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EFFICACY AND TOLERABILITY OF FLUPENTHIXOL DECANOATE IN THE TREATMENT OF DEPRESSION AND PSYCHOSOMATIC DISORDERS: A MULTICENTER TRIAL IN GENERAL PRACTICE

GISELA BUDDE

Medical Department, Troponwerke GmbH & Co. KG, Köln, FRG

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Abstract

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1. A number of controlled as well as uncontrolled studies indicate that flupenthixol in a low-dose regimen is effective in treating syndromes with depression, anxiety, and psychosomatic disorders.

2. In view of the low compliance rates among patients suffering from depressive syndromes, the author evaluated the efficacy and tolerability of flupenthixol decanoate i.m. in an unselected collective of such patients treated in general practices.

3. Flupenthixol decanoate i.m. induced remission in 25 % of patients suffering from chronic pain, in 29 % of patients with psychosomatic disorders. Patients with depression and anxiety remitted in 27 % of the cases. Therapeutic benefit was seen in more than 90 % of the patients.

4. The best results were observed in patients
   1) who had not been treated with psychotropic drugs before,
   2) whose disease had a duration of less than one year,
   3) who were under 40 years of age, and
   4) who were treated with a dose lower than 0.5 ml (10 mg flupenthixol decanoate).

Keywords: anxiety, chronic pain, depression, flupenthixol, flupenthixol decanoate, psychosomatic disorders.

Introduction

Low-dose neuroleptics have been applied increasingly in recent years to treat anxiety and depression (Ovhed 1976, Robertson and Trimble 1981, Valle-Jones and Swarbrick 1981). This has become quite common especially in Germany and several other European countries with doctors in general practice as well as with specialists for internal medicine (Pöldinger and Sieberns 1983). Low dose neuroleptics now are sometimes seen as alternative to benzodiazepines, which have received more criticism lately due to the risk of physical and psychological dependence.

Flupenthixol and flupenthixol decanoate, neuroleptics of the thioxanthene group, initially were used in the treatment of schizophrenic psychoses. The application of flupenthixol in low dose as an antidepressant was first described by Holst (1964), and Reiter (1969) reported on the first clinical studies.

Today, flupenthixol is a well documented neuroleptic and was in many controlled studies compared with placebo (Ovhed 1976), classic antidepressants (Maragakis 1990, Young et al 1976, Tam 1982, Hostmaelingen et al 1989, Johnson 1983, Jokinen et al 1984), and benzodiazepines (Hamilton et al 1989, Majid 1986, Conway 1981). The studies document a mood-stimulating and anxiety-reducing effect in patients with depressive mood, neurotic and endogenous depression of a mild to moderate level, with psychosomatic disorders, and depression in older patients (Valle-Jones and Swarbrick 1981) and anxious neurotics. Apathic, inactive patients and those with inhibitons are especially helped by the activating effect of flupenthixol. When compared to classic antidepressants, flupenthixol works quicker, in only two to three days, and has less unwanted, vegetative side effects.

While the antidepressive and anxiolytic efficacy of oral flupenthixol is very well documented, the depot form, flupenthixol decanoate, has only been examined in a few studies (Tam et al 1982, Budde et al 1990, Tegeler et al 1990). Therefore, a new, comprehensive study of treatment with flupenthixoldecanoate in general practices was carried out with patients suffering from depression, neurotic anxiety, chronic pain, and psychosomatic disorders. In addition to assessing the efficacy and tolerability of the drug, the study was intended to provide a general overview of prescription habits such as previous treatment and co-medication, selection of patients, and length of disease in general practices. Further questions concerned the onset of clinical effect and the course of the disease as well as the dependence of the efficacy on co-medication, age, and length of disease.

Methods

Patients

A total of 4,772 patients about 70 % women and 30 % men, was enrolled in this study. The age of the patients varied from 15 to 94 years (Table 1).

At the start of the study, more than 80 % of the patients suffered from depression, 50 % had anxiety or psychosomatic disorders, and 25 % were affected by chronic pain. More than 70 % of the patients complained of more than one of the above mentioned syndromes. The average length of sickness of the patients was 2.8 years with a range from half a month to 70 years (Table 2).

2,424 patients (50.8 %) had been treated with psychopharmacological drugs (Table 3) where the accompanying psychoactive drugs were supposed to be kept to a minimum. This was not possible in 12.1 % of the cases.

Table 1

Distribution of Patients according to Sex and Age

	male		female		total	
pat. no.	1,355 (28.4 %)*		3,345 (70.1%)*		4,772	
mean age	51 ± 15**		54 ± 15**		53 ± 15**	
range	15 - 92		18 - 94		15 - 94	
age	abs.	%	abs.	%	abs.	%
< 20	7	0.6	16	0.5	23	0.5
21 - 30	105	8.3	213	6.8	321	7.2
31 - 40	170	13.4	436	14.0	614	13.8
41 - 50	338	26.7	676	21.6	1.025	23.0
51 - 60	299	23.6	686	21.9	999	22.4
61 - 70	203	16.0	582	18.6	800	18.0
71 - 80	112	8.8	410	13.1	528	11.8
> 80	33	2.6	108	3.5	149	3.3

* sex not recorded in 72 cases

** age not recorded in 313 cases

Table 2

Pretreatment Status of 4,772 Patients

	total n = 4,772 abs.	%	male n = 1,355 abs.	%	female n = 3,345 abs.	%
depressive syndrome	3.886	81.4	1.058	78.1	2.765	82.7
anxiety	2.818	59.1	765	56.5	2.009	60.1
pain	1.230	25.8	355	26.2	855	25.6
psychosomatic disorder	2.506	52.5	723	53.4	1.752	52.4
patients with 1 symptom	1.129	23.7	342	25.2	768	23.0
patients with 2 symptoms	1.964	41.2	562	41.5	1.374	41.1
patients with 3 symptoms	1.289	27.0	349	25.8	923	27.6
patients with 4 symptoms	379	7.9	97	7.2	274	8.2
duration of disorder*** (years)	3.0 ± 4.0;		2.8 ± 4.0;		3.1 ± 4.0;	
range	1/2 month-70 years		1 month-70 years		1/2 month-60 years	

* symptoms not recorded in 11 cases
** sex not recorded in 72 cases
*** arithm. mean ± standard deviation

Table 3

Previous and Concomitant Treatment with Psychotropic Drugs (n = 4.772)

treatment*	pretreatment total	%	ongoing** treatment total	%
	2,424	50.8	579	12.1
neuroleptics	692	14.5	117	2.5
antidepressants	981	20.6	266	5.6
minor tranquilizers	833	17.5	200	4.2
other psychotropic drugs	361	7.6	82	1.7

* one or more psychotropic drugs per patients
** at least one psychotropic drug was not discontinued

Drugs

The patients in the study were treated with a variable dosage of 6 to 14 mg of flupenthixol decanoate (0.3-0.7 ml of flupenthixol decanoate 2 %) every 14 days, depending on clinical necessity. The average initial dose was 14 mg every two weeks. The average dose at the end of the study was 10 mg every two weeks.

Assessments

Several different checklists were used to diagnose and evaluate the symptoms and side effects. The patients were examined on days 0, 14, 28, 42, 56, and 70.

Data Analysis

A comprehensive evaluation of efficacy and tolerability was undertaken at the end of the study. The results follow with the aid of descriptive statistical methods.

The frequency of unwanted side effects of fluanxol depot was measured twice with 95 %-confidence-intervals, based on Pearson-Clopper.

Results and Discussion

Efficacy

Approximately 70 % of the patients exhibited a depressive mood at the onset of the study. Only 25 % showed the same degree of psychopathology after 14 days of treatment, and at the end of the study, another 8 weeks later, only about 4 % of the patients remained seriously depressed (Fig 1). The comprehensive evaluation at the end of the study showed that 27 % of the patients experienced a remission of their symptoms while in 66 % a definite improvement of depression took place (Fig 2).

Similar results were found with the other syndromes. At the beginning of the study, 70 % of the patients exhibited distinct anxiety whereas this was only the case with 4 % at the end of the study (Fig 3). Initially, vegetative symptoms were apparent in 65 % and chronic pain in 76 % of the patients. After ten weeks, only 4 % continued to have clear-cut psychosomatic disorders, and only 6 % still had chronic pain (Fig 5 and 7). According to the final evaluation, 27 % of the patients suffering from anxiety had a remission, and 67 %

were substantially improved. The figures for patients with psychosomatic disorders were 29 % and 64 %, respectively, and for patients with chronic pain, 24 % and 67 %, respectively (Fig 4, 6 and 8).

Forty % of the doctors involved in the study described efficacy of flupenthixol decanoate as "excellent", 41 % as "good", and 12 % as "satisfactory". Only 7 % of the doctors rated it as "unsatisfactory". The tolerability of flupenthixol decanoate was described by 60 % of the patients involved as "excellent", by 34 % as "good", and by 3.5 % as "satisfactory". It was described as having an "unsatisfactory" tolerability by only 2.5 % of the patients.

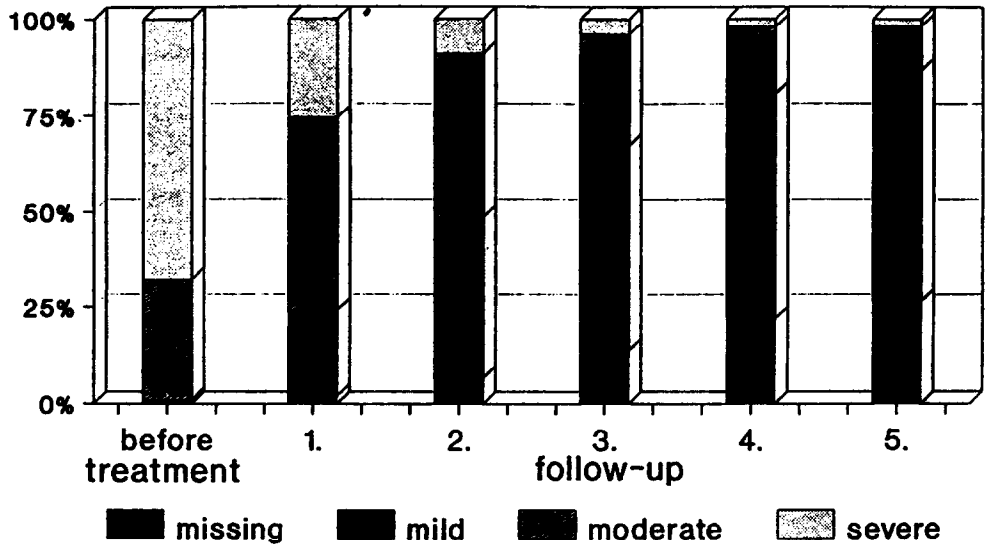

Fig 1. Depressive syndromes in the course of treatment with fluanxol depot 2 %

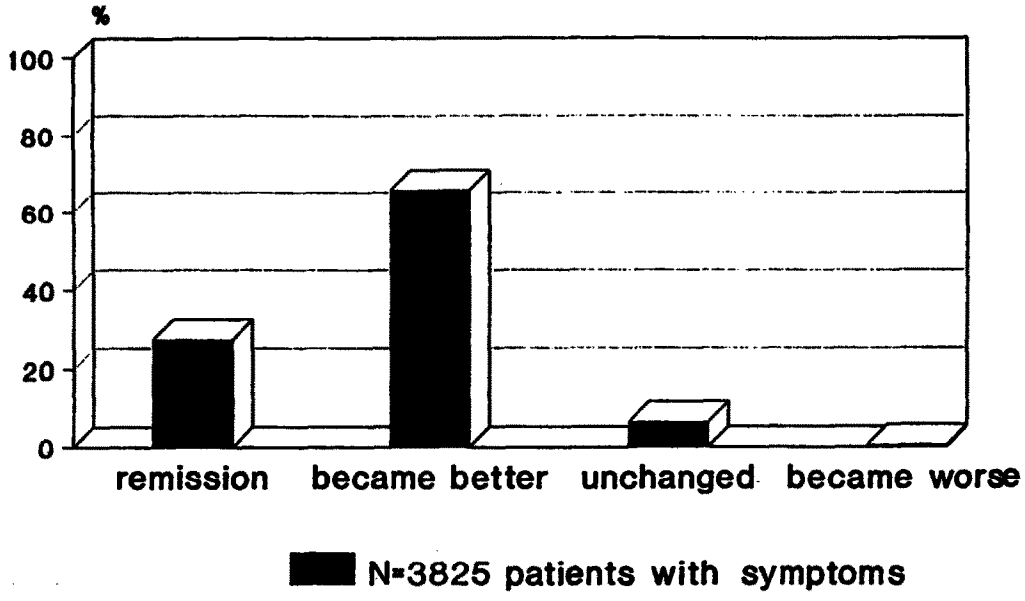

Fig 2. Depressive syndromes - response rates

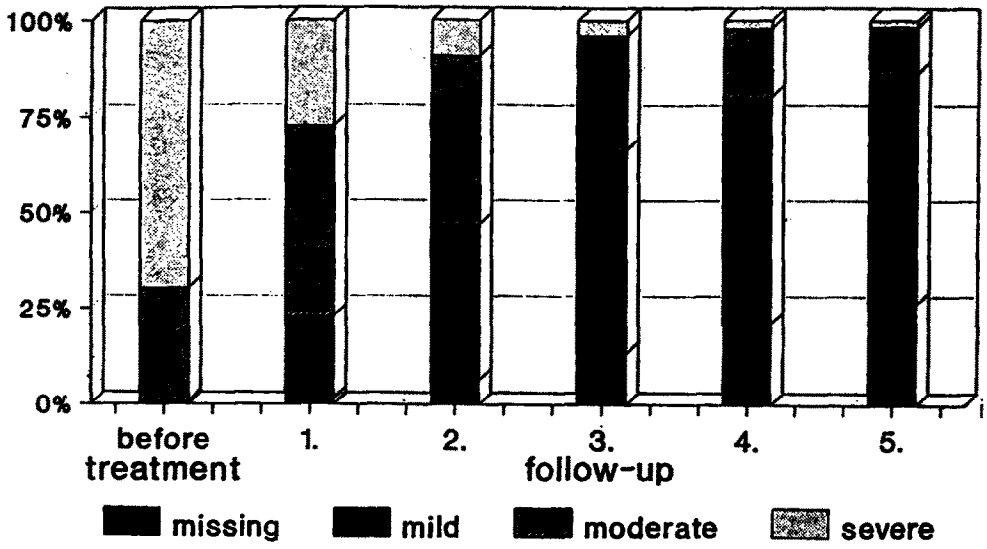

Fig 3. Anxiety in the course of treatment with fluanxol depot 2 %

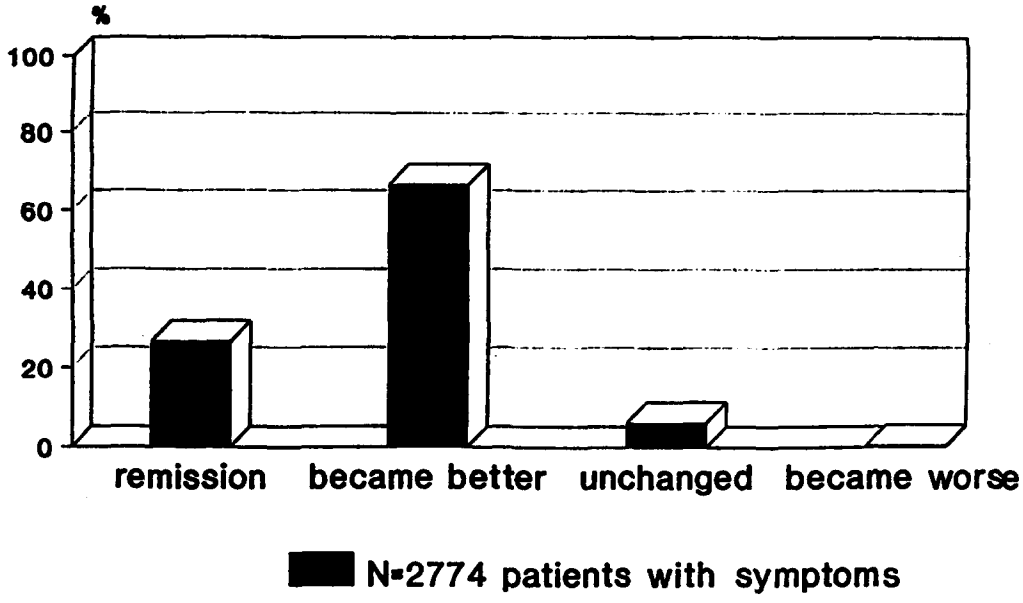

Fig 4. Anxiety response rates

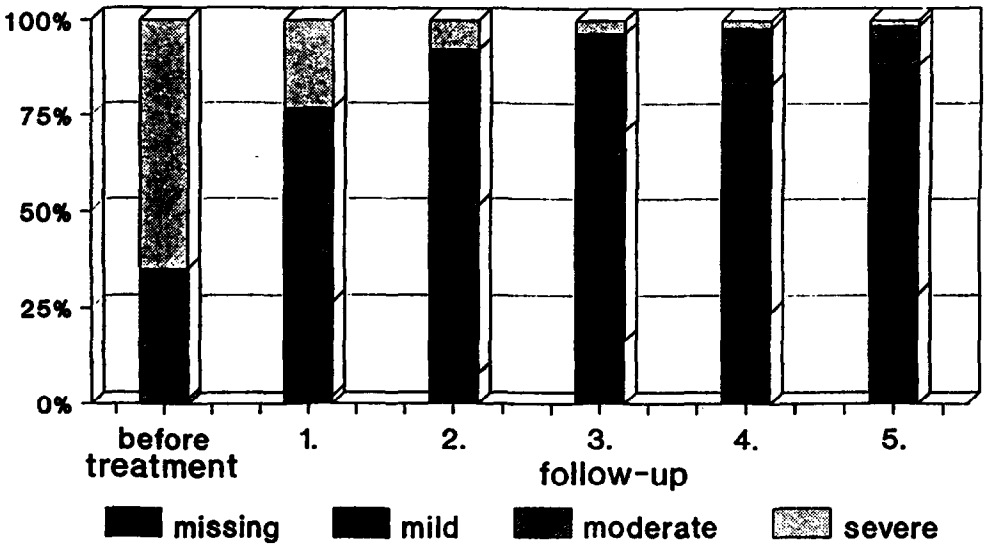

Fig 5. Psychosomatic disorder in the course of treatment with fluanxol

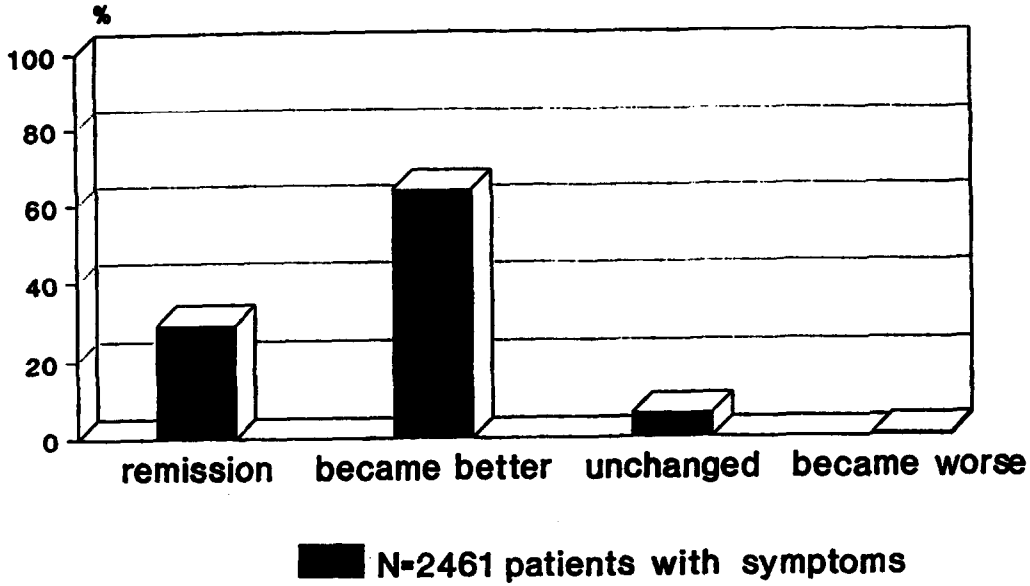

Fig 6. Psychosomatic disorder response rates

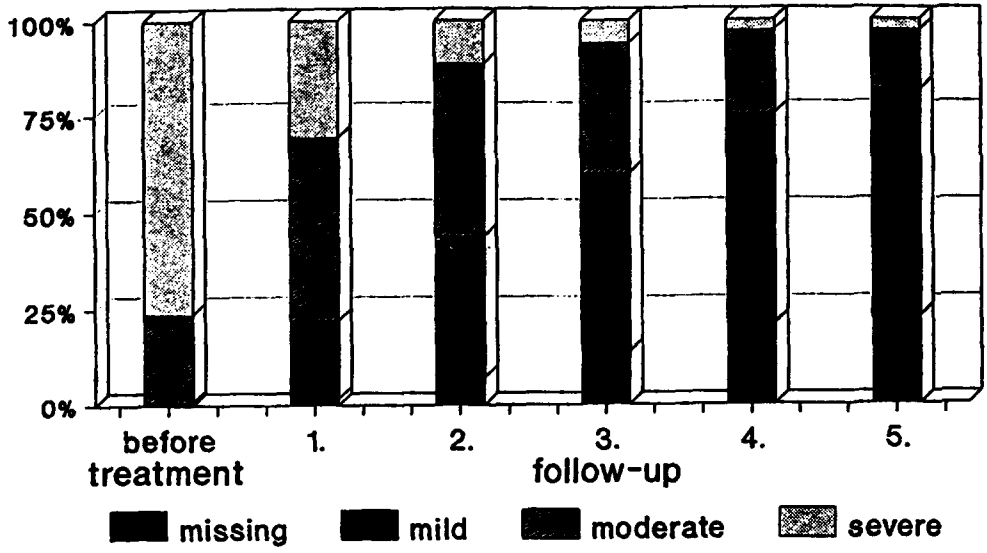

Fig 7. Pain in the course of treatment with fluanxol depot 2 %

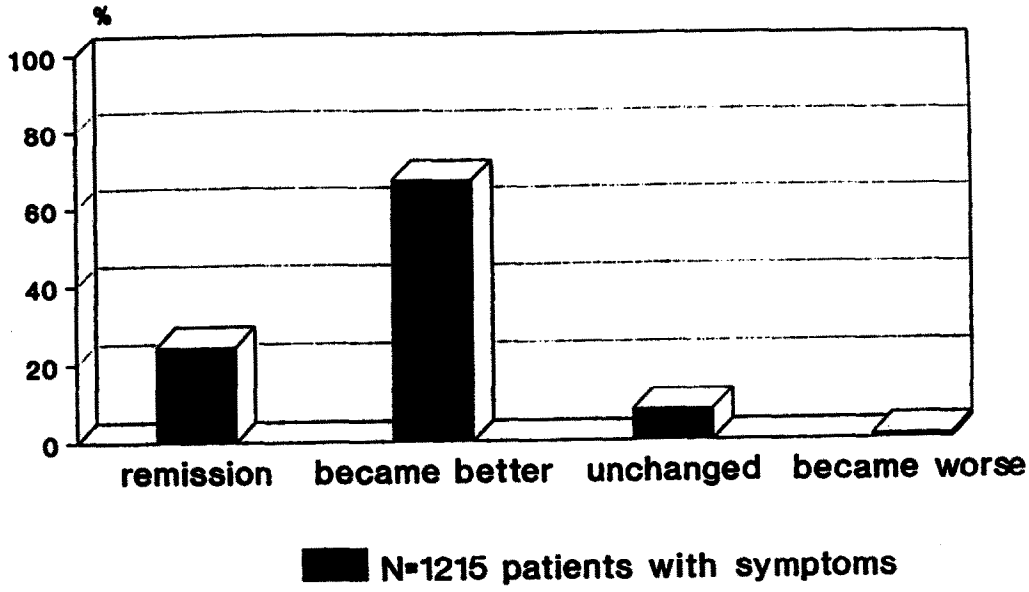

Fig 8. Pain - response rates

The efficacy of the therapy was definitely lower in patients that had taken neuroleptics before, or were taking drugs in addition to flupenthixol decanoate during the study. The length of sickness was negatively correlated to the outcome of the therapy. The best results were obtained in the patient group that was older than 40 years, and whose disease lasted less than one year.

Side Effects

Side effects from the treatment with flupenthixoldecanoate were observed in 439 patients (9.2 %) (tab. 4). One-hundred and five patients (2.1 %) developed mild EPS. Weight loss (0.6 %) was mentioned less in this study than in others.

One-hundred and twenty-one patients (2.5%) dropped out of the study due to their side effects. Other reasons for premature ending of the study were premature remissions (4.7 %), marked improvement (1.5 %), ineffectiveness of the treatment (2.4 %), and non-compliance (1.8 %).

Table 4

Incidence of Side Effects in 4.772 Patients

symptom*	no of reports	percentage
EPS	94	1.9
Akathisia	11	0.2
Drowsiness	97	2.0
Gastroenteropathy	74	1.6
Vertigo	50	1.0
Dry mouth	41	0.9
Restlessness	32	0.7
Weight gain	31	0.6
cardiovascular disorder	21	0.4
Nausea	14	0.3
Urinary retention	7	0.1
sleep disorders	13	0.3
local reactions	11	0.2
Headache	13	0.3
Sweating	7	0.1
Blurred vision	6	0.1

* multiple registrations are possible

Conclusion

In conclusion, flupenthixoldecanoate in a dose of about 10 mg every two weeks is efficient in patients with anxiety and depression with good tolerability.

The effects of treatment with the depot seem to take longer to become evident when compared to Fluanxol.

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Inquiries and reprint requests should be addressed to:

Dr. Gisela Budde
Medical Service Department
Troponwerke GmbH & Co. KG
Berliner Str. 156, D-5000 Köln 80
Germany