Pain in end-stage renal disease: a frequent and neglected clinical problem

Domenico Santoro, Ersilia Satta, Salvatore Messina, Giuseppe Costantino, Vincenzo Savica and Guido Bellinghieri

Department of Nephrology, University of Messina, Messina, Italy

Key words
ESRD – pain – uremic neuropathy – renal bone disease – electrotherapy

Abstract. Pain is a major health problem in end-stage renal disease (ESRD) affecting half of the dialysis patients; most of them experience a moderate to severe degree of pain. Nevertheless, the impact of chronic pain and its consequences are often underestimated. Sources of pain related to the uremic environment are renal bone disease (osteitis fibrosa cystica, amyloidosis, osteomalacia), osteoarthritis, calcific uremic arteriolopathy and peripheral neuropathy. Moreover, comorbid conditions such as ischemic peripheral artery disease, diabetic neuropathy, osteopenia/osteoporosis (due to long-standing hypertension, diabetes, or old age) result in various kinds of pain. Also the primary kidney disease (e.g. autosomal dominant polycystic kidney disease (ADPKD)) as well as performance of hemodialysis or peritoneal dialysis are important causes of pain. Potential consequences of persistent pain are disturbed sleep, weakened memory/attention, altered mood (anxiety and depressive disorder), impotence, poorer physical state, less social activities and consideration of withdrawal from dialysis. Consequently the health-related quality of life (HRQOL) is diminished, associated with a higher morbidity and mortality. In the therapy of pain the WHO three-step analgesic ladder adapted for ESRD, was shown to be effective in dialysis patients. Of fundamental importance are various forms of non-pharmacological strategies including electrotherapy. Recently the so-called high tone external muscle stimulation (HTEMS) was very effective in the management of neuropathic pain in ESRD patients.

Types and causes of pain in ESRD

Pain can be acute, intermittent or chronic (usually more than 3 months). There are three broad categories:

- **Nociceptive pain** is poorly localized and described as cramping, deep, and throbbing. Here the nerves are not damaged. Pain results from stimulation of peripheral or visceral nociceptors which subsequently send their signals via the spinal cord to the brain. Somatic pain can be due to trauma, inflammation, muscle spasm etc. while visceral pain results
from serosal irritation, distension or ischemia of tissues, as well as inflammation of internal organs. Nociceptive pain is often time limited.

- **Neuropathic pain** is aching, stabbing, paroxysmal and electric shock-like. Pain is generated from an alteration of the different somato-sensory pathways caused by damage of the peripheral-(PNS) or central nervous system (CNS). It is associated with changes in sensitivity such as numbness, allodynia and hyperalgiesia [10].

- **Mixed pain** represents a combination of the two above mentioned forms.

A broad variety of conditions and different pathophysiological mechanisms are involved in pain manifestations. As consequence of the progressive course of renal failure, osteodystrophy, osteoarthritis, calciphylaxis and peripheral neuropathy may develop. Other kinds of pain are related to co-morbidities such as critical limb ischemia, non-uremic peripheral neuropathy or osteoporosis/osteopenia due to long-lasting hypertension, diabetes mellitus, advanced age as well as inflammatory/immunological diseases. Pain may also result from the primary kidney disease (e.g., autosomal dominant polycystic kidney disease (ADPKD), from drug treatment (statins), diagnostic procedures, (gadolinium MRI), chronic infections (e.g., osteomyelitis, discitis, infection of the arteriovenous (AV) fistula) [2]. During hemodialysis sessions pain results from needle insertion, muscle cramps, abdominal and cardiac pain (due to intradialytic ischemia) and headaches [11] (Table 1), while peritoneal dialysis induces discomfort and pain from dialysate instillation, abdominal distension and peritonitis [6]. It is necessary to distinguish the different causes of pain for a more effective therapeutic management. For example, patients with neuropathic pain are less responsive to opioids but respond much better to antidepressants and anticonvulsants.

**Bone pain in ESRD**

Disturbances in mineral metabolism and bone diseases are common complications of chronic kidney disease (CKD). They are called Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) and include abnormal mineral metabolism, alterations of structure and composition of the bone, and extraskeletal calcification. In general the classical osteitis fibrosa is mostly without clinical symptoms. In the case of osteitis fibrosa cystica, induced by secondary hyperparathyroidism, pain and fragility of the bone is a frequent complication. Also osteomalacia, caused by vitamin D deficiency, as well as the adynamic bone disease are often associated with pain and fractures [12]. Manifestation of osteoarthritis may be caused by deposition of calcium pyrophosphate dehydrate (CPPD) as well as by β2-microglobulin amyloidosis. Fibromyalgia induces more diffuse muscle and soft tissue pain. Radiography may reveal pseudofractures of the pelvis, femurs, metatarsals, or lateral margins of the scapulae. Therapy of chronic pain has to be adapted to the individual patient with special regard to the presence of a high or low bone turnover osteopathy.

**Calcific uremic arteriolopathy**

Calcific uremic arteriolopathy (CUA), or calciphylaxis, is an under-recognized and rare disease with an incidence of ~ 1 – 4% in dialysis patients [13]. It is characterized by a progressive calcification of arterioles of the skin resulting in ischemia, indurated nodules, necrotic eschars, dry gangrene or infections [13]. The lesions develop symmetrically in the thighs and calves as well as less often in heart, lung and penis. CUA is extremely painful and associated with high mortality. Its pathogenesis is poorly understood. Potential factors are elevated parathyroid hormone (PTH) levels with a high bone turnover, elevated serum concentration of calcium and phosphate (not always observed), hypercoagulability and enhanced pro-inflammatory cytokines. Deposition of calcium and phosphate crystals is assumed to be an active cell-mediated process [14]. Other risk factors are malnutrition (low serum albumin concentration), use of calcium salts and/or vitamin D analogues, exposure to high doses of iron salts, use of glucocorticoids or warfarin.

Treatment of CUA involves rigorous wound care, strict control of mineral me-
metabolism, avoidance of calcium and vitamin D supplementation as well as pain control. Drug treatment includes bisphosphonates, which lower bone turnover and sodium thiosulfate. This drug induces antioxidant effects (via enhanced glutathione formation) and may enhance the calcium solubility from deposits in the arterioles. Furthermore hyperbaric oxygen therapy, and/or daily hemodialysis using a low-calcium dialysate are recommended [15]. However, even with all treatment possibilities, CUA is associated with a high morbidity and mortality [13].

### Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) develops in the setting of acute or chronic renal failure after application of gadolinium-based contrast media (GBC) during magnetic resonance imaging (MRI) [16]. The lesions are typically symmetric and develop on limbs and trunk. In the affected areas, joint contractures, itch, causalgia and sharp pain may occur. Free gadolinium is assumed to activate circulating fibrocytes to synthesize hyaluronan and to invade the skin. Also monocytes and macrophages are activated and produce profibrotic cytokines [17]. Other factors associated with NSF include coagulation abnormalities, activation of transglutaminases, recent surgery, hyperphosphatemia and the use of recombinant erythropoietin.

Currently, there is no effective therapy for NSF. Intense physiotherapy is advised to prevent or reverse the disabilities and contractures of the joints [17]. Interestingly, an improved renal function after kidney transplantation or in the recovery phase of acute renal failure seems to slow or arrest NSF. Thanks to warnings from the Food and Drug Administration (FDA) and the European Medicine Agency (EMA), the incidence of NSF has dramatically declined. In the new guidelines of the European Society of Urogenital Radiology (ESUR) X-ray media with the highest NSF risk (gadodiamid and gadoversetamide) are contra-indicated in CKD Stage 4 and 5 as well as in acute renal failure.

### Uremic neuropathy

Occurrence of uremic neuropathy was suspected by Charcot and Ossler at the end of 19th century. With introduction of hemodialysis and renal transplantation for ESRD in the early 1960s, uremic neuropathy found great attention. It is a chronic progressive sensorimotor disease and characterized by a symmetric length-dependent axonal degeneration with greater involvement of lower than upper extremities [18]. Nerve biopsy studies showed that demyelination is secondary to axonal degeneration of the distal nerve [19]. Earliest clinical symptoms are paresthesia, pain, numbness, creeping and paradoxical heat sensation. In later stages, involvement of

<table>
<thead>
<tr>
<th>Important causes of pain in ESRD and during dialysis treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important causes of pain in ESRD</strong></td>
</tr>
<tr>
<td><strong>Peripheral polyneuropathy</strong></td>
</tr>
<tr>
<td>Uremia, diabetes, vasculitis, Fabry disease</td>
</tr>
<tr>
<td>Renal bone disease</td>
</tr>
<tr>
<td>Osteitis fibrosa cystica, osteomalacia, low bone turnover osteopathy</td>
</tr>
<tr>
<td><strong>Mononeuropathy</strong></td>
</tr>
<tr>
<td>Carpal tunnel syndrome, ulnar or femoral neuropathy</td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Deposition of calcium pyrophosphate (DCPP) or β2-microglobulin amyloidosis</td>
</tr>
<tr>
<td><strong>Ischemic monomelic neuropathy</strong></td>
</tr>
<tr>
<td>Calcific uremic arteriopathy (Calciphylaxis)</td>
</tr>
<tr>
<td><strong>Critical lower limb ischemia</strong></td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td><strong>Chronic infections</strong></td>
</tr>
<tr>
<td>Osteomyelitis, discitis, shunt infection</td>
</tr>
<tr>
<td>Primary kidney disorder</td>
</tr>
<tr>
<td>Renal stone disease, pyelonephritis, autosomal dominant polycystic kidney disease</td>
</tr>
<tr>
<td><strong>Nephrogenic systemic fibrosis</strong></td>
</tr>
<tr>
<td>Gastrointestinal complains</td>
</tr>
<tr>
<td><strong>Hemodialysis</strong></td>
</tr>
<tr>
<td><strong>Needle insertion, muscle cramps, headaches, abdominal or cardiac pain due to volume contraction</strong></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>Dialysate installation, abdominal distention, peritonitis</td>
</tr>
</tbody>
</table>
motor neurons results in weakness and muscle atrophy. Deep tendon reflexes are reduced at first in the ankles; the vibratory threshold is elevated. A slowing of motor and sensory nerve velocity is observed in symptomatic and asymptomatic patients [20, 21].

Manifestation of uremic neuropathy is tightly related to the severity of renal impairment. In general it becomes clinically manifest when the glomerular filtration rate (GFR) is less than 10% [14, 18]. However, electrophysiological and histological manifestations occur earlier [18]. Among the dialysis patients, between 10 to 41% show neuropathic symptoms [2, 4]. In ESRD also autonomic neuropathy may develop characterized by postural hypotension, impaired sweating, diarrhea, constipation or impotence [22, 23].

Pathogenesis of uremic neuropathy is still not fully understood. Hegström et al. [24] postulated the role of accumulated dialyzable toxins, since intermittent hemodialysis in patients with severe uremic intoxication resulted in an improvement of neuropathy. In the following years, the so-called “middle molecules” such as advanced glycation end products (AGEs), β-2 microglobulin and PTH were regarded as potential neurotoxins [25, 26]. Recently, the fundamental role of hyperkalemia has been demonstrated [27]. Using a novel nerve-excitability technique (as an indirect assessment of the activity of various axonal ion channels) in the predialysis phase the abnormalities were directly related to the serum potassium concentration. After a single hemodialysis an improvement of excitability abnormalities and hyperkalemia occurred [27]. The authors hypothesized that prolonged hyperkalemia disrupts the normal ionic gradient of the neurons by activating a calcium-mediated process, that leads to axonal damage [28]. Inhibition of the axonal Na+/K+ pump in ESRD, as postulated earlier [21, 22] could not be confirmed in recent investigations [27].

Successful kidney transplantation results in a cure or an improvement of peripheral uremic neuropathy within a period of weeks or several months [29]. Beneficial effects could also be demonstrated by daily hemodialysis, change to high flux dialysis membranes as well as drug therapy with pyridoxine, thiamine, methylcobalamin or erythropoietin [30]. An optimal serum potassium during the interdialytic phase is absolutely necessary. Furthermore painful neuropathy may be improved by physical activities, an anticonvulsive therapy with gabapentin and/or application of electrotherapy (see below).

Among the non-uremic neuropathies in ESRD the diabetes-induced nerve damage is a frequent complication. It occurs mostly in the form of a generalized symmetrical sensorimotoric polyneuropathy. Usually its course is more severe than uremic neuropathy, probably due to an amplifying effect of the uremic state [31]. Other causes of peripheral neuropathy are polyarteritis nodosa, Wegener’s granulomatosis, systemic Lupus erythemathodes or Fabry disease.

### Important determinants of chronic pain in ESRD

In a prospective study of ESRD patients the disturbed mineral metabolism was associated with muscle pain and skin complaints [32]. A relationship with elevated serum levels of calcium, phosphorus and iPTH levels could be demonstrated. Similar findings were reported in a cross-sectional study [4]. In this investigation there was also an association between pain and lowered levels of calcitriol. Based on these findings the authors postulated that the altered mineral metabolism could be involved in various kinds of pain in ESRD. Indeed, other authors implicated a direct relationship of calcium overload and vitamin D deficiency in pain manifestation [33, 34].

### Mononeuropathies in ESRD

In ESRD mononeuropathies typically affect the median and ulnar nerves. The most important one is carpal-tunnel syndrome (CTS), which is observed in up to 30% of dialysis patients [35]. CTS is caused by an entrapment of the median nerve with subsequent pain of the first three fingers, diffuse pain of the hand, followed by thenar atrophy. In its pathogenesis deposition of amyloid, uremic tumoral calcinosis and “a steal” effect of the AV fistula were identified. Manifestation of CTS symptoms in both hands
suggests a strengthening effect of a generalized uremic neuropathy.

Manifestation of ulnar neuropathy may occur in up to 50% of dialysis patients [36]. It is characterized by pain, weakness and sensory symptoms in the hand (the small and ring fingers and the hypothenar), elbow and distal arm with functional impairments. Ulnar neuropathy may occur also without pain and may thereby be overlooked until profound weakness occurs. Risk factors include external pressure on the ulnar groove (in particular during hemodialysis), amyloid deposition, uremic tumoral calcinosis and a steal effect of the vascular access of the upper limb.

Ischemic monomelic neuropathy is a vascular steal syndrome due to a newly-created AV fistula of an upper limb [37]. It induces symptoms of median and ulnar neuropathy with sensory loss and weakness of the forearm and hand. Symptoms occur immediately after creation of the fistula due to shunting of the arterial blood with a subsequent blood pressure decline in the distal limb. Diabetic patients are in an enhanced risk [37].

Uremic chronic cystic disease

In contrast to ADPKD the frequent occurrence of acquired renal cystic disease in ESRD is not associated with manifestation of pain. The biggest problem of acquired renal cysts is the development of renal carcinoma, which mostly is also not associated with pain symptoms [41].

Pain in autosomal dominant polycystic kidney disease (ADPKD)

ADPKD is frequently associated with various types of pain, even in the presence of a normal kidney function. Pain afflicts ~60% of patients after age of 40 and has been located in the low back (71%), abdomen (61%), head (49%), chest (30%), and legs (27%), often with radicular features (38, 39). Back pain is induced by kidney enlargement as well as rupture, hemorrhage or infection of cysts. Other causes of pain are the frequent nephrolithiasis (in ~1/3 of the patients due to stasis of urine) and urinary tract infections (due to ureter compression). Moreover, cysts of the liver frequently cause pain due to the hepatomegaly as well as infection, rupture and hemorrhage of cysts. Other non-renal factors of pain are colon diverticulitis and abdominal wall hernias, which are more frequently observed in ADPKD. Episodes of pain may occur several times per day, per week or only a few times per month and are unforeseeable. This also contributes to the impaired mood of the patients and their limited social activities [39].

Pain management of ADPKD patients should be based on psychological behavior modifications (including Alexander technique), physical therapy (ice massage, heating pad), transcutaneous nerve stimulation (TENS), treatment of infections, application of systemic analgesics and surgical approaches (decompression procedures, aspiration, fenestration or resection of cysts, renal denervation or nephrectomy) (Figure 1) [39].
Pain in endstage-renal disease: a frequent and neglected clinical problem

Personal relationships and the desire of certain patients to withdraw from dialysis [44]. The HRQOL is diminished which is associated with enhanced hospitalization and mortality [42, 43, 44, 45, 46]. On the other hand the threshold of pain is markedly influenced by the degree of insomnia and depression which may enhance discomfort and pain resulting in a vicious circle [46]. Interestingly chronic pain exerts marked effects on various brain areas. Beyond original pain it may lead to abnormal brain chemistry and loss of neocortical gray matter [47, 48] which favor the perpetuation of pain and development of further complications. Chronic pain may also promote cardiovascular complications in part due to development of hypertension [49].

Management of pain in ESRD

First of all the deranged mineral metabolism, the lowered vitamin D levels and the PTH excess should be corrected. It is conceivable that thereby the severity of pain can be modulated in many patients.

For the drug management of pain the World Health Organization (WHO) three-step analgesic ladder is generally accepted. Severity of pain is evaluated on visual 10-point analog scale, where 1 – 3 represents mild pain, 4 – 6 moderate pain and 7 – 10 severe pain. The “first step” recommends non-opioid analgesics such as acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs) or specific cyclooxygenase-2 (COX-2) inhibitors. In persisting pain or moderate pain the “second step” advises weak opioid analgesics. If pain still persists or pain is severe the “third step” advocates strong opioid analgesics. A combination with non-opioid analgesics (acetaminophen) may be performed in moderate or severe pain.

In ESRD the WHO analgesic ladder in its current form is unsuitable. The pharmacokinetics of many analgesics, in particular of opioids, is markedly altered, resulting in numerous adverse effects. Disturbed pharmacokinetics is caused by the lowered renal excretion of the parent compound and/or their active metabolites in renal failure. Moreover the biotransformation and hepatic removal of opioids may be altered [50]. There are also data that in ESRD the sensitivity to adverse effects of opioids is enhanced. Certain opioids may even exacerbate symptoms of renal failure. Therefore, the WHO three-step analgesic ladder has to be adapted to the needs in ESRD [43, 51].

An adjustment of the WHO analgesic ladder for ESRD patients is shown in Table 2 [5]. In Step 1 NSAIDs and COX-2 inhibitors should be avoided for chronic pain treatment due to their risk of gastrointestinal bleeding, development of hypertension and compromise of residual renal function. Acetaminophen (paracetamol) is regarded as a safe medication, except in higher doses, which are hepatotoxic.

In Step 2 (moderate pain) codeine medication is not recommended, since its elimination half-life is markedly prolonged, associated with enhanced neurotoxicity [52]. However, other authors still advise codeine in ESRD in a modified dose [53, 54]. The centrally acting tramadol is effective in a reduced dose and well tolerated. This is explained by its non-opioid mechanism of action due to inhibition of the noradrenaline and serotonin reuptake. Another advantage of tramadol is it’s less abuse potential. Hydrocodone is a semi-synthetic centrally acting opioid needing dose adjustment. Its use is widespread but may be hepatotoxic. An alternative is the semisynthetic opioid oxycodone, administered in a lower dose.

In Step 3 (severe pain) morphine should be avoided, since its metabolites morphine-3-glucuronide and morphine-6-glucuronide accumulate, resulting in multiple adverse effects such as orthostatic hypotension.
nausea, constipation, pruritus and respiratory depression (Table 3). A promising alternative is the synthetic opioid fentanyl. It is 100 times more potent than morphine and characterized by a rapid onset and short duration of action (strong agonist of µ-opioids). Fentanyl is probably safe, since its metabolites are inactive [52]. It can be administered transdermally. A dose adjustment is necessary. The analgesic effect of Methadone, a synthetic opioid, is associated with an anti-addictive action for patients with opioid dependency. Methadone is indicated for severe chronic pain and characterized by long duration of action. Hydromorphone (dihydromorphinone) is a semi-synthetic derivative of morphine. It is a potent, centrally-acting analgesic, showing also antitussive effects.

In neuropathic pain treatment with opioids is less effective. In these patients anticonvulsants such as gabapentin are recommended in ESRD in a lower dose. Also tricyclic antidepressive agents such as amitriptyline exert analgesic effects, particularly in combination with opioids [51]. However side effects such as sedation, dry mouth, weight gain and orthostatic hypotension limit their application in ESRD [56].

The efficacy of the adjusted WHO analgesic ladder to ESRD patients was recently demonstrated in a small group of dialysis patients. However, in elderly patients more adverse effects were observed [5]. An improved pain control in ESRD patients through the adapted version of the WHO analgesic ladder was also observed in another study [53]. However, up to now there are no randomized trials or proven guidelines as yet.

### Non-pharmacological treatment of pain

With regard to their few side effects non-pharmacological strategies are a challenge. They include a psychological and cognitive behavioral therapy such as relaxation technique, biofeedback, meditation, hypnosis, breathing-exercises, Yoga and spiritual counseling [46, 57]. Furthermore distraction techniques can reduce attention to pain by TV watching, playing cards, crossword puzzles, etc. Of particular importance is regular physical activity which can relieve or even prevent various kinds of pain as shown in animal experiments [58] and in humans [59]. In dialysis patients a Yoga-based exercise program reduced pain by 37% in HD patients [60].

In pain treatment also different forms of electrotherapy are effective. Most commonly used forms are transcutaneous nerve stimulation (TENS), percutaneous nerve stimulation (PENS), spinal cord stimulation (SCS) and high tone external muscle stimulation (HTEMS). TENS is an application of electrical currents to the skin above the painful area. The portable battery-powered device can be applied with low (< 10 Hz) or high (50 – 120 Hz) frequencies [61]. TENS was effective in postoperative pain, osteoarthritis and diabetic neuropathy but not in lower back pain [61]. Application of PENS combines the effect of low frequency TENS and acupuncture-like needle probes. For spinal cord stimulation (SCS) an electrode is implanted in an appropriate segment of the epidural space. SCS proved successful in severe pain due to diabetic neuropathy, refractory angina pectoris, ischemic peripheral artery disease and back pain. However SCS is associated with severe complications such as life threatening infections.

In the past several years the so-called high tone external muscle stimulation (HTEMS) was developed. Its carrier frequency varies in short intervals between 4,096 Hz and 32,786 Hz. Simultaneously the amplitude is modulated. In a short term comparative study in patients with symptomatic painful diabetic neuropathy HTEMS was three times more effective than TENS [62]. In a chronic study of patients with symptomatic diabetic neuropathy HTEMS therapy improved the discomfort in 3/4 of the patients [63].

<table>
<thead>
<tr>
<th>Opioids: side effects</th>
<th>Absolute risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>16% (10 – 22%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15% (11 – 19%)</td>
</tr>
<tr>
<td>Dizziness or Vertigo</td>
<td>8% (5 – 12%)</td>
</tr>
<tr>
<td>Somnolence or Drowsiness</td>
<td>9% (5 – 13%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5% (2 – 7%)</td>
</tr>
<tr>
<td>Dry Skin, Itching or Pruritus</td>
<td>4% (1 – 6%)</td>
</tr>
</tbody>
</table>
HTEMS therapy was also successful in a prospective clinical pilot study in dialysis patients with symptomatic diabetic or uremic peripheral neuropathy [64]. Both lower extremities were treated intradialytically three times a week for one hour. After a period of one to three months a significant amelioration in neuropathic symptoms such as burning, pain, tingling, numbness and numbness in painful areas was achieved [47]. There was also a significant improvement of sleep disturbances.

Our group recently performed a three month study of HTEMS therapy on neuropathic and nociceptive pain in a cohort of 30 CKD patients (Stage 4 – 5) unpublished data). HTEMS treatment led to a significant relief of five neuropathic symptoms and to a significant reduction of sleep disorders. Generally, a better relief of pain was achieved in patients who were treated daily versus three times per week. Interestingly, also the restless-legs-syndrome was significantly improved. To the best of our knowledge this is the first observation of HTEMS treatment of this disturbance. According to our findings HTEMS can be regarded as a useful strategy in pain treatment of ESRD patients which did not respond to standard methods.

**Conclusion**

Prevalence of pain in ESRD patients is rather high and caused by uremic environment, co-morbid conditions, underlying kidney disease and dialysis therapy. Unfortunately, only one quarter of the patients are effectively treated. If not treated, persistent pain may lead to various physical, mental or social consequences. Therefore, an early and effective therapy is a challenge. First of all a better recognition by the physicians and a better understanding of the current therapeutic strategies is necessary [46]. In the drug therapy the WHO three-step analgesic ladder in its adapted forms to the needs in ESRD has been successfully applied. With regard to the polypharmacy of the patients and the potential of adverse effects of many drugs, non-pharmacological strategies should be recommended. They include a cognitive/behavioral therapy, physical exercise and modern forms of electrotherapy including HTEMS.

**References**

Pain in endstage-renal disease: a frequent and neglected clinical problem


