Comparison of Intramuscular Ziprasidone, Olanzapine, or Aripiprazole for Agitation: A Quantitative Review of Efficacy and Safety

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Objective: To compare the efficacy and safety of the intramuscular formulations of ziprasidone, olanzapine, and aripiprazole in treating agitation.

Data sources: The pivotal registration trials were accessed by querying on-line literature and clinical trial databases. Pharmacovigilance data and posters were requested from the manufacturers. No date or language constraints were applied.

Study Selection: Nine double-blind, randomized, controlled clinical trials were identified.

Data Extraction: Number needed to treat (NNT) for response to treatment for agitation and number needed to harm (NNH) for extrapyramidal effects were calculated from the study reports. Additional safety outcomes subject to NNH analysis were obtained from product labeling.

Data Synthesis: Using the a priori definitions of response at 2 hours after the first injection, NNT for response versus placebo (or placebo equivalent) in treating agitation for the pooled data at the recommended dose of ziprasidone 10–20 mg was 3 (95% CI = 2 to 4), for olanzapine 10 mg was 3 (95% CI = 2 to 3), and for aripiprazole 9.75 mg was 5 (95% CI = 4 to 8). Treatment-emergent adverse events occurring during the pivotal trials revealed statistically significant NNH versus placebo (or placebo equivalent) for aripiprazole for headache (NNH = 20, 95% CI = 11 to 170) and nausea (NNH = 17, 95% CI = 11 to 38), for ziprasidone in the treatment of headache (NNH = 15, 95% CI = 8 to 703), and for olanzapine in treatment-emergent hypotension (NNH = 50, 95% CI = 30 to 154). Olanzapine and aripiprazole had a more favorable extrapyramidal side effect profile compared to haloperidol. (There was no haloperidol treatment arm in the ziprasidone studies.)

Conclusions: Although the lowest NNT, and hence strongest therapeutic effect, was seen for the studies of ziprasidone and olanzapine as opposed to aripiprazole, head-to-head controlled studies directly comparing these 3 agents are needed.

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In the United States, 3 second-generation antipsychotics are now available in a rapid-acting intramuscular formulation. An important question is whether these newer agents offer any clinical advantages in the treatment of agitation associated with schizophrenia or bipolar mania over older medications such as haloperidol or lorazepam.

Ziprasidone intramuscular was commercially launched in 2002 for the indication of agitation associated with schizophrenia, olanzapine intramuscular in 2004 for agitation associated with schizophrenia or bipolar mania, and aripiprazole intramuscular in 2006 for agitation associated with schizophrenia or bipolar mania. The specific disease states for which these agents were approved reflect the specific pivotal studies done to demonstrate efficacy and safety. The nature of these studies precludes the inclusion of the most severely ill patients seen in clinical practice because of the requirement of informed consent. Nevertheless, these studies do provide a level of evidence from which we can confidently measure treatment effect over placebo and active comparators when available. The purpose of this review is to calculate the effect sizes for both efficacy and tolerability for the new agents compared to placebo or active comparators, using the metrics of number needed to treat (NNT) and number needed to harm (NNH). More general overviews of these agents, with the exception of aripiprazole intramuscular, can be found elsewhere.[1–4]

METHOD

Data Sources

The pivotal trials referred to in the United States product labeling for ziprasidone,[5] olanzapine,[6] and aripipra-

zole[7] were accessed by querying http://www.pubmed.gov, http://www.lillytrials.com, http://ctr.bms.com/ctd/, http://www.clinicalstudyresults.org, http://www.fda.gov, and http://www.clinicaltrials.gov. Keywords used were *intramuscular*, *ziprasidone*, *olanzapine*, and *aripiprazole*. No date or language constraints were used. Pharmacovigilance data were requested from representatives of the manufacturers. When studies were not yet published, information was extracted from posters that were presented at international conferences, as supplied by the manufacturers. When numerical information is not explicitly provided in the poster text, it was physically measured from printed figures.

Product labeling for the 3 second-generation antipsychotics[5–7] was inspected with regard to incidence of adverse events.

Study Selection

Nine double-blind randomized controlled clinical trials were identified (Table 1).

Data Extraction

NNT and NNH comparing ziprasidone, olanzapine, and aripiprazole to placebo or active comparators were calculated for both efficacy and safety outcomes, and 95% CIs were determined. The methodology of this technique is described in detail elsewhere,[21–23] but essentially NNT and NNH are measures of effect size and indicate how many patients would need to be treated with one agent instead of the comparator in order to see a difference in outcome. Lower NNTs are evidenced when there are large differences between the interventions in question. For example, an NNT of 2 would be a very big effect size, as a difference is seen after treating just 2 patients with one of the interventions versus the other. An NNT of 50 would mean little difference between the 2 interventions, as it would take treating 50 patients to see a difference in outcome. NNH is used when referring to undesirable events. A useful medication is one with a low NNT and a high NNH when comparing it with another intervention. Kraemer and Kupfer[23] put forth that an NNT of 2.3, 3.6, and 8.9 correspond to a Cohen's d of 0.8, 0.5, and 0.2, respectively, representing effect sizes that are large, medium, and small, respectively.

The data from the respective a priori–defined responder analyses were used for the calculation of NNT. Response for the ziprasidone studies was defined as at least a 2-point reduction in the Behavioral Activity Rating Scale (BARS) score 2 hours after the first injection. Response for the olanzapine and aripiprazole studies was defined as a 40% reduction or more on the Positive and Negative Syndrome Scale (PANSS) Excited Component (EC) score 2 hours after the first injection. In addition to calculating NNT for the antipsychotics for each pivotal trial, data were pooled for the individual antipsychotics to calculate NNT at the doses recommended in product labeling.

The safety outcomes subject to NNH analysis were obtained from product labeling (the 4 most frequently reported adverse events for each agent), as the details provided allowed for the determination of both NNH and the corresponding CI pooled across all available data. NNH for extrapyramidal symptoms was calculated from the study reports.

For each NNT or NNH, 95% CIs are provided. When the difference between the 2 treatments is not statistically significant, the CI for NNT or NNH is difficult to describe.[24] Because NNT and NNH are calculated by taking the reciprocal of the difference in percentages of the outcome of interest, a zero difference would generate an NNT or NNH of infinity, and thus, if the NNT or NNH is not statistically significant, the CI would include infinity. Mathematically, 2 ranges are possible for a CI for a nonstatistically significant result: one limited by "positive" infinity, the other limited by "negative" infinity. For clarity, this is expressed in the tables as $-x$ *to* $-\infty$ *and* y *to* ∞. When the rates being compared are both zero, the CI can be expressed as $-\infty$ *to* ∞.

RESULTS

Data Synthesis

Pivotal clinical trials and product-labeling information. The pivotal clinical trials identified are included in Table 1. Published articles were found for all studies,[8–19] with the exception of one study for aripiprazole in the treatment of agitation associated with acute mania.[20]

Ziprasidone intramuscular was approved for the indication of acute agitation in patients with schizophrenia on the basis of two 1-day, double-blind trials[8,9] of hospitalized subjects considered by the investigators to be acutely agitated and in need of intramuscular antipsychotic medication.[5] In product labeling, the usual recommended dose is 10 to 20 mg.[5] Safety concerns specific to intramuscular ziprasidone as noted in product labeling include caution in patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration. Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure. (For more information, see the U.S. Food and Drug Administration [FDA] briefing document for ziprasidone.[25])

Olanzapine was approved for the indication of agitation associated with schizophrenia or bipolar I mania on the basis of three 1-day, placebo-controlled trials[10–15] in inpatients considered by the investigators to be "clinically agitated" and clinically appropriate candidates for treatment with intramuscular medication.[6] A fourth pivotal

Table 1. Pivotal Clinical Trials for Agitation: Fast-Acting Intramuscular Formulations of Second-Generation Antipsychotics

Reference	Agent; Indication	N	Study Arms (N)	Entry Criterion for Severity of Agitation	Primary Outcome Measure(s)	Results
Lesem et al,[8] 2001	Ziprasidone; schizophrenia[a]	117	Ziprasidone 2 mg (54) Ziprasidone 10 mg (63)	Score of ≥ 3 (mild) on at least 3 of the following items on the PANSS: anxiety, tension, hostility, and excitement	BARS; CGI-S[b]	10 mg superior on BARS at 0 to 2 hours, but not on CGI-S
Daniel et al,[9] 2001	Ziprasidone; schizophrenia[a]	79	Ziprasidone 2 mg (38) Ziprasidone 20 mg (41)	Score of ≥ 3 (mild) on at least 3 of the following items on the PANSS: anxiety, tension, hostility, and excitement	BARS; CGI-S[b]	20 mg superior on BARS at 0 to 4 hours, and on CGI-S at 4 hours
Breier et al,[10,11] 2002	Olanzapine; schizophrenia	270	Olanzapine 2.5 mg (48) Olanzapine 5 mg (45) Olanzapine 7.5 mg (46) Olanzapine 10 mg (46) Haloperidol 7.5 mg (40) Placebo (45)	Score of ≥ 14 on PANSS-EC, and at least 1 item score of ≥ 4 (moderate)	PANSS-EC[c]	All doses of olanzapine superior to placebo on PANSS-EC; effect larger and more consistent for 5, 7.5, and 10 mg
Wright et al,[12,13] 2001	Olanzapine; schizophrenia	311	Olanzapine 10 mg (131) Haloperidol 7.5 mg (126) Placebo (54)	Score of ≥ 14 on PANSS-EC, and at least 1 item score of ≥ 4 (moderate)	PANSS-EC[c]	Olanzapine superior to placebo on PANSS-EC
Meehan et al,[14,15] 2001	Olanzapine; bipolar, manic or mixed	201	Olanzapine 10 mg (99) Lorazepam 2 mg (51) Placebo (51)	Score of ≥ 14 on PANSS-EC, and at least 1 item score of ≥ 4 (moderate)	PANSS-EC[c]	Olanzapine superior to placebo on PANSS-EC
Meehan et al,[16,17] 2002	Olanzapine; dementia[d]	272	Olanzapine 2.5 mg (71) Olanzapine 5 mg (66) Lorazepam 1 mg (68) Placebo (67)	Score of ≥ 14 on PANSS-EC, and at least 1 item score of ≥ 4 (moderate)	PANSS-EC[c]	Both olanzapine doses were superior to placebo on the PANSS-EC
Andrezina et al,[18] 2006	Aripiprazole; schizophrenia	448	Aripiprazole 9.75 mg (175) Haloperidol 6.5 mg (185) Placebo (88)	Score of ≥ 15 on PANSS-EC, and at least 2 item scores of ≥ 4 (moderate)	PANSS-EC[c]	Aripiprazole superior to placebo on PANSS-EC
Tran-Johnson et al,[19] 2007	Aripiprazole; schizophrenia	357	Aripiprazole 1 mg (57) Aripiprazole 5.25 mg (63) Aripiprazole 9.75 mg (57) Aripiprazole 15 mg (58) Haloperidol 7.5 mg (60) Placebo (62)	Score of ≥ 15 on PANSS-EC, and at least 2 item scores of ≥ 4 (moderate)	PANSS-EC[c]	All but the 1-mg dose of aripiprazole were superior to placebo on PANSS-EC
Oren et al,[20] 2005[e]	Aripiprazole; bipolar, manic or mixed	291	Aripiprazole 10 mg (75) Aripiprazole 15 mg (75) Lorazepam 2 mg (68) Placebo (73)	Score of ≥ 15 on PANSS-EC, and at least 2 items score ≥ 4 (moderate)	PANSS-EC[c]	Both doses of aripiprazole superior to placebo on PANSS-EC

[a]Patients had a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, delusional disorder, or psychotic disorder not otherwise specified (DSM-IV). Approximately 80% of the subjects had schizophrenia or schizoaffective disorder.
[b]For the ziprasidone studies, the CGI-S scores were based on the patient's behavior, specifically the severity of agitation present since the previous rating.
[c]PANSS-EC comprises the following 5 items from the PANSS: poor impulse control, tension, hostility, uncooperativeness, and excitement.
[d]Not an FDA-approved indication; subjects were hospitalized or nursing home residents, aged 55 or older, who met either National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association or *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, criteria for possible or probable Alzheimer's disease, vascular dementia, or a combination of both.
[e]Dose of 10 mg in the poster was rounded up from the actual dose of 9.75 mg.
Abbreviations: BARS = Behavioral Activity Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, FDA = U.S. Food and Drug Administration, PANSS = Positive and Negative Syndrome Scale, PANSS-EC = Positive and Negative Syndrome Scale-Excited Component.

trial was done in patients with agitation associated with dementia,[16,17] for which regulatory approval was not pursued. In product labeling, the usual recommended dose is 10 mg.[6] Safety concerns specific to intramuscular olanzapine, as noted in product labeling include hypotension, bradycardia with or without hypotension, tachycardia, and syncope as reported during the clinical trials. As per the product label, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. [6] (For more information, see the FDA briefing document for olanzapine.[26])

Aripiprazole intramuscular was approved for the indication of agitation associated with schizophrenia or bipolar mania on the basis of three 1-day, placebo-controlled trials[18–20] in inpatients considered by the investigators to be "clinically agitated" and clinically appropriate candidates for treatment with intramuscular medication.[7] In product labeling, the usual recommended dose is 9.75 mg.[7] Safety concerns specific to intramuscular aripiprazole as noted in

Table 2. Response and Number Needed to Treat

Comparison	Disease State	Study Reference	Dose of Drug of Interest (mg)	Dose of Comparator (mg)	NNT[a,b]	95% Confidence Interval[c]
Second-Generation Antipsychotic vs Placebo or Placebo Equivalent						
Ziprasidone vs ziprasidone 2mg (placebo equivalent)	Schizophrenia	Lesem et al,[8] 2001	10	2	4	3 to 10
	Schizophrenia	Daniel et al,[9] 2001	20	2	2	2 to 3
Olanzapine vs placebo	Schizophrenia	Breier et al,[10,11] 2002	2.5	Placebo	4	3 to 9
			5	Placebo	3	2 to 5
			7.5	Placebo	2	2 to 3
			10	Placebo	2	2 to 3
	Schizophrenia	Wright et al,[12,13] 2001	10	Placebo	3	2 to 4
	Bipolar mania	Meehan et al,[14,15] 2001	10	Placebo	3	2 to 5
	Dementia[d]	Meehan et al,[16,17] 2002	2.5	Placebo	5	3 to 12
			5.0	Placebo	4	3 to 8
Aripiprazole vs placebo	Schizophrenia	Tran-Johnson et al,[19] 2007	1	Placebo	70	NS* (–7 to –∞ and 6 to ∞)
			5.25	Placebo	8	NS* (–30 to –∞ and 4 to ∞)
			9.75	Placebo	6	NS* (–376 to –∞ and 3 to ∞)
			15	Placebo	6	3 to 66
	Schizophrenia	Andrezina et al,[18] 2006	9.75	Placebo	6	4 to 16
	Bipolar mania	Oren et al,[20] 2005	10	Placebo	4	3 to 6
			15	Placebo	4	3 to 10
Second-Generation Antipsychotic vs Active Comparator						
Olanzapine vs haloperidol	Schizophrenia	Breier et al,[10,11] 2002	2.5	7.5	–10	NS* (–4 to –∞ and 10 to ∞)
			5	7.5	39	NS* (–6 to –∞ and 5 to ∞)
			7.5	7.5	8	NS* (–17 to –∞ and 3 to ∞)
			10	7.5	5	3 to 73
	Schizophrenia	Wright et al,[12,13] 2001	10	7.5	24	NS* (–7 to –∞ and 5 to ∞)
Aripiprazole vs haloperidol	Schizophrenia	Tran-Johnson et al,[19] 2007	1	7.5	–5	–3 to –24
			5.25	7.5	–11	NS* (–4 to –∞ and 13 to ∞)
			9.75	7.5	–17	NS* (–5 to –∞ and 9 to ∞)
			15	7.5	–23	NS* (–5 to –∞ and 8 to ∞)
	Schizophrenia	Andrezina et al,[18] 2006	9.75	6.5	–34	NS* (–8 to –∞ and 14 to ∞)
Olanzapine vs lorazepam	Bipolar mania	Meehan et al,[14,15] 2001	10	2	7	4 to 160
	Dementia[d]	Meehan et al,[16,17] 2002	2.5	1	–10	NS* (–4 to –∞ and 19 to ∞)
			5.0	1	–19	NS* (–5 to –∞ and 10 to ∞)
Aripiprazole vs lorazepam	Bipolar mania	Oren et al,[20] 2005	10	2	ND[e]	NS* (–7 to –∞ and 7 to ∞)
			15	2	–17	NS* (–5 to –∞ and 11 to ∞)
Active Comparator vs Placebo						
Haloperidol vs placebo	Schizophrenia	Breier et al,[10,11] 2002	7.5	Placebo	3	2 to 5
	Schizophrenia	Wright et al,[12,13] 2001	7.5	Placebo	3	2 to 5
	Schizophrenia	Andrezina et al,[18] 2006	6.5	Placebo	5	3 to 11
		Tran-Johnson et al,[19] 2007	7.5	Placebo	5	3 to 17
Lorazepam vs placebo	Bipolar mania	Meehan et al,[14,15] 2001	2	Placebo	5	3 to 60
	Bipolar mania	Oren et al,[20] 2005	2	Placebo	4	3 to 7
	Dementia	Meehan et al,[16,17] 2002	1	Placebo	3	2 to 6

*Not statistically significant at $p < .05$.
[a]Response for the ziprasidone studies defined as at least a 2-point reduction in Behavioral Activity Rating Scale 2 hours after the first injection; response for the olanzapine and aripiprazole studies (and thus for the active comparators of haloperidol and lorazepam) was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.
[b]A negative number for NNT implies a disadvantage for ziprasidone, olanzapine, or aripiprazole over the comparator.
[c]When not statistically significant, the 95% confidence interval represents both positive and negative numbers. (See text.)
[d]Not an FDA-approved indication.
[e]Response (nonzero) is the same for the 2 interventions being compared.
Abbreviations: FDA = U.S. Food and Drug Administration, ND = no difference, NNT = number needed to treat, NS = not significant.

product labeling include greater sedation and orthostatic hypotension with the combination of lorazepam and aripiprazole as compared to that observed with aripiprazole alone.[7]

For the studies that included a haloperidol intramuscular treatment arm,[10–13,18,19] prophylactic anticholinergic medication such as benztropine was not used.

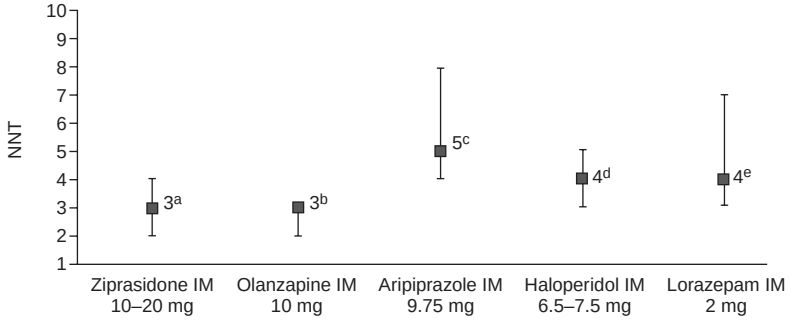
Response: number needed to treat. Using the a priori definitions of response, NNTs for achieving response at 2 hours are reported in Table 2. Statistically significant superiority over placebo is noted for ziprasidone 10 mg and 20 mg; olanzapine 2.5 mg, 5 mg, 7.5 mg, and 10 mg; and aripiprazole 9.75 mg and 15 mg. The strongest effect sizes (lowest NNT) were evident for ziprasidone 20 mg and olanzapine 7.5 mg or 10 mg in the treatment of agitation associated with schizophrenia and olanzapine 10 mg in the treatment of agitation associated with bipolar mania. A dose-response relationship appears to be evident for ziprasidone across studies (NNT strengthens from 4 to 2 when going from 10 mg to 20 mg, respectively) and

olanzapine (NNT strengthens from 4 to 3 to 2 when going from 2.5 mg to 5 mg to 7.5 mg, respectively). A clear dose response for aripiprazole is not evident between 5.25 mg, 9.75 mg, and 15 mg, with NNTs of 8 (not significant), 6 (not significant), and 6, respectively, for schizophrenia or between 10 mg and 15 mg for the study in bipolar mania (NNT of 4 for each dose of aripiprazole). Overall, these NNTs are comparable to the performance of the active controls in which NNTs ranged from 3 to 5 for haloperidol or lorazepam. Figure 1 provides the NNT and CIs for the pooled data that tested the recommended doses of ziprasidone 10 to 20 mg,[8,9] olanzapine 10 mg,[10–15] and aripiprazole 9.75 mg versus placebo,[18–20] and the NNT and CIs for pooled data across studies that compared haloperidol 6.5 mg or 7.5 mg versus placebo[10–13,18,19] and lorazepam 2 mg versus placebo.[14,15,20]

Information is available regarding the direct comparison of olanzapine or aripiprazole versus haloperidol or lorazepam. Statistically significant NNTs were evident for the comparison of olanzapine 10 mg versus haloperidol 7.5 mg in patients with schizophrenia (NNT = 5), for the comparison of olanzapine 10 mg versus lorazepam 2 mg in patients with bipolar mania (NNT = 7), and for the comparison of aripiprazole 1 mg versus haloperidol 7.5 mg in patients with schizophrenia (NNT = –5), indicating superiority of haloperidol to this subtherapeutic low dose of aripiprazole.

Safety outcomes: number needed to harm. The incidence of the most commonly reported adverse events as outlined in product labeling[5–7] can be converted into the metric of NNH, together with a 95% CI (Table 3). NNHs range from 17 to 100, indicating that these events occur only occasionally, and less frequently than a therapeutic response as seen in the NNT analysis (where response versus placebo was evident every 2 to 6 patients). Some of the NNHs were statistically significant: hypotension with olanzapine (NNH = 50), headache with ziprasidone and aripiprazole (NNH = 15 and NNH = 20, respectively), and nausea with aripiprazole (NNH = 17).

Figure 1. Response and Number Needed to Treat for Ziprasidone, Olanzapine, and Aripiprazole at the Doses Recommended by the Manufacturer, and Comparators



[a]Response for ziprasidone defined as at least a 2-point reduction in Behavioral Activity Rating Scale 2 hours after the first injection.[8,9] NNT = 3, 95% CI = 2 to 4.
[b]Response for olanzapine was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[10–15] NNT = 3, 95% CI = 2 to 3.
[c]Response for aripiprazole was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[18–20] NNT = 5, 95% CI = 4 to 8.
[d]Response for haloperidol was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[10–13,18,19] NNT = 4, 95% CI = 3 to 5.
[e]Response for lorazepam was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[14,15,20] NNT = 4, 95% CI = 3 to 7.
Abbreviations: IM = intramuscular, NNT = number needed to treat.

Table 3. Treatment-Emergent Adverse Events Reported in Product Labeling

Second-Generation Antipsychotic	Adverse Event	NNH Versus Placebo	95% Confidence Interval[d]
Ziprasidone[a]	Somnolence	22	NS* (–27 to –∞ and 8 to ∞)
	Nausea	18	NS* (–74 to –∞ and 8 to ∞)
	Dizziness	37	NS* (–35 to –∞ and 12 to ∞)
	Headache	15	8 to 703
Olanzapine[b]	Somnolence	34	NS* (–179 to –∞ and 16 to ∞)
	Dizziness	50	NS* (–108 to –∞ and 21 to ∞)
	Hypotension	50	30 to 154
	Asthenia	100	NS* (–93 to –∞ and 33 to ∞)
Aripiprazole[c]	Headache	20	11 to 170
	Nausea	17	11 to 38
	Dizziness	34	NS* (–137 to –∞ and 15 to ∞)
	Somnolence	34	NS* (–238 to –∞ and 16 to ∞)

*NS = not statistically significant at $p < .05$.
[a]Data from Pfizer,[5] Table 5, calculated by combining data regarding ziprasidone 10 mg and 20 mg, and comparing this with the placebo-equivalent dose of ziprasidone 2 mg.
[b]Data from Eli Lilly,[6] Table 3.
[c]Data from Bristol-Myers Squibb,[7] Table 3.
[d]When not statistically significant, the 95% confidence interval represents both positive and negative numbers. (See text.)
Abbreviation: NNH = number needed to harm.

Extrapyramidal symptoms can also be examined using NNH (Table 4). Because there is no active comparator, the clinical trials of ziprasidone are not included in this analysis.[8,9] In any event, no signal for an increase in these symptoms was evident in the clinical trial of ziprasidone 20 mg, in which extrapyramidal syndrome was not reported in the 20-mg group,[9] and no clear pattern emerged from the ziprasidone 10-mg study, in which 1 patient in

Table 4. Treatment-Emergent Extrapyramidal Symptoms

Antipsychotic	Disease State	Study Reference	Dose of Haloperidol or Lorazepam	Adverse Event	NNH Versus Placebo[a]	95% Confidence Interval[b]	NNH Versus Active Comparator[a]	95% Confidence Interval[b]
Olanzapine	Schizophrenia	Breier et al,[10,11] 2002[d]	Haloperidol, 7.5 mg	Acute dystonia	ND[c]	NS* (–∞ to ∞)	–20	NS* (–9 to –∞ and 57 to ∞)
				Parkinsonism	142	NS* (–149 to –∞ and 49 to ∞)	–7	–4 to –27
				Akathisia	86	NS* (–227 to –∞ and 36 to ∞)	–15	NS* (–7 to –∞ and 50 to ∞)
				Requiring anticholinergic medication	NA		–15	NS* (–7 to –∞ and 79 to ∞)
	Schizophrenia	Wright et al,[12,13] 2001	Haloperidol, 7.5 mg	Acute dystonia	ND[c]	NS* (–∞ to ∞)	–14	–9 to –38
				Extrapyramidal syndrome	–92	NS* (–21 to –∞ and 36 to ∞)	–21	–11 to –191
				Requiring anticholinergic medication	115	NS* (–19 to –∞ and 15 to ∞)	–7	–5 to –13
	Bipolar mania	Meehan et al,[14,15] 2001	Lorazepam, 2 mg	Acute dystonia	ND[c]	NS* (–∞ to ∞)	ND[c]	NS* (–∞ to ∞)
				Akathisia	99	NS* (–105 to –∞ and 34 to ∞)	–106	NS* (–20 to –∞ and 30 to ∞)
				Requiring anticholinergic medication	46	NS* (–17 to –∞ and 10 to ∞)	17	NS* (–218 to –∞ and 8 to ∞)
	Dementia	Meehan et al,[16,17] 2002[d]	Lorazepam, 1 mg	Acute dystonia	ND[c]	NS* (–∞ to ∞)	ND[c]	NS* (–∞ to ∞)
				Parkinsonism	69	NS* (–183 to –∞ and 29 to ∞)	69	NS* (–183 to –∞ and 29 to ∞)
				Akathisia	ND[c]	NS* (–∞ to ∞)	ND[c]	NS* (–∞ to ∞)
Aripiprazole	Schizophrenia	Andrezina et al,[18] 2006	Haloperidol, 6.5 mg	Extrapyramidal symptoms	–167	NS* (–24 to –∞ and 33 to ∞)	–10	–7 to –18
	Schizophrenia	Tran-Johnson et al,[19] 2007[d]	Haloperidol, 7.5 mg	Acute dystonia	116	NS* (–306 to – and 49 to ∞)	–17	NS* (–8 to –∞ and 172 to ∞)
				Akathisia	47	25 to 349	–12	– 6 to –533
	Bipolar mania	Oren et al,[20] 2005[d,e]	Lorazepam, 2 mg	Acute dystonia	–144	NS* (–28 to –∞ and 46 to ∞)	156	NS* (–164 to –∞ and 53 to ∞)
				Parkinsonism	11	7 to 26	10	7 to 18
				Akathisia	20	12 to 62	20	12 to 62
Haloperidol	Schizophrenia	Breier et al,[10,11] 2002[d]	Haloperidol, 7.5 mg	Acute dystonia	20	NS* (–27 to –∞ and 8 to ∞)		
				Parkinsonism	6	4 to 23		
				Akathisia	13	NS* (–27 to –∞ and 8 to ∞)		
	Schizophrenia	Wright et al,[12,13] 2001	Haloperidol, 7.5 mg	Acute dystonia	14	9 to 38		
				Extrapyramidal syndrome	27	NS* (–27 to –∞ and 8 to ∞)		
				Requiring anticholinergic medication	6	4 to 13		
	Schizophrenia	Andrezina et al,[18] 2006	Haloperidol, 6.5 mg	Extrapyramidal symptoms	10	7 to 22		
	Schizophrenia	Tran-Johnson et al,[19] 2007[d]	Haloperidol, 7.5 mg	Acute dystonia	15	8 to 259		
				Akathisia	10	6 to 40		

*NS = not statistically significant at $p < .05$.
[a]A negative number for NNH implies an advantage for olanzapine or aripiprazole over the comparator.
[b]When not statistically significant, the 95% confidence interval represents both positive and negative numbers. (See text.)
[c]Incidence for the event is zero for the 2 interventions being compared.
[d]Data from all doses of the second-generation antipsychotic were pooled.
[e]Numerical data were determined by physically measuring the printed bar graph on the copy of the poster provided by Bristol-Myers Squibb Company.
Abbreviations: NA = not available, ND = no difference, NNH = number needed to harm.

the 10-mg group experienced moderate akathisia, and 1 patient in the 2-mg group experienced mild extrapyramidal symptoms.[8] Table 4 provides the NNH for events for which incidence data are provided. Different aspects of extrapyramidal symptoms are inconsistently reported from study to study. Incidence data may be provided for the active control and not necessarily for placebo. For olanzapine, statistically significant advantages were seen compared to haloperidol, in that cases of adverse events were avoided every 7 patients treated in terms of parkinsonism, every 14 patients for acute dystonia, every 21 patients for extrapyramidal syndrome, and every 7 patients for prescription of an anticholinergic medication. Similarly for aripiprazole versus haloperidol, extrapyramidal symptoms were avoided every 10 patients. However, among patients in one of the studies of aripiprazole in schizophrenia,[19] risk of akathisia in terms of NNH versus placebo was 47, and in the study in mania[20] NNH for akathisia versus both placebo and lorazepam was 20. In this latter study, NNH for parkinsonism with aripiprazole versus placebo was 11 (and 10 vs. lorazepam).

Examining treatment-emergent extrapyramidal symptoms with haloperidol in the clinical trials of olanzapine or aripiprazole in agitation associated with schizophrenia, NNH versus placebo for "parkinsonism" was relatively strong at 6 in one of the studies,[10,11] and NNH versus placebo for use of anticholinergic medicine was also 6 in another.[12,13] Other studies also evidenced an effect–NNH for "extrapyramidal symptoms" was 10 and NNH for acute dystonia was 15 in one report,[18] and NNH for akathisia was 10 in another study.[19] These NNH magnitudes indicate a stronger adverse effect on these parameters with haloperidol than with either olanzapine or aripiprazole.

Ziprasidone's product label contains a bolded warning about QTc prolongation and sudden death.[5] Data are not available to evaluate this in terms of NNH, and over 5 years' clinical availability has not resulted in evidence that ziprasidone by itself poses a substantial clinical problem in this regard.[4] Comparative intramuscular antipsychotic data are available—the product information[5] includes details of a study evaluating the QTc-prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, which revealed a mean increase in QTc from baseline for ziprasidone of 4.6 ms following the first injection and 12.8 ms following the second injection, compared with 6.0 ms and 14.7 ms for haloperidol, respectively, and with no patients having had a QTc exceeding 500 ms.

Pharmacovigilance. Rare events are usually not detected in pivotal trials. There are no pharmacovigilance studies published regarding the new intramuscular formulations of the second-generation antipsychotics. Data from the first 21 months of postmarketing safety experience with olanzapine IM have been presented in a poster.[27] There were 29 fatalities reported among an estimated worldwide patient exposure to olanzapine intramuscular of 539,000. These cases were complicated by multiple concomitant medications, including benzodiazepines or other antipsychotics, and medically significant risk factors. The manufacturer has issued guidance that olanzapine intramuscular should not be administered to patients with unstable medical conditions and that patients treated with olanzapine intramuscular should have their heart and respiratory rates, blood pressure, and level of consciousness carefully observed for 2 to 4 hours following administration.[28,29] Simultaneous injection of olanzapine intramuscular and parenteral benzodiazepines is not recommended.

Pharmacovigilance data regarding ziprasidone intramuscular or aripiprazole intramuscular are not available for review, the latter having been approved for marketing only recently.

DISCUSSION

Compared with placebo, or placebo equivalent, all 3 of the intramuscular second-generation antipsychotics show impressive efficacy in reducing agitation in the tested populations. Using response as defined by a prespecified amount of reduction on the primary outcome measure as the desired degree of overall efficacy, NNT was strongest (i.e., lowest) for ziprasidone and olanzapine and appeared dose-dependent for these agents. Active comparators were not used in the pivotal trials for ziprasidone, making comparison of that agent with other efficacious interventions difficult. Consistent with the pattern of results as reported in the published pivotal trials, olanzapine demonstrated a degree of superiority in terms of NNT for response against haloperidol in one of the studies (NNT for olanzapine 10 mg versus haloperidol 7.5 mg was 5, 95% CI = 3 to 73),[10,11] and lorazepam in another (NNT for olanzapine 10 mg versus lorazepam 2 mg was 7, 95% CI = 4 to 160).[14,15] The published studies of intramuscular aripiprazole[18,19] demonstrated a disadvantage in terms of NNT for response versus haloperidol; however, this disadvantage was not statistically significant for aripiprazole doses of 5.25, 9.75, or 15 mg.

Product labeling for each of the 3 available intramuscular second-generation antipsychotics provided incidence data for adverse events. Adverse-event profiles differed from agent to agent, but all 3 of the second-generation antipsychotics had a more favorable extrapyramidal side effect profile compared to haloperidol. As per the NNH analysis, a small signal for extrapyramidal effects was noted for aripiprazole; however, it clearly has a lower propensity for these effects compared to haloperidol.

Treatment-emergent adverse events occurring during the pivotal trials revealed statistically significant NNH for aripiprazole in terms of headache (NNH = 20) and

nausea (NNH = 17), and for ziprasidone for headache (NNH = 15). Olanzapine was associated with treatment-emergent hypotension, with an NNH of 50. Although the magnitude of this NNH is large, and thus the effect size is small, the possible consequences of hypotension necessitate closer monitoring. This conclusion is supported by the pharmacovigilance study undertaken by olanzapine's manufacturer and the guidance suggesting the prudent monitoring of blood pressure and pulse. Product labeling for aripiprazole also notes the possibility of orthostatic hypotension and carries a caveat regarding combining that agent with a benzodiazepine.

Although the pivotal trials examined here were all rigorously conducted and provide us with controlled data that we can evaluate with confidence, they suffer from the limitation that the subjects were generally not as severely ill as some patients commonly seen in clinical practice. Moreover, patients with comorbid medical conditions and those taking multiple psychotropic medications are generally excluded from registration studies. Thus, generalizability from these studies may be limited. Although there are published articles systematically describing the "real-world" use of second-generation intramuscular antipsychotics,[30] they are not controlled as a double blind, randomized clinical trial is, and effect size, such as NNT, cannot be adequately calculated. In terms of safety and rare events, pharmacovigilance studies are needed, but very little has so far been reported and not enough for us to compare the different intramuscular second-generation antipsychotics.

The metrics of NNT and NNH are limited to dichotomous or binary outcomes. Although we have calculated NNT based on response as measured by the individual protocol's principal outcome measure, this was a responder analysis and not the same as the primary analysis in the registration studies (for ziprasidone the outcome of interest was area under the curve for the BARS, and for the olanzapine and aripiprazole studies it was change from baseline in the PANSS Excited Component at 2 hours postinjection).

The difference in the definitions of response makes it difficult to compare ziprasidone with olanzapine or aripiprazole. It is not known if a decrease in at least 2 points on the BARS is clinically as important as a reduction of at least 40% on the PANSS-EC. The BARS is a single-item, 7-point scale, and a 2-point decrease represents an improvement of 29% and may be easier to demonstrate at 2 hours than the criterion of response used in the studies of olanzapine and aripiprazole. Moreover, the BARS is essentially a sedation scale, with scores that range from a state of sedation to a state of agitation.[31] This is different from the broader-based PANSS-EC. However, the BARS and the PANSS agitation items (anxiety, tension, hostility, and excitement) do exhibit a statistically significant degree of correlation.[31]

Placebo response rates can fundamentally affect the NNT calculations, and a lower placebo response rate will render a stronger NNT for the drug of interest, all else being equal. The response rates for ziprasidone 2 mg (a placebo-equivalent dose) were 30%[8] and 34%.[9] The response rates for placebo in the olanzapine studies were 20%,[10,11] 33%,[12,13] 44%,[14,15] and 37%.[16,17] The response rates for placebo in the aripiprazole studies were 36%,[18] 36%,[19] and 37%.[20]

Even for studies that share similar design features (such as the ones for olanzapine and aripiprazole), the dose of the haloperidol comparator differs, complicating comparisons. A lower dose of the haloperidol comparator, 6.5 mg[18] versus 7.5 mg,[10–13,19] may make it easier to demonstrate efficacy equivalence for the second-generation antipsychotic being tested. The influence of this choice of a lower haloperidol comparator dose is probably small, given that NNT for response for haloperidol versus placebo was 5 for the aripiprazole study using 6.5 mg as the haloperidol dose[18] and also 5 for the aripiprazole study that used a haloperidol comparator dose of 7.5 mg.[19]

Patient eligibility criteria differed for the studies of ziprasidone, olanzapine, and aripiprazole (Table 1); however, baseline measures of agitation across the studies appear similar—for the studies of aripiprazole, the mean baseline PANSS-EC score was 19, and the range was 15 to 34,[7] while that for olanzapine was 18.4, with a range of 13 to 32.[6] Dividing the mean baseline PANSS-EC score by the number of items yields an average score of 3.8 and 3.7 per component item for the studies of aripiprazole and olanzapine, respectively. The ziprasidone studies did not use PANSS-EC but did report on similar PANSS agitation items at baseline, yielding an average item score ranging from 3.6 to 3.8, depending on the study. The patients themselves shared similar demographics across the published studies (mean ages between 33 and 42 years, male gender 53% to 79%, white race/ethnicity 60% to 73%), except for the study of olanzapine in agitation associated with dementia (mean age = 78 years, percentage male = 39%, percentage white race/ethnicity = 92%).

Acquisition costs can be a significant barrier to adoption of the intramuscular formulations of the second-generation antipsychotics. The price for ziprasidone 20 mg is $9.58, olanzapine 10 mg $19.18, and aripiprazole 9.75 mg $10.68, compared with $2.84 for a 5-mg dose of intramuscular generic haloperidol, $9.36 for a 5-mg dose of intramuscular branded haloperidol, or $0.86 for a 2-mg dose of intramuscular lorazepam (cost to Rockland Psychiatric Center pharmacy, Orangeburg, N.Y., February 26, 2007). However, it is not uncommon for combinations of haloperidol and lorazepam to be used,[32] increasing acquisition costs for the use of first-generation antipsychotics. Cost of using first-generation antipsychotics increases further when prophylactic anti-

cholinergic agents are also used—for example, the cost of benztropine intramuscular 2 mg is $36.95 (cost to Rockland Psychiatric Center pharmacy, February 26, 2007). Any cost analysis should factor in the substantial cost savings in medical and nursing care when an episode of an acute dystonic reaction is avoided by using a second-generation antipsychotic or when future compliance is enhanced by having a more favorable acute treatment experience.

Head-to-head randomized, controlled studies comparing the newer agents, as well as additional pharmacovigilance studies, would be highly desirable.

CONCLUSIONS

Rapid-acting intramuscular second-generation antipsychotics are available for the indication of agitation associated with schizophrenia or bipolar mania. The use of the evidence-based medicine metrics of NNT and NNH help place the newer agents into clinical perspective and lead us to conclude that the newer intramuscular agents differ from the first-generation antipsychotics principally by a lower propensity for extrapyramidal adverse effects, making them easier to use in terms of avoiding the complications of treating acute dystonia and enhancing future compliance by avoiding the unpleasant sensation of akathisia and the nuisance of a tremor. Response rates in terms of reduction of agitation may show a small advantage for some of the agents, as evidenced by data regarding olanzapine over haloperidol. Safety concerns include the small signal for hypotensive events as evidenced for olanzapine, making pharmacovigilance studies imperative.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), ziprasidone (Geodon).

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