WHY IS THE MAIN EFFECT OF BENZODIAZEPINES, IN CLINICAL COMPARISON STUDIES OF NEUROLEPTICS ON ACUTE AGITATION, NOT REPORTED AS SUCH? AN OPINION

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Abstract

Object: There is a need for effective and tolerated medication for the sedation of acutely agitated patients in clinical settings. Benzodiazepines and antipsychotics have already been shown to yield comparable effects on acute agitation from 1979. Both antipsychotics and benzodiazepines are used for this purpose, but only the former are handled as main effect medication in recent comparison studies.

Method: We searched for studies comparing the use of different antipsychotics, where information on the concomitant use of benzodiazepines was given explicitly in the core text. Three relevant Cochrane Collaboration Reviews were also scrutinized. The use of benzodiazepines under focus in the present study was, however, not directly searchable. The study is therefore not at all comprehensive, but explorative and illustrative of the clinical use of benzodiazepines for sedation.

Results: Seven single studies from 2002 and onwards were identified reporting the use of variable doses of benzodiazepines. A statistical evaluation of the separate effect of concomitant use of benzodiazepines with the same rigour as with the main comparison drugs could not be found.

Conclusions: The results strongly indicate that newer studies do not handle benzodiazepines given for agitation in the same way as antipsychotics or placebo in comparisons between neuroleptics. Even though the presence of a comparable effect has been known for 25 years. The true results of comparisons may be distorted, and may mislead clinicians treating acutely agitated patients.

Keywords*:* Antipsychotics – Benzodiazepines – Acute Agitation – Emergency Psychiatry

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Introduction

Treatment of agitation in resident psychiatric settings is a challenging task. First generation antipsychotics do not always calm the patient sufficiently for the acute ward to handle them, and panoply of other medications is often added. The clinical frustration of attending physicians or psychiatrists may explain the frequent use of other calming agents, such as the benzodiazepines. When neuroleptics did calm the patient, the level of adverse effects was sometimes high (Chengappa 2004). Studies introducing new neuroleptics addressing this issue may state that the new agent has no sedative effect, which is deemed good for the patient in the long run, and the use of other calming medication is openly recommended. Or, the studies claim that the new neuroleptic has sedative effects, which is also deemed good for the patient, and, henceforth, no other calming medication would be needed. The advent of second-generation antipsychotics has given us both good sedative and sedation-free agents.

Benzodiazepines are already documented as separate effective medication in the treatment of acute agitation in severe mental illness at least since 1979 (Lerner et al. 1979). They compared haloperidol (20-35 mg intravenously) and diazepam (30-40 mg intravenously) in the treatment of psychosis in 40 patients, after two days of drug-free observation. Post-treatment ratings at 4 and 24 hours with the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions Scale (CGI) revealed significant improvement in both groups, but no significant differences between the treatments. Specifically the authors underscore "that high-dose parenteral haloperidol is not specifically effective in the alleviation of psychotic symptoms within the first day of treatment. This lack of specific effectiveness is apparent when… compared with diazepam". Battaglia et al. and Foster et al. compared 2mg lorazepam or 5mg haloperidol in

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repeated injections over 12 hours and 4 hours, respectively (Battaglia et al. 1997, Foster et al. 1997). Both groups observed that either medication achieved effective symptom reduction. Foster et al. concluded, "Lorazepam may provide an excellent alternative for rapid tranquillisation of the acutely agitated psychotic patient in the emergency room setting". Battaglia et al. also compared the combination and found it superior to administration of only one part.

Given this information, clinicians would be tempted to believe that benzodiazepines are as effective as antipsychotics to calm patients. Whether this observation is treated as a main effect in comparisons would then be the purpose of the following exposé of recent studies.

Materials and methods

We searched for studies comparing the use of different antipsychotics, where information on the concomitant use of benzodiazepines was given explicitly in the core text. The last search of Pub-med was done at the end of 2007. Three relevant Cochrane Collaboration Reviews were also scrutinized. They were edited by Gilles, Belgamwar and Volz, respectively (Belgamwar and Fenton 2005, Gillies et al. 2005, Volz et al. 2007).

The use of benzodiazepines under focus in the present study was, however, not directly searchable, as we were looking for studies comparing antipsychotics and or placebo, but where reading of the core text of the papers would reveal the use of benzodiazepines for calming purposes. The present study is therefore not at all comprehensive, but explorative and illustrative of the clinical use of benzodiazepines for sedation.

In the review by Gilles et al. the following is stated: "As a global impression, people allocated benzodiazepines did not clearly need additional medication compared with those given antipsychotics (n=216, 2 RCTs) suggesting an equivalent level of effect." p. 10.

In the Cochrane review by Volz, where Gillies is a co-author, on the use of benzodiazepines in schizophrenia, the authors state that "there was too little... evidence... for efficacy and tolerability… At best, the effectiveness of benzodiazepines to calm acutely ill patients early in treatment has been documented." P.16.

Many studies comparing antipsychotics with or without placebo control had to be excluded because the information on the use of benzodiazepines was too fragmentary for evaluation in the present context.

Studies using benzodiazepines as adjuvant treatment without statistical evaluation of concomitant or main effect, table 1.

Vieta et al. compared 372 patients with acute bipolar mania given either aripiprazole or haloperidol (Vieta et al. 2005). Patients were given, at the discretion of the doctor, either lorazepam, up to 4mg per day, or oxazepam up to 60mg per day. The separate effect of the benzodiazepines was not disclosed in the study.

Hovens et al. compared risperidone with lorazepam versus zuclopenthixol with lorazepam in an open study of 75 acute schizophrenic exacerbations (Hovens et al. 2005). Patients were given lorazepam up to 12 mg per day. The authors report that "At the beginning of the study, most of the nursing staff were not confident that risperidone, whether or not in combination with lorazepam, was appropriate in the management of acute psychosis in the emergency setting. However, by the end of the study, most of the nursing staff preferred lorazepam to zuclopenthixol for acute sedation and felt that risperidone plus lorazepam conferred several advantages over zuclopenthixol in the emergency setting; namely, that the combination caused less long-term sedation and fewer extra pyramidal symptoms without loss of efficacy." Despite this pivotal effect of lorazepam, the doses of lorazepam are not further reported as a main effect of the study, although the authors contend in the discussion "high dosages of lorazepam were administered to patients in both... groups, possibly obfuscating the effects of the study drugs." Certainly, such data must have been available.

Kane et al. included 414 patients in a comparison of aripiprazole (15 mg or 30 mg) and haloperidol (10 mg) versus placebo in a 4-week double-blind, randomized study (Kane et al. 2002). Both neuroleptics were equally effective in reducing PANSS scores and clearly superior to placebo. Lorazepam was allowed, but no dosages or duration of treatment are given in the study. Lorazepam was stated used as treatment for emerging agitation and anxiety and insomnia. The imputed difference in sedative effect of aripiprazole and haloperidol is used as an argument for using the former in maintenance treatment, and should have raised the interesting question, would the haloperidol-treated patients need less adjuvant calming?

Potkin et al. compared aripiprazole (20 mg or 30 mg) with risperidone (6 mg) and placebo in 404 patients from the US (Potkin et al. 2003). Both neuroleptics were equally effective in reducing PANSS scores and clearly superior to placebo. Lorazepam was allowed, but no dosages or duration of treatment were disclosed in the study. Lorazepam was stated used as treatment for emerging agitation and anxiety and insomnia. The procedure was the same as in the Kane etal study, and three of the authors were the same, and the investigation time almost the same, and the studies were conducted in US centres, 36 for the Kane and 40 for the Potkin study.

Kasper etal compared aripiprazole and haloperidol in 861 patients over 52 weeks (Kasper et al. 2003). Up to 4 mg of lorazepam was allowed at the discretion of the investigators, with the same indications as in Kane et al. and Potkin et al.

Tohen et al. compared olanzapine and divalproex in the treatment of acute mania for three weeks in 248 patients (Tohen et al. 2002). Lorazepam was allowed up to 2 mg a day, probably at the discretion of the doctor. Symptom rating scales were not given to the patients before 8 hours after an intake of benzodiazepines. A difference in rating scales between patients given benzodiazepines or not is not revealed, and neither a separate effect of the latter.

In a recent study Andrezina et al. studied the effect of aripiprazole IM and haloperidol in 448 patients from a range of centres (Andrezina et al. 2006). At two hours post injection both antipsychotics were superior to placebo. Lorazepam was allowed at the discretion of the clinicians up to 4 mg a day. More placebo-treated

patients got benzodiazepines (19%) than aripiprazole-treated patients (8%) or haloperidol-treated patients (12%). However, the exact doses given was not stated or entered into analysis.

Discussion

When the studies from the last century mentioned are taken into account, finding even one study employing benzodiazepines as adjunct treatment, not calculated as a main effect, would, in my view, indicate a lack of statistical rigour. The results shown in table 1 are thus disappointing. The studies in table 1 are probably only examples of more such studies, employing benzodiazepines concomitantly, in otherwise effective doses, without reporting on those effects. The otherwise proven effect of the benzodiazepines are thus not controlled for, giving the impression that the comparisons of antipsychotics, with or without placebo control, may be fully explained by these medications. Concomitant benzodiazepine use was not reported in the abstracts of the papers of table 1, although some information on the use of benzodiazepines appeared in the methods section, further underscoring the purportedly lack of importance given to its use. There should be no reason for not including an analysis of the benzodiazepines given to the patients. Furthermore, benzodiazepines referred to in table 1 were given at the discretion of the duty doctor, whereas in the study by Lerner they were rigorously controlled for.

The use of such preparations is clinically relevant, and rather self-explicatory to clinicians working with acutely agitated persons. Generally the psychiatrist on duty has a choice of seclusion, constraints, or effective sedating agents as the benzodiazepines, alone or in combination. In many countries the use of seclusion or constraints is restricted or forbidden, although differing from country to country. The use of benzodiazepines, however, is not restricted in hospitals in any country of my knowledge.

One study even controlled for an imputed effect of benzodiazepines on the ratings on psychometric tests, but not for a separate main effect of the benzodiazepines used.

FDA and other controlling agencies have to my knowledge, neither commented on or protested against such an evasion of including an effective agent from the analysis of a purported treatment effect on agitated patients. Neither has the three Cochrane reviews cited.

The collection of papers reviewed are thus not in any way exhaustive, as the aim was to shed light on the untoward use of benzodiazepine data in recent RCT's and comparisons. Further research is needed to evaluate the best use of several effective agents in the treatment of acute agitation. All medications used for sedating purposes should then be included in the final analyses.

Table 1. *Studies of acute agitation comparing antipsychotics (AP) and placebo where benzodiazepines have been used without accounting for the separate effect of BD's, according to demonstrated effect (reviews and metaanalyses studies not in table)*

	N entering/ completing	BD used, fixed dose	BD used, variable dose	BD main effect stated	Medications compared
Vieta 2005	372/139 12-weeks	4mg# 60mg	2mg 30mg	no	Aripiprazole versus haloperidol
Hovens 2005	75 for 14 days + endpoint		4-12mg"	no	Risperidone versus zuclopenthixol
Kasper 2003	861/367 52-weeks		≤ 4mg"	no	Aripiprazole versus haloperidol
Kane 2002	414/248 4-weeks		Dose not stated§	no	Aripiprazole versus haloperidol
Potkin 2003	404/242 4-weeks		Dose not stated§	no	Aripiprazole versus risperidone
Tohen 2002	248/167 3-weeks	≤ 2mg		no	Olanzapine versus valproex
Andrezina 2006	448/ 420? 2hours		≤4mg	no	Aripiprazole versus haloperidol

#) Vieta et al.: Lorazepam 4mg per day, or 60mg of oxazepam per day on day 1-4, further 2mg or 30mg respectively

") Hovens et al.: Lorazepam added, "If necessary" and "high doses of lorazepam were administrated… possibly obfuscating the effects of the study drugs."

") Kasper et al.: Lorazepam given "prescribed for anxiety and insomnia, or intramuscular benzodiazepines administered for emerging agitation as *deemed necessary by the investigator*". (Italics mine)

§) Lorazepam used, but dose not stated

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