Paroxetine drops versus paroxetine tablets: evaluation of compliance in a six-month study

Valutazione della compliance al trattamento con paroxetina in gocce rispetto alle compresse in uno studio di sei mesi

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SUMMARY. Aims. Literature data show that one third of patients discontinue antidepressant therapy within the first month of treatment. The aim of this study was to evaluate whether paroxetine liquid solution 10 mg/ml may influence adherence in patients receiving long-term treatment. **Methods.** 71 subjects affected by mood disorders or panic disorder were monitored for six months. The study sample was divided into two groups: controls (n=33) maintained their own therapy with paroxetine tablets; 38 patients maintained the same dosage of paroxetine, but shifted to liquid formulation 10 mg/ml. Compliance and general wellness were evaluated with the Medication Adherence Rating Scale (MARS) and the World Health Organization Quality of Life questionnaire (WhoQol). Data were analyzed using analysis of variance (ANOVA) and multivariate analysis of covariance (MANCOVA). **Results.** Significant differences were found in MARS scores: patients on oral solution 10 mg/ml showed an improvement of compliance month by month. In addition, age, formulation and quality of life had a significant impact on patient compliance. Significant correlations were found between MARS and quality of life. A specific paroxetine formulation could be a variable able to influence adherence to psychopharmacological treatment. The same consideration can be made for quality of life, sex and age that showed a trend towards improved adherence when compared with controls. In particular, the WhoQol subscale analysis of delta scores showed a significant difference in self-perception of quality of life in patients treated with paroxetine either in tablet or drop formulation. **Discussion.** Formulation in drops 10 mg/ml is equally effective to tablets, but it may allow patients having a higher cognition and control on drug assumption.

KEY WORDS: compliance, long-term treatment, depression, formulation, panic disorder.

RIASSUNTO. Scopo. I dati presenti in letteratura mostrano come un terzo dei pazienti trattati con farmaci antidepressivi non sia costante nell'assunzione della terapia nel primo mese di trattamento. L'obiettivo dello studio è stato quello di valutare se la formulazione liquida di paroxetina 10 mg/ml potesse influenzare l'aderenza al trattamento in pazienti trattati con una terapia a lungo termine. **Metodi.** 71 soggetti affetti da disturbo dell'umore o disturbo di panico sono stati monitorati per sei mesi. Il campione è stato diviso in due gruppi: il gruppo di controllo (n=33) ha mantenuto la terapia con paroxetina in compresse; 38 pazienti, pur mantenendo lo stesso dosaggio di paroxetina, sono passati alla formulazione liquida 10 mg/ml. La compliance e il benessere generale sono stati rispettivamente valutati con Medication Adherence Rating Scale (MARS) e World Health Organization Quality of Life (WhoQol). I dati sono stati analizzati tramite l'analisi della varianza (ANOVA) e l'analisi multivariata della covarianza (MANCOVA). **Risultati.** Differenze significative sono state riscontrate nei punteggi alla scala MARS: il gruppo che assumeva la soluzione orale 10 mg/ml mostrava un incremento di compliance che aumentava nel tempo. Anche l'età, la formulazione e la qualità della vita influenzano significativamente la compliance. Sono state trovate correlazioni significative tra MARS e qualità della vita, valutata tramite la scala WhoQol. Una specifica formulazione di paroxetina potrebbe essere una variabile in grado di influenzare l'aderenza al trattamento psico-farmacologico. La medesima considerazione potrebbe essere fatta per la qualità della vita, il sesso e l'età, variabili che sembrano in grado di incrementare l'aderenza al trattamento quando confrontate con il gruppo di controllo. In particolare, l'analisi dei delta delle sottoscale della WhoQol evidenzia una differenza significativa nella percezione della propria qualità di vita tra i pazienti dei due gruppi. **Discussione.** La formulazione in gocce del farmaco è efficace quanto quella in compresse, ma sembra portare i pazienti ad avere maggiore consapevolezza e controllo sull'assunzione del farmaco.

PAROLE CHIAVE: compliance, trattamento a lungo termine, depressione, formulazione, disturbo di panico.

INTRODUCTION

Mental disorder is associated with enormous personal suffering for affected patients, great distress for their family and friends and major socio-economic costs (1,2). Antidepressant medication reduces acute symptoms (3,4) and its premature discontinuation increases the risk for relapse (5). Nevertheless, between 30% and 83% of patients who begin antidepressants discontinue treatment prematurely (5-7).

More than other diseases, depression is associated with high rates of relapse and recurrence during a patient's lifetime (5). For this reason, a life-long antidepressant treatment is recommended (8).

The treatment of depressive episodes has 3 phases (3,5):

1. the goal of the acute treatment phase is relief of symptoms and the length of this phase depends on responsiveness to treatment and the need to find an optimal regimen;
2. continuation therapy is recommended for a period of 4-9 months following the acute phase to allow more complete resolution of the episode and to prevent the relapse that is the re-emergence of the existing episode (5);
3. the need for long-term maintenance phase depends on the number of prior episodes (9,10) and other risk factors such as associated anxiety (11,12).

Recent data show that nearly one third of patients discontinue quickly antidepressants within the first month of treatment (13,14) and 44% of patients discontinue therapy within the first three months (15,16). Lingam and Scott (17) reviewed data published from 1976 to 2001 regarding the prevalence of psychotropic medication non-adherence in affective disorders: the authors showed that for these disorders the incidence of non-adherence ranged from 10% to 60% with a median of 40%. They further assured that the trend of non-adherence had not changed significantly in recent years (14,16-21).

In parallel with a development of a notion that depression is an illness requiring a continuous and regular medication treatment, the psychiatric community started to focus its attention on compliance with antidepressant medication regimens (22). Many studies quantify the percentage of subjects who early interrupt antidepressant therapy, but only few ones focused on the causes of this diffused behaviour.

Compliance has been defined as the extent to which a person's behaviour in terms of taking medication or executing a lifestyle changes coincides with medical or heath advice (23). Because this term is sometimes perceived as too authoritarian, other terms have appeared sporadically in the literature such as adherence, maintenance, self-regulation, alliance or concordance (24).

Non-compliance can be manifested in several ways (24,25): 1) failure to have the prescription filled; 2) having the prescription filled but failing to take the medication; 3) not follow the frequency or dosage instructions of the prescription; 4) errors of purpose or use of inadvertent combinations.

There appears to be a broad range of reasons why patients discontinue antidepressants prematurely. Bulloch and Patten found that simply forgetting to take medication was the main reason for patient non-adherence (26).

Willingness to take the prescribed antidepressant is tightly linked to beliefs about medication. For example, patients report that treatment effectiveness and barriers are among the most critical aspects of depression care (27). Data also show that pre-treatment perceptions of the benefits of and barriers to antidepressants predict initial medication adherence, and that primary care patients frequently attribute their early discontinuation to their perception that they do not need an antidepressant (16). Moreover, some authors (16) suggested that severe daytime somnolence was significantly associated with early non-adherence, while fatigue, blurred vision, difficulty in falling asleep, feeling anxious or jumpy, changes in appetite, and weight gain were significantly associated with late non-adherence. Long-term adherence may gradually diminish as clinically improved patients begin to conclude that they no longer need medication or become less willing to continue tolerating previously acceptable medication problems such as sexual side effects. Maintenance phase may also be relatively more affected by fears of potential long-term cumulative or insidious adverse effects such as personality changes, addiction or toxicity (27). Deterrents to adherence may also include other personality disorder symptoms, above all those included in DSM-IV Cluster B personality disorders (28).

Aikens et al. (29) suggested that perceived necessity of medications is related to age, thus older patients reported greater perceived necessity.

Although it is generally assumed that elderly patients are more likely to be non-compliant than younger patients because of the high number of medications prescribed and complexity of dose regimens, this relationship has not yet been fully established (9). Compliance in elderly patients remains a focus of interest because the large number of medication used increases the risk of side effects.

Horne (30) has asserted that beliefs of medication are "the hidden determinant of treatment outcome",

thus, in relation to antidepressants, beliefs appear to be a major predictor of adherence.

Demyttenaere concluded that antidepressant adherence improves when patient-clinician communication focuses on patient's personalized belief about how to best manage their depressive symptoms, which often conflict with medical models of treatment. Thus, adherence may improve if clinicians carefully clarified the patient's specific concerns (e.g. adverse effects, addiction, personality changes, financial costs, stigma) and then offered a conservative dosing (29).

The strength of the physician-patient relationship, the severity of psychopathology, side effects, and patient education and personality may be considered predictors of antidepressant medication adherence (31). Consistent evidence indicates that a therapeutic alliance with the patient through educational techniques increases behavioural compliance, physicians may be able to enhance patient adherence to antidepressant treatment by offering detailed information about their treatment regimens (10,16).

Paroxetine is indicated for the treatment and prevention of depression and anxiety disorders. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and increases serotonin levels by inhibiting the reuptake transporters. Paroxetine is available as hydrochloride (HCl) and as mesylate salt. Some patients may have difficulty in swallowing tablets and thus may be less likely to adhere to their medication regimen. Swallowing problems can occur for physical or psychological reasons. Physical swallowing problems can be caused by abnormalities of the head and neck, age-related degeneration of the esophagus, trauma or surgery, neurogenic or muscular disorders, or the side effects of medications (32). Some patients may simply experience discomfort when trying to swallow tablets due to pill size or texture (33).

Navarro (34) found that orodispersible tablet formulations may improve compliance among patients with depression who have physical or anxiety-based swallowing difficulties, nausea, or limited liquid intake, and may also prove preferable for patients without these difficulties. Obviously, pill-swallowing problems can occur for a number of reasons and these may not be readily identified by patients. For such patients a liquid formulation of paroxetine could be beneficial and improve their compliance. Compliance to treatment protocol is crucial since long-term treatment of depression is important to prevent relapses (35).

The aim of this study was to evaluate wheter the recent introduction of paroxetine liquid solution 10 mg/ml into the Italian market may influence patient adherence to long-term treatment.

MATERIALS AND METHODS

There is a growing body of evidence on the therapeutic efficacy of paroxetine: it is indicated for the treatment and prevention of depression and also for the treatment of generalized anxiety disorder, social anxiety disorder, panic disorder and obsessive-compulsive disorder (36); moreover, it can be used during the acute phase of illness and for a long-term treatment during the maintenance phase.

The aim of this study was to evaluate how paroxetine formulation (tablet and drops) could influence adherence to long-term antidepressant therapy in a sample of patients treated at the Department of Clinical Neurosciences of San Raffaele Hospital.

Paroxetine oral solution 10 mg/ml has been introduced into the Italian market as well as tablets; because adherence to treatment may also depend on medication assumption, we supposed that drops could be easier to assume than tablets. Our aim was to compare these two different formulations to identify, if possible, when and who should be prescribed with one or the other formulation.

More than six months of euthymia were required for the inclusion in the study and all patients were treated with paroxetine tablets with different dosages.

The study sample consisted of 71 subjects (14 male and 57 female), 57 affected by mood disorder (44 major depressive disorder and 13 comorbidity of mood and panic disorder) and 14 affected by panic disorder. In case of comorbidity, mood disorder is the principal diagnosis. They were monitored for six months and administered with a battery of self-administered scales in four consecutive times: at baseline, and after 1, 3 and 6 months.

Patients were divided into two groups: controls (n=33) maintained their own therapy with paroxetine tablets; patients included in the control group participated in qualitative interviews and expressed a reluctance or refusal to shift to paroxetine liquid solution 10 mg/ml; the remaining 38 patients maintained the dosage of paroxetine recommended by the physician, but shifted to the liquid formulation 10 mg/ml.

After the first month, three patients preferred to come back to the tablet formulation because of a subjective nasty taste of drug and for greater convenience of tablets. No drop-outs were recorded in the control group.

Compliance was evaluated with the Medical Adherence Rating Scale (MARS) (35,37-39), a self-administered scale, at baseline, after the first month, after the third month and at the end of the study, as well as after six months from the shift.

Wellness was evaluated using the World Health Organization Quality of Life questionnaire (WhoQol). This scale evaluates the influence of four different variables on person's life; from these depends subjective wellness: Psychological Area, Physical Area, Interpersonal Relations and Environment. The addition of scores from these areas provides a comprehensive score of quality of life perceived.

Before the inclusion in the study and at every step, the physician visited the patients and administered Hamilton Rating Scale for Depression and MADRS to test the euthymia.

RESULTS

Clinical and socio-demographic variables of the study population are shown in **Table 1** and did not show any significant differences.

Repeated measure ANOVA showed significant differences (p<0.0272) in MARS scores during six months of monitoring between the two groups; in particular, the group receiving oral solution 10 mg/ml showed an improvement of compliance month by month (**Figure 1**).

Analyzing MARS scores, we verified whether some clinical-demographic variables could affect adherence to treatment; MANCOVA analysis was performed using MARS scores as dependent variables, time as within factor, age and formulation and quality of life (total WhoQol score) at baseline as between factor. Results obtained showed how significant variables explained variance of compliance at baseline (p=0.011), and after the first (p<0.000), third (p<0.000) and sixth month (p<.000). Formulation significantly explained variance of MARS scores (λ di Wilks: p=0.000).

Post-hoc analysis confirmed significant differences in MARS scores between the two groups from the beginning to the end of the study period (LSD Fisher on: baseline (p=0.0036), and after the first (p=0.020), third (p=0.005) and sixth month (p=0.005).

As MARS and WhoQol scores were different at baseline, we decided to analyze also the delta scores in order to point out the variation during the three periods of observation (first period: baseline-1 month; second period: 1-3 months; third period: 3-6 months).

As shown in **Figure 2**, mean MARS delta scores did not show a variation during the time (p=0.41) in ANOVA analysis, whereas mean WhoQol subscales delta scores (**Figures 3-6**) showed statistical significant differences between the two groups. Each WhoQol area showed a difference during the time for patients receiving paroxetine tablet and drops.

Spearman rank correlation analysis showed significant correlations between MARS scores and WhoQol scores (**Table 2**).

Table 1. Clinical and socio-demographic variables of the study population

	Drops	Tablets
No. subjects	38	33
Sex (M/F)	5/33	9/24
Age (years)	46.21±15.26	47.81±13.74
Instruction (age)	11.29±4.45	12.63±3.96
Diagnosis		
UP	22	22
DAP	10	4
DAP+UP	6	7
Dosage	25.55±11.26	24.19±9.58
Onset	36.14±14.75	33.22±17.39

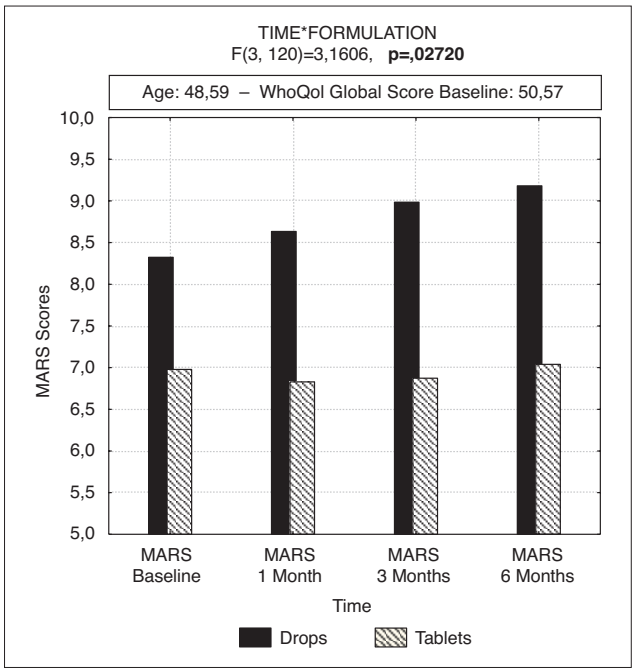

Figure 1. ANOVA, variation during the time in MARS scores.

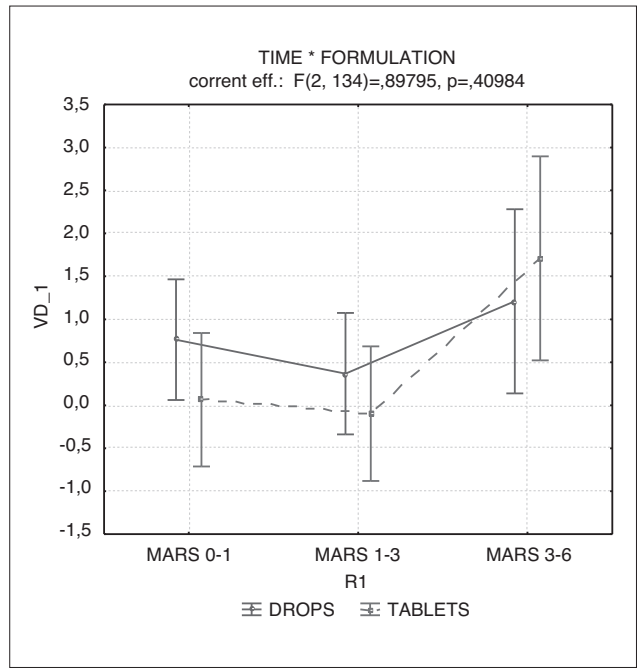

Figure 2. ANOVA, variation during the time of mean delta MARS scores.

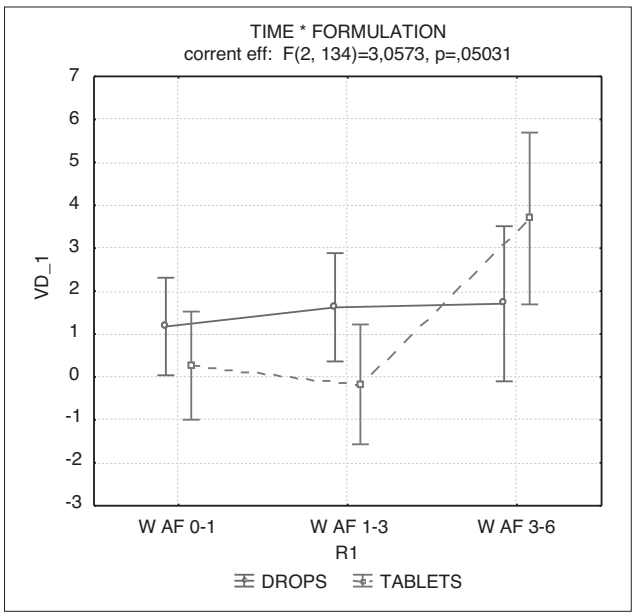

Figure 3. ANOVA, variation during the time of mean delta Physical Area (AF) WhoQol scores.

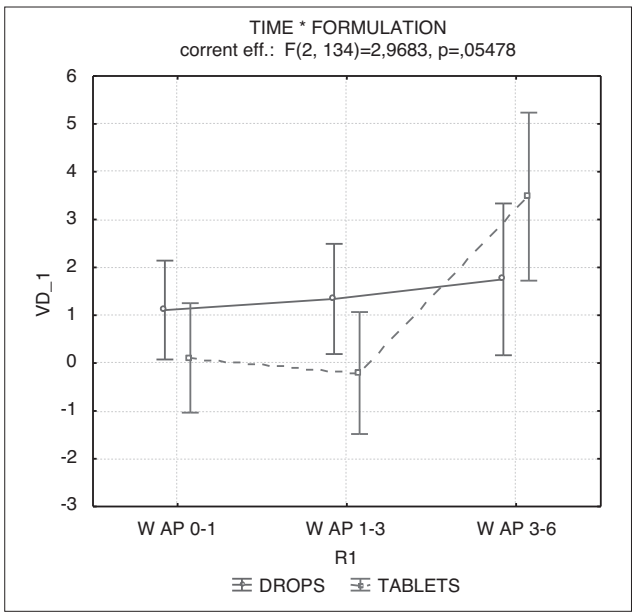

Figure 4. ANOVA, variation during the time of mean delta Psychological Area (AP) WhoQol scores.

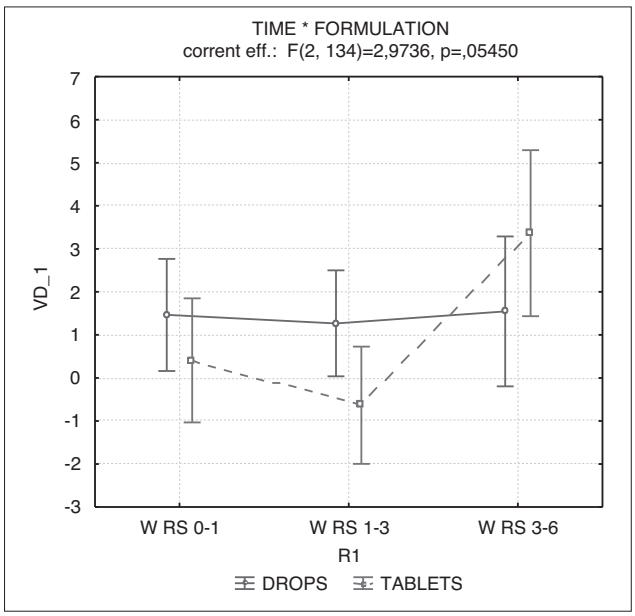

Figure 6. ANOVA, variation during the time of mean delta Social Relations (RS) WHOQOL scores.

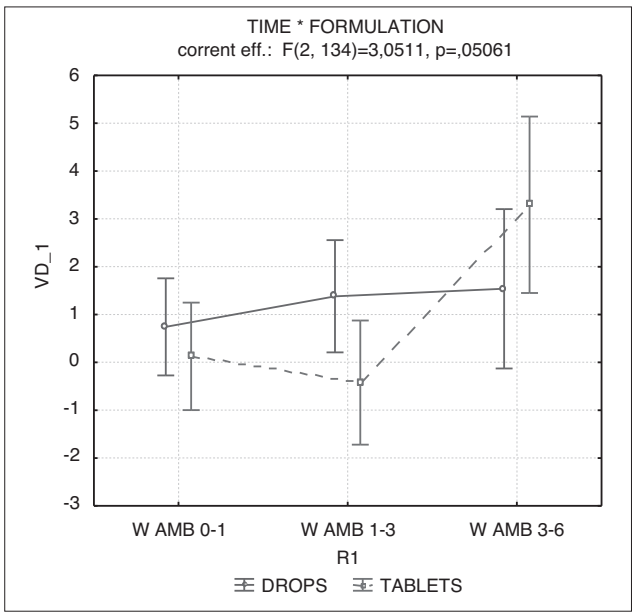

Figure 5. ANOVA, variation during the time of mean delta Environmental Area (AMB) WhoQol scores.

Table 2. Spearman rank correlation (p<0.05)

MARS	WhoQol			
	Baseline	**1 month**	**3 months**	**6 months**
Baseline	0.311*			
1 month		0.379*		
3 months			0.405*	
6 months				0.543*

*p<0.05

DISCUSSION AND CONCLUSIONS

Our results showed how a specific paroxetine formulation could be one of many variables able to influence adherence to a psychopharmacological treatment. Also quality of life is another variable of interest: patients with higher scores in WhoQol are more open to change formulation and show a progressive

improvement. Moreover, sex and age were found to influence adherence to antidepressant therapy: women on paroxetine oral solution 10 mg/ml had higher MARS scores and a slighter improvement than men of the same group and controls, but the effect did not reach statistical significance. We also observed a trend in elderly people towards a slight improvement when compared to the control group.

As reported in our previous analysis, there was a statistical significant variation during time for mean delta WhoQol scores in each area. In particular, patients receiving paroxetine in drops showed a stable self-perception of quality of life during the time, while patients receiving paroxetine in tablets showed a progressive worsening of this parameter in each area.

These data go in the same direction as the following considerations. It may be hypothesized that patients choosing paroxetine in drops maintain an adequate self-perception, while patients receiving the tablet formulation tend to express a progressive demoralization with respect to their life conditions.

From a clinical point of view, the formulation in drops is equally effective to tablets, but it may allow patients to have a higher cognition, consciousness and control on drug assumption; in fact, patients who accepted to change tablets with drops sustain that the latter formulation is more simple to administer than the former, making them sure to assume the appropriate dose according to their needs; conversely, attempts at dividing tablets may lead to inappropriate dosing. A liquid formulation of paroxetine (10 mg/ml) could offer a straightforward way to taper treatment by reducing the dose drop by drop. An advantage of the liquid formulation is that it allows to adopt slow titration. This would allow a very gradual reduction in the plasma levels of paroxetine. The great benefit of this formulation is that it will allow the physician to design individualized tapering off regimens to avoid withdrawal symptoms (36).

Finally, three different areas affecting adherence to therapies can be identified: the main predictors of adherence (or non-adherence) to antidepressant treatment can be due to the physician, the patient, or specific drugs. The physician may build a therapeutic alliance with the patient, take a psycho-educational intervention, let alone regularly visit the patient during the follow-up. These behaviors can help the patient to feel sustained during the first period of treatment, when drugs do not provide positive effects on depressive symptoms and the patient asks to change therapy. By the patient depends motivation to begin and continue treatment that has potential side effects or drug-drug interactions. Moreover, the formulation of drug assumption may influence treatment adherence and success but up to date there are insufficient data about a specific drug formulation.

The use of custom doses permits to minimize side effects. It also allows a better doctor-patient relationship and a greater continuity and constancy in therapy assumption. The patient may feel more involved in the choice of therapy, without suffering from it.

The choice of using paroxetine is due to the fact that it is one of the most prescribed drugs. In our sample, no patients reported side effects due to its anticholinergic effect (40).

Further studies are warranted to investigate the impact of the drop formulation using other drugs.

All subjects of our study sample received only paroxetine and they were clinically euthymic for at least six months before entering into the study. Although the use of hypnotic drugs was permitted (rarely), no patient took other psychotropic drugs during the follow-up.

These findings match the interest of the clinician in understanding the causes underlying discontinuation of antidepressant treatment. Further studies on larger samples and longer follow-up may provide more precise answers about the impact of formulation type on patient compliance.

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