EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 4
09-13
Year: 2016

EFFICACY AND TOLERABILITY OF PAROXETINE HYDROCLORIDE SOLUTION: SLOW TITRATION VS STANDARD TITRATION

Camilla Callegari*[1], Marta Ielmini[1], Lucia Bianchi[1], Melissa Lucano[1], Celeste Isella[1], Lorenza Bertù[2], Simone Vender[1]

[1]Department of Clinical and Experimental Medicine, Via O. Rossi 9, 21100 Varese (Italy) Azienda Ospedaliera di Circolo e Fondazione Macchi - 21100 Varese Italy.
[2]Centro di Ricerca EPIMED – Epidemiology and Preventive Medicina, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy.

***Author for Correspondence: Camilla Callegari**
Department of Clinical and Experimental Medicine, Via O. Rossi 9, 21100 Varese (Italy) Azienda Ospedaliera di Circolo e Fondazione Macchi - 21100 Varese Italy.

Article Received on 03/02/2016 **Article Revised on 24/02/2016** **Article Accepted on 15/03/2016**

ABSTRACT
In the recent years, the psychiatric activity in Northern Italy have shown an increase of patients with anxiety and depressive disorders. SSRIs, including the formulation in drops, seem to be the first choice. The objective of this trial is to investigate the efficacy, safety and tolerability of paroxetine hydrochloride, extending the comparison between slow (starting dose 5 mg/die increased by 5 mg on the 7th day) and standard up titration (starting dose of 10 mg/die), already tested by other trials among specific populations, to an outpatient population with depressive and/or generalized anxiety disorder. Clinical analysis was based on a naturalistic trial performed on 186 patients. Treatment setting was a public outpatient center for anxiety and depression in Varese. The efficacy of paroxetine was confirmed in both kind of titration by the number of patient in clinical remission. Instead, about safety and tolerability there were found more frequent adverse events among the standard titration group (35.7 % vs 9.7% , $p < 0.001$). Comparing the other scales' scores between the two groups at T 1 and T2 emerged a statistically significant difference in the WHOQOL-Bref scale ($p= 0.003$, highest scores in slow titration group), and in the TAS ($p <0.0003$, highest scores in slow titration group); these data may be due to a higher quality of life, probably consequent to fewer perceived side effects. Our results are consistent with increased tolerability and safety of slow titration of paroxetine. However, these findings, need to be replicated in clinical trials.

KEYWORDS: Paroxetine hydrochloride, Slow titration, Mood disorder, Antidepressant, SSRI.

INTRODUCTION
In the recent years, in keeping to literature, epidemiological data related to the psychiatric activity in North Italy have shown an increase of patients with anxiety disorders with and without panic attacks, generalized anxiety disorders, anxiety-depressive syndromes, depressive disorders and reactive adaptation disorders with mixed anxiety and depressed mood. Therefore, the choice was made to offer specific therapeutic Outpatient Service for Anxiety and Depression.

In the guidelines for the treatment of depressive disorders associated or not with anxiety, antidepressant medications are the first choice,[1] including selective serotonin reuptake inhibitors (SSRIs). These are associated sometimes to the onset of adverse events that may occur in some patients, but they tend to disappear after the first 2 weeks of treatment.[2]

The main cause of interruption in the first stage of treatment, although of proven efficacy, seems to be the appearance of a high number of side effects, which influence the quality of life of the patient and consequently induce him to interrupt the therapy.[3]

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 SSRI. The great benefit of this formulation is that it will allow the physician to design individualized tapering of regimens to avoid withdrawal symptoms.[4]

In line with these consideration our study aimed to investigate the efficacy, safety and tolerability of paroxetine hydrochloride, comparing slower with standard up titration in a population of outpatients.

METHODS
The primary efficacy assessment was performed by comparing the clinical remission, defined by a total score

of ≤ 7, on the HDRS at 12 weeks (T2) between the two populations.

Secondary safety and tolerability were evaluated monitoring and recording side effects throughout the study through an unstructured global approach based on self-reports.

Secondary efficacy assessment was evaluated by comparing the benefits of therapies through the clinician rating scales WHOQOOL, TAS and CES-D between the two groups.

This is a retrospective and observational trial.
There were 186 patients fullfilling the following inclusion criteria:

- age≥ 18 years old;
- have a diagnosis of depressive disorder and/or generalized anxiety disorder (the diagnosis were defined as DSM 5 criteria for DD and GAD);
- be an outpatient of the Anxiety and Depression Ambulatory of the "Ospedale di Circolo";
- be in therapy with paroxetine hydrochloride slow or standard titration (drug naive or switch from another treatment);
- sign a written informed consent.
  Patients were excluded from the study if they had the following exclusion criteria:
- have a diagnosis of antisocial personality disorder;
- have a diagnosis of substance-related and alcohol addictive disorders.

Patients were recruited consecutively from December 2013 to October 2015.
This trial was carried out to observe the up-titration of paroxetine from a starting dose of 10 mg/die (standard titration) or from a lower dose of 5 mg, increased by 5 mg on up to 10 mg on the 7th day (slow titration) based on the routine clinical activity of the physicians. Then (during the second control 4 weeks later –T1) paroxetine dose based on the clinical response was maintained at 10 mg or increased until 15 mg or other.

The last control was done at the 12th weak (T2).

The maximum dose reached was 40 mg/die.

Patients were evaluated at the recruitment (T 0), at weeks 4th (T1) and 12th (T2). During each evaluation they were visited by a psychiatrist and tested through the following scales:

Hamilton Depression Rating Scale (HDRS): it is a rating scale developed to quantify depression. It consists of items representing different levels of gravity: no depressive symptoms (0-7), mild symptoms (8-17), moderate symptoms (17-24), severe symptoms (> 25).[5]

Center for Epidemiological Studies-Depression scale (CES-D), a widely used self-reported screening test assessing the frequency of depressive symptoms within the previous week.[6]

Each item is rated on a 4-point scale ranging from 0 (rarely or none of the time-less than 1 day-) to 3 (most or all of the time-5/7 days-). Total CES-D scores ranges from 0 to 60, and is computed as the sum of items, with items 4, 8, 12, and 16 reversed. A cut-off score ≥16 is often used as threshold used to define depressed mood. CES-D≥16 aids in identifying individuals at risk for clinical depression, with good sensitivity and specificity and high internal consistency.

Toronto Alexithymia Scale, 20 items alexithymia self-assessment based on a 5-point Likert scale: not disagree (1 point), I am not very well (2 points), are neither agree nor disagree (3 points) are partly agree (4 points), I fully agree (5 points). In calculating the total scores obtained in the test are considered: non alexithymic subjects that get scores <51, borderline subjects who obtain scores between 51 and 60, alexithymic subjects that get scores greater than or equal to 61.[7]

World Health Organization Quality of Life Scale Bref, composed of 26 items (WHOQOL-BREF), which provides a quantitative estimate of the quality of life (the WHOQOL Group, 1998) orientated dimensional. It consists of 26 domains designed to assess physical (items 3, 4, 10, 15, 16, 17, 18), psychological well-being (items 5, 6, 7, 19, 26), interpersonal relationships (items 20, 21 and 22), relations with the environment (items 8, 9, 12, 13, 14, 23, 24, 25); the items 1 and 2 do not fall under any domain but are included in the calculation of the total score. Each item is given a score on a Likert scale from 1 to 5 expressing increasingly satisfaction of the subject. Exceptions are items 3, 4 and 26, where the scoring is decreasing.

The scores of the scales administered were calculated as the sum of the numbers of items.

As the number of patients amounted to 176 (considering the population that has participated in the analysis, excluding the drop out, 10 patients who did not attend all the meetings) it assumes normal trends. Approximating the normal distribution of the data we have seen fit to use parametric t-tests.

Proportions were compared using the Fisher'S exact test.
To evaluate the primary endpoint, we calculated the number of remitters (patients with HDRS' score ≤ 7 among the two groups at T2) comparing the two groups by the Fisher'S exact test.

All statistical tests were two-tailed, with $p< 0.05$ considered statistically significant.
Statistical analysis was performed with GraphPad Prism Version 5.1 for Windows (GraphPad software, San Diego, CA).

RESULTS AND DISCUSSION

Sample

186 patients meeting the inclusion criteria were enrolled consecutively into 2 groups: 95 into the slow titration group and 91 into the standard titration group. Ten of them dropped out (5,6% of all patients), 3 in the slow titration and 7 in the standard titration. Their demographic characteristics are given in Table1.

No significant differences in age, sex distribution or severity of depression were found between the 2 groups at T0. Clinical variables were not statistically different in slow and standard titration patients before treatment.

Table 1.Baseline Demographics, by Titration Group

Demographic Variables	Slow	Standard	P value
Age, mean (SD)	50,23 (11,61)	48,26 (11,20)	0.262
Sex, **Female (%)** **Male (%)**	 56 (61%) 36 (39%)	 31 (37%) 53 (43%)	1,000
HDRS, mean (SD)	26,63 (6,84)	28,54 (10,63)	0,1478

Legend: SD=standard deviation.

Primary efficacy result

The patients achieving a score ≤ 7, index of clinical remission, at 12 weeks were 53% of the standard titration group and 58% of the slow titration group (table 2), without differences between the two populations.

These data confirm the documented efficacy of paroxetine, without differences in the two kind of titration, as already demonstrated in another trial comparing the two kinds of titration in a cancer population.[3]

Differently, in a comparison between the two kind of titration in a elderly population the slow titration group was characterized by a larger number of remitters (84% vs 54,5, 0 =0.028) and -similarly to our trial- fewer dropout cases (20% vs 73", p<0.001).[8]

Table 2: patients in clinical remission at 12 weeks

	HDRS ≤ 7	P value
Slow titr	54 (58%)	0,54
Standard titr	45 (53%)	

Legend: titr=titration

Secondary safety and tolerability results

In both populations there were found adverse events (AEs), more frequent in the standard titration group (35.7 % vs 9.7% , p < 0.001). Sexual dysfunction and nausea were the side effects most represented in this population. For the other AEs reported there were no statistically significant differences between the two groups of patients, as shown in table 3.

As just stated, despite the therapeutic efficacy was comparable in the two groups, there was a difference in the occurrence of adverse effects, with a preponderance in the "standard titration group". This data is confirmed also by Serretti and Olgiati.[8]

The most commonly affected system organ classes were gastrointestinal disorders and sexual disorders, with a statistically significant difference between the two groups (15.5% vs 2%, respectively, p <.005 for sexual dysfunction and 15% vs 4%, p <0.03 for nausea). Particularly sexual dysfunction was reported as responsible of 4 drop out while 1 was due to headache. It's known that many psychiatric medications, including SSRI and SNRI, can also adversely affect normal sexual response.[9]

Table 3: Adverse events

	Rapid	Slow	p
Diarrhea	5 (6%)	1 (1%)	0,11
Nausea	13(15%)	4 (4%)	**0,03**
Sexualdisf	13(15%)	2 (2%)	**0,005**
Sedation	3 (3,5%)	1 (1%)	0,354
Restlessness	1 (1%)	0	0,48
Headache	10 (12%)	5 (5,4%)	0,1

Legend: AEs= adverse events.

Secondary efficacy results

Depression has a negative impact on quality of life, often with a negative impact on social by functioning.[10] Despite the short term treatment period evaluated "slow titration group" achieved greater scores in WHOQOL at 4 and 12 weeks (p<0.00 and p<0.00), as shown in Table 4. These results, based on broad measurements of patient well-being, may indicate a greater quality of life probably due to fewer side effects.

About TAS we have found higher scores among "standard titration group", showing that this population had greater difficulty in expressing their discomfort. In both groups we have seen a decrease of the scores, with lower values in the slow titration group.

Table 4: comparison between the scales'scores in the 2 population at T1

T1	Slow titr		Standard titr		P value
	mean	SD	mean	SD	
CES-D	27.52	11.50	30	12.53	0.17
TAS	41.9	9.09	53.32	17.8	0,0001
WOHQ	49.12	9.1	43.58	8.8	0,0001

Legend: titr=titration; DS= standard deviation.

Repeating the same comparison at T2, except for the scale CES-D in which the difference of the scores obtained in the two groups was not statistically significant shown, for all the other scales we obtained statistically significant results (Table 5).

Table 5: comparison between the scales' scores in the 2 population at T2

	Slow titr		Standard titr		P value
	mean	SD	mean	SD	
CES-D	16.8	8.67	14.9	8.55	0.14
TAS	32.25	9.7	43.22	19.85	0.0001
WHOQ	65.42	10.42	57.64	11.04	0.0001

Legend: titr = titration; DS= standard deviation.

CONCLUSION

The measurements performed by the HDRS scores throughout the study period (Figure 1-2) and the number of remitters in the two groups confirm the documented efficacy of paroxetine, without differences in the two kind of titration.

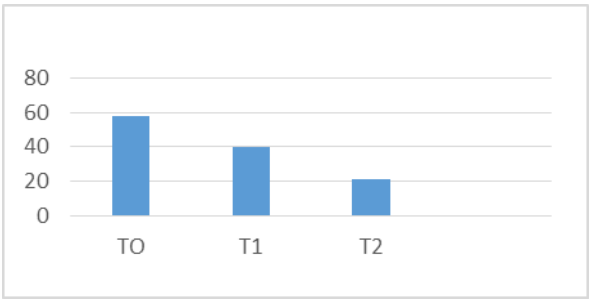

Figure 1: HDRS trand among the standard titration group

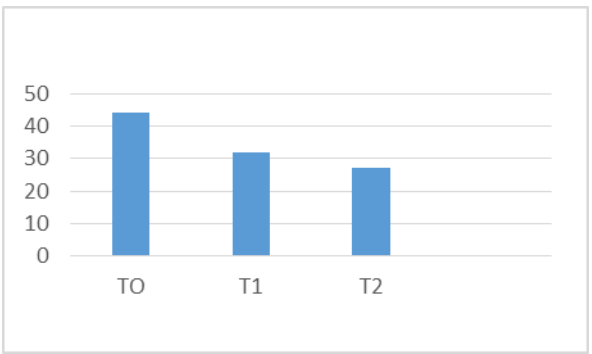

Figure 2: HDRS trand among the slow titration group

The most interest data dealing with safety and tolerability: side effects were more frequent among standard titration group, as described in literature. If paroxetine is gradually titrated and therapeutic dose reached slowly, there might be less accumulation with advantages in terms of tolerability, and that occurred also among our population. Instead standard titration is often difficult and can result in prolonged effects even after its reduction or discontinuation.[8] also in our trial there were more dropout cases among the "standard titration group", probably due to the higher incidence of adverse events (AEs) in this population. It is also interest to note the higher quality of life described among the slow titration group, probably due to the fewer perceived side effects.

The current study, due to its short duration of 12 weeks, limits the implication of these outcomes in longer-term treatments. Other limits of this trial are the lack of data about medication adherence, that is a decisive factor in the therapeutic efficacy and that we did not use any objective measures for estimating side effects.

REFERENCES

1. APA. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition, The American Journal of Psychiatry. October 2010 American Psychiatric Publishing, Inc.
2. James M, Ferguson M.D. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry. 2001 Feb; 3(1): 22–27.
3. Amodeo L, Castelli L, Leombruni P, Cipriani D et al. Slow versus standard up-titration of paroxetine for the treatment of depression in cancer patients: a pilot study. International Review of Psychiatry, 2012; 20: 375-384.
4. Van den Tweel ERW, Relleke M, Muniz Piniella P. Paroxetine oral solution is bioequivalent to paroxetine tablets: advantages of the solution. Int J ClinPharmacolTher, 2007; 45: 611-6.
5. Miller I, Bishop S, Norman W et al. The modified Hamilton rating scale for depression: Reliability and validity. Psychiatry Research 1985.
6. Radloff L. The CES-D Scale - A Self-Report Depression Scale for Research in the General

Population - Center for Epidemiologic Studies National Institute of Mental Health. Applied Psychological Measurement 1977.
7. Bagby RM, Parker JDA, Taylor GJ. The twenty-item Toronto Alexithymia Scale I. Item selection and cross-validation of the factor structure. Journal of psychosomatic research, 1994.
8. Olgiati P., Serretti A. Persistent benefits of slow titration of paroxetine in a six-monyh follow-up. Human psychopharmacology, 2015; 10: 1002/hup 2478.
9. Garthlener G., Hansen RA., Morgan LC. et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Inter Med., 2011; 155: 722-785.
10. Iren Akbyyik D., Berkusun OE, Sumbuloglu V et al. Quality of life of Turkish patients with depression in Ankara and in Berlin. EurPsychiatry, 2008; 23(1): 4-9.