Scandinavian Journal of Pain 5 (2014) 63–71

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Observational study

Long-term efficacy of spironolactone on pain, mood, and quality of life in women with fibromyalgia: An observational case series

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HIGHLIGHTS

- Spironolactone as add-on medication improved symptoms in women with treatment-resistant fibromyalgia syndrome.
- Fifteen of 31 women responded to spironolactone and were observed for 12–14 months.
- Spironolactone improved pain, stiffness, fatigue, anxiety, depression, and mood.
- Beneficial effects were obvious at 4–6 weeks and persisted over the whole observation period.

ARTICLE INFO

Article history:
Received 25 October 2013
Received in revised form 2 December 2013
Accepted 30 December 2013

Keywords:
Aldosterone
Analgesics
Fibromyalgia syndrome
Mineralocorticoid-receptor
Neurosteroids

ABSTRACT

Objective: No single drug is broadly efficacious in the long-term treatment of fibromyalgia syndrome (FMS). Spironolactone is known to ameliorate mood and tension headache or migraine in women with premenstrual syndrome or clinical signs of hyperandrogenism. In a case series of women with treatment resistant FMS spironolactone was therefore added to their medication, and they were observed for at least 12 months.

Methods: 31 women with treatment-resistant FMS received spironolactone as add-on medication to various pain modulating drugs. 15 women responded to spironolactone and baseline data were compared with assessments over 12–14 months on treatment with spironolactone (ALDACTONE®) in dose range 100–200 mg/day. The efficacy was evaluated by the fibromyalgia impact questionnaire (FIQ) total score and 8 FIQ subtests, a German mood inventory (BSKE-EWL), and further assessments of changes in relevant psychological and physical complaints. 16 women had no effect and stopped the treatment early.

Results: The subsequent data refer to the 15 responders. The FIQ total score (maximal score = 80) decreased from 56.6 ± 10.0 at baseline to 17.1 ± 11.9 (mean ± SD) 12–14 months later, and pain intensity on an 11 point numeric rating scale (NRS) decreased from 8.8 ± 1.6 to 2.6 ± 1.9 (mean ± SD). Similar changes in FIQ subscores were found for fatigue, morning tiredness, stiffness, anxiety, and depression. Emotional functioning consistently improved: positive mood from 20.0 ± 5.4 to 37.7 ± 5.4 (maximal score = 48), and negative mood from 35.4 ± 5.3 to 10.0 ± 4.4 (maximal score = 60) (each mean ± SD) as well as other mental and physical dysfunctions including non-restorative sleep. All these changes at 4–6 weeks remained on this level for 11–13 months. The drug was well-tolerated and safe, no serious adverse effects were observed. Regular monitoring of serum potassium did not reveal hyperkalemia. All 15 women were able to reduce or discontinue concomitant drugs.

Conclusion: Fifteen of 31 women with otherwise treatment-resistant FMS experienced a number of prolonged beneficial effects from spironolactone on their complex pain-condition.

Implications and discussion: We hypothesise that spironolactone affects several central and peripheral neurotransmitter systems such as γ-aminobutyric acid (GABA) activity and dopaminergic transmission. The high rate of non-responsive patients underlines that FMS may represent several subgroups. Pain relief and improvement of associated FHS-symptoms and positive effects on additional diseases or dysfunctions give reasons for marked and sustained improvement in the quality of life.

Well-controlled, double-blind, and randomised trials are necessary to confirm our potentially very important observations.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2014.02.006.
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1877-8860/$ – see front matter
http://dx.doi.org/10.1016/j.sjpain.2013.12.003

1. Introduction

The fibromyalgia syndrome (FMS) is a complex generalised chronic pain disorder most likely resulting from not only disordered central pain processing, but also associated symptoms such as fatigue and sleep disturbance as well as cognitive difficulty, headache, paraesthesia or morning stiffness also involving the spinal tract level [1–3]. Drug treatment of pain and other symptoms are unsatisfactory. Within the concept of multicomponent treatment, the recommended analgesics comprise antidepressants and antiepileptics which are used as co-analgesics for classical neuropathic pain syndromes [4]. These agents may offer benefit for at least some patients in short-term studies [5,6]. The prevailing polysymptomatology frequently requires combined medications, however, most therapeutic responses are rarely effective long-term, or side effects of drugs limit long-term administration. The present explorative case series was prompted by earlier clinical observations showing that spironolactone administered during the luteal phase in women with premenstrual syndrome (PMS) achieved a marked improvement in mood and headache [7]. Practice-based observations confirmed that patients with PMS or women with clinical hyperandrogenism (hirsutism, acne, alopecia) experienced sustained amelioration or complete relief of tension headache or migraine attacks. Both, pain disorders and PMS commonly coexist with FMS [8]. Positive treatment effects of spironolactone on the mental state and other aspects of psychological functioning in women were described in the thesis by J. Niemeyer (1996; University of Würzburg; no electronic version available). These early findings encouraged this explorative and long-term observational case series on the possible effects of spironolactone on pain and other symptoms in treatment-resistant FMS-patients.

2. Patients and methods

2.1. Patients

We evaluated 31 out-patients with chronic widespread treatment-resistant pain from FMS. They were referred by medical practitioners, rheumatologists, neurologists, or self-referred in search of various treatment approaches. All women went through the initial assessment and started the spironolactone treatment. Fifteen women responded to the treatment and subsequently underwent three assessments on treatment after 4–6 weeks, 6 months, and 12–14 months. Six patients could be followed-up to six years and more, one of them over 12 years.

Sixteen patients declared at the first follow-up visit after 4–6 weeks that they had no or low pain relief and therefore did not continue the spironolactone-medication, and they could not be followed-up. These patients did not reveal markedly different baseline profiles of various measures apart from emotional dysfunction which revealed a tendency towards lower positive mood scores.

At baseline, all patients received a medical and psychological history evaluation. The physical examination regarding pain confirmed that all patients had high pain levels, a high number of "tender points", and various other bodily disturbances. The laboratory analysis included indicators of liver and renal function as well as recordings of metabolic and electrolyte values. Subject demographics, duration of suffering, comorbidities and additional health problems, prior medications, and pain characteristics are listed in Table 1.

The diagnosis was classified according to the American College of Rheumatology diagnostic criteria [9].

Table 1
Baseline characteristics of the 15 responders Subject characteristics, duration of pain disorder, comorbidities, last prior medications, and individual baseline measures (tender point count, FIQ total score and pain level).

Patient number	Age (years)	Weight (kg)	Duration of pain (years)	Comorbidities	Prior medications	Tender point count	FIQ total score	Pain level (FIQ subscore)
1	55	67	7	Hypertension, migraine	NSAID, tramadol, oestrogen	14	43.6	10
2	59	94	13	Hypertension, obesity, FRS, GAD, panic disorder	TCA, tramadol, AG, MR, zopiclone, SSRI, clonazepam	18	73.4	10
3	45	53	17	CMD, FRS, RLS, asthma, fructose intolerance, GAD, panic disorder	TCA, NSAID, MR, tramadol, levodopa	15	73	9
4	58	69	9	Asthma, polyarthrosis (finger)	TCA, NSAID, MR, oestrogen	16	63	10
5	36	61	7	Androgenic alopecia	NSAID, AG, TCA, MR, OC	12	63.5	9
6	41	92	10	Obesity, CMD, PMS, hirsutism	TCA, NSAID, AG, OC	13	57.3	8
7	53	68	7	Overweight, hypertension, migraine, tinnitus	TCA, NSAID, MR, AG, bromazepam	14	47.2	10
8	55	66	6	CMD, migraine, hirsutism, rosacea, burning-mouth syndrome	TCA, NSAID, AG	12	52.9	8
9	54	62	7	irritable bowel syndrome, multiple allergies, FRS, carpal tunnel syndrome	NSAID, AG, TCA, oxycodone, pregabalin, progesterone	17	67.9	8,5
10	41	62	15	Hypertension, FRS, androgenic alopecia	NSAID, carvedilol, duloxetine, L-thyroxin, tetrazepam	16	43	5
11	47	83	10	Obesity, BED, hypertension, acne, hyperlipidemia	TCA, NSAID, AG	14	45.6	6
12	50	62	16	Migraine, BED	TCA, hydrocortison, NSAID, AG	17	51.6	9
13	34	74	8	Overweight, PMS, FRS, multiple food allergies	TCA, hydrocortison, NSAID	16	52.2	10
14	54	90	11	Obesity	NSAID, AG	17	54.5	10
15	43	75	10	Overweight, FRS, acne	TCA, AG, oxycodone	16	55.1	10

Comorbidities: BED, binge eating disorder; CMD, craniomandibular dysfunction; GAD, generalised anxiety disorder; FRS, fluid retention syndrome; PMS, premenstrual syndrome; RLS, restless leg syndrome *Drugs*: AG, other not specified analgesics; MR, muscle relaxant; NSAID, nonsteroidal analgesic/anti-inflammatory drug; OC, oral contraceptive; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

2.2. Outcome measures

With regard to the multiplicity of somatic and psychological dysfunctions of FMS patients, it is mandatory to assess a wide array of clinical variables also integrating patients' view on treatment efficacy. The following measures seemed appropriate.

2.2.1. The fibromyalgia impact questionnaire (FIQ)

This established and validated instrument assesses physical functioning, days felt good, pain, morning tiredness, fatigue, stiffness, anxiety, and depressive mood [10]. Each item ranges from 0 to 10 score points, the first two items address the status after normalisation. The composite index of the FIQ comprises a total score from 0 to 80 without cut-off due to the wide-range of FMS. This simple measure is sensitive to change, meaningful, easy to handle, cheap, applicable to all patients, and quickly evaluated by clinical practitioners. FIQ's disadvantage is that the time frame only covers the last week.

2.2.2. Emotional functioning

Emotional functioning was assessed by a German self-report *multidimensional mood questionnaire BSKE* (*EWL*) [11]. This questionnaire contains 8 items to describe positive mood dimensions, and 10 items reflecting negative mood states. Responders rated each item from 0 (not at all) to 6 (very strong) indicating the level during past four weeks. The sums of the respective items give the total score, for positive mood ranging from 0 to 48, and for negative mood from 0 to 60. There was also one addendum item as a brief index of "perceived stress" related to workplace, family, partner, interpersonal conflicts, and environmental factors. It was rated on the same seven point scale.

2.2.3. Additional measures regarding mental and physical domains

Because the multidimensional mood questionnaire contains important issues of interest which could selectively strengthen the evidence of changes on any treatment, four items were calculated separately: concentration, lack of energy, fatigue (day time), and feeling drowsy. Due to the difficulties of applying additional lengthy validated questionnaires in clinical practice, further important psychophysical and bodily complaints were presented as written items which had to be answered on seven point ordinal scales scored from "never (0) to always (6)" for the past four weeks. The questions are worded: restorative sleep, bodily weakness/exhaustion, forgetfulness, muscle tension, and dizziness.

2.2.4. Further appropriate indicators of change

At the endpoint of the study, patients were asked to assess the *global impression of improvement*, rated on a transition scale anchored: 1 = very much worse, 4 = unchanged, and 7 = very much improved. Another set of questions was used to confirm and specify the spectrum of changes more detailed over the whole treatment period by the items: (1) improvement in health related quality of life; (2) increase in physical activity; (3) amelioration in mobility and endurance; (4) reduction in pain; (5) intake of concurrent medications and (6) frequency of visiting medical practitioners or specialists during the observation period. These items were rated as percentage of changes compared to the baseline condition.

2.2.5. Changes in medication

The number of different drugs was counted and the change of this number was given as percentage value. This mode of pharmaco-therapeutic recording (irrespective of the daily dosages) of analgesics during chronic pain syndromes is considered as an objective procedure.

2.3. Treatment

Patients were treated with spironolactone [ALDACTONE®] after they consented to comply with a written instruction (2 pages) on all modalities of treatment and *off-label use* because of missing worldwide approval for any other indication than primary and secondary hyperaldosteronism. Depending on body weight, patients started with 25–50 mg spironolactone after breakfast for the first 3–5 days. Provided that there were no side effects, patients were advised to raise their dose up to 100–200 mg/day within two weeks. Depending on prevailing personal conditions, such as days with exaggerated psychological distress, bodily exertion, or other environmental (weather) factors, patients were further advised to keep their dosage somewhat flexible instead of staying consistently on a fixed dose regimen in order to minimise the risk of hyperkalemia. Consequentially, they also could decide on their own to schedule drug intake either once in the morning or twice daily. The majority of women preferred the intake of the entire dosage in the morning.

Initially, patients were allowed to continue prior medications but were requested to try to reduce doses or to discontinue intake of other drugs.

Based on earlier and recent reports of some women (suffering from severe hirsutism) on lower effectiveness of some spironolactone generics, we exclusively prescribe ALDACTONE® which is worldwide available in order to assure comparability.

2.3.1. Pharmacokinetics of spironolactone

It is quickly cleared from plasma after oral intake with a mean elimination half life ($t_{1/2}$) of 1.4 h, whereas the active metabolites 7α-thiomethylspironolactone, 6β-hydroxy-7α-thiomethylspironolactone, and canrenone had $t_{1/2}$ values of 13.8, 15, and 16.5 h, respectively [12].

2.4. Descriptive statistical analysis

Results are presented by descriptive statistics, i.e. presentation of mean and SD, or changes of means from baseline values.

3. Results

3.1. Fibromyalgia impact questionnaire (FIQ)

Spironolactone treatment resulted in an early, substantial, and sustained reduction in FIQ total score (Table 2) at all follow-up visits with changes over the entire observation period. Considering the magnitude of improvement in FIQ total score, a similar change in individual components of FIQ could be expected (Table 2). Apart from pain relief, mean scores of all other subtests showed marked improvement within 4–6 weeks such as physical functioning, days felt good, fatigue, morning tiredness, stiffness, anxiety, and depression. These items were also found to be markedly improved at six and 12–14 months.

3.2. Emotional functioning and additional measures of mental or somatic symptoms

The measures of emotional functioning which were psychometrically evaluated by the opponent mood indices, demonstrated an early and sustained increase in positive mood, and a substantial reduction in negative mood. These improvements could be demonstrated already at both intermediate evaluations with highly significant differences from baseline (Fig. 1). Noteworthy, two patients with less pronounced pain relief were also found to display smaller changes in both mood indices at six and 12–14 months.

Table 2
Baseline, assessments at six and 12–14 months (mean ± SD) of FIQ total score, FIQ subscores, and additional items describing physical and psychological measures among 15 women with FMS who completed the case series on spironolactone treatment.

Efficacy measures	Baseline (n = 15)	4–6 weeks (n = 14)[a]	6 months (n = 15)	12–14 months (n = 15)
Fibromyalgia impact questionnaire (FIQ)				
FIQ total score (range 0–80)	56.6 ± 10	19.5 ± 9.7	16.3 ± 11.9	17.1 ± 11.9
FIQ subscores (range 0–10)				
Physical functioning	4.3 ± 1.3	1.9 ± 1.3	1.4 ± 1.3	1.5 ± 1.5
Days felt good[b]	8.6 ± 2.0	2.9 ± 1.8	2.0 ± 2.3	2.3 ± 1.8
Pain	8.8 ± 1.6	3.4 ± 1.9	2.7 ± 1.8	2.6 ± 1.9
Fatigue	8.3 ± 1.0	2.8 ± 1.6	2.3 ± 1.3	2.3 ± 1.7
Morning tiredness	8.3 ± 1.2	2.7 ± 2.4	2.4 ± 1.9	2.4 ± 2.1
Stiffness	6.7 ± 2.3	2.7 ± 1.8	2.1 ± 1.8	2.5 ± 1.4
Anxiety	5.9 ± 2.7	1.9 ± 1.4	1.9 ± 2.0	2.0 ± 1.7
Depression	5.6 ± 2.8	0.9 ± 1.1	1.2 ± 1.5	1.1 ± 1.4
Additional psychological and physical symptoms (range 0–6)				
Concentration	2.60 ± 1.1	4.14 ± 0.7	4.26 ± 1.1	4.33 ± 1.1
Fatigue (Day-time)	4.76 ± 0.9	1.54 ± 1.2	1.83 ± 1.0	1.47 ± 1.3
Lack of energy	4.70 ± 1.6	1.14 ± 1.3	0.66 ± 0.9	1.13 ± 1.3
Drowsiness	3.53 ± 1.5	1.14 ± 1.0	0.73 ± 1.1	0.67 ± 0.8
Forgetfulness	3.80 ± 1.1	2.20 ± 1.3	2.20 ± 1.1	2.20 ± 1.0
Feeling stressed	4.57 ± 1.1	2.29 ± 1.2	1.53 ± 1.0	1.40 ± 1.2
Restorative sleep	0.93 ± 1.4	3.96 ± 1.9	4.00 ± 1.9	4.27 ± 1.9
Bodily weakness/exhaustion	4.56 ± 0.8	1.82 ± 0.9	1.50 ± 1.2	1.36 ± 1.1
Muscle tension	4.73 ± 0.8	1.64 ± 1.3	1.40 ± 1.2	1.77 ± 1.4
Dizziness	3.63 ± 1.4	1.07 ± 1.3	0.53 ± 1.0	0.67 ± 1.1

[a] One woman failed at second visit.
[b] High score = less good days, low score = more good days.

As compared with pre-treatment evaluation, impressive improvement in lack of energy and concentration, as well as in fatigue, feeling stressed, feeling drowsy and forgetfulness, important complaints of FMS patients (13) could be observed during the entire period of assessment (Table 2). Moreover, patients achieved very noticeable changes regarding non-restorative sleep, bodily weakness/exhaustion, muscle tension and dizziness.

One additional woman, who is not among the 31 patients in the observational case series, experienced rapid and pronounced pain relief, but discontinued spironolactone treatment due to nausea (see Section 3.6).

3.3. Global impression of change

Patients' evaluation of global impression of changes using a transition scale provided the following results: two patients scored the treatment as "moderately improved", seven patients as "much improved", and six patients as "very much improved". Furthermore, specific ratings of global treatment efficacy at 12–14 months were compared with baseline values (Fig. 2). These semi-quantitative results demonstrate that the majority of patients experienced a clinically impressive amelioration in their mental and physical health. The means of pain levels were reduced by 76%, and this

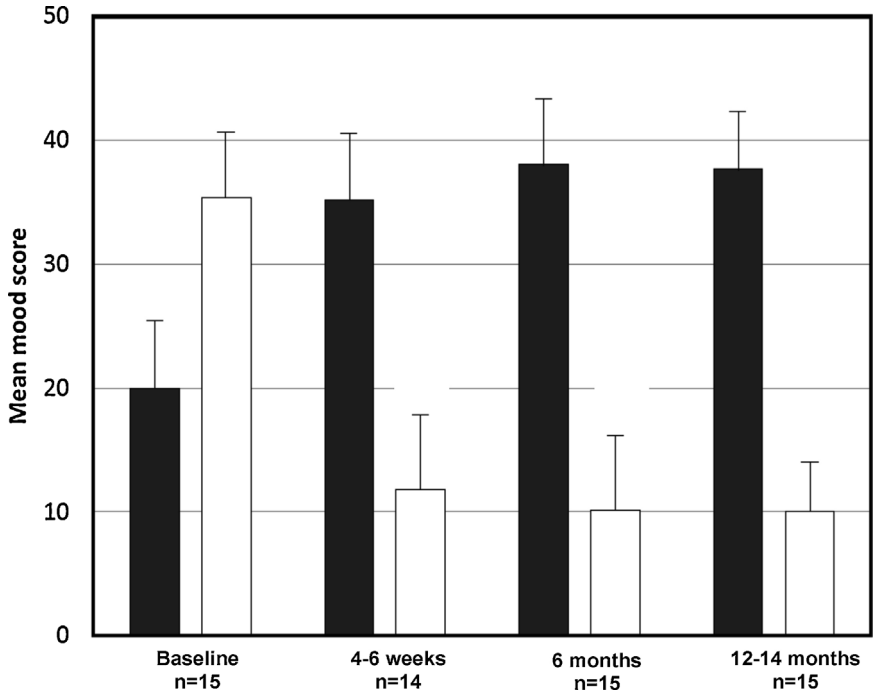

Fig. 1. Mood scores (mean ± SD) calculated as positive mood (sum of 8 items [black bars]) and negative mood (sum of 10 items [open bars]) at baseline and different time intervals among 15 women with FMS on treatment with spironolactone. One woman could not perform the second visit.

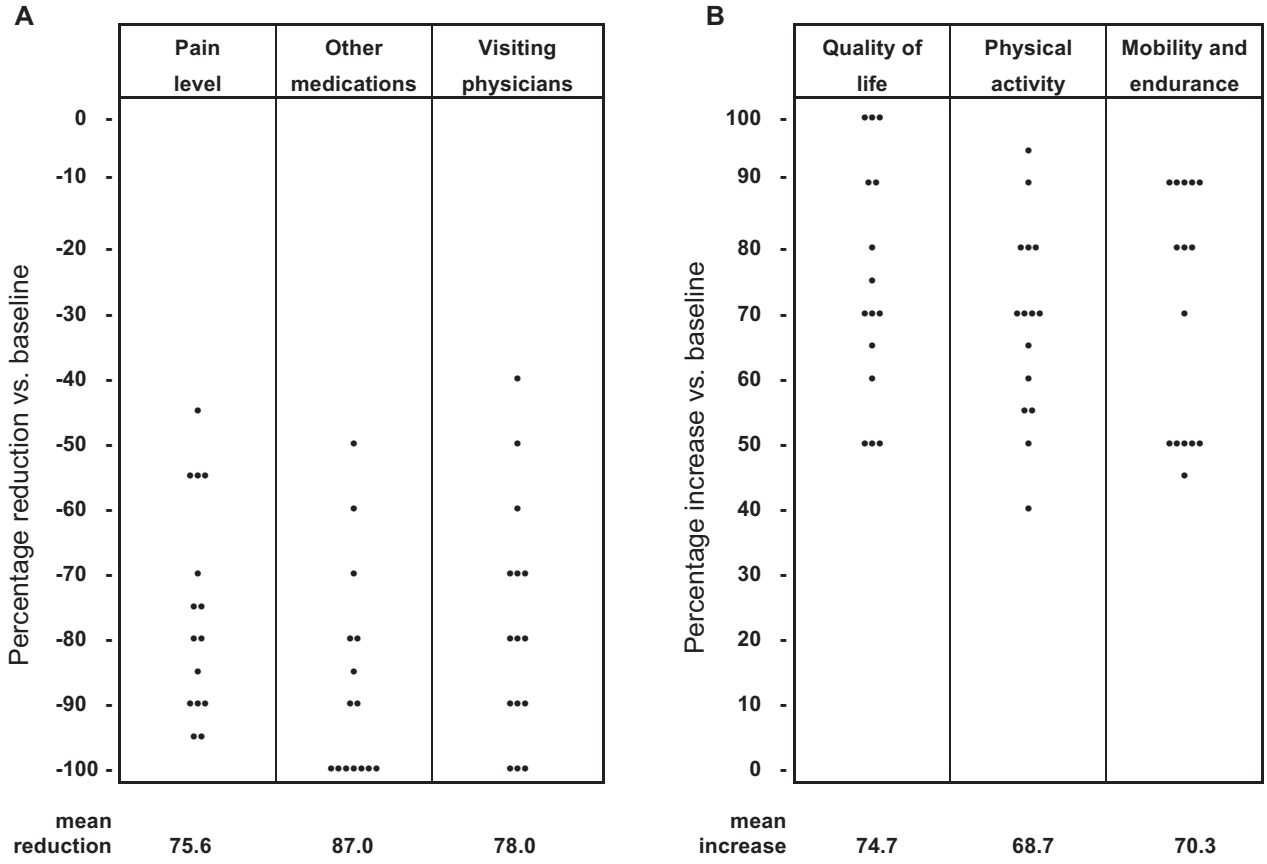

Fig. 2. Individual efficacy evaluation (one point gives one patient) of spironolactone treatment concerning six important domains at last observation. All patients rated change compared to the baseline condition either as percentage reduction (A) or increase (B) in each of the outcome measures.

beneficial change was reflected by increases in means of quality of life, physical activity as well as mobility and endurance by 75%, 69% and 70% (Fig. 2).

3.4. Reduction in concomitant drug therapy

Most importantly, all patients were able to reduce medications they used at start of spironolactone treatment (mean −87%) (Fig. 2). Seven women were even able to do completely without any other drugs, and most patients could even completely abstain from opioids. This reduction in the number of medications was 87% (i.e. by average a reduction from 5–6 different drugs to 0–1 drug). Moreover, the frequency of visiting medical practitioners or specialists during the observation period was markedly reduced (mean −78%) (Fig. 2).

3.5. Additional observations and clinically relevant effects

3.5.1. Prediction of efficacy

A rapid onset of response within a few days according to what the patients have reported to the physician at the first follow-up-visit, has proven as the best predictor for long-term efficiency, whereas severe emotional disturbances at baseline, appeared to characterise poor or non-responders (data not shown).

Some women achieved an early improvement in activity level, sleep and fatigue on lower dosage, but acceptable pain relief requested a dosage ≥100 mg/day. Abrupt discontinuation of drug (during a travel abroad) exacerbated pain in two women.

3.5.2. Duration of effect

Six responsive patients have been followed for six years, one for over 12 years. They adhered to spironolactone without loss of activity or side effects apart from transient hyperkalemia in one woman.

3.5.3. Weight reduction in obese patients

The majority of FMS patients suffered from a variety of other diseases either representing a family of medical and psychiatric disorders with a common pathophysiology [14] or general medical diseases not related to FMS (see Table 1). Overweight or obesity is frequently associated with FMS. Indeed, this was also true for seven cases (47% of 15 patients). The weight loss in patients ranged from 1.1 kg to 9.8 kg (mean 2.6 ± 2.2 kg) at the third visit.

3.5.4. Clinical hyperandrogenism and hypertension

Hirsutism, acne or alopecia, typical symptoms of hyperandrogenism [15,16] were improved in five women, hypertension was lowered in five women, and two patients showed improvements in both symptoms.

3.5.5. Antimigraine effect

It is noteworthy that four (out of 15) patients with concomitant migraine, one of them with a history of 30 years, did not suffer from headache attacks during the observation period and beyond.

3.5.6. Restless legs syndrome

One woman experienced complete and sustained reduction of restless legs syndrome and leg cramps and could abstain from levodopa. The omission of levodopa supports our hypothesis, that the

beneficial actions of spironolactone might also involve increase in dopamine effects (see Section 4).

3.5.7. Anxiolytic effect

The same woman did not experience any more her frequent panic attacks associated with the hyperventilation syndrome.

3.5.8. Eating disorders

Two patients with binge eating disorder (BED), possibly related to persistent pain and negative affectivity, had lost eating abnormalities under spironolactone already at the 6-months visit. This normalisation in eating behaviour remained stable throughout the observation period and was documented by an eating disorder inventory. The co-occurrence of FMS with eating disorders [17] has already been recognised earlier.

3.6. Adverse effects

No serious treatment related side effects were recorded during the entire observation period except for nausea in one woman. That patient discontinued spironolactone. Dose dependent menstrual cycle irregularities occurred in one premenopausal woman. These irregularities are known to happen in 15–25 percent of women on higher dosage, and normalise after discontinuation of medication. Possibly because of the antiandrogenic potency and dosage, five patients noticed dry skin.

Breast tenderness, another known side effect, did not occur during the present study. On the contrary, four patients reported consistent relief of breast tenderness while on spironolactone treatment particularly in the premenstrual period.

The obligatory control of various blood variables at intervals of 2–3 months did not reveal any negative effects of spironolactone. Serum sodium, potassium, and creatinine levels were in the normal ranges, as well as the conventional indicators of liver function and uric acid level. The widely feared hyperkalemia was observed only in one patient who was followed up for 6 years. Her hyperkalemia was mild and transient.

4. Discussion

4.1. Substantial and sustained improvement in all aspects of FMS

The effect of pharmacological treatments in women with FMS is generally small and transient as documented for the use of antidepressants [18] or even deteriorate the symptoms [19]. Our observations demonstrate that fifteen out of thirty-one women with FMS responded well to the mineralocorticoid-receptor antagonist (erroneously named aldosterone antagonist) spironolactone (100–200 mg per day) as add-on medication. Sixteen patients did not experience a substantial improvement, they stopped taking the spironolactone treatment early, and they were not followed up any longer.

The pronounced effects of spironolactone comprised reduction in pain and core symptoms such as fatigue, sleep disturbances, and physical weakness/exhaustion. In addition, spironolactone improved concentration, energy, forgetfulness and drowsiness that are important complaints of FMS-patients [13]. All of these beneficial effects were consistently improved during the 12–14 months of the observation period.

The majority of FMS-patients suffer from emotional disturbances that contribute importantly to the reduced quality of life. It is another remarkable observation that spironolactone persistently raised positive mood and impressively diminished negative mood. These effects are favourable for pain modulation and pain relief in chronic FMS patients [20–22]. Most importantly, all patients adhered to spironolactone while concomitant analgesic medications, including opioids, were reduced or even discontinued.

4.2. Possible modes of action: observations from animal and human reseach

4.2.1. Effects on GABA transmission

Spironolactone blocks mineralocorticoid and androgen receptors dose-dependently, and has agonistic activity on progesterone receptors. In contrast to the peripheral endocrine effects, the mechanisms of actions of spironolactone in the central nervous system (CNS) are incompletely understood. Mineralocorticoid receptors (MR) as primary target on spironolactone express highest density in the septo-hippocampal area [23,24]. Inhibition of these receptors by spironolactone, or synthetic analogues, administered either systemically or intraventricularly, provokes a variety of behavioural and molecular changes in rodents, e.g. anxiolytic [25] and anticonvulsant effects. Furthermore, cognitive dysfunctions induced by the anticholinergic drug scopolamine, were markedly antagonised [26].

FMS is a complex syndrome with apparent dysregulation of several body systems, mainly in the brain. Interestingly, spironolactone has also been shown to act directly on the membrane-bound γ-aminobutyric acid (GABA) – receptor complex [27]. Based on endocrinological studies in man [28,29], spironolactone enhances the circulating levels of deoxycorticosterone and progesterone. Their naturally occurring 3α,5α-reduced metabolites (3α,5α-tetrahydroprogesterone [3α,5α THP] and 3α,5α-tetrahydrodeoxycorticosterone [3α,5α THDOC]), both generated by enzymes in various tissues including brain [30], were shown to enhance GABAergic transmission [31]. These metabolites, also termed neuroactive steroids (neurosteroids), exert a broad spectrum of behavioural changes including sedative, hypnotic, anxiolytic, anti-aggressive, anticonvulsant, and sleep modulating effects in animals and humans [32]. THP or THDOC administration to rats reduces plasma corticosterone levels in response to stress. Thus, these neurosteroids attenuate the function of hypothalamic-pituitary-adrenal (HPA) axis possibly by GABAergic action in the hypothalamus [33] which suppresses sympathetic overactivity, too. THP and the synthetic 3α-5α neuroactive steroid alphaxalone effectively alleviate thermal and mechanical hyperalgesia in a rat model of neuropathic pain [34].

Furthermore, the 3α-reduced neurosteroids modulate depressive behaviour and realise the action of antidepressants [35–37].Thus, animal research provides strong evidence that spironolactone can increase the GABAergic transmission with consequent attenuation of central pain responses [38]. Moreover, it increases the presence of neuroactive steroids which in turn attenuates central stress responses and enhances anxiolysis or sedation.

Besides the improvement in emotional functioning by GABAergic mechanisms, GABA activation plays a well known predominant role in the amelioration of restorative sleep disturbances. Interestingly, that reinforcement of GABA transmission positively affects the slow wave pattern [39], which is one established abnormality in patients with FMS [40]. Non-restorative sleep is discussed as the common denominator for multiple somatic and mental complaints and is rated as an FMS-aggravating factor in 79% of patients ($n = 2596$) based on an internet survey [41].

4.2.2. Effect on dopamine transmission

In FMS-patients, levels of dopamine (DA) metabolites are reduced in the cerebrospinal fluid [42] and PET studies have confirmed the hypo-dopaminergic state in FMS [43]. In line with this observation, hypo-dopaminergic alterations reflect prolonged stress, a distinct feature of FMS-patients [44–46]. We speculate

that the GABA activation by the anti-mineralocorticoid itself, its sulphur containing metabolites, or by induced release of neurosteroids might also affect the dopaminergic system. Both, GABA and the neurosteroid THP (also called allopregnanolone) reinforce the dopaminergic system and antagonise anti-dopaminergic effects [47–50]. Thus, a decreased GABAergic tone associated with low DAergic activity could be defined as a further neurobiological characteristic at least in a subgroup of women with FMS. It is tempting to speculate that the inactive GABA-dopamine-axis contributes to pain perception and emotional dysfunction as well as to dyscognition, perception speed, and memory dysfunction, often referred to as "fibro-fog".

4.2.3. Effects on the nociceptive system

Recent observations have reported a pro-nociceptive role of an activation of the mineralocorticoid-receptor (MR) in the pathogenesis of painful diabetic polyneuropathy [51] whereas MR blockade by the MR antagonist eplerenone reduces pain behaviour and decreases excitability in small-diameter sensory neurons [52] Spironolactone was found to elevate the concentration of morphine fourfold in the brain, and it was hypothesised that spironolactone inhibits the outward-directed P-gp transporter [53]. A substantial subset of FMS patients show symptoms of small-fibre polyneuropathy (SFPN) [54,55], and it is a challenging hypothesis to test whether spironolactone might affect clinical aspects of SFPN.

4.2.4. Clinical observations of spironolactone related to FMS

Spironolactone has already been studied to treat tension headache and migraine, however, there are no reports on chronic pain disorders [56]. Already 35 years ago, mood stabilisation was seen in 5 of 6 patients with bipolar disorder on spironolactone treatment (100 mg daily) between 12 and 18 months without any side effects [57]. In women suffering from premenstrual syndrome (PMS) during 14 premenstrual days, a placebo controlled trial demonstrated a significant decrease in negative emotions such as anxiety and tension, irritability, fatigue and depression, whereas the positive affect indices were increased comprising cheerfulness, well-being, friendliness, and feeling energetic [58]. Older conference abstracts reported on mood enhancing as well as stress tolerance improving effects of spironolactone as documented in hyperandrogenised women (J. Niemeyer; medical thesis 1996; University of Würzburg; no electronic version available).

Finally, prolonged stress is often associated with hypocortisolemia and diminished adrenal responsiveness despite hyperactive ACTH release [59], that sometimes is found in FMS patients. Interestingly, inhibition of central MR by spironolactone elevates the plasma cortisol levels in healthy adults [60], and these effects might help to normalise the decreased adrenal responsiveness in FMS-patients. Moreover, activation of central MR under chronic stress conditions attenuates serotonin release and turnover, and this can be reversed by MR inhibition [60].

Spironolactone has a proven safety profile, and it has beneficial metabolic [61], cardiovascular [62] and anti-inflammatory [63] effects. It could be an option for those patients with various symptoms such as dyscognition ("fibro-fog") and psychological distress. Spironolactone might not only improve pain syndromes in FMS, but also further symptoms in overlapping conditions of the so called "central sensitivity syndrome" [8] such as tension and migraine headache, restless legs syndrome, and pre-menstrual syndrome (PMS).

4.3. Critical aspects

The observations in the present case series are limited by the lack of a placebo control group. The observed effects of spironolactone have to be validated in strictly controlled double blinded, randomised clinical studies with different subgroups of FMS-patients. Such randomised-controlled-trials (RCT) also should address the hypothesis that spironolactone is superior to, or non-inferior to active drugs as recommended by FMS-specialists, e.g.tramadol, pregabalin, and antidepressants.

We have treated only female patients with FMS. Higher doses of spironolactone may induce painful gynecomastia and sexual dysfunction in man. Spironolactone does have anti-androgenic effects, therefore male patients with FMS may react differently from what we have observed in our female FMS-patients. Spironolactone treatment in male patients with FMS must be explored with utmost care. Interestingly, a recent open-label study of spironolactone that was given to mostly male patients with treatment-resistant hypertension and obstructive sleep apnoea [64] documented beneficial effects on apnoea-periods also in men.

4.4. Conclusions

This observational case series provide evidence that spironolactone is an effective pharmacological option for the treatment of pre- and postmenopausal women suffering from FMS, not only against pain, but also against various affective, cognitive, endocrine, and vegetative disturbances. Our data suggest a superior safety and long-term effectiveness of spironolactone that is at least comparable to that of generally recommended analgesics and other neuropharmacological drugs for FMS. Therapy of FMS with spironolactone can be easily conducted in a medical practice using the fibromyalgia impact questionnaire (FIQ) for pre- and post-treatment evaluation.

4.5. Implications

The use of spironolactone offers a novel option for drug treatment of FMS patients. It is easy to check for its responsiveness, lacks major drug-interactions and adverse side effects, and spironolactone can be added in multimodal therapies. Based on clinical observations that patients with FMS represent several subgroups with different pathophysiological background, pharmacotherapy was proposed as a potential tool to clarify different pathogenic mechanisms [65]. In this regard spironolactone seems to be a very promising candidate.

Conflict of interest

The authors receive no funds and declare no conflict of interests.

Contribution of authors

The clinical part of this observational case series that started in 2001, and the intellectual design of the manuscript were exclusively performed by H. W.

T. H. contributed to the writing and submission of the manuscript.

Acknowledgements

We are grateful to B.A. Schoelkens, MD, Professor of pharmacology, Univ. of Frankfurt/Germany and I. Auer, MD, Professor of Internal Medicine and Rheumatology, Wuerzburg/Germany for critical reading of the manuscript. We also thank our colleagues U. Moser, MD, practitioner and pain therapist, Mönchberg/Germany, and M. Klein, MD, Neurologist/Wuerzburg/Germany for their active support by referring treatment resistant FMS patients as well Roswitha Gerhard and Birte Wolf for technical help.

Spironolactone (ALDACTONE®) is produced by Riemser AG, 17493 Greifswald/Germany. Finally, we thank Dr. Kirstin Reinecke for her help on the manuscript.

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