

Impact of olanzapine on quality of life of patients with schizophrenia: one-year follow-up with the Seville Quality of Life Questionnaire

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Impacto de la olanzapina sobre la calidad de vida en pacientes con esquizofrenia: seguimiento a un año con el Cuestionario Sevilla de Calidad de Vida

Summary

Introduction. Our objective is to present the impact on quality of life of long-term olanzapine treatment in a significant number of schizophrenics as determined by the Seville Quality of Life Questionnaire (SQLQ), an instrument that addresses the aspects that particularly affect these patients, and to evaluate the sensitivity of this instrument to the changes induced by this treatment.

Methods. Three hundred and seventy two patients with the diagnosis of schizophrenia as per the ICD-10 classification were evaluated in a 1 year prospective study after switching to olanzapine. The SQLQ, Lehman's structured interview and short version of the disability assessment scale were used to evaluate patient's subjective experience; in addition, other instruments were used to evaluate psychopathology.

Results. Significant increases in the scores of the favorable scale and decreases in the unfavorable scale of the SQLQ were found. There were also significant improvements in quality of life as measured with Lehman's structured interview. This improvement continued until the end of the 1 year follow-up after switching to olanzapine. Both instruments show a good correlation. Changes in psychopathology were also remarkable, including the negative symptoms.

Conclusions. The SQLQ has proven to be a sensitive instrument to measure quality of life in schizophrenic patients treated with olanzapine. It focuses on aspects that are relevant for patients that were frequently overlooked by treating physicians. This drug has been proven to have a favorable subjective impact upon patients, besides improving psychopathology.

Key words: Seville's Quality of Life Questionnaire. Olanzapine. Schizophrenia. Sensitivity.

Resumen

Introducción. Nuestro objetivo es presentar el impacto sobre la calidad de vida del tratamiento a largo plazo con olanzapina en un número importante de pacientes esquizofrénicos, medido con el Cuestionario Sevilla de Calidad de Vida (CSCV), un instrumento que recoge los aspectos que afectan especialmente a estos pacientes, y evaluar la sensibilidad de este instrumento a los cambios inducidos por este tratamiento.

Métodos. Se evaluaron 372 pacientes diagnosticados de esquizofrenia según la clasificación CIE-10 en un estudio prospectivo de 1 año después de cambiar a olanzapina. Para evaluar la experiencia subjetiva se utilizaron el CSCV, la entrevista estructurada de Lehman y la versión abreviada de la escala de evaluación de la discapacidad; además se utilizaron otros instrumentos para evaluar la psicopatología.

Resultados. Se observaron aumentos significativos en las puntuaciones de la escala favorable y reducciones significativas en las puntuaciones de la escala desfavorable del CSCV. También se observó una mejoría significativa en la calidad de vida medida con la entrevista estructurada de Lehman. Esta mejoría continuó hasta el final del seguimiento 1 año después del cambio a olanzapina. Ambos instrumentos muestran una buena correlación. Los cambios en la psicopatología también fueron considerables, incluyendo los síntomas negativos.

Conclusiones. El CSCV ha demostrado ser un instrumento sensible para medir la calidad de vida en pacientes esquizofrénicos tratados con olanzapina. Se centra en los aspectos que son importantes para los pacientes y que los médicos frecuentemente han pasado por alto. Este fármaco ha demostrado tener un impacto subjetivo favorable en los pacientes además de mejorar la psicopatología.

Palabras clave: Cuestionario Sevilla de Calidad de Vida. Olanzapina. Esquizofrenia. Sensibilidad.

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INTRODUCTION

Characterization of the subjective quality of life (QL) (self-evaluated) in psychiatric patients represents a greater challenge than in other subjects. As the QL refers to

subjective and specific aspects of each individual, it can vary significantly from one to another, even in the cases in which the objective circumstances (physical) seem to be similar. The cognitive, emotional and behavioral disorders that are included in mental diseases, and especially schizophrenia, hinder the efforts made by these patients to define their understanding of the QL and, consequently, that of their physician to find the relevant aspects to evaluate it.

In spite of these difficulties, recent studies have demonstrated that it is possible to characterize the subjective QL of the schizophrenics, since clinically stable patients can distinguish between favorable and unfavorable aspects that cause suffering and affect their QL¹. They have also demonstrated that they provide stable, reliable and valid self-evaluations of their psychological well being and of the subjective evaluation of the pharmacological treatments. These achievements have been possible thanks to the identification of those factors that the schizophrenics consider relevant to define their quality of life. In this way, it has been observed that the subjective evaluation of the patient in the context of a clinical model of quality of life is partially determined by the severity of the psychopathological symptoms, especially the negative ones, the adverse drug effects and the psychosocial performance^{2,3}.

The Seville Quality of Life Questionnaire (SQLQ) was made based on this perspective. It has been shown to have psychometric properties⁴ and it is a multidimensional instrument, that is disease specific and self-evaluated. It focuses in an interesting way on the evaluation of the relevant factors of the subjective experience of the subject with their unfavorable scale. Furthermore, it has been observed that the score of this unfavorable scale is associated significantly with the scores of the affective block of the AMDP scale, especially with the depressive and anxious components¹, that make up a part of the subjective experience of the patient who is less psychotic but that play an important role in determining quality of life in schizophrenia. The importance of the affective status and, in general, of the psychological distress symptoms (in which the drug side effects—including the dysphoric response which is clearer for the patient than for the clinicians— present a significance importance) have been recently reinforced in the study by Ritsner M, et al. that included them in a 3 factor model of quality of life in severe mental disorders together with the clinical factor (psychopathology) and the social factor⁵. On the other hand, Awad et al. provided a list of factors that should be considered to measure quality of life in schizophrenia: its multidimensional character, the predominance of self-evaluation over the evaluation of the expert and suitability for the population studied, as well as the establishment of the psychometric properties of the instrument used⁶. Thus, the SQLQ can be considered a good specific instrument that contemplates those aspects related with the disease that the patients consider that affect their quality of life⁷, and that fulfills the already mentioned recommendations.

For the assessment of the benefits of the treatment, evaluation of the subjective effects of the anti-psychotic agents is being recognized as a principal component. Subjective well being has been associated with an increase in compliance and the probability of a satisfactory rehabilitation⁹. Social disability and depressive symptoms, in addition to the presence of the pure psychotic symptoms, are being considered as determining factors of the prognosis. This means that the perspective of the patient, that may sometimes vary from that of the psychiatrist, should be considered for correct therapeutic management.

The characteristics of the atypical antipsychotic agents, with better tolerability and potential profiles to relieve the negative symptoms and cognitive deficits, make them good candidates to improve quality of life. Evaluation of their therapeutic outcome, however, has been commonly measured by psychopathology more than by their subjective effects, but there are some empiric data. In a study of Naber et al.⁸, the effects of risperidone, clozapine and olanzapine on well being, assessed both by objective instruments based on the symptoms focused on psychopathology as well as by subjective instruments based on the patient, were compared. They found a poor correlation of the results measured by both types of instruments and they observed that mental functioning was evaluated more extensively with the latter instruments. Furthermore, the olanzapine treated patients showed greater improvement in their subjective well being than those treated with clozapine or risperidone. These data stress the importance of measuring QL in the management of antipsychotic treatment.

In this context, we contribute a long term study on the results of the treatment in an important number of schizophrenics who began to receive olanzapine, in whom the SQLQ was used to verify its adequacy. The patients were also evaluated with Lehman's structured interview of quality of life, some psychopathology instruments (AMDP, PANSS, CGI), the Calgary scale of depression in schizophrenia and the Hamilton anxiety scale.

The principal objective of this article is to present the impact on the quality of life of long term treatment with olanzapine in an important number of schizophrenics, measured by SQLQ and to evaluate the sensitivity of this instrument to the changes induced by this treatment. Correlation with the scores of Lehman's structured interview of quality of life will also be presented.

METHODS

Patient population

This study sample included patients diagnosed of schizophrenia according to the ICD-10 classification, with ages ranging from 18 to 65 years, in whom the onset of an antipsychotic treatment with olanzapine was indicated. Pregnant women, patients with organic brain diseases, other severe concomitant diseases or alcohol or drug abuse were excluded. Patients who

discontinued olanzapine or who received another antipsychotic agent concomitantly for more than two weeks during the study were withdrawn. The participants or their legal representatives granted their informed consent before the beginning of the study and the study was communicated to the Spanish Drug Agency.

Study design and assessment instruments

This is an observational, prospective, open labeled and non-controlled study. The initial dose of olanzapine had to be 10 mg/day, which the investigators could modify afterwards. The patients were evaluated on the baseline visit and at 1, 3, 6, 9 and 12 months. The instruments used were the SQLQ (favorable and unfavorable scales, score range from 1 to 5 each one), Lehman's structured interview of quality of life¹⁰, the short version of the disability evaluation scale¹¹, system of the Association for Methodology and Documentation in Psychiatry (AMDP)¹², positive and negative syndromes scale (PANSS)¹³, clinical global impressions scale, Calgary scale of depression in schizophrenia¹⁴ and Hamilton anxiety scale¹⁵.

To guarantee interrater reliability, a weighted kappa correlation coefficient was calculated on the investigators after the evaluation of a fictitious case with the PANSS. A minimum value of 0.4 was established to be able to participate in the study.

The side effects were systematically evaluated with the UKU scale of extrapyramidal side effects¹⁶ as well as open questions to the patients in each study visit.

Statistical analysis

The principal objective of the analysis was to evaluate the sensitivity of the SQLQ in olanzapine treated patients. To do so, a single methodological procedure was followed to evaluate the changes observed in the different general scales. A last-operation carry forward technique (LOCF) was used to attribute the absent values in patients with at least one valid determination after the baseline one. In order to evaluate the changes within each scale globally, an analysis of the variance was used with contrast techniques to detect differences between the mean values in each visit and the baseline value as intrasubject variables. Furthermore, the 95% confidence intervals of the mean values in each visit were calculated.

Simple product-moment Spearman correlation coefficients were also calculated to assess convergent and discriminant validity of the SQLQ with Lehman's structured interview and PANSS subscales scores.

Finally, the same approach was used with the UKU scale as for the principal analysis. The non-systematic information on adverse events was analyzed descriptively.

RESULTS

This study sample included 428 enrolled patients, of whom only 372 presented valid data after baseline. The latter were included in the LOCF population to perform the analysis. A total of 66.5% of these patients were male. Their age (mean \pm SD) was 34.2 ± 10.52 years and duration of the disease after diagnosis was 10.6 ± 8.88 years. The reason for the change to olanzapine was lack of efficacy of the previous antipsychotic treatment in 43.0% of the patients, poor tolerability in 18.0%, both in 26.9% and not determined in 12%. The mean dose of olanzapine increased during the follow-up, it being 13.58 mg/day on the last visit. Compliance with the treatment was considered very good in up to 76% of the patients.

Evolution of the SQLQ scores is shown in figure 1. Quality of life described increased in regards to the baseline until the end of the follow-up period of the study both in the favorable scale (increase of mean scores) as well as the unfavorable one (decrease of the mean scores). Observing the confidence intervals, it can be concluded that there were significant changes between the baseline evaluations and month 3 on both scales. Furthermore, in the favorable scale, significant changes were observed between month 3 and month 12 evaluations and also in the unfavorable scale between month 3 and month 6 evaluations and between month 6 and month 12 evaluations. The changes in the three domains of each scale (life satisfaction, self-esteem and harmony in the favorable one and in the aggregates inhibition, incomprehension and irritation in the unfavorable one) were coherent with these results: significant improvements were observed from baseline to month 3 in all the domains and, between month 3 and month 12, in all the domains except in that of self-esteem on the favorable scale (see

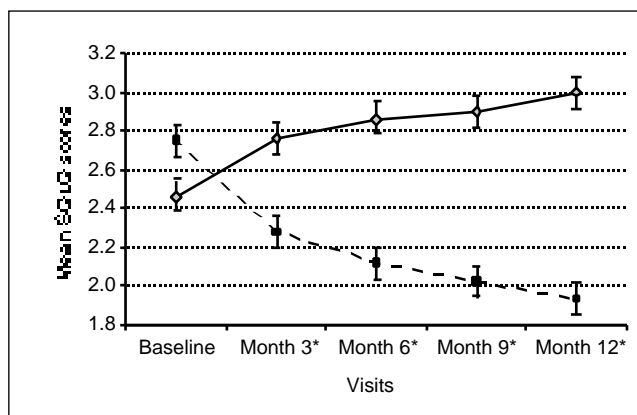


Figure 1. Mean scores on the favorable scale (continuous trace) and on the unfavorable scale (discontinuous trace) of the Seville Quality of Life Questionnaire in the LOCF population. The points indicate the mean value in the evaluation times indicated. The error bars represent the 95% confidence intervals for each mean. The asterisks indicate a value of $p < 0.001$ for the comparison between the value on the specified visits and the baseline value.

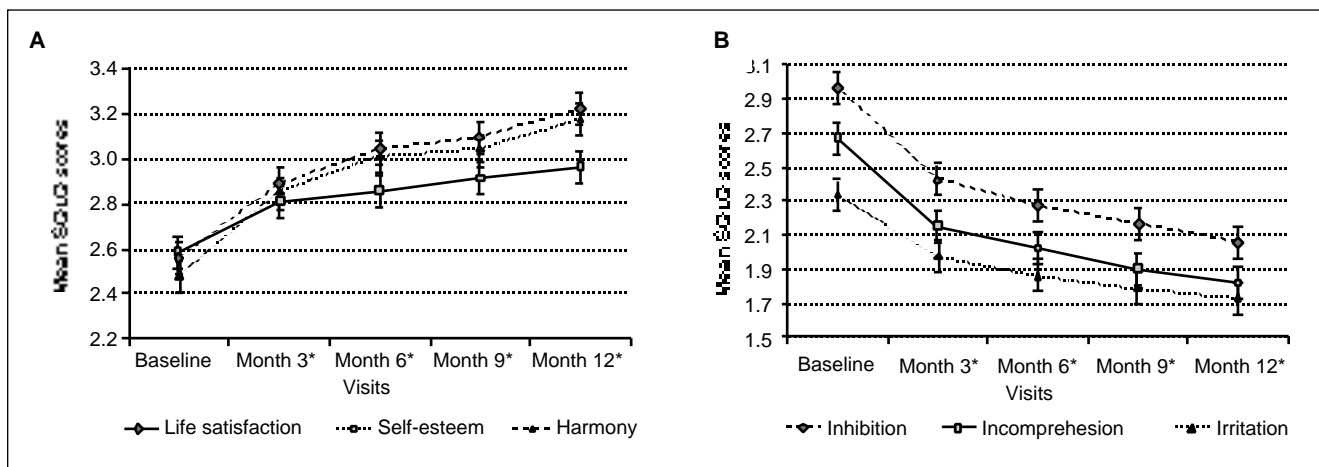


Figure 2. A: Mean scores in the domains of the favorable scale (life satisfaction, self-esteem and harmony) of the Seville Quality of Life Questionnaire in the LOCF population. The points indicate the mean value in the times of evaluation indicated. The error bars represents the 95% confidence intervals for each mean. The asterisks indicate a $p < 0.001$ value for the comparison between the values of each subscale in the specified visits and the corresponding baseline value. B: Mean scores in the domains of the unfavorable scale (inhibition, incomprehension and irritation) of the Seville Quality of Life Questionnaire in the LOCF population. The points indicate the mean value in the evaluation times indicated. The error bars represent the 95% confidence intervals for each mean. The asterisks indicate a $p < 0.001$ value for the comparison between the values of each subscale in the specific visits and the corresponding baseline value.

the 95% confidence intervals in figures 2 A and B). In general, improvements were more important on the unfavorable scale than on the favorable one. The scores of each domain as well as those of each subscale in all the visits were compared with the corresponding baseline values, obtaining a p value less than 0.001 in all the cases. These results indicate that the SQLQ has been sensitive to the changes induced by the antipsychotic treatment with olanzapine, and the response pattern (more important improvements in the unfavorable scale than those observed in the favorable one) was coherent with the known effects of this drug, which is effective, also improving the negative symptoms. Interestingly, the patients continued to show improvements at least up to 12 months after beginning treatment.

Regarding Lehman's structured interview on quality of life, significant improvements were found at the end of the treatment in all the domains (table 1). These changes were already significant from the 3rd month except for the place of residence (significant from month 9), finances (only significant at month 12), work (only significant at month 12) and legal and safety aspects (only significant at month 12).

The correlations between the SQLQ scores and Lehman's structured interview are summarized in table 2. The total score of the SQLQ presented a significant positive correlations with the scores of the domains of Lehman's structured interview ($p < 0.001$ except for legal and safety aspects). The SQLQ unfavorable scale score presented a significant negative correlations with the scores of all the domains of Lehman's structured interview ($p < 0.001$ in all the cases). The favorable scale score of the SQLQ presented a significant positive correla-

tion with some of the domains of Lehman's structured interview. In general, the correlation between the favorable scale of the SQLQ was small for some domains of Lehman's structured interview (place of residence, family, finances and legal and safety aspects) and moderate to high for the others (general satisfaction with life, daily activities and functioning, social relationships, work, health, global score and mean score). The correlations between the unfavorable score and the total score of the SQLQ with the domains of Lehman's structured interview were small to moderate and moderate to high, respectively.

Only 15.7% of the patients notified at least one adverse event. The adverse events described with greatest frequency were weight gain (6.8% of the patients), erectile dysfunction (2.3% of the patients) and drowsiness (2.3% of the patients). Global score of the UKU scale of extrapyramidal side effects noticeably decreased between baseline and month 3, but continued to decrease from this time until the end of the follow-up (fig. 3). The changes in this scale were significant from month 1.

CONCLUSIONS

The disagreement existing in the past between the opinions of the clinicians and the patients in relationship with the perceptions on the efficacy of the drugs in the treatment of schizophrenia, the former being based on the control of the symptoms and the latter on the absence of adverse effects, is being overcome, since it is presently recognized that the experience of the patient predicts compliance and outcome^{17,18}. At present, with

TABLE 1. Results of Lehman's structure interview of quality of life before treatment (baseline) and after treatment (month 12)

Domain	95% CI of the mean						
	Visit	Mean	SD	Inferior	Superior	Difference of means	p
General satisfaction with life	Baseline	3.23	1.48	3.0716	3.3829	1.21	<0.0001
	Month 12	4.44	1.35	4.3053	4.5811		
Place of residence	Baseline	4.92	1.46	4.7864	5.0650	0.30	<0.0001
	Month 12	5.22	1.15	5.1039	5.3394		
Daily activities and functioning	Baseline	3.29	1.26	3.1604	3.4178	1.08	<0.0001
	Month 12	4.37	1.21	4.2466	4.4938		
Family	Baseline	4.51	1.52	4.3559	4.6685	0.47	<0.0001
	Month 12	4.98	1.38	4.8409	5.1239		
Social relationships	Baseline	3.44	1.37	3.2975	3.5792	0.82	<0.0001
	Month 12	4.26	1.33	4.1226	4.3942		
Finances	Baseline	3.72	1.58	3.5551	3.8789	0.36	<0.0001
	Month 12	4.08	1.45	3.9321	4.2283		
Work	Baseline	4.02	1.52	3.7238	4.3136	0.37	0.0022
	Month 12	4.39	1.39	4.1633	4.6171		
Legal and safety aspects	Baseline	4.62	1.55	4.4587	4.7770	0.23	0.0002
	Month 12	4.85	1.38	4.7118	4.9944		
Salud	Baseline	3.71	1.29	3.5815	3.8459	0.89	<0.0001
	Month 12	4.60	1.26	4.4741	4.7312		
Global score	Baseline	3.49	1.34	3.3502	3.6276	1.14	<0.0001
	Month 12	4.63	1.26	4.5027	4.7601		
Mean score	Baseline	3.37	1.32	3.2391	3.5095	1.18	<0.0001
	Month 12	4.55	1.23	4.4239	4.6757		

The results are expressed as mean values in the visits indicated for all the LOCF population together with the standard deviation (SD) and the 95 % confidence interval (CI). The p value of the difference is that obtained by the ANOVA model used for the comparison of the means expressed.

TABLE 2. Simple product-moment Spearman correlation coefficient between the scores of the Seville Quality of Life Questionnaire (SQLQ) and those of Lehman's structured interview of the LOCF population after 12 months of treatment

Lehman's structured interview	SQLQ		
	Total favorable	Total unfavorable	Total score
General satisfaction with life	0.59492 [‡]	-0.38465 [‡]	0.58867 [‡]
Place of residence	0.14772 [*]	-0.33805 [‡]	0.27774 [‡]
Daily activities and functioning	0.56573 [‡]	-0.39208 [‡]	0.57492 [‡]
Family	0.18012 [†]	-0.19933 [‡]	0.22189 [‡]
Social relationships	0.53830 [‡]	-0.37470 [‡]	0.54647 [‡]
Finances	0.14891 [*]	-0.26004 [‡]	0.24260 [‡]
Work	0.36202 [‡]	-0.43766 [‡]	0.47629 [‡]
Legal and safety aspects	0.08953	-0.22531 [‡]	0.17730 [†]
Health	0.42800 [‡]	-0.38226 [‡]	0.47502 [‡]
Global score	0.48047 [‡]	-0.37594 [‡]	0.50331 [‡]
Mean score	0.58225 [‡]	-0.41323 [‡]	0.59022 [‡]

*p < 0.05; †p < 0.01; ‡p < 0.001.

the introduction of atypical antipsychotics, the traditionally negative evaluations made by the patients and their family on the treatments and poor subjective tolerability are less frequent with the introduction of the atypical

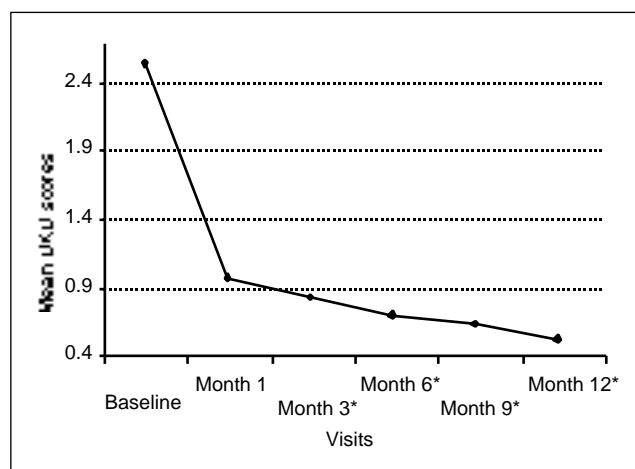


Figure 3. Evolution of the UKU scale scores for extrapyramidal side effects. The changes regarding the baseline value begin to be significant from the month 1 visit.

antipsychotic agents, since they are capable of reducing the extrapyramidal and subjective adverse effects, maintaining the efficacy on the psychopathology presented by the typical drugs, facts that have provided an improvement in the subjective response¹⁹. However, in spite of being aware of the importance of the subjective experience of the patients, serious investigations on subjective well being and quality of life of the schizophrenics treated with antipsychotic agents (atypical) have only recently been carried out. These efforts include the development of adequate instruments as well as the performance of well designed clinical studies to assess the therapeutic outcome under this perspective.

Development of the SQLQ corresponds to these efforts. In addition to the applicable generic instruments, several specific scales have been developed with the purpose of measuring subjective well being or quality of life of these patients. However, there is no agreement on their reliability²⁰. The results presented with the SQLQ indicate that it is a strong instrument to assess the effects of long term treatment with olanzapine. It has been shown to be sensitive and to have a good correlation with Lehman's structured interview, that is considered to be the preferred procedure for the evaluation of quality of life in schizophrenia. Furthermore, as has already been mentioned, it focuses on the evaluation of the relevant factors of the subjective experience of the patient with the unfavorable scale. Thus, in previous works, important correlations have been found between this instrument with the PANSS⁷. However, this should not be considered a defect in its validity, but rather the fact that the SQLQ is a well directed survey on the factors that influence in quality of life of these patients. In fact, we have performed an analysis of the correlation with the PANSS scores obtained in the population of this study (data not presented in this article) and have found that it was, in general, inferior to that observed with Lehman's structured interview. The SQLQ also has the advantage of being easy to use and that it requires a short time to be filled out.

Another interesting question of this study is that it provides information on the treatment outcome with olanzapine; since, up to now, little, although encouraging, information has been published in regards to the experience with this drug. In the Bartkó et al.¹⁸ study, the assessment of their subjective experience with olanzapine performed by the patients was superior to that of the previous antipsychotic treatment and in the Naber et al.⁹ comparative study, the patients treated with other atypical antipsychotics (clozapine and risperidone) presented an improvement in their psychopathology that was as important as that of the patients treated with olanzapine, however the changes in the well being measured by the short version of the well being scale with neuroleptics (SWN, by the same authors) were greater in the patients treated with olanzapine. Nevertheless, the follow-up in these two studies mentioned was short. In fact, Naber et al. suggested that the differences in the subjective result between the atypical antipsychotic agents could come from the short duration of the study,

since the most relevant side effects with risperidone principally appear in the first weeks, while weight gain, the principal problem associated with olanzapine, is more outstanding after, so that these differences can vary over time. We provide long term data with our study. Our results have indicated that quality of life continues to improve with olanzapine from month 3 on. There were even significant differences between month 3 and month 12 in the improvement of the SQLQ domains, including all the factors of the unfavorable scale.

The patients almost did not spontaneously describe their weight gain, which suggests that they did not perceive it as a problem. However, the safety outcomes presented are not convincing, since the number of events is unusually low. This may be due to a deficient unsystematic gathering of the appearance of adverse events, given the observational character of this study, so that it may not be reliable. On the contrary, the information obtained with the UKU scale was more reliable, since it was administered to almost all the patients, and the results verify that olanzapine had a low potential of extrapyramidal side effects.

This study has clear limitations; it includes a single cohort treated in an open way and without comparator. However, it is a large long term study, and has focused on the subjective experience of the patients under treatment with olanzapine, this being done by few studies published up to the present date. As there is no agreement on the reliability of the QL instruments in relationship to which scale should be used for this purpose, any new information based on experience is welcome.

In conclusion, the SQLG has been shown to be a sensitive and easy to use instrument to measure the subjective experience of the patients in schizophrenics treated with olanzapine. This drug has provided an important improvement in the patients' quality of life, that continues up to one year after onset of the treatment. This improvement has been detected by both the SQLQ as well as by Lehman's structured interview.

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