INTRAMUSCULAR OLANZAPINE: A CRITICAL-META-ANALYTIC OVERVIEW OF SOME RECENT ISSUES

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Summary

Object: To compare some of the effects of intramuscular (IM) olanzapine with other drugs used in agitated psychotic disorders and Alzheimer's disease.

Method: Broad searching yielded four studies providing data regarding lack of effect within the first two hours, patients leaving the study early, requiring further IM injection, requiring further benzodiazepines, any adverse events, extrapyramidal side effects requiring anticoligercic medication, dystonia, extrapyramidal syndrome, treatment emergent akathisia. We scored study-quality, tested between-study variance, and examined efficacy and safety of IM olanzapine vs. haloperidol, bezodiazepines, and placebo by meta-analyses using conservative random-effects methods to model risk ratios.

Results: In the four reports suitable for meta-analysis, involving the above mentioned measures of efficacy and safety, IM olanzapine was always superior to other treatments. For each variable considered we presented a forest plot figure which presents the conbined odds ratio. Such combined value demostrates that IM olanzapine was always superior to other medications involved in the management of a particular feature of disorders considered.

Conclusions: IM olanzapine showed high efficacy and safety compared with haloperidol, benzodiazepines and placebo. Our results point to a reconsideration of such medication in acutely agitated patients. A calming effect has been observed during IM olanzapine treatment which may facilitate further stages of drug therapy.

Key Words: Intramuscolar Olanzapine – Agitated Psychotic Disorders

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Intramuscular olanzapine (Zyprexa®) is a rapid-acting atypical antipsychotic drug that is also indicated for agitation associated with schizophrenia or bipolar mania. Intramuscular olanzapine has also been used in acutely agitated patients with dementia (Meehan et al. 2002).

Comprehensive reviews have recently provided up-to-date information on therapeutic efficacy and tolerability (Wagstaff et al. 2005, Belgamwar and Fenton 2005).

Wright et al. (2001) performed a double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation. These authors found that for the excited component of the Positive and Negative Syndrome Scale both intramuscular (IM) olanzapine and intramuscular haloperidol reduced agitation significantly more than intramuscular placebo at 2 and 24 hours following the first injection. They also found that IM olanzapine reduced agitation significantly more than IM haloperidol; olanzapine treated patients did not experience acute dystonia compared with 7% of haloperidol treated patients. Meehan et al. (2001) carried out a double-blind, randomized placebo-controlled comparison of the efficacy and safety of IM olanzapine and lorazepam in treating acutely agitated patients diagnosed with bipolar mania. These authors measured agitation at baseline, every 30 minutes for the first two hours after the first injection using the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) subscale and two additional agitation scales. At 2 hours after the first injection, patients treated with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either lorazepam or placebo. At 24 hours after the first injection, olanzapine remained statistically superior to placebo in reducing agitation in patients with acute mania, whereas the results of patients treated with lorazepam were not significantly better than those treated with placebo or olanzapine.

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Breier et al. (2002) carried-out a double-blind, placebo-controlled dose-response comparison of IM olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. These authors found that olanzapine exhibited a dose-response relationship for reduction in agitation. Mean PANSS-EC reductions two hours after the first injection of olanzapine (2.5 mg) were superior to those with placebo, but not with haloperidol. Doses of 5.0, 7.5 and 10.0 mg of olanzapine caused greater reductions in agitation than placebo 30 minutes after the first injection. Greater response rates were observed with IM olanzapine at 7.5 mg and 10.0 mg.

Meehan et al. (2002) tested IM olanzapine vs. lorazepam and vs. placebo in a double-blind, randomized study involving acutely agitated patients with dementia. These authors found that at two hours, olanzapine and lorazepam showed significant improvement over placebo on the PANSS-EC and Agitation-Calmness Evaluation Scale. Olanzapine group maintained over time superiority vs, placebo but lorazepam did not.

The aim of this study was to provide meta-analytic results on some of the key issues surrounding IM olanzapine.

Materials and Methods

We conducted careful MedLine, Excerpta Medica and PsycLit searches to find papers in English until 2006. Search terms were "olanzapine", "intramuscular", "rapidly acting agents" "schizophrenia", "mania". Each term was also cross-referenced with the others using the MeSH method (Medical Subjects Headings). Using the same databases and methods, we also cross-referenced the above mentioned terms with key words such as "agitation" or "calming" and "dementia".

We tabulated rates of side effects during treatment with IM olanzapine and compared them with rates in study arms involving alternative treatment conditions. Our initial analysis evaluated crude pooled rates.

Results

Included were all randomized, placebo controlled trials on IM olanzapine. Four papers were identified and carefully read. Table 1 provides information on variables included in the statistical analysis.

Discussion

Dealing with an agitated psychotic patient or with any kind of agitated patient is a difficult task. Sleep seems to be not essential for decreasing agitation, moreover excessive sedation is an important side effect in rapid tranquilization. Patients are often affected by medical conditions and are dehydrated. There is

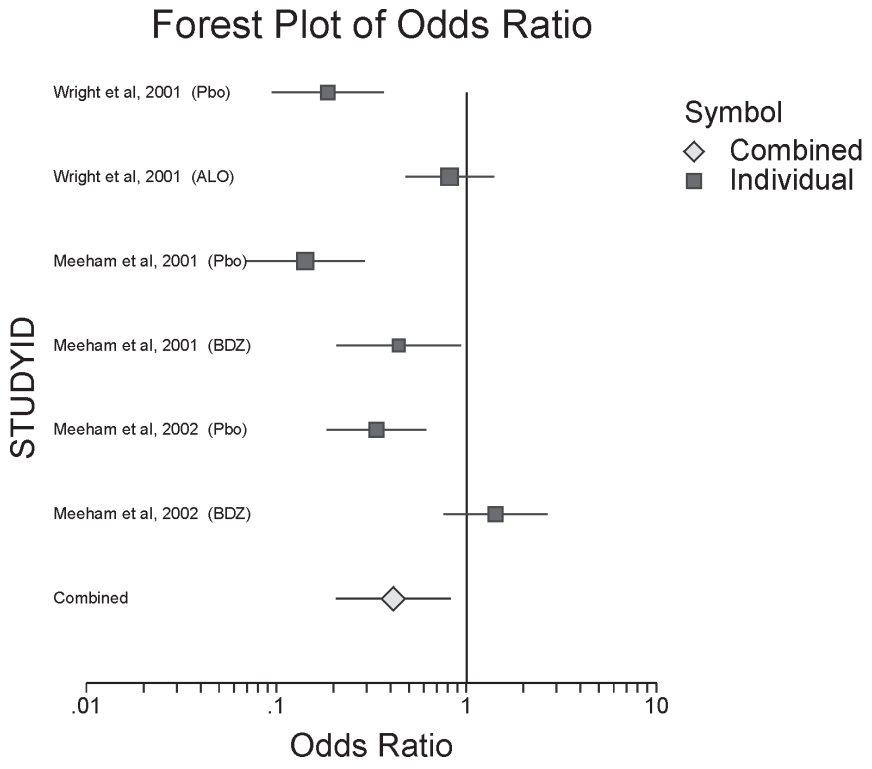

Figure 1. *Forest plot of lack of effect within the first 2 hours*

Table 1. *Summary of reports on IM olanzapine vs. other treatments*

Study, year	Quality Score	Other Rx	Trial design	Diagnosis	Time	*With IM Olanzapine* n/N	Rate	*Without IM* n/N	Rate	Odds ratio	Risk ratio
Lack of effect by 2 hours											
Wright et al. 2001	100	Pbo	RCT	SCHI	2 h	35/131	0.2672	36/54	0.6667	0.1865	0.4053
		HAL			2 h	35/131	0.2672	39/126	0.3095	0.8149	0.8647
Meeham et al. 2001	100	Pbo	RCT	BP	2 h	19/199	0.0955	22/51	0.4314	0.1416	0.2253
		BDZ			2 h	19/99	0.1919	18/51	0.3529	0.4386	0.5481
Meeham et al. 2002	100	Pbo	RCT	ALZ	2 h	49/137	0.3577	42/67	0.6269	0.3356	0.5739
		BDZ			2 h	49/137	0.3577	19/68	0.2794	1.4168	1.2692
Leaving the study early											
Meeham et al. 2001	100	Pbo	RCT	BP	24 h	1/99	0.0101	5/51	0.0980	0.1287	0.1418
		BDZ			24 h	1/99	0.0101	3/51	0.0588	0.2110	0.2229
Meeham et al. 2002	100	Pbo	RCT	ALZ	24 h	8/137	0.0584	7/67	0.1045	0.5295	0.5585
	100	BDZ			24 h	9/137	0.0657	7/68	0.1029	0.6062	0.6333
Wright et ak, 2001	100	HAL			24 h	9/131	0.0687	10/126	0.0794	0.8604	0.8705
Requiring further IM injection											
Wright et al. 2001	100	Pbo	RCT	SCHI	24 h	31/131	0.2666	27/54	0.5000	0.3134	0.4773
		HAL			24 h	31/131	0.2666	36/126	0.2857	0.7771	0.8303
Meeham et al. 2001	100	PbO	RCT	BP	24 h	26/99	0.2626	27/51	0.5294	0.3212	0.5011
Meehan et al. 2001		BDZ			24 h	26/99	0.2626	27/51	0.5694	0.3212	0.5011
Meeham et al. 2002	100	Pbo	RCT	ALZ	24 h	29/137	0.2117	31/67	0.4627	0.3150	0.4615
		BDZ			24 h	29/137	0.2117	14/68	0.2059	1.0219	1.0172
Requiring further BDZ											
Wright et al. 2001	100	Pbo	RCT	SCHI	24 h	21/131	0.1603	21/54	0.3889	0.3032	0.4167
Wright et al. 2001	100	HAL			24 h	21/131	0.1603	25/126	0.1984	0.7745	0.8112
Adverse event											
Any											
Meehan et al. 2001	100	Bpo	RCT	SCHI	24 h	34/99	0.3434	13/51	0.2549	1.5021	1.3289
		BDZ			24 h	35/99	0.3535	29/51	0.5686	0.4198	0.6258
EPS requiring anticoligercig med.											
Meeham et al. 2001	100	Bpo	RCT	BP	24 h	8/99	0.0808	3/51	0.0588	1.2873	1.2629
		BDZ			24 h	9/99	0.0909	4/51	0.0784	1.1080	1.0978
Wright et al. 2001	100	Bpo	RCT	SCHI	24 h	6/131	0.0458	2/54	0.0370	1.0876	1.0833
Wright et al. 2001	100	HAL			24 h	6/131	0.0458	26/126	0.2063	0.1964	0.2360
Breier et al. 2002	100	HAL			24 h	1/185	0.0054	3/40	0.0750	0.0871	0.0945
Dystonia											
Wright et al. 2001	100	HAL	RCT	SCHI	24 h	0/131	0.0000	9/126	0.0714	0.0470	0.0506
Breier et al. 2002	100	HAL	RCT	SCHI	24 h	0/185	0.0000	2/40	0.0500	0.0415	0.0441
		Bpo			24 h	0/185	0.0000	0/45	0.0000	0.2453	0.2473
Extrapiramidal Syndrome											
Wright et al. 2001	100	HAL	RCT	SCHI	24 h	1/131	0.0076	7/126	0.0556	0.1831	0.1924
Breier et al. 2002	100	HAL	RCT	SCHI	24 h	1/142	0.0000	6/36	0.1667	0.0497	0.0597
		Pbo			24 h	1/142	0.0070	0/37	0.0000	0.7951	0.7972
Treatment emergent akathisia											
Breier et al. 2002	100	HAL	RCT	SCHI	24 h	2/171	0.0117	3/38	0.0789	0.1498	0.1620
		Pbo			24 h	2/171	0.0117	0/42	0.0000	1.2537	1.2500

Legend for Table 1:

Quality in the 4 reports was scored as: presence of subjects observed both with and without IM olanazapine (1 point), randomized treatment-assignment and blind clinical assessments (1 or 2 points), Ne"100subjects/treatment group (1 or 2 points), and presented as percentage of the maximum score of 5.0.

*Abbreviation*s: HAL = haloperidol, BDZ = benzodiazepine, Pbo = placebo

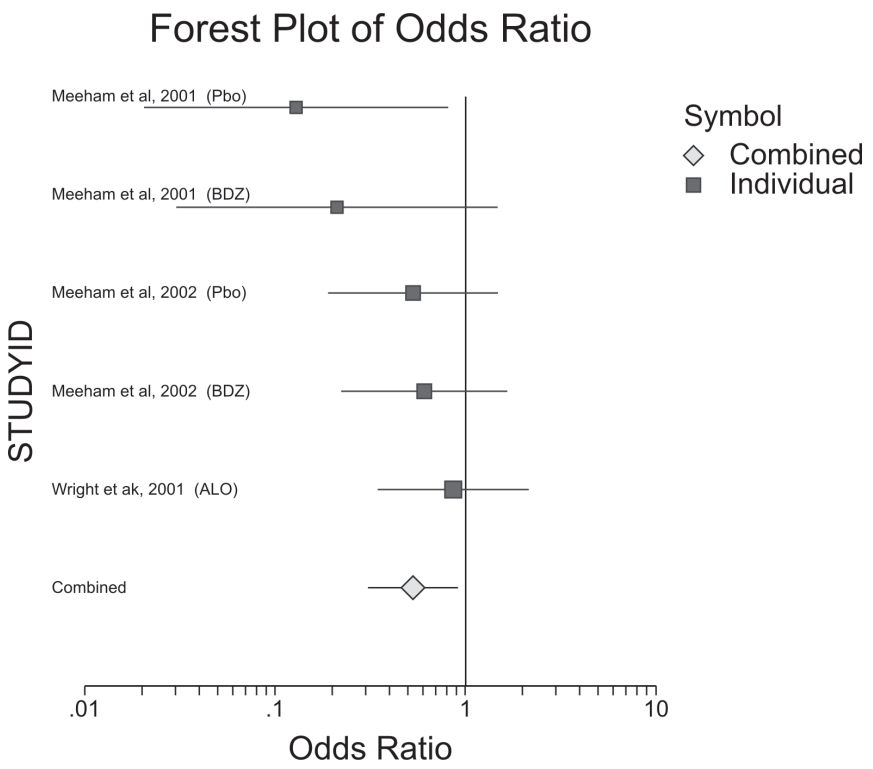

Figure 2. *Patients leaving the study early*

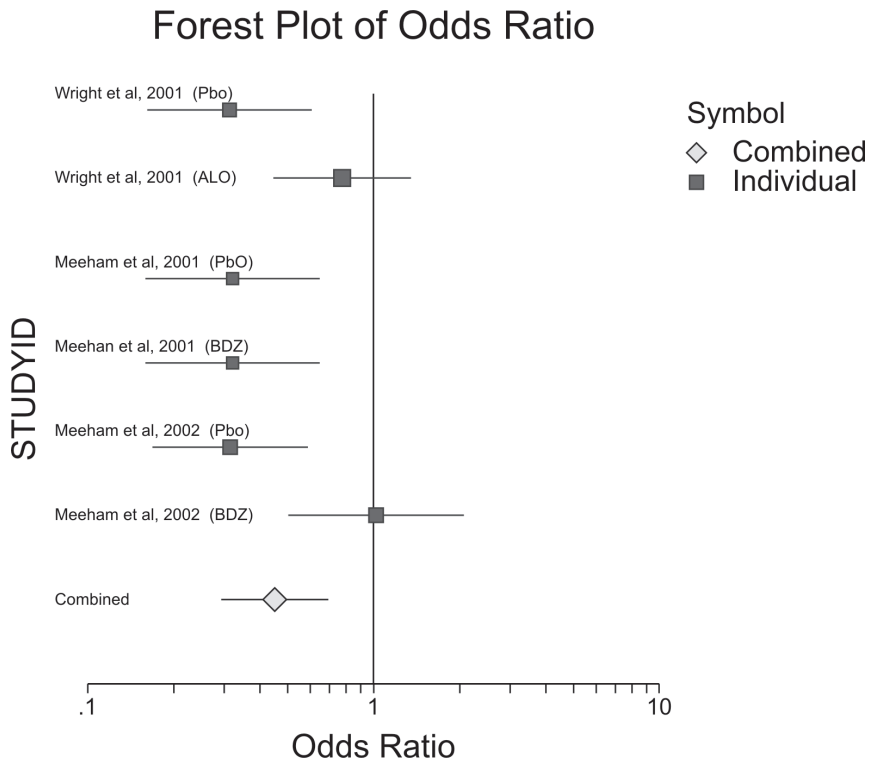

Figure 3. *Requiring further IM injection*

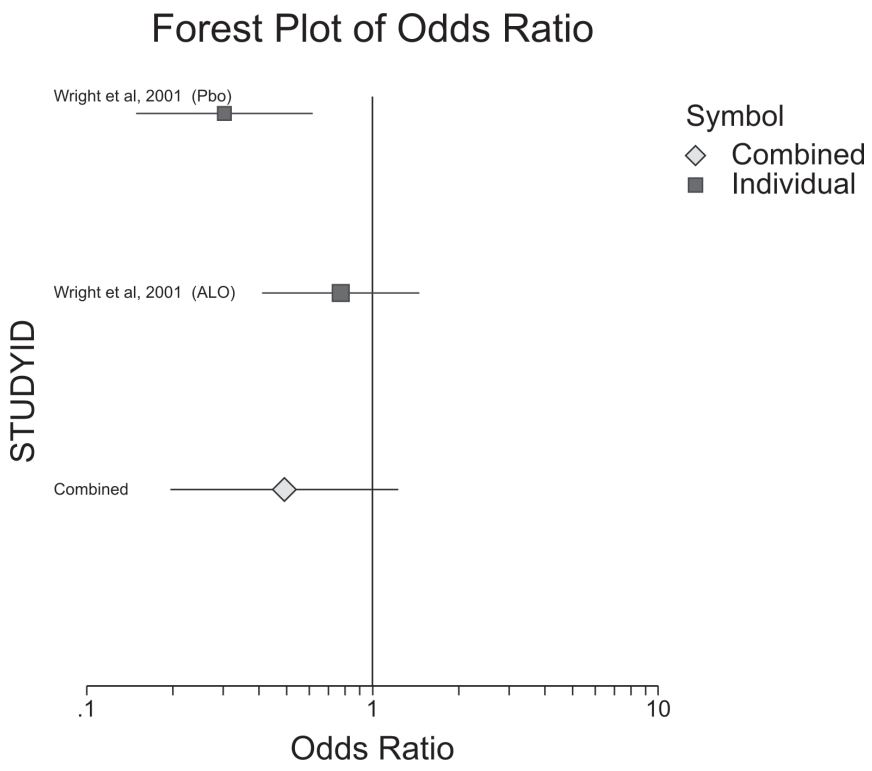

Figure 4. *Requiring further BDZ*

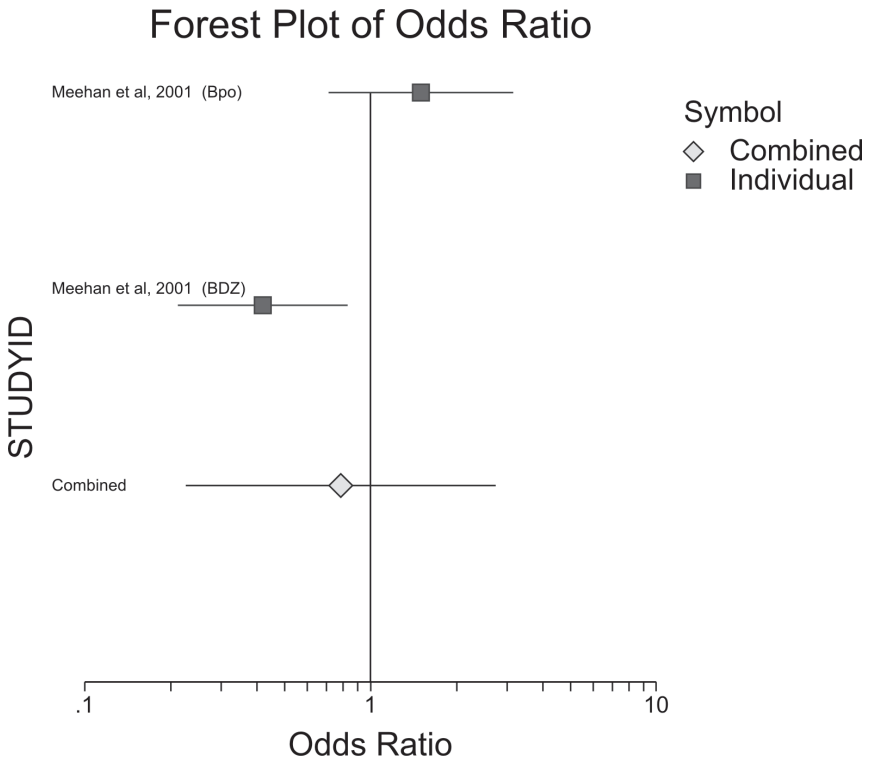

Figure 5. *Adverse events (any)*

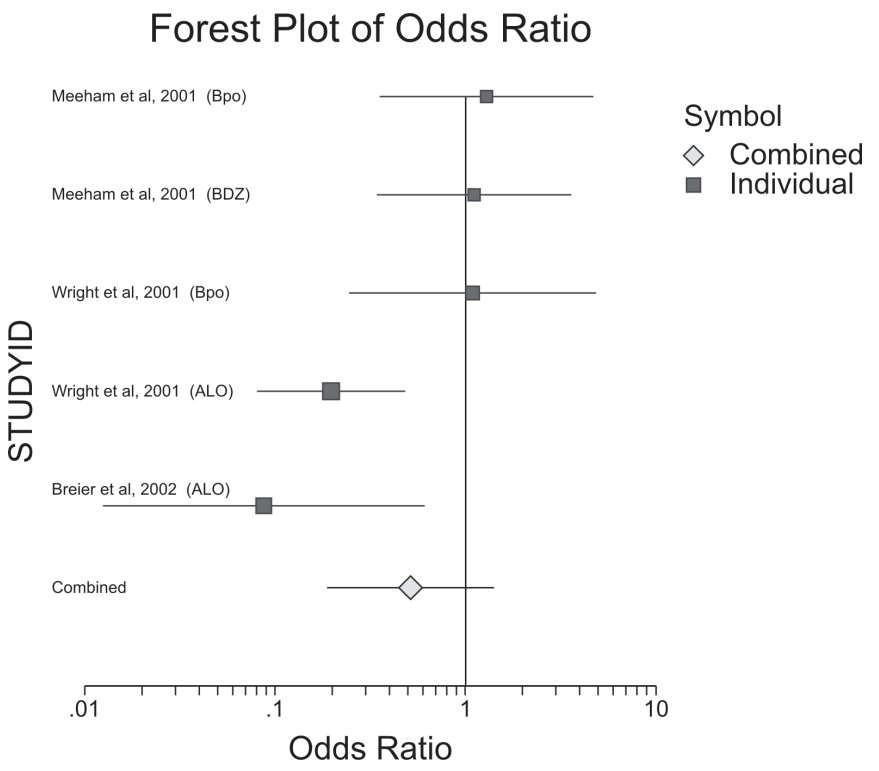

Figure 6. *EPS requiring anticolinergic medications*

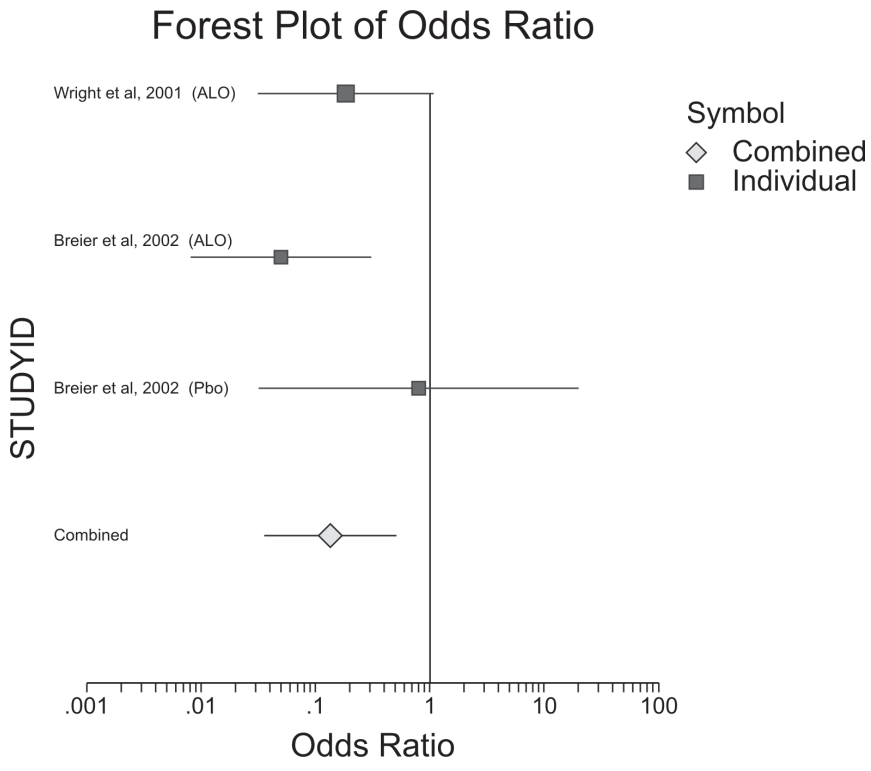

Figure 7. *Dystonia*

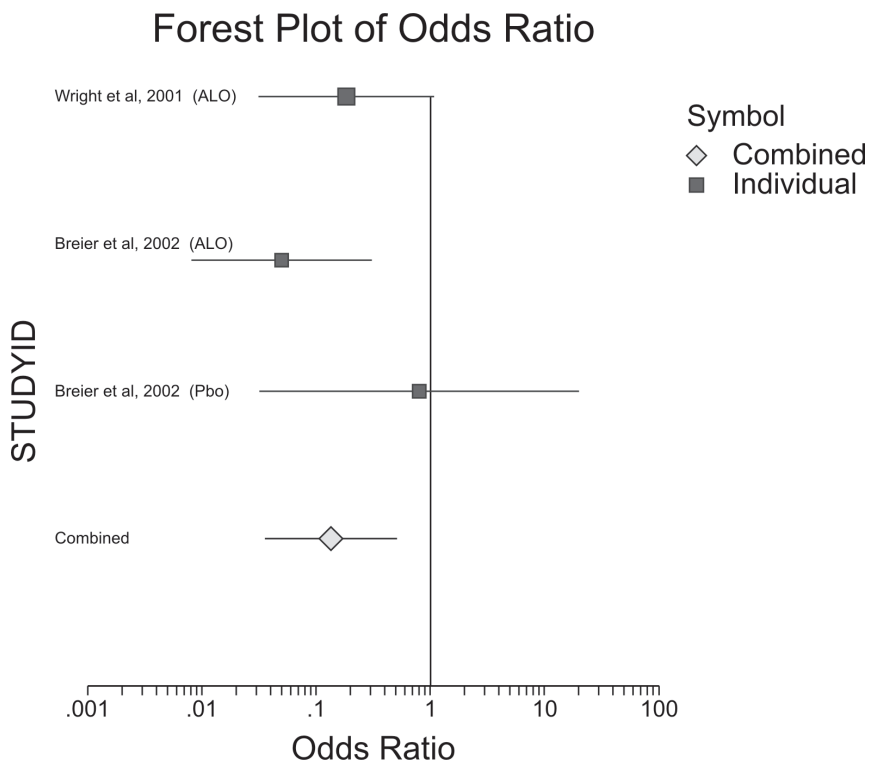

Figure 8. *Extrapyramidal syndrome*

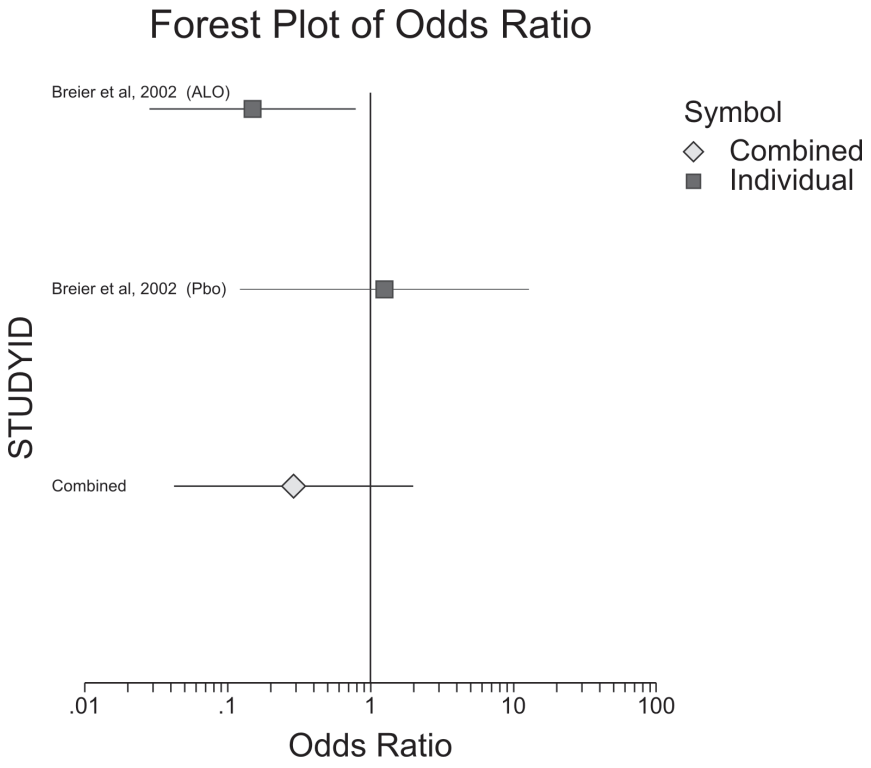

Figure 9. *Treatment emergent akathisia*

evidence to suppose that sleep is not essential for decreasing agitation, also high-potency neuroleptics, such as haloperidol, have extrapyramidal symptoms which often impair proper treatment. Benzodiazepines, such as lorazepam, although not associated with extrapyramidal symptoms and efficacious for agitation, may cause respiratory depression and excessive sedation. Also, combination treatment, such as haloperidol and lorazepam, although superior to either agent alone, does not provide favorable safety.

Intramuscular olanzapine has been proving as having a favorable safety and efficacy profile. IM olanzapine reaches mean maximum plasma concentration 15 to 45 minutes after injection and therefore represents one of the newest medications in the armamentarium for the treatment of acute agitation in psychotic states.

In their analysis of published clinical trials Battaglia et al. (2003) reported that IM olanzapine, was no more sedating than IM haloperidol in the treatment of agitation in patients with schizophrenia, schizophreniform or schizoaffective disorder, and IM olanzapine was no more sedating than IM lorazepam in the treatment of agitation in patients with bipolar mania or dementia. These authors concluded an appropriate level of calming rather than sedation was achieved during IM olanzapine.

Our study considered all data available from trials whose results were published in medical journals. We pooled and processed data regarding lack of effect within the first two hours as well as patients either leaving the study early, requiring further IM injection, or requiring further IM benzodiazepines, in addition to, patients experiencing a number of side effects, such as dystonia, treatment emergent akathisia and extrapyramidal syndrome.

Results of our meta-analysis showed that IM olanzapine was always superior to other treatments for the variables taken into account.

Manufacturer of IM olanzapine provided careful information on how to use the drug safely. In reviewing warnings on safety issues of this drug, one cannot avoid noticing how such warnings apply to any IM psychotropic drug. Also, when adverse events occurred, it is worth noticing that IM olanzapine might have been underestimated for its treating properties and, therefore, more or higher doses were administered to agitated patients.

Our study considered some, but not all, issues regarding IM olanzapine. Meta-analysis is a powerful tool that poses numerous problems, a few of which occurred in this investigation as well (Bulpitt 1988). Limitations of this study include lack of meta-analytic investigation on efficacy of IM olanzapine (literature provided ample evidence of efficacy of such drug). Another limitation regards inclusion criteria; in facts in each trial if substance abuse was the primary cause of illness, patients were not included. Also, patients with serious, unstable medical illness were not included as well. Another limitation regards the number of trials included in our work being only four and limited to published works only. To our knowledge, based on the search criteria described above, literature in French and/or in German is not available at this time.

One important issue of investigations involving drugs concerns sponsorships from pharmaceutical industries. Heres et al. (2006) reviewed trials involving second-generation antipsychotics and investigated 42 reports of which 33 were sponsored by a pharmceutical company and in 90% of the studies, the reported overall outcome was in favor of the sponsor's drug. Moreover, Montgomery et al. (2004) reported that industry-funded studies significantly favor second generation over first generation antipsychotics when compared to non-industry funded studies. Procyshyn et al. (2004) also stresses in their review paper that one-third of the published clincal trials involving clozapine, risperidone, or olanzapine were funded by their respective manufacturers and that the reported outcomes of the sponsored trials highly favour the manufacturers' product. Although our meta-analysis does include trials that may have been funded by pharmaceutical companies, we perfomed our study spontaneously and the fact that one of the authors (MP) received an unrestricted research grant from manufactures of IM olanzapine and that other two authors (MM and SF) are employees of such company did not affect our scientific method and statistical processing of data in any possible way.

More studies are needed to further clarify issues regarding safety and efficacy of IM olanzapine. One key point to consider when using such drug is its proper usage by medical personnel. Caregivers should follow carefully how and when to use IM olanzapine. There is evidence to suppose that adverse events outlined by warning issues by producers of IM olanzapine were the result of improper use of the drug. Future studies should also focus on the investigation on how such drug may interfere with other medications and, therefore, follow more structured guidelines.

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