SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
68° CONGRESSO NAZIONALE SIGG
Ritorno al futuro
FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

Il trattamento del dolore nell'anziano

Raffaele Antonelli Incalzi

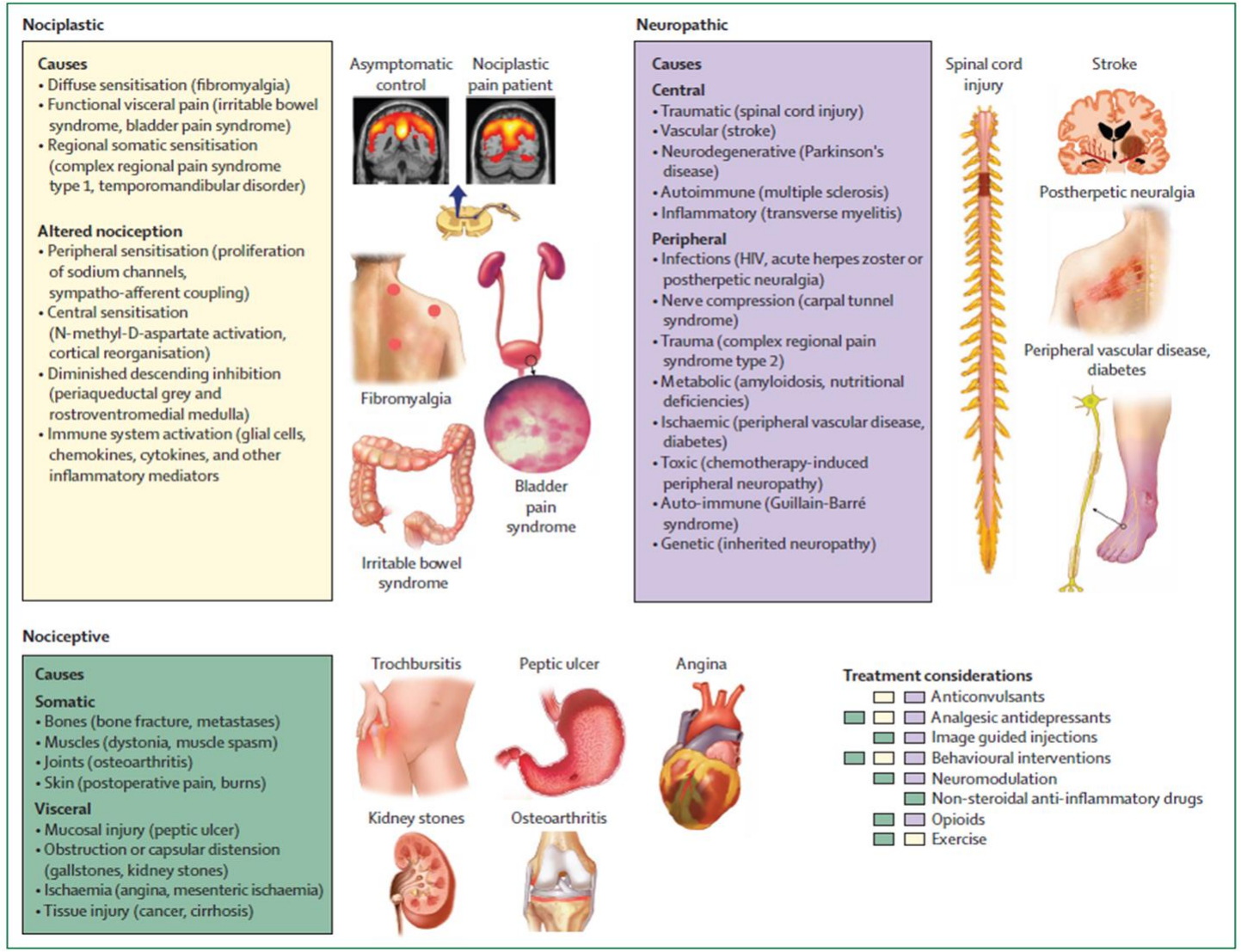
Università Campus Bio Medico

Roma

Che cosa è il dolore cronico (Cohen SP et al. *Lancet* 2021; 397: 2082–97)

- The IASP defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.
- Although there is no clear threshold of when acute pain becomes chronic, it is generally accepted that pain persisting beyond the expected healing period (3 months according to International Classification of Diseases, 11th edition criteria) is pathological.
- In contrast to acute pain, chronic pain contains little evolutionary benefit. In viewing chronic pain as a disease, patients and providers might shift their expectations from eradicating the problem to controlling it (ie, functional and emotional restoration).

I tipi di dolore cronico, ma, specie nell'anziano, attenzione al mixed pain (Cohen SP et al. *Lancet* 2021; 397: 2082–97)



	Nociceptive pain	Neuropathic pain	Nociplastic pain
Causes	Tissue or potential tissue damage	Disease or injury affecting the nervous system	Maladaptive changes that affect nociceptive processing and modulation without objective evidence of tissue or nerve damage
Examples and mechanisms	Degenerative changes that occur via normal wear and tear (degenerative disc disease, facet arthropathy, primary osteoarthritis), trauma, (eg, burns, muscle tears, traumatic arthritis), muscle spasm, visceral pathology (eg, ulcers, renal stones, pancreatitis)	Nerve or nerve root compression (eg, radiculopathy, carpal tunnel syndrome), toxins (eg, chemotherapy), metabolic (eg, liver disease, diabetes), ischaemia (eg, peripheral vascular disease, diabetes), trauma (eg, postsurgical pain), infectious (eg, shingles, HIV), inflammatory (eg, acute and chronic inflammatory demyelinating polyradiculoneuropathy), hereditary (eg, Charcot-Marie Tooth)	Central sensitisation, wind-up, glial and chronic immune system activation, disturbed response to psychosocial stressors, reduced central inhibition. Examples include bladder pain syndrome, fibromyalgia, irritable bowel syndrome, temporomandibular disorder, some tension-type headaches and non-specific back pain
Descriptors	Throbbing, aching, pressure-like	Lancinating, shooting, electrical-like, stabbing	Similar to neuropathic pain; visceral pain (eg, interstitial cystitis, irritable bowel syndrome), might be described as diffuse, gnawing, aching, sharp
Sensory deficits	Infrequent and, if present, in non-dermatomal or non-nerve distribution	Frequent (eg, numbness, tingling, pricking)	Not uncommon, in non-dermatomal and non-nerve distribution
Motor deficits	Might have pain-induced weakness	Neurological weakness might be present if motor nerve affected; dystonia or spasticity may be associated with CNS lesions, and sometimes peripheral lesions (eg, complex regional pain syndrome type 2, other forms of peripheral nerve trauma)	Generalised fatigue common; weakness might be related to deconditioning
Hypersensitivity	Uncommon except for hypersensitivity in the immediate area of an acute injury	Pain frequently evoked with non-painful (allodynia) or painful (exaggerated response) stimuli	Common, often diffuse; hyperalgesia and sensitivity to mechanical stressors more common than allodynia
Pain pattern	Distal radiation less common; proximal radiation frequent around area of anatomical structure	Distal radiation common in a nerve or nerve root (dermatomal) distribution	Diffuse spread not confined to an anatomical referral pattern; patients often have multiple nociplastic conditions
Precipitating or relieving factors	Exacerbations less common and often associated with activity	Exacerbations common and unpredictable	Common, often related to psychosocial stress
Autonomic signs	Uncommon	Colour changes, temperature changes, swelling, or sudomotor (sweating) activity, or a combination, occur in a third to half of patients	Sympathetic nervous system hyperactivity common in diffuse pain (fibromyalgia) and visceral pain conditions (irritable bowel syndrome)
Accompanying symptoms	Higher rates of psychopathology including depression and anxiety than controls	Greater psychological distress and concomitant disability than observed in nociceptive pain	Psychological distress affects most individuals. Cognitive symptoms, insomnia, and fatigue are common. Gastrointestinal complaints and sensitivity to other sensory stimuli often occur. Association with multiple sensitivity reactions to chemicals
Concomitant conditions	Higher rates of psychopathology, insomnia, obesity, other pain conditions, cognitive impairment, hypertension, and cardiovascular disease	Higher rates of psychopathology, insomnia, cognitive impairment (eg, dementia), and hypertension and cardiovascular disease. Many diseases that cause neuropathic pain result from conditions that can lead to pain and other symptoms (diabetes, rheumatoid arthritis, lupus, coeliac disease, HIV, and other infections). Severe neuropathy can result in autonomic symptoms (eg, gastroparesis, dizziness, and syncope)	Similar to nociceptive pain. Nociplastic conditions have high co-prevalence rates with each other, and with other chronic pain conditions such as spine pain, arthritis and headaches, cataplexy, and psychiatric conditions such as post-traumatic stress and eating disorders
Effective non-opioid pharmacological treatments	Non-steroidal anti-inflammatory drugs (topical and systemic), muscle relaxants (more effective for acute and subacute spinal pain), serotonin–norepinephrine reuptake inhibitors and tricyclic antidepressants, disease modifying anti-rheumatic drugs (inflammatory arthritis), nerve growth factor	Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, high concentration capsaicin patch (regional pain), lidocaine patch (regional pain), tramadol	Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, ketamine infusions

Il dolore cronico: una malattia multidimensionale per eccellenza (Cohen SP et al. *Lancet* 2021; 397: 2082–97)

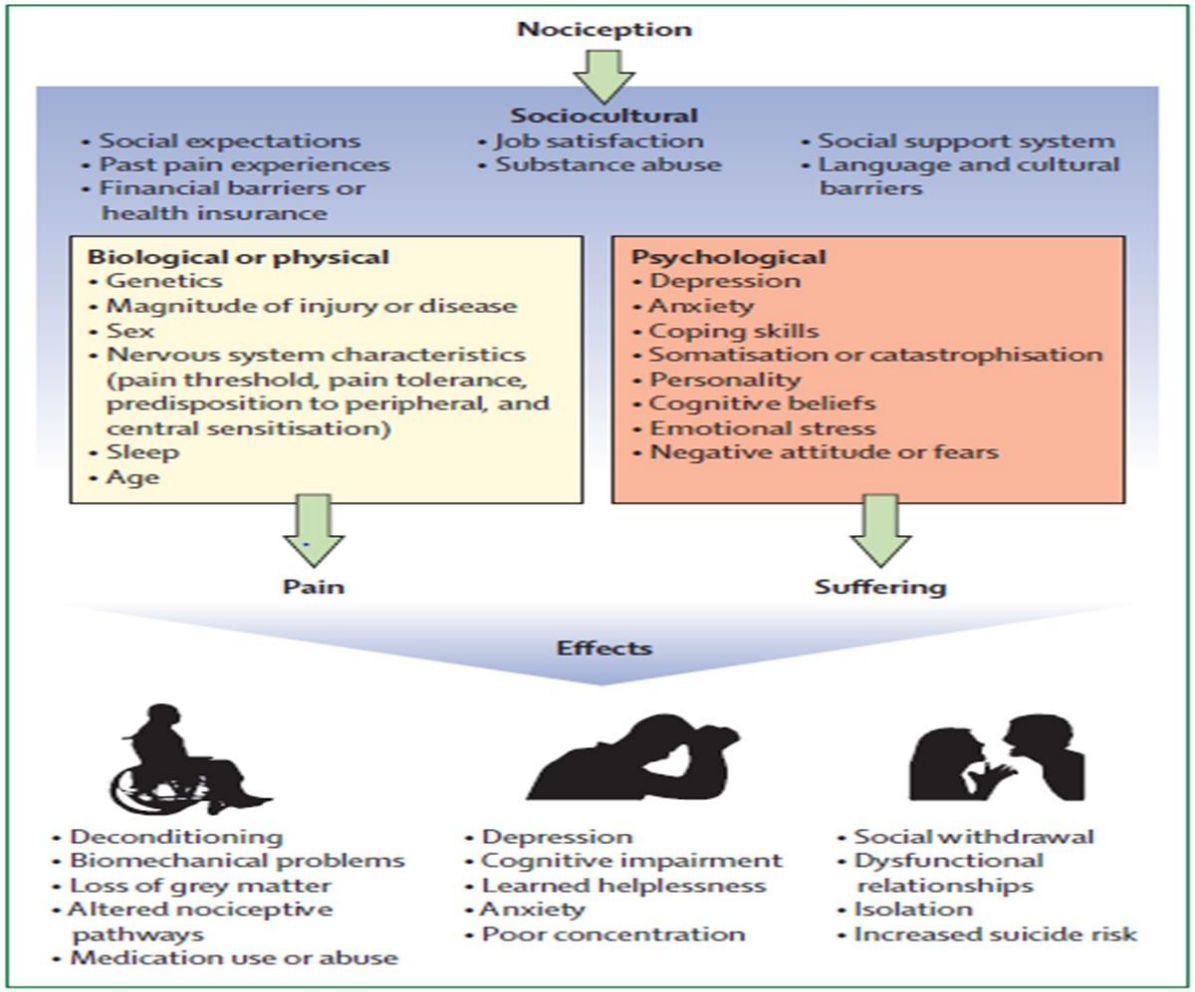
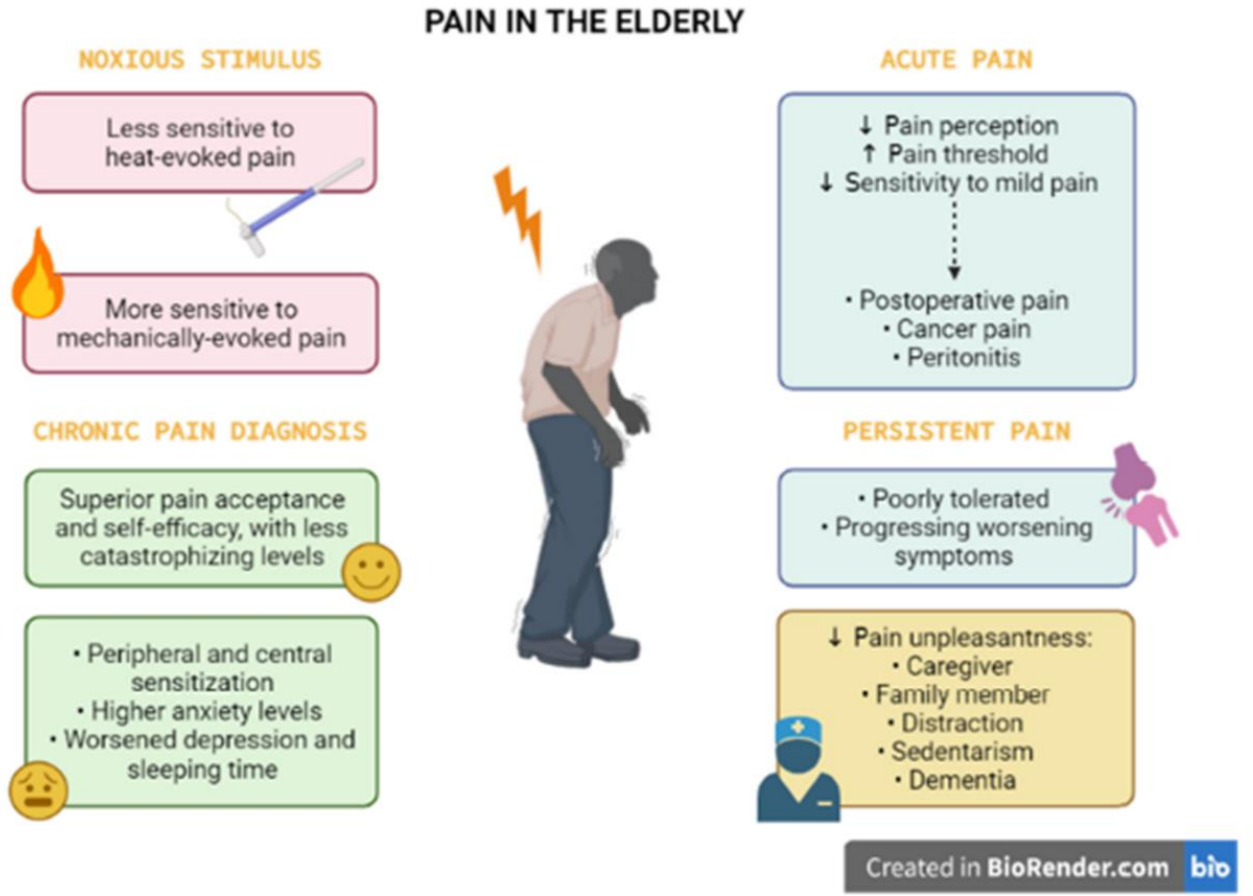
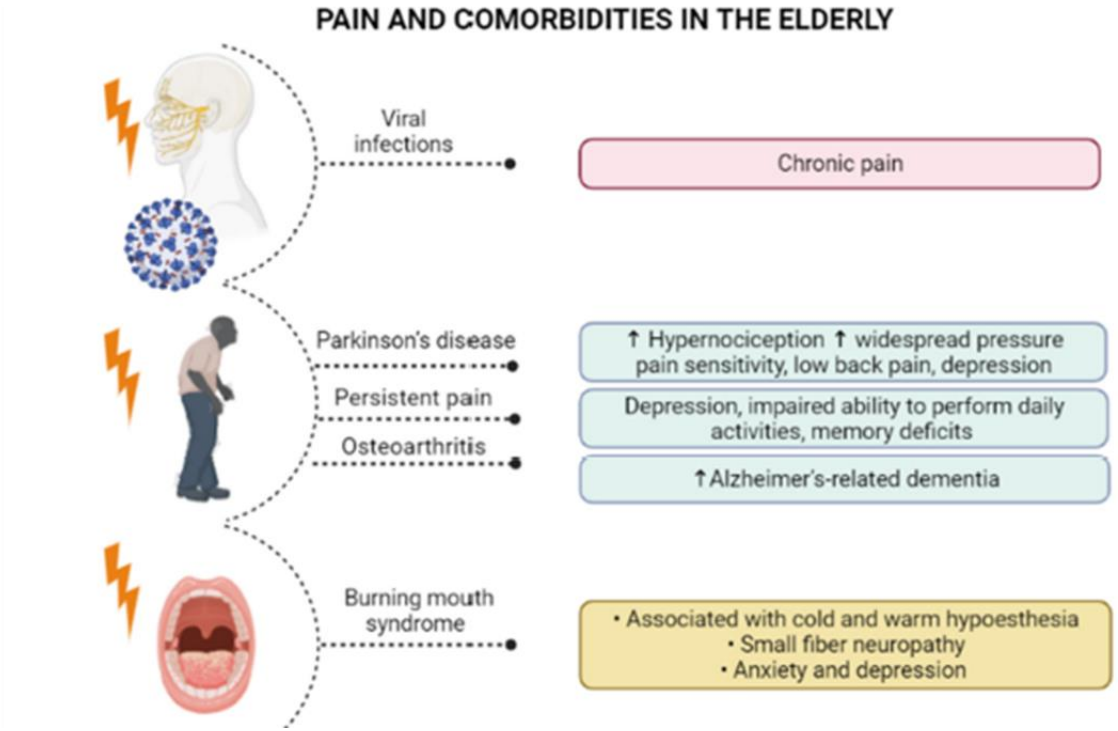


Figure 1: **Biopsychosocial model of pain showing the complex interaction between chronic pain and biological, psychological, and social factors**

Il dolore nell'anziano: elementi di specificità (Dagnino A et al. Front. Hum. Neurosci. 16:736688. doi: 10.3389/fnhum.2022.736688)



In sintesi


PAIN AND COMORBIDITIES IN THE ELDERLY
Viral infections
Chronic pain
Parkinson's disease
↑ Hypernociception ↑ widespread pressure pain sensitivity, low back pain, depression
Persistent pain
Depression, impaired ability to perform daily activities, memory deficits
Osteoarthritis
↑ Alzheimer's-related dementia
Burning mouth syndrome
• Associated with cold and warm hypoesthesia
• Small fiber neuropathy
• Anxiety and depression

Malattie neurodegenerative e dolore: Parkinson (Dagnino A et al. Front. Hum. Neurosci. 16:736688. doi: 10.3389/fnhum.2022.736688)

Osservazioni

- ..hypernociception precedes the development of motor symptoms in Parkinson's disease…
- .. about 40% of low back pain carriers had painful
- symptoms before the Parkinson's diagnosis…
- .. Pain in patients carrying out Parkinson's disease has also been linked with the severity of motor symptoms, in addition to sleep and mood disturbances…
- … a significant correlation of pain intensity, pain-related disability, as well as pain interference, with depression symptoms in Parkinson's disease….

Meccanismi

- One hypothesis that is currently gaining attention is that dopaminergic deficits are associated with anhedonia and chronic pain.
- The activity of GABAergic neurons is eliminated by the activation of postsynaptic dopamine D2 receptors.
- The D2/D3R availability in the ventral striatum was reduced in chronic non neuropathic back pain patients (CNBP)
- The dopaminergic neural mechanisms of cognitive flexibility are affected by aging and dopamine has been associated with cognition and executive functions changes in adults

Malattie neurodegenerative e dolore: Alzheimer (Dagnino A et al. Front. Hum. Neurosci. 16:736688. doi: 10.3389/fnhum.2022.736688)

Osservazioni

- A longitudinal study evaluating more than 1,000 > 70-year-old communitydwelling individuals, throughout 21 years (Einstein Aging Study), demonstrated that high levels of pain interference in usual skills were associated with an elevated risk of developing all-cause and Alzheimer's-related dementia, irrespective of no significant correlation between pain intensity and the latency for dementia (Ezzati et al., 2019).
- In institutionalized elders with dementia, there was a positive correlation between pain diagnosis and depression, what accounts for the complexity of pain evaluation and management in this specific population (Malara et al., 2016)

Meccanismi

- Besides, it has been demonstrated that acetylcholinesterase inhibitors, such as
- neostigmine and rivastigmine, that had been used for the management of dementia in patients with Alzheimer's or Parkinson's disease, display beneficial effects on chronic pain, considering that acetylcholine deficits are implicated in either cognitive impairment or persistent pain. (Eldufani and Blaise,
- 2019)

Ma nel demente è difficile stimare il dolore (*Hadjistavropoulos T et al. Lancet Neurol* 2014; 13: 1216–27)

- Nevertheless, observers display substantial biases in their investigation of pain in others. Studies have documented general bias, in which observers consistently underestimate pain in others.
- The underestimation bias is enhanced among observers with clinical experience with pain suff erers (Prkachin KM et al. *Can J Nurs Res* 2007; **39:** 88–106).
- Autonomic reactions, such as diaphoresis or increase of blood
- pressure, heart rate, and respiratory rate, can indicate the presence of acute pain; however, such measures are not as useful to identify persistent pain (Kunz M et al. *Eur J Pain* 2009; **13:** 317–25.).
- Furthermore, evidence that these autonomic reactions are blunted in
- people with dementia has been reported (Kunz M et al. *Gerontology* 2009; **55:** 674–82).

Vi sono molte linee guida sulla stima del dolore nel demente

***Panel 3:* Key guidelines of pain assessment in the patient with dementia**

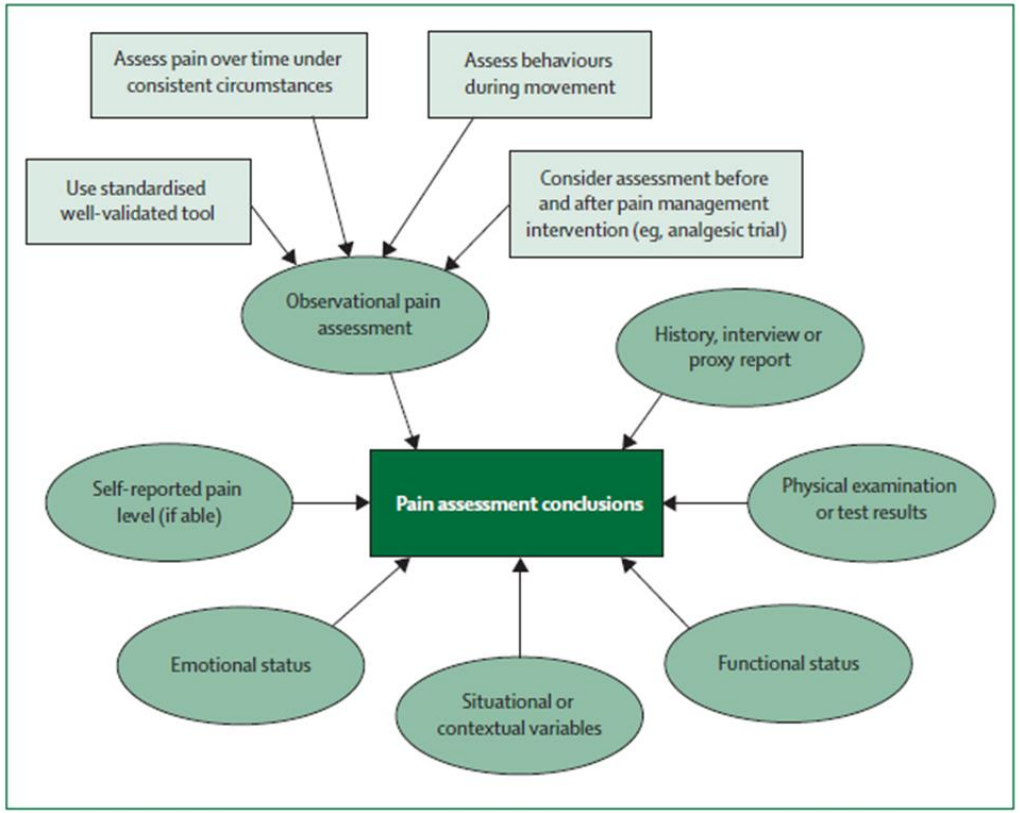
- International Interdisciplinary Consensus Statement on Pain Assessment in Older Persons[1]
- National Nursing Home Pain Collaborative[41]
- American Geriatrics Society (AGS)[116,117]
- American Medical Directors' Association (AMDA) Pain Management Guideline[124]
- Pain in residential aged care facilities (Australian Pain Society)[125]
- Task force of the American Society for Pain Management Nursing (ASPMN)[126]
- The British National Guideline for Assessment of Pain in Older People[127]
- Transforming pain management in long-term care pain management in North America[128]
- Australian and New Zealand Society for Geriatric Medicine[129]
- Multidisciplinary guideline (Dutch)[130]

E molte scale, ma…

***Panel 1*: Instruments suitable for the assessment of pain in the elderly adult with dementia**

- Abbey Pain Scale[77,82–84]
- Checklist of Non-Verbal Pain Indicators (CNPI)[78,84,85]
- Certified Nursing Assistant Pain Assessment Tool (CPAT)[75,86]
- DOLOPLUS-2[87,88–90]
- Discomfort Scale in Dementia of the Alzheimer's Type (DS-DAT/DS-DAT modified)[91–95]
- EPCA-2[96]
- Mahoney Pain Scale[97]
- Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID and MOBID-2) Pain Scale[74,98,99]
- Non-Communicative Patient's Pain Assessment Instrument (NOPPAIN)[57,72,85,100]
- Pain Assessment in the Communicatively Impaired (PACI)[101–103]
- Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACLSAC and PACSLAC-II)[2,73,85,104–107]
- Pain Assessment for the Dementing Elderly (PADE)[85,108]
- Pain Assessment in Advanced Dementia (PAINAD)[57,71,82,85,109]
- Pain Assessment in Noncommunicative Elderly Persons (PAINE)[76]
- The Rotterdam Elderly Pain Observation Scale (REPOS)[110]

…alla fine, è una valutazione multidimensionale



Come trattare il dolore: inquadrare bene le raccomandazioni del CDC (

Recommendations and Reports / Vol. 71 / No. 3 November 4, 2022)

BOX 2. Intended use of CDC's Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

This clinical practice guideline is

- a clinical tool to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together;
- intended for primary care clinicians and other clinicians providing pain care for outpatients aged ≥18 years with
  - acute pain (duration of <1 month),
  - subacute pain (duration of 1–3 months), or
  - chronic pain (duration of >3 months); and
- intended to be flexible to enable person-centered decision-making, taking into account a patient's expected health outcomes and well-being.

This clinical practice guideline is not

- a replacement for clinical judgment or individualized, person-centered care;
- intended to be applied as inflexible standards of care across patients or patient populations by health care professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or abrupt discontinuation of opioids for patients;
- a law, regulation, or policy that dictates clinical practice or as a substitute for Food and Drug Administration–approved labeling;
- applicable to
  - management of pain related to sickle cell disease,
  - management of cancer-related pain, or
  - palliative care or end-of-life care; or
- focused on opioids prescribed for opioid use disorder.

Approccio a tre gradini OMS

SCALA ANALGESICA WHO

Morfina (sc/eve/epidurale/intratecale)
Fentanyl (transmucosale/transdermico)
Ossicodone (+naloxone o +paracetamolo)
Idromorfone
BUPRENORFINA

Oppiacei forti
± Fans
± adiuvanti

3° GRADINO

DOLORE SEVERO

«4°GRADINO»
BLOCCHI NERVOSI
POMPE per ANALGESIA CONTROLLATA dal PAZIENTE
ANALGESIA EPIDURALE
STIMOLATORI SPINALI

Tramadolo
Codeina

Associazioni precostituite:
- Tramadolo/paracetamolo
- Tramadolo/FANS
- Codeina/paracetamolo
- Codeina/ibuprofene

Oppiacei deboli
± Fans
± adiuvanti

2° GRADINO

DOLORE MODERATO

Fans ± adiuvanti

1° GRADINO

DOLORE LIEVE

Paracetamolo
Ibuprofene
Ketoprofene/Dexketoprofene
Diclofenac
COX2 inibitori

Associazioni precostituite:
- Codeina/ibuprofene
- paracetamolo/ibuprofene

PARACETAMOLO

- Ancora cardine della terapia antalgica nell'anziano
- Ben tollerato, poche controindicazioni
- Efficace nel dolore acuto di intensità moderata non specifico e nel dolore severo
- In associazione con FANS potenzia effetto analgesico, consentendo uso dosi minori
- Dose max raccomandata/die 4 g per breve periodo, ≤3 g se somministrazione cronica, 2 g/die in soggetti ≤50 kg

Ennis ZN et al. Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. Basic Clin Pharmacol Toxicol. 2016 Mar;118(3):184-9

FANS

- **Se** fallite altre terapie
- **Dopo** accurata valutazione rischio complicanze (rivalutazione seriata):
  - Gruppi a rischio: long term users, over65, assunzione concomitante steroidi/ASA/NAO e TAO
  - Interazioni farmacologiche: ASA/FANS, ASA/COX2, warfarin/FANS, FANS/steroidi
- Raccomandata minore dose possibile nel tempo
- **Nota 66**: artropatia gottosa, connettiviti, osteoartrosi, neoplasia

- Controindicazione assoluta: ulcera peptica attiva, nefropatia cronica, CHF
- Controindicazione relativa: HP, ipertensione arteriosa, steroidi, anamnesi di ulcera peptica

Schwan J et al Chronic Pain Management in the Elderly. Anesthesiol Clin. 2019 Sep;37(3):547-560.

ADIUVANTI

Farmaci la cui indicazione non è l'analgesia,ma che in determinate circostanze possono fornire o aiutare a fornire sollievo al dolore (in modo diretto/indiretto/antidoto di effetti collaterali)

- STEROIDI
- ANESTETICI PER USO TOPICO
  - Lidocaina
- ADIUVANTI PER IL DOLORE OSSEO e MUSCOLO-SCHELETRICO (es. bifosfonati, miorilassanti)

- ADIUVANTI PER IL DOLORE NEUROPATICO
  - GABAPENTIN
  - PREGABALIN
  - AMITRIPTILINA
  - TRAZODONE
  - SSRI
  - Anticonvulsivanti (dolore neuropatico periferico lancinante)
  - CANNABINOIDI

Portenoy RK. A Practical Approach to Using Adjuvant Analgesics in Older Adults. J Am Geriatr Soc. 2020 Apr;68(4):691-698.

STEREOTIPI sui FARMACI OPPIOIDI – il medico

- «La morfina è indicata nella fase terminale della vita»
- «La morfina porta alla morte»
- «La morfina non funziona»
  - Somministrazione scorretta
  - Dolore non sensibile ad oppiodi
  - Aspetti psicosociali
- Provocano effetti collaterali inaccettabili (stipsi, nausea, sonnolenza)
- Paura/timore di:
  - Tolleranza
  - Dipendenza fisica o psicologica

STEREOTIPI sui FARMACI OPPIOIDI – il paziente

- «sto per morire quindi»
- «sono allergico alla morfina»
- «non avrò altri farmaci a disposizione, diventerò un tossico»
- «non posso assumere la morfina per i suoi effetti collaterali»
- «non funziona»

ROTAZIONE DEGLI OPPIOIDI

(EAPC – European Association of Palliative Care)

Se l'incremento della dose non genera più analgesia (TOLLERANZA)

Se presente un rapporto negativo tra effetti collaterali e analgesia

VARIARE l'OPPIOIDE O LA VIA DI SOMMINISTRAZIONE:

Sfruttare tolleranza crociata incompleta agli oppioidi per utilizzare recettori ancora non saturati dal farmaco

BUPRENORFINA

- Oppioide derivato sintetico tebaina, altamente liposolubile in grado di penetrare barriera cutanea
- Meccanismo di azione: parziale stimolazione dei recettori mu e delta, azione di blocco sui k
- Agonista parziale: produce effetti simili ad agonisti puri, ma in maniera meno pronunciata
- Basso rischio depressione respiratoria e abuso
- Lenta dissociazione e relativa lunga durata d'azione analgesica

Evans HC, Easthope SE. Transdermal buprenorphine. Drugs. 2003;63(19):1999-2010; discussion 2011-2.

BUPRENORFINA

- Efficacia analgesica
  - Circa 25-40 volte più della morfina
  - Classificato tra gli oppioidi forti secondo OMS
- Formulazioni a basso dosaggio:
  - Indicato negli adulti
  - Trattamento del dolore non maligno di intensità moderata quando è necessario un oppioide per ottenere una analgesia adeguata(non indicazioni su tipo di dolore specifico)
  - Non è adatto per il trattamento del dolore acuto (studi su dolore osteoarticolare reumatico, dolore erpetico)

Pergolizzi JV Jr et al. Transdermal Buprenorphine for Acute Pain in the Clinical Setting: A Narrative Review. J Pain Res. 2021 Mar 31;14:871-879.

Ahn JS et al. Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. J Pain Res. 2017 Aug 18;10:1963-1972.

BUPRENORFINA

Farmacocinetica [17]

La formulazione transdermica di buprenorfina fornisce concentrazioni plasmatiche più stabili e una somministrazione controllata e sostenuta rispetto a una dose terapeutica costante [19].

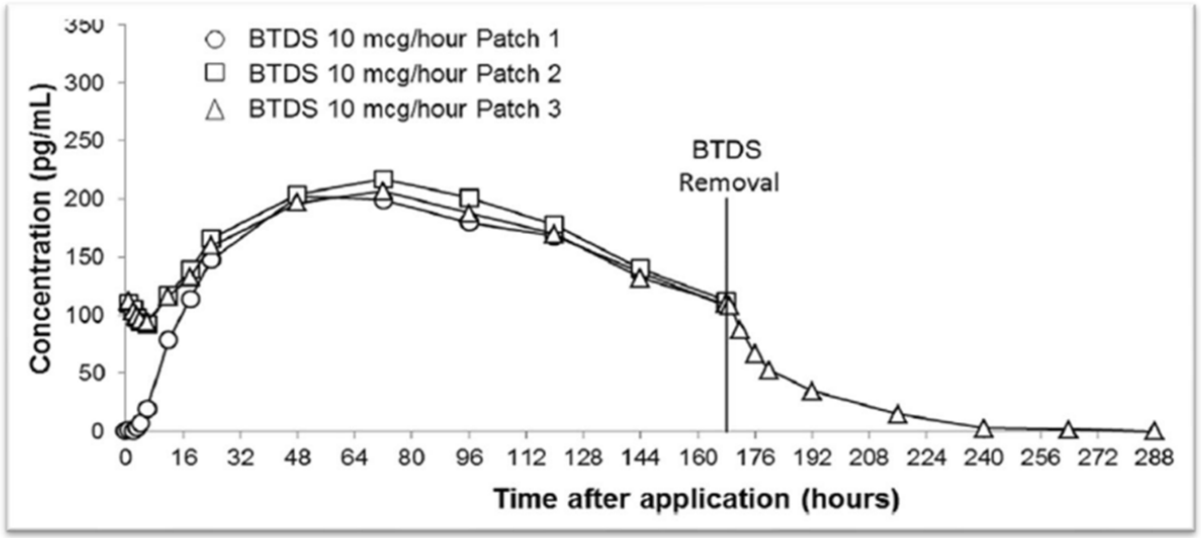


Fig. 3B: concentrazioni plasmatiche medie di Buprenorfina sovrapponibili durante tre applicazioni consecutive ogni 7 giorni [19]

17 Kapil RP, et al. Once-weekly transdermal buprenorphine application results in sustained and consistent steady-state plasma levels. J Pain Symptom Manage [Internet]. 2013

BUPRENORFINA

- Utile in diversi scenari clinici grazie a proprietà farmacologiche favorevoli
- Raccomandata da linee guida come prima linea di oppioidi per dolore cronico non oncologico, soprattutto in pazienti anziani
- Utilizzo transdermico semplice
- Gestione terapeutica sotto stretto controllo specialistico

Alcune raccomandazioni del CDC di particolare rilievo per l'anziano 1

When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids (recommendation category: A; evidence type: 4).	Because of the longer half-life and longer duration of effects (e.g., respiratory depression) of ER/LA opioids (e.g., methadone, fentanyl patches, or extended-release versions of oxycodone, hydromorphone, hydrocodone, or morphine). Methadone: late respiratory depressant effect, Qt prolongation. Fentanyl: variable, heat dependent absorption.
For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy …	Patients receiving long-term, high-dosage opioid therapy for chronic pain are at increased risk for adverse events including overdose death (*55*,*72*,*202*,*203*,*209*). However, discontinuation of long-term, high-dosage opioid therapy has been associated with adverse events including mental health crisis, overdose events, and overdose death

Alcune raccomandazioni del CDC di particolare rilievo per l'anziano 2

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone (recommendation category: A; evidence type: 4).	Clinicians should offer naloxone when prescribing opioids, particularly to patients at increased risk for overdose, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11), and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering ….
Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B; evidence type: 3).	Benzodiazepines and opioids both cause central nervous system depression, and benzodiazepines can potentiate opioid-induced decreases in respiratory drive. In addition, experts noted that long-term, stable use might be safer than erratic, unpredictable use.

Alcune raccomandazioni del CDC di particolare rilievo per l'anziano 3

Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A; evidence type: 1).	FDA-approved medications indicated for the treatment of opioid use disorder include buprenorphine (a partial agonist opioid), methadone (a full agonist opioid), and naltrexone (an opioid antagonist). Experts from OWG stated that partial agonist opioid, full agonist opioid, and opioid antagonist treatment should not be framed as equal options for opioid use disorder, noting that partial and full agonist opioid treatments have stronger evidence for better outcomes, do not require abstinence, have less challenges with initiation, and are much more widely used than opioid antagonist treatment.

Attenti alla conversione!

TABLE. Morphine milligram equivalent doses for commonly prescribed opioids for pain management

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1.0
Hydromorphone	5.0
Methadone	4.7
Morphine	1.0
Oxycodone	1.5
Oxymorphone	3.0
Tapentadol†	0.4
Tramadol§	0.2

Sources: Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7 and Nielsen S, Degenhardt L, Hoban B, Gisev N. Pharmacoepidemiol Drug Saf 2016;25:733–7.
Abbreviations: mcg/hr = microgram per hour; mg = milligram; MME = morphine milligram equivalent.

Stipsi da oppiacei: una definizione non banale e un problema maggiore nell'anziano

(Lacy BE et al. Gastroenterology 2016;150:1393–1407)

C6. Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:
   a. Straining during more than one-fourth (25%) of defecations
   b. Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
   c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives

Prima di colpevolizzare gli oppioidi

Table 7. Drugs With Strong Anticholinergic Properties

Antiarrhythmic	Promethazine
Disopyramide	Pyrilamine
	Triprolidine
Antidepressants	
Amitriptyline	
Amoxapine	
Clomipramine	Antimuscarinics
Desipramine	(urinary incontinence)
Doxepin (>6 mg)	Darifenacin
Imipramine	Fesoterodine
Nortriptyline	Flavoxate
Paroxetine	Oxybutynin
Protriptyline	Solifenacin
Trimipramine	Tolterodine
	Trospium
Antiemetics	
Prochlorperazine	Antiparkinsonian agents
Promethazine	Benztropine
	Trihexyphenidyl
Antihistamines (first generation)	
Brompheniramine	Antipsychotics
Carbinoxamine	Chlorpromazine
Chlorpheniramine	Clozapine
Clemastine	Loxapine
Cyproheptadine	Olanzapine
Dexbrompheniramine	Perphenazine
Dexchlorpheniramine	Thioridazine
Dimenhydrinate	Trifluoperazine
Diphenhydramine (oral)	
Doxylamine	Antispasmodics
Hydroxyzine	Atropine (excludes ophthalmic)
Meclizine	Belladonna alkaloids
Clidinium-chlordiazepoxide	Scopolamine (excludes ophthalmic)
Dicyclomine	
Homatropine (excludes ophthalmic)	Skeletal muscle relaxants
Hyoscyamine	Cyclobenzaprine
Methscopolamine	Orphenadrine
Propantheline	

Stipsi da oppioidi: non solo stipsi (in pazienti neoplastici)

(Candrilli SD et al. Journal of Pain & Palliative Care Pharmacotherapy, 2009; 23: 231-241)

TABLE 3. Incidence of Other Opioid-Related Side Effects in Opioid Initiators During the 12-Month Period Following Opioid Initiation, by Constipation Status[a]

	With Constipation ($n = 821$)		Without Constipation ($n = 821$)		
	n	%	*n*	%	*P* Value
Nausea (alone)	175	21.32	93	11.33	<.0001
Vomiting (alone)	97	11.81	52	6.33	.0001
Nausea with vomiting	274	33.37	161	19.61	<.0001
Pruritus	11	1.34	18	2.19	.1899
Intestinal obstruction	164	19.98	53	6.46	<.0001
Delirium/disorientation	36	4.38	20	2.44	.0296
Myoclonus	5	.61	4	.49	.7384
Respiratory depression/dyspnea	211	25.70	151	18.39	.0003
Urine retention	64	7.80	23	2.80	<.0001

[a]Outcomes compared between opioid initiators with constipation and a demographically matched cohort (1:1 ratio) of opioid initiators without evidence of constipation during the 12-month follow-up period.

PAMORAs: Peripherally acting mu-opioid receptor antagonists. Azione preminente sui mu.

(Wald A. JAMA. 2016;315(2):185-191)

Table 3. Available Opioid Antagonists

Drug	Receptor Antagonism[a] μ	κ	δ	Permeable to Blood-Brain Barrier
Naloxone	+++	++	++	Yes
Naltrexone	+++	++	++	Yes
Methylnaltrexone	+++	++	++	No
Alvimopan	+++	None	None	No
Naloxegol	+++	None	None	No

[a] Affinity for the receptor: ++ = moderate; +++ = strong.

A more biologically plausible approach to OIC is to combine a strong opiate agent with an effective opioid receptor antagonist that will not counteract the benefits of pain reduction. An example of this is oxycodone/naloxone. Naloxone is an opioid receptor antagonist that exhibits a local effect on gastrointestinal opioid receptors but is nearly completely inactivated by the liver after oral administration.

A variation on this theme is the development of naloxegol, a pe Gylated derivative of naloxone that limits the ability of naloxegol to cross the blood-brain barrier so that it acts only on peripheral μ-opioid receptors.

Naldemedina: non passa la barriera ematoencefalica e tale effetto non è mediato dalla Glicoproteina P

(Watari R et al. Drug Metabolism and Pharmacokinetics 34 (2019) 126e133)

Table 3
Radioactivity concentrations after a single oral administration of [^{14}C]-naldemedine tosylate to ferrets.

Tissues	Radioactivity concentration (ng eq./g)	
	0.5 h	4 h
Plasma	152	39.7
Area postrema	198	102
Caudate nucleus	1.73	1.46
Cerebrum	1.88	1.41
Choroid plexus	168	38.0
Hippocampus	1.49	1.01
Hypothalamus	2.02	1.87
Brain stem	1.37	1.03
Periaqueductal gray	1.55	0.477
Pituitary	334	124
Putamen	1.04	0.581
Thalamus	2.14	1.25

n = 1 at each time point.

These results suggest that the low brain distribution of naldemedine was due to the limited ability to cross the BBB rather than efflux by P-gp and therefore brain distribution of naldemedine would not be affected by concomitant administration of P-gp inhibitors or functional disorder of P-gp.

Efficace indipendentemente dal pregresso uso di lassativi: dati integrati da COMPOSE 1 e COMPOSE 2

(Hale ME et al. Ther Adv Gastroenterol 2021, Vol. 14: 1–11)

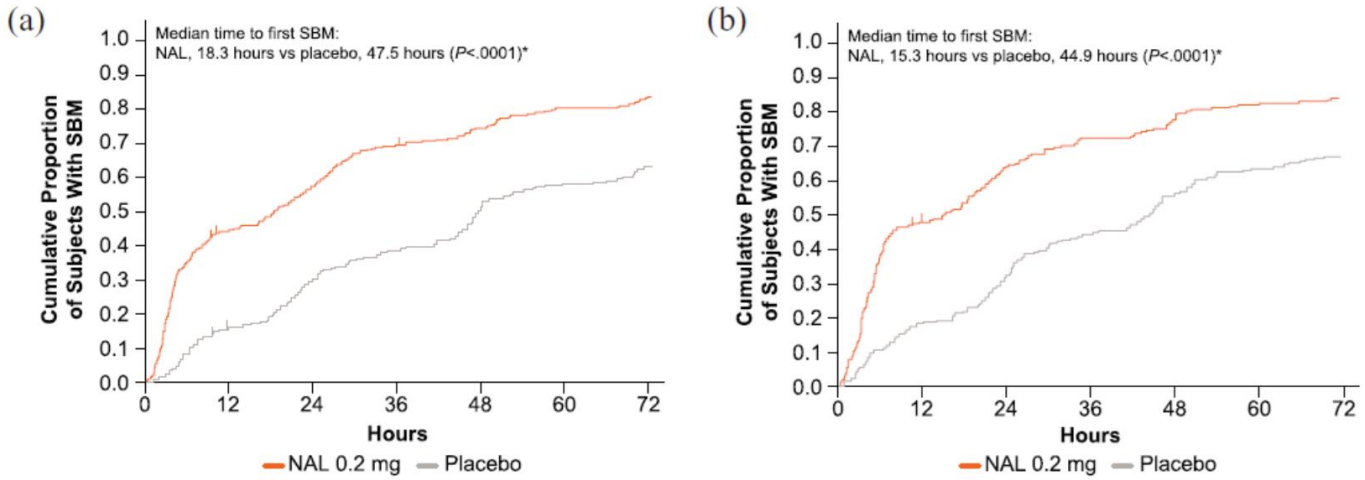


Figure 5. Kaplan–Meier estimate of time to first spontaneous bowel movement in (a) PLR and (b) non-PLR subgroups
The time to first SBM was significantly shorter for the naldemedine groups *versus* the placebo groups (Figure 5). In the PLR subgroup, the median time to first SBM was 18.3 h for naldemedine and 47.5 h for placebo ($p < 0.0001$) [Figure 5a]. In the non-PLR subgroup, the median time to first SBM was 15.3 h for naldemedine and 44.9 h for placebo ($p < 0.0001$) [Figure 5b].

L'effetto cumulativo dei fattori di rischio per diarrea da Naldemedina

(Hashizume J et al. Biol. Pharm. Bull. 2021; 44, 1081–1087)

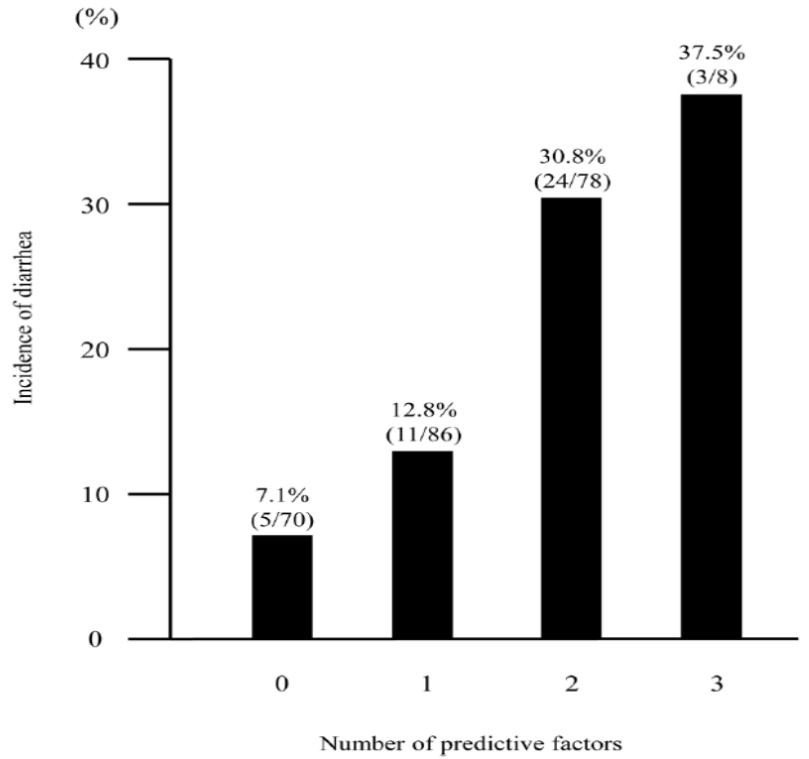


Fig. 1. The Combination of Opioid Analgesics for More than 8 d, Laxatives and CYP3A4 Inhibitors Are Predictors of Naldemedine-Induced Diarrhea

Patients with higher number of these predictors are more likely to develop naldemedine-induced diarrhea.

Cannabinoidi: una possibile aggiunta agli oppioidi? Almeno nell'adulto, pare di no. (Boland EG, et al. BMJ Supportive & Palliative Care 2020;**10**:14–24)

- There is an increased recent interest in cannabinoids (including cannabis) for pain management along with more permissive legislative changes in many countries. The medicinal use of cannabis is already legal in 40 countries and 29 US states. The WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents suggest that data analysis is needed on cannabinoids for cancer pain

Cannabinoidi: una possibile aggiunta agli oppioidi? Almeno nell'adulto, pare di no. (Boland EG, et al. BMJ Supportive & Palliative Care 2020;**10**:14–24)

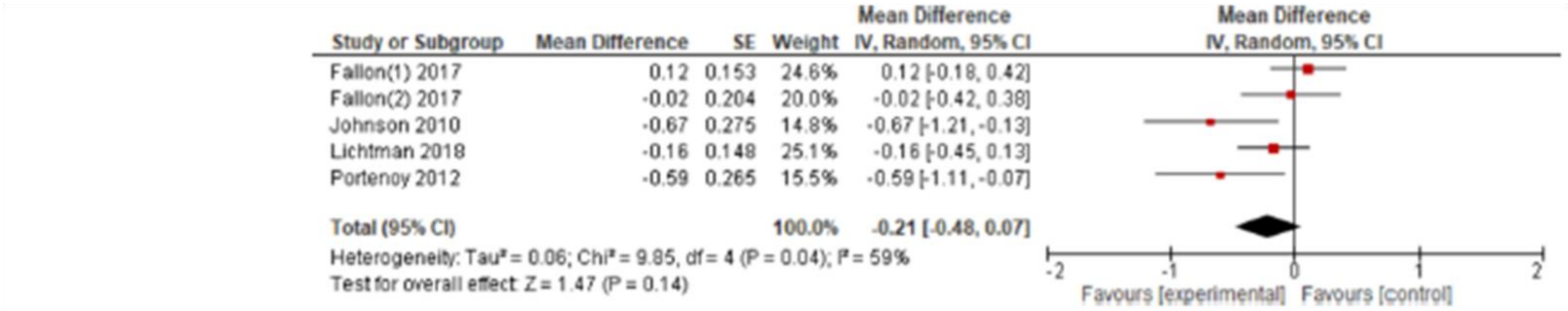


Figure 2 Forest plot for change in pain intensity for the phase II and III studies.

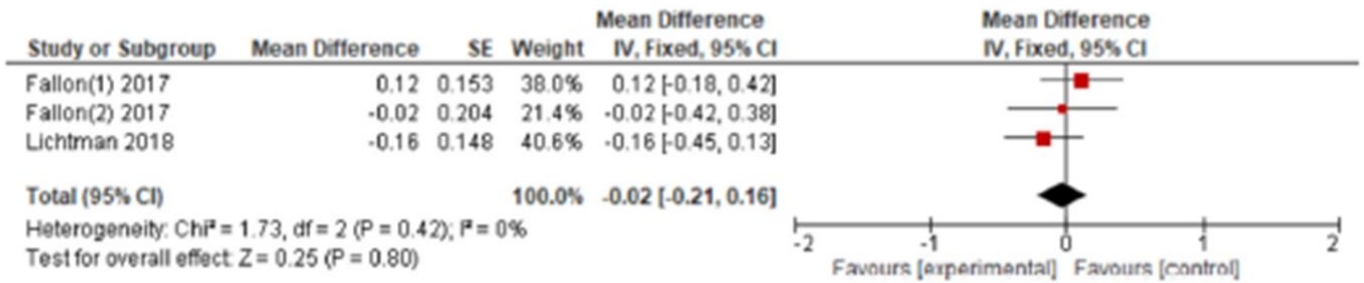


Figure 3 Forest plot for change in pain intensity for the phase III studies.

Opioids for Chronic Non cancer Pain: comparable to non opioid therapy?

(Busse J et al. *JAMA*. 2018;320(23):2448-2460)

Key Points

Question Is the use of opioids to treat chronic noncancer pain associated with greater benefits or harms compared with placebo and alternative analgesics?

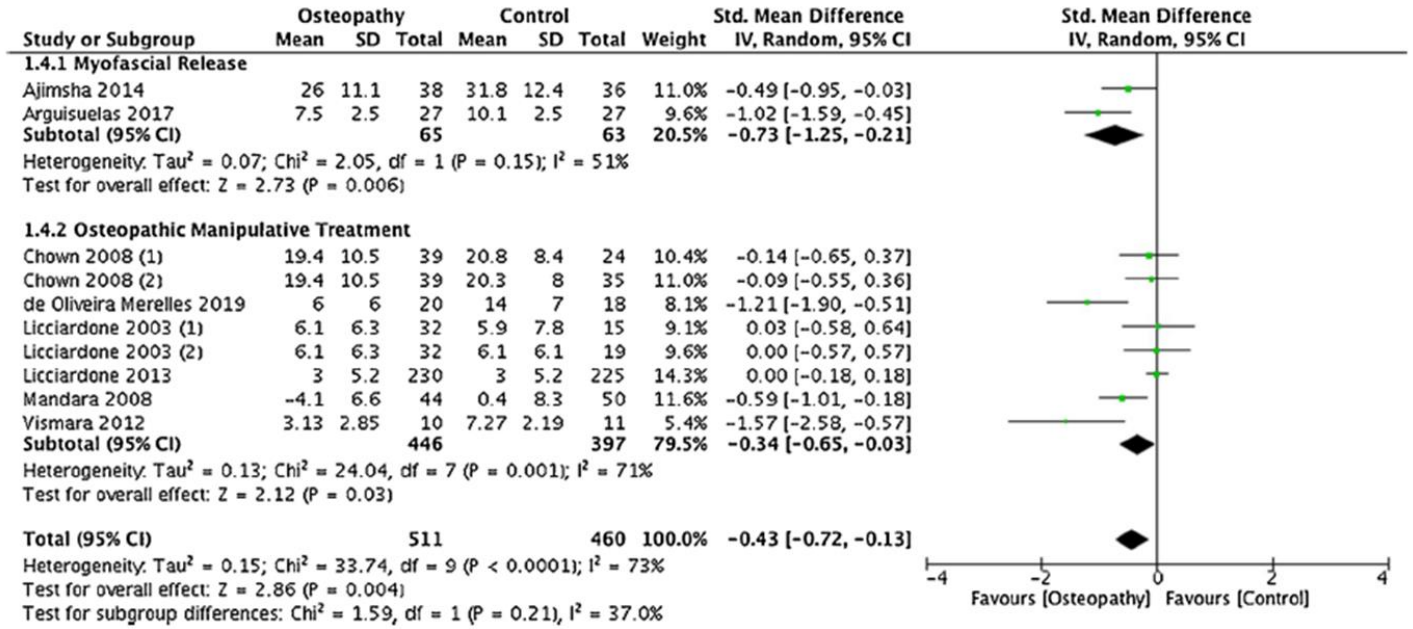
Findings In this meta-analysis that included 96 randomized clinical trials and 26 169 patients with chronic noncancer pain, the use of opioids compared with placebo was associated with significantly less pain (−0.69 cm on a 10-cm scale) and significantly improved physical functioning (2.04 of 100 points), but the magnitude of the association was small. Opioid use was significantly associated with increased risk of vomiting.

Meaning Opioids may provide benefit for chronic noncancer pain, but the magnitude is likely to be small.

Non solo farmaci: lo yoga nel low back pain (Wieland LS et al. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD010671)

- **Authors' conclusions**
- There is low- to moderate-certainty evidence that yoga compared to non-exercise controls results in small to moderate improvements in back-related function at three and six months. Yoga may also be slightly more effective for pain at three and six months, however the effect size did not meet predefined levels of minimum clinical importance. It is uncertain whether there is any diFerence between yoga and other exercise for back-related function or pain, or whether yoga added to exercise is more effective than exercise alone. Yoga is associated with more adverse events than non-exercise controls, but may have the same risk of adverse events as other back-focused exercise. Yoga is not associated with serious adverse events. There is a need for additional high-quality research to improve confidence in estimates of effect, to evaluate long-term outcomes, and to provide additional information on comparisons between yoga and other exercise for chronic nonspecific low back pain.

Non solo farmaci: l'osteopatia nel low back pain (Dal Farra F Complementary Therapies in Medicine 56 (2021) 102616)



Study or Subgroup	Osteopathy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Myofascial Release								
Ajimsha 2014	26	11.1	38	31.8	12.4	36	11.0%	-0.49 [-0.95, -0.03]
Arguisuelas 2017	7.5	2.5	27	10.1	2.5	27	9.6%	-1.02 [-1.59, -0.45]
Subtotal (95% CI)			**65**			**63**	**20.5%**	**-0.73 [-1.25, -0.21]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.05$, df = 1 (P = 0.15); $I^2 = 51\%$								
Test for overall effect: Z = 2.73 (P = 0.006)								
1.4.2 Osteopathic Manipulative Treatment								
Chown 2008 (1)	19.4	10.5	39	20.8	8.4	24	10.4%	-0.14 [-0.65, 0.37]
Chown 2008 (2)	19.4	10.5	39	20.3	8	35	11.0%	-0.09 [-0.55, 0.36]
de Oliveira Merelles 2019	6	6	20	14	7	18	8.1%	-1.21 [-1.90, -0.51]
Licciardone 2003 (1)	6.1	6.3	32	5.9	7.8	15	9.1%	0.03 [-0.58, 0.64]
Licciardone 2003 (2)	6.1	6.3	32	6.1	6.1	19	9.6%	0.00 [-0.57, 0.57]
Licciardone 2013	3	5.2	230	3	5.2	225	14.3%	0.00 [-0.18, 0.18]
Mandara 2008	-4.1	6.6	44	0.4	8.3	50	11.6%	-0.59 [-1.01, -0.18]
Vismara 2012	3.13	2.85	10	7.27	2.19	11	5.4%	-1.57 [-2.58, -0.57]
Subtotal (95% CI)			**446**			**397**	**79.5%**	**-0.34 [-0.65, -0.03]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 24.04$, df = 7 (P = 0.001); $I^2 = 71\%$								
Test for overall effect: Z = 2.12 (P = 0.03)								
Total (95% CI)			**511**			**460**	**100.0%**	**-0.43 [-0.72, -0.13]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 33.74$, df = 9 (P < 0.0001); $I^2 = 73\%$								
Test for overall effect: Z = 2.86 (P = 0.004)								
Test for subgroup differences: $Chi^2 = 1.59$, df = 1 (P = 0.21), $I^2 = 37.0\%$								

Fig. 7. Forest plot of comparison: Subgroup analysis (category of intervention) and overall effect analysis comparing the effect of Osteopathy vs Control for Chronic Low Back Pain. Outcome: functional status. Abbreviations: CI, confidence interval; SD, standard deviation.

Review Article

Management of Chronic Pain in Long-Term Care: A Systematic Review and Meta-Analysis

Jennifer A. Knopp-Sihota PhD [a,b,*], Tara MacGregor BA [b], Jennifer T.H. Reeves BA [b], Megan Kennedy MLIS [b], Ahsan Saleem PhD [b]

https://doi.org/10.1016/j.jamda.2022.04.008

[a] *Faculty of Health Disciplines, Athabasca University, Athabasca, Alberta, Canada*
[b] *Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada*

Results: We included 42 trials in the meta-analysis and described 13 more studies narratively. Studies included 26 nondrug alternative treatments, 8 education interventions, 7 system modifications, 3 nonanalgesic drug treatments, 2 analgesic treatments, and 9 combined interventions. Pooled results at trial completion revealed that, except for nonanalgesic drugs and health system modification interventions, all interventions were at least moderately effective in reducing pain. Analgesic treatments (SMD −0.80; 95% CI −1.47 to −0.12; $P = .02$) showed the greatest treatment effect, followed by nondrug alternative treatments (SMD −0.70; 95% CI −0.95 to −0.45; $P < .001$), combined interventions (SMD −0.37; 95% CI −0.60 to −0.13; $P = .002$), and education interventions (SMD −0.31; 95% CI −0.48 to −0.15; $P < .001$).

Non solo farmaci: interventi non farmacologici per low back pain (Fernandez-Rodriguez R et al. *J Orthop Sports Phys Ther 2022;52(8):505-521)*

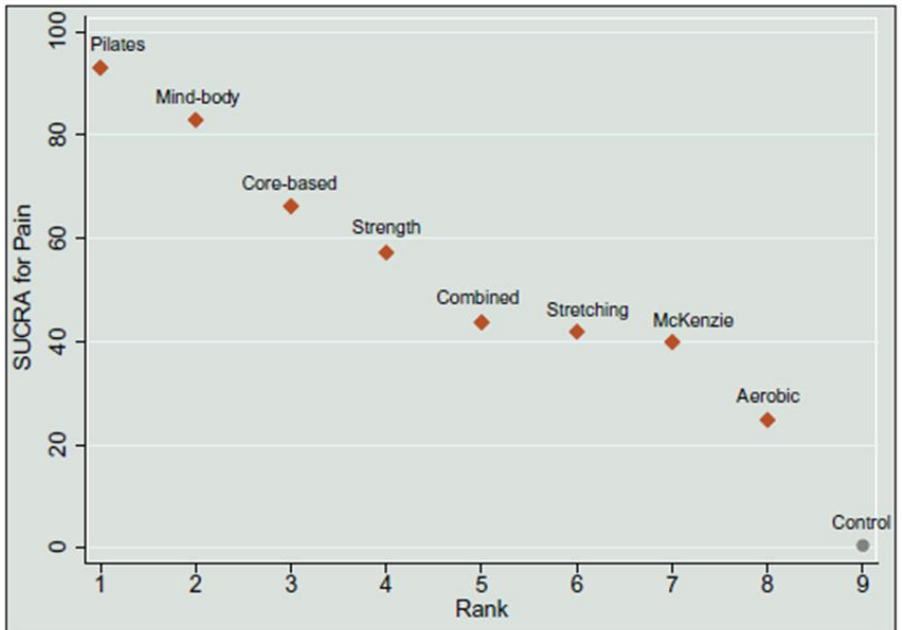


FIGURE 4. Ranking for each intervention on pain (SUCRA). Abbreviation: SUCRA, surface under the cumulative ranking curve.

Received: 29 January 2020 | Revised: 19 May 2020 | Accepted: 14 June 2020

DOI: 10.1111/eci.13347

REVIEW

WILEY

Comprehensive geriatric assessment in older adults with cancer: Recommendations by the Italian Society of Geriatrics and Gerontology (SIGG)

Domenico Fusco[1] | Alessandro Ferrini[2] | Giuseppe Pasqualetti[3] | Chiara Giannotti[4,5] | Matteo Cesari[6,7] | Alice Laudisio[2] | Alberto Ballestrero[4,5] | Stefano Scabini[5] | Patrizio R. Odetti[4,5] | Giuseppe F. Colloca[1] | Fabio Monzani[3] | Alessio Nencioni[4,5] | Raffaele Antonelli Incalzi[2] | Fiammetta Monacelli[4,5] | the Oncogeriatrics Group of the Italian Society of Gerontology, Geriatrics

[1]Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of the Sacred Heart School of Medicine, Teaching Hospital 'Agostino Gemelli', Rome, Italy

[2]Geriatric Unit, Campus Bio-Medico University, Rome, Italy

[3]Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa4, Pisa PI, Italy

[4]Department of Internal Medicine and Medical Specialties (DIMI), Section of Geriatrics, University of Genoa, Genoa, Italy

[5]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[6]Geriatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[7]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Terapia del dolore nell'anziano: conclusioni

- Dolore, entità complessa e multidimensionale >> Terapia multidimensionale
- Quantificazione, ma anche definizione di componenti e impatti
- Nei casi ipocomunicativi, i proxy del dolore
- Lo screening degli effetti avversi della terapia
- A monte e ove possibile, ottimizzare la terapia della/e patologia/e di fondo