The pharmacological management of agitated and aggressive behaviour : a systematic review and meta-analysis

The pharmacological management of agitated and aggressive behaviour: a sysetemtic review and meta-analysis (or A European Psychiatry Guidance Paper)

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Abstract

Introduction

Non-pharmacological interventions peferably precede pharmacologcal interventions in acute agitation. Reviews of pharmacological interventions remain descriptive or compare only one compound with several other compounds. The goal of this study is to compute a systematic review and meta-analysis of the effect on reaching calmness after a pharamcological intervention, so a more precise recommendation is possible.

Method

A search in Pubmed and Embase was done to isolate RCT's considering pharmacological interventions in acute agitation. The outcome is reaching calmness within maximum of 2 hours, assessed by the psychometric scales of PANSS-EC, CGI or ACES. Also the percentages of adverse effects was assessed.

Results

Fifty-three papers are used for a systematic review and meta-analysis. Most studied drug is olanzapine. Changes on PANNS-EC and ACES at 2 hours showed the stronest changes for haloperidol plus promethazine, risperidon, olanzapine and aripiprazole. However, incomplete data showed that the effcet of risperidon is overestimated. Adverse effects are most prminet for haloperidol and heloperidol plus lorazepam.

Conclusion

Olzanzapine, haloperidol plus promethazine or droperidol are most effective and safe for use as rapid tranquilisation. Midazolam sedates most quickly. But due to increased saturation problems, midazolam is restricted to use within an emergency department of a general hospital.

Introduction

During any hospital admission, either in a mental hospital, emergency department (ED) or at a general hospital ward, aggression and agitated behaviour is a ~~most~~ challenging problem. Even more challenging is management of aggressive or agitated behaviour in psychiatric patients outside the hospital as met by assertive outreach teams, community care or 24u/7 psychiatric crisis services. Aggressive, agitated behaviour or excitement might originate from or coincide with a mental disorder, but this is not a condition sine qua non. Hereafter, agitated behaviour refers to the spectrum of behaviours presented as excitement, agitated behaviour or agression. Assessment of agitated behaviour is part of a medical psychiatric condition or not is problematic. Generally agitated behaviour ~~hampers~~ complicates the evaluation of the underlying somatic and psychiatric problems or disease. To enable diagnostic assessment calmness is conditional. Beside agitated behaviour is a very stressful and may become life-threatening due to physical exhaustion. Finally, agitated behviour may corrobate with safety of staff and other patients on a psychiatric ward or ED.

The prevalence of aggression in the USA is estimated at 16% in psychiatric patients. The prevalence is estitmated at 7% among people without a psychiatric illness {NIMH, 2011 #6}. Agitated behaviours are important reasons for psychiatric admittance into a psychiatric hospital. About 8.8% - 10% of the patients admitted to the emergency department are at risk of developing agitation symptoms {Allen, 2004 #7}. A recent meta-analysis showed that the pooled prevalence of inpatients who committed at least one act of violence was 17% (range 3- 44%) {Lozzino, 2015 #84}.

The literature is unclear in defining agitation or aggression or violence. Even the terms irritability or excitement are used. It seems that these terms and consepts are used with overlapping definitions, and are used interchangeably. The DSM-5 defines agitation as an excessive motor activity associated with a feeling of inner tension, resulting in non-

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productive and repetitious behaviour {Garriga, 2016 #197}. The course or at which level of agitation interventions and treatment are most effective remain unclear {Cohen-Mansfield, 1989 #177; Deksnyte, 2012 #174}. Irritability is a mood of partially physiological agitation characterised by increased sensitivity to sensory stimuli and non-cognitive mediated lowered threshold for responding with anger and/ or aggression to typically less vexing stimuli {Toohey, 2017 #198}. Aggression is defined as behaviour that is intended to harm another individual who does not wish to be harmed {Jhangiani, 2014 #195}. Social psychologists refer to violence if the goal of the aggression has become extreme physical harm such as injury of death {Jhangiani, 2014 #195}. The most recent NICE guidelines offer the following definition: "Violence and aggression refer to a range of behaviours or actions that can result in harm, hurt or injury to another person, regardless of whether the violence or aggression is physically or verbally expressed, physical harm is sustained or the intention is clear" {NICE, 2015 #102}.

It seems we may recognise a continuum of severity that may also represent an evolutionary path towards violence, that starts with agitation, followed by irritability, aggression and ultimate violence. Therefore, prevention of violence focus on interventions as early as agitation starts. The acute presentation of agitation is the focus of the paper and in agreement with NICE guidelines on rapid tranquilisation {NICE, 2015 #102}.

The primary goal of any interventions towards agitated behaviour is to facilitate assessment of underlying problems and prevent further escalation, through achieving calmness and collaboration {Allen, 2004 #7; Allen, 2005 #8}. Calmness is reached if the situation has de-escalated and the aggressive behaviour is reduced and under control. In this calm state a patient is able to collaborate with the diagnostic process and intervention planning. In a pharmacological intervention, this asks for fast and non-complicated, rapid and safe

interventions, considering all possible side-effects and often within a context of limited access to sophisticated and thorough diagnostic assessment and monitoring systems.

The management and treatment of acute agitation is more than emphasizing pharmacological interventions or rapid tranquillisation {Allison, 2014 #17}. Psychosocial interventions and de-escalating measures may prevent acute agitation or escalation towards aggression and are thought to be less physically harmful and may help to restore patient - staff interaction, and thus coopreration, more easily {NICE, 2015 #102}.

Before strating a pharmacological intervention targeting agitation some basic principles need to be considered: 1. Safety for patient and staff – the context and staff experience determine the decision whether acute pharmacological intervention is needed or other options are still available; 2. Pharmacological interventions are limited to specific situations and target symptoms; 3. Not all target symptoms are likely to respond – generally the main goal is reaching calmness; 4. Drug selection and preferred route of administration {Jibson, 2007 #71}.

Consistently, prescribing preferences may not always be based on evidence-based guidelines, although the use of pharmacological interventions for agtitation is widely spread {Bervoets, 2015 #27; De Fruyt, 2004 #182; Marder, 2006 #181}. Several (systematic) reviews on pharmacological interventions conclude that the quality of studies on rapid tranquilisation lack high quality standards {Pratt, 2008 #112}. Multiple reviews and guidelines come to the conclusion that either antipsychotics or benzodiazepines are first choices in treating acute agitation pharmacologically {Jibson, 2007 #71; Bak, 2011 #24; Nice 2015 #102}. The general advise is that pharmacologic interventions should be based on assessment of the most likely cause; e.g. antipsychotic medication incase of psychosis or mania and preferably oral over intramuscular medication or intraveneus {Wilson, 2012 #150}. Second generation antipsychotics (SGA) are recommended over first generations antipsychotics (FGA). Despite

these guidelines, FGA's are more likely to be used than SGA's {Wilson, 2014 #151; Campillo, 2015 #44}. ~~Noteworthy is that preferences of pharmacological interventions differ accordingly to medical specialty treating acute agitation (psychiatrist versus emergency physician) {Bervoets, 2015 #27}.~~

Improvements and standardization, based upon a sound scientific basis, of the overall treatment of these patients is crucial and at the core of the psychiatric professional competencies. Indeed, treatment interventions for these patients are increasingly looked upon critically from many angles, i.e. mental health professionals, consumers and their families, and the public opinion. First, although high quality guidelines and systematic reviews are available {NICE, 2015 #102;Bak, 2011 #24;Huf, 2016 #159;Kishi, 2015 #79; Khokhar, 2016 #160;Ostinelli, 2017 #158}, there remains a great diversity within day-to-day practices between clinical centres, medical speciaity (emergency physiciansversus psychiatrists), regions and countries {Bervoets, 2015 #27}. ~~Noteworthy is that preferences of pharmacological interventions differ accordingly to medical specialty treating acute agitation (psychiatrist versus emergency physician) {Bervoets, 2015 #27}.~~

Pharmacological interventions need to be targeted on reaching calmness and cooperativeness within a short timeframe {Canas, 2007 #47}. The purpose of acute pharmacological intervention is reaching calmness and cooperation {Garriga, 2016 #197}. Reaching calmness is meant to restore personal and staff safety, as well as patient-doctor relationship, and offers treatment or diagnostic assessment The standard maximum time of evaluation is 2 hours. However, desirably the outcome measure is reached as soon as possible.

Although r~~R~~ecently several comprehensive reviews have been published, there remain weaknesses in the results that warrant improvement to allow for clinical translations and guidance. First, four ~~, four~~ Cochrane meta-analyses on pharmacological interventions for

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Met opmerkingen [MOU1]: GD Deze paragraaf is me wat onduidelijk waarom hier – je doet een eigen search >> misschien de resulaten afzetten tegen de Cochrane bevindingen in de discussie….

Met opmerkingen [MB2R1]: Ik denk dat het beter is de Cochrane en eventuele belangrijke reviews hier al te noemen, omdat bepaalt waarom we een andere aanpak en een nieuwe search doen. De data van Cochrane zijn uiteraard heel goed, maar hebben ook beperkingen. Het aantal studies is bijna altijd 1, aantal subjecten is weinig. En daar bouwen we dan ons beleid op? Plus hun strategie is om 1 middel te vergelijken met de rest. Aslof dat dan echt iets zegt over de middelen die niet direct met elkaar worden vergeleken?

rapid tranquillisation have been published {Belgamwar, 2005 #164;Huf, 2016 #159;Khokhar, 2016 #160;Ostinelli, 2017 #158}. The Cochrane on Olanzapine is outdated {Belgamwar, 2005 #164}. Therefore, a more recent review is added {Kishi, 2015 #79}. Table S1 (Suplementary material) presents an overview of the most common use medications assessed in those meta-analyses. The general results are that haloperidol is more effective than placebo, whereas effects of haloperidol are similar as lorazepam and droperidol. Haloperidol plus midazolam, haloperidol plus lorazepam and haloperidol plus promethazine are more effective than haloperidol alone. Olanzapine is more effective than placebo and lorazepam. Comparison of haloperidol and olanzapine is are comparable in effectivity. Olanzapine is more less as effective as haloperidol plus promethazine and droperidol (see table 1).

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Table 1 about here >> in supplementary material ??

Overview of meta-analyses comparing 1 medicine with other pharmacological interventions

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~~The~~ However, several problems with these (Cochrane) meta-analyses limit their interpretation. First, in these meta-analyses ~~is that~~ one medication is compared with several other prescriptions and effectsizes are calculated. The available Cochrane meta-analyses and the of Kishi {Kishi, 2015 #79} are methological very sound. As a result most outcome measures are based on 1 study that meets the inclusion criteria. The Cochrane reviews allow for comparison for one drug with various others. This does not clarify differences between those other drugs. ~~This strategy only offers data on those drugs that are directly studied in a RCT's.~~ ~~Also~~ Next, the number of inlcuded studies is very small, which questions the generability. Finally, some questions remain; i.e. p~~P~~eculiar is that the effectsizes slightly differ between the meta-analyses, while based on the same RCT's. Haloperidol versus haloperidol plus promethazine has an effectsize of 0.76 (0.39 – 1.47) reaching calmness after 2 hour {Ostinelli, 2017 #158}. Whereas in the other study by Huf the effectsize is 0,55 (0.32 – 1.23) for the same comparison {Huf, 2016 #159}.

The objective of ~~this~~ the current paper is to systematically summarize the current state of the art on the use of pharmacological interventions in the management of agitated beaviour. The main outcome is change in agitated behaviour as assessed with various validated scales. This strategy allows for a more direct comparison between various pharmacological interventions in reaching calmness, with comparing differences in raw effects on reaching calmness. First, the present status of pharmacological rapid tranquillization (RT) is reviewed and discussed. A systemic review and meta-analyis measuring the level of change on sclae used for assessment of agitated behanviour are conducted. Second, pharmacological intervention strategies for reaching calmness in children and adolescents are discussed separately. Third, a systematic review of the number and severity of adverse effects of the various medications to evaluate

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Met opmerkingen [MB3R1]: Geert vind jij di took onduidelijk. Met Cochrane wordt 1 middel vergelijken met meerder andere middelen. Dat zegt niets over het verschillen in effectiviteit tussen die 'andere' middelen. Ik weet nie hoe ik nog anders moet opschrijven. Jij een idee? Graag dan neerschrijven.

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Met opmerkingen [MDR4]: Ik vind dat je dit niet zo open kan laten. Dan moet je eigenlijk de oorspronkelijke artikelen er even bij pakken. Heeft de ene meta de gecorrigeerde en de andere de ongecorrigeerde resultaten gebruikt ofzo?

Met opmerkingen [MB5R4]: Ga ik uitzoeken waarom dit verschil

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Met opmerkingen [JDF6]: Nog onduidelijk waarin juist verschillend van bv. Cochrane papers.

Met opmerkingen [JDF7]: Andere aanpak t.o.v. Cochrane reviews/meta-analyses zouden we nog scherper moeten kunnen stellen?

Met opmerkingen [MB8R7]: Alininea hierboven iets aangepast. Geert vind jij dit duidelijker zo?

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safety aspects of the medications used for rapid tranquilisation. Finally, all findings will be summarized in recommendations for clinical use and future research projects.

Method

Inclusion criteria and study evaluation

The aim of the search was to identify randomised controled trials where subjects were randomised into intervention groups classified per medication to treat acute agitation and aggression.

The inclusion criteria were:

1. Agitation or aggression
2. Psychiatric disorder or intoxication
3. Rapid tranquilisation or pharmacological intervention
4. Randomised control trial, controlled clinical trial, clinical trial or Phase IV clinical trial with adequate control group.
5. Raw follow-up data of period of 2 hours.
6. End date December 31st 2017

Patients with a delirium were excluded from the study, as these patients have a clear organic origin and good protocols exist. Childeren or adolescents under 18 years of age were searched seperatly with the same search team but age limit < 18 years. Generally, these patients are excluded from most studies. Data needed to be presented with raw outcome variables of the scale used per timeframe. Studies that only report effect sizes, only indicated statitiscal significant difference by mentioning p-values or effectsizes without raw data, were excluded. The focus of the study is to explore the degree of change after an intervention with a certain medication. The studies presenting only effect sizes or p-values authors were contacted to receive raw data

Exclusion criteria were:

1. Trials only presenting data of more than 2 hours.
2. Presenting only effect sizes or p-values as outcome variable.

Outcome scales

The identified outcome was change on several general accepted psychometrics; PANNS-EC (Positive and Negative Symptom Scale – Excitement Components, also called the PEC) {Kay, 1987 #157}, ACES (Agitation-Calmness Evaluation Scale; a scale developed by Eli-Lilly pharmaceuticals) and the OASS (Overt Agitation Severity Scale) {Baldaca, 2011 #25}, mean minutes of reaching calmness and repeated medication within two hours.

PANSS-EC: A clincal scale to assess the agitation level in patients. PANSS-EC is a subscore of thensists of 5 items derived from the PANSS {Kay, 1987 #157} and that are associated with agitation: poor inpuls control, tension, hostility, uncooperativeness and excitement. The PANSS-EC has become accepted as the scale for assessing agitation {Leucht, 2005 #189}. Validity and reliability have been demonstrated to be comparable with a strong correlation with the CGI and ACES in agitated patients {Montoya, 2011 #101}. The PANSS-EC and CGI are linearly related with avarge increase of 3.4 point ($p<0.001$) and linearly inversely related with ACES of 5.5 points ($P<0.001$). Crohnbach's alpha was 0.86 {Montoya, 2011 #101}.

ACES: The ACES consistes of a single item that rates overall agitation and sedation. It has a 9-point Likert scale: 1 – marked agitation, 2 – moderate agitation, 3 – mild agitation, 4 – normal behaviour, 5 – mild calmness, 6 – moderate calmness, 7 – marked calmness, 8 – deep sleep, 9 – unarousable. This scale has convergent validity and reliabiality compared with PANSS-EC {Battaglia, 2003 #190; Meehan, 2002 #35; Montoya, 2011 #101}. Spearman colrelation with PANNS-EC showed correlaytion coefficients of 0.73 – 0.8. The Crohnbach'

alpha varied from 0.86 (at admission) till 0.9 (at discharge) of patients {Montoya, 2011 #101}

OASS: The OASS contains 47 observable characteristics of agiation, which are subcategorised into 12 behaviourally related units. Each subcategory is scored with likert-scale of 0 - no symptoms, 1- indicating mild symptoms to 4 - indicating very severe symptoms. The OASS exclusively rates observable manifastations of agitation. Iterrater reliablity is 0.97 (at 15minutes) and 0.91 after 1 hour, whereas validity 0.81 compared with PAS (Pittsburg Agiation Scale {Rosen, 1994 #245}) suggesting reasonble reliablity and validity{Yudofsky, 1997 #244}.

Quality assessment

Quality assessment was based on the items given in the MOOSE checklist, which summarises recommendations of an expert panel for reporting meta-analyses and systematic reviews of observational studies {Stroup, 2000 #183}. Methodological issues evalualted with the checklist were presence of a clearly focussed study question, an appopriate study type, an adequate recruitement of patients and controls, an unbiased measurement of outcomes, the identification of an statistical control of important confouding factors, the completeness of follow-up and the precesion of estimates.

All paper were reviewed by independent researchers (MB and EB), who studied the papers closely on methodology and outcome measure based on the MOOSE checklist criteria. In case of doubt papers were discussed with IW and concensus reached. Additionally JdF checked the completeness of the search.

Data sources and search strategy

A systematic search was performed in Pubmed and Embase search libraries. The search terms in Pubmed were: ((((((((((("Psychomotor Agitation"[Mesh]) OR Psychomotor Agitation) OR Agitation) OR Acute agitation)) AND ((("Drug Therapy"[Mesh]) OR Drug Therapy) OR Pharmacological treatment)) AND ((((("Mental Disorders"[Mesh]) OR Mental Disorders) OR psychiatric disorders) OR intoxication)) AND ((Therapy/Broad[filter]) AND (acute agitation AND mental disorder))) NOT (("Review"[Publication Type]) OR Review)) NOT (("Case Reports"[Publication Type]) OR Case Reports)) NOT (("Delirium"[Mesh]) OR Delirium)) NOT (("Pain"[Mesh]) OR Pain) Filters: Humans; Adult: 19+ years.

The search in EMBASE was: (((Acute agitation and lorazepam) or (Acute agitation and midazolam) or (Acute agitation and haloperidol) or (Acute agitation and olanzapine) or (Acute agitation and droperidol) or (Acute agitation and loxapine) or (Acute agitation and quetiapine) or (Acute agitation and aripiprazole) or (Acute agitation and ziprasidone) or (Acute agitation and lurasidone) or (Acute agitation and levopromazine) or (Acute agitation and risperidone)) not Review not Case reports not Delirium not Pain).

First authors were contacted in case of missing or ambiguous information, or in case of only presenting p-values or only effect sizes. In case papers were not in the library of Maastricht University, first authors were also contacted for the requested article.

Data extraction

Per medicine baseline data as number of patients, age, mean dose in mg and route (oral, inhalation, intramuscular or intravenous administration) and diagnosis are noted in the data base. Per medicine baseline data of PANSS-EC, CGI and ACES are noted. Per medicine and per scale (PANNS-EC, ACES, CGI and OASS) follow-up data are extracted at the follow-up times of 15-20 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes of. The mean duration of becoming calm in minutes is noted per medication. The percentage of patients

reaching calmness in 2 hours. The percentage of patients that needed repeated medications within 2 hours per medicine. Per medicine the reported percentage of adverse effects as noted in the papers.

Outcomes

In the systematic review descriptve data per medicine and paper are noted of dose number of patients, diagnosis, administration route, raw data of the psychometric scales (for the consecutive time intervals at follow-up), recall of a doctor within 2 hours and the percentage of the adverse effects at hours noted.

The meta-analyse adresses the changes on PANSS-EC, CGI and ACES at 2 hours follow-up

Statistical analyses

All analyses were performed using Stata {Statacorp, 2012 #242}. In order to examine the outcomes per antipsychotic for each scale (PANSS-EC, ACES and CGI), the Stata command *metan* {Bradburn, 2009 #241} generated forest plots including pooled estimates (absolute changes) with their corresponding 95% confidence interval (95% CI). This same procedure was performed for the rates, but because of the transformation of the rates before analyses, the R-program was used to make forest plots of the back-transformed results {R-Core-Team, 2013 #243}.

The computation of summary effects was carried out under the random-effects model, in which Tau was estimated using the DerSimonian-Laird method. Heterogeneity analyses were carried out using the chi-square, I-square, and Tau-square statistics. Tau-square estimates the total amount of variability (heterogeneity) among the effect sizes, but does not differentiate between sources. Heterogeneity may be due to random or systematic differences between the

estimated effect sizes. I-square estimates the proportion of the total variability in the effect size estimates that is due to heterogeneity among the true effects.

Results

The Pubmed search yielded 167 citations. The Embase search yielded 58 citations. Using backward citation tracking resulted in 15 extra studies. After removing duplicates between Pubmed and Embase 212 studies remained. These 212 papers were screened on title and abstract. Ninety-eight papers that did not meet the inclusion criteria and were excluded. This left 114 articles eligible for full screening of the paper. This full screening resulted in a rejection of 61 papers because these papers did not study rapid tranquillisation after all, presented only data only beyond the 2 hours' time period, appeared to be a review paper, a case report only, no data per medication but only medication groups, only report of effect size no raw data on PANNS-EC, ACES or CGI (see appendix: all excluded papers and reason of exclusion). This resulted in 61 papers that entered qualitative assessment. Seven papers met all inclusion criteria and qualitative data, but presented no raw data and contacting authors did not result in retrieving these data. Ultimately 54 papers were used for data extraction (see figure 1).

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Figure 1 about here. Prisma flow diagram

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In total of seventeen drugs or combinations of drugs RCT were included. These RCT comprise 8829 subjects. In total 5 papers have data on lorazepam with 390 subject, 4 papers on midazolam (n= 273), 15 papers on haloperidol with 1176 subjects, 7 papers with data on the combination of haloperidol plus promethazine (n= 465), 4 papers on the combination of

haloperidol plus lorazepam (n= 149) and 2 papers about the combination of haloperidol plus midazolam (n-=55). In total 7 papers have data about droperidol (n=570) and 3 papers are about the droperidol plus midazolam (n=159). For loxapine 4 papers (n=558) are extracted of which 3 have 2 different dosages. Two studies have included levopromazine (n=62). Of the second-generation antipsychotics olanzapine is the most studied medicine with 19 papers (n=2498). Aripiprazole is studied in 8 RCT's (n=1065). For risperidone 4 papers (n=137) are isolated, with additionally 3 papers on the combination of risperidone and lorazepam (n=113) and 1 paper with risperidone and clonazepam (n=104). On ziprasidone 4 papers (n=359) are included. Finally, in 10 papers data are available on placebo (n=696).

Primary outcome reduction of agitated behaviour, main outcomes of systematic review

Lorazepam has a reduction of 7 points on the PANNS-EC, with haloperidol the reduction is between 7 and 8 points, the reduction with haloperidol plus promethazine is assessed in only 1 study but shows a reduction of 15 point after 2 hours. The combination of haloperidol plus lorazepam shows a reduction of 8 to 10 points after 2 hours. The combination of haloperidol with midazolam results in a reduction of 15 points after 90 minutes (only 1 study). There are no data available with droperidol or droperidol plus midazolam. Levopromazine is used in two studies in a more elderly population, resulting in a decrease of 5 – 6 points. The reduction with aripiprazole is between 7 and 8 points with one exception where only 3 points reduction is reported {De Filippis, 2013 #194}. Olanzapine shows a decrease around 7 and 10 points on the PANNS-EC. Risperidone shows a reduction of PANNS-EC in 2 hours of 7 – 8 points in two papers {Hatta, 2008 #62;Lim, 2010 #83}, and one study reports a reduction of 14 points after two hours {Walther, 2014 #147}. Addition of lorazepam of clonazepam to risperidone does not result in extra decrease on the PANSS-EC score. Ziprasidone shows a reduction of PANS-EC score of 3 – 15. Loxapine which is used through nasal inhalation

results in 9 – 11 points reduction. Finally, placebo also shows some reduction after two hours on PANSS-EC of 2 – 6 points.

Primary outcome decreasing agitated behaviour, meta-analytic findings

Not all RCT's, discussed in the systematic overview as presented in table 2, could be used for meta-analysis. Only studies that showed baseline PANSS-EC, ACES or CGI data and standard deviation plus end-point data with standard deviation were fit for use in this meta-analysis. Unfortunately, in a proportion of the studies end-point standard deviation with raw data were not presented. Contacting corresponding author was not always possible as email address were out of order. Of those authors contacted no additional data were obtained. So, for PANN-EC, ACES and CGI changes, meta-analysis was only possible for limited number of medications and RCT's (see figure 2, 3 & 4, supplement tables S1 – S3 and supplement figures S2, S3 and S4)

Per medication the weighted mean differences at 2 hours' follow-up are calculated. The changes after 2 hours' follow-up are presented in figure 2. For more detailed information see table S2 (PANNS_EC meta-analyses data), table S3 (ACES meta-analyses data) and table S4 (CGI meta-analyses data).

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figure 2 about here

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The CGI and ACES indicate the level of agitation. The level of change is associated with the level of agitation diminution. The figures 3 and 4 show the results of changes at 2 hours' follow-up with ACES respectively CGI.).

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Figure 3 and 4 about here

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Percentage of patients reaching calmness

With lorazepam about 78% reaches calmness with in 15 – 20 minutes. After 2 hours, the percentage of patients that is calm with lorazepam is around 63 – 88%. With midazolam 55 – 89% reaches calmness with 15 – 20 minutes. Only 1 study reports that 95% reaches calmness after 120 minutes {Huf, 2003 #68}. The results of the number of patients that reaches calmness with haloperidol is inconsistent with 1 study reporting 92% reaching calmness in 15-20 minutes {Calver, 2015 #39} but another study reports 55% {Huf, 2007 #52}, whereas after 120 minutes 60 – 89% reaches calmness after 120 minutes {Andrezina, 2006 #22;Huf, 2007 #52;Wright, 2001 #152}. The combination of haloperidol plus promethazine has a strong effect in the short term of around 67 – 91% reaching calmness within 15-20 minutes. After two hours, this combination results in about 89 – 97% of patients who reaches calmness. Studies with droperidol only report short term outcome data. About 53 – 92% reaches calmness with 15-20 minutes and one study report 96% of the patients has reached calmness after 60 minutes {Richards, 1998 #133}. Only one study reports data on the combination of droperidol plus midazolam through IV administration, where 89% reaches calmness with 15-20 minutes and 98% after 60% minutes. Aripiprazole results in calmness in 60 – 84% of the patients after 120 minutes. Olanzapine results in 73 – 91% of the patients in calmness after 2 hours. One study reports that 66% of the patients reaches calmness after 15-20 minutes by IV administration {Taylor, 2017 #98}. With ziprasidone 29 – 90% reached calmness after 2 hours. Reaching calmness varied from 66 – 74% within 2 hours in patients who received loxapine. Placebo results in 28 – 44% of the patients in calmness after 2 hours.

No data available for haloperidol plus lorazepam, haloperidol plus midazolam, risperidone, risperidone plus lorazepam or risperidone plus clonazepam and levopromazine.

Mean duration reaching calmness

Some studies reported the mean time in minutes that patients reached calmness. For lorazepam 1 study reported that calmness is reached after 48 minutes. Midazolam shows a mean time of 20 – 24 minutes. With haloperidol, the mean duration of reaching calmness is only given in 1 study and is 30 minutes {Calver, 2013 #57}. The combination of haloperidol plus promethazine is results in calmness at 20 – 30 minutes. Adding lorazepam to haloperidol results in mean time of 44 minutes {Currier, 2001 #192}. The combination of haloperidol plus midazolam is quite fast and is reaches calmness in about 10 minutes {Calver, 2013 #57}. The mean time with droperidol is about 8 – 25 minutes. Adding midazolam results in reaching calmness in 25 minutes, although Intravenous (IV) administration results in reaching calmness within 5 minutes. Olanzapine results in calmness with 11 – 30 minutes, be noted that the 11 minutes' period is by IV administration. Risperidone plus lorazepam resulted in reaching calmness within 43 minutes. Loxapine intranasal administration results in reaching calmness in about 57 – 67 minutes. No data are available for aripiprazole, risperidone, levopromazine, ziprasidone or placebo.

Doctor called back – repeated medication

The number of cases a doctor is called back for re-evaluation and / or the need for another medication administration within two hours is varies highly per study. For lorazepam, the number time a doctor is called back is around 18% in 1 study. The number of repeated medication is not assessed. The frequency of reiterated medication is with midazolam is around 62%. For haloperidol, the number of repeated medication is between 8 and 55% of the

cases. The combination of haloperidol plus promethazine reports a frequency of 5 – 19% of the cases that needs medication again with 2 hours. For the combination of haloperidol plus lorazepam 1 study mentions that 30% of the cases are re-medicated within 60 minutes. The number of cases that received repeated medication is 20% with haloperidol plus midazolam. The number of patients that needs additional droperidol within 2 hours is between 5 – 60%. Adding midazolam to droperidol leads to repeat medication in 28 – 41% of the patients. The number of repeated medication with aripiprazole is between 31 – 54% of the cases. For olanzapine, this number is about 4– 16%. One study reports that in 61% of the cases repeated medication is needed {Taylor, 2017 #98}. In 33% (and 43% after 4 hours) of the cases who received olanzapine the doctor is called back (within 4 hours). The number of cases that need repeated medication after risperidone varies from 9 – 25%. After use of ziprasidone only 1 study reported the number of repeated medication in 35% of the cases {Mantovani, 2013 #87}. For placebo, the number of repeated medication is 30 – 78%. No data reported on risperidone plus lorazepam, risperidone plus clonazepam, levopromazine, loxapine.

Adverse effects

Description of the unwanted effects related to the medications varies quite strongly. Some medication is related with oversedation of around 10% with lorazepam, 0 – 36% with haloperidol, 3% with the combination of haloperidol plus promethazine, between 13 and 70% with the combination of haloperidol plus lorazepam and 40% with the combination of haloperidol plus midazolam. Droperidol results in 1% of the cases in oversedation. There are no data reported of oversedation with droperidol plus midazolam. With aripiprazole oversedation is reported between 4 – 9%. Olanzapine results in 3 – 13% of the cases to oversedation, which is the same for risperidone with 13% or risperidone plus lorazepam with also 13% leading to oversedation. Levopromazine leads in 8% of the cases to oversedation.

After use of ziprasidone the percentage of oversedation is 10%. In loxapine the report of oversedation is between 11 – 13%. Even placebo results in some cases of oversedation of around 2 – 10%.

Movement disorders

The reported number of patients with movement disorders, more specific EPS, dystonia and akathisia, is absent with lorazepam, with only 1 study that report data on akathisia which is in 2% of the cases. For midazolam, no reports of movement disorders are given. Haloperidol shows increased number of patients with movement disorders, EPS in 6 – 55% of the cases, reports of acute dystonia is between 0 – 17% and akathisia is reported in 8 – 46%. The reports of movement disorders with haloperidol plus promethazine varies highly; percentages of EPS are between 0 – 74%, acute dystonia absent and akathisia is not reported. Haloperidol plus lorazepam shows some reports of EPS of 5%, acute dystonia of 3% and haloperidol plus midazolam has a percentage of acute dystonia 10% and EPS of 44%. Droperidol is mild in movement disorders with no reports of EPS, acute dystonia in 0 – 1% and no reports of akathisia. Adding midazolam to droperidol does not change these outcomes. For aripiprazole, there is one study that reports EPS (2%), acute dystonia is about 1 – 2% and akathisia is around 3 %. Olanzapine results in low rates of movement disorders; EPS in 0 – 5%, acute dystonia in 0 – 4% and akathisia in 0 – 2% of the cases. For risperidone, the rates are modest EPS 6 – 8% and acute dystonia 2%. Adding lorazepam or clonazepam does not change the percentages of EPS or acute dystonia. Levopromazine does not result in EPS or acute dystonia but akathisia is reported in 8% of the cases. Ziprasidone is does not result in acute dystonia and EPS, except for 1 study that reports EPS in 52% of the cases {Mantovani, 2013 #87}. For loxapine intranasal administration there are no reports of movement disorders.

Finally, placebo results in some movement disorders EPS in 2 – 7%, but no reports of acute dystonia of akathisia.

Cardiovascular adverse effects

Antipsychotics increase the risk of the QT-elongation (> 500ms) resulting in arrhythmias. The percentage of cases with QT-elongation is absent in lorazepam except for 1 study that report that QT-elongation is present in 7% of the cases {Zimbroff, 2007 #156}. Midazolam results in between 3 – 7% of the cases in QT-elongation. Haloperidol shows QT-elongation in 0 – 6% of the cases. The combination of haloperidol plus promethazine or plus lorazepam or plus midazolam has no reports of QT-elongation. The percentage of reported cases with droperidol is between 1 – 6%. Studies addressing QT-time elongation in droperidol are presented in table 3. Adding midazolam to droperidol results in a percentage of 1 – 14%. Aripiprazole results in 0 – 6% of the cases having QT-elongation. For olanzapine, the percentages vary between 0 and 3%. There are no reports for risperidone. Levopromazine and ziprasidone both do not result in QT-elongation. There are no data for loxapine. Placebo does not result in QT-elongation except in 2 studies with 5% and 8% of the cases showing QT-elongation {Tran-Johnson, 2007 #142;Zimbroff, 2007 #156}.

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Table 3 about here

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Hypotension / hypertension

Hypertension is mentioned with lorazepam in 3% of the cases. With midazolam, some reports of hypotension are mentioned in 5% of the cases. For haloperidol, hypotension is reported in

0 – 17%, as well as hypertension in 7% of the cases. Hypotension is reported with haloperidol plus promethazine in 10% of the cases. With regard to the combination of haloperidol plus lorazepam only one study reports hypotension in 3% of the cases. Hypotension is reported in 10% of the patients after administration of haloperidol plus midazolam. For droperidol, the percentage of hypotension is 0 – 4%. Adding midazolam to droperidol seems to increase the percentage of cases with hypotension up to 41%, although another study reports only 2% of the cases develop hypotension. No blood pressure problems are reported for aripiprazole. Olanzapine results in 0 – 4% of the cases in hypotension, whereas hypertension is reported in 3 – 5% of the cases. There are no reports of blood pressure changes with risperidone, risperidone with lorazepam or with clonazepam. Levopromazine resulted in hypertension in 3 % and hypotension in 16% of the patients. For ziprasidone or loxapine no report of blood pressure changes are presented. Placebo shows in one study hypertension in 2% of the patients.

Hypoventilation

Midazolam increases the rate of saturation problems in those who intoxicated with alcohol. Between 1 and 30% of the cases that are reported that needed ventilation support.

Throat irritations

Loxapine shows some small increase in dysgeusia and throat irritation of respectively 4 – 17% and 1 – 7%.

Discussion

Pharmacological intervention in patients with agitated behaviour is serious event. Whether this is at an emergency department or in ward of a psychiatric hospital. This calls for solid studies. This study assembles data of several pharmacological interventions in decreasing the level of agitated behaviour in a systematic review and also computing a meta-analysis of weighted mean reduction of agitated behaviour per medicine. The primary outcome is the level of change on PANNS-EC or ACES or CGI or the more subjective measures the percentage patients being calm after 2 hours and the duration of reaching calmness or noted in a systematic descriptive review. Second, a meta-analysis has been computed only on those data that presents baseline data of severity and data after 2 hours or data on level of change assessed by the psychometric scales. This results in only a small proportion of drugs eligible for a meta-analytic approach. Calculating changes with the PANNS-EC shows to be only possible for 12 drugs, ACES 7 drugs and CGI 4 drugs. Changes assessed with OASS can not be analyses with a meta-analytic approach. The systematic review further shows an overview of another outcome measure; the number of times doctor is called back within 2 hours. Finally, the review notes the percentages of adverse effects, so the safety of the specific drug can be judged.

Despite a specific search no studies have been found on rapid tranquillisation in children and adolescents that fulfills the inclusion criteria. Of interest is the number of studies about the old age patients which is also limited in number. Only 3 studies meet the inclusion criteria {Meehan, 2001 #200;Suzuki, 2013 #139;Suzuki, 2014 #141}. This is most peculiar as agitated behaviour in the old ages might be a problem but also dosage issues and adverse effects, should be studied

The outcomes in the systematic review suggests that haloperidol plus promethazine is strongest in decreasing the agitation measured with PANSS-EC and CGI. The number of patients reaching calmness in 2 hours-period is high (between 89 – 97%) and the side-affects

profile is relative safe. The meta-analyses comparing the changes on the PANSS-EC show that also haloperidol shows the strongest in comparison with the other drug change after 2 hours. Although, we cannot whether this is a statistical significant difference as we could not control for this. Additionally, only 1 study was apparent in the meta-analysis on haloperidol plus promethazine. However, the finding is in accordance with the Cochrane reviews {Huf, 2016 #159;Ostinelli, 2017 #158} where the combination of haloperidol plus promethazine shows strong effects on decrease of agitated behaviour compared to other drugs. Olanzapine was the most studied drug and also showed good improvements on PANNS-EC, ACES and CGI, no only based upon data in the review but also the meta-analysis showed that olanzapine was in top region of improving agitated behaviour. Mean time in reaching calmness is also quite fast between 15 – 30 minutes with a good proportion of patients reaching calmness in 2 hours (73 – 91%).

Aripiprazole shows a good effect on decreasing the level of agitation and this medication is also safe. Rapid tranquillisation studies with aripiprazole are mainly performed in patients with mania. In the meta-analysis aripiprazole shows comparable changes with olanzapine on the various scales, which makes a pharmacological intervention with aripiprazole suitable in patients with mania. Haloperidol + lorazepam is often prescribed in daily practice. The number of studies is limited and all 4 studies present different outcome effects. Data reaching calmness is mediocre compared to the previous mentioned medications. The reported number of side effects is relative high, especially the acute dystonia and other movement disorders are more severe. The Cochrane review advises not to use haloperidol or haloperidol + lorazepam because of these adverse effects {Huf, 2016 #159;Ostinelli, 2017 #158}. The combination of haloperidol plus midazolam is only presented data till 60 or 90 minutes. One review shows comparable change on PANNS-EC as with haloperidol + promethazine. This combination reaches calmness fast, although it seems that calmness is not sustainable over

time and the side-effect profile shows high number of adverse effects like higher levels of acute dystonia.

Loxapine is interesting as the route of administration is nasal. The results show that the effects rather weak in reaching calmness.

Midazolam and droperidol are both rather effective, but unfortunately no studies are available that show PANSS-EC or ACES data. These medications reach calmness very fast, even in minutes if administered IV or IM within. However, the sustainability of the effect is weak. IM administration of midazolam needs quite often repeated administration. The side effect profile shows the possibility of reaching oversedation and ventilation problems. Therefore, midazolam is more suitable for use at ED, where safety measures are available, but where fast interventions are needed as well. Droperidol administered intravenous results in calmness very fast, and remains reasonably fast via the intramuscular route. Droperidol has been abandoned for some years because of QT-time prolongation. However, recent studies have shown that the prevalence of exceeding unsafe QT-times is rare and not more than with other antipsychotics (see also table 3) {Khokhar, 2016 #160}.

Risperidone showed a strong effect on the PANNS-EC. However, this result is based on 1 study {Walther, 2014 #147}. Two other studies show a more modest effect of 7 points decrease on the PANSS-EC {Hatta, 2008 #62;Lim, 2010 #83}. Also, risperidone plus lorazepam or plus clonazepam do not increase the outcome effect reaching calmness substantially (see table 2).

Studies with droperidol only reported data on time to reach calmness and percentages on number of patients being calm at the shorter time intervals then 2 hours. Here, the effects are reasonable compared to other drugs. The question is whether these effects last at 2 hours. At least the effects of reduction of agitated behaviour seems to quite fast, which is welcomed in daily practice.

The reported adverse effects are generally mild for haloperidol + promethazine, olanzapine, aripiprazole or droperidol. So, being the more extensive studied drugs or showing the more robust changes toward improvement of agitated behaviour, the drug also show the least adverse effects. The problem of QT-elongation in droperidol appears a rather smaller problem and not more prevalent compared to other antipsychotics.

The route of administration matters in duration of reaching calmness. In general, intravenous (IV) administration is much faster that intramuscular (IM) administration, whereas oral medication is the slowest in reducing agitated behaviour. Most studies chose the rout of IM. The number of IV or oral administration is limited. Only two studies use IV administration {Richards, 1998 #133;Taylor, 2017 #98}, which shows a very quick response. Given the increased risk of respiratory adverse effects and the IV administration this method of administration is only available for ED, as specific monitoring of physical parameters is required. Here midazolam or droperidol plus midazolam are good options as they act sedative within minutes. The oral route of taking medication is studied in 6 studies, all involving risperidone {Hatta, 2008 #62;Lim, 2010 #83;Yildiz, 2003 #193;Currier, 2004 #58;Currier, 2001 #192;Fang, 2012 #205}. In clinical practice taking medication is often preferred as it adds to the feeling of remaining control to some extent {Bak, 2011 #24;Rocca, 2006 #134}. Being in control might help in containing agitated behaviour

Despite guidelines it seems that most psychiatrist and physicians at emergency departments or acute psychiatric wards prescribe a wide range of medications for pharmaceutical interventions in agitated or aggressive behaviour {Bervoets, 2015 #27}. Guidelines advocate the use of second-generation antipsychotics {NICE, 2015 #102}, but despite these guidelines doctors preferably use the older antipsychotics or benzodiazepines {Bervoets, 2015 #27;Wilson, 2014 #151}. Most guidelines or review are only descriptive and offer an overview of the opportunities of pharmacological interventions {Garriga, 2016

#197;Hockenhull, 2012 #188;Jibson, 2007 #71;Pratt, 2008 #112;Rocca, 2006 #134} The general criticism is that the quality of the studies on rapid tranquillisation is poor. Here, the number of studies per medicine and the number of patients included is relatively small, given the impact of rapid tranquillisation. Rapid tranquillisation is performed in acute situations, with very disturbing behaviour based upon often unknown medical diagnose or background knowledge of the patient. Apparently, clinicians rely heavily on clinical experience based evidence rather than thorough clinical studies. This problem is also seen in the number of studies that is included in the Cochrane surveys {Huf, 2016 #159;Khokhar, 2016 #160;Ostinelli, 2017 #158;Zaman, 2017 #240}. These Cochrane studies indicate that most RCT's cannot enter the review because of methodological shortcomings. The result is that almost all effect measurements in the Cochrane reviews end up with 1 RCT per drug. Although, the Cochrane reviews are very strict on methodological issues, one may argue that for the acute pharmacological intervention meeting the strict Cochrane criteria are presumably very difficult to meet for this type of research. This makes the level of evidence based on the Cochrane reviews rather low.

In the daily practice of meeting agitated behaviour leaves the doctor more or less blind-folded in addressing this behaviour. Daily practice interventions should not be ruled by experience based evidence, but as much as possible being evidence based. In this study, the inclusion criteria are practice based, albeit the RCT's need to meet minimal methodological conditions as described in the method section. The systematic review shows that midazolam reaches calmness very fast if administered IV, and that haloperidol + promathazine and olanzapine are most effective in reaching calmness. Also, droperidol has good properties in decreasing the level of agitated behaviour, although the this is only based on the data in systematic review. The RCT's on droperidol and midazolam all use a shorter time period of assessment outcome. This makes more difficult for direct comparison. In patients with mania,

aripiprazole has good results in decreasing agitated behaviour and is safe. Haloperidol and especially haloperidol plus lorazepam are often used in daily practise. But in agreement with the Cochrane reviews, the primary effect of reducing agitated behaviour is not on all scales good enough, but the risk of adverse effects more specific acute dystonia and parkinsonism is too high. Therefore, is not recommended to use haloperidol or haloperidol plus lorazepam for agitated behaviour

Limitations

Some various limitations must be considered in interpreting the outcome. The number of studies and subjects is limited. This is complicated by the use of different psychometrics. Although the scale are most likely comparable the results are not completely comparative. If studies would report at least a uniform set of data, like PANNS-EC reduction, number of patients that reaches calmness, mean score of reaching calmness at 2 hours.

The meta-analytic approach needs data that are clear and up to a certain standard. A fair number of studies did not provide the complete data, more specific raw data of changes including standard deviation. Contacting the authors did not result in new viable information.

The studies also report primary outcome and adverse effects at different time points. Assessment of speed of onset is important. However, time points vary between studies. Also, it the assessment of adverse effects varies from end of the study at 2 hours or the occurrence of adverse effects within 24 hours. Studies on midazolam and droperidol defined the end-point at 60 minutes. This hampers the comparability at 2 hours. May be the medications show a less numbers of patients being calm at 2 hours.

Despite the poor evidence for some medications this systematic review and meta-analysis does not allow for direct comparison between the various drugs, as this is not formally tested.

The number of studies of the elderly agitated patients or children and adolescents are sparse or absent. Only 4 studies were isolated studying pharmacological interventions in agitated older patients. Given that the world population grows older and in the western countries dementia is definitely a growing problem with increased risks for agitation in the elderly, further research is needed definitely. The pharmacological management of agitated behaviour in adolescents is even more understudied. Young patients are with developing brains are vulnerable.

Conclusions and recommendations

Agitated or aggressive patients impedes the diagnostic and treatment process. A good enough contact and collaboration are general conditional in the diagnostic process. Agitated behaviour may originate from various medical causes or intoxications. Before the conclusion that the agitated behaviour is explained by a psychiatric illness, a medical illness needs to be ruled out. Consider non-pharmacological interventions before a pharmacological intervention as rapid tranquillisation is applied, to reach calmness and contact may be restored. Based on previous work the observation period of effect is set at 2 hours maximum. Depending on the context one may judge that a patient need to become calm in a shorter period of time, as non-pharmacological interventions are not mastered by trained personnel or in emergency departments in General Hospitals a more rapid onset of sedation is required, for safety reasons in a more fragile environment. At an ED medical safety equipment is at hand. This might offer possibilities prescribing midazolam, droperidol or droperidol plus midazolam IV or IM. However, choosing haloperidol plus promethazine or olanzapine might be first choice drugs as well.

At a psychiatric admission ward the possibilities to deal with agitated behanviour are more extensive, because of building facilities and presence of trained staff. Haloperidol +

promethazine is quite fast, does not need re-medication and is a safe combination. Olanzapine is most extensive studied for this indication and almost equally in reducing agitated behaviour. A fair number of patients reaches calmness in 2 hours and the level of adverse effects is acceptable. The change of re-medication is slim. In case of diagnostic insecurity or the probability of suspected contra-indications, lorazepam is a safe alternative.

Future directions

Elaborate comparison of effectivity and safety between drugs, data presentation need detailed and standardised information. We propose that at least PANNS-EC and ACES or CGI is used for measuring the primary outcome of decrease of agitation and aggression. Report of start data plus SD and endpoint data plus SD are essential. The primary outcome is at 2 hours, but the rate in which calmness is reach is also important. So, assessment at different time points (15-30-60-90-120 minutes) is also crucial. The number of patients that reached calmness as a fraction of the total study population in 2 hours is another important informative factor. Plus, the mean time of reaching calmness, which is indicative for the time outcome effect is reached adds to the clinical understanding of effect. Last but not least a standardised assessment of adverse effects ensure that most unwanted effects of antipsychotics and benzodiazepines are listed properly. So, assessment of adverse effect by standardized scales in recommended