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Benzodiazepines for Psychosis-Induced Aggression or Agitation

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Background

Acute psychotic illness, especially when associated with agitated or violent behavior, can require urgent pharmacological tranquillization or sedation. In many countries, benzodiazepines (either alone or in combination with antipsychotics) are often used in this situation (1).

Objectives

To examine whether benzodiazepines, alone or in combination with other pharmacological agents, are an effective treatment for psychosis-induced aggression or agitation when compared with placebo, other pharmacological agents (alone or in combination) or non-pharmacological approaches.

Search Methods

We searched the Cochrane Schizophrenia Group's register (January 2012, August 20, 2015 and August 3, 2016), inspected reference lists of included and excluded studies, and contacted authors of relevant studies.

Selection Criteria

We included all randomized controlled trials (RCTs) comparing benzodiazepines alone or in combination (with antipsychotics), vs placebo or antipsychotics alone or in combination (with other antipsychotics, benzodiazepines or antihistamines) for people who were aggressive or agitated due to psychosis.

Data Collection and Analysis

We reliably selected studies, quality assessed them, and extracted data. For binary outcomes, we calculated standard estimates of risk ratio (RR) and their 95% CI using a fixed-effect model. For continuous outcomes, we calculated the mean difference (MD) between groups. If there was heterogeneity, this was explored using a random-effects model. We assessed the risk of bias and created a "Summary of findings" table using GRADE (table 1).

Main Results

Twenty trials including 695 participants are included in this review. The quality of evidence for the main outcomes was low or very low due to the very small sample sizes of included studies and serious risk of bias (randomization, allocation concealment and blinding were not well conducted in the included trials, and 6 out of the 20 trials were supported by pharmaceutical institutes). There was no clear effect for most outcomes.

Benzodiazepines Alone vs Placebo

One trial compared benzodiazepines alone (IM lorazepam) with placebo. There was no difference in the number sedated at 24 hours (very low quality of evidence). However, more people receiving placebo showed no improvement in global state in the medium term (1 to 48 h) (n = 102, 1 RCT, RR 0.62, 95% CI 0.40 to 0.97, very low quality of evidence).

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Table 1. Summary of Findings: Benzodiazepines Compared to Antipsychotics for Psychosis-Induced Aggression or Agitation

Patient or population: people with psychosis-induced aggression or agitation

Settings: hospitals (United States, Canada, Israel, China, Australia)
Intervention: benzodiazepines
Comparison: antipsychotics

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antipsychotics	Benzodiazepines				
Tranquillisation or asleep: sedation - medium term vs haloperidol Number of participants sedated Follow-up: mean 16 h	Low 100 per 1000 Moderate[e] 227 per 1000 High 500 per 1000	 113 per 1000 (83 to 154) 257 per 1000 (189 to 350) 565 per 1000 (415 to 770)	RR 1.13 (0.83 to 1.54)	434 (8 studies)	⊕⊕⊖⊖ Low[a,b]	—
Global state: no improvement - vs haloperidol - medium term As defined in each study Follow-up: 24 h	Low 77 per 1000 Moderate[c] 619 per 1000 High 933 per 1000	 68 per 1000 (55 to 85) 551 per 1000 (439 to 687) 830 per 1000 (662 to 1000)	RR 0.89 (0.71 to 1.11)	188 (5 studies)	⊕⊕⊖⊖ Low[a,b]	—
Global state: no improvement - vs olanzapine - medium term As defined in each study Follow-up: 24 h	192 per 1000	353 per 1000 (203 to 610)	RR 1.84 (1.06 to 3.18)	150 (1 study)	⊕⊖⊖⊖ Very low[a,b,g]	—
Global state: need for additional medication - medium term Number of participants requiring additional medication Follow-up: 24 h	See comment	See comment	Not estimable	216 (2 studies)	⊕⊖⊖⊖ Very low[a,b,d]	High levels of heterogeneity between included studies ($\chi^2 = 16.41$; $I^2 = 94\%$) − data not pooled.[d]

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Table 1. *Continued*

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Antipsychotics	Corresponding risk Benzodiazepines				
Adverse effects/events: extrapyramidal symptoms - vs haloperidol - medium term Number of instances of extrapyramidal symptoms Follow-up: 21 h	Low 0 per 1000 Moderate[f] 186 per 1000 High 500 per 1000	 0 per 1000 (0 to 0) 24 per 1000 (7 to 76) 65 per 1000 (20 to 205)	RR 0.13 (0.04 to 0.41)	233 (6 studies)	⊕⊕⊖⊖ Low[a,b]	—
Satisfaction with treatment: from the perspective of consumer, family and informal care givers or professionals/carers at any point during the acute management stage	See comment	See comment	Not estimable	0 (0)	See comment	No study reported this outcome.
Economic outcomes: cost-effectiveness	See comment	See comment	Not estimable	0 (0)	See comment	No study reported this outcome.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Note: The basis for the "assumed risk" (eg, the median control group risk across studies) is provided in footnotes. The "corresponding risk" (and its 95% CI) is based on the assumed risk in the comparison group and the "relative effect" of the intervention (and its 95% CI). RR, risk ratio.
[a]Risk of bias: "serious"—most trials received funding from a pharmaceutical institute, and there was a potential risk of selection bias.
[b]Imprecision: "serious"—CIs for the best estimate of effect included both "no effect" and appreciable benefit/harm.
[c]Assumed risk: calculated from the included studies—presented 3 risks based on the control group risks—"moderate" risk equates with that of the control group (61.9%).
[d]Inconsistency: "serious"—one study indicated significant favor of antipsychotics, while the other study indicated favor for benzodiazepines (nonsignificant).
[e]Assumed risk: calculated from the included studies—presented 3 risks based on the control group risks—"moderate" risk equates with that of the control group (22.7%).
[f]Assumed risk: calculated from the included studies—presented 3 risks based on the control group risks—"moderate" risk equates with that of the control group (18.6%).
[g]Only one small study reporting data.

Benzodiazepines Alone vs Antipsychotics

Eleven trials compared benzodiazepines with antipsychotics. Compared with haloperidol there was no difference for sedation at 16 hours (n = 434, 8 RCTs, RR 1.13, 95% CI 0.83 to 1.54, low quality of evidence) or improvement (global state) in the medium term (n = 188, 5 RCTs, RR 0.89, 95% CI 0.71 to 1.11, low quality of evidence).

In one small trial, fewer participants improved (global state) in the medium term when receiving lorazepam compared with olanzapine (n = 150, 1 RCT, RR 1.84, 95% CI 1.06 to 3.18, very low quality of evidence).

People receiving benzodiazepines were less likely to experience extrapyramidal effects (EPS) in the medium term compared to people receiving haloperidol (n = 233, 6 RCTs, RR 0.13, 95% CI 0.04 to 0.41, low quality of evidence).

Benzodiazepines Alone vs Combined Antipsychotics/ Antihistamines

When benzodiazepines (lorazepam or midazolam) were compared with combined antipsychotics/antihistamines (haloperidol plus promethazine), there was a higher risk of no improvement (global state) for benzodiazepines alone in the medium term (n = 200, 1 RCT, RR 2.17, 95% CI 1.16 to 4.05, low quality of evidence). However, for sedation in the medium term, the results were unclear: compared with combined antipsychotics/antihistamines, lorazepam led to a lower risk of sedation (n = 200, 1 RCT, RR 0.91, 95% CI 0.84 to 0.98, low quality of evidence); while, midazolam led to a higher risk of sedation (n = 200, 1 RCT, RR 1.13, 95% CI 1.04 to 1.23, low quality of evidence).

Other Combinations

Benzodiazepines (lorazepam or clonazepam) plus antipsychotics (haloperidol or risperidone) vs benzodiazepines alone did not yield any clear differences for global state. When comparing combined benzodiazepines/antipsychotics (a haloperidol combination in all studies) with haloperidol alone, there was no difference in medium-term improvement for global state (n = 185, 4 RCTs, RR 1.17, 95% CI 0.93 to 1.46, low quality of evidence), but sedation was more likely in the short-term for people who received the combination therapy (n = 172, 3 RCTs, RR 1.75, 95% CI 1.14 to 2.67, very low quality of evidence). Only one trial compared combined benzodiazepines/antipsychotics with antipsychotics; however, this study did not report our primary outcomes. One small trial compared combined benzodiazepines/antipsychotics (midazolam and haloperidol) with combined antihistamines/antipsychotics (promethazine and haloperidol). The combined benzodiazepines/antipsychotics group had a higher risk of no improvement (global state) (n = 60, 1 RCT, RR 25.00, 95% CI 1.55 to 403.99, very low quality of evidence) and higher levels of sedation in the medium term (n = 60, 1 RCT, RR 12.00, 95% CI 1.66 to 86.59, very low quality of evidence).

Authors' Conclusions

The small amount of evidence is of poor quality. Most trials were too small to highlight differences. A direct comparison of single agent benzodiazepines vs antipsychotics demonstrated a possible small advantage of antipsychotics. However, caution must be exercised as older antipsychotic agents also had a disadvantage in terms of side effects (EPS). Adding benzodiazepines to other drugs does not seem to confer clear advantage and has the potential for adding unnecessary adverse effects. It would appear that antihistamines would be a better choice of additive agent to antipsychotics than benzodiazepines; however, the quality of evidence was very low. Much more high-quality research is still needed in this area.

Reference

1. Zaman H, Sampson SJ, Beck ALS, et al. Benzodiazepines for psychosis-induced aggression or agitation. *Cochrane Database Syst Rev*. 2017;12:CD003079. doi:10.1002/14651858.CD003079.pub4

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