ORIGINAL ARTICLE

# Pharmacological management of agitation in emergency settings

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**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.

Agitation is a non-specific constellation of comparatively unrelated behaviours that possess a risk to the safety of the patient or caregiver, impedes the process of care giving or impairs a person's function.[1 2] Representing a state of poorly organised and aimless psychomotor activity stemming from physical or mental unease; agitation, can be seen in a variety of clinical situations, such as; delirium, dementia, psychoactive substance intoxication and withdrawal, schizophrenia, delusional disorder, psychotic disorder NOS, bipolar disorder, major depressive disorder, anxiety disorder, acute reaction to stress, post-traumatic stress disorder, antisocial/borderline/paranoid personality disorder, autism, mental retardation, attention deficit hyperactivity disorder, conduct disorder, and akathisia.[1 3] Given the diversity of clinical entities from which agitation may arise it is not surprising that it is among the most commonly encountered clinical problems in psychiatric facilities and hospital emergency services. However, quite surprisingly this area has received such little attention and has not been a target for clinical trials until recently. Thus, tremendous variability exists in approach to agitation, both across geographical regions and across providers within regions.[4]

During the past decade or so classic antipsychotics and benzodiazepines have been used to control agitation/aggression first as monotherapy and then in combination as a result of some potentially serious adverse effects of these agents.[5–14] While, the question of best clinical practice among the classic antipsychotics versus benzodiazepines versus combination of both waits for an answer, atypical antipsychotics have been introduced recently. Stemming from the observations based on a longer term use, a few investigators have investigated the usefulness of atypical antipsychotics specifically in the first a few hours of treatment of agitated patients.[15] Although, data coming from these initial trials are quite encouraging, the use of atypical antipsychotics in emergency services before the use of traditional antipsychotics like haloperidol needs to be incorporated into the service guidelines in emergency settings. This may in part relate to the unfortunate clinical impression that these novel drugs may not be very effective in the acutely agitated and psychotic patient and intramuscular route of administration is an absolute necessity in such emergency situations.[16] Indeed, in many settings, intramuscular medications are first line treatment for agitation with or without psychosis and intramuscular formulations of the novel agents are yet to be available for common use.[16] Unfortunately, an emergency practice over-reliance on classic intramuscular antipsychotics without evidence of necessity, not only puts these patients with psychotic disorders who require emergency intramuscular treatment still at risk of adverse effects of these agents during critical phases of their illness, but also delays the start of treatment with novel antipsychotics with superior efficacy and safety profile.[17]

Originating from an unmet clinical need on the management of agitation in emergency situations, this article has three objectives: (1) To examine published studies comparing conventional antipsychotics, benzodiazepines, and/or combination of both to achieve calm in acutely agitated psychiatric patients. (2) To review available data on the use of atypical antipsychotic medications for acute treatment of agitation associated with psychiatric illness. (3) To present an evidence based discussion on the route of administration of anti-agitation treatment.

## METHOD

A computer assisted literature search of the National Library of Medicine's Medline has been completed with the use of

**Table 1** Demographic and diagnostic features of the studies comparing benzodiazepines, classic antipsychotics, and the combination of both in the treatment of acute agitation

| Source/year | Mean baseline agitation score SD | | | Assessment scale | Sample size male/female | | | Age mean[a]–median[b] SD[c]/range[d] | | | Final diagnostic impression (in the order of frequency) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Comb | Cl Aps | Benz | | Comb | Cl Aps | Benz | Comb | Cl Aps | Benz | |
| Battaglia/1997 | 49*<br>Not stated | 46.7*<br>Not stated | 50.6*<br>Not stated | BPRS<br>(11 selected item) | 25/7 | 25/10 | 23/8 | 34.4[a]<br>18–54[d] | 34.3[a]<br>18–56[d] | 33.9[a]<br>19–57[d] | Schizophrenia, psychosis NOS, psychoactive substance use, mania, schizophreniform disorder |
| GarzaTrevino/ 1989 | Median baseline score<br>60 | | | VAS | 15/9 | 9/12 | 17/6 | Not stated† | Not stated† | Not stated† | Mania, schizophrenia, atypical psychosis, miscellaneous diagnosis |
| Bieniek/1998 | 5.2*<br>Not stated | | 5.5*<br>Not stated | OAS | 5/4 | | 8/3 | 41[b]<br>18–50[d] | | 35[b]<br>18–50[d] | Mania, psychosis NOS, Sch paranoid, substance induced, brief reactive psychosis, Sch undifferentiated |
| Barbea/1992 | 18.5<br>6.8 | 18.1<br>3.5 | | BPRS<br>(Psychoticism subscale) | 8/6 | 3/11 | | 33.4[a]<br>5.8[c]<br>18–60[d] | 32.5[a]<br>6.2[c]<br>18–60[d] | | Schizophrenic patients in psychotic relapse |
| Dorevitch/1999 | | 49.0<br>6.6 | 45.4<br>6.7 | BPRS | | 5/8 | 8/7 | | 36.8[a]<br>15.1[c] | 34.9[a]<br>8.1[c] | Schizophrenia, schizoaffective disorder, bipolar disorder |
| Chouinard/ 1993 | | 16.6<br>5.2 | 16.8<br>3.0 | IMPS manic symptoms subscale | | 4/4 | 6/2 | | 34.6[a]<br>10.3[c]<br>18–60 | 35.3[a]<br>9.7[c]<br>18–60 | Bipolar disorder, schizophrenia, schizoaffective disorder, brief reactive psychosis |
| Salzman/1991 | | 7.1<br>Not stated | 9.0<br>Not stated | OAS | | Not stated | Not stated | | 37.9[a]<br>Not stated | 30.5[a]<br>Not stated | Schizophrenia, other (psychotic depression, personality dis, deferred), bipolar disorder, organic mental disorder, schizoaffective disorder |
| Richards/1998 | | 5.6<br>0.6 | 5.3<br>0.7 | Sedation scale score<br>(6 point) | | 62/40 | 63/37 | | 33.2[a]<br>10.2[c]<br>>18[d] | 34.6[a]<br>10.8[c]<br>>18[d] | Methamphetamine toxicity, cocaine toxicity, psychiatric illness, ethanol withdrawal |
| Foster/1997 | | 61.5<br>10.7 | 60.4<br>11.6 | BPRS | | 14/6 | 12/5 | | 42.4[a]<br>12.0[c]<br>18–61 | 41.4[a]<br>10.6[c]<br>18–61 | Schizophrenia, bipolar disorder, psychotic disorder NOS, schizoaffective disorder |
| Wyant/1990 | | Not stated | Not stated | No baseline evaluation | | 5/0 | 5/0 | | 43.4[a]<br>11.0[c]<br>28–59 | 35.6[a]<br>5.2[c]<br>28–59 | Chronic undifferentiated schizophrenia, chronic paranoid schizophrenia |
| Richards/1997 | | 5.5<br>0.6 | 5.1<br>0.7 | Sedation scale score<br>(6 point) | | 46/26 | 52/22 | | 34.6[a]<br>10.5[c] | 32.3[a]<br>10.2[c] | Methamphetamine toxicity |

*Numeric data are estimated from the graphic presentation. Comb, combination treatment; Cl 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); BPRS, brief psychiatric rating scale; IMPS, inpatient multidimensional psychiatric scale (manic symptoms subscale: motor overactivity, elevated mood, pressure of speech, logorrhea and insight); Sch, schizophrenia. †Authors have indicated that the distributions of age ranges were comparable across the three treatment groups and were similar to the age range in their pilot study (17–52 years; median age of 31 years).

**Table 2** Summary of the studies comparing benzodiazepines, classic antipsychotics, and the combination of both in the treatment of acute agitation

| Source/year/design | Study drugs and dosing (mg/injection or dose) and adm route | Improvement rate (%) | | | Sample size (number included in the analysis) | | | Definition of improvement | Time for defined improvement | Incidence of EPS side effects (%) | | | Conclusion | Study environment and duration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Comb | Cl Aps | Benz | Comb | Cl Aps | Benz | | | Comb | Cl Aps | Benz | | |
| Battaglia/1997/DBR | Lorazepam 2 mg im/haloperidol 5 mg im/combination of them im | 91 | 71 | 74 | 32 | 35 | 31 | Need for 3 or less doses of study medication | 3 hours | 6 | 20 | 3 | Combination is significantly more effective | ED/24 hours |
| GarzaTrevino/1989/random | Lorazepam 4 mg im/haloperidol 5 mg im/combination of them im | 100 | 71 | 83 | 24 | 21 | 23 | VAS becoming ⩽20 mm | 60 minutes | Not stated | Not stated | Not stated | Combination is significantly more effective | Not stated/210 minutes |
| Bieniek/1998/DBR | Lorazepam 2 mg im/haloperidol 5 mg im plus lorazepam 2 mg im | 100 | | 55 | 9 | | 11 | Decrease of 4 or more points on OAS | 60 minutes | 0 | | 0 | Combination is significantly more effective | ED/3 hours |
| Barbea/1992/DBR | Alprozolam 1 mg po plus haloperidol 5 mg po/haloperidol 5 mg po | 93 | 64 | | 14 | 14 | | BPRS psychotism subscale <12, or sedated | 4 hours | 36 | 64 | | Combination is significantly more effective | ED/72 hours |
| Dorevitch/1999/DBR | Flunitrazepam 1 mg im/haloperidol 5 mg im | | 92 | 80 | | 13 | 15 | Improvement of at least 50% in OAS | 90 minutes | | 0 | 0 | No significant difference in efficacy | Inpatient/2 hours |
| Chouinard/1993/DBR | Clonazepam 1–2 mg im/haloperidol 5–10 mg im | | 75 | 63 | | 8 | 8 | Improvement of 50% on IMPS manic symptoms subscale | 2 hours | | 13 | 0 | No significant difference in efficacy (Cl Aps faster action) | Inpatient and ED/2 hours |
| Salzman/1991/DB | Lorazepam 2 mg im/haloperidol 5 mg im | | 27 | 59 | | 26 | 22 | % of patients who had greater than mean improvement on OAS | 2 hours | | 50 | 5 | Benz has a significantly superior efficacy | Inpatient/ 24 hours |
| Richards/1998/random | Lorazepam 2–4 mg iv/droperidol 2.5–5 mg iv | | 92 | 60 | | 102 | 100 | Sedation scale score being <4 | 30 minutes | | 1 | 0 | Droperidol (Cl Aps) has a significantly superior efficacy | ED/1 hour |
| Foster/1997/DBR | Lorazepam 2 mg im/po / haloperidol 5 mg im/po | | 35 | 36 | | 20 | 17 | % Improvement in BPRS according to baseline | 4 hours | | 0 | 0 | No significant difference in efficacy (Benz po is recommended by authors) | ED/4 hours |
| Wyant/1990/SBR | Midazolam 5 mg im/haloperidol 10 mg im/sodium amytal 250 mg im | | 34* | 75* | | 5 | 5 | Improvement indicated by CGRS on motor agit mean score, according to maximum possible improvement) | 2 hours | | Not stated | Not stated | Benz more effective than Cl Aps on motor agitation | Inpatient/2 hours |
| Richards/1997/random | Lorazepam 2–4 mg iv/droperidol 2.5–5 mg iv | | 71 | 55 | | 72 | 74 | % Improvement in sedation scale score according to baseline | 60 minutes | | 1 | 0 | Droperidol (Cl Aps) produces more rapid and profound sedation | ED/60 minutes |

*Numeric data are estimated from the graphic presentation. DBR, double blind randomised; SBR, single blind randomised; DB, double blind; random, 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

| Source/ year | Mean baseline agitation score SD | | | | Assessment scale | Sample size male/female | | | | Age mean[a]–median[b] SD[c]/range[d] | | | | Final diagnostic impression (in the order of frequency) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Atyp Aps | CI Aps | Placebo | Benz | | Atyp Aps | CI Aps | Placebo | Benz | Atyp Aps | CI Aps | Placebo | Benz | |
| Currier/ 2001 | 26.7<br>5.2 | 28.5<br>5.7 | | | PANSS‡ (5 observable item) | 23/7 | 16/14 | | | 37.6[a]<br>11.3[c]<br>18–65[d] | 37.3[a]<br>10.7[c]<br>18–65[d] | | | Psychosis NOS, mania, schizophrenia |
| Brook/ 2000 | 45.9<br>10.5 | 47.5<br>9.3 | | | BPRS (total score) | 83/7 | 40/2 | | | 34.5[a]<br>20–66[d] | 32.8[a]<br>19–53[d] | | | Schizophrenia, schizoaffective dis, brief psychotic dis, schizophrenif dis, bipolar dis, delusional dis, psychosis NOS |
| Jones/ 2001* | 10.7<br>3.8 | Not stated | Not stated | | BPRS (positive subscale) | (stated for the entire sample) | 205/106 | | | | 38.2[a]<br>11.6[c] | | | Schizophrenia, schizophrenif dis, schizoaffective dis |
| Wright/ 2001* | 18.4<br>3.4 | 18.2<br>3.2 | 18.4<br>3.5 | | PANSS§ (excited component) | Not stated | Not stated | Not stated | | (stated for the entire sample) | 38.2[a]<br>11.6[c] | | | Schizophrenia, schizophrenif dis, schizoaffective dis |
| Meehan/ 2001 | 13.0<br>3.2 | | 12.7<br>3.1 | 12.4<br>3.0 | PANSS§ (excited component) | 57/42 | | 29/22 | 21/30 | 40.2[a]<br>12.4[c] | | 40.5[a]<br>10.5[c] | 39.0[a]<br>9.7[c] | Bipolar-manic |
| Yildiz/ 2003† | 69.75<br>18.75 | 63.60<br>15.18 | | | BPRS | 1/7 | 8/2 | | | 39.3[a]<br>8.5[c] | 30.6[a]<br>10.0[c] | | | Bipolar-manic, depression, psychosis NOS, schizophrenia, borderline personality disorder |

*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. Atyp Aps, atypical antipsychotic PANSS‡, positive and negative syndrome scale (five directly observable items: excitement, hostility, hallucinatory behaviour, uncooperativeness, and poor impulse control); PANSS§, positive and negative syndrome scale (excited component: tension, uncooperativeness, hostility, poor impulse control, and excitement); schizophrenif, schizophreniform; dis, disorder. Other abbreviations as in table 1.

main search terms "treatment of acute agitation", "psychiatric emergency", "chemical restraint", "benzodiazepines", and "conventional antipsychotics". Augmented by the use of the references listed in the articles identified with the search, this process yielded 128 citations. We selected for further review the reports in which adult psychiatric patients with acute agitation were randomly assigned to treatment with a classic high potency neuroleptic available in the United States or a benzodiazepine or combination of both drugs. For studies to be considered in this review, treatment had to be rendered immediately, and reassessment had to occur in minutes to a maximum of four hours, as the time required for the onset of therapeutic effect is critical in the emergency treatment of agitation. 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.[9 18–27] 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.[18–21] 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.[18 19] 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 4** Summary of the studies comparing comparing atypical antipsychotics with classic antipsychotics and/or benzodiazepines and/or placebo in the treatment of acute agitation

| Source/ year/design | Study drugs and dosing (mg/injection or dose) and adm route | Improvement rate (%) | | | | Sample size (n included in the analysis) | | | | Definition of improvement | Time for defined improvement | Incidence of EPS side effects (%) | | | | Conclusion | Study environment and duration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Atyp Aps | Cl Aps | Placebo | Benz . | Atyp Aps | Cl Aps | Placebo | Benz | | | Atyp Aps | Cl Aps | Placebo | Benz | | |
| Currier/ 2001/rater blinded | Risperidone 2 mg po plus lorazepam 2 mg po/ haloperidol 5 mg im plus lorazepam 2 mg im | 62 | 71 | | | 30 | 30 | | | % Improvement in PANSS according to baseline | 60 minutes | 0 | 3 | | | No significant difference between the two treatment groups | ED/24 hours |
| Brook/ 2000/ random | Ziprasidone 10 mg im/ haloperidol 2.5–10 mg im | 13 | 7 | | | 83 | 40 | | | % Improvement in BPRS according to baseline | 72 hours | 0 | 21.4 | | | Ziprasidone is significantly more effective and better tolerated | Inpatient/ 72 hours |
| Jones/ 2001* / DBR | Olanzapine 10 mg im/ haloperidol 7.5 mg im/ placebo im | 27 | Not stated | Not stated | | 122 | 116 | 47 | | % Improvement in BPRS positive subscale according to baseline | 2 hours | Not stated | Not stated | Not stated | | Olanzapine and haloperidol are superior to placebo but not significantly differ from each other | Inpatient/ 24 hours |
| Wright/ 2001* / DBR | Olanzapine 10 mg im/ haloperidol 7.5 mg im/ placebo im | 73 | 69 | 33 | | 131 | 126 | 54 | | Improvement of at least 40% in excited component of PANSS | 2 hours | 0.8 | 5.6 | Not stated | | Olanzapine is not inferior to haloperidol in efficacy; has a significantly more rapid onset of action | Inpatient/ 24 hours |
| Meehan/ 2001/DBR. | Olanzapine 10 mg im/ lorazepam 2 mg im / placebo im | 74 | | 38 | 54 | 98 | | 50 | 51 | % Improvement in excited component of PANSS according to baseline | 2 hours | No significant difference in EPS side effects | | | | Olanzapine is superior to placebo and lorazepam in reducing agitation | Not stated/ 24 hours |
| Yildiz/ 2003†/ observ | Risperidone 1–2 mg po ± lorazepam 1 mg po/ haloperidol 2–5 mg im or po ± lorazepam 1–2 mg im or po | 57 | 41 | | | 8 | 10 | | | % Improvement in BPRS according to baseline | 2 hours | 0 | 0 | | | Risperidone is not inferior to haloperidol in efficacy | ED/2 hours |

*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.[9 22–27] However, two studies reported an insignificant difference in efficacy, while in the other two, droperidol was the classic antipsychotic agent used,[25 27] 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 agent.[28–33] Three of these studies used a blind design.[28 31 32] The total number of subjects was 711 (five trials), of which 15% (104) was assigned to the placebo arm (tables 3 and table 4 ).

Improvement rates with atypical antipsychotic agents were higher than the corresponding active comparator (in two studies, haloperidol; in one study, lorazepam) in four of the six reports,[29 31–33] this difference was found significant in three of them.[29 31 32] The other three reports indicated that the atypical antipsychotic agent was found to be as effective as its active comparator and/or significantly superior to placebo. All the five trials have evaluated the side effects, with three reporting fewer incidences of EPS side effects in the atypical antipsychotic group than the classic antipsychotic group (table 4). In two studies route of administration was orally (table 4).[28 33] In the first report with orally atypical antipsychotic, Currier and Simpson showed that a substantial number of patients who are in an emergency setting would otherwise have received intramuscular drugs were indeed willing to accept an oral alternative.[28] Furthermore, in this population, oral atypical antipsychotic in combination with an oral benzodiazepine seem to be equally calming and at least as tolerable as injectable alternatives.[28] Our own experience in the pilot study is totally in accordance with this.[33]

## DISCUSSION

This review found that atypical antipsychotics in moderate doses are effective treatment alternatives for agitation in emergency situations. Given the postulated mechanisms underlying agitation in different psychiatric conditions, atypical antipsychotic agents by virtue of their activities on various dopaminergic, serotonergic, noradrenergic, and histaminergic receptors are likely to provide a distinctive anti-agitation effect.[1]

As reflected in the clinical data, among the available atypical antipsychotics, supportive information is available for the use of risperidone, ziprasidone, and olanzapine, which seem to be proper alternatives in the treatment of acute agitation (table 4). In addition to their broader efficacy, and better safety profiles, using these compounds for the treatment of acute agitation offers an opportunity for a pharmacological continuum by transferring the patients to oral maintenance treatment as indicated once their acute symptoms have been ameliorated.[34] Moreover, protection against EPS with these compounds is important as EPS experienced in the acute emergency setting may have an adverse effect on subsequent treatment compliance and cooperation by the patient in the long term. This benefit of atypical antipsychotics is particularly significant, as non-compliance is thought to be responsible for about 40% of hospital readmissions two years after discharge.[17]

In addition, 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 to effect the vital signs including blood pressure compromise the vital in that sense. None the less, the emergency physician should give the highest possible attempt to establish the underlying diagnosis behind the agitation before making any treatment decision. Excluding the cases with organicity, treatment alternatives should be explained to the agitated patient. Besides, the patient should be offered to take an active role in the treatment decision whenever possible.

### 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.[15] 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.[36] 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.[36] 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.[4] 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.[37] As a result, this can influence the establishment of therapeutic alliance between the patient and caregivers and affect compliance and cooperation with subsequent treatment.[37]

The clinicians need to understand the dynamics of agitation/aggression. Aggressive behaviour is frequently the result of an acute narcissistic injury.[3] 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.[3] 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.[3]

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.[38–42] In a recent study, Foster *et al* found no significant interaction between administration route and improvement rates.[9] Indeed, the most important "advantage" of an intramuscular route is in involuntary treatment.

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.[28 38–42]

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.[4] 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.[36 37] Thus, safety of the anti-agitation compound is at least as important as its efficacy; and atypical antipsychotics have a better 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.[36] 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

Aysegul 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. Aysegul Yildiz and Atilla Turgay are the authors who will act as "guarantors".

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