

## CLINICAL REPORT

# Treatment of Chronic Pruritus with the Selective Serotonin Re-uptake Inhibitors Paroxetine and Fluvoxamine: Results of an Open-labelled, Two-arm Proof-of-concept Study

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**Chronic pruritus is difficult to treat and requires the evaluation of new therapeutic modalities. We initiated an open-labelled, two-arm prospective, proof-of-concept study applying two selective serotonin re-uptake inhibitors on a long-term basis. Paroxetine and fluvoxamine were tested in a total of 72 pruritic patients (27 men, 45 women, age range 28–88 years, mean age 59.2 years). The reduction in pruritus was evaluated by analysis of visual analogue scores and determination of the maximal antipruritic effect (maximal percentual reduction in pruritus). Forty-nine of 72 patients (68.0%) experienced a weak ( $n=9$ ), good ( $n=16$ ) or very good ( $n=24$ ) antipruritic effect. Statistical analysis proved the efficacy of paroxetine and fluvoxamine with no significant difference. The best response was observed in patients with pruritus due to atopic dermatitis, systemic lymphoma and solid carcinoma. Chronic scratch lesions healed completely in 14/31 patients and partially in 17/31 patients. Adverse drug effects were observed in 70.8% of patients, resulting in discontinuation of treatment in 18 patients. These results support previous reports of high antipruritic potency of selective serotonin re-uptake inhibitors, which are a good alternative treatment modality in chronic pruritus. This should be confirmed in future double-blind studies. Key words: itch; therapy; prurigo nodularis; antipruritic effect, paroxetine, fluvoxamine; SSRI.**

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Chronic pruritus of any origin is difficult to treat and has a high impact on patients' quality of life and psychological well-being (1, 2). The development and evaluation of new therapeutic concepts is necessary to improve this situation. During the past years, clinical research has focussed on the antipruritic efficacy of centrally acting substances, such as opioid receptor agonists and antagonists as well as on serotonin subtype 3 receptor

(5-HT<sub>3</sub>) antagonists (3–7). While mu-opioid antagonists and kappa-opioid agonists demonstrated clinical benefit in certain forms of chronic pruritus, 5-HT<sub>3</sub>-antagonists did not prove significant antipruritic effects (8). Among the conventionally applied centrally acting antipruritic drugs, tricyclic and tetracyclic antidepressants, such as doxepine, amitriptyline or mirtazapine, were regularly used to combat chronic pruritus with moderate effects but show a variable efficacy and a high level of side-effects (9, 10). The selective serotonin re-uptake inhibitors (SSRI) are thought to mediate effects on the serotonin as well as on the opioid system. Consequently, in case series and two randomized control trials, the SSRI paroxetine, sertraline and fluoxetine were demonstrated to influence severe systemic and paraneoplastic pruritus (11, 12), pruritus due to polycythaemia vera (13, 14), primary biliary cirrhosis (15), liver disease (16) and psychogenic itch (17). In this proof-of-concept (POC) study, we describe the antipruritic efficacy and treatment safety of the two SSRI in a large group of patients with chronic pruritus of various origins, with special attention on the onset and stability of the antipruritic effect upon long-term use. We selected paroxetine, which was demonstrated to have the highest serotonin re-uptake inhibitory effect, and fluvoxamine, which was reported to have a favourable benefit-side-effect profile (18, 19).

## PATIENTS AND METHODS

A total of 72 patients with severe chronic pruritus (27 men, 45 women, age range 28–88 years, mean age 59.2 years, standard deviation 13.3) were randomly selected to participate in this open-labelled, two-therapy-arm prospective, POC trial. Before treatment, patients were examined thoroughly using clinical and laboratory measures for any underlying disease inducing pruritus. In 20 patients an underlying origin was determined. These patients had: atopic dermatitis ( $n=3$ ), diabetes mellitus ( $n=7$ ), hydroxyethyl starch-induced pruritus ( $n=2$ ), pruritus due to contact with water of unknown cause (aquagenic pruritus, no polycythaemia present,  $n=1$ ), mycosis fungoides ( $n=2$ ), cutaneous B-cell-lymphoma ( $n=1$ ), Hodgkin's disease ( $n=1$ ), non-Hodgkin's lymphoma ( $n=1$ ), lymphatic leukaemia ( $n=1$ ), and rectal carcinoma ( $n=1$ ). In 52 patients no underlying origin of chronic pruritus could be determined. Fifty of the 72 patients showed chronic scratch lesions of prurigo nodularis. In all patients pruritus was refractory to at least one therapeutic attempt; the number of previous unsatisfactory therapies ranged

individually from 1 to 8 (mean 3.4). Previous therapies included, among others, topical and systemic steroids, antihistamines, capsaicin, naltrexone and ultraviolet (UV) phototherapy.

Before starting the medication, psychosomatic diagnostics were performed, including a clinical interview by an experienced medical psychotherapist from the Department of Psychosomatics and Psychotherapy (GS), with assessment of psychiatric ICD-10-diagnoses. Six patients refused the clinical interview, which was replaced by the written German version of the Hospital Anxiety and Depression scale (HADS) (20, 21). These patients also did not show clinically relevant anxiety or depression. The psychometric properties of the HADS scale are excellent, with a reported inner consistency (Cronbach's alpha) of 0.80 for the anxiety scale and 0.81 for the depression scale and a global retest-reliability of 0.71 (22). The convergent validity was supported by correlating the sub-scales with other known scales used in recording anxiety and depression (22).

Ethics committee approval and written informed consent were obtained before any protocol-specific procedure was undertaken. All previous systemic antipruritic treatments, including phototherapy, were stopped one month before treatment; topical treatment (i.e. corticosteroids, capsaicin) was stopped 2 weeks before starting study treatment. Use of concomitant topical treatment (except skin moisturizer) or any systemic treatment that could affect chronic pruritus was not permitted until the end of the study. The patients alternately received either the SSRI paroxetine (GlaxoSmithKline, Munich, Germany) ( $n=39$ ) or fluvoxamine (Neuraxpharm, Langenfeld, Germany) ( $n=33$ ). After 3 days on 10 mg paroxetine or 25 mg fluvoxamine, medication was increased to the maintenance dose of paroxetine 20 mg (17/39 patients) or fluvoxamine 50 mg (17/33 patients). Two patients (one on paroxetine and one on fluvoxamine) were maintained on the low starting dose due to side-effects. According to clinical efficacy, the dose was increased to paroxetine 40 mg in 19/39 and to 60 mg in 2/39 patients. Fluvoxamine was increased to a dosage of 100 mg in 12/33 patients and to 150 mg in 3/33 patients.

One aim of the study was to evaluate the stability of the antipruritic effect in long-term use (more than 2 weeks treatment, as described in previous studies). After a minimal treatment period of 2 weeks the therapy was continued for 4-week intervals in cases of therapeutic success. According to this, study visits were scheduled 2 weeks after initiation of treatment and thereafter every 4 week. At each visit, the therapeutic effect was measured by a dynamic rating score (i.e. total percentual reduction in pruritus intensity). In order to obtain the dynamic rating score, patients were regularly asked about the percentage reduction in their pruritus, considering the initial pruritus as 100%. The maximal antipruritic effect (MAE) was defined as maximal percentual reduction in pruritus during total treatment time. Reduction in pruritus by 0% was regarded as no therapeutic effect; reduction by 1–30% as weak therapeutic effect; 31–70% as good therapeutic effect; and 71–100% as very good therapeutic effect. During visits, patients were also asked for the average visual analogue scale (VAS) score (average of the past 24 h). Patients were examined regularly for adverse drug effects, including laboratory tests of liver and kidney function and red and white blood cell counts. Patients with skin lesions underwent clinical investigation and repeated photodocumentation.

#### Statistical analysis

Data were collected and encoded in routine data bank formats. Statistical analysis was carried out by intention-to-treat with the SPSS-software package (Version 14.0). Possible differences between groups were evaluated using Fisher's exact test in the case of categorical data, Mann-Whitney  $U$  test and analysis of variance (ANOVA) in the case of continuous data. The tests

were performed as two-paired tests.  $p$ -values less than 0.05 were considered statistically significant.

## RESULTS

Sixty-nine of 72 patients completed the study; three patients interrupted the study in the first days of treatment (counted as 0% reduction in pruritus). In two patients, the therapy had to be discontinued after two days due to side-effects; one patient developed hypertension (180/100 mmHg) and one patient suffered from vertigo and fatigue. Symptoms promptly resolved after discontinuation of therapy. Both patients were in the fluvoxamine treatment group. A third patient discontinued fluvoxamine 4 days after initial treatment because he was afraid of possible adverse drug effects, although fluvoxamine was well-tolerated until then. These cases were regarded as failures to treatment.

Forty-nine of 72 patients (68.0%) responded to the treatment; 55.5% with good or very good response (Fig. 1). In the paroxetine group, a considerable pruritus reduction was achieved in 23/39 (59.0%) patients, in the fluvoxamine group in 17/33 (51.5%) patients. The average value for the MAE achieved in patients treated with paroxetine was 67.6% ( $\pm 26.5$ ), in patients treated with fluvoxamine 64.9% ( $\pm 32.2$ ); (considering patients with antipruritic effect 1–100%, Fig. 1). The initial average VAS value ranged from 2 to 10 points (paroxetine, median,  $7.2 \pm 2.3$ ; fluvoxamine, median,  $5.88 \pm 2.3$ ; Fig. 2). The mean VAS reduction was  $3.7 \pm 3.1$  (paroxetine) and  $3.2 \pm 2.7$  (fluvoxamine). Between the two substances, statistical analysis (ANOVA) of MAE and VAS reduction showed no significant difference ( $p=0.826$ ). Regarding the subgroups of patients, patients with pruritus due to atopic dermatitis (MAE average score,  $45.0 \pm 7.1$ ), Hodgkin's disease and non-Hodgkin's lymphoma ( $88.3 \pm 16.1$ ) as well as rectal carcinoma

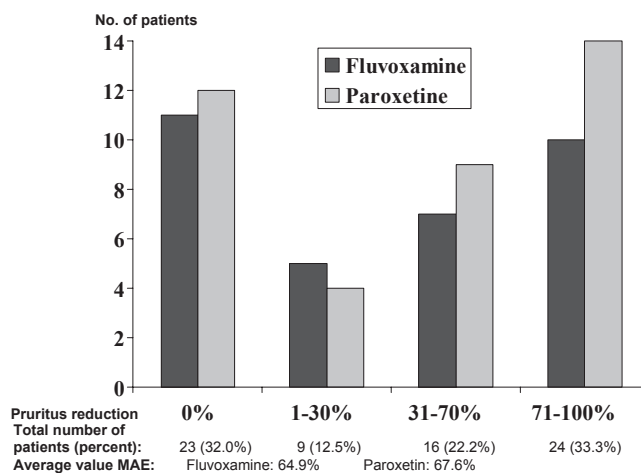


Fig. 1. Maximal antipruritic effect (MAE) of all patients ( $n=72$ ) included in the study.

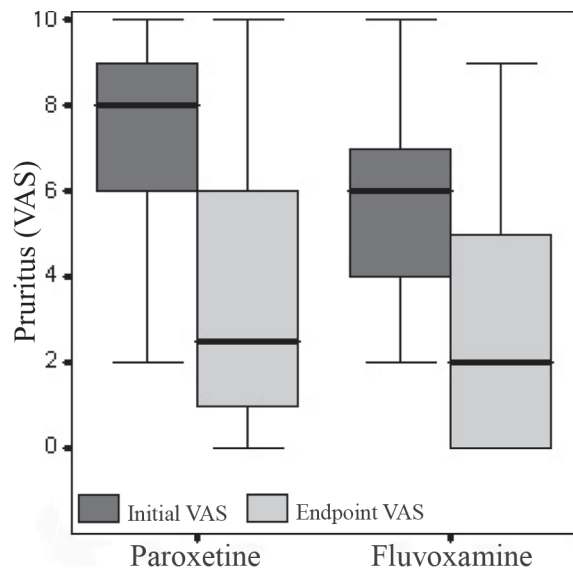


Fig. 2. Initial and end-point visual analogue scale (VAS) points of all patients ( $n=72$ ) included in the study. Average VAS value (0–10 points; y-axis) at the beginning and end of treatment with paroxetine and fluvoxamine. Mean values are shown with a bold line.

(80.0,  $n=1$ ) responded with considerable reduction in pruritus, respectively. In pruritus of unknown origin, the results were variable; 52.8% of patients showed a major reduction in pruritus, while 13.2% experienced weak and 34.0% no reduction. Interestingly, patients with pruritus due to either cutaneous T- or B-cell lymphoma did not respond to SSRI therapy. In patients showing prurigo nodularis ( $n=50$ ), lesions healed completely in 14/31 patients (45.2%) and partially in 17/31 patients (54.8%) (Fig. 3).

None of the patients had psychiatric contraindications for the use of a SSRI therapy, such as suicide intentions or suicide attempts. In 37/72 patients (51.4%) no psychiatric diagnosis was found. In 21/72 (29.2%) patients psychological co-factors in the course of the

disease were identified (ICD-10 diagnosis: F54). Five patients fulfilled ICD-10 criteria for the diagnosis of depressive disorders (F32, F33). Six patients showed an adjustment disorder to the chronic pruritus (F43.2). Four patients fulfilled the diagnosis of somatoform or dissociative disorder (F44, F45); 5 patients for anxiety disorders (F40, F 41) and in 3 patients other neurotic disorders (F48.8) were diagnosed. Twenty-six out of 35 patients fulfilled criteria for one psychiatric diagnosis, 9/35 patients fulfilled criteria for two psychiatric diagnoses. There was a slight difference in the response rate of patients with or without psychological factors (Table. I). Of the patients with psychiatric findings 71.4% had a treatment benefit, while only 64.9% of patients without psychiatric findings showed response. This difference was not statistically significant, and, again, no significant difference between the fluvoxamine and paroxetine groups was discovered ( $p=0.206$ ).

Interestingly, the onset of the antipruritic effect showed a broad inter-individual variability. Patients presented after 2 weeks of beginning of the study and then every 4 weeks for a study visit. The antipruritic effect was experienced within the first week by 12/49 patients (24.5% of responding patients), within the second week by 12/49 patients (24.5%), up to the fourth week by 11/49 patients (22.5%) or up to the 8th week by 8/49 patients (16.3%), while 6/49 patients responded after 8 weeks (12.2%). Accordingly, the duration to achieve the MAE ranged from 3 days to 34 weeks. The majority of patients (35/49; 71.4%) experienced the MAE within the first month of therapy, mean 4.9 weeks. The MAE was achieved earlier in the paroxetine group (paroxetine group: average value 3.6 weeks; fluvoxamine group: average value 6.4 weeks), but this was not statistically significant ( $p=0.989$ ). The duration of the treatment was established according to the stability of the antipruritic effect and relief of scratch lesions and ranged from 2 to 143 weeks. The average duration in the fluvoxamine

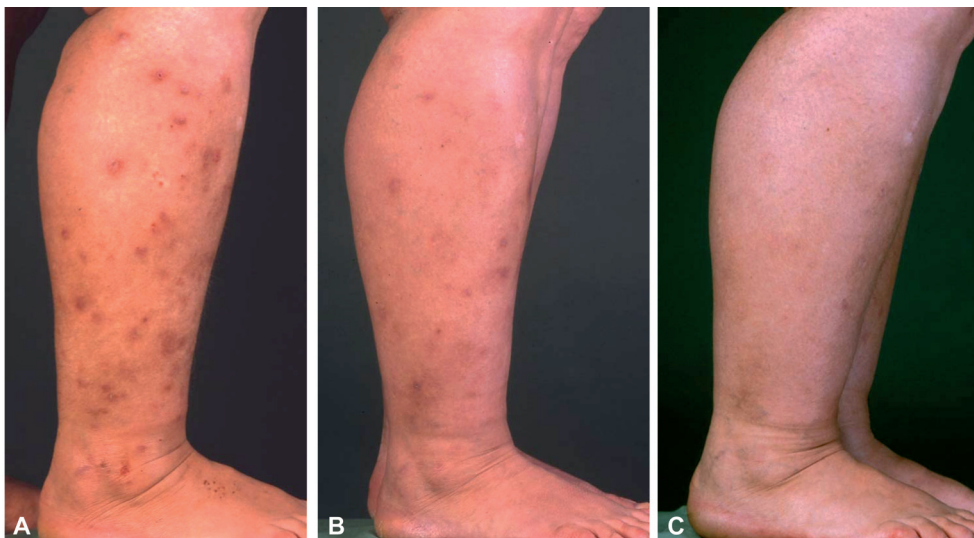


Fig. 3. A 43-year-old female patient with prurigo nodularis of unknown origin. (A) Before, (B) after 3 months and (C) after 11 months on paroxetine 20 mg. Three days after being on paroxetine her pruritus was relieved completely.

Table I. Antipruritic effect in patients with or without psychological co-factors

	SSRI medication	Number of patients with MAE			
		0%	1–30%	31–70%	71–100%
Patients with psychological factors	Fluvoxamine <i>n</i> =15	4	3	4	4
	Paroxetine <i>n</i> =20	6	1	7	6
	Total <i>n</i> =35	10 (28.6%)	4 (11.4%)	11 (31.4%)	10 (28.6%)
Patients without psychological factors	Fluvoxamine <i>n</i> =18	7	2	3	6
	Paroxetine <i>n</i> =19	6	3	2	8
	Total <i>n</i> =37	13 (35.1%)	5 (13.5%)	5 (13.5%)	14 (37.9%)

Mean maximal antipruritic effect (MAE) (1–100% response): 71.4% (patients with psychological factors), 64.9% (patients without psychological factors). SSRI: selective serotonin re-uptake inhibitors.

group was 21.5 weeks; the average duration in the paroxetine group was slightly longer (26.3 weeks). In most of the patients (54/72, 75%), study medication was discontinued during the first 6 months. In patients without antipruritic effect, therapy was discontinued after 4–10 weeks (Table II).

Of all the patients, 70.8% experienced some kind of expected adverse drug effect (fluvoxamine group, 66.6% of patients; paroxetine group, 74.3% of patients). Patients complained most frequently about symptoms regarding the central nervous system, the gastrointestinal tract, the vegetative system and the cardiovascular system (Table III). Symptoms were mostly mild and transient and were relieved completely after interruption of therapy. In 18 patients, study medication had to be stopped due to adverse drug effects (fluvoxamine group *n*=10; paroxetine group *n*=8). No side-effects were experienced by 29.2% of the patients (11 patients in the fluvoxamine group, 10 patients in the paroxetine group). No unexpected or severe adverse drug effects occurred. No clinically considerable alteration in laboratory values associated with the SSRI therapy was detected.

## DISCUSSION

This open-labelled, two-arm POC study aimed to investigate the antipruritic potency of SSRI in a large group of patients with chronic pruritus, focussing on the onset and stability of the antipruritic effect with long-term use. Moreover, given that most conventional antidepressants exhibit high levels of side-effects, we aimed to record the benefit/side-effect profile of the SSRI. In previous reports, SSRI were demonstrated to mediate high antipruritic effects (11–16). Zyllicz et al. (11) were the first to describe five patients with

paraneoplastic pruritus due to solid cancers, which responded rapidly to administration of paroxetine 5–20 mg. Five years later, the same group published a one-week, placebo-controlled, cross-over study with 24 patients with chronic pruritus due to systemic disease (12). Of these patients, 37.5% responded to 20 mg paroxetine therapy despite the short-term application. In polycythemia vera, 8/10 patients on paroxetine 20 mg (*n*=9) or fluoxetine (*n*=1) reported complete or near-complete resolution of pruritus within 48 h (13). In an epidemiological study on polycythemia vera, 5/39 were documented to receive paroxetine 20 mg with high antipruritic effect within one week (14). Furthermore, one patient with psychogenic pruritus was reported to respond to paroxetine 20 mg (17). In cholestatic pruritus, antipruritic effect of sertraline 50–100 mg/day was demonstrated in a case series (15) and a recent randomized, double-blind, placebo-controlled trial (16).

In our study we applied paroxetine, which is the most potent inhibitor of serotonin re-uptake among SSRIs, and fluvoxamine, which was reported to have a favourable side-effect profile in comparison with other SSRIs (18, 19). However, there was no statistical difference ( $p=0.604$ ) in the occurrence of side-effects between the two substances apart from less vegetative symptoms such as hyperhidrosis, weight gain or xerostomia in the fluvoxamine group. This is underlined by recent studies showing that fluvoxamine shows no difference in tolerability in comparison with other SSRI (23). The side-effects occurred at the beginning of the therapy, were mild and disappeared within time. No irreversible side-effect occurred. Importantly, before starting SSRI therapy a psychiatric or psychosomatic evaluation is essential. Given that SSRI may lead to excitatory side-

Table II. Duration of treatment

SSRI medication	Number of patients with duration of therapy						Average value (weeks)
	≤1 month	≤3 months	≤6 months	≤12 months	≤24 Months	>24 months	
Fluvoxamine <i>n</i> =33	10	12	6	1	3	1	21.5
Paroxetine <i>n</i> =39	5	13	11	5	3	2	26.3
Total <i>n</i> =72	15	25	17	6	6	3	24.2

SSRI: selective serotonin re-uptake inhibitors.

Table III. Side-effects of fluvoxamine ( $n = 33$ ) and paroxetine ( $n = 39$ ) therapy

Side-effects	Symptom* (number of affected patients)	Total number of affected patients
Central nervous system	Drowsiness ( $n=6$ ), vertigo ( $n=6$ ), fatigue ( $n=9$ ), headache ( $n=2$ ), sexual dysfunction ( $n=3$ ), tremor ( $n=2$ ), agitation ( $n=1$ )	22/39 (paroxetine)
	Drowsiness ( $n=2$ ), vertigo ( $n=5$ ), fatigue ( $n=6$ ), headache ( $n=2$ ), sexual dysfunction ( $n=2$ ), tremor ( $n=1$ ), agitation ( $n=1$ )	18/33 (fluvoxamine)
Gastrointestinal	Gastrointestinal pain ( $n=1$ ), nausea ( $n=6$ ), vomiting ( $n=1$ ), obstipation ( $n=1$ )	7/39 (paroxetine)
	Gastrointestinal pain ( $n=6$ ), nausea ( $n=5$ ), vomiting ( $n=1$ ), diarrhoea ( $n=1$ ), obstipation ( $n=1$ )	9/33 (fluvoxamine)
Vegetative	Hyperhidrosis ( $n=3$ ), weight gain ( $n=5$ ), xerostomia ( $n=1$ ), difficulties in urination ( $n=1$ )	10/39 (paroxetine)
	Xerostomia ( $n=1$ ), weight gain ( $n=1$ ), cramps in the calf ( $n=1$ )	3/33 (fluvoxamine)
Cardiovascular	Hypertension ( $n=1$ ), tachycardia ( $n=1$ ), palpitations ( $n=1$ )	1/39 (paroxetine)
	Hypertension ( $n=2$ ), palpitations ( $n=1$ ), oedema ( $n=2$ )	4/33 (fluvoxamine)
No side-effects	–	10/39 (paroxetine)
	–	11/33 (fluvoxamine)

\*More than one side-effect in several patients.

effects before the antidepressant effect starts, patients with manifest depression may be initiated to commit suicide. Furthermore, in elderly patients over 65 years of age the usage of SSRI is controversial due to possible excessive central nervous system stimulation, sleep disturbances and increased agitation (24). In this study, we did not observe this; however, a thorough consideration of the benefit/side-effect profile of SSRI in elderly patients has to be recommended.

Our results show that both substances mediate considerable and stable antipruritic effects in chronic generalized pruritus, as measured by patient's subjective recording of pruritus intensity reduction (VAS, MAE). The results have to be interpreted with care since we performed a non-placebo-controlled study and have to be confirmed in future randomized, controlled, double-blind studies that should also clarify the optimal dosage of the substances. Moreover, since both arms contained an active substance, placebo effects cannot be excluded. However, comparing both substances, no significant difference was observed in treatment response (paroxetine, 67.6% MAE; fluvoxamine, 64.9% MAE;  $p = 0.826$ ). According to previous studies, the antipruritic effect established only in a fraction of patients (24.5%) in the first 2 weeks and could be enhanced by maintaining the treatment. To the best of our knowledge, this report is the first study to describe long-term treatment with SSRI in chronic pruritus. Our results demonstrated that the antipruritic effect was achieved, on average, after 4.9 weeks. Comparing the mean duration up to the full antipruritic efficacy, an advantage for paroxetine over fluvoxamine could be observed; however, this was not statistically significant ( $p = 0.989$ ). As a consequence, therapy should not be stopped too early in patients with initial weak response.

A stable antipruritic effect was produced by both substances, which is especially important in the treatment of chronic pruritus and chronic scratch lesions including prurigo nodularis. An itch-scratch-cycle is currently regarded to be one major factor in the maintenance of

pruritic nodules. It is speculated that due to repeated scratching, cutaneous nerve fibres start to sprout and develop hypersensitivity, which may be responsible for pruritus and induction of epidermal thickening (25). One aim of this study was to investigate whether a stable antipruritic effect could be produced by long-term treatment with SSRI, contributing to the interruption of scratching and the healing of chronic scratch lesions. Indeed, we could observe healing or improvement of scratch lesions upon cessation of pruritus under SSRI treatment. Our results confirm further the response of systemic paraneoplastic pruritus to SSRI. However, patients with an underlying cutaneous lymphoma did not respond to SSRI. The reason for response of systemic, but not cutaneous, lymphoma to SSRI is unknown, but it supports the theory of a central mode of antipruritic action. Interestingly, patients with psychological co-morbidity influencing pruritus showed slight but insignificantly higher response rates. This finding again supports the theory that SSRI interfere with central mechanisms involved in pruritus perception or modulation. We did not record whether psychiatric disorders/depressive mood improved during SSRI therapy, which would further underline these considerations.

SSRI were developed and approved for the treatment of depression; the underlying mechanism of the antipruritic effect is not yet clarified. SSRI target the serotonergic system and the serotonin (5-HT) receptors, which are widely distributed in the peripheral and central nervous system. The serotonergic system is involved in numerous central functions including nociception, analgesia, sleep-wakefulness and autonomic regulation (26, 27). Experimental studies demonstrated that intracutaneous administration of serotonin excites nociceptive C-fibres and induces itch (28, 29). However, the inhibitory effect of SSRI was mainly demonstrated in the central nervous system but not clearly in peripheral sites (30). It seems likely that the antipruritic effect of SSRI is due to its central action rather than peripheral effects. In the central nervous system, SSRI target

Na<sup>+</sup>/Cl<sup>-</sup>-dependent transporters (syn.: neurotransmitter sodium symporters) on synaptic membranes (31). These transporters convey released neuromediators, i.e. serotonin, into presynaptic cell bodies after they were released. The inhibition of this mechanism results in increased serotonin concentration acting on postsynaptic receptors. It was speculated that the antipruritic effect of SSRI is due to a down-regulation of 5-HT<sub>3</sub> receptors upon continuous stimulation of the receptors (12). This is underlined by the fact that ondansetron, a 5-HT<sub>3</sub>-receptor antagonist, was shown to inhibit an antinociceptive effect of paroxetine (27).

Another hypothesis focuses on the effect of SSRI on opioid receptors. Recent animal studies demonstrated that the anti-nociceptive effect of paroxetine was significantly inhibited by naloxone, an opioid receptor antagonist, suggesting the involvement of opioidergic mechanisms (27). However, while these authors suggested paroxetine to increase the level of opioids, other studies demonstrated down-regulation of opioids by paroxetine (32). The CYP2D6 hepatic isoenzyme is speculated to activate morphine and other opioid pruritogens (33). Paroxetine was demonstrated to inhibit the activity of this enzyme, leading to a down-regulation of pruritogenic opioids (33). Inter-individual variability in CYP2D6 inhibition by paroxetine is well-known and is related to the basal enzyme activity prior to drug administration (34). It may therefore be speculated that the patients who did not respond to paroxetine therapy have altered CYP2D6 enzyme activity. Although the exact mechanisms leading to suppression of pruritus are not fully understood, a cerebral suppression of pruritus can be assumed, explaining the response of several forms of pruritus to SSRI therapy.

Finally, comparing the antipruritic efficacy, side-effect profile and costs of treatment for months with other modern antipruritic therapies, e.g. the opioid receptor antagonist naltrexone, SSRI has several medical and economic advantages, e.g. side-effects are milder and therapy costs are lower. In summary, previous case series, controlled studies and this POC study suggest SSRI as an alternative treatment modality for chronic pruritus, although this needs to be confirmed in future double-blind studies.

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*The authors declare no conflict of interest.*

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