Pharmacological management of agitation in emergency settings

A Yildiz, G S Sachs, A Turgay

Objective: To review, firstly, published studies comparing classic antipsychotics, benzodiazepines, and/or combination of both; and secondly, available data on the use of atypical antipsychotic medications in controlling agitation and aggressive behaviour seen in psychiatric patients in emergency.

Method: In the first review, studies comparing antipsychotics, benzodiazepines, and combination of both; and in the second review, efficacy trials of atypical antipsychotics that include an active and/or inactive comparator for the treatment of acute agitation were identified and reviewed. Data from clinical trials meeting the inclusion criteria were summarised by recording improvement rates, definition of improvement, and timing of defined improvement for individual studies.

Results: In the first review, 11 trials were identified meeting the inclusion criteria, eight with a blind design. The total number of subjects was 701. These studies taken together suggest that combination treatment may be superior to the either agent alone with higher improvement rates and lower incidence of extrapyramidal side effects. In the review of atypical antipsychotic agents as acute antiagitation compounds, five studies were identified, three with a blind design. The total number of subjects was 711, of which 15% (104) was assigned to the placebo arm. This review found atypical antipsychotics to be as effective as the classic ones and more advantageous in many aspects.

Conclusion: Atypical antipsychotics such as risperidone, ziprasidone, and olanzapine with or without benzodiazepines should be considered first in the treatment of acute agitation. If these agents are not available the combination of a classic antipsychotic and a benzodiazepine would be a reasonable alternative. An oral treatment should always be offered first for building up an alliance with the patient and suggesting an internal rather than external locus of control.
### Table 1: Demographic and diagnostic features of the studies comparing benzodiazepines, classic antipsychotics, and the combination of both in the treatment of acute agitation

<table>
<thead>
<tr>
<th>Source/year</th>
<th>Mean baseline agitation score SD</th>
<th>Sample size male/female</th>
<th>Age mean±median SD/range</th>
<th>Final diagnostic impression (in the order of frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battaglia/1997</td>
<td>49*</td>
<td>Not stated/Not stated</td>
<td>25/7</td>
<td>25/10</td>
</tr>
<tr>
<td>GarzaTrevino/1989</td>
<td>Median baseline score 60</td>
<td>Not stated</td>
<td>15/9</td>
<td>9/12</td>
</tr>
<tr>
<td>Bieniek/1998</td>
<td>5.2*</td>
<td>5.5*</td>
<td>5/4</td>
<td>8/3</td>
</tr>
<tr>
<td>Barbea/1992</td>
<td>18.5</td>
<td>18.1</td>
<td>8/6</td>
<td>3/11</td>
</tr>
<tr>
<td>Dorevitch/1999</td>
<td>49</td>
<td>45.4</td>
<td>5/8</td>
<td>8/7</td>
</tr>
<tr>
<td>Chouinard/1993</td>
<td>16.6</td>
<td>16.8</td>
<td>4/4</td>
<td>6/2</td>
</tr>
<tr>
<td>Salzman/1991</td>
<td>7.1</td>
<td>9.0</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Richards/1998</td>
<td>5.6</td>
<td>5.3</td>
<td>Sedation scale score (6 point)</td>
<td>62/40</td>
</tr>
<tr>
<td>Foster/1997</td>
<td>61.5</td>
<td>10.7</td>
<td>BPRS</td>
<td>14/6</td>
</tr>
<tr>
<td>Wyant/1990</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No baseline evaluation</td>
<td>5/0</td>
</tr>
<tr>
<td>Richards/1997</td>
<td>5.5</td>
<td>5.1</td>
<td>Sedation scale score (6 point)</td>
<td>46/26</td>
</tr>
</tbody>
</table>

*Numeric data are estimated from the graphic presentation. Comb, combination treatment; CI Aps, classic antipsychotic; benz, benzodiazepine. BPRS, brief psychiatric rating scale (11 selected item: hostility, suspiciousness, uncooperativeness, unusual thought content, disorganised conceptualisation, hallucinatory behaviour, grandiosity, anxiety, excitement, tension, mannerisms/posturing); VAS, visual analogue scale for agitation (100 mm); OAS, overt aggression scale; BPRS, brief psychiatric rating scale (psychoticism subscale: suspiciousness, conceptual disorganisation, hallucinatory behaviour, uncooperativeness, unusual thought content, and excitement); IMPs, brief psychiatric rating scale (psychoticism subscale: suspiciousness, conceptual disorganisation, hallucinatory behaviour, uncooperativeness, unusual thought content, and excitement).
<table>
<thead>
<tr>
<th>Source/year/ design</th>
<th>Study drugs and dosing (mg/injection or dose) and adm route</th>
<th>Improvement rate (%)</th>
<th>Sample size (number included in the analysis)</th>
<th>Definition of improvement</th>
<th>Time for defined improvement</th>
<th>Incidence of EPS side effects (%)</th>
<th>Conclusion</th>
<th>Study environment and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battaglia/ 1997/DBR</td>
<td>Lorazepam 2 mg im/haloperidol 5 mg im/combination of them im</td>
<td>91 71 74</td>
<td>32 35 31</td>
<td>Need for 3 or less doses of study medication</td>
<td>3 hours</td>
<td>6 20 3</td>
<td>Combination is significantly more effective</td>
<td>ED/24 hours</td>
</tr>
<tr>
<td>GarzaTrevino/ 1989/random</td>
<td>Lorazepam 4 mg im/haloperidol 5 mg im/combination of them im</td>
<td>100 71 83</td>
<td>24 21 23</td>
<td>VAS becoming &lt;20 mm</td>
<td>60 minutes Not stated Not stated Not stated</td>
<td>Combination is significantly more effective</td>
<td>Not stated/ 210 minutes</td>
<td></td>
</tr>
<tr>
<td>Bieniek/1998/ DBR</td>
<td>Lorazepam 2 mg im/haloperidol 5 mg im plus lorazepam 2 mg im</td>
<td>100 55 59</td>
<td>9 11</td>
<td>Decrease of 4 or more points on OAS</td>
<td>60 minutes 0 0</td>
<td>Combination is significantly more effective</td>
<td>ED/3 hours</td>
<td></td>
</tr>
<tr>
<td>Barbea/1992/ DBR</td>
<td>Alprozolam 1 mg po plus haloperidol 5 mg po/lorazepam 2 mg po</td>
<td>93 64 14</td>
<td>14 14</td>
<td>BPRS psychosis subscale &lt;12, or sedated</td>
<td>4 hours 36 64</td>
<td>Combination is significantly more effective</td>
<td>ED/72 hours</td>
<td></td>
</tr>
<tr>
<td>Dorevitch/1999/DBR</td>
<td>Flunitrazepam 1 mg im/haloperidol 5 mg im</td>
<td>92 80 13</td>
<td>15 15</td>
<td>Improvement of at least 50% in OAS</td>
<td>90 minutes</td>
<td>0 0</td>
<td>No significant difference in efficacy</td>
<td>Inpatient/2 hours</td>
</tr>
<tr>
<td>Chouinard/1993/DBR</td>
<td>Clonazepam 1–2 mg im/haloperidol 5–10 mg im</td>
<td>75 63 8</td>
<td>8 8</td>
<td>Improvement of 50% on IMPS manic symptoms subscale</td>
<td>2 hours</td>
<td>13 0</td>
<td>No significant difference in efficacy (Cl Aps faster action)</td>
<td>Inpatient and ED/2 hours</td>
</tr>
<tr>
<td>Salzman/1991/DB</td>
<td>Lorazepam 2 mg im/haloperidol 5 mg im</td>
<td>27 59 26</td>
<td>22 22</td>
<td>% of patients who had greater than mean improvement on OAS</td>
<td>2 hours</td>
<td>50 5</td>
<td>Benz has a significantly superior efficacy</td>
<td>Inpatient/ 24 hours</td>
</tr>
<tr>
<td>Richards/1998/random</td>
<td>Lorazepam 2–4 mg iv/droperidol 2.5–5 mg iv</td>
<td>92 60 102</td>
<td>100 100</td>
<td>Sedation scale score being &lt;4</td>
<td>30 minutes</td>
<td>1 0</td>
<td>Droperidol (Cl Aps) has a significantly superior efficacy</td>
<td>ED/1 hour</td>
</tr>
<tr>
<td>Foster/1997/ DBR</td>
<td>Lorazepam 2 mg im/po/haloperidol 5 mg im/po</td>
<td>35 36 20</td>
<td>17 17</td>
<td>% Improvement in BPRS according to baseline</td>
<td>4 hours</td>
<td>0 0</td>
<td>No significant difference in efficacy (Benz po is recommended by authors)</td>
<td>ED/4 hours</td>
</tr>
<tr>
<td>Wyant/1990/ SBR</td>
<td>Midazolam 5 mg im/haloperidol 10 mg im/sodium amytal 250 mg im</td>
<td>34* 75* 5</td>
<td>5 5</td>
<td>Improvement indicated by CGRS on motor agitation mean score, according to maximum possible improvement</td>
<td>2 hours Not stated Not stated</td>
<td>Benz more effective than Cl Aps on motor agitation</td>
<td>Inpatient/2 hours</td>
<td></td>
</tr>
<tr>
<td>Richards/1997/random</td>
<td>Lorazepam 2–4 mg iv/droperidol 2.5–5 mg iv</td>
<td>71 55 72</td>
<td>74 74</td>
<td>% Improvement in sedation scale score according to baseline</td>
<td>60 minutes</td>
<td>1 0</td>
<td>Droperidol (Cl Aps) produces more rapid and profound sedation</td>
<td>ED/60 minutes</td>
</tr>
</tbody>
</table>

* Numeric data are estimated from the graphic presentation. DBR, double blind randomised; SBR, single blind randomised; DB, double blind; randomised; ED, emergency department. Other abbreviations as in table 1.
Table 3  Demographic and diagnostic features of the studies comparing atypical antipsychotics with classic antipsychotics and/or benzodiazepines and/or placebo in the treatment of acute agitation

<table>
<thead>
<tr>
<th>Source/yyy</th>
<th>Final diagnostic impression (in the order of frequency)</th>
<th>Atyp Aps</th>
<th>Cl Aps</th>
<th>Placebo</th>
<th>Benz Aps</th>
<th>Atyp Aps</th>
<th>Cl Aps</th>
<th>Placebo</th>
<th>Benz Aps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currier/2001</td>
<td>psychosis NOS, mania, schizophrenia</td>
<td>37.3a</td>
<td>32.8</td>
<td>10.5</td>
<td>9.3</td>
<td>18.4</td>
<td>18.2</td>
<td>8.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Brook/2000</td>
<td>schizophrenia, schizoaffective dis, brief psychotic dis, schizophreniform dis, bipolar dis, delusional dis, psychosis NOS</td>
<td>3.8 (positive subscale) (stated for the entire sample)</td>
<td>11.6</td>
<td>18.75</td>
<td>15.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones/2001*</td>
<td></td>
<td>18.4</td>
<td>13.4</td>
<td>3.0</td>
<td>1.0</td>
<td>19.0</td>
<td>13.2</td>
<td>6.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Wright/2001*</td>
<td></td>
<td>18.4</td>
<td>13.4</td>
<td>3.0</td>
<td>1.0</td>
<td>19.0</td>
<td>13.2</td>
<td>6.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Meehan/2001</td>
<td></td>
<td>18.4</td>
<td>13.4</td>
<td>3.0</td>
<td>1.0</td>
<td>19.0</td>
<td>13.2</td>
<td>6.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Yildiz/2003†</td>
<td></td>
<td>18.4</td>
<td>13.4</td>
<td>3.0</td>
<td>1.0</td>
<td>19.0</td>
<td>13.2</td>
<td>6.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>

*Same study reported in different ways. †The study was conducted at the Harvard Medical School, Massachusetts General Hospital, and the article is in press. Age, Aps, Atyp, Benz, CI, Cl, Female, Male, Median, Mean, Male/Female, Mean baseline agitation score, Sample size, SD, Standard deviation.

The main search terms “treatment of acute agitation”, “psychiatric emergency”, “chemical restraint”, “benzodiazepines”, and “conventional antipsychotics”. Augmented by the use of the key words, we identified all efficacy trials of atypical antipsychotics, which included an active and/or inactive comparator for the treatment of acute agitation that has appeared in English since the advent of atypical antipsychotics. Augmented by the use of citations of the review articles on this topic, this process provided 16 citations. We selected for further review the reports in which adult psychiatric patients with acute agitation were assigned to treatment with a novel antipsychotic or a classic high potency neuroleptic or a benzodiazepine or placebo. Retrospective studies or the studies comparing the efficacy of two or more neuroleptic agents or two or more benzodiazepines or two or more combination treatments unless either of them was used as a control were excluded.

In a second review through a computer assisted literature search of the National Library of Medicine’s Medline, by using “treatment of acute agitation”, “atypical antipsychotics” as the key words, we identified all efficacy trials of atypical antipsychotics, which included an active and/or inactive comparator for the treatment of acute agitation that has appeared in English since the advent of atypical antipsychotics. Augmented by the use of citations of the review articles on this topic, this process provided 16 citations. We selected for further review the reports in which adult psychiatric patients with acute agitation were assigned to treatment with a novel antipsychotic or a classic high potency neuroleptic or a benzodiazepine or placebo. Retrospective studies or the studies comparing the efficacy of two or more atypical antipsychotic agents or an atypical antipsychotic in two or more different doses are excluded. As the efficacy trials of the novel antipsychotics on the short-term management of agitation are limited; in this review, we included studies in which reassessment scores within the first 72 hours of the pharmacological interventions were reported.

Issues of diagnosis, relative efficacy, dose, route of administration, study duration/environment, sample size, sex, age, assessment scale, and timing for defined improvement are considered. Because of lack of consistency among studies in design, patient selection, rating scales, definition of improvement, and duration of treatment, we could not perform meta-analyses of the published treatment studies in this field. However, we report improvement rates, definition of improvement, and timing of the defined improvement for individual studies, in an attempt to aid an easy interpretation of the relative actions of these drugs in emergency in controlling agitation/aggression. The improvement rates for the individual studies are calculated by the authors based on the data provided in the corresponding studies unless they were originally given as percentages.

RESULTS

Review 1 Classic antipsychotics versus benzodiazepines and/or combination of both

In our first review, 11 trials meeting our inclusion criteria were identified. Of these 11 trials, eight used a blind design. The total number of subjects was 701 (tables 1 and 2).

There were four studies rendering the combination treatment as a study arm. All of the four trials reported the combination treatment to be significantly more effective than the comparison group. Two of them were three armed studies comparing lorazepam plus haloperidol to each drug alone. They established that combination treatment was superior to either drug alone. Three studies evaluating the side effects reported fewer incidences of extrapyramidal system (EPS) side effects in the combination group than the group taking classic antipsychotic alone (table 2).
<table>
<thead>
<tr>
<th>Source/year/design</th>
<th>Study drugs and dosing (mg/injection or dose) and adm route</th>
<th>Improvement rate (%)</th>
<th>Sample size (n included in the analysis)</th>
<th>Definition of improvement</th>
<th>Time for defined improvement</th>
<th>Incidence of EPS side effects (%)</th>
<th>Conclusion</th>
<th>Study environment and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currier/2001/rater blinded</td>
<td>Risperidone 2 mg po plus lorazepam 2 mg po/haloperidol 5 mg im</td>
<td>62 71</td>
<td>30 30</td>
<td>% Improvement in PANSS according to baseline</td>
<td>60 minutes</td>
<td>0 3</td>
<td>No significant difference between the two treatment groups</td>
<td>ED/24 hours</td>
</tr>
<tr>
<td>Brook/2000/random</td>
<td>Ziprasidone 10 mg im/haloperidol 2.5–10 mg im</td>
<td>13 7</td>
<td>83 40</td>
<td>% Improvement in BPRS according to baseline</td>
<td>72 hours</td>
<td>0 21.4</td>
<td>Ziprasidone is significantly more effective and better tolerated</td>
<td>Inpatient/72 hours</td>
</tr>
<tr>
<td>Jones/2001* / DBR</td>
<td>Olanzapine 10 mg im/haloperidol 7.5 mg im/placebo im</td>
<td>27</td>
<td>Not stated Not stated</td>
<td>% Improvement in BPRS positive subscale according to baseline</td>
<td>2 hours Not stated Not stated Not stated</td>
<td>Olanzapine and haloperidol are superior to placebo but not significantly differ from each other</td>
<td>Inpatient/24 hours</td>
<td></td>
</tr>
<tr>
<td>Wright/2001* / DBR</td>
<td>Olanzapine 10 mg im/haloperidol 7.5 mg im/placebo im</td>
<td>73 69 33</td>
<td>131 126 54</td>
<td>Improvement of at least 40% in excited component of PANSS</td>
<td>2 hours</td>
<td>0 8 Not stated 5.6</td>
<td>Olanzapine is not inferior to haloperidol in efficacy; has a significantly more rapid onset of action</td>
<td>Inpatient/24 hours</td>
</tr>
<tr>
<td>Meehan/2001/DBR</td>
<td>Olanzapine 10 mg im/haloperidol 2 mg im/placebo im</td>
<td>74</td>
<td>38 54 98 50 51</td>
<td>% Improvement in excited component of PANSS according to baseline</td>
<td>2 hours</td>
<td>No significant difference in EPS side effects Not stated</td>
<td>Olanzapine is superior to placebo and lorazepam in reducing agitation Not stated/24 hours</td>
<td></td>
</tr>
<tr>
<td>Yildiz/2003†/observ</td>
<td>Risperidone 1–2 mg po ± lorazepam 1 mg po/haloperidol 2–5 mg im or po ± lorazepam 1–2 mg im or po</td>
<td>57 41</td>
<td>8 10</td>
<td>% Improvement in BPRS according to baseline</td>
<td>2 hours</td>
<td>0 0</td>
<td>Risperidone is not inferior to haloperidol in efficacy</td>
<td>ED/2 hours</td>
</tr>
</tbody>
</table>

*Same study reported in different ways. †The study was conducted at the Harvard Medical School, Massachusetts General Hospital, Acute Psychiatry Service; and the article is in press. Observ, observational. Other abbreviations as in table 1.
Among the seven studies comparing a benzodiazepine with a classic antipsychotic, improvement rates with the classic antipsychotic group were higher than the benzodiazepine group in four studies. However, two studies reported an insignificant difference in efficacy, while in the other two, droperidol was the classic antipsychotic agent used, which was found to have a significantly superior efficacy than the benzodiazepine comparator. In three studies, improvement rates in the benzodiazepine group were higher than the classic antipsychotic group. Two of these studies found a significant difference in the anti-agitation effect of the benzodiazepine over the classic antipsychotic comparator. In one study, the difference in the improvement rates was found insignificant, however, the authors have recommended the use of benzodiazepine by mouth as a first line anti-agitation compound. Six studies evaluating the side effects reported fewer incidences of EPS side effects in the benzodiazepine group than the group taking classic antipsychotic (table 2).

These studies taken together suggest that combining haloperidol, 5 mg, and lorazepam, 2 mg, orally or intramuscularly (in the same syringe) as required is an effective approach to the rapid tranquilisation of the agitated patient in emergency settings.

Review 2 Atypical versus classic antipsychotics and/or benzodiazepines and/or placebo

In our review of atypical antipsychotic agents as acute anti-agitation compounds, five comparison trials (six reports) were identified using a classic antipsychotic or a benzodiazepine or placebo as a comparator to an atypical antipsychotic. Among the seven studies comparing a benzodiazepine with a classic antipsychotic, improvement rates with the classic antipsychotic group were higher than the benzodiazepine group in four studies. However, two studies reported an insignificant difference in efficacy, while in the other two, droperidol was the classic antipsychotic agent used, which was found to have a significantly superior efficacy than the benzodiazepine comparator. In three studies, improvement rates in the benzodiazepine group were higher than the classic antipsychotic group. Two of these studies found a significant difference in the anti-agitation effect of the benzodiazepine over the classic antipsychotic comparator. In one study, the difference in the improvement rates was found insignificant, however, the authors have recommended the use of benzodiazepine by mouth as a first line anti-agitation compound. Six studies evaluating the side effects reported fewer incidences of EPS side effects in the benzodiazepine group than the group taking classic antipsychotic (table 2).

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**Intramuscular compared with oral route of administration in emergency treatment of agitation**

When an agitated patient walks in an emergency department the primary focus is often to stabilise the positive symptoms and parapositive symptoms in a rapid time course, which may lead to overuse of physical/chemical restraints. As a result of documentation of the traumatic aspects of restraints, the US Health Care Finance Administration’s (HCFA) new interim final rules concerning use of physical and chemical restraints. According to this, “A drug used as a restraint is not a standard treatment for the patient’s medical and psychiatric condition” and patient participation in the planning and conduct of treatment and the right to refuse unwanted treatment are the central premises of the regulations. In that sense, the indications for the use of involuntary treatment with an intramuscular route need to be re-evaluated in the light of some of the commonly overlooked potential impacts on the patients’ acute and subacute course.

Compliance of the patients with medication treatment may be influenced by their experiences in emergency setting. An injectable medication use is likely to be experienced as an assault invoking images of punishment and incarceration for the patient rather than those of therapy and relief. As a result, this can influence the establishment of therapeutic alliance between the patient and caregivers and affect compliance and cooperation with subsequent treatment.

The clinicians need to understand the dynamics of agitation/aggression. Aggressive behaviour is frequently the result of an acute narcissistic injury. Besides, the aggressive patient’s behaviour frequently leads to circumstances that cause additional shame and embarrassment, such as police action, restraint and seclusion, and psychiatric evaluation. The clinician must avoid responding to the patient’s aggression in a punitive manner, instead take action with a respectful, non-judgmental, and reassuring attitude such as offering the patient an active choice in their treatment suggesting an internal rather than an external locus of control.

The advantages and disadvantages of choosing an intramuscular route have to be considered seriously for a rapid behavioural control in agitation. Interestingly, there is evidence indicating that oral drugs can be as effective as the intramuscular ones, and the onset of action of intramuscular drugs is not significantly more rapid to warrant its use as a first intervention. Moreover, it seems that parapositive symptoms are less problematic with intramuscular route of administration. In addition, the intramuscular route is more appropriate in patients with multiple comorbidities, such as those with significant cognitive impairment, who may have difficulty swallowing or vomiting. Furthermore, intramuscular administration is preferred in patients with oral dyskinesia, which can be triggered by oral administration of antipsychotics and potentially worsen the agitation.

In summary, the choice of route of administration should be made based on the specific needs and preferences of the patient, as well as the clinical situation. Intramuscular administration may be preferred in some situations, but oral administration should also be considered as an effective and less invasive alternative.
However, despite the belief that patients may be too agitated and uncooperative to take oral drugs, it has been shown that that most patients will indeed cooperate with an oral dosing regimen.\textsuperscript{35-37} In a recent survey, it was found that most medical directors of psychiatric emergency programmes would prefer to administer an oral atypical agent if such an agent were found to be effective, safe, reliable, and practical to use.\textsuperscript{38} Consequently, intramuscular treatment should be reserved for the agitated patients for whom parenteral treatment is the only feasible alternative.

CONCLUSIONS

This review provided support from the literature for the effective use of antipsychotic medications and benzodiazepines in controlling agitation and aggression in emergency settings. The conclusions of the review were: (1) A combined use of a classic antipsychotic and a benzodiazepine may produce an anti-agitation effect superior to either drug alone in a safer manner. (2) Some of the atypical antipsychotic agents are at least as effective as the classic high potency alternatives and/or benzodiazepines providing a better safety profile. (3) Agitation and aggressive behaviour seem to be linked to abnormalities in dopaminergic, serotonergic, noradrenergic, and sometimes glutamatergic-GABAergic systems. Accordingly, atypical antipsychotic agents by virtue of their activities on various dopaminergic, serotonergic, noradrenergic, and histaminergic receptors may possess a distinctive anti-agitation effect. In situations where a reduced GABAergic transmission is suspected combining an atypical antipsychotic with a benzodiazepine would be beneficial. (4) As drugs are often prescribed before assessment in emergency settings, associated physical and psychiatric illnesses may be overlooked.\textsuperscript{35-37} Thus, safety of the anti-agitation compound is at least as important as its efficacy; and atypical antipsychotics have a safer safety profile than the classic ones. While the investigations are taking place to rule out organicity behind the agitation, it will be safer to use atypical antipsychotics as they have less risk for affecting the vital signs including blood pressure. (5) This review indicates that a comparatively benign psychopharmacological intervention may be adequate to calm agitated psychiatric patients and an oral route of administration should always be offered first. This would build up an alliance with the patient and suggest an internal rather than external locus of control. Present data suggest that oral treatment with an atypical antipsychotic (with or without a benzodiazepine) may be as effective as the intramuscular injection route with a classic antipsychotic drug. Therefore, an overreliance on an intramuscular route of administration should be avoided and intramuscular treatment should be reserved for patients who cannot cooperate with the treatment/physician or favour the intramuscular treatment. In these cases, where an injection is required, the least offensive drug should be used. Timing for reassessment of agitation should then be adjusted according to the route of administration; and should occur in about 30 minutes after intramuscular administration and 30 to 60 minutes after oral administration of drugs.\textsuperscript{39} Non-responders may receive additional medications in oral or intramuscular formulations as needed. (6) Based on the available data to date, among the present novel antipsychotic agents, risperidone, ziprasidone, and olanzapine seem to be more fitting as acute antiagitation compounds.

As more data become available on the use of atypical compared with classic antipsychotics and benzodiazepines in emergency situations, further refinement of the treatment of agitation/aggression and the development of specific algorithms will be viable.

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Contributors

Ayselgül Yildiz initiated and formulated the primary study hypothesis, designed the protocol, collected and documented the data and wrote the paper. Gary Sachs discussed core ideas, participated in the design, and execution of the study particularly data documentation and quality control. Atilla Turgay discussed core ideas and interpretation of the findings, and edited the paper. Ayselgül Yildiz and Atilla Turgay are the authors who will act as “guarantors”.

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