Testphase – Katheterverfahren versus single-shot: Pro Katheter

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Conflict of Interest:

Vortragshonorare und Advisory Boards
Wissenschaftsunterstützungen

Grünenthal, Gerot Lannacher, Gebro-Pharma, CSC-Pharma, Böhringer Ingelheim, Sintetico, Reckitt Benkiser, Fresenius,Bionorica,Trigal

Table 6. Disease Indications for Intrathecal Drug Delivery.

- Axial neck or back pain; not a surgical candidate
  - Multiple compression fractures
  - Discogenic pain
  - Spinal stenosis
  - Diffuse multiple-level spondylosis
- Failed back surgery syndrome
- Abdominal/pelvic pain
  - Visceral
  - Somatic
- Extremity pain
  - Radicular pain
  - Joint pain
- Complex regional pain syndrome (CRPS)
- Trunk pain
  - Postherpetic neuralgia
  - Post-thoracotomy syndromes
- Cancer pain, direct invasion and chemotherapy related
- Analgesic efficacy with systemic opioid delivery complicated by intolerable side effects

Persistent spinal pain syndrome (failed back surgery syndrome)

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

Schmerzbehandlungsplan

- Übungsprogramme
- Biofeedback
- Entspannungsverfahren
- Nicht-Opioid-Analgetika
- Co-Analgetika
- Physiotherapie
- Rehabilitationstraining
- Kognitive Verhaltenstherapie
- somatische, sympathische Nervenblockaden
- Orale Opioide/subkutan
- Rückenmarksnahe Stimulation
- intraspinale Infusionsanalgesie
- neurodestruktive Verfahren

RECOMMENDATIONS OF THE PACC TO REDUCE MORBIDITY AND MORTALITY

General Recommendations

1. The use of IDDS to treat chronic pain should be part of a treatment algorithm that involves the failure of more conservative attempts at treatment. IDDS should be considered prior to other options when unacceptable side-effects or lack of efficacy is established.

2. The use of IDDS should be based on an analysis of safety, efficacy, a goal of economic neutrality and appropriateness for the individual patient. These factors have been described as the S.A.F.E. principles.(safety,appropriateness,fiscal neutrality,efficacy)

3. Spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), and hybrids of both SCS and PNS should be considered inappropriate candidates prior to considering an IDDS.

4. Psychological evaluation and stability should be confirmed prior to proceeding with an IDDS in noncancer patients.

Portenoy RK, Hassenbusch SJ. Polyanalgesic Consensus Conference 2000. J Pain Symptom Manage 2000;20:S3; Krames E, Poree L, Deer T, Levy R. Implementing the SAFE principles for the development of pain medicine therapeutic algorithms that include neuromodulation techniques. Neuromodulation 2009;12:104–113;Deer TR.A critical time for practice change in the treatment continuum:we need to reconsider the role of pumps in the patient care algorithm. Pain Med 2010;11:987– 989; Deer TR, Smith HS, Cousins M et al. Consensus guidelines for the selection and implantation of patients with non-cancer pain for intrathecal drug delivery. Pain Physician 2010; 13:E175–E213.

5. In patients with cancer and those at the end of life, the use of IDDS should be combined with spiritual, psychological, and social support. While this practice may not change the measurable mortality and morbidity, the panel feels that this is an important component of the patient care team.

6. Prior to implanting an IDDS, the patient should undergo a trial of the planned drug with an emphasis on evaluating side-effects and efficacy. **In some cases such as advanced cancer pain, the panel agrees that the need for a trial may be negated based on a risk to benefit ratio.** In those cases, a careful analysis of life expectancy should be performed with therapy limited to those who do not have impending death in the immediate postoperative period.

7. Oral or transdermal opioids should be reduced as much as possible either prior to the implant or in the first 12 weeks of surgery. **IDDS is a different route of delivering opioid, but the reduction of additional routes may improve outcome.**

Deer TR, Smith HS, Burton AWet al. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. Pain Physicain 2011;14:E283–E312; Burton AW, Deer TR,Wallace MS, Rauck RL, Grigsby E. Considerations and methodology for trialing ziconotide. Pain Physician 2010;13:23–33.

8. The use of CNS depressants, including opioids, benzodiazepines, barbiturates, antipsychotic drugs, and other applicable drug classes, should be assessed and doses reduced or discontinued if possible prior to implant. The primary care doctor and those involved in the patient care team should notify the doctor managing the IDDS when adding drugs that may impact brain stem respiratory centers.

9. Alcoholism and other illicit drug habits should be evaluated and addressed prior to implant. The addition of any CNS suppressant can worsen outcomes and those that are illicit may greatly increase risks.

10. Avoid rapid IDDS drug escalation and doses that exceed the PACC guidelines.

11. When therapy is discontinued because of catheter disruption, pump failure, or elective stoppage of the pump, the therapy must be reinitiated at a starting dose consistent with that of an opioid-naive patient. Starting at a dose higher than those recommended can potentially lead to death.

Deer TR, Prager J , Levy R, et all; Polyanalgesic Consensus Conference 2012: Recommendations to Reduce Morbidity and Mortality in Intrathecal Drug Delivery in the Treatment of Chronic Pain; Neuromodulation 2012; Centers for Disease Control. Policy impact: prescription painkiller overdoses. JAMA 2011;305:1315–1321;Deer T, Levy RM, Prager J et al. Polyanalgesic Consensus Conference. 2012: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. (in press)

12. The PACC recommends starting at the lowest reasonable dose of opioid when initiating IT drug therapy, or after revising a pump following an interruption in drug delivery.

13. In the elderly, the use of IDDS is often very helpful since they may have difficulty tolerating oral or transdermal medications. **They may also exhibit extreme sensitivity to opioid dosing, and a lower dose should be initiated in the elderly or chronically ill.**

Deer TR, Prager J , Levy R, et all; Polyanalgesic Consensus Conference 2012: Recommendations to Reduce Morbidity and Mortality in Intrathecal Drug Delivery in the Treatment of Chronic Pain; Neuromodulation 2012; Centers for Disease Control. Policy impact: prescription painkiller overdoses. JAMA 2011;305:1315–1321;Deer T, Levy RM, Prager J et al. Polyanalgesic Consensus Conference. 2012: Recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. (in press)

Pain care algorithm for non-cancer pain

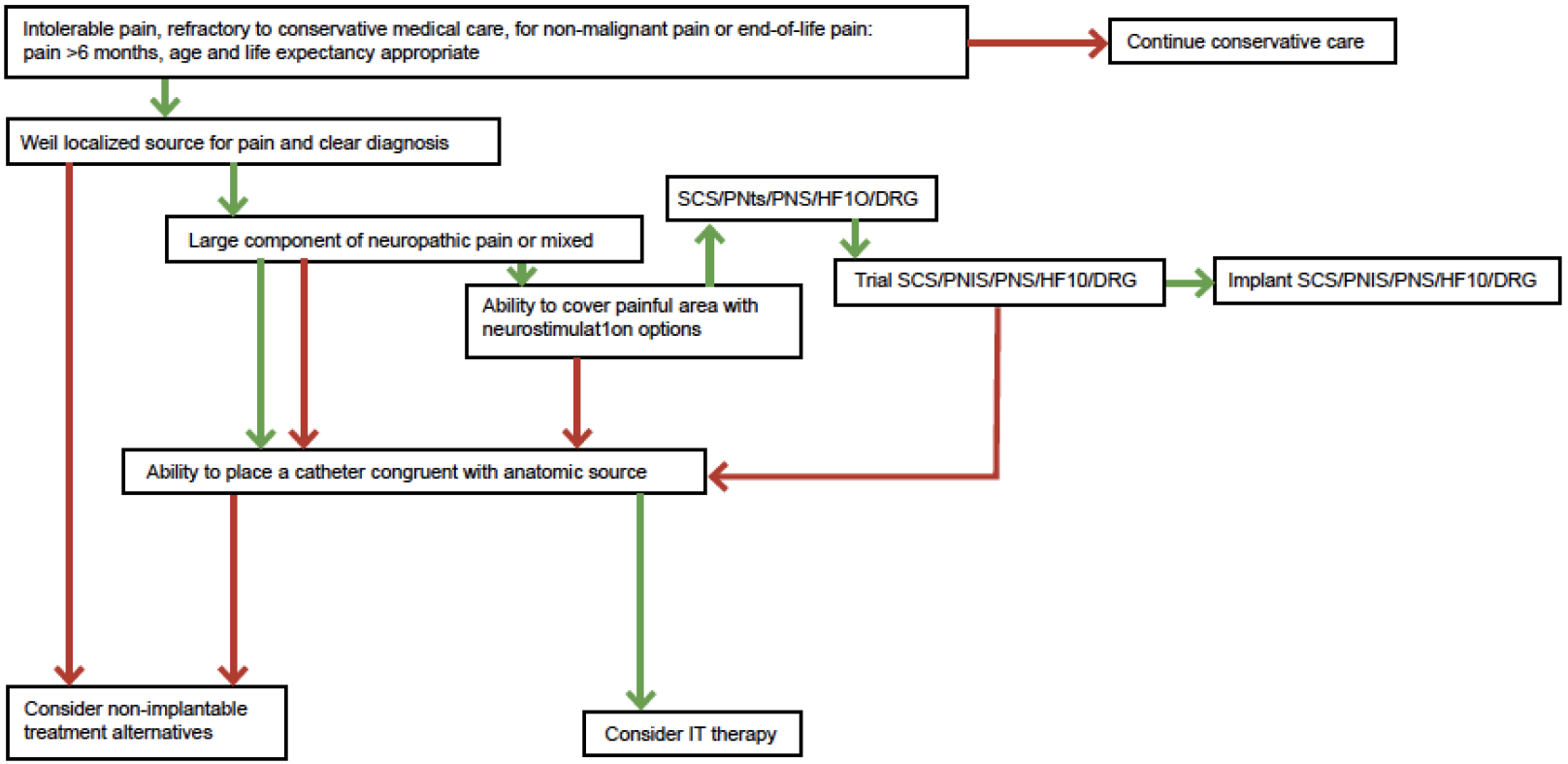

Figure 2. Algorithm for placement within the pain care algorithm for noncancer or non-end-of-life pain. DRG, dorsal root ganglion; HF10, high frequency stimulation; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation. Green arrows indicate affirmation or positive response; red arrows signify negative response.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

Pain care algorithm for cancer-related pain

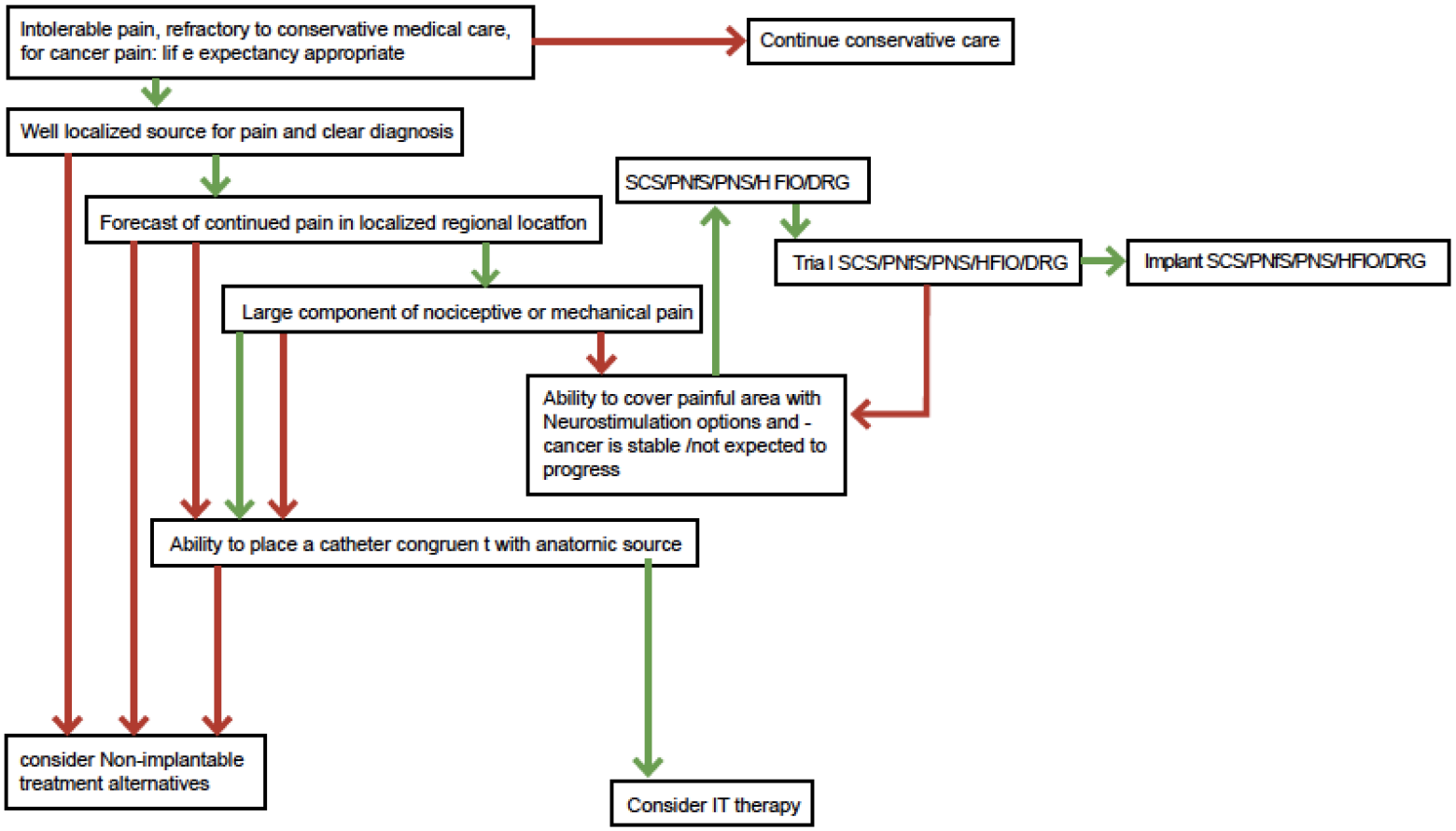

Figure 3. Pain care algorithm for cancer-related pain. DRG, dorsal root ganglion; HF10, high frequency stimulation; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation. Green arrows indicate affirmation or positive response; red arrows signify negative response.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

Schmerzpumpenplan

- **Neurologische, neurophysiologische, neurochirurgische und radiologische Abklärung**
- **Psychiatrische, psychologische und soziökonomische Evaluierung**
- **Multiinterdisziplinäre Entscheidung für spinale Testphase**
- **Durchführung einer einfach blinden Testphase (Singleshot bzw. kontinuierlich mit intrathekalen Katheter und Port). In Ausnahmefällen placebokontrollierte Testphase.**

Prager JP. Spine 2002; 27(22);2593-2605

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force, Ref [7]).

Evidence level	Study type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well designed-controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences
III	Clinical experience-based opinions, descriptive studies, clinical observations or reports of expert committees.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, International Neuromodulation Society, 2017, 20:155-176.

Table 2. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force, Ref [7]).

Degree of recommendation	Meaning
A	Highly recommended (good evidence that the measure is effective and benefits outweigh the harms)
B	Recommended (at least, moderate evidence that the measure is effective and benefits exceed harms)
C	Neither recommend nor advise (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Not advisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low quality, or contradictory evidence; the balance between benefit and harms cannot be determined.

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Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, International Neuromodulation Society, 2017, 20:155-176.

Table 3. Strength of Consensus.

Strength of consensus	Definition*
Strong	>80% consensus
Moderate	50–79% consensus
Weak	<50% consensus

*Quorum defined as 80% of participants available for vote.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, International Neuromodulation Society, 2017, 20:155-176.

PACC - Trailing

Table 4. Does Trialing Predict Therapy Outcome? Recommendations by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence level	Recommendation strength	Consensus level
A trial should be considered before initiating IT drug delivery for noncancer pain.	II-3	B	moderate
A trial is not a necessity before initiating IT drug delivery for cancer pain.	III	I	moderate
If a trial is performed, delivery of the medication within the IT space is an acceptable method.	II	C	strong
IT trials should be monitored in a safe setting, with due vigilance, appropriate monitoring of the patient, and appreciation for patient comorbidities.	II-3	B	strong
IT ziconotide trials should be monitored in a safe setting, with due vigilance, and appropriate monitoring of the patient.	II-3	B	strong

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Trailing of Intrathecal Drug Delivery Infusion Therapy, International Neuromodulation Society, 2017, 20:133-154.

Table 10. Possible Outcomes of Bolus IT Trials.

Outcome	Consideration
Relief without side effects	Successful trial, medication and dose considered for chronic delivery
Relief with side effects	May be appropriate IT medication; consider reduction in medication dose for retrial or medication switch
No relief, side effects noted	Medication switch recommended for retrial
No relief, no side effects	Consider retrial with higher dose or medication switch

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Trailing of Intrathecal Drug Delivery Infusion Therapy, International Neuromodulation Society, 2017, 20:133-154.

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Non-cancer related pain with localized nociceptive and neuropathic pain

Table 16. Noncancer-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide		Morphine	
Line 1B	Fentanyl		Fentanyl + bupivacaine	
Line 2	Fentanyl + clonidine	Hydromorphone or morphine + bupivacaine	Fentanyl + bupivacaine + clonidine	Bupivacaine
Line 3	Fentanyl + ziconotide + bupivacaine	Morphine or hydromorphone + clonidine	Ziconotide + clonidine or bupivacaine or both	Bupivacaine + clonidine
Line 4	Sufentanil + bupivacaine or clonidine	Baclofen	Bupivacaine + clonidine + ziconotide	
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

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Non-cancer pain with diffuse nociceptive and neuropathic pain

Table 18. Noncancer-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

Line 1A	Morphine		Ziconotide*	
Line 1B	Hydromorphone		Morphine or hydromorphone + bupivacaine	
Line 3	Hydromorphone or morphine + clonidine		Fentanyl + bupivacaine	Ziconotide + morphine or hydromorphone
Line 4	Hydromorphone or morphine + bupivacaine + clonidine	Fentanyl + ziconotide	Sufentanil + bupivacaine or clonidine	Ziconotide + clonidine or bupivacaine or both
Line 5	Fentanyl or sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	Baclofen
Line 6	Opioid + ziconotide + bupivacaine or clonidine			

*Ziconotide should be first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of history of psychosis.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

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Cancer Pain with localized nociceptive and neuropathic pain

Table 12. Cancer or Other Terminal Condition-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide			Morphine		
Line 1B	Fentanyl			Morphine or fentanyl + bupivacaine		
Line 2	Hydromorphone	Hydromorphone + bupivacaine		Hydromorphone or fentanyl or morphine + clonidine	Morphine or hydromorphone or fentanyl + ziconotide	
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Sufentanil + bupivacaine	Baclofen	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine					
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, octreotide.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

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Cancer Pain with diffuse nociceptive and neuropathic pain

Table 14. Cancer or Other Terminal Condition-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide			Morphine		
Line 1B	Hydromorphone			Morphine or hydromorphone + bupivacaine		
Line 2	Hydromorphone or morphine + clonidine			Morphine or hydromorphone + ziconotide		
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Baclofen	Sufentanil + bupivacaine	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + bupivacaine + ziconotide		Sufentanil + clonidine + ziconotide	
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, octreotide.

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

Table 4. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Therapy (3).

Statement	Evidence level	Recommendation grade	Consensus strength
Intrathecal therapy should be utilized for active cancer-related pain.	I for opioids; I for ziconotide	A	Strong
Intrathecal therapy should be utilized for noncancer-related pain.	III-2 for opioids; II-3 for opioids in combination with bupivacaine; I for ziconotide	B	Strong

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, International Neuromodulation Society, 2017, 20:155-176.

Table 5. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations for Intrathecal Opioid Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Intrathecal opioid delivery is a relatively safe and effective method for chronic infusion to treat cancer and noncancer-related pain.	II-2	A	Strong
Respiratory depression can occur with intrathecal opioid administration, and careful dosing is critical to avoid this complication.	II-3	B	Strong
Concurrent use of sedative medications in patients receiving opioids should be minimized or avoided.	II-2	A	Strong
Single-shot trialing with intrathecal opioids is a safe strategy, with an observation period of at least six hours, in an outpatient or inpatient site of service. Outpatients should have continued observation after discharge with a responsible adult.	II-3	B	Moderate
Endocrinopathic side effects are a consequence of intrathecal opioids, and preoperative surveillance and monitoring is recommended.	II-3	A	Strong
Lower extremity edema can occur by an unknown mechanism and can be mitigated by transition to a more lipophilic opioid.	III	C	Strong
Urinary retention is a complication that may be mitigated by the administration of parasympathomimetic medications.	III	C	Moderate
Nausea, vomiting, and pruritus are consequences of intrathecal delivery of opioids and, although they typically resolve with time, should be considered when employing opioids for chronic infusion.	III	C	Moderate
Consideration of patient candidacy for intrathecal opioid therapy is crucial, and evaluation should consider the pain generator(s), patient age, location and type of pain, previous opioid exposure, and patient comorbidities (3).	II-2	B	Strong

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, International Neuromodulation Society, 2017, 20:155-176.

Table 25. Recommendations Regarding Intrathecal Baclofen Treatment by the PACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus strength
Baclofen should be considered an intrathecal medication for use to treat spasticity.	II-2	A	Strong
Baclofen can be used as an adjuvant to treat pain.	II-3	B	Moderate
Care regarding mitigating withdrawal from baclofen is suggested.	II-2	A	Strong
Ancillary resources regarding physical therapy to aid in titration and assessment when employing baclofen is recommended.	III	C	Moderate
Using bolus or flex dosing strategies to improve spasticity demonstrates promise.	II-3	B	Moderate

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practice and Guidelines, International Neuromodulation Society, 2017, 20:96-132

Table 4. Does Trialing Predict Therapy Outcome? Recommendations by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence level	Recommendation strength	Consensus level
A trial should be considered before initiating IT drug delivery for noncancer pain.	II-3	B	moderate
A trial is not a necessity before initiating IT drug delivery for cancer pain.	III	I	moderate
If a trial is performed, delivery of the medication within the IT space is an acceptable method.	II	C	strong
IT trials should be monitored in a safe setting, with due vigilance, appropriate monitoring of the patient, and appreciation for patient comorbidities.	II-3	B	strong
IT ziconotide trials should be monitored in a safe setting, with due vigilance, and appropriate monitoring of the patient.	II-3	B	strong

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Trailing of Intrathecal Drug Delivery Infusion Therapy, International Neuromodulation Society, 2017, 20:133-154.

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Recommendations for trailing Ziconotide

Table 8. Recommendations for Trialing Ziconotide by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence levels	Recommendation strength	Consensus level
A trial should be administered before initiating ziconotide.	II-2 Ver Donck II-3 others	B	strong
A bolus ziconotide trial is preferred over continuous trial.	II-3	B	strong
Patients trialed with IT ziconotide should be monitored in a clinical setting for at least 6 hours, in the absence of any neurologic findings.	II-3	B	strong
Ziconotide should be considered "first in patient" for both neuropathic and nociceptive pain.	III	B	moderate

Deer et al., The Polyanalgesic Consensus Conference (PACC): Recommendations for Trailing of Intrathecal Drug Delivery Infusion Therapy, International Neuromodulation Society, 2017, 20:133-154.

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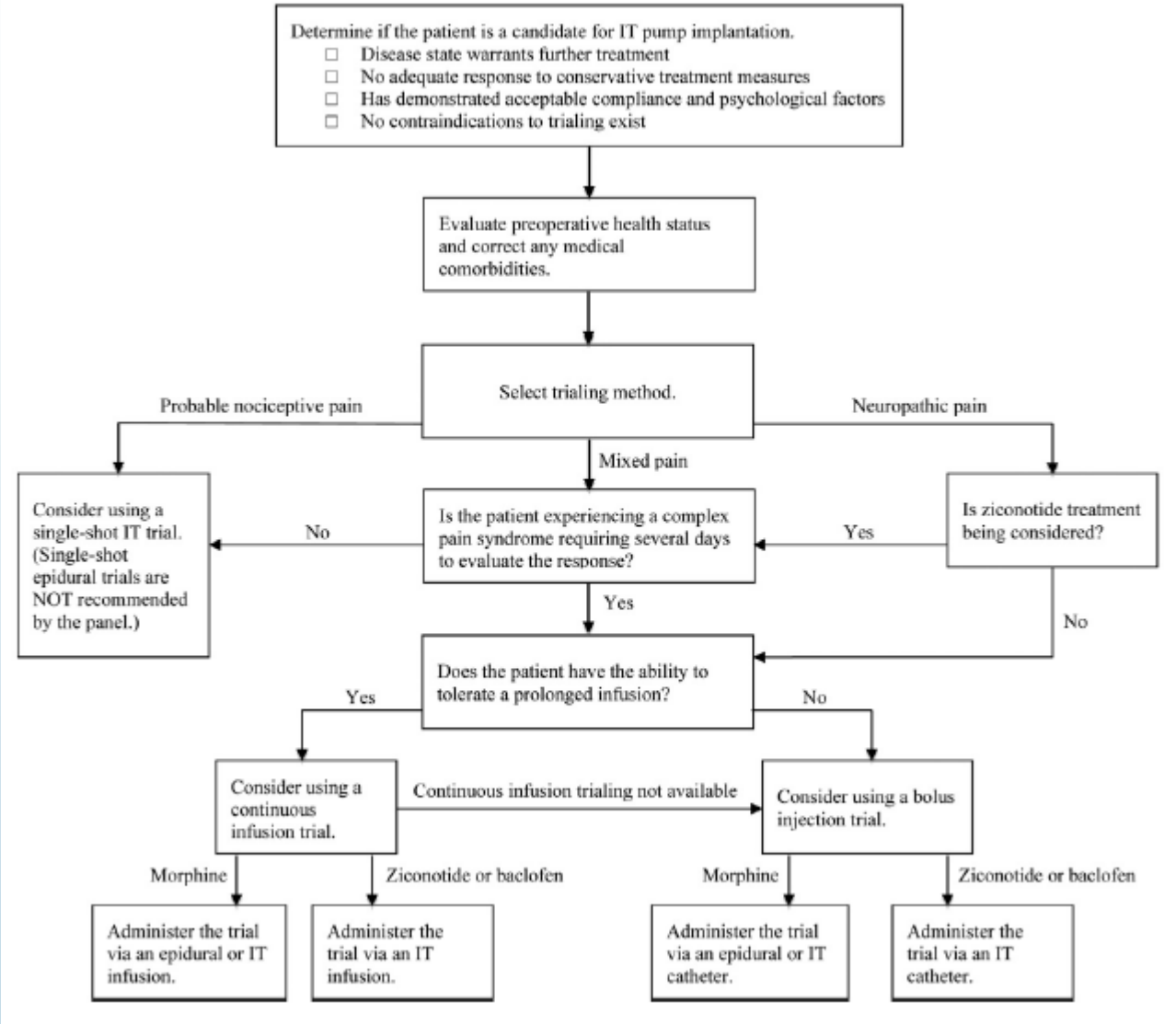
Trialing algorithm. IT, intrathecal



Timothy R. Deer, Joshua Prager et al; Polyanalgesic Consensus Conference—2012: Recommendations on Trialing for Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel; Neuromodulation 2012

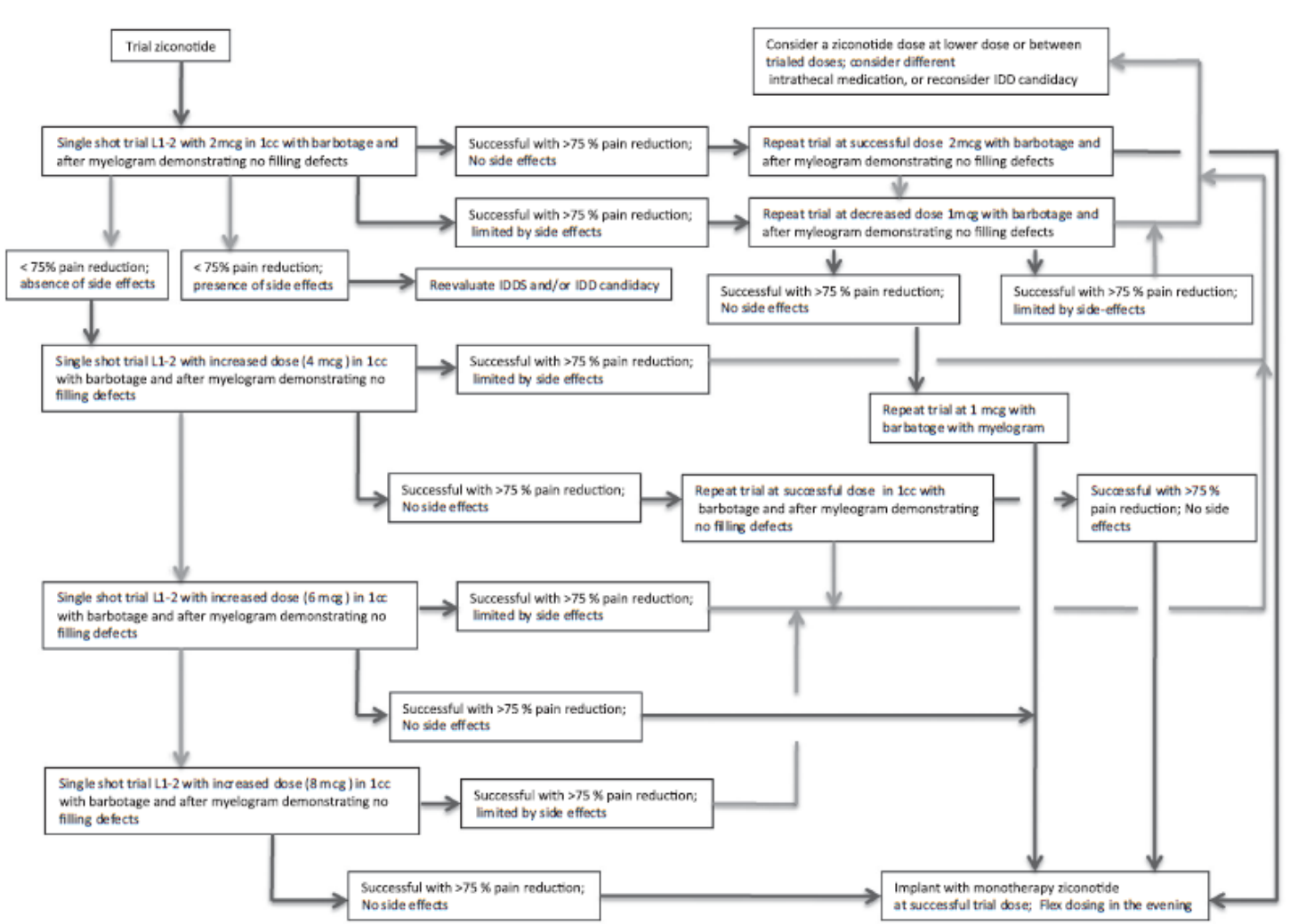


Figure 1. Flow diagram for methodology of trialing ziconotide and subsequent long-term dosing. Dark grey arrows: desired outcome achieved. Light grey arrows signify failure.

Pope Je, Deer TR. Intrathecal Pharmacology Update: Novel Dosing Strategy for Intrathecal Monotherapy Ziconotide on Efficacy and Sustainability. Neuromodulation 2015 Jul;18(5):414-20.

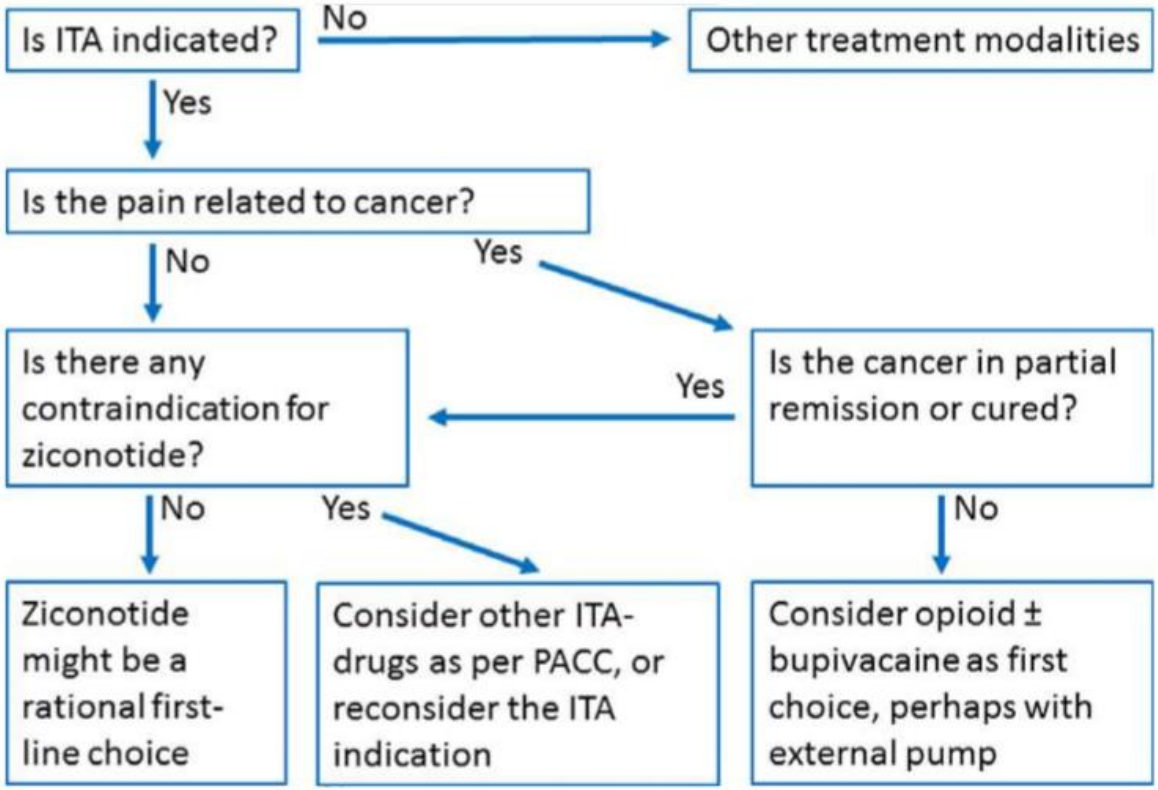


Figure 4 Overall decision-making algorithm focusing on ziconotide. ITA, intrathecal analgesia; PACC, polyanalgesic consensus conference (Deer et al., 2017b).

Bäckryd E. et al.; Do the potential benefits outweigh the risks? An update on the use of ziconotide in clinical practice; European Journal of Pain; 2018.

Dosing and Titration Scheme for IT Ziconotide

Table 7. Dosing and titration schemes for IT ziconotide

Dosing/Titration Scheme	Summary
Continuous dosing per prescribing information [12] FDA	• Starting dose: ≤2.4 mcg/d (0.1 mcg/h) • Titration schedule: dose increase of ≤2.4 mcg/d every 2 to 4 days • Maximum dose: 19.2 mcg/d • Doses should be adjusted based on severity of pain, response to therapy, and occurrence of side effects
Low dose/slow titration [53,57,78]	• Starting dose: ≤0.5 mcg/d • Titration schedule: ≤0.5 mcg/d every week • Doses should be adjusted to achieve a balance of effective analgesia and AEs • Doses may also be adjusted by altering either the ziconotide concentration in the pump reservoir or the pump's flow rate; however, changes to the flow rate may affect dosing of concomitant IT agents
Night time bolus (flex) dosing [55]	• Optional background continuous infusion of ziconotide • Pump delivers daily bolus dose of IT ziconotide, as programmed by the clinician • Starting dose: 1–3 mcg/d, based on trialing • Titration schedule: 0.1 mcg/d • Doses should be adjusted to optimize efficacy and minimize AEs • May be used as monotherapy or in combination with other IT medications
Patient-controlled analgesia [55]	• Background continuous infusion of IT ziconotide • Patients administer additional doses via PTM; bolus dose, dosing interval, and maximum number programmed by clinician • Each bolus dose is ~10% of continuous dose (reported dose range for bolus = 0.15–0.25 mcg) • Doses should be adjusted to optimize efficacy and minimize AEs • May be used as monotherapy or in combination with other IT medications

Portions of this table were adapted with permission from: McDowell GC, Pope JE. Intrathecal ziconotide: Dosing and administration strategies in patients with refractory chronic pain. Neuromodulation 2016;19(5):522–32; via a Creative Commons Attribution-NonCommercial-NoDerivs License [55].

AE = adverse event; IT = intrathecal; PTM = personal therapy manager.

Deer T. et al.; American Academy of Pain Medicine: Intrathecal Therapy for Chronic Pain: A Review of Morphine and Ziconotide as Firstline Options. Pain Medicine, 20(4), 2019, 784-798.

Parameter	FDA SmPC	EMA SmPC	Other recommendations
Maximum daily dose	19.2 µg/day (*0.8* µg/h)	21.6 µg/day	19.2 µg/day (*0.8* µg/h)[a]
Starting dose	≤2.4 µg/day (*0.1* µg/h)	2.4 µg/day	0.5–1.2 µg/day (*0.02–0.05* µg/h)[a]; initiation with ≤ 0.5 µg/day (*0.02* µg/h) may be preferred[b]
Dose increments	≤2.4 µg/day (*0.1* µg/h)	≤2.4 µg/day	≤0.5 µg/day (≤*0.02* µg/h) on a no more than weekly basis[b], according to individual patient's pain reduction and tolerability (Fisher; Prager[b])
Minimum interval between dose increases	≤2–3/week (*56–84* h)	24 hr	Titration slow and not more than once weekly[b]
Recommended interval (safety)	≤2.4 µg/day and ≤2–3/week	≥48 hr	Not more than once weekly[b]
Minimum concentration, external pump reservoir	5 µg/ml; change dose rate by adjusting flow rate or solution concentration	5 µg/ml	–
Minimum concentration, internal pump reservoir	25 µg/ml	25 µg/ml	–

Note: **Sources:** (FDA SmPC, 2019); (EMA SmPC, 2019).

[a](Deer, Hayek, Pope, et al., 2017; Deer, Pope, Hayek, Bux, et al., 2017; Deer, Pope, Hayek, Lamer, Veizi, et al., 2017).

[b](Fisher et al., 2005; McDowell & Pope, 2016; Prager et al., 2014).

Matis G. et al.; Intrathecal pain management with ziconotide: Time for consensus?. Brain and Behavior. 2021;11.

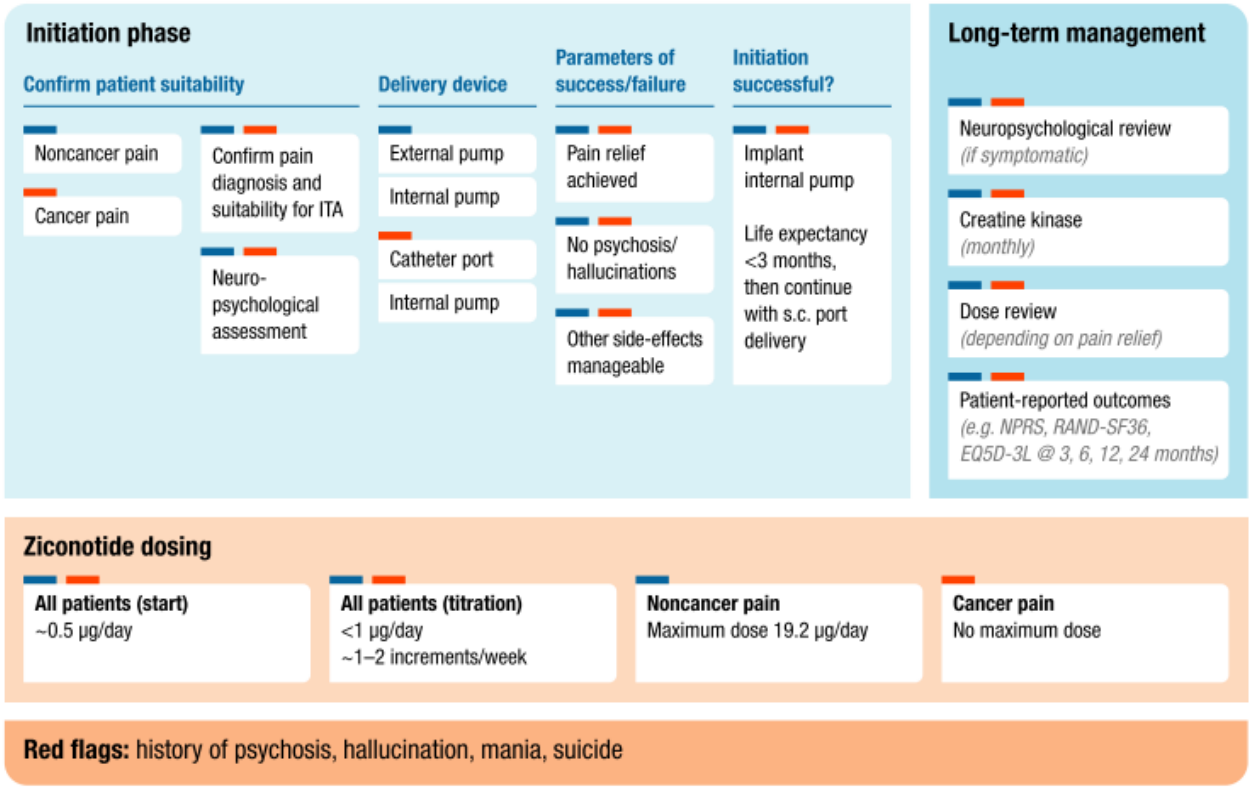


FIGURE 3 Infographic summarizing the key requirements for consideration in of any European Consensus Statement for initiation and long-term management phases of ziconotide intrathecal analgesia (continuous infusion) (ITA). s.c., spinal catheter; NPRS, numeric pain rating scale; RAND-SF36, Research and Development Corporation short-form 36; EQ5D-3L, EuroQol five-dimension three-level

Matis G. et al.; Intrathecal pain management with ziconotide: Time for consensus?. Brain and Behavior. 2021;11.

Die häufigsten aufgetretenen Nebenwirkungen während der Behandlungsdauer (Inzidenz mehr als 10% in jeder Behandlungsgruppe)

Nebenwirkung	Patienten in % Ziconitid (n = 112)	Patienten in % Placebo (n = 108)
Alle Nebenwirkungen	104 (92,9)	89 (82,4)
Schwindel	53 (47,3)	14 (13,0)
Übelkeit	46 (41,1)	33 (30,6)
Körperliche Schwäche	25 (22,3)	13 (12,0)
Schläfrigkeit	25 (22,3)	16 (14,8)
Durchfall	21 (18,8)	18 (16,7)
Verwirrtheit	20 (17,9)	5 (4,6)
Ataxie	18 (16,1)	2 (1,9)
Kopfschmerzen	17 (15,2)	13 (12,0)
Erbrechen	17 (15,2)	14 (13,0)
Abnormer Gang	17 (15,2)	2 (1,9)
Beeinträchtigung der Denkleistung	13 (11,6)	1 (0,9)
Schmerzen	12 (10,7)	8 (7,4)
CK Anstieg	12 (10,7)	4 (3,7)
Juckreiz	9 (8,0)	11 (10,2)
Schlaflosigkeit	7 (6,3)	13 (12,0)

Zeit des Auftretens der ersten Nebenwirkungen (nur Ziconotid – behandelte Patienten)

Nebenwirkung	Inzidenz (%)	Tagesmittelwert	Durchschnittsdosis/h
Abnormer Gang (inkl. Ataxie)	34 (30,4)	4,5 (0-24)	0,20 (0,1-4,0)
Abnormes Sehen (inkl. Sehschwäche)	11 (9,8)	8,0 (0-30)	0,20 (0,1-0,6)
Aphasie bzw. Sprachstörung	19 (17,0)	16,0 (4-24)	0,30 (0,1-0,6)
Körperliche Schwäche (inkl. Myasthenie)	27 (24,1)	3,0 (0-30)	0,15 (0,1-0,6)
Verwirrtheit	20 (17,9)	9,5 (0-24)	0,28 (0,1-0,6)
Schwindel	53 (47,3)	3,0 (0-24)	0,15 (0,1-0,6)
Kognitive Beeinträchtigung oder Amnesie	16 (14,3)	7,5 (2-29)	0,16 (0,1-0,6)
Übelkeit (inkl. Erbrechen)	53 (47,3)	4,0 (0,32)	0,13 (0,1-0,4)
Nystagmus	9 (8,0)	8,0 (4-16)	0,16 (0,1-0,7)
Somnolenz	25 (22,3)	4,0 (0-24)	0,11 (0,1-0,5)
Abnormes Denken (inkl. Denkschwierigkeiten)	8 (7,1)	4,0 (0-18)	0,12 (0,1-0,5)
Harnretention	10 (8,9)	7,5 (1-24)	0,15 (0,0-0,6)

Rauck RL et al: A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain; J Pain Symptom Manage, 2006; 31(5): 393-406

Table 5. Common* AEs Associated with IT Ziconotide Therapy

Ziconotide[23–25]	Ziconotide[23–25]
• Abnormal gait	• Headache
• Asthenia	• Nausea
• Ataxia	• Nystagmus
• Confusion	• Pain
• Constipation	• Postural hypotension
• Diarrhea	• Somnolence
• Dizziness	• Urinary retention
• Fever	• Vomiting

* Occuring in ≥15% of patients in any study.
AEs, adverse events; IT, intrathecal.

Table 6. Common* AEs Associated with IT Morphine Therapy

Morphine[59]	Morphine[59]
• Constipation	• Insomnia
• Depression	• Loss of appetite
• Disturbance of libido	• Myoclonic jerk/spasm
• Disturbance of micturition	• Nausea
• Dizziness	• Nightmare
• Dry mouth	• Provocation of asthma
• Edema	• Pruritus
• Fatigue	• Sweating
• Hallucinations	

* Occuring in ≥15% of patients.
AEs, adverse events; IT, intrathecal.

Placebo -Response

Rauck R.L., Wallace M. S., Burton A. W., Kapural L., North J. M. Intrathecal Ziconotide for Neuropathic Pain: A Review Pain Practice, Volume 9, Issue 5, 2009 327-337

Methods: Literature search through EMBASE, Medline, Cochrane databases, and systematic reviews as well as peer-reviewed non-indexed journals from 1980 to December 2010. Studies are assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies and the Cochrane Musculoskeletal Review Group criteria for randomized trials. **The level of evidence was determined using 5 levels of evidence, ranging from Level I to III with 3 subcategories in Level II, based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).**

Outcome Measures: The primary outcome measure for chronic non-cancer is pain relief (short-term relief ≤ one-year and long-term > one-year), whereas it is 3 months for cancer. Secondary outcome measures of improvement in functional status, psychological status, return to work, and reduction in opioid intake.

Hayek S.M.; Intrathecal Therapy for Cancer and Non-Cancer Pain. Pain Physician 2011; 14:219-248.

Results: The level of evidence for this systematic review of non-cancer pain studies meeting the inclusion criteria of continuous use of an intrathecal drug delivery system (IDDS) for at least 12 months duration with at least 25 patients in the cohort, **is Level II-3 based on USPSTF criteria. The level of evidence for this systemic review for cancer-related pain studies meeting the inclusion criteria of continuous use of IDDS for at least 3 months duration with at least 25 patients in the cohort is Level II-2 based on USPSTF criteria.**

Conclusion: Based on the available evidence, the recommendation for intrathecal infusion systems for cancer-related pain is moderate recommendation based on the high quality of evidence and the recommendation is limited to moderate based on the moderate quality of evidence from nonrandomized studies for non-cancer related pain.

Hayek S.M.; Intrathecal Therapy for Cancer and Non-Cancer Pain. Pain Physician 2011; 14:219-248.

Danke für Ihre Aufmerksamkeit

Bei Fragen zu dieser Präsentation wenden Sie sich bitte per e-mail an tanja.maier@kabeg.at