ARTICLE: “A Naturalistic Study of Intramuscular Haloperidol Versus Intramuscular Olanzapine for the Management of Acute Agitation”
- **Citation:** Kai MacDonald, MD et al. Journal of Clinical Psychopharmacology & Volume 32, Number 3, June 2012. pp 317-322
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PURPOSE:
- **Research Question(s):** Is there a difference in efficacy and/or safety in the use of haloperidol and olanzapine either alone or in combination with a benzodiazapine in the treatment of agitated patients in a “naturalistic” ED setting.
- **Hypothesis:** The deviation from the “gold standard” of haloperidol and benzodiazapine in recent ED practice does not have the same efficacy as initially thought.

DESIGN:
- **Study Design:** A Structured multicenter retrospective chart review study
- **Outcomes:** Overall, these finding suggest that in a naturalistic emergency department setting, haloperidol monotherapy is less effective at least in requiring Additional Medical Intervention than olanzapine with or without a benzodiazapine or haloperidol plus a benzodiazapine. Moreover, these later 3 regimens seemed comparable.

SUBJECTS:
- **Subjects:** as below
- **Number of Studies / Subjects:** 146 consecutive emergency department patients who received either IM haloperidol or IM olanzapine for agitation
- **Inclusion / Exclusion criteria:** Inclusion criteria consisted of all emergency department patients who received either IM haloperidol or olanzapine with or without concomitant medications during the study period. Exclusion criteria
included treatment with any parenteral medication other than haloperidol or olanzapine for agitation.

- **Demographics:** 2 emergency departments: one serving primarily an urban region and one in a community setting with a combined census of 65,000 visits per year.

**METHODS:**
- **Interventions:** Patient received various doses of haloperidol or olanzapine, with and without various doses of benzodiazepines. They were rated based on a common “agitation” scale and if required they received multiple doses.

- **Study Groups:** Regarding the patient’s presenting complaint, they categorized these as ‘‘psychiatric-related’’ or ‘‘non-psychiatric-related’’ based on a common understanding of emergency department triage. They coded patients as positive for drugs and alcohol (D/A (+)) if they had a urine drug screen (UDS) that contained amphetamines, cocaine, alcohol, or marijuana or had chart notes indicating the presence of alcohol, a positive result in the breathalyzer, or blood alcohol level; benzodiazepine or opioids were not coded positive to avoid potential confounding prescription medications.

**DATA ANALYSIS:**
- **Statistics Used:** The statistics used in this report are primarily descriptive; the study was not powered to detect statistically significant differences between treatments.

- **What, if any, confounding variables were controlled for / adjusted for:** Given the heterogeneous, individualized nature of emergency department charting, adverse effects and clinical significance were ascertained on a case-by-case basis using clinical judgment from the actual recorded nursing and physician observations (ie, “pt groggy” in chart = clinically significant sedation). A subset of charts with sufficiently detailed preintervention and postintervention documentation were abstracted and blinded for demographic information and medication administered. These charts were further analyzed and rated (using pretreatment and posttreatment Clinical Global Impression Y Severity [CGI-S] scale for agitation/psychosis, CGI-S for Adverse Events, and Global CGI-I, which balances clinical efficacy and AE) by a group of blinded doctoral-level clinicians with extensive experience in the assessment and treatment of agitation.

**RESULTS:**
- **Brief answers to research questions:** Across all doses, they found that substantially fewer agitated patients given haloperidol in combination with a benzodiazepine required AMI compared with those treated with haloperidol alone (43% vs 18%). Using the primary outcome measure of ‘‘requiring additional
medication intervention for agitation” (AMI), they found that the addition of a benzodiazepine to haloperidol decreased the proportion of patients who needed AMI for agitation in the subsequent 3-hour period. Overall, the percentage of patients who needed AMI after being treated with IM olanzapine, whether given alone (29%) or in combination with a benzodiazepine (9%), was substantially lower than haloperidol monotherapy (43%) and similar to the haloperidol plus benzodiazepine group (18%). Comparing the most commonly prescribed doses of haloperidol (5 mg) and olanzapine (10 mg), given with or without additional medications, rates of AMI were 26% (25/95) for haloperidol and 4.5% for olanzapine (1/22).

The only charted adverse effect they noted was sedation, and predictably, the addition of lorazepam to either haloperidol or olanzapine yielded higher adverse effect ratings.

- **Limitations:** Lack of randomized treatment assignment, standardized treatment regimens, and systematic assessment of efficacy and adverse effects. Notably, this design results in comparisons of nonequivalent groups. Moreover, a relatively small sample size limited the power to detect statistically significant differences between regimens, and the primary outcome measure need for additional medication for agitation is rather blunt, insensitive to the difference between overt sedation and the calm, wakeful state that facilitates engagement in ongoing care.

**IMPLICATIONS FOR PRACTICE:**
- **Applicable to this clinical practice:** Not a great study but, based on this study, don’t give haloperidol alone. Olanzapine alone at 10mg may be okay, but not better than the usual practice of 5&2.

- **Feasibility (cost, resources, etc):** Is olanzapine in Pyxis, especially in critical care.

- **Clinically Relevant:** No reason to change current practice.

**LEVEL OF EVIDENCE / DECISION FOR USE:**
- **Background** [Consider Replication] Ready for use

- **Level of Evidence:**
  - Ia Evidence obtained from meta-analysis of randomized controlled trials
  - Ib Evidence obtained from at least one RCT
  - IIa Evidence obtained from at least one well-designed controlled study without randomization
  - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study

**III Well-designed non-experimental studies**

- IV Expert committee reports, opinions of experts