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# Olanzapine orally-disintegrating tablet in severe psychotic agitation: a naturalistic study

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**Introduction.** This study was conducted to determine effectiveness and safety of olanzapine in patients with severe agitation.

**Method.** A naturalistic, open-label study in 80 acutely agitated psychotic patients visited in our psychiatric emergency department. Patients received either a 20-mg olanzapine orally-disintegrating tablet or conventional treatment depending on attending psychiatrist's preference. Efficacy was assessed by the Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC), the Agitation-Calmness Evaluation Scale (ACES) and pragmatic variables (second pharmacological intervention and need for physical restraints).

**Results:** 60 % patients completed a 6 hour trial. Both groups showed a significant reduction in mean PANSS-EC score. The olanzapine-treated group showed statistically significant improvements: PANSS-EC (F = 122.9; df = 2.4; p = 0.000), ACES (F = 68.2; df = 2.8; p = 0.000). Treatment was well-tolerated and no serious side-effects were observed.

**Conclusions.** In this naturalistic study in patients with severe agitation, 20-mg oral olanzapine was effective, rapid and safe.

**Key words:**
Agitation. Olanzapine. Naturalistic study.

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## Olanzapina bucodispersable en la agitación psicótica severa: estudio naturalístico

**Introducción.** El objetivo de este estudio fue determinar la efectividad y seguridad de la olanzapina en pacientes con agitación severa.

**Método.** Estudio naturalístico y abierto en 80 pacientes psicóticos con agitación psicomotriz severa que fueron atendidos en el servicio de urgencias de psiquiatría. Los pacientes recibieron 20 mg de olanzapina bucodispersable o el tratamiento convencional dependiendo de la preferencia del psiquiatra que los evaluó. La eficacia se determinó mediante los componentes de excitación de la escala de evaluación de los síntomas positivos y negativos (PANSS-EC), la escala de evaluación agitación-calma (ACES) y variables pragmáticas (necesidad de segunda intervención farmacológica y necesidad de contención física).

**Resultados.** El 60% de los pacientes completaron el estudio de 6 h de duración. Ambos grupos mostraron una reducción significativa en la media de la puntuación PANSS-EC. El grupo tratado con olanzapina mostró una mejoría estadísticamente significativa: PANSS-EC (F = 122,9; gl = 2,4; p = 0,000), ACES (F = 68,2; gl = 2,8; p = 0,000). El tratamiento fue bien tolerado y no se observaron efectos secundarios severos.

**Conclusiones.** Según este estudio naturalístico en pacientes con agitación psicotica severa la administración de 20 mg de olanzapina oral fue efectiva, rápida y segura.

**Palabras clave:**
Agitación. Olanzapina. Estudio naturalístico.

## INTRODUCTION

Psychomotor agitation is a common event in Emergency Psychiatric Services (PES) with a prevalence of approximately 10 %[1]. Immediate and effective intervention is essential to rapidly control the symptoms. Physical restraints may give rise to traumatic experiences, thereby affecting the future therapeutic alliance[2,3].

Based on our previous naturalistic study[4], 4.3 % of patients who arrived at our PES presented acute agitation. Only 39 % were mechanically restrained, 52 % accepted oral therapy and haloperidol was the most frequent oral treatment. However, in a survey as to patient preference amongst individuals attending PES[5], pharmacological treatment was preferred to physical restraints, and oral treatment was preferred to intramuscular administration. Benzodiazepines were the drug of choice, while typical neuroleptics ranked last.

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Acute agitation is a therapeutic dilemma and there is no general consensus regarding management[2,3]. Benzodiazepines have demonstrated their efficacy[6,7], although they are also known to produce marked sedation and cause respiratory depression, ataxia, disinhibition and confusion[6,8]. These adverse effects are more likely to emerge when the patient has consumed alcohol or toxics or if administered in combination with typical antipsychotics and/ or intravenously[9,10]. Conventional antipsychotics administered orally or parenterally have been the usual treatment for controlling agitated psychotic patients[2,9]. However, these agents are associated with dysphoria and severe extrapyramidal symptoms (EPS), such as acute dystonia and akathisia[6,11].

Atypical antipsychotics are recommended as first-line agents for ongoing therapy because they are better tolerated and have a favorable side-effect profile[12]. Currently available data indicate that they may also be efficacious for controlling psychomotor agitation[13,14]. Olanzapine is an atypical antipsychotic with a favorable efficacy and safety profile due to its lower potential for causing extrapyramidal symptoms[15]. Studies performed with olanzapine also appear to confirm its efficacy and safety in treating agitation. Oral olanzapine at a dose range of 5-20 mg/day has demonstrated similar efficacy to oral haloperidol in controlling moderate agitation[16]; a 40 mg dose of olanzapine has proven to be faster and more efficacious in agitated patients and was as well tolerated as 20 mg of olanzapine[17]. At doses of between 2.5 and 10 mg, intramuscular olanzapine was seen to be more efficacious than placebo and similar to haloperidol in moderately agitated patients, and demonstrated better tolerance[18].

Although randomized clinical trials have demonstrated the safety and efficacy of these agents, there is a concern that the patients in these trials are not representatives of patients in «real-life» emergency department populations[13].

Based on the observations from these studies and given the need for data on severe agitation, the aim of our naturalistic study was to evaluate the effectiveness and safety of 20 mg dose of olanzapine orally-disintegrating tablets as monotherapy in the treatment of patients with severe psychomotor agitation

## MATERIAL AND METHOD

### Subjects and design

This naturalistic, prospective, open-label study was conducted in agitated psychotic patients visited at our PES. Inclusion criteria were: *a)* patients of both sexes aged 18-65 years; *b)* DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, non-specified psychotic disorder or acute bipolar mania; *c)* PANSS Excitement Component score[19] of ≥ 20; *d)* Clinical Global Impression of Severity (CGI-S)[20] score ≥ 5; *e)* patients willing to accept oral medication; *f)* no severe medical illness or central nervous system pathology, and *g)* agitation not due to intoxication of substances of abuse.

Individuals under treatment with olanzapine in the previous one week were excluded from participation, as were patients who had received ECT in the 72 hours prior to treatment initiation, patients who had received depot antipsychotics in the previous two weeks or who had been treated with benzodiazepines or antipsychotics during the four hours prior to administering the drug, and pregnant or nursing women. No concomitant psychoactive drugs were permitted during the course of the study period.

Patients received either a single dose of 20 mg olanzapine orally-disintegrating or conventional oral therapy depending on the attending psychiatrist's choice. The study duration was six hours; participants remained hospitalised in the Emergency Psychiatry Service throughout the entire treatment period. Scores recorded at pre-treatment were considered baseline values; assessments were made at 1, 2, 4 and 6 hours following treatment administration.

In light of the characteristics of the agitated patient on arrival at PES, informed consent for data utilization was allowed to be obtained after the acute treatment phase. The study was approved by the Clinical Research Ethics Committee of the Hospital de Sant Pau.

### Material

The main measure used to evaluate efficacy was the Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC)[19]: tension, uncooperativeness, hostility, poor impulse control, and excitement. The Agitation Calmness Evaluation Scale (ACES) (copyright Eli Lilly and Company, 1998) was also used. It is a single-item, 9 point scale developed by Eli Lilly and Company on which 1 indicates marked agitation; 2, moderate agitation; 3, mild agitation; 4, normal behavior; 5, mild calmness; 6, moderate calmness; 7, marked calmness; 8, deep sleep, and 9, unarousable. The patients' general psychopathological status was assessed by means of the Clinical Global Impression–Severity (CGI-S) scale[20].

In addition to the clinical scales, pragmatic variables were also used to evaluate effectiveness. The need for a second pharmacological intervention as well as physical restraint measures with nursing supervision was also recorded.

During the 6 hour study period, safety was assessed by means of vital signs (blood pressure, heart rate, and temperature) at each evaluation time point and by recording spontaneously reported adverse effects. The presence of extrapyramidal effects was evaluated by the UKU-Modified Rating Scale[21].

## Statistical analyses

Data were analyzed using SPSS 11.0 software. All analyses were conducted using intent-to-treat methodology. The chi-square test for categorical variables and Student's *t* test for continuous variables were used to assess demographic data and baseline values. Analysis of variance (ANOVA) of repeated measurements was used to evaluate efficacy and safety. The end-point was based on a last-observation-carried-forward strategy (LOCF). All tests of hypotheses were performed using a two-sided significance level of 0.05.

# RESULTS

## Patient demographics and baseline clinical characteristics

The study included 40 olanzapine-treated patients and 40 patients treated with standard therapy: 30 received a single dose of 10 mg haloperidol, 7 benzodiazepines (2 mg of clonazepam) and 3 haloperidol plus benzodiazepine. The mean age was 35.04 (SD: 11.9; range: 18-66 years); 63.8 % were males. The total mean baseline scores were as follows: PANSS-EC, 24.2 (SD: 13.8); ACES, 2.1 (SD: 10.7), and CGI-S, 5.7 (SD: 10.8).

There were no between-group differences regarding demographic variables or DSM-IV diagnoses at baseline. Neither were there differences in mean baseline scores between the two groups with the exception of the PANSS-EC hostility item (p = 0.011) (Table 1).

**Table 1** Clinical characteristics and outcomes at baseline for 40 olanzapine-treated patients and 40 patients treated with standard therapy

| Sample characteristics | Olanzapine | Standard therapy |
|---|---|---|
| Age (mean, SD)* | 34.1 (11.9) | 36.0 (12.0) |
| Gender (% males)** | 65 | 62.5 |
| Diagnosis (n)** | | |
| Schizophrenic D | 10 | 15 |
| Schizophreniform D | 5 | 4 |
| Schizoaffective | 5 | 5 |
| Mania bipolar D | 7 | 5 |
| Non-specified psychotic D | 13 | 11 |
| Physical restraint (%)** | 30 | 30 |
| Scales (mean, SD)* | | |
| PANSS-EC tension | 5.18 (0.8) | 5.25 (1.2) |
| PANSS-EC uncooperativeness | 4.50 (1.4) | 4.38 (1.5) |
| PANSS-EC poor impulse control | 4.50 (0.8) | 4.70 (0.8) |
| PANSS-EC excitement | 5.53 (0.7) | 5.33 (0.9) |
| PANSS-EC hostility | 4.10 (1.4)*** | 4.90 (1.3)*** |
| PANSS-EC total | 23.83 (3.3) | 24.58 (4.2) |
| ACES | 1.98 (0.6) | 2.20 (0.7) |
| CGI-S | 5.75 (0.7) | 5.65 (0.9) |

* T-test-T-Student. ** Chi square test. *** p = 0.011. SD: standar deviation; D: disorders.

## Efficacy outcomes

Following pharmacological intervention, both groups showed a significant reduction in the mean PANSS-EC score. In the ANOVA analysis of differences between-groups, the olanzapine-treated group showed a statistically significant improvement in the PANSS-EC (F = 122.9; df = 2.4; p = 0.000). Significant differences were observed at 1 hour after treatment (fig. 1). Mean changes in PANSS-EC from baseline to 6 hours were -12.9 for patients given olanzapine and –13.6 for patients given standard therapy. Statistically significant improvements were also achieved on the ACES (F = 68.2; df = 2.8; p = 0.000) (fig. 2).

Efficacy measurements of pragmatic variables such as the number of subjects who required extra drug treatment and the need for contention and special nursing supervision were also evaluated. There were significant differences between groups in the need for second intervention (p = 0.04). In olanzapine-treated group, 70 % (N = 28) completed the study without needing any additional medication; twelve subjects failed to complete the study because of the need for extra medication. In the conventional therapy-treated group, 50 % needed extra medication. The need for physical restraints and special measures was also analyzed. At baseline, 30 % patients required physical restraint without differences between groups. This need decreased throughout the study period in both groups and at the final 6 hour time point, only five patients treated with olanzapine (13 %) and nine patients (22 %) treated with standard therapy needed mechanical restraint. There were no between-group differences in physical restraints at final point.

## Safety results

No differences were detected between-groups concerning secondary effects as spontaneously reported by the subjects nor in movement disorders with respect to UKU-Modified Rating Scale scores. Three olanzapine-treated patients revealed hypotension (diastolic pressure below 50), but this was well tolerated. Bradycardia was observed in one case (heart rate under 40 beats per minute), but showed no clinical significance. No symptomatic treatment was needed nor was it necessary to withdraw any patient from the study. No movement disorders were spontaneously reported by

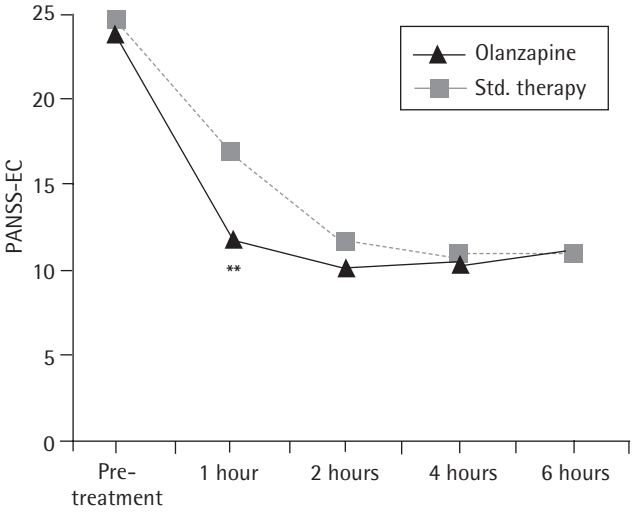


**Figure 1** *Mean change in the Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC) from baseline during the 6 hour study period. Last observation carried forward. ANOVA anlysis (F = 122,9; df = 2,4; p = 0.000). ** Significant differences between olanzapine and standard therapy were observed at 1 hour (t = -2.77; df = 78; p = 0.007).*

the patients. Three patients presented akinesia and mild tremor.

With haloperidol, two patients presented excessive sedation and one hypotension (diastolic pressure below 50). With haloperidol plus benzodiacepine, one patient presented excessive sedation. With conventional therapy, no dystonia, rigidity, or hyperkinesias were detected. Two patients presented akinesia and 3 mild tremor.

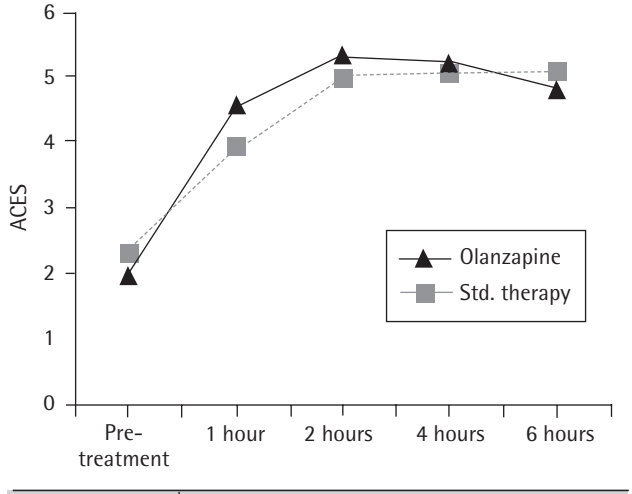


**Figure 2** *Mean change in the Agitation-Calmness Evaluation Scale (ACES) from baseline during the 6 hour study period. Last observation carried forward. ANOVA analysis (F = 68.2; df = 2.8; p = 0.000).*

## DISCUSSION

The results of this naturalistic study suggest that a 20 mg dose of olanzapine orally-disintegrating tablet administered as monotherapy in severely agitated patients can be effective in reducing agitation. In addition, a short latency time was observed with this treatment, since statistically significant improvements were obtained 1 hour after administration. Our results appear to be in line with those emerging from controlled clinical trials with olanzapine in patients with less severe agitation than that observed in the present participants[14,16,17]. Moreover, there were significant differences between groups regarding the need for a second intervention: 70 % in the olanzapine-treated group as compared to 50 % in the standard therapy group.

Patients in clinical trials are not always representatives of «real-life» emergency department patients. As severely agitated individuals tend to be uncooperative, obtaining informed consent prior to initiating treatment (as is mandatory in clinical trials) may bias the sample towards a less severe patient group. In our study, in an attempt to comply with a naturalistic approach based on clinical reality, informed consent for data utilization was obtained after the acute treatment in some cases. In addition, the present study was conducted in emergency rooms, where severely agitated patients require immediate intervention. Minimum PANSS-EC score for the study was ≥ 20 and GCI-S score ≥ 5. Patients who failed to respond to treatment were withdrawn from the study and given a second therapeutic option. Finally, pragmatic response measures such as the number of patients who required a second drug intervention and patients who no longer required physical restraints for their agitation were also evaluated. It is vitally important to reduce the time during which physical restraint is used. The National Association of State Mental Health Program Directors (NASMHPD) Position Statement read that seclusion and restraint should be considered a safety measure, not a form of medical treatment, and should be used only as a «last resort measure». Deleterious effects have been described in patients who perceive such measures to be coercive and traumatic[2].

All treatments were well tolerated; in no cases were the few mild adverse effects cause for withdrawal from the study. Consistent with the findings of other prior studies with olanzapine, no extrapyramidal effects were detected[18,4]. Although atypical antipsychotics are recommended as the first-line agents for ongoing therapy of schizophrenia, they have not, up to now, been as widely used as the conventional agents in emergency settings. According to our study, atypical antipsychotics, such olanzapine, appears to be more effective than the conventional antipsychotics in the treatment of agitation[12,2].

It should be pointed out that 24 patients (30 %) in our sample were diagnosed as non-specific psychotic disorder

and DSM-IV diagnosis was made on the basis of the information available. As a complete history or structured interview is not usually feasible in the case of an agitated patient visited in the Emergency Room, diagnosis tends to be syndromic or non-specific.

The main limitation of this study is that it was a non-randomized trial in which patients received either olanzapine or standard medication depending on the attending psychiatrist's preference. It is therefore difficult to draw any conclusions about comparative efficacy.

In summary, a single dose of 20 mg of olanzapine orally-disintegrating tablet proved to be effective, rapid and safe in the treatment of patients with severe agitation. It will be of interest to conduct future controlled trials in order to obtain a higher level of evidence using pragmatic variables and randomized controlled design.

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