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# Olanzapine (Zyprexa®) Treatment in Patients Pre-treated with other Antipsychotics: Pharmacovigilance Data from a Large Drug Utilization Observation (DUO) Study in Germany

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## Abstract

*Objective: To observe tolerability-related aspects of drug-utilization and outcome of olanzapine (Zyprexa®) treatment in daily practice in patients pre-treated with other antipsychotics. Method: Outpatients with schizophrenia (ICD-10) or other psychiatric disorders pre-treated with antipsychotic medication other than olanzapine participated in this non-interventional drug utilization observation (DUO) study. At baseline, demographics and tolerability of antipsychotic pre-treatment were documented for patients theoretically eligible for olanzapine treatment. Patients actually starting olanzapine (OLZ group) were followed-up in a 6-month observational phase. Tolerability data collected included adverse events, laboratory, EEG and ECG findings, extrapyramidal symptoms (EPS) and CGI tolerability ratings (CGI-T). Results: Of 3358 pre-treated patients documented at baseline, 1654 continued previous treatment, while 1704 started olanzapine and follow-up. Hospitalizations and side effects of previous medication, concomitant diseases and co-medication all were significantly higher in patients subsequently treated with OLZ. During the observation, 582 adverse events were reported in 24.4% of patients, with weight gain reported most frequently (13.6%). Over the 6-month observation, mean body weight increased by 2.6±5.0 kg. All other adverse events had incidences of <3%. Olanzapine was generally well tolerated, as supported by favorable CGI-T ratings (96% of patients not or only minimally impaired by adverse events). Conclusions: This naturalistic study suggested that olanzapine was generally well tolerated in outpatients with schizophrenia treated in community clinical practices and had a tolerability profile consistent with that found in previous controlled trials. Of note, this study involved a patient population with high EPS rates at baseline due to prior antipsychotic treatment (German J Psychiatry 2005;8:49-58).*

*Keywords: Antipsychotic agents, adverse effects, olanzapine, haloperidol, risperidone, schizophrenia*

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## Introduction

Since the first neuroleptic drugs have been introduced in the 1950´s, antipsychotic treatment has made substantial steps forward in terms of both effectiveness and tolerability profile of the newer atypical antipsychotics. However, a high percentage of patients still treated with typical neuroleptics have an insufficient response to treatment, as well as a frequent experience of severe extrapyramidal side effects (Brenner et al., 1990). In controlled trials, atypical antipsychotics were superior to conventional neuroleptics with regard to several clinical characteristics: atypicals significantly improved both the positive and the negative symptoms of schizophrenia (Tollefson et al., 1997; Lieber-

man et al., 2003), were effective in patients resistant to conventional neuroleptics (Lindenmeyer et al., 2004), enhanced cognitive function (Jann, 2004), had a lower incidence of extrapyramidal symptoms (EPS) (Carlson et al., 2003) and had a better benefit to safety profile (Tollefson et al. 1997; Lieberman et al. 2003).

Various randomized placebo-controlled trials have shown the efficacy and tolerability of olanzapine (Beasley et al., 1996a, 1996b), also in comparison with risperidone (Tran et al., 1996), haloperidol (Tollefson et al., 1997; Beasley et al., 1997a), and clozapine (Naber et al., 2005). Overall, olanzapine treatment under the rigorous condition of a randomized clinical trial has been shown to be generally well tolerated (Beasley et al., 1997b). Randomized controlled clinical trials are considered the gold standard for investigating tolerability and efficacy of new therapeutic options. However, there are major discrepancies between the conditions of controlled studies and the situation in routine treatment. Particularly in psychiatric disorders such as schizophrenia the experimental situation in randomized controlled studies is often substantially different from daily practice (Linden, 1997).

Therefore, the main objective of the present study was to observe the utilization and outcome of olanzapine treatment in the context of daily practice in patients pre-treated for schizophrenia or other psychiatric disorders with other antipsychotics. Pharmacovigilance data were documented for pre-treatment with different antipsychotics and after initiation of olanzapine treatment by the investigator during a 6-month observational phase. Data were gathered as spontaneously reported adverse events, rating of EPS, and global clinical impression of tolerability (CGI-T) score.

# Methods

## Design and Ethical Considerations

This study was a drug utilization observation (DUO) study comprising a baseline documentation and a 6-month observational phase. It was designed to pursue relevant pharmacovigilance aspects of antipsychotic pre-treatment in the baseline documentation as well as those of olanzapine treatment during the observational phase. All patients the investigator considered theoretically suitable for treatment with olanzapine were documented at baseline. After the baseline evaluation the investigator decided whether to initiate olanzapine treatment or not. Those patients who changed medication to olanzapine were observed for 6 months. The study was conducted according to the applicable German laws and regulations. The present study had been notified to and reviewed by the independent ethics committee (IEC) of the University Hospital Benjamin Franklin, Berlin, Germany. No concerns regarding the conduct of the study were raised by the IEC.

## Sample Size Considerations

The baseline documentation of the study was planned for a total of 4000 patients. Of these, 2000 patients for whom olanzapine treatment was initiated by the physician were planned to be observed for 6 months. For this sample size at least one event as rare as 0.1% can be detected with a probability of 95%. The sample size was chosen to allow for detection of uncommon adverse events (i.e. 0.1% - 1% according to European guidelines; CHMP 2005).

Data were documented by a total of 495 psychiatrists from psychiatric practices or specialized outpatient clinics. Each participating psychiatrist was instructed to document schizophrenic patients pre-treated with antipsychotics other than olanzapine until completing a maximum of 8 patients, 4 patients who started olanzapine and 4 patients who did not (i.e., who either continued pre-treatment or changed to treatment other than olanzapine). To limit selection bias, sampling was continued until data had been documented for 4 patients treated with olanzapine. If data from more than 4 patients not treated with olanzapine were documented, only the data of the first 4 patients were analyzed.

## Patient Population

All outpatients receiving antipsychotic treatment other than olanzapine and rated as theoretically suited for olanzapine treatment by the physician were eligible for documentation in the epidemiological survey. Patients could be treated for any type and course of schizophrenia (F.20 of ICD-10 code for type and DSM-IV code for course), or any other psychiatric diagnosis. Physicians were asked to document only patients who were on antipsychotic medication at the start of observation. However, the observational design of the study made it impossible to achieve full compliance, i.e. to completely avoid documentation of patients not on antipsychotic medication at baseline.

In order to reflect conditions as naturalistic as possible, no specific exclusion criteria were defined. Patients were neither subject to any experimental intervention, nor were there any restrictions on the current and further treatment of patients.

## Treatment and Conduct

### Baseline Documentation

At start of the study, demographic data and baseline characteristics were recorded for all patients theoretically suited for treatment with olanzapine. This included the documentation of age, weight, height, gender, type and course of schizophrenia, as well as previous and current antipsychotic and non-antipsychotic medication. In addition, previous and current concomitant diseases were documented.

To assess the tolerability of previous antipsychotic therapy, physician-assessed side effects (i.e., treatment-related adverse events) were collected and separately documented for EPS

and other events. The severity of EPS (parkinsonism, akathisia, dyskinesia, motor retardation) was noted by means of 7-point Likert scales. Other physician-assessed side effects of previous antipsychotic treatment (EPS excluded) were documented by severity (mild, moderate, severe), date of first occurrence and name of the antipsychotic agent probably causing the side effect.

**Observational Phase**

Patients who had olanzapine treatment initiated by the physician were followed up over a 6-month observational phase, starting directly after the baseline documentation. Within this phase, 4 documentations were planned after approximately 2 weeks, 4 weeks, 3 months, and 6 months. The following tolerability-relevant parameters were to be documented at each follow-up visit: i) all adverse events (with physician assessed relatedness to treatment), ii) EPS, iii) change of concomitant medication, and iiii) tolerability of olanzapine treatment noted by the clinical global impression of tolerability (CGI-T) scale (grade of impairment due to adverse events). Any event that was life-threatening, required hospitalization, lead to permanent injury, or congenital anomaly, was a malignant disease, or resulted in death was considered as serious adverse event (SAE). In addition to collecting the date and severity of an adverse event, the physicians were requested to assess and record the following parameters: i) relationship to olanzapine (possibly related, not related, not assessable), ii) discontinuation of olanzapine treatment, and iii) outcome of the adverse event (abated, improved, unknown, not assessable).

No specific tolerability examination was mandatory in the course of the study (ECG, EEG, laboratory investigation, vital signs), since none of these are usually carried out in clinical routine in patients with schizophrenia. However, physicians were asked to record any relevant finding observed in clinical routine such as laboratory findings, vital signs (blood pressure, pulse frequency), as well as additional examinations (ECG, EEG, other). Each of the additional laboratory findings had to be given with date, unit and standard range value, if present. No protocol violations were defined due to the naturalistic setting of the study; nevertheless, reasons for discontinuation of olanzapine treatment were to be documented by the investigator. Documentation started in June 1999 and the last documentations were collected in July 2001.

## Statistical Analysis

For statistical analysis of baseline documentation data, all patients in whom olanzapine treatment was initiated were included in the olanzapine group (OLZ), while patients who continued their previous treatment or received treatment other than olanzapine were included in the non-olanzapine group (Non-OLZ). All study data were analyzed descriptively. All statistical tests performed were exploratory in nature. Demographic data of both groups were checked for homogeneity by appropriate statistical tests. Wilcoxon tests were used for continuous variables, chi-square tests for categorical variables. Side effects of prior antipsychotic treatment were evaluated separately for haloperidol, risperidone, and clozapine. If no prior antipsychotic agent was specified, the most recent previous antipsychotic medication was assumed to have caused the side effect.

Tolerability of olanzapine was assessed in all patients who received olanzapine and for whom at least one documentation during the observational phase was obtained. All documented side effects of pre-treatment and all adverse events reported during olanzapine treatment were listed and coded using the COSTART dictionary (1990). Abnormal laboratory findings, vital signs, EEG and ECG results and abnormal changes of these parameters were evaluated descriptively.

# Results

## Patient Disposition

A total of 3358 patients were documented at baseline, 3048 (90.8%) had been pre-treated with antipsychotics other than olanzapine. Of these, 1654 patients either continued their previous antipsychotic treatment or received medication other than olanzapine, and thus were not followed-up (Non-OLZ). In 1704 patients, antipsychotic treatment with olanzapine was started after the initial documentation (OLZ; see Figure 1). This subset of patients was followed up in the observational phase for 6 months. During this phase, 305 patients (17.9%) discontinued olanzapine treatment due to different reasons. Nevertheless, these patients were followed up in order to record any long-term data. A total of 102 patients discontinued the observation permanently; therefore, 6 month data were available for 1602 patients (94.0%).

## Demographics and Clinical Characteristics

Demographic variables and clinical characteristics of Non-OLZ and OLZ patients documented at baseline are shown in Table 1 (N=3358). Generally, baseline characteristics were similar in both groups. However, due to the large sample size most of the statistical comparisons rendered statistically significant results. Therefore, the clinical relevance of the actual differences has to be taken into account. Statistical tests revealed homogeneity between groups for height and gender. Between group differences in demographic parameters were observed with regard to age, weight and BMI. However, the numerical values of these differences were low (OLZ patients were, on average, 0.7 years younger, 1.7 kg leaner, and had a 0.6 $kg/m^2$ lower BMI) and therefore of low clinical relevance.

**Table 1. Demographic data and baseline characteristics (SD = Standard deviation. [a] Wilcoxon test; [b] Chi-square test)**

| Characteristics | OLZ (N = 1704) | Non-OLZ (N = 1654) | p-value |
|---|---|---|---|
| **Age [years]** | | | |
| Mean ± SD | 41.5 ± 14.5 | 42.2 ± 12.8 | 0.049[a] |
| Range | 17-92 | 17-99 | - |
| **Height [cm]** | | | |
| Mean ± SD | 171.7 ± 8.5 | 171.8 ± 8.2 | 0.838[a] |
| **Weight [kg]** | | | |
| Mean ± SD | 74.5 ± 12.7 | 76.2 ± 13.6 | < 0.001[a] |
| **BMI [kg/m$^2$]** | | | |
| Mean ± SD | 25.2 ± 3.7 | 25.8 ± 4.1 | < 0.001[a] |
| **Gender [%]** | | | |
| Male/Female | 48.8/51.2 | 50.9/49.1 | 0.220[b] |
| **Schizophrenia Subtype [%]** | | | 0.003[b] |
| Paranoid | 66.8 | 67.2 | - |
| Undifferentiated | 6.3 | 4.8 | - |
| Residual | 7.0 | 11.0 | - |
| Hebephrenic | 6.5 | 6.6 | - |
| Catatonic | 2.0 | 1.7 | - |
| **Course [%]** | | | < 0.001[b] |
| Continuous | 15.4 | 15.0 | - |
| Episodic with progressive deficit | 18.3 | 16.2 | - |
| Episodic with stable deficit | 14.8 | 21.3 | - |
| Episodic remittent | 22.5 | 18.5 | - |
| Incomplete remission | 12.5 | 13.7 | - |
| **Duration of current episode [months]** | 7.2 ± 20.3 | 13.2 ± 32.0 | < 0.001[a] |
| **Other psychiatric diagnoses, Yes [%]** | 10.9 | 6.9 | - |
| **Hospitalizations, yes [%]** | 24.0 | 16.1 | < 0.001[b] |

In addition, there was a statistically significant difference regarding type and course of schizophrenia between the two groups due to the large sample size. Furthermore, the duration of the current episode was significantly shorter for the patients later subjected to olanzapine treatment. Other psychiatric diagnoses present in more than 1% of the patients were Schizoaffective Disorders in 3.8% of OLZ and 3.0% of Non-OLZ patients, Persistent Delusional Disorders in 1.3% of OLZ and 0.4% of non-OLZ patients, and Depressive Episodes in 1.1% of OLZ and 0.2% of non-OLZ patients.

**Figure 1. Disposition of patients**

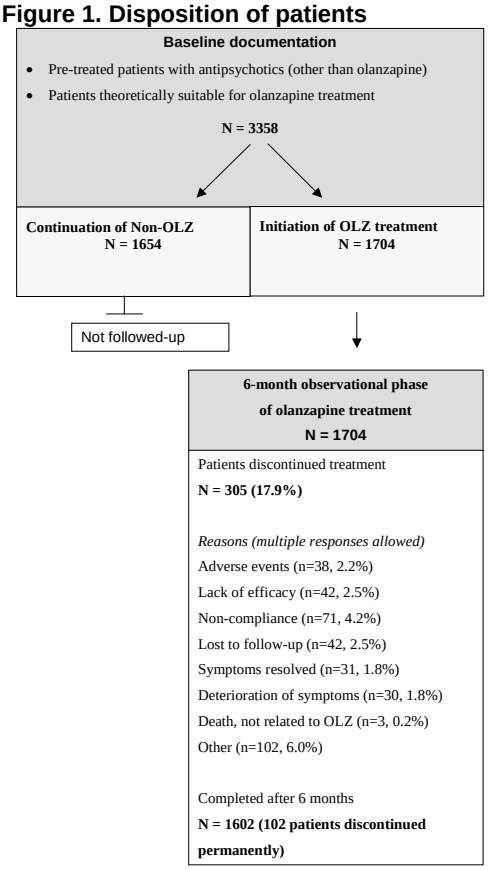



**Table 2. Previous principal antipsychotic medication reported most frequently (≥ 3% of patients, previous 2 weeks)**

| | OLZ (N = 1704) n (%) | Non-OLZ (N = 1654) n (%) |
|---|---|---|
| Haloperidol | 459 (26.9) | 340 (20.6) |
| Risperidone | 293 (17.2) | 263 (15.9) |
| Flupentixole | 211 (12.4) | 275 (16.6) |
| Fluphenazine | 149 (8.7) | 146 (8.8) |
| Clozapine | 126 (7.4) | 248 (15.0) |
| Chlorprothixene | 75 (4.4) | 78 (4.7) |
| Amisulpride | 38 (2.2) | 91 (5.5) |
| Zotepine | 71 (4.2) | 57 (3.4) |
| Levomepromazine | 60 (3.5) | 67 (4.1) |
| *None* | *117 (7.1%)* | *193 (11.2%)* |

More OLZ patients had experienced prior hospitalizations within the last 6 months compared to patients who did not initiate olanzapine. The major reasons for hospitalization in both groups were acute psychiatric symptoms.

# Tolerability Results

### Baseline Documentation

It was planned to document only patients who were already on antipsychotic medication at the start of observation. However, only 3048 of 3358 patients (90.8%) actually received antipsychotic treatment at the time of baseline documentation while 310 (9.2%) did not. The majority of patients had received prior treatment with a single antipsychotic agent (73.6% of N=3358), 17.1% of all documented patients had received 2 or more antipsychotic agents. The most frequently reported previous antipsychotic drugs are given in Table 2. Overall, the majority of patients in both groups had received haloperidol (23.8%), followed by risperidone (16.6%), flupentixol (14.5%) and clozapine (11.1%). Pretreatment was similar in both groups of patients, with the exception that clozapine and amisulpride treatment had been given less frequently to patients in whom olanzapine treatment was initiated later on.

**Table 3. Side effects of antipsychotic pre-treatment by selected pre-treatment subgroups of the total cohort at baseline (N = 3358)**

| | Haloperidol N = 799 n (%) | Risperidone N = 556 n (%) | Clozapine N = 374 n (%) |
|---|---|---|---|
| **Any side effects** | 169 (21.2) | 88 (15.8) | 95 (25.4) |
| **Affected body system** | | | |
| Nervous | 136 (17.0) | 57 (10.3) | 28 (7.5) |
| Body as a whole | 21 (2.6) | 11 (2.0) | 32 (8.6) |
| Metabolic and nutritional | 13 (1.6) | 12 (2.2) | 19 (5.1) |
| Digestive | 10 (1.3) | 3 (0.5) | 29 (7.8) |
| Urogenital | 2 (0.3) | 7 (1.3) | 1 (0.3) |
| Cardio-vascular | - | - | 5 (1.3) |
| Skin and append-ages | 1 (0.1) | 1 (0.2) | - |
| Other | 1 (0.1) | - | 8 (2.1) |
| **Side effect, COSTART term** | | | |
| EPS | 57 (7.1) | 23 (4.1) | 2 (0.5) |
| Asthenia | 15 (1.9) | 8 (1.4) | 29 (7.8) |
| Akathisia | 24 (3.0) | 12 (2.2) | 2 (0.5) |
| Dyskinesia | 12 (1.5) | 5 (0.9) | - |
| Hypokinesia | 15 (1.9) | 10 (1.8) | 7 (1.9) |
| Weight gain | 9 (1.1) | 11 (2.0) | 15 (4.0) |
| Increased salivation | 4 (0.5) | 1 (0.2) | 26 (7.0) |

Physician-assessed side effects of previous antipsychotic treatment are summarized by previous antipsychotic medication, i.e., haloperidol, risperidone, or clozapine (Table 3), and by patient cohort (Table 4).

In general, fewer side effects were documented for risperidone than for haloperidol and clozapine. EPS and akathisia were primarily responsible for the high frequency of pretreatment side effects reported for haloperidol, whereas the most frequent reports for clozapine were asthenia and increased salivation, followed by weight gain. For EPS, there was a clear gradient from high to low EPS prevalence from haloperidol (7.1%) over risperidone (4.1%) to clozapine (0.5%), similar results were observed for akathisia and dyskinesia.

At baseline, patients who initiated olanzapine experienced more severe EPS than patients who did not start olanzapine (Table 4; overall difference in EPS rates: $p<0.005$). The rate of patients free of EPS at baseline was markedly lower in the OLZ group (33.9%) than in the Non-Olz group (51.4%). Side effects other than EPS were also significantly more frequently reported in patients starting olanzapine (29.3%) than in the Non-Olz group (9.8%).

Although already solicited separately, physicians also often additionally reported EPS as a side effect. Pre-existing and concomitant diseases or complaints were reported in a total of 863 patients (25.7%) at baseline documentation. In general, those patients subsequently starting olanzapine treatment suffered more frequently from previous diseases than the Non-OLZ group, with 478 patients (28.1%) in the OLZ versus 385 (23.3%) in the Non-OLZ group ($p = 0.005$). Diseases of the nervous system (OLZ 8.6%, Non-OLZ 7.0%) and mental and behavioral disorders (OLZ 7.2%, Non-OLZ 5.9%) were reported most frequently. Looking at individual diseases, depressive episodes (OLZ 4.0%, Non-OLZ 3.9%) and sleep disorders (OLZ 3.5%, Non-OLZ 2.2%) were prevailing. However, there were no marked differences regarding the disease profile reported between both groups of patients.

Physicians reported intake of one or more non-antipsychotic medications in 45.1% of all patients (N=3358), with the rate being higher in the group of future OLZ patients ($p=0.0001$). Drugs affecting the nervous system (including anti-parkinson medication) were most frequently reported by far, reflecting the type of the most frequent concomitant diseases.

### Observational Phase

In total, 1704 patients were treated with olanzapine for a mean duration of treatment of 170 ± 54 days. The median and modal daily dose given was 10 mg/day at all visits. Individual doses given ranged from 2.5 mg/day up to 40 mg/day (40 mg/day only in 1 patient).

For a high percentage of patients (66.8%) the concomitant antipsychotic medication was modified when they initiated olanzapine treatment. This overall rate decreased to 12.9% after 2 weeks and 6.9% after 6 months of olanzapine treatment.

The antipsychotic agents given most frequently (haloperidol, risperidone, flupentixole) were discontinued in approximately half of the patients upon initiation of olanzapine treatment and were still given to less than 6% of the patients after 6 months of treatment. Upon initiation of olanzapine treatment, 40% of patients had received other concomitant medication relating to the nervous system. This rate decreased to 32.3% after 2 weeks and to 31.6% after 6 months of olanzapine treatment. Most commonly documented were psycholeptics (20.4% at initiation, 14.9% after 2 weeks and 15.2% after 6 months) and psychoanaleptics (13.7% at initiation, 12.2% after 2 weeks and 14.4% after 6 months). A considerable decrease was seen in anticholinergics from 10.6% upon initiation of olanzapine treatment to 7.2% after 2 weeks and 5.7% after 6 months of treatment.

**Table 4. Tolerability of previous antipsychotic medication at baseline. All side effects relate to the previous medication given during the last 2 weeks. Patients listed in the OLZ-column had olanzapine treatment initiated after this baseline documentation.**

| | OLZ (N=1704) n (%) | Non-OLZ (N=1654) n (%) |
|---|---|---|
| **Any side effects** | 600 (35.2) | 172 (10.4) |
| **Affected body system** | | |
| Nervous | 345 (20.2) | 64 (3.9) |
| Body as a whole | 101 (5.9) | 30 (1.8) |
| Metabolic and nutritional | 39 (2.3) | 39 (2.4) |
| Digestive | 39 (2.3) | 28 (1.7) |
| Urogenital | 26 (1.5) | 7 (0.4) |
| Cardiovascular | 13 (0.8) | 4 (0.2) |
| Others | 23 (1.3) | 6 (0.4) |
| **Side effect, COSTART term** | | |
| **> 1.5% in any group** | | |
| Extrapyramidal syndrome | 131 (7.7) | 24 (1.5) |
| Asthenia | 84 (4.9) | 22 (1.3) |
| Akathisia | 63 (3.7) | 7 (0.4) |
| Weight gain | 32 (1.9) | 32 (1.9) |
| Hypokinesia | 46 (2.7) | 13 (0.8) |
| Somnolence | 35 (2.1) | 7 (0.4) |
| Dyskinesia | 27 (1.6) | 7 (0.4) |
| **Solicited EPS (at least mild symptoms multiple denominations allowed)** | | |
| Parkinsonism | 712 (42.2) | 271 (16.6) |
| Akathisia | 648 (38.7) | 236 (14.6) |
| Dyskinesia | 482 (28.7) | 166 (10.2) |
| Motor retardation | 960 (56.6) | 552 (33.9) |

**Table 5. Overview of adverse events during the 6-month observation (OLZ group only)**

| | Number (%) of patients N = 1704 | Number (%) of events n = 582 |
|---|---|---|
| Treatment-emergent adverse events (TEAE) | 415 (24.4) | 582 (100) |
| Serious adverse events (SAEs) | 80 (4.7) | 95 (16.3) |
| SAEs considered related to olanzapine | 14 (0.8) | 16 (2.7) |
| Clinically significant adverse events (resulting in discontinuation) | 38 (2.2) | 38 (6.5) |
| Deaths (no relation to OLZ) | 3 (0.2) | 3 (0.5) |

During the observational phase, a total of 582 adverse events were reported in 415 of 1704 patients (24.4%) treated with olanzapine (Table 5). Frequently reported treatment-emergent adverse events are listed in Table 6. Weight gain was reported most frequently, and more often in female (15.1%) than in male patients (11.9%). Apart from weight

**Table 6. Treatment emergent adverse events during the 6-Month observation by body system and COSTART term (> 5 patients)**

| | Number (%) of patients; N = 1704 n (%) |
|---|---|
| **Affected body system** | |
| Metabolic and nutritional | 237 (13.9) |
| Nervous | 133 (7.8) |
| Body as a whole | 51 (3.0) |
| Digestive | 38 (2.2) |
| Cardiovascular | 11 (0.6) |
| Urogenital | 7 (0.4) |
| Skin and appendages | 5 (0.3) |
| **Adverse event, COSTART term** | |
| Weight gain | 231 (13.6) |
| Personality disorder | 49 (2.9) |
| Asthenia | 33 (1.9) |
| Liver function tests abnormal | 18 (1.1) |
| GGTP increased | 13 (0.8) |
| Depression | 12 (0.7) |
| Nervousness | 12 (0.7) |
| Anxiety | 10 (0.6) |
| Psychosis | 9 (0.5) |
| Sleep disorder | 9 (0.5) |
| Somnolence | 8 (0.5) |
| Schizophrenic reaction | 7 (0.4) |
| Akathisia | 6 (0.4) |

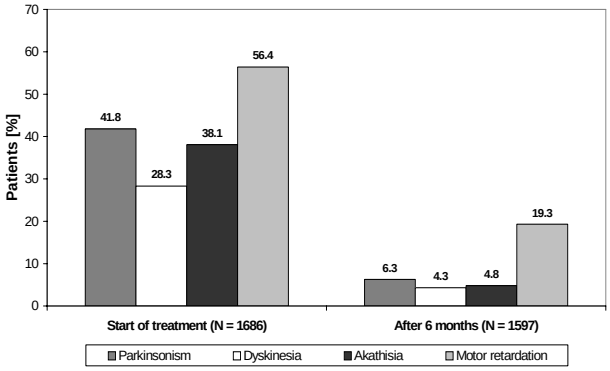
**Table 7. Rates of abnormal laboratory findings in patients treated with olanzapine during the 6-month observation**

| Parameters | Patients (N = 1704) n (%) |
|---|---|
| **Hepatic enzymes** | |
| GPT (ALAT) | 36 (2.1) |
| GOT (ASAT) | 24 (1.4) |
| AP | 4 (0.2) |
| Gamma-GT | 49 (2.9) |
| **Hematologic parameters** | |
| Erythrocytes | 10 (0.6) |
| Hemoglobin | 7 (0.4) |
| Hematokrit | 3 (0.2) |
| Leucocytes | 23 (1.3) |
| Neutrophil granulocytes | 6 (0.4) |
| Eosinophil granulocytes | 5 (0.3) |
| Basophil granulocytes | 1 (0.1) |
| Monocytes | 1 (0.1) |
| Lymphocytes | 5 (0.3) |
| Thrombocytes | 3 (0.2) |
| **Metabolic parameters** | |
| Cholesterol | 13 (0.8) |
| Triclycerides | 8 (0.5) |
| Glucose | 5 (0.3) |
| Urea | 1 (0.1) |
| Uric acid | 4 (0.2) |
| Creatinine | 5 (0.3) |
| **Electrolyte** | |
| Potassium | 1 (0.1) |
| **Other parameters** | |
| Prolactin | 4 (0.2) |
| Others | 10 (0.6) |
| **Any abnormal laboratory finding** | 232 (13.6) |

gain, personality disorder, asthenia, and abnormal liver function tests were the only adverse events reported in more than 1% of patients but all had an incidence < 3%.

Information about the physician-assessed relationship to olanzapine, severity and outcome was available for a minority of adverse events only. Information on the physician-assessed relationship of adverse events to olanzapine was available for 142 of 582 events (24.4%). Among those events with information available, 62.8% (N = 123/196) were of mild or moderate severity, and 35.5% (N = 134/377) resolved completely during the observation period. Of these, 76 events (53.5%) were considered as related. Only one hyperglycemia (serious adverse event) and one reversible case of diabetes mellitus (duration approximately 3 weeks, no antidiabetic treatment, olanzapine continued) were reported. Thus, adverse events related to glucose metabolism disturbances were reported in 0.12% of the patients accounting for less than 0.4% (2/582) of all adverse events. No cases of agranulocytosis were reported.

**Figure 2. Extrapyramidal symptoms in patients treated with olanzapine at start and during the 6-month observation**




Thirty-eight (6.5%) out of the 582 treatment-emergent adverse events led to a discontinuation of olanzapine treatment (i.e. 2.2% of all OLZ patients). A total of 95 serious adverse events (SAEs) were documented for 80 patients. The SAEs reported most frequently were personality disorder (43 patients, 2.5%), followed by psychosis and schizophrenic reaction. Only 14 out of these were considered to be likely related or of unknown relationship. All but three of these events referred to patients who required hospitalization due to an aggravation of the underlying disease. The other serious adverse events with physician-assessed possible or unknown relationship to olanzapine treatment were dyskinesia, hyperglycemia, and an infection (pneumonia). Three patients died during the study (myocardial infarction, heart failure, suicide), but none of these deaths was considered as related to olanzapine.

The rate of patients free from EPS more than doubled throughout the 6-month observation period from 34.6% at start to 77.6% after 6 months of olanzapine treatment. Accordingly, the rate of patients with parkinsonism, dyskinesia, akathisia as well as motor retardation decreased after 6 months (Figure 2). The rates of patients with severe or extreme parkinsonism, dyskinesia or akathisia also decreased from 6.3%, 4.0% and 5.9% at baseline documentation to 0.3%, 0.2% and 0.1%, respectively, after 6 months of olanzapine treatment.

The mean body weight in patients increased by 2.6 ± 5.0 kg throughout the 6-month observational phase (Figure 3). Accordingly, the mean body mass index increased from 25.2 ± 3.7 kg/m² to 26.1 ± 3.8 kg/m² after 6 months of olanzapine treatment. The 5% and 95% quantiles of body weight changes from initiation to 6 months were -4.0 kg and 11.0 kg, respectively.

Physicians were asked to document any spontaneous abnormal findings with regard to laboratory, vital signs, EEG and ECG measurements. Rates of abnormal laboratory findings (physician rating) are shown in Table 7.

For a total of 232 patients (13.6%) abnormal laboratory findings were documented. The majority of abnormalities related to increased hepatic enzyme levels.

Mean systolic and diastolic blood pressure as well as heart rates remained unchanged throughout the 6-month observational period (N=1521 patients with data available). EEG and ECG measurements were performed and documented by the physicians in only 12.5% and 8.4% of patients, respectively. No clinically relevant findings were observed. Of note, no treatment-emergent prolongation of the QTc interval was reported during this observation among those patients who had an ECG measurement. Physicians were also asked to rate the global impression of impairment by adverse events (CGI-T). They assessed that the vast majority of patients (96.0%) was not or not significantly impaired after 6 months of treatment.

# Discussion

This observational study is one of the largest studies collecting pharmacovigilance data in patients suffering from schizophrenia or other psychiatric disorders and treated with olanzapine. In order to collect naturalistic tolerability data in a large number of patients, drug utilization observation (DUO) studies are well suited. Randomized controlled studies are the gold standard for investigating efficacy and tolerability of a treatment option. However, they may not provide all the information needed in psychiatric practice. Thus, investigations in a naturalistic setting should always be performed in addition to randomized controlled studies (Linden, 1997). Nevertheless, typical difficulties and limitations of observational studies are the non-randomized nature, frequent use of concomitant medication, heterogeneous patient groups with various concomitant diseases, and a lack of source data verification. Acknowledging these limitations, however, in the current DUO study almost completely filled data documentation forms and a high retention rate were achieved due to the scientifically focused observational plan and the highly motivated physicians.

## Baseline Documentation

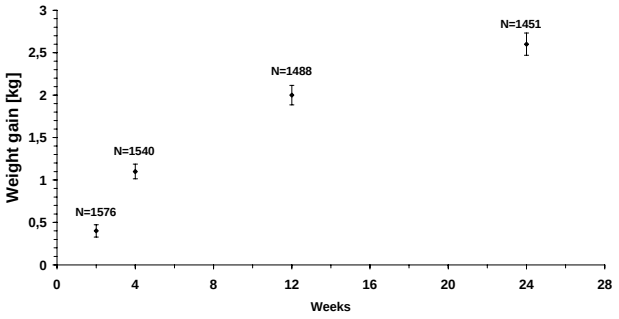
The baseline documentation provided evidence that the treatment decisions of the physicians lead to differences between the two groups of patients who were later subject to olanzapine treatment or not. Generally, more seriously ill patients with marked EPS were preferentially transferred to olanzapine treatment (OLZ). Furthermore, the patients subject to olanzapine initiation had significantly higher rates of previous hospitalizations, of side effects of previous medication, and of concomitant diseases and medications. Apart from this, a comparison of demographic and baseline characteristics in both patient groups revealed broad similarity. However, due to the high number of patients observed, some statistically significant differences with regard to age, weight, BMI, and type and course of schizophrenia were found but were considered not to be of major clinical relevance. In conclusion, the physicians' decision of whether to change the antipsychotic treatment to olanzapine or not was primarily influenced by disease severity and tolerability of pre-treatments. Comparing the tolerability profiles of the various previous antipsychotic medications, nervous system side effects were most frequently reported in haloperidol- and risperidone treated patients, but not in clozapine-treated patients; the highest percentage of side effects affecting the nervous system was found in the haloperidol group (17%). Correspondingly, EPS were most frequently reported with the conventional neuroleptic. These observations are well in accordance with previous findings (Tollefson et al., 1997; Beasley et al., 1997b).

## Observational Phase

The rate of patients completing the 6-month observational phase after initiation of olanzapine was very high (82%), a result even superior to controlled clinical trials. The most frequent reason for discontinuation of documentation was loss to follow-up. This finding might reflect the situation in normal practice when treating patients with schizophrenia and other psychiatric diseases. Remarkably, only 38 patients (2.2%) discontinued due to adverse events, suggesting high compliance and good overall tolerability of olanzapine treatment in a naturalistic setting. Previous observational studies with olanzapine have shown comparable results (Gómez et al., 2000, Lambert et al., 2005). However, during the first weeks of olanzapine treatment in particular, a high proportion of patients (12.9%) had modifications of the concomitant antipsychotic medication they received in addition to olanzapine treatment. Therefore it is difficult to attribute adverse events unequivocally to olanzapine or the co-medication.

Nevertheless, the low number of reported EPS in this study is consistent with the results of controlled trials suggesting that patients treated with olanzapine had lower rates of EPS than patients treated with haloperidol or risperidone (Tran et al., 1997; Tollefson et al., 1997), and with the results of a more recent integrated meta-analysis (Carlson et al. 2003). As expected from previous clinical trial data weight gain was the most often spontaneously reported treatment-emergent adverse event, occurring in 13.6% of all patients. However, the mean change in body weight after 6 months of treatment

**Figure 3. Mean changes in body weight (± SD) in patients treated with olanzapine during the 6-month observation**



was limited to 2.6 kg. Generally, reported adverse events were consistent with those mentioned in the summary of product characteristics (SPC) of olanzapine. The reported rate of anticholinergic effects (such as dry mouth, constipation, diplopia, urinary retention, difficulties in concentration, or confusion), which have been observed during olanzapine treatment in single investigations (Tollefson et al., 1997), was low (<0.4% of patients) in our observational study as compared to clinical trials. As observed in controlled clinical trials (Tran et al., 1997; Beasley et al., 1997b), increased hepatic enzyme levels were also reported for some patients in this study (GPT 2.1%, GOT 1.4%, AP 0.2%, Gamma-GT 2.9% ), but in no case lead to discontinuation of olanzapine treatment within 6 months. Consistent with previous studies of the prolactin safety profile of olanzapine (Beasley et al., 1996a, 1996b), only 4 cases of abnormal prolactin levels were spontaneously reported during this observation. No case of agranulocytosis, which is observed in approximately 0.5-2% of patients treated with clozapine (Mendelowitz et al. 1995, Casey 1997) but is rare with other antipsychotics, was reported after initiation of olanzapine. Also, new onset diabetes mellitus or hyperglycemic events, which have been previously described patients treated with olanzapine (Seaburg et al., 2001; Kropp et al. 2004), were observed in only 0.2% of the patients. Overall, the adverse events observed in this study were consistent with those in controlled clinical trials.

In conclusion, the pharmacovigilance data of the baseline and the observational phase of the present study suggest that atypical antipsychotics provide a favorable EPMS profile as compared to typical antipsychotics. Furthermore, this study shows that the observed adverse event profile of olanzapine is similar to that seen in controlled clinical trials.

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