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Effectiveness results of olanzapine in acute psychotic patients with agitation in the emergency room setting: results from NATURA study

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Introduction. Patterns of use of antipsychotics are not well described in emergency units. The objective of this study was to describe the effectiveness and safety of use of olanzapine in patients with acute psychosis and agitation in the emergency rooms.

Methods. In this prospective observational study 278 patients with acute psychosis and agitation were consecutively admitted in 16 psychiatric emergency wards and treated with any oral psychopharmacology treatment, including olanzapine, according to investigators clinical criteria. Data were collected prospectively including demographics, diagnosis, concomitant medications, utilization of mechanical restraints, and severity of agitation. Clinical evolution during emergency room stay was assessed with PANSS-Excitement Component, CGI-S and Agitation and Calmness Evaluation Scale (ACES) at baseline, before any re-intervention (if needed) and at discharge from the emergency room. Safety was also evaluated.

Results. Olanzapine alone was used in 148 (53.2 %) patients. Most of them (77.7 %) were diagnosed of Schizophrenia and related psychoses. Up to 38 patients (25.7 %) required mechanical restraints. Mean change (confidence interval [CI] 95 %) from baseline to discharge was significant in all rating scales; PANSS-EC: –7.46 (–8.2, –6.7); CGI-S: –1.82 (–2, –1.6) ACES: 1.28 (1.1, 1.5). At discharge 70.3 % of patients went to inpatient units. Five patients (3.4 %) reported adverse events including: bradycardia, dry mouth, sedation, hypertension, hypotension, and orthostatic hypotension. None of them was serious.

Conclusions. The utilization of olanzapine alone decreased agitation in psychotic patients in emergency room settings. Incidence of adverse events was low and it was well tolerated.

Key words:
Olanzapine. Schizophrenia. Agitation. Emergency medical services.

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Resultados de efectividad de olanzapina en pacientes psicóticos agudos con agitación en servicios de urgencias: resultados del estudio NATURA

Introducción. Se carece de descripciones adecuadas de los patrones de uso de antipsicóticos en urgencias. El objetivo del presente estudio es describir la efectividad y eficacia del uso de olanzapina en pacientes con psicosis aguda y agitación en urgencias.

Métodos. En este estudio prospectivo observacional realizado en 16 servicios de urgencias se incluyeron 278 pacientes consecutivos con psicosis aguda y agitación los cuales recibieron tratamiento psicofarmacológico, que incluyó olanzapina, según el criterio clínico del investigador. Se recogieron datos prospectivos de demografía, diagnóstico, medicación concomitante, utilización de contención mecánica y grado de agitación. La evolución clínica durante la estancia en urgencias se evaluó mediante la componente de excitación de la PANSS, la ICG-G y la escala de evaluación de agitación-sedación (ACES) al ingreso, antes de cualquier reintervención (si procedió) y al alta del servicio de urgencias, evaluándose asimismo la seguridad.

Resultados. Olanzapina como monoterapia se administró a 148 pacientes (53,2 %), la mayoría (77,7 %) con diagnóstico de esquizofrenia y psicosis relacionadas. Fueron 38 (25,7 %) los pacientes que precisaron contención mecánica. El cambio medio (intervalo de confianza [IC] 95 %) de basal al alta fue significativo en todas las escalas: PANSS-CE: –7,46 (–8,2, –6,7); ICG-G: –1,82 (–2, –1,6); ACES: 1,28 (1,1, 1,5). Al alta, el 70,3 % de los pacientes se trasladó a unidades de hospitalización. Cinco pacientes (3,4 %) presentaron acontecimientos adversos: bradicardia, boca seca, sedación, hipertensión, hipotensión e hipotensión ortostática, ninguno de los cuales fue grave.

Conclusiones. La utilización de olanzapina empleada como monoterapia disminuyó la agitación en pacientes psicóticos en urgencias, con una baja incidencia de acontecimientos adversos.

Palabras clave:
Olanzapina. Esquizofrenia. Agitación. Servicios de urgencias.

INTRODUCTION

Psychomotor agitation that requires hospitalization is a common event during the course of certain major psychiatric disorders, including schizophrenia and bipolar disorders. Emergency psychiatric services (EPS) are the first doorway for the control of agitation and behavioural disturbances of the mentally ill in order to avoid dangerousness and aggression towards themselves and/or others. Contrasting the broad data regarding hospitalization only some studies have evaluated the management of agitation in emergency psychiatry services[1-4] and several counselling guidelines[5] have been published in an attempt to provide some standards for the control of agitation of the mentally ill.

Traditionally, the emergency psychiatry has primarily focused to look for efficiency in making a quick assessment, containment and referral of the patient, but nowadays, more attention is being paid to an extended evaluation that would allow for a refined diagnosis followed by a well supported referral to community or inpatient services. In addition, safety and tolerability are gaining importance besides efficiency. Along with this, the use of psychotropic drugs should help to handle with agitation and aggression, rapidly rendering people calm and/or sedated without producing distressing or dangerous adverse events, and facilitating extended assessment and definitive treatment[2].

Standard practice at EPS often consists of using a combination of a conventional antipsychotic (i.e., haloperidol) and a benzodiazepine, which is generally administered via a parenteral route[1,3]. However, there are serious potential complications using those medications, including hypotension[6,2], cardiotoxicity[2], extrapyramidal side effects (EPS)[2,7,8], sedation, or neuroleptic malignant syndrome (NMS)[2,8]. In addition, parenteral route is frequently perceived as coercive by certain patients that can influence the establishment of a therapeutic alliance between the patients and caregivers and affect compliance and cooperation with subsequent treatment[4].

Atypical antipsychotics have gained acceptance as first line treatment for psychotic disorders, as they generally offer similar efficacy and improved adverse event profiles over conventional antipsychotic medications[9-11]. Consensus guidelines (American Psychiatric Association) recommend atypical antipsychotics as first line treatment for schizophrenia in most clinical situations. Moreover, several recent surveys at EPS revealed that both physicians and patients generally prefer atypical antipsychotics as well as oral agents[9,12]. However the utility of atypical antipsychotics in the emergency setting is relatively unexplored, and there is even less evidence from oral agents. The recent availability of several rapid acting preparations, intramuscular (im) or oral, of some atypical antipsychotics like olanzapine[10,11,13,14] represents significant advancements in this setting that needs to be investigated.

An observational approach can mimic the normal conditions of clinical practice in order to describe the characteristics of patients usually attending an EPS and to explore the utility of atypical antipsychotics like olanzapine. Consequently, a naturalistic study on the use of olanzapine, among other antipsychotropic drugs (first orally and then intramuscularly if requested by non-collaborative patient) in the management of acute psychosis and agitation in patients attended in the emergency room setting was performed.

METHODS

Study design

This was a prospective observational study performed in 16 psychiatric hospitals in Spain from February 2004 to January 2005. Study participants were outpatients aged 18 or older admitted at the psychiatry emergency room because of acute psychosis and agitation requiring treatment with oral antipsychotics. There was not washout period for previous antipsychotic and/or anticholinergic medications at admission. Patients who received treatment with antipsychotics or benzodiazepines within 4 hours prior to initial treatment, required parenteral drugs, had a diagnosis of delirium or dementia, or were participating in any research clinical trial were excluded.

Informed consent was obtained from all subjects and/or their legal representatives at the moment of initial data collection, or once the patient had recovered from the acute psychotic episode should the patient was unable to give his/her informed consent at that moment. The study was conducted according to the Declaration of Helsinki guidelines and approved by regulatory authorities of Spain and by each centre's ethics committees.

Treatment

At time of entry into the emergency room oral psychopharmacological treatment, including olanzapine, was prescribed to the patient according to investigators clinical criteria. There was no study-specific treatment selection nor diagnosis nor follow-up intervention; all procedures were according to clinical practice.

Patients were observed from the time of admission into the emergency room until they were discharged or transferred out of the psychiatric emergency service. In case of no improvement, re-intervention (including but not limited to benzodiazepines and intramuscular/parenteral antipsychotics) was possible.

Assessments

Primary efficacy measures included assessment of the type and dose of antipsychotic treatment initially received

and type of medication prescribed at re-intervention. This article will focus on the cohort of patients who received olanzapine as psychotic treatment, thus only the latter will be discussed here. During the study observation, other data were prospectively explored including; use of mechanical restraints, time to first re-intervention, destination following emergency room discharge and length of stay, and occurrence of adverse events as well as clinically significant changes in vital signs.

Secondary measures including demographic data and severity of illness were also prospectively collected. These included patient characteristics at baseline like sex, age, current diagnosis and years since diagnosis, and severity of agitation at admission.

Severity of agitation and clinical evolution were assessed at admission, before any re-intervention (if needed) and at discharge from the emergency room. Assessment scales included the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales, the PANSS Excited Component Scale (PANSS-EC) and Agitation-Calmness Evaluation Scale (ACES). The CGI-I, was specifically applied to agitation improvement (and not to global improvement) and recorded at re-intervention and at discharge.

The CGI-S and CGI-I scales are well-recognized and established psychometric instruments15 which are suitable to measure the severity of agitation and its improvement (or worsening) compared with the condition at baseline in the subject. The Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) is a validated subscale of the PANSS used for measuring agitation symptoms, and assesses 5 items: poor impulse control, tension, hostility, uncooperativeness and excitement[16]. Each item is rated by the physician on a scale of 1 (absent) to 7 (extreme). The agitation and calmness evaluation scale (ACES) is a Lilly internally developed scale consisting of a single item that rates overall agitation and sedation at the time of evaluation ranging from 1: marked agitation, to 9: unarousable. This scale has a high convergent validity and high reliability[17].

Statistical methods

Because of the naturalistic nature of the study, all patients who received olanzapine as initial treatment were included in the analyses. Demographic, baseline data, vital signs and adverse reactions were analysed by means of descriptive statistics using means, standard deviations (SD), and ranges when quantitative variables and frequency distributions when qualitative variables.

Time to pharmacological re-intervention and time to discharge from emergency room curves were estimated using the Kaplan-Meier method, censuring times for those patients that did not require pharmacological re-intervention by carrying forward the last observation. Data were expressed as median and 95% confidence interval..

The Wilcoxon Signed-Rank test for paired data was used to test for significant pre- to post-intervention changes in the PANSS-EC, ACES and CGI-S mean scores from baseline, to first intervention (if any) and to discharge. It was also used for change in PANSS-EC mean score in the 5 items of PANSS-EC. Analysis was also performed in the subpopulation of re-intervened patients.

RESULTS

Patient characteristics at baseline

A total 278 subjects with acute psychosis and agitation were consecutively admitted in 16 Spanish psychiatric emergency wards and treated with any oral psychopharmacological treatment according to investigators clinical criteria. Olanzapine alone was administered to 148 (53.2%) of these patients, and 15 (5.4%) patients received olanzapine in combination with other antipsychotics. Only the former cohort was considered for the analyses in the present article. Patients' baseline characteristics are summarized in table 1. Patients were mainly men (64.9%) with a mean age of 36 ± 11.8 (SD) years old. Most of them (77.7%) received the diagnosis of schizophrenia and related psychoses and had chronic illness, with a mean duration of illness of 11 ± 10.1 years. Severity of agitation at admission was measured by the CGI-S, ACES and PANSS-CE scales. Scale scores indicated that a majority of the patients had moderate or marked illness. Most patients were categorized as «markedly ill» (19,6%), «moderately ill» (34.5%) or «mildly ill» (28.4%) according to CGI-S scores; with «mild» (44.6%) to «moderate» agitation (47.3%) as per ACES scale, and between «mild» and «severe» in each of the 5 PANSS-EC subscales.

Re-intervention

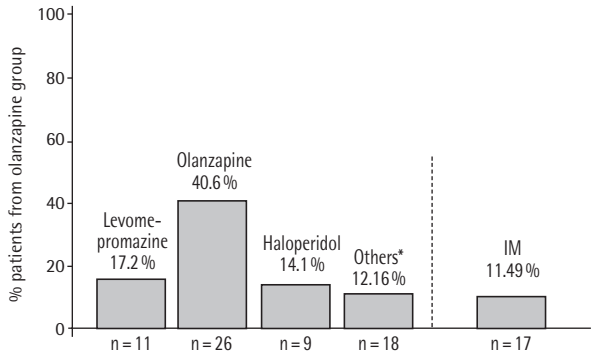
During emergency stay, over one third (34.5%, n = 51) of the cohort of olanzapine patients required at least one kind of re-intervention. Only four of these patients required a second and another four (2.7%) even further re-interventions. The median time from admission to first re-intervention was of 6.03 hours (CI 95% median 3.78-8.80 hours).

At first re-intervention, one or two medications were prescribed in 40 (78.4%) and 10 patients (19.6%), respectively. Olanzapine, haloperidol and levomepromazine were among the most prescribed. Seventeen out of 51 (11%) patients required intramuscular antipsychotic re-intervention. Type and dose of medication prescribed at re-intervention is illustrated in figure 1. Up to 38 patients (25.7%) required mechanical restraints and in 22 (57.9%) of them mechanical restraints were removed before discharge.

Table 1 Patients' demographic and baseline characteristics

Total, (%)	148
Sex	
Men (%)	96 (64.9)
Age (years)	
Mean (SD)	35.82 (11.8)
Years from diagnosis	
Mean (SD)	10.99 (10.1)
Current diagnosis, n (%)	
Schizophrenia and related psychoses	115 (77.7)
Bipolar affective disorders	18 (12.2)
Others	13 (8.8)
Unknown	2 (1.4)
Initial dose (mg)	
Olanzapine alone N (%)	148 (53.2)
Mean (SD)	11.54 (4.87)
Range	(2.5-20)
Olanzapine in combination N (%)	15 (5.4)
Mean (SD)	12 (4.55)
Range	(5.0-20)
Proportion of patients receiving treatment one week prior to baseline	
N (%)	83 (56.1)
CI (proportion)	48.09 (64.08)

SD: standar desviation.



* Clonazepam, cloracepate, clothiapine, diazepam, flufenazin, lorazepam, oxcarbamazepine, risperidone, ziprasidone and zuclopenthixol.

	Mean dose (mg)	Mean dose (mg)
Haloperidol	6,72	5
Olanzapina	9,42	10
Levomepromazina	39,32	25

Figure 1 *Medications prescribed at re-intervention.*

Clinical course of agitation during emergency room stay

Agitation mean change (CI 95 %) from admission to discharge was significant ($p < 0.0001$ as per Wilcoxon signed-rank test) in all rating scales: PANSS-EC: –7.46 (–8.2, –6.7); CGI-S: –1.82 (–2.0, –1.6); ACES: 1.28 (1.1, 1.5). Overall, no re-intervened patients exhibited less agitation at admission than patients needing re-intervention as per their mean values at all study scales. After treatment with olanzapine both subgroups achieved similar scores at discharge from the emergency room. Figure 2 show mean CGI-S, ACES and PANSS-EC scores at admission, first re-intervention and discharge, respectively for the totality of olanzapine group and for the subgroups of re-intervened and not re-intervened patients.

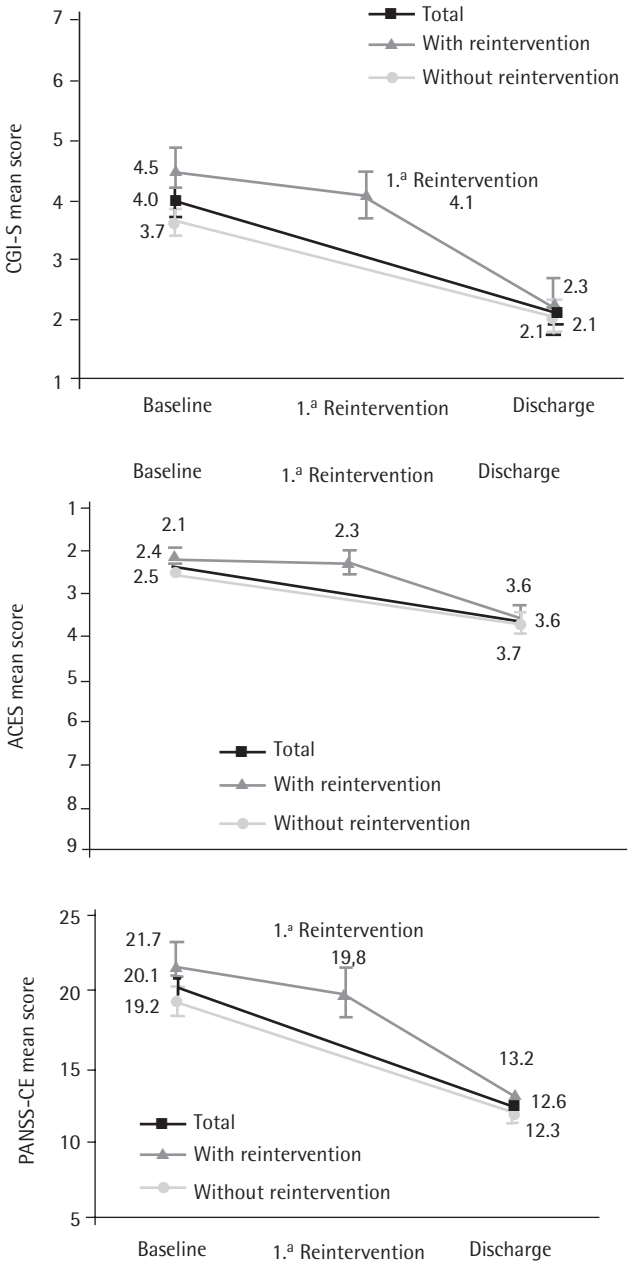
At discharge, most patients were «mildly ill» (23 %), «borderline ill» (19.6 %) or «not at all ill» (44.6 %) according to CGI-S scores; as per ACES scale the majority presented values around the normality (37.8 % patients were «normal» and 38.5 % patients with «mild agitation») or calmness («mild» to «marked», 14.3 %) and only a small proportion had «marked» to «moderate» agitation (9.5 %). According to the PANSS-EC scale, more than 70 % of patients observed a displacement in each of the subscales scores to the «absent», «minimal» or «mild» categories in comparison scores registered at admission.

Mean change in CGI-I scores achieved at discharge in the olanzapine cohort of patients was 2.11 which corresponds to the «much improved» category. When considering the subgroup of re-intervened patients a mean CGI-I value of 3.43, which is between «minimally improved» and «no change» is obtained at first re-intervention but, the same scale at discharge obtains a mean value of 2.3. Agitation improvement was achieved in the great majority of the cohort of olanzapine treated patients as per CGI-I scale scores at discharge: 27.7 % «very much improved», 39.9 % «much im-proved», 26.4 % «minimally improved» and only 6.1 % with «no change» (fig. 3).

Median length of stay at emergency room was 2.02 hours (95 % CI median 1.62-2.5 h). After discharge, 70.3 % (n = 104) of patients were transferred to inpatient units, 6.1 % (n = 9) to other center, 1.4 % (n = 2) to the observational unit, 20.9 % (n = 31) sent to home and the rest (n = 2) were considered missing or other.

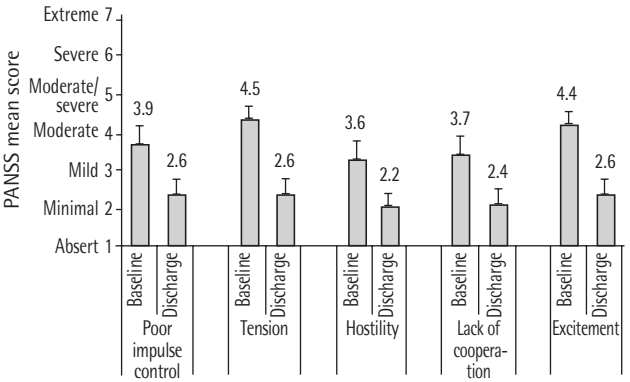
Adverse events

Patients in the olanzapine group, reported no significant adverse effects during the course of emergency room stay. Only 3.4 % of patients reported any adverse events and included bradycardia, dry mouth, sedation, hypertension, hypotension, and orthostatic hypotension. Cardiovascular side effects, such as bradicardia and orthostatic hypotension, were just reported in a 0.7 %, of patients. No treat-



*p < 0.0001 of the change from baseline to release for each item as per sign-rank test.

Figure 2 *CGI-S, ACES and PANSS-EC mean scores at baseline, at 1st re-intervention and at discharge.*



*p < 0.0001 of the change from baseline to release for each item as per sign-rank test.

Figure 2 *Mean scores in the 5 items of PANSS-EC at baseline and at discharge.*

ment-emergent extrapyramidal symptoms were observed in this study. Number and frequencies of adverse events are shown in table 2. None of them was serious.

DISCUSSION AND CONCLUSIONS

In last years, pharmacological interventions for acute agitation in psychotic patients in psychiatry emergency services are changing from chemical restraint to rapid tranquilization, which literally means calming without sedation, preserving a normal physician-patient relation and allowing physician to make an accurate patient's diagnosis[2,9]. The emergent use of atypical antipsychotics in the emergency setting[10,11] and the development of newer oral drug forms (such as the oro-dispersible form developed for olanzapine) facilitates the therapeutic alliance and contributes to patient acceptance[13].

The present article describes the characteristics of a cohort of 148 out of 278 (53.2%) patients with acute psychosis and agitation in an EPS and treated with olanzapine. The results showed a majority of these patients presenting an underlying chronic psychotic illness (77.7% had a diagnosis of schizophrenia and related psychoses and 12.2% of bipo-

Table 2 **Adverse events in olanzapine population (n = 148)**

	n (%)
Total number of AE	6 (4.1)
Serious AE	0 (0)
Discontinuations due to serious AE	0 (0)
Patients with at least one AE	5 (3.4)
Type of adverse event	
Bradycardia	1 (0.7)
Dry mouth	1 (0.7)
Sedation	1 (0.7)
Hypertension	1 (0.7)
Hypotension	1 (0.7)
Orthostatic hypotension	1 (0.7)

*Baseline HR(bpm): 88. Discharge HR: 76. Baseline BP (mmHg): 130/75. Discharge BP: 90/50. Baseline BP (mmHg): 100/65. Discharge BP: 95/65.

lar affective disorders) for more than 10 years. In a recent survey a panel of experts found that provisional diagnosis made at EPS is quite accurate and also that pharmacological interventions are selected differentially based on diagnosis together with other relevant demographic and medical features.9 The great proportion of psychotic illness observed may suggest that the agitation symptoms are the result of a relapse in the underlying disease due to suboptimal therapeutic efficacy, either because of poor compliance or because of inadequate prescription (dosage or active drug) for their illness.

Results from the present study point out to a clear benefit from olanzapine treatment, demonstrating that the behavioural alterations present in patients diagnosed of schizophrenia or bipolar disorders are well controlled with atypical antipsychotics[12,18,19]. Oral olanzapine alone or combined with a benzodiazepine was considered a first line for treatment of agitation related to schizophrenia or mania in the respondents to the aforementioned survey. As expected, at admission most patients exhibited moderate to marked agitation. Pharmacologic treatment significantly ($p < 0.001$) improved severity of agitation from baseline as measured by the CGI-S, ACES and PANSS-CE scales thus at discharge most patients were around the normality or with absent or mild agitation.

Approximately one third of patients required at least one kind of re-intervention in a median time of 6.03 hours. No re-intervened patients exhibited less agitation at admission than patients needing re-intervention as per their mean baseline values at all study scales. The most prescribed drug (in nearly 40 % of patients) in this first intervention was olanzapine which probably reflects a dosage adjustment in suboptimally treated patients. The second and third most prescribed drugs were two conventional antipsychotics (levomepromazine and haloperidol). In those who needed, first intervention resulted effective and only a few patients required second or further re-interventions.

For the evaluation of agitation PANSS-EC subscale and ACES rating scales have been used in this study. A major disadvantage of PANSS-EC scale is that it assesses from agitation to absence of agitation, without assessing desirable or undesirable sedation/lowering of consciousness. Recently ACES scale has been designed for studies with olanzapine, which differentiates between extreme agitation and extreme sedation (unable to arouse). Although it offers a less detailed description of agitation, it has the advantage of including normal activity (being quiet and awake to rouse): thereby being in line with the most recent concept of «calm rather than sedated». Accordingly, the analysis of ACES scale results shows that less than 1 % of patients were rated as «deep sleep» and none was «unarousable» at discharge. The majority of patients presented values around the normality (76.3 %) or calmness (14.3 %) at discharge. Some authors have analyzed the sedation degree observed in several olanzapine studies as per ACES scale observing that the incidence of sedation with olanzapine was similar to that observed with haloperidol and lorazepam[20].

A major advantage of olanzapine treatment is that it is available in both a tablet form and an orally disintegrating oral form (oro-dispersible) which is preferred by physicians and patients, in order to avoid the perception of coercion associated with the injection of antipsychotic medication[4,14,24]. Oral formulation is desirable in terms of patient's cooperation and treatment compliance, length of hospitalization and continuity of treatment in the long term. In a recent survey by Allen et al.[1] respondents preferred liquid preparations to tablets, perhaps because the former may offer advantages in speed and may improve patient's compliance. In our study, an oral route of administration was offered first, although an intramuscular medication was prescribed in no more than 11.5 % of the patients who needed a therapeutic intervention. When comparing the differential efficacy between intramuscular vs oral route of administration some authors have found that approximately 55 % of severely agitated patients could be treated with oral medication only[2].

Using olanzapine in the emergency setting has the advantage of allowing for continuity of care between emergency, acute and chronic care and between inpatient and outpatient care. This is supported by several studies who have reported that the efficacy of oral olanzapine, as orodispersible[13,22,23] or rapid initial dose escalation standard tablets[24] in agitation or during transition from the intramuscular route[18], can be as effective as the intramuscular ones in the acute and long term care.

A number of limitations to the present study can be considered which are inherent to its own naturalistic nature. First of all, as it was conducted within a routine clinical emergency psychiatric service, the real patient's length of stay is confounded by hospital's bureaucracy. Also the shortness of length of stay at emergency room (median: 2.02 hours) did not allow for a complete safety evaluation in order to determine frequency of adverse events at emergency setting. Moreover, treatment and assessment bias cannot be ruled out because of the open-label nature of the study.

Despite these limitations, the present prospective naturalistic study provides information from real life emergency psychiatry practice covering the gap between current clinical practice and expert based/evidence based guidelines. The results support the utility of the oral atypical antipsychotic olanzapine as first line treatment for psychotic disorders in the emergency setting. In view that a majority of patients (70.3 %) were transferred to inpatient units at discharge of the emergency room, perhaps a complete observational study from emergency entry to inpatient unit discharge will be interesting in order to follow compliance of treatment in the long term.

In conclusion, use of oral olanzapine as monotherapy decreases agitation in psychotic patients in emergency room

settings, rapidly rendering people calm without sedation and and is well tolerated. Olanzapine treatment can be started in the psychiatric emergency room facilitating extended assessment and could be continued as definitive treatment in the long term which enables treatment compliance and good patient-physician cooperation.

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