines were more sedated (in short-term) when compared to the use of droperidol (RR=2.71 CI95%=1.55-4.73). Regarding the decrease in the agitation condition, there was less agitated behavior in patients using olanzapine (MD=2.91 CI95%=0.80-5.02) and there was no difference in clonazepam or lorazepam compared to haloperidol. There was no difference in the use of haloperidol or lorazepam in relation to the improvement of mental conditions. Individuals using olanzapine presented better results compared to the use of lorazepam (MD=2.85 CI95%=1.14-4.56). There was no difference between the interventions in the treatment early dropout (RR=1.48 CI95%=0.70-3.3).	Individuals using benzodiazepines presented fewer adverse drug reactions compared to the ones using haloperidol (n=233, RR=0.13 CI95%=0.04-0.41) and other antipsychotic (n = 536, RR=0.15 CI95%=0.06-0.39). There were no differences between benzodiazepines and antipsychotic for adverse drug reactions (airway obstruction, blood pressure alterations, dry mouth, hypoxia, nausea, vomit, seizure, and tremor)
LORAZEPAM + ANTIPSYCHOTIC versus LORAZEPAM (n=4, N= 216) [12, 14, 37, 92]	The association lorazepam + haloperidol + risperidone were compared to lorazepam. In the evaluation of the global outcome: "no improvement in medium-term", there was no difference between lorazepam + haloperidol (RR=0.11 CI95%=0.01-1.74) and lorazepam + risperidone (RR=0.86 CI95%=0.45-1.64) in relation to lorazepam. There were no differences between the	The groups did not present differences for specific adverse drug reactions, such as ataxia, dizziness, dry mouth, or speech disturbances.

	groups in the" number of participants that needed additional drug" (RR=1.02 ICI95%=0.79-1.32), however, lorazepam + haloperidol presented a higher level of sedation in short-term (RR=1.92 CI95%=1.10-3.35). There were no differences between the groups as "agitated behavior" (RR=-1.60 CI95%=-5.94-2.74). There was no difference in "mental conditions" of the associations (lorazepam + antipsychotic) compared to lorazepam (MD=3.20 CI95%=-29.41-35.81). There was no difference between the groups in the treatment early dropout.	
BENZODIAZEPÍNES + HALOPERIDOL versus HALOPERIDOL (n=4, N= 759) [6, 7, 12, 37]	Benzodiazepine associations (lorazepam or midazolam) with haloperidol were compared to haloperidol. There was no difference for the outcome "no improvement in the 12-hour period" between the associations compared to haloperidol (RR=1.27 CI95%=0.94–1.70). Patients using lorazepam + haloperidol were more inclined to receive additional drug (RR=0.95 CI95%=0.79-1.15). The combination midazolam + haloperidol presented better result for short-term sedation (MD=0.50 CI95%=0.01-1.01). The use of haloperidol alone showed benefit in "improvement in behavior and aggression in medium-term" (MD=2.40 CI95%=0.59-4.21). There was no difference for the combination of midazolam + haloperidol as for the need of additional drug (MD=0.20 CI95%=-0.33-0.73) neither for mental health conditions (MD=0.01 CI95%=-7.26-7.28) compared to haloperidol. The groups did not present differences for "early treatment dropout" (RR=0.90 CI95%=0.54-1.50).	No differences between the groups were found regarding adverse drug reactions related to extrapyramidal symptoms (RR=0.44 CI95%=0.16-1.17).
BENZODIAZEPÍNE + ANTIPSYCHOTIC versus ANTIPSYCHOTIC (n=5, N=565) [95, 93, 97, 42, 6]	Benzodiazepines (clonazepam or midazolam) were compared to different antipsychotic. For the global outcome "no important response to treatment in 12 hours", the use of midazolam + haloperidol compared to olanzapine presented better results (RR=25.00 CI95%=1.55-403.99). For the outcome "use of additional drug", patients using midazolam + haloperidol were more inclined to receive additional drug when compared to haloperidol. However, individuals using midazolam + haloperidol compared to olanzapine were more sedated in short-term. Aggression and agitation were significantly higher in patients using midazolam + haloperidol compared to olanzapine and ziprasidone (MD=2.10 CI95%=1.00-3.20). The improvement in mental conditions was most frequent with the use of clonazepam + risperidone compared to clozapine (MD=2.50 CI95%=0.32-4.68). Results about treatment early dropout were not presented.	There were no differences between the groups regarding adverse drug reactions for most comparisons. Only the combination of clonazepam + risperidone presented fewer adverse drug reactions when compared to haloperidol (RR=0.05 CI95%=0.00-0.85).
BENZODIAZEPÍNES + ANTIPSYCHOTIC versus	Only the outcomes "alteration in behavior" and "early dropout" were evaluated. There were no differences between the groups	No data on adverse drug reactions were reported.

ANTIPSYCHOTIC + ANTIPSYCHOTIC N=60) [14]	**(n=1,**	"lorazepam + haloperidol" and clotiapine + haloperidol" (MD=-5.83 CI95%=-27.60-15.94) in improvement to the treatment. No groups had early dropouts.	
BENZODIAZEPÍNES HALOPERIDOL + PROMETHAZINE N=200) [2, 46]	**versus (n=2,**	In the evaluation of the outcome "no important response in a two-week period", it was observed that individuals using haloperidol + promethazine presented improvement in immediate treatment (RR=1.79 ICI95%=1.36-2.37), short-term treatment (RR=2.47 CI95%=1.51-4.03) and medium-term treatment (RR=2.17 CI95%=1.16-4.05) compared to the use of lorazepam. No need for additional drug in any group (RR=3.00 CI95%=0.12-72.77). However, patients using lorazepam presented worse results for sedation onset (RR=0.88 CI95%=0.77-0.99), while midazolam presented a faster onset compared to the combination (RR=1.32, CI95%=1.16-1.49). There were no differences for early treatment dropout (RR=0.43 CI95%=0.06-2.87).	The groups did not present differences regarding specific adverse drug reactions: airway alteration (RR=2.99 CI95%=0.31-28.54), nausea (RR=3.00 CI95%=0.12-72.77) and seizure (RR=0.33 CI95%=0.01-8.06).
MIDAZOLAM + HALOPERIDOL versus HALOPERIDOL + PROMETHAZINE N=150) [6]	**(n=1,**	For the outcome "global evaluation for a 12-hour follow-up" patients using midazolam + haloperidol did not present improvement (RR=25.00 CI95%=1.55-403.99) and needed more additional drug (MD=0.63 CI95%=0.15-1.11) compared to haloperidol + promethazine, but presented higher level of sedation (MD=0.00 CI95%=-0.46-0.46) and lower level of agitation and aggression (MD=-3.30 CI95%=-5.25-1.35. No groups had early dropouts.	There were no differences between the groups regarding adverse drug reactions: extrapyramidal effects (RR=0.60 CI95%=0.16-2.29) nor hypotension (RR=1.67 CI95%=0.44-6.36).

n= number of studies. N= number of participants. RR= relative risk. CI95%=confidence interval 95%, MD=mean difference.

4. Discussion

The present study identified four systematic reviews in a total of 61 RCTs and 8,021 participants aiming to verify the available evidence regarding efficacy and safety of drugs used for rapid tranquilization in patients with psychomotor agitation of a psychotic nature. The findings showed that the association of haloperidol with promethazine was effective to promote tranquilization in patients and presented the best safety profile, with moderate quality evidence. Olanzapine demonstrated benefit for tranquilization and good safety profile, however, additional dose was necessary.

There was no benefit in the use of haloperidol alone or associated to other psychotropic or benzodiazepines for the majority of the outcomes assessed, neither in the use of benzodiazepines alone or associated to antipsychotics, with a low quality evidence for most of these interventions.

All trials selected for the review used drugs intramuscularly injected. This choice must have been done due to patient´s lack of collaboration, intramuscular injection is used when the patient does not present the conditions to receive the drug orally; moreover, oral doses are less used due to a longer onset and lesser response time [3]. Even though intravenous administration has an immediate onset, it is not recommended because it may expose the patients even more to the adverse drug reactions [43,73,69].

Huf et al [45] verified that all interventions were effective for the assessed outcomes, but they differ as to onset. Midazolam is the fastest, but the least safe when compared to the use of haloperidol plus promethazine. Even though olanzapine seemed safe, it was necessary to repeat its dosage due to the shorter duration of its effect. Based on the results, the authors emphasize that the choice of the best intervention must be founded on safety criteria in the use of those drugs, observing the fewer number of effects with the use of the combination.

Among the effects observed, Huf et al [45] point to the severity of the respiratory depression caused by benzodiazepines, midazolam being the most common [6,73]. According to the authors of the review, even though this effect occurred in only one patient that used midazolam, it must be considered due to the fact that it is necessary to have a health team preparation for reversing respiratory depression besides the costs associated to the need of using flumazenil [6], which is

the antagonist for the benzodiazepine receptor, with powers to revert the sedative, anxiolytic and anticonvulsive effects of benzodiazepines [24].

The administration of haloperidol causes more adverse drug reactions, but, the association with promethazine presents good results due to the drug's sedative and anticholinergic effects [46]. Somnolence and sedation caused by promethazine with consequent reduction of the memory and cognitive functions as well as the psychomotor performance contribute for tranquilization [76].

Powney et al [77] verified weak evidence that haloperidol tranquilizes patients more than placebo and other treatments, moreover, the adverse drug reactions observed with its use may be as anguishing as the psychosis. The authors also observed that there is no good evidence for the use of haloperidol with benzodiazepines and the use of other antipsychotic; wherein first generation antipsychotic (haloperidol, chlorpromazine, levomepromazine and zuclopenthixol) as well as second generation (aripiprazol, olanzapine, quetiapine, risperidone, sertindol, ziprasidone, droperidol, perphenazine, thiothixene and magnesium valproate) founded in studies evaluated.

While Powney et al [77] included an elevated number of clinical trials and participants, countless interventions were observed and there were few studies for most of them, along with a reduced sample of participants, and different outcomes, which justifies the evidence as weak. Other observation made by the authors is regarding the importance of the outcomes assessed, since most studies did not evaluate outcomes which were relevant for clinical practice, such as treatment satisfaction with the treatment, life quality and their costs. Only the studies of Huf et al [45]; Currier et al [25]; Fruensgaard et al [36] evaluated whether the patient was "tranquil or sleeping", considered as important outcomes for the daily routine of professionals who deal with those patients.

Powney et al [77] and Huf et al [45] had in common the inclusion of a clinical trial from Huf et al [48] which demonstrated the benefits and better safety profile in the use of haloperidol with promethazine, with moderate quality evidence. This association is considered as low cost and besides that, these drugs are part of the list of essential drugs from the World Health Organization [49].

Belgamwar and Fenton [13] verified important clinical response in the use of olanzapine in relation to tranquilization, indicating some benefit this psychotropic has

in controlling aggression or agitation in patients with mixed or manic bipolar disorder and dementia; and higher safety profile compared to haloperidol and lower compared to lorazepam. This review included Huf et al [46], clinical trial also present in Huf et al [45] which compared lorazepam to olanzapine. The authors state that the available evidence is not enough for a decision-making, pointing the need for further studies that report relevant outcomes for the clinical practice. Moreover, olanzapine has high cost when compared to haloperidol, which limits its use in the practice and studies related to costs comparing these interventions are scarce.

Breier et al [16] was the only clinical trial included in Belgamwar and Fenton [13] and Powney et al [77]. This study compared olanzapine to haloperidol and was observed benefit in use of olanzapine in relation to the outcome “24-hour tranquilization” and better safety profile; however, most of the outcomes reported were different in two reviews.

Pacciardi et al [74] clinical guidelines review study points to the trend to the parenteral use of atypical antipsychotics (olanzapine and ziprasidone) as first line option for rapid tranquilization treatment due to more favorable adverse drug reactions. However, Belgamwar and Fenton [13] demonstrated that these interventions must be better studied regarding safety and efficacy profiles, due to the few available clinical trials and limited number of participants.

Gilles et al [38] observed that the use of benzodiazepines alone (clonazepam, lorazepam e diazepam) did not present advantages in relation to antipsychotics (haloperidol and olanzapine) for most efficacy outcomes (low quality evidence), but it demonstrated benefit regarding safety profile. The association of benzodiazepine (clonazepam or midazolam) with psychotropic (haloperidol, or risperidone or olanzapine), in general, did not present benefit in relation to the use of benzodiazepine or haloperidol alone, but it is low quality evidence.

Huf et al [45] and Gilles et al [38] included the same clinical trial twice in their reviews, Huf et al [46] study which verified that the evidence favors the use of haloperidol with promethazine. Powney et al [77] and Gilles et al [38] when comparing haloperidol to benzodiazepines verified that midazolam presented favorable results regarding patient sedation, but a higher number of patients needed additional drug. Both reviews included the studies of Battaglia et al [12]; Dorevitch et al [31]; Garza et al [37]; Huf et al [45]; Foster et al [35]; Salzman et al [82].

Gillies et al [38], Belgamwar and Fenton [13] did not include the same clinical trials. The summary of their findings tend to show a better safety profile and similar efficacy of lorazepam and olanzapine. Clonazepam and diazepam were not more effective than haloperidol and olanzapine, even though they also presented a better safety profile. The authors warn again for the need of further clinical trials that confirm these findings.

The reviews included in this overview compared different drugs and their associations, and most clinical trials present different outcomes, which enable the presentation of the results in a descriptive way. Due to these differences, it is also necessary to choose the outcomes with higher clinical relevance for the construction of this review's results, which is considered as a limiting factor for this study.

Gathering information in the literature from high quality methodology systematic reviews, this study demonstrated the available evidence concerning fast tranquilization aiming to inform the professionals that work in this area about the aspects related to the efficacy and safety present in these interventions, therefore contributing for the decision-making process.

The summary of the findings demonstrated that the association of haloperidol with promethazine demonstrated efficacy and safety, and a tendency to use this association was observed, however, further studies are recommended. In general, the evidence was considered as low quality due to the limitations of the clinical trials in relation to the small sized sample for most interventions found; which allowed the conclusion that further clinical trials are necessary so that enough evidence will be formulated for a recommendation of the interventions assessed.

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5 CONSIDERAÇÕES FINAIS

Este estudo selecionou quatro revisões sistemáticas que avaliaram o uso de diferentes intervenções medicamentosas para tranquilização rápida em pacientes psiquiátricos com agitação psicomotora.

- A associação haloperidol com prometazina se mostrou mais segura se comparada ao uso de haloperidol isolado, embora a evidência tenha sido considerada como moderada.

- A administração de Olanzapina se mostrou eficaz no controle da agressão e agitação de pacientes com transtorno bipolar maníaco/misto e demência, com maior perfil de segurança comparado ao haloperidol, no entanto a evidência é fraca. Além disso, seu custo é elevado comparado a outras intervenções e faltam estudos comparando o custo-benefício desta intervenção.

- Não se observou evidência suficiente para afirmar a eficácia e segurança do uso de haloperidol associado a benzodiazepínicos, ou do uso associado ou não de outros antipsicóticos. Além disso, o uso de antipsicóticos de segunda geração para tranquilização rápida é questionável, pois apesar de apresentarem resultados positivos relacionados aos efeitos adversos, a evidência é fraca devido aos poucos ECCR existentes.

- Ao comparar o uso de benzodiazepínicos (sozinhos ou associados) em relação aos antipsicóticos observou-se que clonazepam ou diazepam não apresentaram vantagens em relação ao uso de haloperidol ou olanzapina; e embora pareçam ser mais seguros, a evidência é de baixa qualidade. A associação de benzodiazepínico com antipsicóticos também não apresentou benefício em relação ao uso do benzodiazepínico ou haloperidol sozinho. É importante destacar o risco da depressão respiratória associada ao uso dos benzodiazepínicos sendo este evento adverso considerado grave, e que pode ocorrer em especial com o uso de midazolam.

Embora exista uma tendência em indicar o uso do haloperidol associado à prometazina devido aos melhores perfis de eficácia e segurança entre estudos avaliados, a evidência é de qualidade moderada o que sugere a necessidade de novos estudos para afirmar estes resultados.

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ANEXO A: AMSTAR (ASSESSING THE METHODOLOGICAL QUALITY OF SYSTEMATHIC REVIEWS)

1. Foi elaborado um projeto previamente? A questão de investigação e os critérios de inclusão devem ser estabelecidos no antes do início da revisão.	Sim □	Não □	Não aplicável □	Sem resposta □
2. Foi realizada uma dupla seleção de estudos e recolha de dados? Deve existir pelo menos dois revisores independentes na recolha dados e deve ser estabelecido um procedimento consensual para a resolução de casos de desacordo.	Sim □	Não □	Não aplicável □	Sem resposta □
3. Foi realizada uma pesquisa bibliográfica abrangente? Deve ser realizada pelo menos em duas fontes electrónicas. O relatório deve conter os anos e as bases de dados usadas (ex. Central, EMBASE, e MEDLINE). As palavras-chave e/ou termos MESH devem ser referenciados e sempre que possível a estratégia de pesquisa deve ser apresentada. Todas as pesquisas devem ser complementadas com conteúdos atuais, revisões, livros, peritos na área do estudo em questão e, por último, revendo as referências do próprio estudo.	Sim □	Não □	Não aplicável □	Sem resposta □
4. O *status* de publicação (ex. literatura cinzenta) foi considerado um dos critérios de inclusão? Os autores devem declarar se pesquisaram artigos independentemente do seu tipo de publicação. Os autores devem referir se excluíram ou não alguns trabalhos (da revisão sistemática), baseado no tipo de publicação, na linguagem, etc.	Sim □	Não □	Não aplicável □	Sem resposta □
5. Foi fornecida a lista dos estudos (incluídos e excluídos)? A lista dos estudos incluídos e excluídos deve ser providenciada.	Sim □	Não □	Não aplicável □	Sem resposta □
6. Foram apresentadas as caraterísticas dos estudos incluídos? De forma compilada, como por exemplo numa tabela, os dados dos estudos originais sobre participantes, intervenientes e resultados devem ser apresentados. Os intervalos referentes às caraterísticas dos estudos analisados, por exemplo, a idade, a raça, o sexo, a relevância socioeconómica, o estado de saúde, a duração, a gravidade da doença, devem ser mencionados.	Sim □	Não □	Não aplicável □	Sem resposta □

7. A qualidade científica dos estudos incluídos foi avaliada e documentada? Os métodos de avaliação devem ser fornecidos previamente (ex. a eficiência dos estudo se os autores escolherem incluir estudos aleatórios, *double-blind* e com grupo de controlo, ou *allocation concealment* como critério de inclusão); para outros tipos de estudos os parâmetros alternativos são relevantes.	Sim ☐	Não ☐	Não aplicável ☐	Sem resposta ☐
8. A qualidade científica dos estudos utilizados foi considerada para a formulação das conclusões? Os resultados do rigor metodológico e da qualidade científica devem ser considerados na análise e na conclusão da revisão e, devem ser explicitamente referenciados na formulação das recomendações	Sim ☐	Não ☐	Não aplicável ☐	Sem resposta ☐
9. Os métodos utilizados para associar as conclusões dos estudos foram apropriados? De modo a compilar os resultados, deve ser realizado um teste para assegurar que os estudos são complementares, avaliando a sua homogeneidade (ex. Teste do Qui-Quadrado para a homogeneidade; I^2). Se a heterogeneidade existir o modelo de efeitos aleatórios deve ser utilizado e/ou a adequação clínica deve ser tomada em consideração (ex. Foram fáceis de conjugar?).	Sim ☐	Não ☐	Não aplicável ☐	Sem resposta ☐
10. A probabilidade de existência de viés no estudo foi avaliada? A avaliação da publicação de viés presente no estudo deve incluir a combinação de gráficos (ex. diagramas de dispersão, ou outros testes disponíveis) e/ou testes estatísticos (ex. teste de regressão de Egger).	Sim ☐	Não ☐	Não aplicável ☐	Sem resposta ☐
11. O conflito de interesses foi apresentado? As potenciais fontes de suporte devem ser clarificadas e reconhecidas tanto na revisão sistemática como nos estudos utilizados.	Sim ☐	Não ☐	Não aplicável ☐	Sem resposta ☐

ANEXO B: ORIENTAÇÕES PARA APRESENTAÇÃO DE DISSERTAÇÕES DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS DA UNIVERSIDADE DE SOROCABA

Orientações para apresentação de dissertações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba

As dissertações de mestrado do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s). Os trabalhos de investigação que possam resultar em patentes poderão ser apresentados na forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos um artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

A dissertação no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Quadro 1 - Elementos para a construção da dissertação no formato de artigo(s) científico(s).

Elementos pré-textuais	*1. Folha de rosto*
	2. Errata (Opcional)
	3. Folha de aprovação
	4. Dedicatória (Opcional)
	5. Agradecimentos (Opcional)
	6. Epígrafe (Opcional)
	7. Resumo na língua vernácula
	8. Resumo em inglês (Abstract)
	9. Lista de abreviaturas e siglas; lista de tabelas e lista de símbolos (opcionais). Estas listas não devem conter as informações apresentadas nos artigos científicos.
	10. Sumário

Elementos textuais	*11. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.
	12. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	13. Objetivos: geral e específico
	14. Material e Métodos (opcional). Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.
	15. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	16. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	17. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.
Elementos pós-textuais	*18. Referências:* Devem seguir as normas do “Manual para normalização de trabalhos acadêmicos” da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	19. Apêndices (Opcional)
	20. Anexos (Opcional)

Encaminhamentos posteriores à defesa da dissertação:

1. A incorporação de correções e alterações sugeridas pela banca no artigo científico deve ser definida pelo orientador e informada ao mestrando;

2. O orientador continua sendo o responsável por aprovar a versão final do trabalho;

3. O trabalho final deve ser entregue na Secretaria da Pós-Graduação, impresso e acompanhado do arquivo digital em pdf (CD);

4. O arquivo digital (em pdf) deve conter o trabalho completo em único arquivo (incluindo capa, elementos pré-textuais, ficha catalográfica e folha de aprovação assinada por todos os membros da banca e demais seções).

4. Um dos exemplares impressos será encaminhado imediatamente à biblioteca, exceto quando for objeto de patente. Neste caso, os procedimentos devem ser discutidos previamente com a coordenação do programa;

5. Dissertações no formato de artigos podem não ser divulgadas imediatamente no site do programa, caso solicitado pelo orientador. Neste caso, apenas o resumo e o abstract serão divulgados no site, junto com a seguinte informação: ***Trabalho completo contendo artigos científicos. Aguardando a publicação dos resultados.***

6. A princípio, a versão eletrônica da dissertação contendo artigos poderá ser retida por até 12 meses. A partir deste prazo, o trabalho completo será divulgado na página do programa. Havendo necessidade de prorrogação dos 12 meses, o orientador deve discutir com a coordenação os encaminhamentos.

7. Os docentes devem informar à Secretaria do Programa (com cópia para a coordenação do programa), sempre que um artigo derivado de dissertação for publicado, acompanhado da referência no formato ABNT. Neste caso, será incluída no site a referência e um hiperlink para acesso do artigo, logo abaixo do resumo.

ANEXO C: COMPROVANTE DE SUBMISSÃO DO ARTIGO PARA EUROPEAN PSYCHIATRY

De: ees.eurpsy.0.373789.ce24aaec@eesmail.elsevier.com <ees.eurpsy.0.373789.ce24aaec@eesmail.elsevier.com> em nome de European Psychiatry <europeanpsychiatry@gmail.com>
Enviado: quarta-feira, 10 de fevereiro de 2016 13:22
Para: Cristiane De Cassia Bergamaschi Motta
Assunto: Submission Confirmation

Dear Dr. Cristiane de Cássia Bergamaschi,

Your submission entitled "Rapid tranquilization for psychiatric patients with psychomotor agitation: What is known about it?" has been received by European Psychiatry

You may check on the progress of your paper by logging on to the Elsevier Editorial System as an author. The URL is http://ees.elsevier.com/eurpsy/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to this journal.

Kind regards,

Elsevier Editorial System
European Psychiatry

APÊNDICE A: DESCRIÇÃO DOS ESTUDOS INCLUÍDOS EM CADA REVISÃO SISTEMÁTICA E TIPOS DE PARTICIPANTES

Quadro 1 - Descrição dos estudos incluídos em cada revisão sistemática e tipos de participantes

Revisões sistemáticas incluídas/número de participantes e diagnóstico	Estudos incluídos
Huf et al. (2009) (N= 1.117) *Esquizofrenia*	Alexander et al. (2004), Huf et al. (2003), Huf et al. (2007), Nirmal et al. (2007).
Belgamwar et al. (2005) (N= 1.059) *Doenças mentais severas (Transtorno bipolar maníaco, demência)*	Breier et al. (2001), Meehan et al. (2001), Meehan et al. (2002), Wright et al. (2001).
Gillies et al. (2013) (N=1.968) *Doenças mentais severas (Transtorno bipolar maníaco, demência), esquizofrenia*	Barbee et al. (1992), Chouinard et al. (1993), Qu et al. (1999), Yang et al. (2003), Wang et al. (2004), Han et al. (2005), Zhang et al (2007), Lerner et al. (1979), Dorevitch et al. (1999), Garza et al. (1989), Salzman et al. 1991), Battaglia et al. (1997), Foster et al. (1997), Subramaney et al. (1998), Bieniek et al. (1998), Battaglia et al. (2001), Alexander et al. (2004), Veser et al. (2006), Huf et al. (2003), Knott et al. (2006), Baldaçara et al. (2011).
Powney et al. (2012) (N= 3.877) *Pacientes com psicoses*	Battaglia et al. (2002), Breier et al. (2001), Bristol et al. (2004), Bristol et al. (2005), Brook et al. (1998), Eli et al. (2004), Garza et al. (1989), Guo et al. (2007), Higashima et al. (2004), Kinon et al. (2001), Lim et al. (2010), Resnick et al. (1984), Shu et al. (2010), Bailine et al. (1987), Battaglia et al. (1997), Currier et al. (2004), Dorevitch et al. (1999), Fitzgerald et al. (1969), Foster et al. (1997), Fruensgaard et al. (1977), Huf et al. (2007), Kewala et al. (1984), Li et al. (2006), Man et al. (1973), Nobay et al. (2004), Paprocki et al. (1977), Reschke et al. (1974), Ritter et al. (1972), Salzman et al. (1991), Stotsky et al. (1977), Taymeeyapradit et al. (2002), Tuason et al. (1986).

APÊNDICE B: DESFECHOS DE EFICÁCIA E SEGURANÇA DO USO DE HALOPERIDOL E PROMETAZINA COMPARADOS A BENZODIAZEPÍNICOS E ANTIPSICÓTICOS

Quadro 2 - Desfechos de eficácia e segurança do uso de haloperidol e prometazina comparados a benzodiazepínicos e antipsicóticos (Huf et al., 2009a)

Intervenções	**Comparações**	**Tempo de início para tranquilização/sedação RR (IC 95%)**	**Número de pacientes com efeitos adversos n (%)**
Haloperidol (10mg)+ prometazina (até 50mg) (H+P)	Midazolam (até 15mg) (M)	RR=2,9 (IC95%=1,75-4,80)	M= depressão respiratória: 1 (0,7%) H+P=epilepsia: 1 (0,65%)
	Lorazepam (até 4mg)	RR=0,26 (IC95%=0,10-0,68)	L= depressão respiratória: 1 (1%) H+P: nenhum
	Haloperidol (até 10mg) (H)	RR=0,65 (IC95%=0,49-0,87)	H= distonia: 10 (6,4%); convulsão: 1 (0,6%) H+P= convulsão 1 (0,6%)
	Olanzapina (até 10 mg) (O)	RR=0,74 (IC95%=0,38-1,41)	H+P= desnutrição: 1(0,66%) O= Acatisia: 2 (1,3%) e náuseas:1 (0,7%)

n: número de pacientes. RR: risco relativo. IC95%: intervalo de confiança 95%.

APÊNDICE C: DESFECHOS DE EFICÁCIA E SEGURANÇA DO USO DE HALOPERIDOL COMPARADO COM 18 TRATAMENTOS DIFERENTES PARA TRANQUILIZAÇÃO RÁPIDA

Quadro 3 - Desfechos de eficácia e segurança do uso de haloperidol comparado com 18 tratamentos diferentes para tranquilização rápida (Powney et al., 2013)

Intervenções	Comparações	Nenhuma Melhora Global RR (IC 95%)	Não tranquilo e / ou necessidade repetida adormecido por tranquilização / agitação	Necessidade de medicamento adicional	Estado Mental (nenhuma alteração importante no estado mental	Evento Adverso	Abandono ao tratamento
Haloperidol	Placebo	P- RR=0,61 (IC95%=44 84)	H- RR=0,88 (IC95%=0,82 - 0,95)	P- RR=0,51 (IC95%=0,42-0,62)	H- DM= -1,04 (IC95% -1,54 - 0,54)	P-RR=1,31 (IC95%=0,61-2,82) (insônia) H- Taquicardia, tontura, efeitos extrapiramidais, náuseas, vômitos e cefaleia.	Não houve diferenças entre os grupos
Haloperidol	Aripiprazol	RR=2.07 (IC95%=0,86 4,98)	H - RR=1,07 (IC95%=0,92-1,26)	A - RR=0,78 (IC95%=0,62 0,99)	DM= -0,23 (IC95%= -1,28 0,82)	H- insônia, tontura, diarreia, vômitos, náuseas, distonia, e sintomas extrapiramidais.	Não houve diferenças entre os grupos quanto a taxa de abandono do estudo.
Haloperidol	Clorpromazina	RR=0,79 (IC95%= 0,61 1,02)	RR=1.93 (IC95%=1,04-3,60)	H e CZ RR=1,50 (IC95%=0,53 4.26)	NR	CZ – apresentou crise epilética, hhipotensão e alteração de TGP H- Leucopenia suave	Não houve diferenças entre os grupos quanto a taxa de abandono do estudo.
Haloperidol	Droperidol	NR	NR	H – RR=2,23 (IC95%=0,99-5,06)	NR	H – distonia RR=2,12 (IC95%=09-47,68)	Não apresentou resultados
Haloperidol	Loxapina	48 horas RR=0,93 (IC95%=0,14-6,15) 72 horas RR=0,39 (IC95%= 0,04 a 3,49)	Diferença não significantes RR=4,31 (IC95%= 0,54-34,48)	NR	DM=6,10 (IC95%=4,48 7,72)	Não houve diferenças entre distúrbios de movimento e excitação	Uma pessoa do grupo loxapina abandonou o tratamento RR=2,84 (IC95%=0,12 a 65,34)
Haloperidol	Olanzapina	NR	O- RR=1,16 (IC95%=1,02-1,32)	RR=1,06 (IC95%= 0,75-1,51) RR=1,05 (IC95%=0,63-1,74)	O - RR=0,35 (IC95%=0,01-8,12) ansiedade O - RR=0,35 (IC95%=0,01-8,12) delírios O - RR=2,17	H – Distúrbios de movimento, aumento da salivação, problemas gástricos e hemorragias nasais.	O grupo Olanzapina apresentou menor abandono do tratamento RR=1,66 (IC95%=1,04-2,65)

					(IC95%=0,70-6,74) nervosismo		
Haloperidol	Perfenazina	PER - RR=0,46 (IC95%=0,04-4,68)	NR	H - RR=2,74 (IC95%=0,62-12,12)	NR	PER - RR=2,74 (IC95%=0,62-12,12) H - RR=1,83 (IC95% 0,18-18,70)	H - uma pessoal abandonou o estudo RR=2,75 (IC95%=0,12-64,04)
Haloperidol	Risperidona	NR	R- RR=0,84 (IC95%=0,74-0,95)	R- RR=0,96 (IC95%=0,79-1,16)	H – RR=-1,90 (IC95%=1,39-2,59)	RR=1,01 (IC95%=0,84 - 1,23)	R – uma paciente foi retirado (RR=0,33 (IC95%=0,01-8,03)
Haloperidol	Tiotixeno	RR=2,50 (IC95%=0,57-11,05)	NR	RR=1,07 (IC95%=0,89-1,28)	RR=0,28 (IC95%=0,01-6,52)	T - RR=1,47 (IC95%=0,97-2,22)	Não foi relatado abandono precoce do estudo
Haloperidol	Ziprazidona	RR=1,11 (IC95%=0,84 1,48) RR=0,71 (IC95%=0,20 2,50)	DM=0,06 (IC95%=-1,13-1,25)	RR=1,11 (IC95%=0,84-1,48)	DM=1,11 (IC95%=-0,45-2,67)	H- RR=1,77 (IC95%=1,49-2,11) Z – Distúrbios de movimento, distonia, taquicardíaca e alterações de ECG.	Não houve diferenças entre os grupos RR=1,77 (IC95%=0,53-5,94)
Haloperidol	Acetato Zuclopentixol	NR	NR	H - RR=2,54 (IC95%=1,19-5,46)	NR	H- 7 haloperidol tremor A Z – 2 tremor	Não houve abando precoce do estudo
Haloperidol	Flunitrazepam	NR	Não apresenta diferenças entre os grupos RR=1,15 (IC95%=0,86-1,55)	NR	NR	Nenhum dos participantes apresentou efeitos extrapiramidais	NR
Haloperidol	Lorazepam	RR=1,64 (IC95%=0,54–5,03)	H- RR=1,05 (IC95%=0,76-1,44)	Não houve diferenças RR=1,14 (IC95% 0,91-1.43) e RR=1,11 (IC95%=0,50- 2,45)	DM=3,26 (IC95%=-4,13-10,65)	H- apresentaram efeitos extrapiramidais RR=15,00 (IC95%=2,11 106,49)	Não foram relatados abando precoce do estudo
Haloperidol	Midazolam	Não apresenta diferenças entre os grupos RR= 1,14 (IC95%=0,46 2,87)	M- RR=1,33 (IC95%=0,48 3,65)	Não houve diferenças RR=1,14 (IC95%=0,46 2,87)	NR	H- Hipotensão e apnéia RR=3,00 (IC95% 0,13 71,61) RR= 3,00 (IC95%=0,13 71,61)	Não foram relatados abando precoce do estudo
Haloperidol	Haloperidol + Levomepromazina	Não houve diferenças entre os grupos (RR=8,18 (IC95%=0,50 133,66)	NR	NR	NR	NR	NR
Haloperidol	Haloperidol + Lorazepam	Em 60 minutos ambos os grupos	H+ L - RR=1,83 (IC95%=1,11-3,02)	H- RR=1,5 (IC95%=0,87-1,27)	NR	H - RR=1,16 (IC95%=0,62 2,18 (distonia, boca seca,	Não foram apresentados resultados sobre abandono

		apresentaram melhora do estado global				hipertensão)	precoce do estudo
Haloperidol	Haloperidol + Prometazina	NR	H+P - RR=1,60 (IC95%=1,18 2,16) (20 minutos) H+P- RR=1,26 (IC95%=0,83 1,91) (40 minutos)	H- RR=1,67 (IC95%=0,71 3,91)	H- RR=11,28 (IC95%=1,47 86,35)	H- RR=11,28 (IC95%=1,47 86,35) H- RR= 19,48 (IC95%=1,14 331,92) (distonia aguda) H+P - RR=5,2 (IC95%=0,19-22,39) (convulsão)	Não houve diferenças entre os grupos RR=3,1 (IC95%=0,06-16,25)
Haloperidol	Quetiapina + Valproato de Magnésio	NR	RR=1,17 (IC95%=0,44-3,06)	NR	NR	NR	NR

H- haloperidol, PZ- prometazina, L- lorazepam, M- midazolam, DM- diferença entre as médias, RR- risco relativo, IC95%- intervalo de confiança 95%, T- tiotixeno, R- risperidona, PER- perfenazina, O- olanzapina, CZ- clorpromazina, A- aripiprazol, P- placebo, NR – não reportado.

APÊNDICE D: DESFECHOS DE EFICÁCIA E SEGURANÇA DO USO DE OLANZAPINA COMPARADA COM HALOPERIDOL, LORAZEPAM E PLACEBO

Quadro 4 - Desfechos de eficácia e segurança do uso de olanzapina comparada com haloperidol, lorazepam e placebo (Belgamwar e Fenton, 2005)

Intervenções	Comparações	Desfecho global (nenhuma resposta clínica importante) RR (IC 95%)	Abandono ao tratamento	Necessidade de medicamento adicional	Número (%) de pacientes com efeitos adversos
Olanzapina (O) (2,5, 5, 7,5 e 10mg) (n=769)	Placebo (P) (n=217)	RR=0,49 (IC95%=95%0,42-0,59)	RR=0,31 (IC95%=0,06-1,55)	RR=0,48 (IC95%=0,40-0,58)	O= *anemia e alteração no eletrocardiograma n=1 (0,13%)
Olanzapina (O) (2,5, 5, 7,5 e 10mg) (n=316)	Haloperidol (H) (n=166)	RR=1,00 (IC95%=0,73-1,38)	RR=0,87 (IC95%=0,36-2,06)	RR=0,95 (IC95%= 0,57-1,60)	H= acatisia n=NR; angústia n=11 (6,62%). O=*anemia e alteração no eletrocardiograma n=1 (0,31%) Ansiedade, cefaleia e insônia (sem diferença entre os grupos)
Olanzapina (O) (2,5, 5, 7,5 e 10mg) (n=316)	Lorazepam (L) (n=166)	RR=92 (IC95%=0,66-1,30)	RR=0,50 (IC95%=0,21-1,16)	RR=0,68 (IC95%= 0,49-0,95)	O e L= Lesões acidentais em idosos, tonturas, ECG anormalidade, dor de cabeça, sonolência. L = Náuseas / vômitos 0,31%

NR: não reportado *efeito adverso grave. n: número de pacientes. RR: risco relativo. IC95%: intervalo de confiança 95%, O: olanzapina, L: lorazepam e H: haloperidol.

APÊNDICE E: RESULTADOS DE EFICÁCIA E SEGURANÇA DO USO DE BENZODIAZEPÍNICOS (SOZINHOS OU ASSOCIADOS À ANTIPSICÓTICOS) COMPARADOS A ANTIPSICÓTICOS, BENZODIAZEPÍNICOS E ANTI-HISTAMÍNICOS

Quadro 5 - Desfechos de eficácia e segurança do uso de benzodiazepínicos (sozinhos ou associados à antipsicóticos) comparados a antipsicóticos, benzodiazepínicos e anti-histamínicos (Gillies et al., 2013)

Intervenções	Comparações	Desfecho global (nenhuma resposta clínica importante) RR (IC95%)	Necessidade de medicamento adicional	Comportamento	Estado Mental	Abandono ao tratamento	Evento Adverso
Benzodiazepínico: lorazepam (L)	Placebo (P)	RR=0,89 (IC95%=0,69-1,16) (L comparado P)	RR=1,00 (IC95%=0,69-1,44) (L comparado a P)	DM=3,61 (IC95%=5,92 -1,30) (L comparado a P)	DM=-2,57 (IC95%=-6,23-1,09) (L comparado a P)	RR=0,60 (IC95%=0,15-2,38) (L comparado a P)	tonturas, náuseas e vômitos (p>0,05)
Benzodiazepínicos (B)	Antipsicóticos: olanzapina (O) ou haloperidol (H) ou droperidol (D)	RR=1,84 (IC95%=3,18-1,06) (B comparado O) RR=0,88 (IC95%=0,66-1,17) (B comparado ao H)	RR=1,87 (IC95%=0,83-4,19) (D comparado aos B) RR= 0,87 (IC95%=0,70-1,09) (H comparado aos B)	H comparado a L= SD H x C = SD	H comparado a L = SD	RR=1,48 (IC95%=0,70-3,13) (B comparado a A)	Obstrução de vias aéreas, alteração de pressão arterial, boca seca, hipóxia, náuseas, vômitos, convulsões e tremor (p>0,05)
Benzodiazepínico + Antipsicótico	Benzodiazepínico	RR= 0,11 (IC95%=0,01-1,74) (L+H comparado L) RR=0,86 (IC95%=0,45 1,64) (L+ R comparado L)	RR=1,02 (IC95%=0,79-1,32)	RR=-1,60 (IC95%=-5,94 - 2,74) (L+H RR=1,92 (IC95%=1,10-3,35) sedação maior)	DM=3,20 (IC95%=-29,41 35,81)	L+ H (RR=0,71 (IC95%=0,34-1,50) L+R (RR=0,86 (IC95%=0,45-1,64)	Ataxia, tonturas, boca seca ou distúrbios da fala.
Benzodiazepínico + Antipsicótico	Antipsicótico	RR=1,27 (IC95%=0,94 – 1,70)	L+H RR=0,95 (IC95%=0,79-1,15) M+H DM=0,20 (IC95%=-0,33 a 0,73)	M+H DM=0,50, (IC95%=0,01 1,01) (sedação maior) H DM=2,40 (IC95%=0,59-4,21)	DM=0,01 (IC95%=-7,26 a 7,28)	RR=0.90, 95% (IC95%=0.54-1.50)	Não houve diferenças entre os efeitos adversos e sintomas extrapiramidais RR=0,44 (IC95%=0,16-1,17)
Benzodiazepínico + Antipsicótico	Diferentes Antipsicóticos	M+H X O RR=25,00 (IC95%=1,55 - 403, 99)	NR	M+HxO RR=12,00 (IC95%=1,66-86,59)	C+R x CZ DM 2,50 (IC95%=0,32 4,68)	Sem resultados	Não houve diferenças entre os efeitos adversos e sintomas

				(sedação maior) M+H x Z RR=4,00 IC95%=1,25-12,75) (sedação maior)			extrapiramidais HipotensãoO- RR= 5,00 (IC95%=0,62- 40,28) e Z- RR=0,83 (IC95%=0,28-2,44)
Benzodiazepínico + Antipsicótico	Antipsicóticos + Antipsicóticos	DM= -5,83 (IC95%=- 27,60-15,94)	NR	NR	NR	Não houve abandono em nenhum dos grupos	NR
Benzodiazepínico + Antipsicótico	Anti-histamínicos	I - RR=1,79 (IC95%=1,36-2,37) CP- RR=2,47 (IC95%=1,51-4,03) MP- RR=2,17 (IC95%=1.16-4,05)	RR=3,00 (IC95%=0,12-72,77)	H+PZ- RR=0,88 (IC95%=0,77-0,99) (sedação)	NR	RR=0,43, (IC95%=0,06- 2,87)	SD= Vias aéreas (RR=2,99 (IC95%=0,31- 28,54), náuseas (RR=3,00 (IC95%=0,12- 72,77), ou apreensão (RR=0,33 (IC95%=0,01-8,06)
Benzodiazepínico + Antipsicótico	Antipsicóticos + Anti- histamínicos	RR=25,00 (IC95%=1,55- 403,99)	DM=0,63 (IC95%=0,15-1,11)	DM=0,00 (IC95%=- 0,46 a 0,46) (sedação) M+H - DM= -3,30 (IC95%=-5,25 -1,35) (agitação e agressão)	NR	Não houve abandono em nenhum dos grupos	Sintomas extrapiramidais (RR=0,60 (IC95%=0,16-2,29) Hipotensão (RR=1,67 (IC95%=0,44-6,36)

L- Lorazepam, A-Antipsicóticos, Benzodiazepínicos, O- Olanzapina, H- Haloperidol, D- Droperidol. M- Midazolam, P- Placebo, SD sem diferenças, R- Risperidona, Z- Ziprazidona, CZ- Clozapina, C-Clonazepam, I- Imediato, CP- Curto Prazo, MP- Médio Prazo, PZ- Prometazina, NR – não reportado.