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LEADING ARTICLE

Managing Chronic Non-Malignant Pain in the Elderly: Intrathecal Therapy

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Abstract
Intrathecal drug delivery (IDD) was first described in 1981 by Onofrio, who used a pump for continuous and intrathecal delivery of morphine to treat cancer pain. Over the following four decades, many reports supported this treatment method with implanted pumps for cancer and non-cancer pain. To date, more than 300,000 pumps for pain therapy and spasticity have been implanted worldwide. This article reviews current knowledge regarding intrathecal opioid therapy, focusing particularly on the use of IDD in elderly patients. Current literature is presented, and the arguments in favor of and against this therapy in elderly patients are discussed.

Key Points

Elderly patients often experience chronic pain.

Oral opioid therapy can incur unwanted side effects.

Treatment of pain via intrathecal drug delivery has yielded favorable results in a vast number of studies, including randomized controlled trials.

Intrathecal drug delivery may have advantages in elderly patients because it is efficacious and avoids the side effects of oral or transdermal application.

1 Pain in the Elderly

Elderly patients have traditionally been defined as those aged ≥ 65 years. This definition was introduced according to historical contexts rather than physiological factors. In fact, the first national pension plans in Germany used this age as a qualification limit [1]. In 2014 the US National Institute on Aging estimated that more than half of the elderly people reported bothersome pain in the last month [2]. No exact data exist about the real incidence of chronic pain in patients aged > 65 years, because this population group tend to underreport pain. The prevalence of pain increases with age and is higher in women and the obese elderly. Patel et al. [3] analyzed data from the 2011 National Health and Aging Trends study in 7601 adults aged ≥ 65 years to determine the prevalence and impact of pain. In this study, 52.9% of participants reported pain in the previous months. The majority reported multiple sites of pain and showed depressive symptoms [3].

With global demographic development, pain treatment in elderly patients will become a special point of interest, particularly in the West [4, 5]. In these patients, sufficient pain reduction is of great importance to quality of life. Moreover, the American Health and Retirement Study showed a possible correlation between chronic pain and memory decline. Elderly patients with chronic pain had a 26.7% elevated risk of dementia in a 10-year follow-up compared with the control group [6].

There seems to be an age-related difference in perception and reporting of pain [7]. On one hand, the pain threshold appears to increase, whereas the response to mild pain reduces; on the other hand, the elderly seem to be more sensitive to severe pain. The reasons for these observations remain unclear [8].

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1.1 Common Sources of Pain in the Elderly

The most common sources of chronic pain in the elderly are musculoskeletal diseases such as osteoporosis, with and without fractures of the vertebrae, osteoarthrosis, rheumatoid arthritis and polymyalgia, peripheral vascular disease and neuropathic pain due to diabetes and stroke or postherpetic neuralgia [9–11].

1.2 Pain Treatment in the Elderly

Pain treatment in this patient group must consider some physiological characteristics, e.g., reduced hepatorenal function and increased sensitivity to centrally active medications due to structural, biochemical and functional changes in the peripheral and central nervous system [6].

Further, the volume of distribution is lower in elderly than in younger people. This may lead to increased plasma drug levels, which may affect the pharmacology of analgesics, leading to unwanted side effects, particularly with centrally active drugs such as opioids. Also, age-correlated comorbidities, frailty and polypharmacy may increase the risk of drug interactions and side effects such as confusion [12]. Reduced hepatic function may lead to greater bioavailability of various drugs [5].

First-line therapies for neuropathic or mixed pain, such as nonsteroidal anti-inflammatory drugs, can have cardiovascular and gastrointestinal toxicities, and tricyclic antidepressants and anticonvulsants may have intolerable side effects. Combining these first-line therapies with an opioid may allow the dosages to be reduced [13, 14], albeit opioid efficacy in neuropathic pain seems limited, with a number needed to treat of 3.4–5.8 for morphine and oxycodone [15].

1.3 Oral Opioid Applications in Pain Therapy of the Elderly

The clinical efficacy of opioids has been shown in cancer pain in general (high level: Ib or IIb), but data concerning the efficacy of opioids in cancer pain of the elderly are limited. Some studies show growing evidence of efficacy of opioid treatment in non-cancer pain in the elderly [5]. Comparative studies have shown that elderly patients with pain have a response to opioid treatment that is equal to or even stronger than that of younger patients [8, 16].

Dementia and other cognitive impairments leading to compliance problems in the elderly must be taken into account when treating with opioids. Other age-related changes such as renal dysfunction must also be considered. The opioid dose must be reduced because of an increased half-life of the drugs and their partially toxic metabolites, particularly in the case of morphine. Longer time intervals are also recommended for these drugs. The only exception to these recommendations is buprenorphine, which also shows a ceiling for respiratory depression. Respiratory depression and hypoventilation under opioid treatment is more frequent in the elderly, particularly those with respiratory tract diseases and pre-existing impairment of the central ventilatory drive [5].

The long-term use of opioids in the management of chronic non-cancer pain is a matter of debate, not only because of the intrinsic side effects, such as sedation, constipation, and cognitive deficits, but also because of the possible development of addiction or tolerance to opioids with necessary dose escalation [17]. Dose escalation can be necessary with oral or intrathecal opioid therapy in non-cancer patients. Some authors regard the phenomenon "dose escalation" as an expression of tolerance [18–24].

In 2008, a consensus statement from an international expert panel focusing on the most frequently used high-potency opioids (World Health Organization [WHO] step III opioids: buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone) in the management of chronic severe pain in the elderly summed up the most important recommendations on the optimal use of these medications in elderly patients. It was emphasized that significant data were available for the WHO step III opioids in general but not specifically in the treatment of the elderly [5]. All in all, not only should the "right opioid" be selected for the individual patient but also longer dosing intervals and possibly dosage reduction should be considered. Moreover, given the narrow therapeutic window, patients should be closely monitored for possible adverse effects.

Concerns regarding opioid use in the elderly include obstipation [25, 26], urinary retention, intoxication—particularly in patients with reduced hepatic or renal function—difficulties in dose finding in patients with dementia and an increased risk of falls [27].

2 Intrathecal Pain Therapy: Indications, Procedure and Outcomes

2.1 Indications

Intrathecal drug delivery (IDD) systems are used in the control of cancer pain and non-cancer pain as well as in the treatment of severe spasticity. The use of an intrathecal pump was first described in 1981 by Onofrio et al. [28] for the continuous and intrathecal delivery of morphine in cancer pain. Many reports followed that showed beneficial outcomes from this treatment method for cancer and non-cancer pain [19, 29–34] (Table 1). To date, more than 300,000 pumps have been implanted to treat pain and spasticity [35].

Table 1 Overview of selected studies on outcomes of intrathecal opioid therapy in non-cancer pain

Study	*N*	Study type	Follow-up	Outcome
Winkelmuller and Winkelmuller [19]	120	Retrospective	6 months–5.7 years	60% of the patients experienced pain reduction, 81% significant improvement of QoL
Roberts et al. [30]	88	Retrospective	≥ 6 months	Improved analgesia and self-reported activity levels, reduced medication
Thimineur et al. [31]	38	Prospective	6, 12, 18, 24, 30, 36 months	Improved pain, function and mood
Deer et al. [29]	Enrolled 166; implanted 136	Prospective	6, 12 months	80% satisfied, 87% would undergo procedure again, trial success rate 93%
Rauck et al. [32]	110	Prospective	6 months	Significantly improved pain and function, no serious AEs
Veizi et al. [33]	126	Retrospective	3, 6, 12 months	Significant pain reduction, no major AEs
Hamza et al. [34]	58	Prospective	6, 12, 18, 24 months	Significant pain relief, reduced oral opioids, functional improvement
Raphael et al. [96]	15	Randomized, controlled double blind	10 weeks	20% dose reduction led to significantly higher pain scores
Kleinmann and Wolter [65]	Eligible 50; analyzed 36	Retrospective	Mean 11.8 years	Significant pain reduction, self-reported improved mobility and sleep

AE adverse event, *QoL* quality of life

The intrathecal application of opioids allows extensive dose reduction compared with oral or parenteral application and thereby reduces the typical drug-induced side effects [36]. Indications for IDD in chronic non-cancer pain include nociceptive and neuropathic pain mechanisms. Most patients have pain originating from the spine, e.g., failed back surgery, compression fractures, spondylolisthesis and spinal cord injury-induced spasticity, complex regional pain syndrome, neuropathies, or chronic pancreatitis [37]. Standard procedures and algorithms have been developed to maintain the safety and efficacy of this treatment option [35]. Currently, the only drugs approved by the US FDA and the European Medicines Agency [38] for intrathecal administration are morphine, baclofen and ziconotide. Morphine and ziconotide are recommended as first-line therapy for nociceptive and mixed pain [37, 39]. If side effects from the on-label FDA-approved medications are intolerable, other opioid and non-opioid medications, such as hydromorphone are fentanyl or clonidine, can be used off-label as second- or third-line treatments [39–41], but data for their intrathecal use in chronic pain are limited [42]. In case of side effects or loss of efficacy, conversion to intrathecal opioids is recommended [39].

Baclofen, a derivative of gamma-aminobutyric acid (GABA) is used primarily in the management of spasticity of spinal or cerebral origin [43, 44]. It is also used in the treatment of pain and dystonia as a rare part of the complex regional pain syndrome [45]. A recent randomized trial in 60 patients [46] reported that baclofen can also reduce pain in patients with post-stroke pain and spasticity.

Ziconotide, a non-opioid calcium channel blocker, is the synthetic form of a marine snail conotoxin. Three randomized controlled trials [47–49] and several observational studies [50–52] have shown efficacy in the treatment of moderate to severe pain when delivered intrathecally. It is characterized by a narrow therapeutic window and must be carefully titrated, as neuropsychiatric and cognitive adverse events have been described secondary to rapid dose escalation [38]. It is recommended to "start low and go slow" to reduce side effects [53]. Concomitant drugs such as antidepressants and anticonvulsants may accelerate the risk for side effects observed with ziconotide.

Currently, within a study on ziconotide as first-line therapy, a study on intrathecal morphine as an alternative to oral opioids and a study on intrathecal morphine microdoses are recruiting. In our institution, morphine is used as a first-line treatment. If side effects are intolerable, hydromorphone or buprenorphine may be employed.

In 2003, the first Polyanalgesic Consensus Conference (PACC) developed an algorithm for the indication and trialing of IDD and choice of drugs. Since 2000, the implantation growth rate has been flat [54]. It is possible that the acceptance of and indications for IDD, especially for non-cancer pain, have changed slowly over the last 10–15 years as more multidisciplinary pain programs have been implemented. The PACC guidelines were updated in 2012 and 2017 [39,

55–59]. Algorithms were developed as an evidence-based decision support for intrathecal medication choices according to the pain mechanism, e.g., nociceptive and neuropathic pain, cancer and non-cancer pain, terminal illness, and localized versus diffuse pain. Multiple reviews have considered the efficacy and safety of IDD, and it has been found to be a safe and efficient method of pain therapy [35, 59–64]. IDD was also effective in long-term applications, with a mean duration of 11.8 years; unwanted side effects were not reported as a limiting factor for patient satisfaction [65].

However, the lack of firm scientific proof of evidence for intrathecal opioids has also been criticized, as no RCTs have been conducted [66].

The PACC strongly recommended (grade A recommendation) intrathecal therapy in patients with cancer. Opioids and ziconotide are effective in the treatment of patients with cancer (evidence level I); the evidence is lower for non-cancer pain (grade B recommendation) [39, 59].

2.2 Procedure

2.2.1 Patient Selection

Prior to IDD implantation, a multidisciplinary pain exploration, including a psychological examination, is mandatory to rule out psychiatric comorbidities, such as severe depression, psychosis or substance abuse, that might constitute a contraindication for IDD [35, 61, 67]. The presence of psychosocial factors influencing the perception of pain can also be assessed with a psychological examination. These psychosocial factors may be a relative contraindication for IDD [39]. In any case, the knowledge of these factors may facilitate decisions for or against pump implantation and improve the outcome of this therapy when used.

IDD should be considered in all severe refractory painful conditions where pain persists despite oral or transdermal opioids or where drug-induced side effects are intolerable [68, 69]. Typical side effects, such as sedation, constipation and cognitive deficits, are likely to be reduced with IDD, but other problems such as pruritus, edema and hypogonadism are described more frequently [70–72]. Benzodiazepines, antidepressants, anticonvulsants and muscle relaxants can augment opioid-induced respiratory depression [55].

2.2.2 Trialing

Prior to implantation in non-cancer patients, a trial is recommended to check the analgesic effect or possible side effects of the opioids or other drugs. The trial can be performed with an intrathecal bolus injection or with a continuous intrathecal infusion via a spinal catheter. Several studies have discussed whether to perform a single bolus, double bolus or continuous trialing via an intrathecal catheter [34, 73, 74] but none have yielded clear results. Therefore, the PACC does not give general advice about whether to administer a single shot as a trial or a continuous infusion, instead presenting data from the Medtronic Product Surveillance Registry. Here, 68.4% of patients received a continuous intrathecal infusion, 26.3% received a single intrathecal bolus injection, and 5.3% received a continuous epidural infusion as a trial method. No patient received multiple intrathecal bolus injections [59]. A study on the prognostic value of the infusion test is currently recruiting (Table 2).

When performing a continuous infusion, a catheter is first placed under local anesthesia with the help of fluoroscopy. The usual insertion site is L2–3 or L3–4, but the catheter tip is located in the lower thoracic spine. The exact location of the spinal catheter tip depends on the level of the intended

Table 2 Overview of selected studies on intrathecal ziconotide in cancer and non-cancer pain

Study	*N*	Study type	Follow-up	Outcome
Staats et al. [47]	111 cancer pain	RCT	5 days	53.1% pain reduction with ziconotide vs. 18.1% with placebo
Wallace et al. [48]	264	RCT	6 days	31.2% pain reduction with ziconotide vs. 6.0% with placebo, starting dose 0.4 µg/h, reduced to 0.1 µg/h due to AE
Rauck et al. [49]	220	RCT	3 weeks	Significantly improved pain and other outcome measures, AEs: dizziness, confusion, ataxia, abnormal gait and memory impairment, slow titration was better tolerated
Ellis et al. [51]	155 (cancer and non-cancer pain)	Prospective		36.9% mean decrease in VAS score; 147 patients reported AEs, 39.4% of patients discontinued treatment because of AEs
Raffaeli et al. [52]	104 (cancer and non-cancer pain)	Retrospective	6 months	72 patients reported > 30% pain reduction; 66 patients had at least one side effect
Prusik et al. [99]	15	Retrospective	13 months	8 patients reported > 30% pain reduction, initial dose 1.2 µg/day titration dose 1.1–2.8 µg/day

AE adverse event, *RCT* randomized controlled trial, *VAS* visual analog scale

analgesia so it exerts a predominantly localized effect. IDD therefore cannot be used for widespread or "full-body" pain.

The PACC panel 2017 recommended starting dosage ranges for intrathecal medications [59]. A 50% reduction in pain is considered a prerequisite for pump implantation and successful IDD. Starting doses of 0.1–0.5 mg/day for morphine and 1–2 µg for ziconotide are recommended, with an increase of not more than 1.2 µg per day [59]. Pain relief of > 50% is generally regarded as trial success [58]. However, possible unwanted side effects must also be considered.

2.2.3 Implantation of the Intrathecal Pump/Pump Types

Pumps are usually implanted under general anesthesia. The pump is placed in the abdominal region (alternatively, in the buttocks), and the spinal catheter is tunneled subcutaneously and connected with the pump [40]. There are fixed-rate delivery systems (gas pressure-operated pumps) and systems of various sizes and delivery rates (programmable and battery-driven pumps), e.g., for breakthrough pain or—for baclofen application—for time-dependent changes in spasticity. The medication is intermittently (only programmable pumps) or continuously transported from the drug reservoir into the spinal space. Most new devices are magnetic resonance imaging (MRI) compatible.

The first implantable pumps for intrathecal drug application were gas driven [75]. These pumps comprised a flexible drug reservoir inserted in a propellant chamber filled with an inert gas. Gas pressure slowly pressed the drug out of the drug reservoir through a chip capillary that served as an outlet restrictor. These pumps had prefixed flow rates, for instance, 0.5 or 1 ml. To change the drug dose in these pumps, the pump had to be refilled with a drug solution of a different concentration.

In 1987, the Synchromed pump (Medtronic) was introduced for systemic drug infusion [76] and 1 year later for intrathecal application [77]. Since then, numerous papers have been published on the application of programmable intrathecal pumps. Unlike gas-driven constant flow pumps, the Synchromed pump was propelled by a small battery-driven peristaltic pump. This pump type meant that, for the first time, the drug dose could be changed with a telemetric programming device, obviating the need to refill the pump. As such, circadian dosing rhythms or boluses could also be programmed according to patient need. Further, using a special device, patients were also able to apply drug boluses according to prefixed schemes [78]. The Prometra pump (Flowonix) is also programmable but, unlike the Synchromed pump, is driven by a valve-gated bellow-delivery mechanism [32].

Apart from considerable differences in cost, several arguments can be considered for or against these two pump types. First, the possibility of telemetric changes to the drug dose and the ability to implement individual drug regimens, notwithstanding the risk of programming errors [79], is a strong argument in favor of the programmable pumps. On the other hand, battery depletion means these pumps must be exchanged after 5–10 years, requiring an additional operation. In contrast, constant flow pumps have, at least in theory, an infinite lifetime. A German supplier for constant flow pumps (tricumed Medizintechnik GmbH, Kiel, Germany) states that the durability of the pump is 20 years if 25 punctures per year are performed. Belverud et al. [80] state that non-programmable pumps should be used only when pump replacement is necessary and the patient is on a stable dose for a long period of time.

The current PACC guidelines do not make a clear recommendation on this question, advising only that constant flow pumps are no longer used [55]. Constant flow pumps are no longer available in the USA but remain available and implanted in individual cases in Europe, South America and elsewhere in the world.

2.2.4 Dosing

In intrathecal testing, initial daily drug doses of 0.5–1.0 mg/day are usually applied [59]. Drug doses generally increase slowly within the first 3–5 years and then normally reach a plateau of primarily 3–8 mg/day [65, 81].

Recently, weaning strategies have been proposed to enhance the efficiency of intrathecal morphine application. Prior to first implantation of a pump, patients were completely weaned off oral opioids for 4–6 weeks. Intrathecal opioid therapy was then started with low to very low doses. These studies have also shown favorable results with comparatively low opioid doses [34, 82].

Bolus application has also been discussed and reportedly leads to a wider spread of the agent within the spinal canal [83]. However, to date, no clear benefit from bolus application has been shown.

2.2.5 Follow-up, Programming and Pump Refills

Implanted intrathecal pumps must be regularly refilled transcutaneously through the reservoir fill port according to the daily dose of the drug and the size of the pump. Follow-up support for patients with implanted intrathecal pumps should be carried out by an experienced team. Pocket fills, where the morphine solution is accidentally placed not into the pump but subcutaneously outside it, have been described [84], as have programming errors [79] and sudden motor stalls [85] or leakages of the silicone septum of the pump [86]. As these complications can have devastating consequences, clinical experience with intrathecal drug devices is warranted, and the PACC has also proposed a two-person validation model [55].

2.3 Complications

The following possible complications have been described: mechanical complications, such as catheter displacements or catheter pump disconnection requiring a surgical procedure; substance-induced and pharmacological complications, such as overdose of morphine with respiratory depression, urinary retention and constipation; surgical complications, such as meningitis infection, cerebrospinal fluid leakage and seroma formation; patient-specific complications such as hormonal suppression with sexual dysfunction; and refill complications such as reprogramming errors and refilling with the wrong medication. Further, catheter tip granulomas must be considered, especially in high-dose and low-flow intrathecal application of opioids such as morphine or hydromorphine [40]. To assure a more favorable risk-to-benefit ratio, the PACC summarizes consensus guidance on best practices of trialing for IDD system implants [55].

2.4 Outcomes

A recent review by Deer et al. [37] listed several retrospective single-arm prospective studies about intrathecal morphine applications in cancer and non-cancer pain [28, 32, 34, 87–97]. These studies show results ranging between 100% good pain relief [87] and 50% of patients experiencing > 25% pain reduction [89]. Favorable results were also reported in several studies not included in this analysis [34, 65, 69]. Interestingly, one randomized controlled double-blind study reported significant increases in pain intensity when the intrathecal morphine dose was reduced by 20% [96].

Three RCTs [47–49] and several prospective open-label [50, 51] and retrospective studies [52, 98, 99] reported significant improvements with intrathecal ziconotide compared with placebo. Raffaeli et al. [98] reported a pain reduction of > 50% in 54% of treated patients, and Prusik et al. [99] reported a minimum 30% improvement in pain intensity, activities of daily living or both in 53% of treated patients.

3 Indications for Intrathecal Opioids in Non-cancer-Related Pain in the Elderly

Generally, pain therapy should always strive to use the least-invasive application route, regardless of patient age. Therefore, the decision to use an invasive drug-delivery system must be justified by substantial advantages for the elderly patient. Intense pain can be reduced using opioids, regardless of the patient's age [21]; however, opioids need careful titration to reduce possible problems with balance and motor function, particularly in the elderly [100]. We believe these problems may be reduced by significant reduction of the intrathecal opioid dose as proposed by recent studies on low-dose intrathecal morphine [34, 82].

Scientific knowledge concerning possible age-related changes to the central nervous system is limited. Because the brain shrinks with age, the cranial cerebrovascular fluid volume increases and flow distribution changes [101]. A decrease in neurotransmitters such as GABA in the occipital cortex has also been shown, which plays an important role in pain perception [102]. The vascularized choroid plexus is part of the continuous turnover of cerebrospinal fluid. A decline of both has been shown in animal studies [103]. Whether these changes are clinically relevant to opioid treatment of the elderly remains unclear.

Escalating doses have been reported in cancer and non-cancer patients with oral and intrathecal opioids [18, 19, 22, 104]. Buntin-Mushock et al. [21] conducted a retrospective chart study of 206 patients and age-dependent behavior with increasing long-acting opioids over time. Patients aged ≤ 50 and ≥ 60 years differed in their dose escalation and pain level: dose escalation was higher in younger than in older patients, and the older patients showed a decrease in the visual analog scale despite a lower escalation of opioid consumption. The investigators concluded that older patients may have a reduced rate of tolerance development [21]. Vigano et al. [105] noted that elderly patients with cancer required smaller amounts of opioids than did younger adults despite similar pain intensity. Patients with cancer aged ˂65, 65–74, and ≥ 75 years required lower doses than younger patients but showed no difference in opioid effects during opioid titration [106].

One RCT has investigated IDD in cancer pain but, to our knowledge, no studies have examined the difference in pain control between oral, transdermal and intrathecal opioid delivery in non-cancer pain [91]. Further, no studies have investigated the possible reduction of risk for cognitive deterioration.

Only few retrospective studies concern a possible age-dependent influence on the effect of IDD in chronic non-cancer pain. Hayek et al. [63] examined 135 patients with chronic non-cancer pain with an intrathecal pump delivery of opioids and found a similar pain relief 12 months post-implant in the groups aged ≤ 50 and > 50 years. During the same 12-month follow-up period, the older patient population reduced their oral opioid consumption significantly compared with the younger population. Hayek et al. [63] discussed an age-dependent change in nociception in the elderly, differences in behavioral and psychological determinants in pain reporting and opioid-induced hyperalgesia as possible factors for the different opioid consumption. Raffaeli et al. [107] reported that patients aged > 65 years showed a 60% reduction in pain scores, which was further enhanced at 48-month follow-up, with the mean visual analogue scale values decreasing from 8.09 prior to

implantation to 1.68 after implantation. In total, 50% of patients reported side effects, most frequently constipation, drowsiness, nausea and urinary retention [107]. A re-analysis of a study of the long-term effects of IDD [65] showed no significant differences between patients aged < 65 years and elderly patients in terms of either pain scores or unwanted side effects (Wolter and Kleinmann, unpublished data).

4 Conclusion

Opioids are effective in cancer and non-cancer pain and in intrathecal therapy [63]. Applied orally or transdermally, opioids can incur substance-induced side effects, especially in the elderly. Age-dependent changes in the organism and in nociception may influence the effectiveness of pain therapy and its potential complications. The narrow therapeutic window of oral and transdermal opioids could be a case for intrathecal delivery.

The major advantage of intrathecal delivery of opioids is the reduction of side effects on the central nervous system because of the reduced oral drug dose. Careful patient selection and sustainable patient care are essential fundamental factors for successful IDD. Moreover, before pump implantation is considered, it must be recognized that the procedure will require the elderly patient to undergo an invasive procedure and need regular pump fillings.

If intrathecal pain therapy is successful, polypharmacy may be reduced or terminated. In individual cases, age-dependent central nervous system changes may also play a role in decisions for or against IDD. However, prospective and controlled studies of oral and transdermal opioids versus intrathecal delivery and their associated side effects are lacking.

To date, data that exhaustively discuss all arguments in favor of and against IDD in the elderly patient are scarce. More prospective and, ideally, randomized studies in pain therapy in the elderly are warranted, particularly regarding IDD, and more clinical research is required in this field.

Compliance with Ethical Standards

Conflict of interest BK and TW have no conflicts of interest that might be relevant to the contents of this manuscript.

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