

# Dolore Aggiornamenti Clinici

Organo ufficiale della Associazione Italiana per lo Studio del Dolore





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### TRIMESTRALE

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Copia omaggio riservata ai soci.

Tutti i diritti riservati.

A causa dei rapidi progressi della scienza medica si raccomanda  
 sempre una verifica indipendente delle diagnosi e dei dosaggi  
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# Pain Neuroscience Education: uno strumento evidence based per aumentare l'efficacia dell'intervento riabilitativo

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## Introduzione

Il dolore è un'esperienza normale nella vita delle persone e l'incapacità di percepirlo mette a rischio la sopravvivenza stessa. Ma convivere con il dolore non è un'esperienza normale ed è ciò che motiva le persone a ricercare aiuto (Bernard and Wright 2004).

Il dolore rappresenta una sfida importante per i professionisti della riabilitazione e solo un approccio di tipo biopsicosociale può render conto alla complessità della soggettiva esperienza dolorosa. Intuitivamente il dolore è un'esperienza inequivocabile e trasparente, facilmente interpretabile, tramite un modello patologico-strutturale, come un danno tissutale. Mentre il dolore acuto può essere considerato una spia di un qualcosa che non va nell'organismo e gli riconosciamo quindi una funzione utile, il dolore cronico diventa esso stesso malattia (Ercolani e Pasquini 2007). Negli ultimi trent'anni la nostra conoscenza sul dolore cronico e i suoi meccanismi è aumentata notevolmente grazie anche ai contributi delle tecniche di neuroimaging, dell'immunologia, delle neuroscienze, della psicologia...

Proprio alla luce di tali contributi, nel 2020

l'International Association for the Study of Pain (IASP) ha ridefinito il termine dolore come un'esperienza sensoriale ed emotiva spiacevole associata, o simile a quella associata, ad un danno tissutale attuale o potenziale (Raja, Carr et al. 2020) e ha sottolineato la complessità dell'esperienza dolorosa aggiungendo alcune note:

- Il dolore è sempre un'esperienza personale che è influenzata a vari livelli da fattori biologici, psicologici e sociali.
- Il dolore e la nocicezione sono fenomeni diversi, il dolore non può essere dedotto unicamente dall'attività nei neuroni sensoriali.
- Attraverso le loro esperienze di vita, gli individui apprendono il concetto di dolore.
- Il resoconto di una persona di un'esperienza come dolore dovrebbe essere rispettato.
- Sebbene il dolore di solito svolga un ruolo adattivo, può avere effetti negativi sulla funzione e sul benessere sociale e psicologico.
- La descrizione verbale è solo uno dei tanti comportamenti per esprimere dolore; l'incapacità di comunicare non nega la possibilità che un uomo o un animale provino dolore.

## La Pain Neuroscience Education

La letteratura suggerisce che l'approccio biopsicosociale e l'intervento multidisciplinare sono più efficaci a lungo termine nel trattamento del dolore cronico. Ma la natura del sistema sanitario e la formazione di base dei professionisti non sempre consentono l'applicazione di tale modello al paziente con sintomatologia dolorosa (Eneberg-Boldon, Schaack et al. 2020). Una possibilità per colmare questo gap ed aumentare l'efficacia delle terapie può derivare da un approccio psicoeducativo integrato alla pratica riabilitativa. In tal senso, la Pain Neuroscience Education (PNE), ovvero l'insieme di sedute educative per i pazienti per illustrare le basi neurobiologiche e neurofisiologiche del dolore e l'elaborazione del dolore da parte del sistema nervoso, allo scopo di rendere più consapevoli e coinvolti i pazienti stessi nel processo terapeutico, si inserisce a pieno titolo tra le competenze necessarie per il personale riabilitativo.

Nella letteratura scientifica l'approccio è definito con diversi termini quali *therapeutic neuroscience education* (Zimney, Louw et al. 2014), *explain pain* (Butler and Moseley 2003) e *pain neuroscience education* (Nijs, Paul van Wilgen et al. 2011). I primi studi degli anni '90 incitano alla ricerca nel campo, nel 1999 si tiene una prima presentazione del modello ad una conferenza della International Association for the Study of Pain a Vienna (Gifford and Muncey 1999) per arrivare tra il 2000 e il 2020 alla pubblicazione di numerosi RCT (randomized controlled trials) e di alcune revisioni sistematiche che sottolineano l'evidenza di efficacia dell'utilizzo dell'approccio PNE per il dolore muscoloscheletrico nel ridurre il dolore, la disabilità, la catastrofizzazione, le limitazioni fisiche al movimento e, non ultimo, l'utilizzo del sistema sanitario (Louw, Zimney et al. 2016).

### RESULTS BY YEAR

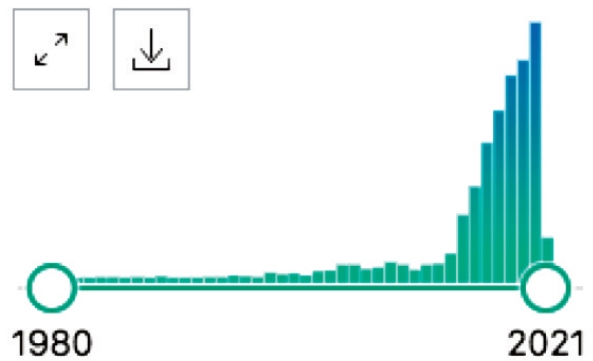


Figura 1

Timeline results by year Source: PubMed  
Search query: Pain Neuroscience Education

La figura 1 dà un'idea dell'incremento del numero di pubblicazioni negli anni.

## Valutazione biopsicosociale

Il primo passo per applicare la PNE nella pratica clinica è una corretta valutazione di tipo biopsicosociale. Qui presentiamo il modello **PSCEBSM** proposto da Wijma e colleghi nel 2016 (Wijma, van Wilgen et al. 2016) che si basa sulla valutazione dei seguenti aspetti:

### *P: pain*

Allo scopo di fornire un'adeguata PNE al paziente occorre innanzitutto valutare e differenziare la presenza dei tre tipi principali di dolore.

Diciotto esperti, provenienti da sette diversi Paesi, nel 2014 hanno indicato un set di criteri classificatori per distinguere la predominanza del tipo di dolore nocicettivo, neuropatico, da sensibilizzazione centrale (CS, central sensitization) nei pazienti con sintomatologia muscoloscheletrica (Nijs, Torres-Cueco et al. 2014). La tabella 1 riassume la differenziazione clinica.

Il primo step consiste nel riconoscere l'eventuale predominanza del dolore neuropatico, che può distinguersi da quello da CS per la presenza o assenza di un danno a livello del sistema nervoso somatosensoriale (Treede, Jensen et al. 2008).

Dolore nocicettivo	Dolore neuropatico	Dolore non neuropatico da CS
Storia di danno tissutale nelle precedenti 6-8 settimane.	Storia di lesioni o malattie del sistema nervoso o danno post-traumatico/post-chirurgico del sistema nervoso.	No storia di lesione, danno o malattia a livello del sistema nervoso.
Il dolore si riduce seguendo la naturale fase di guarigione.	Gli esami diagnostici rivelano anomalie a livello del sistema nervoso.	Non ci sono indicazioni particolari a livello delle indagini diagnostiche.
Connesso al danno tissutale o al danno potenziale	Connesso a una causa medica o sistemica come stoke, herpes, diabete o una forma di malattia neurodegenerativa.	Non vi sono cause mediche stabilite a giustificare il dolore.
Dolore localizzato, spesso con segni diagnostici quali edema, ematoma...	La distribuzione del dolore e l'eventuale disfunzione sensoriale sono neuroanatomicamente logici.	La distribuzione del dolore è neuroanatomicamente illogica e, a livello segmentario, non correlata alla fonte primaria di nocicezione.
Il dolore è descritto come acuto, definito, dolorante, pulsante.	Il dolore è spesso descritto come bruciante, pungente, formicolante.	Il dolore è spesso descritto in modo vago e sfumato.

**Tabella 1** - Criteri di differenziazione clinica tra dolore prevalentemente nocicettivo, neuropatico, da sensibilizzazione centrale (CS) (Wijma, van Wilgen et al. 2016).

Il secondo passo consiste nel differenziare tra la predominanza di dolore nocicettivo o di dolore da CS. Si tratta probabilmente di CS quando il dolore percepito e la conseguente disabilità sono sproporzionati rispetto alla natura della lesione o della patologia. Ciò accompagnato da uno dei seguenti due criteri: 1) la presenza di una distribuzione del dolore diffusa o neuroanatomicamente illogica, quindi non correlata a dermatomeri e miomeri; 2) ipersensibilità non correlata al sistema muscoloscheletrico.

Per il criterio 1 si può utilizzare il Widespread Pain Index (WPI) che valuta la distribuzione del dolore mappando la sua localizzazione. Include 19 regioni corporee, assegnando 1 punto per ogni regione dolorante si ottiene quindi un punteggio che se supera il 7 è suggestivo di dolore diffuso (Margolis, Tait et al. 1986, Margolis, Chibnall et al. 1988).

Per il criterio 2 si può utilizzare il Central Sensitization Inventory (CSI) che, tra le altre cose, valuta l'ipersensibilità alla luce, agli odori, al tatto e l'ipersensibilità cutanea.

Comprende 25 item e, in base agli studi di validazione, un punteggio superiore a 40 è fortemente suggestivo di presenza di dolore da CS. Validazione italiana a cura di Chiarotto e coll.

(Chiarotto, Viti et al. 2018).

L'outcome della valutazione del tipo di dolore può quindi essere predominante nocicettivo, predominante neuropatico, predominante da CS o di tipo misto.

Il modello PSCEBSM descrive poi i successivi passi per identificare quali fattori giocano un ruolo fondamentale nel perseverare della sintomatologia dolorifica.

#### *S: Somatic and Medical Factors*

L'utilizzo di farmaci che interagiscono con il sistema nervoso centrale e la presenza di altre patologie presenti o passate, il non uso, o l'uso improprio, di segmenti corporei, cambiamenti di pattern di movimento, di forza, di tono e tensione muscolare sono tutti fattori che vanno indagati. L'esame fisioterapico deve quindi tenere conto della qualità del movimento, dell'evocazione di sintomi e dell'eventuale paura del movimento. Sarà poi il ragionamento clinico a valutare quanto questi fattori possono contribuire alla persistenza del dolore e alla CS.

#### *C: Cognition/Perceptions*

La percezione del paziente degli aspetti fisici e mentali del dolore e delle sue conseguenze, le

aspettative di prognosi e cura, pattern cognitivi quali tendenza alla catastrofizzazione, ingiustizia percepita ecc. possono contribuire al mantenimento di meccanismi di CS e possono essere valutati tramite appositi questionari (Wijma, van Wilgen et al. 2016).

#### *E: Emotional Factors*

I fattori emozionali, correlati a cognizione e percezione, includono ansia, rabbia, paura, depressione, stress post-traumatico. Dove il professionista lo ritenga necessario, possono essere approfonditi tramite test ad hoc (Wijma, van Wilgen et al. 2016).

#### *B: Behavioral Factors*

È importante valutare il comportamento e gli adattamenti adottati in conseguenza del dolore, quali l'evitamento o la persistenza di attività.

#### *S: Social Factors*

Variabili sociali e/o ambientali possono causare stress e avere effetti negativi sul dolore (per esempio fattori abitativi, lavorativi, relazionali, supporto sociale...).

#### *M: Motivation*

Determinare la motivazione e la prontezza al cambiamento è vitale per il trattamento riabilitativo. La percezione della causa del dolore e le aspettative di trattamento vanno comprese e valutate per fornire adeguata PNE.

## L'intervento di PNE

Valutare il dolore da una prospettiva biopsicosociale, comprendendo l'essenza della problematica del paziente, richiede tempo ma dà i suoi frutti. Ovviamente è importante concentrarsi sui fattori modificabili ed essere consapevoli degli aspetti non modificabili.

Le aspettative del paziente riguardano spesso farmaci, chirurgia e procedure veloci ma queste sono speranze non sempre realistiche nella cura del dolore persistente.

Cambiamenti nell'attività fisica, nei comporta-

menti psicosociali e nello stile di vita possono avere risultati promettenti a lungo termine (Seers 2002). La sfida è motivare il paziente. La PNE può creare le fondamenta per un approccio più intenzionale da parte di un paziente coinvolto e consapevole. La teoria andragogica ci dice che quando gli adulti comprendono il perché qualcosa deve essere fatto in un determinato modo e il come funzionano le cose si viene a stabilire un maggiore livello di motivazione intrinseca (Breese e French 2012).

Aiutare il paziente a comprendere la sua condizione individuale di dolore può portare a un miglioramento nella qualità di vita e a un aumento dei progressi funzionali (Louw, Nijs et al. 2017). Una maggiore compliance da parte del paziente e rilevanti cambiamenti comportamentali, quali rafforzata capacità decisionale e indipendenza in tecniche di trattamento autonome, possono essere ulteriori conseguenze di un approccio di cura efficiente ed efficace nel rompere il circolo del dolore (Stones e Cole 2014).

Una terapia individualizzata può iniziare spiegando la diagnosi biopsicosociale al paziente, rassicurandolo del fatto che il suo dolore è reale e rendendogli comprensibili le cause del dolore (neurofisiologia del dolore, meccanismi nocicettivi, neuropatici, da CS). I fattori modificabili e la ricettività del paziente al cambiamento guideranno quindi i contenuti e l'attitudine del fisioterapista durante la PNE. I meccanismi di plasticità del sistema nervoso, i contributi dei fattori psicosociali e delle credenze che concorrono al mantenimento del dolore sono altri aspetti che il paziente dovrebbe interiorizzare per poter meglio affrontare i cambiamenti richiesti dal processo di presa in carico e diventare self-manager del suo dolore, capendo e controllando la varietà dei fattori influenti.

La PNE è più efficace quando integrata alla terapia manuale e alla prescrizione di esercizi al domicilio. Il fisioterapista esperto è in grado di applicare la terapia manuale accanto all'esercizio fisico di appropriata intensità, fre-

quenza e durata. La prescrizione di un piano di esercizio progressivo da svolgere in autonomia che tiene conto dei bisogni clinici e delle preferenze individuali contribuirà ad aumentare la funzionalità e a diminuire la paura e l'evitamento del movimento verso l'indipendenza. Se non vi sono controindicazioni, l'obiettivo è un programma che combini esercizi in progressione per la flessibilità, la forza, l'equilibrio e la resistenza che il paziente possa tollerare e modificare autonomamente.

## Approccio multidisciplinare

Ferma restando la competenza del fisioterapista nel fornire adeguata PNE, integrata a un opportuno programma riabilitativo, la letteratura sottolinea come, soprattutto in casi di dolore persistente, un approccio multidisciplinare possa sortire maggior efficacia. Tecniche di Mindfulness, Training Autogeno, Acceptance and Commitment Therapy,

Terapia Cognitivo Comportamentale, apprese con il supporto di un esperto psicologo del dolore, possono infatti incidere maggiormente su fattori psicologici quali problemi relazionali, dipendenze, ansia, depressione, stress e agire positivamente su paura del movimento, alleanza terapeutica, aderenza al programma di cura (Daniel, Narewska et al. 2008, Casey, Cotter et al. 2020, Markfelder and Pauli 2020). Similmente, nutrizionisti esperti, possono contribuire nell'incoraggiare strategie di dieta salutari (Brain, Burrows et al. 2019).

Un team che si occupa di dolore deve assicurarsi che ogni membro abbia chiari i punti chiave e lo stato dell'arte della ricerca, al fine di fornire messaggi coerenti di PNE e di dare al paziente con sintomatologia complessa di dolore persistente un piano di trattamento integrato, diretto, comprensivo che possa raggiungere il miglior livello di qualità di vita possibile.

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# Gestione del paziente con dolore cronico durante la pandemia da SARS Covid 19

## L'esperienza della ASL 4 Chiavarese, Regione Liguria

Enrico Cinque, Monica Bonfiglio, Sara Casanova, Kathia Licciardi

Centro Spoke – Area Metropolitana della Rete Ligure di Terapia del Dolore

Il Centro di Medicina del Dolore della A.S.L. 4 Chiavarese – Regione Liguria viene costituito a settembre 2010 in ottemperanza alla Legge 38 del 2010 che ha come finalità quella di garantire alla cittadinanza un centro per la diagnosi e la terapia del dolore. In realtà si andava a colmare il vuoto lasciato qualche anno prima da uno dei pionieri dell'Algologia Italiana, il Dott. Guido Orlandini. A lui, che ha sempre cercato di conferire alla Medicina e Terapia del Dolore una dignità al pari delle altre specializzazioni mediche, dobbiamo la realizzazione di due libri che rappresentano ancora oggi, veri manuali di riferimento per tutti gli Algologi Italiani: - "La Semeiotica del Dolore" e "La Chirurgia percussiva del Dolore" – Edizioni Delfino.

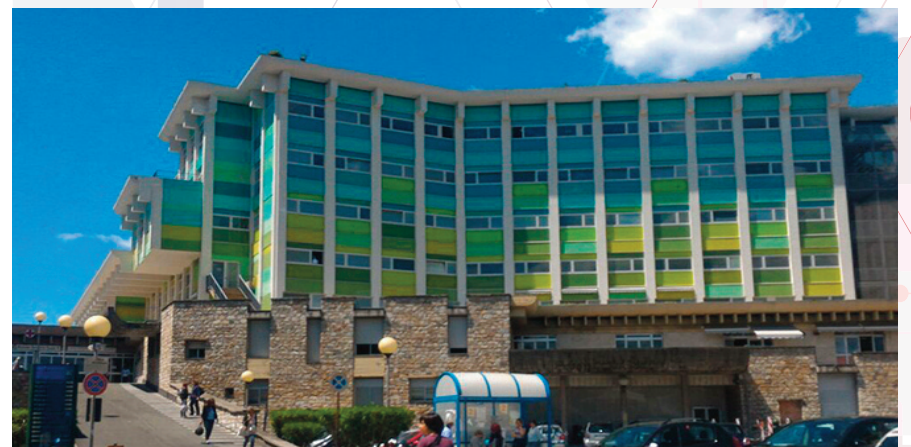
Il primo team è costituito da medici anestesisti: il Dott. G. Altavilla che aveva coadiuvato negli anni precedenti il Dott. Orlandini, dalla Dott.ssa S. Casanova, e dal Dott. E. Cinque che con il Dott. F. Castagnola e la Dott.ssa P. Raganti avevano già maturato esperienza nelle Cure Palliative e Terapia del Dolore presso l'Associazione Gigi Ghirotti di Genova diretta

dal Prof. Franco Henriquet. La responsabilità organizzativa viene affidata alla Dott.ssa M. Bonfiglio allora Responsabile della S.S. Terapia Intensiva. L'inizio di questo nuovo percor-

so algologico, coincide con la partecipazione al 1° Corso di formazione in Semeiotica e Medicina del Dolore presso l'Advanced Algology Research a Bertinoro nel 2010.



(Bertinoro 2010)



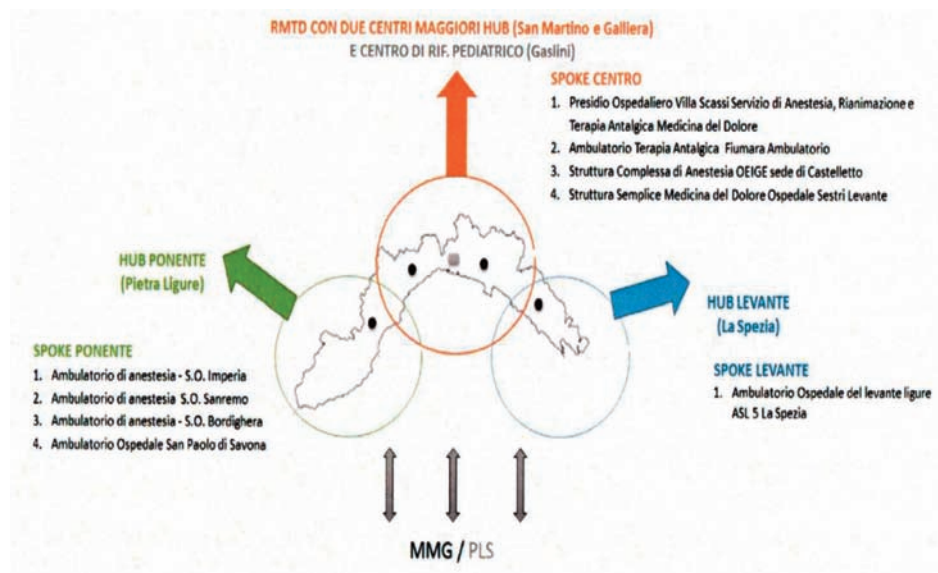
(Ospedale di Sestri Levante 3° piano S.S. Medicina del Dolore)

Negli anni successivi l'attività del nostro centro è aumentata progressivamente: le prime visite algologiche sono passate dalle 125 del 2011 alle 565 del 2019 e le prestazioni totali erogate in un anno sono circa 2000.

L'Ambulatorio diventa S.S. di Medicina del Dolore ed è riconosciuto come Centro Spoke – Area Metropolitana della Rete Ligure di Terapia del Dolore con Delibera Regionale dell'Azienda Sanitaria Ligure n. 347 del 30/09/2020.

Anche nella nostra Regione a Marzo 2020 con l'inizio della pandemia da SARS Covid-19, l'attività della S.S. di Medicina del Dolore ha subito nelle prime fasi una chiusura totale (sola eccezione le poche urgenze), in quanto il personale medico è stato riallocato temporaneamente nell'equipe della Terapia Intensiva Respiratoria per la gestione dei pazienti affetti da grave insufficienza respiratoria acuta. Si è osservata pertanto una drastica riduzione delle attività Ambulatoriale e di Sala Operatoria passando dalle 180 prestazioni di Gennaio e Febbraio a 85 prestazioni nel mese di Marzo, alle 10 prestazioni ad Aprile e 26 prestazioni a Maggio.

Durante tutta la pandemia le vere urgenze algologiche sono state eseguite dal Direttore di Struttura nei ritagli di tempo, rappresentate principalmente da prime visite algologiche urgenti e esecuzioni di iniezioni peridurali per neuropatie infiammatorie lombari su indicazione dei reparti o di

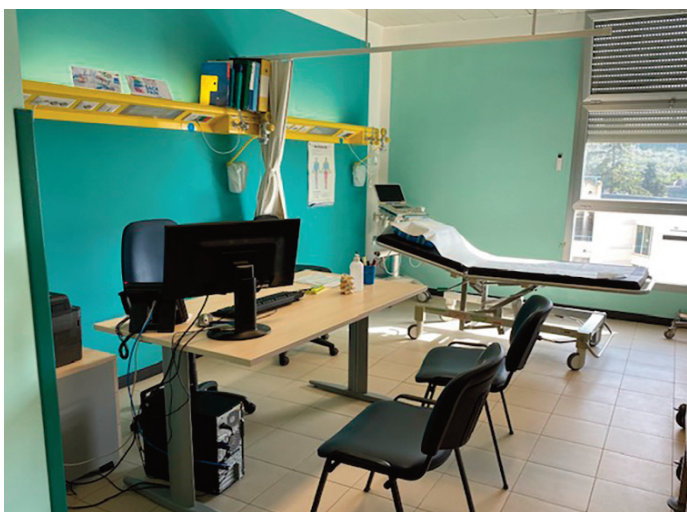


accessi urgenti tramite in Pronto Soccorso. La nostra Assistente Sanitaria e l'Operatrice Sanitaria offrendo una risposta telefonica quotidiana, hanno garantito una continuità assistenziale ai pazienti in carico alla struttura, per tutto il periodo della pandemia, consentendo un prezioso collegamento tra i pazienti e i medici impegnati nell'emergenza. A Maggio 2020 con la chiusura della Terapia Intensiva Respiratoria coincidente con la fine della prima ondata pandemica, riprende l'attività della S.S. Medicina del Dolore: vengono ripristinate le agende ospedaliere per la prenotazione delle prime visite algologiche e delle seconde visite di controllo, si è implementata l'attività ambulatoriale per esterni passando dalle 24 ore a 30 ore settimanali. Tale ampliamento di attività è conseguente all'aumento di richieste per prime visite algologiche e procedure interventistiche,

ma anche alla necessità di garantire all'Ospedale di Sestri Levante (divenuto durante la pandemia Ospedale di riferimento per il ricovero e la cura dei pazienti Covid), la presenza di un Anestesista-Rianimatore per tutta la settimana al fine di garantire le consulenze e le urgenze nei reparti Covid.

Nei mesi estivi, in assenza di disponibilità di sala operatoria le procedure invasive sono state eseguite con tecnica ecografica in Ambulatorio in seduta dedicata. Purtroppo a Novembre 2020 con l'aumento dei contagi, coincidente con l'inizio della seconda ondata pandemica e la nuova riapertura della Terapia Intensiva Respiratoria, ci ha costretto a una riduzione dell'attività al 50% proseguita anche nel mese di dicembre e tutt'ora in corso. Nonostante le difficoltà l'anno 2020 si è concluso con l'erogazione di 1537 prestazioni (con tre mesi di sospensione

Infiltrazione peri-intraarticolare (in scopia o tecnica ecografica)	224	
Iniezione peridurale di anestetico nel canale vertebrale (in scopia)	308	
Prima visita algologica	429	
Seconda visita algologica	575	
Neurolesione branca mediale articolazioni zigoapofisarie	10	
Radiofrequenza pulsata su nervi periferici	10	
Pazienti arruolati in Cannabis Terapeutica	200	



Ambulatorio di Medicina del dolore



(Ospedale di Rapallo – Sale Operatorie)



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Equipe infermieristica dedicata: Kathia Licciardi, Monica Minatore, Barbara De Martini, Monica Cavazzini, Tamara Mannori

Assistente Sanitaria: Laura Rosi

Segreteria: Roberta Paoletti

di attività). Da febbraio 2021 la Regione Liguria sta lavorando allo sviluppo della piattaforma informatica per l'esecuzione della Televisita che sarà operativa a

breve. Il nostro Centro ha accolto con favore l'iniziativa e si sta adoperando perchè questa opzione offerta, consentirà un attento monitoraggio terapeutico in remo-

to dei pazienti con dolore cronico per i quali risulta difficoltosa la visita in presenza presso l'Ambulatorio di Medicina del Dolore.



# Documento di consenso sull'uso degli oppioidi per il dolore cronico non oncologico

*Iniziativa EFIC in collaborazione con nove società scientifiche europee*

*Le raccomandazioni sull'uso di oppioidi nel trattamento del dolore cronico non oncologico sono state elaborate sulla base di un documento di consenso cui hanno collaborato nove società scientifiche europee, coordinate dalla European Pain Federation (EFIC). Il gruppo di lavoro ha esaminato gli studi e le prove di efficacia sull'uso degli oppiacei per il trattamento del dolore cronico non oncologico. Il documento finale è stato pubblicato sull'European Journal of Pain. Obiettivo delle raccomandazioni è fugare le preoccupazioni su una crisi da oppioidi in Europa, come successo invece negli Stati Uniti.*

Le nuove raccomandazioni consigliano che gli oppioidi non dovrebbero essere prescritti nei pazienti con dolore primario cronico, poiché in questi pazienti non funzionano e non dovrebbero essere utilizzati come "terapia di prima linea" nemmeno per le sindromi dolorose seconda-

rie croniche. I medici dovrebbero prima prendere in considerazione farmaci non oppioidi o terapie non farmacologiche consolidate (per esempio, esercizio fisico, terapie psicologiche) e passare alla prescrizione di oppioidi solo se queste terapie di prima linea non funzionassero, non fossero

tollerate o controindicate.

Il dolore cronico primario è definito dall'Organizzazione Mondiale della Sanità come un dolore che dura più di tre mesi, causando un significativo disagio emotivo o disabilità funzionale, ma che non può essere spiegato da un'altra specifica condizione medica, come nel caso di fibromialgia, emicrania cronica, sindrome dell'intestino irritabile e lombalgia aspecifica.

Il dolore secondario cronico, al contrario, è il dolore dovuto a una condizione medica defini-

ta, a seguito di interventi chirurgici o lesioni, malattie interne, malattie muscolari, delle ossa o delle articolazioni, o danni ai nervi.

Circa un quarto degli europei soffre di dolore cronico e in circa l'80% di questi casi il dolore non è correlato al cancro. In passato, gli oppioidi sono stati spesso prescritti per il dolore cronico non oncologico, perché le persone presumono che siano i farmaci antidolorifici più potenti, ma senza una consapevolezza dei potenziali danni derivanti dalla loro assunzione.

Nel corso degli ultimi dieci anni in alcuni paesi europei le prescrizioni di oppioidi sono aumentate e questo incremento ha indotto delle preoccupazioni. Per questo motivo le nuove raccomandazioni intendono fornire un'assistenza più sicura ed efficace alle persone con dolore cronico non oncologico, migliorare la comunicazione tra medici e pazienti su benefici e danni dell'uso di oppioidi prescritti per il dolore cronico e fornire indicazioni ai medici sull'uso appropriato degli oppioidi, oltre a diminuire il consumo dannoso di oppioidi.

Le raccomandazioni invitano i medici, prima di prescrivere gli oppioidi, a stabilire gli obiettivi di trattamento con i loro pazienti, inclusi obiettivi realistici di funzionalità fisica quotidiana e per il dolore. Inoltre, prima di iniziare - e regolarmente durante la terapia con oppioidi - i medici dovrebbero discutere

con i loro pazienti i danni noti e i benefici realistici della terapia con oppioidi (e delle alternative). E se gli oppioidi sono usati per trattare il dolore secondario cronico, dovrebbero sempre essere combinati con antidolorifici e terapie non a base di oppioidi.

I medici devono monitorare attentamente i pazienti dopo l'inizio del trattamento con oppiacei e la terapia deve continuare solo se vi è un miglioramento clinicamente significativo del dolore e della funzionalità fisica superiore ai rischi per la sicurezza del paziente.

Le nuove raccomandazioni EFIC consigliano di iniziare con dosi basse e procedere lentamente. All'inizio i medici dovrebbero prescrivere la dose efficace più bassa: meno di 50 milligrammi equivalenti (MME) di morfina al giorno.

Dovrebbero anche evitare di aumentare il dosaggio oltre i 90 MME /die, o giustificare accuratamente qualsiasi decisione in tal senso.

La terapia con oppioidi deve interrompersi se gli obiettivi concordati all'inizio del trattamento non vengono raggiunti o se si verificano eventi avversi intollerabili. Il trattamento deve anche essere interrotto se gli obiettivi possono essere raggiunti attraverso altri trattamenti non oppiacei o se ci sono preoccupazioni che il paziente sviluppi dipendenza.

Brona Fullen, Presidente dell'EFIC, ha dichiarato che queste raccomandazioni chiari-

scono non solo quale ruolo dovrebbero svolgere gli oppioidi nella gestione del dolore cronico, ma anche il ruolo del trattamento multimodale.

Secondo il coordinatore della stesura del documento, Winfried Häuser, professore di medicina interna, medicina psicosomatica e medicina del dolore a Saarbrücken, il dibattito sulla prescrizione di oppioidi per il dolore cronico non oncologico si è polarizzato: gli oppioidi sono visti o come un rischio pericoloso per tutti i pazienti, che porta alla dipendenza e alla morte, o sono considerati gli antidolorifici più potenti per qualsiasi tipo di dolore. Il documento intende offrire un orientamento tra le prove scientifiche e cliniche e fornire raccomandazioni su quando gli oppioidi potrebbero essere utili per il dolore cronico non oncologico e quando non lo sono. Gli oppioidi sono ancora importanti nella gestione del dolore cronico non oncologico, ma solo in alcune sindromi dolorose croniche selezionate e solo se analgesici non farmacologici e non oppiacei hanno fallito o non sono tollerati.

La professoressa Maria Caterina Pace, presidente dell'Associazione Italiana per lo Studio del Dolore (Capitolo nazionale IASP® ed EFIC®) ha così commentato:

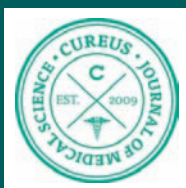
*«L'appropriatezza terapeutica, basata sulle evidenze e sulla conoscenza delle terapie farmacologiche, come guida per la costruzione di percorsi dia-*

*agnostico-terapeutici multidisciplinari, è da anni al centro dell'impegno della nostra associazione, il nuovo documento di consenso promosso dall'European Pain Federation fa chiarezza e offre raccomandazioni basate su criteri di efficacia con spunti di riflessione importanti anche per la pratica clinica dei medici, che non essendo specialisti in terapia del dolore, devono prendersi cura di pazienti con dolore cronico non oncologico».*

Testo completo

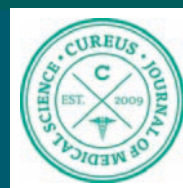
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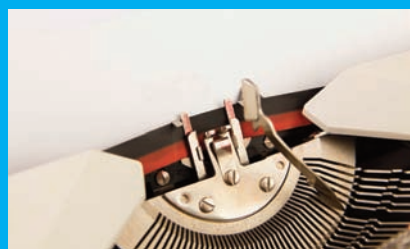
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## A ligand-receptor interactome platform for discovery of pain mechanisms and therapeutic targets

Wangzhou A., Paige C., Neerukonda S.V., Naik D.K., Kume M., David E.T., Dussor G., Ray P.R., Price T.J.  
*Science Signaling* 16 Mar 2021  
 Vol. 14, Issue 674, eabe1648  
 DOI: 10.1126/scisignal.abe1648

**Abstract:** Chronic pain impairs quality of life, is challenging to treat, and accompanies various diseases. Wangzhou et al. integrated bulk and single-cell RNA sequencing of ligand and receptor gene expression in the dorsal root ganglion (DRG) and various peripheral cell types from humans and mice. Computational analysis of these data enabled the construction of a connectome of potential and cell type-specific interaction points between sensory nerves and innervated tissues. With validation in a mouse model of mechanical pain, their findings suggest that blocking heparin-binding epidermal growth factor (HBEGF) signaling may be a common and effective way to alleviate chronic pain in arthritis, colitis, and pancreatic cancer. The resource and the approach, in general, may be used to predict mechanisms of cell-cell communication between various tissues and cell types.

## Altered central pain processing in fibromyalgia-A multimodal neuroimaging case-control study using arterial spin labelling

Müller M, Wüthrich F, Federspiel A, Wiest R, Egloff N, Reichenbach S, Exadaktylos A, Jüni P, Curatolo M, Walther S.

*PLoS One.* 2021 Feb 2;16(2):e0235879

DOI: 10.1371/journal.pone.0235879. eCollection 2021

**Abstract:** Fibromyalgia is characterized by chronic pain and a striking discrepancy between objective signs of tissue damage and severity of pain. Function and structural alterations in brain areas involved in pain processing may explain this feature. Previous case-control studies in fibromyalgia focused on acute pain processing using experimentally-evoked pain paradigms. Yet, these studies do not allow conclusions about chronic, stimulus-independent pain. Resting-state cerebral blood flow (rsCBF) acquired by arterial spin labelling (ASL) may be a more accurate marker for chronic pain. The objective was to integrate four different functional and structural neuroimaging markers to evaluate the neural correlate of chronic, stimulus-independent pain using a resting-state paradigm. In line with the pathophysiological concept of enhanced central pain processing we hypothesized that rsCBF is increased in fibromyalgia in areas involved in processing of acute pain. We performed an age matched case-control study of 32 female fibromyalgia patients and 32 pain-free controls and calculated group differences in rsCBF, resting state functional connectivity, grey matter volume and cortical thickness using whole-brain and region of interest analyses. We adjusted all analyses for depression and anxiety. As centrally acting drugs are likely to interfere with neuroimaging markers, we performed a subgroup analysis limited to patients not taking such drugs. We found no differences between cases and controls in rsCBF of the thalamus, the basal ganglia, the insula, the somatosensory cortex, the prefrontal cortex, the anterior cingulum and supplementary motor area as brain areas previously identified to be involved in acute processing in fibromyalgia. The results remained robust across all neuroimaging markers and when limiting the study



population to patients not taking centrally acting drugs and matched controls. In conclusion, we found no evidence for functional or structural alterations in brain areas involved in acute pain processing in fibromyalgia that could reflect neural correlates of chronic stimulus-independent pain.



## The Evaluation of Nailfold Capillaroscopy Pattern in Patients With Fibromyalgia

Coşkun Benlidayi I, Kayacan Erdoğan E, Sariyildiz A.

*Arch Rheumatol* 2021;36(x):i-viii

DOI: 10.46497/ArchRheumatol.2021.8359

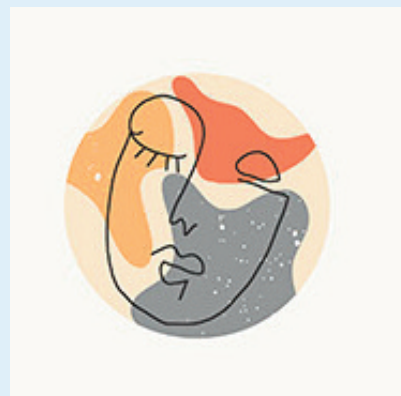
**Objectives:** This study aims to evaluate nailfold capillaroscopic pattern in patients with fibromyalgia and to assess the relation of capillaroscopic parameters with clinical variables and disease-related measures.

**Patients and methods:** This cross-sectional, case-control study included 60 participants (4 males, 56 females; mean age: 44.0±8.2 years; range, 26 to 64 years) between August 2019 and November 2019. All participants were divided into two groups as the primary fibromyalgia group (n=30) who met the 2016 modified American College of Rheumatology Diagnostic Criteria for Fibromyalgia and the control group (n=30) consisting of age- and sex-matched healthy individuals. Nailfold capillaroscopy was performed

by a digital microscope under a magnification of 200×. Capillary density, capillary loop diameter, number of dilated, giant and neoangiogenic capillaries, capillary shape, number of avascular areas, micro-aneurysms and micro-hemorrhages were evaluated by an assessor who was blind to the group allocation. In the fibromyalgia group, Widespread Pain Index, Symptom Severity Scale scores, and Fibromyalgia Severity scores were calculated. Health status and presence of benign joint hypermobility syndrome (BJHS) were evaluated using the Fibromyalgia Impact Questionnaire (FIQ) and revised Brighton criteria, respectively.

**Results:** Of the capillaroscopic parameters, the mean capillary loop diameter, number of micro-aneurysms, avascular areas, and neoangiogenic capillaries were significantly higher in the patient group compared to the controls ( $p<0.001$ ,  $p=0.016$ ,  $p=0.038$ , and  $p=0.04$ , respectively). Nailfold capillaroscopic findings did not significantly differ between the patients with (n=16) and without concomitant BJHS (n=14). Of the disease-related measures, only FIQ score showed a weak correlation with the number of dilated capillaries ( $p=0.324$ ).

**Results:** Patients with fibromyalgia have distinct capillaroscopic patterns than healthy population. Capillaroscopic features, in general, are not related to clinical variables and disease-related measures.



## Live Video Adaptations to a Mind-Body Activity Program for Chronic Pain and Cognitive Decline: Protocol for the Virtual Active Brains Study

Mace RA, Doorley JD, Popok PJ, Vranceanu A.

*JMIR Res Protoc* 2021;10(1):e25351

DOI: 10.2196/25351

**Background:** Chronic pain (CP) and cognitive decline (CD) are costly, challenging to treat, highly prevalent among older adults, and worsen each other over time. We are iteratively developing Active-Brains-Fitbit (AB-F), a live video program for older adults with CP and CD that teaches mind-body skills and gradual increases in step count aided by a Fitbit. AB-F has demonstrated feasibility, acceptability, and signals of improvement in emotional, physical, and cognitive function when delivered in-person to this population.

**Objective:** We are conducting a feasibility randomized controlled trial (RCT) of AB-F versus a time- and dose-matched educational control (Health Enhancement Program; HEP) in older adults with CP and CD. Due to COVID-19 and qualitative feedback from former participants, both programs are delivered in an entirely virtual format via live video (Zoom). Here, we describe our virtual study protocol, manualized treatments, evaluation plan, and study design. We will evaluate feasibility benchmarks and the potential of AB-F to improve physical, emotional, and cognitive function.

**Methods:** This is a single-blind pilot RCT.

Participants are randomized to one of two programs: AB-F or HEP. Patients are recruited through pain clinic referrals, institutional registries, and IRB-approved flyers. Interested participants are screened for eligibility via telephone and provide electronic informed consent.

After randomization, participants are mailed all study documents, including their treatment manual, an ActiGraph accelerometer, and a Fitbit (separate sealed envelope for AB-F only). Both conditions are manualized and delivered over 8 weekly sessions via secure live video. Participants complete self-report and performance-based (6-minute walk test, Montreal Cognitive Assessment) outcome measures via live video at baseline and post-intervention. Primary outcomes

are a-priori set feasibility (recruitment, quantitative measures, adherence), acceptability, credibility, expectancy, and satisfaction benchmarks.

Secondary outcomes are physical, cognitive, and emotional function, as well as intervention targets (social function, pain intensity, pain-specific coping, mindfulness).

**Results:** The trial is ongoing. We have recruited 21 participants (10 AB-F, 11 HEP) across two rounds. Only two participants have withdrawn (1 before baseline, 1 before first session).

All 19 remaining participants have completed the baseline. In the first round, attendance is high (11/12 completed all 4 sessions so far) and AB-F participants are adherent to their Fitbit and step goals (5/6).

**Conclusions:** Preliminary findings are promising for the feasibility of our completely virtual AB-F intervention but need to be confirmed at the trial conclusion. This study will answer important questions about the feasibility of delivering a completely virtual mind-body and activity program to older adults with comorbid CP and CD, which, to our knowledge, is unprecedented. Details on integrating multiple digital platforms for the virtual assessments and intervention delivery will inform treatment development for older adults generally and those with CP-CD specifically, during the COVID-19 pandemic and beyond. Clinical Trial: ClinicalTrial.gov NCT04044183.



## COVID-19 and the Opioid Epidemic: Two Public Health Emergencies That Intersect With Chronic Pain

Manchikanti, L., Vanaparthy, R., Atluri, S. et al.

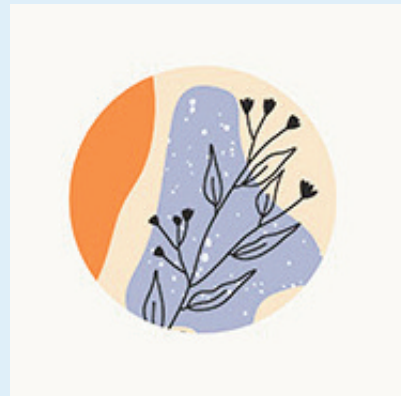
*Pain Ther* (2021)

DOI: 10.1007/s40122-021-00243-2

The COVID-19 pandemic has affected the entire world and catapulted the United States into one of the deepest recessions in history. While this pandemic rages, the opioid crisis worsens. During this period, the pandemic has resulted in the decimation of most conventional medical services, including those of chronic pain management, with the exception of virtual care and telehealth. Many chronic pain patients have been impacted in numerous ways, with increases in cardiovascular disease, mental health problems, cognitive dysfunction, and early death. The epidemic has also resulted in severe economic and physiological consequences for providers.

Drug deaths in America, which fell for the first time in 25 years in 2018, rose to record numbers in 2019 and are continuing to climb, worsened by the coronavirus pandemic. The opioid epidemic was already resurfacing with a 5% increase in overall deaths from 2018; however, the preliminary data show that prescription opioid deaths continued to decline, while at the same time deaths due to fentanyl, methamphetamine, and cocaine climbed, with some reductions in heroin deaths. The health tracker data also showed that along with an almost 88% decline in elective surgeries, pain-related prescriptions declined 15.1%. Despite increases in telehealth, outpatient services declined and only began returning towards normal at an extremely slow pace, accompanied by reduced productivity and increased practice costs.

This review, therefore, emphasizes the devastating consequences of concurrent epidemics on chronic pain management and the need to develop best practice efforts to preserve access to treatment for chronic pain.



## Human surrogate models of central sensitization: a critical review and practical guide

Quesada, C., Kostenko, A., Ho, I., Leone, C., Nochi, Z., Stouffs, A., Wittayer, M., Caspani, O., Finnerup, N.B., Mouraux, A., Pickering, G., Tracey, I., Truini, A., Treede, R.-D. and Garcia-Larrea, L.

(2021), *European Journal of Pain*. Accepted Author Manuscript.

DOI: 10.1002/ejp.1768

**Background:** As in other fields of medicine, development of new medications for management of neuropathic pain has been difficult since preclinical rodent models do not necessarily translate to the clinics. Aside from ongoing pain with burning or shock-like qualities, neuropathic pain is often characterized by pain hypersensitivity (hyperalgesia and allodynia), most often towards mechanical stimuli, reflecting sensitization of neural transmission.

**Data treatment:** We therefore performed a systematic literature review (PubMed-Medline, Cochrane, WoS, ClinicalTrials) and semi-quantitative meta-analysis of human pain models that aim to induce central sensitization, and generate hyperalgesia surrounding a real or simulated injury.

**Results:** From an initial set of 1569 reports, we identified and analyzed 269 studies using more than a dozen human models of sensitization. Five of these models (intra-dermal or topical capsaicin, low- or high-frequency electrical stimulation, thermode-induced heat-injury) were found to reliably induce secondary hyperalgesia to pinprick and have been implemented in multiple laboratories. The ability of these models to induce dynamic mechanical allodynia was however

substantially lower. The proportion of subjects who developed hypersensitivity was rarely provided, giving rise to significant reporting bias. In four of these models pharmacological profiles allowed to verify similarity to some clinical conditions, and therefore may inform basic research for new drug development.

**Conclusions:** While there is no single “optimal” model of central sensitization, the range of validated and easy-to-use procedures in humans should be able to inform preclinical researchers on helpful potential biomarkers, thereby narrowing the translation gap between basic and clinical data.



## Cognitive Load and the Effectiveness of Distraction for Acute Pain in Children

Gaultney, W., Dahlquist, L. and Quito, R  
(2021) *Eur J Pain*. Accepted Author Manuscript.  
DOI: 10.1002/ejp.1770

**Background:** Distraction tasks that place continuous, high demand on executive resources have been shown to reduce pain intensity and pain unpleasantness ratings in healthy adult samples. We examined the effects of a high-demand ‘working memory’ 1-back task compared to a low-demand ‘motor control’ task on pain intensity and unpleasantness ratings in healthy children. Additionally, dispositional mindfulness was examined to explore the mechanisms of distraction on the affective processing of pain.

**Methods:** To examine these hypotheses 57 children (9-13 years old) experienced 3 randomly presented heat levels (not painful, slightly painful, moderately painful) during 2 distraction conditions

involving different levels of cognitive load (a high load ‘working memory’ task and a low load ‘motor’ control task) in counter-balanced order. Children completed measures of dispositional mindfulness.

**Results:** As predicted, children’s pain intensity and pain unpleasantness ratings were lower in the high load condition compared to the low load condition. These differences were amplified in the moderately painful heat trials. In contrast to predictions, dispositional mindfulness did not significantly predict the effectiveness of distraction. Dispositional mindfulness was significantly related to measures of children’s attentional and emotional control abilities; however, a serial mediation model did not produce significant indirect or overall effects to suggest a strong influence of mindfulness on the effectiveness of distraction.

**Conclusions:** Results demonstrate that distraction that places high demand on executive resources is more effective for acute pain management for children. Further research is needed to explore cognitive and affective moderators of the effectiveness of distraction for children.

## Challenges and opportunities in translational pain research - An opinion paper of the working group on translational pain research of the European pain federation (EFIC)

Mouraux, A, Bannister, K, Becker, S, et al  
*Eur J Pain*. 2021; 25: 731– 756  
DOI: 10.1002/ejp.1730

**Abstract:** For decades, basic research on the underlying mechanisms of nociception has held promise to translate into efficacious treatments for patients with pain. Despite great improvement in the understanding of pain physiology and pathophysiology, translation to novel, effective treatments for acute and chronic pain has however been limited, and they remain an unmet medical need. In this opinion paper bringing together pain researchers from very different disciplines, the opportunities and challenges of translational pain research are discussed. The many factors that may prevent the successful translation of bench

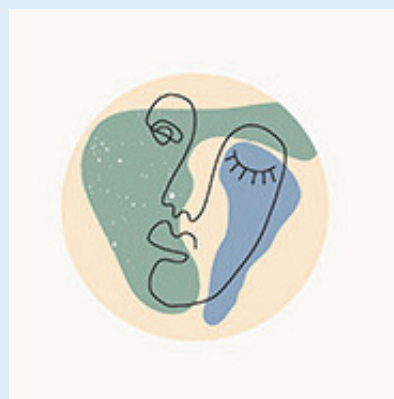
observations into useful and effective clinical applications are reviewed, including interspecies differences, limited validity of currently available preclinical disease models of pain, and limitations of currently used methods to assess nociception and pain in non-human and human models of pain. Many paths are explored to address these issues, including the backward translation of observations made in patients and human volunteers into new disease models that are more clinically relevant, improved generalization by taking into account age and sex differences, and the integration of psychobiology into translational pain research. Finally, it is argued that preclinical and clinical stages of developing new treatments for pain can be improved by better preclinical models of pathological pain conditions alongside revised methods to assess treatment-induced effects on nociception in human and non-human animals.

## Stratification of patients based on the Neuropathic Pain Symptom Inventory: development and validation of a new algorithm

*Bouhassira D., Branders S., Attal N., Fernandes A.M., Demolle D., Barbour J., Ciampi de Andrade D., Pereira A.*  
*PAIN: April 2021 - Volume 162 - Issue 4 - p 1038-1046*  
 doi: 10.1097/j.pain.0000000000002130

**Abstract:** The personalization of neuropathic pain treatment could be improved by identifying specific sensory phenotypes (ie, specific combinations of symptoms and signs) predictive of the response to different classes of drugs. A simple and reliable phenotyping method is required for such a strategy. We investigated the utility of an algorithm for stratifying patients into clusters corresponding to specific combinations of neuropathic symptoms assessed with the Neuropathic Pain Symptom Inventory (NPSI). Consistent with previous results, we first confirmed, in a cohort of 628 patients, the existence of a structure consisting of 3 clusters of patients characterized by higher NPSI scores for: pinpointed pain (cluster 1), evoked pain (cluster 2), or deep pain (cluster 3). From these analyses, we derived a specific algorithm for assigning each

patient to one of these 3 clusters. We then assessed the clinical relevance of this algorithm for predicting treatment response, through post hoc analyses of 2 previous controlled trials of the effects of subcutaneous injections of botulinum toxin A. Each of the 97 patients with neuropathic pain included in these studies was individually allocated to one cluster, by applying the algorithm to their baseline NPSI responses. We found significant effects of botulinum toxin A relative to placebo in clusters 2 and 3, but not in cluster 1, suggesting that this approach was, indeed, relevant. Finally, we developed and performed a preliminary validation of a web-based version of the NPSI and algorithm for the stratification of patients in both research and daily practice.

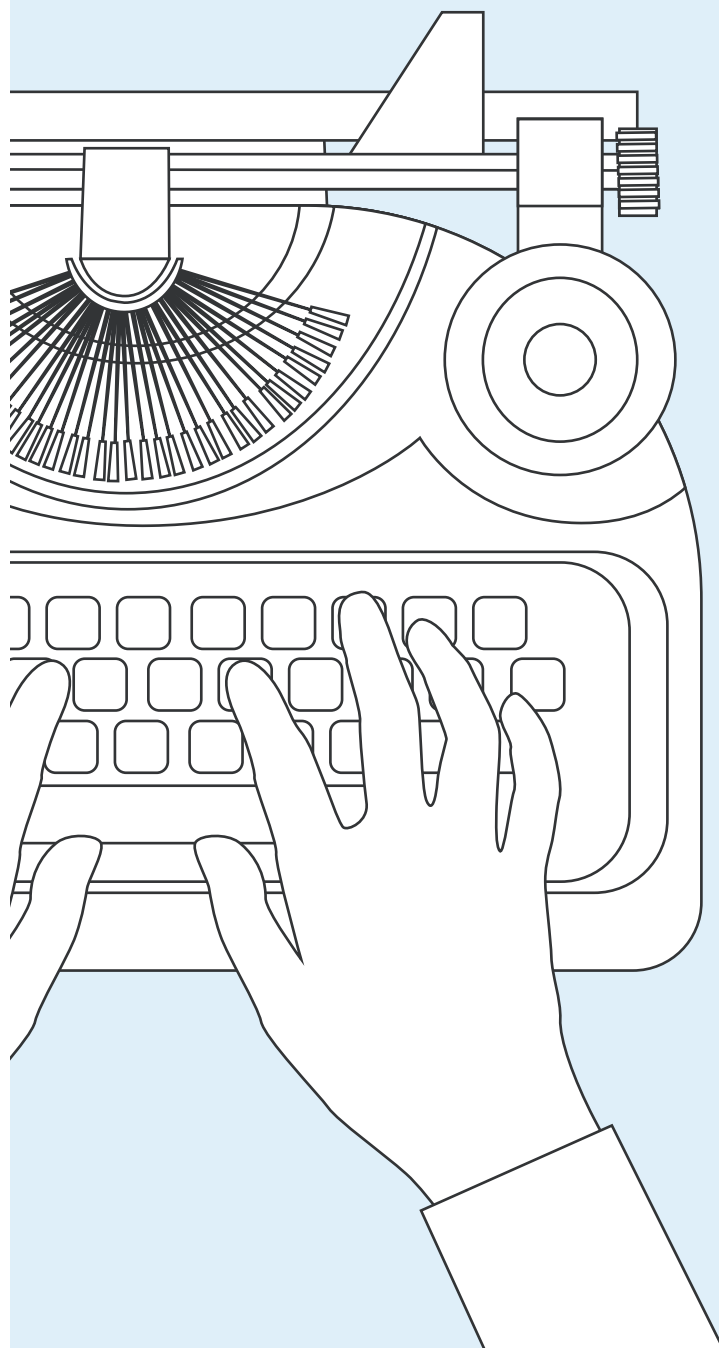


## Effectiveness of placebo interventions for patients with non-specific low back pain - A systematic review

*Wilhelmus Strijkers RH, Schreijenberg M, Gerger H, Koes BW, Chiarotto A.*  
*Pain. 2021 Mar 24. doi: 10.1097/j.pain.0000000000002272.*

**Abstract:** Little is known about the effectiveness of placebo interventions in patients with non-specific low back pain (LBP). This systematic review assessed the magnitude of the effects of placebo interventions as compared to no intervention in randomized controlled trials (RCTs) including patients with LBP. Embase, Medline (Ovid) and Cochrane CENTRAL databases were searched from inception to

December 5th, 2019. RCTs comparing placebo intervention versus no intervention in adult patients with non-specific LBP were included. Pain intensity, physical functioning and health-related quality of life (hrQoL) measured at short-, medium- and long-term follow-up were the outcomes of this review. Twenty-one RCTs were included; one concerning acute LBP and one sub-acute LBP, while 19 studies reported on chronic LBP. In chronic LBP, placebo interventions were more effective than no intervention at short-term for pain intensity [standardized mean difference (SMD) = -0.37, 95% CI = -0.55 to -0.18, moderate quality evidence], physical functioning (SMD -0.19, 95% CI = -0.39 to 0.01, moderate quality evidence), and physical quality of life (Mean Difference = -2.71, 95% CI = -4.71 to 0.71, high quality evidence), respectively. These effects were not significant at medium-term follow-up and no data was available at long-term follow-up. These results show placebo interventions are more effective than no intervention at short-term in patients with chronic LBP. However, the magnitude of the effects is probably not clinically relevant (approximately 8 points on a 0-100 pain scale). Future research should identify effect modifiers and causal mechanisms explaining the short-term effects of placebo interventions in patients with chronic LBP. (PROSPERO Registration number CRD42019127465).



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## Etiology, Diagnosis and Management of Radial Nerve Entrapment

Vij N., Kiernan H., Miller-Gutierrez S., Agusala V., Kaye A.D., Imani F., Zaman B., Varrassi G., Viswanath O., Urits I.  
*Anesth Pain Med. Online ahead of Print; In Press (In Press):e112823.*  
 DOI: 10.5812/aapm.112823

**Context:** The anatomy of the radial nerve is prone to entrapment, each with different symptomology. Compression of entrapment of the radial nerve can occur near the radiocapitellar joint, the spiral groove, the arcade of Frohse, the tendon of the extensor carpi radialis brevis (ECRB), and at the radial tunnel. Those who require repetitive motions are at increased risk of peripheral neuropathy syndromes, including repetitive pronation and supination, trauma, or systemic disease; however, the influence of all risk factors is not well understood.

Depending on the location of entrapment, radial nerve entrapment syndrome presents different symptoms. It may include both a motor component and a sensory component. The motor component includes a dropped arm, and the sensory

component can include pain and paresthesia in the distribution of the radial nerve that resolves with rest and exacerbates by repetitive pronation and supination.

**Evidence Acquisition:** Diagnostic evaluation for radial nerve entrapment, apart from clinical symptoms and physical exam, includes electromyography, nerve conduction studies, ultrasonography, and magnetic resonance imaging. Conservative management for radial nerve entrapment includes oral anti-inflammatory medications, activity modification, and splinting. Some recently performed studies mentioned promising minimally invasive techniques, including corticosteroid injections, peripheral nerve stimulation, and pulsed radiofrequency.

**Results:** When minimally invasive techniques fail, open or endoscopic surgery can be performed to release the nerve.

**Conclusions:** Endoscopic surgery has the benefit of decreasing incision size and reducing time to functional recovery.



## Surgical and Non-surgical Treatment Options for Piriformis Syndrome: A Literature Review

Vij N, Kiernan H, Bisht R, Singleton I, Cornett E M, Kaye A.D., Imani F., Varrassi G., Pournabari M., Viswanath O., Urits I.  
*Anesth Pain Med. Online ahead of Print ; 11(1):e112825*  
 DOI: 10.5812/aapm.112825

**Context:** Piriformis syndrome is a solely clinical diagnosis that often eludes the practitioner and goes underdiagnosed. PS is a pain syndrome and for those it affects, causes persistent pain and limits daily activity and work capacity. It is a form of deep gluteal syndrome that needs to



be considered on the differential of low back pain as it comprises between 0.3% - 6% of all low back pain cases and is frequently underdiagnosed.

Piriformis syndrome may be primary due anatomic anomalies or secondary, though the majority of cases are secondary to some insult. The objective of this manuscript is to provide a description of the epidemiology and presentation of piriformis as well as both non-operative and operative treatment options. We review all of the recent clinical evidence regarding the aforementioned therapies.

**Evidence Acquisition:** Literature searches were performed using the below MeSH Terms using Mendeley version 1.19.4. Search fields were varied until further searches revealed no new articles. All articles were screened by title and abstract. Decision was made to include an article based on its relevance and the list of final articles was approved three of the authors. This included reading the entirety of the article. Any question regarding the inclusion of an article was discussed by all authors until an agreement was reached.

**Results:** Medical management and physical therapy show some promise; however, when conservative treatment fails minimally invasive methods such as steroid injections, botulinum toxin injections, dry needling are all efficacious and there is substantial clinical evidence regarding these therapies. In those patients in which minimally invasive techniques do not result in an adequate relief of pain and return of function, endoscopic release can be considered. Endoscopic release is far superior to open release of the piriformis syndrome given the higher success and lower rate of complications.

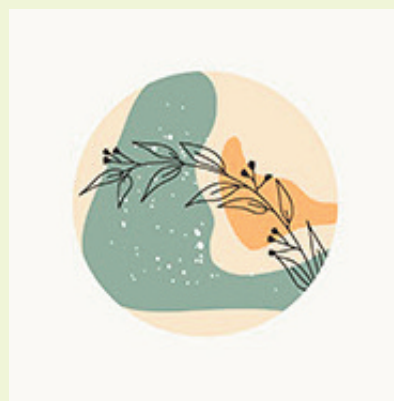
**Conclusions:** Piriformis syndrome is an important differential diagnosis in the work up of lower back pain and should not be ruled out with proper examination and testing. Clinicians should consider medical management and conservative management in the initial treatment plan for piriformis syndrome. There are many options within the conservative management and the literature shows much promise regarding these.

Physical therapy, steroid injections, botulinum toxin injections, and dry needling are all potentially effective therapies with few adverse effects.

Surgical options remain as gold standard, but only when conservative management has failed and the symptoms are significant to affect daily living

activities. Endoscopic decompression of the sciatic nerve with or without release of the piriformis muscle has a reported high likelihood of success and a low complication rate.

Current literature supports the preference of the endoscopic approach over the open approach due to improved outcomes and decreased complications. Further research is to well define the metrics for the diagnosis of piriformis syndrome and may include a need to develop diagnostic criteria.



## Utilization of Magnesium for the Treatment of Chronic Pain

*Urits I, Jung J W, Amgalan A, Fortier L, Anya A., Wesp B., V Orhurhu V., Cornett E.M., Kaye A.D., Imani F., Varrassi G., Liu H., Viswanath O.*

*Anesth Pain Med. Online ahead of Print ; In Press(In Press):e112348*

*DOI: 10.5812/aapm.112348*

**Context:** The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists or recurs for longer than 3 months. Chronic pain has a significant global disease burden with profound effects on health, quality of life, and socioeconomic costs.

**Evidence Acquisition:** Narrative review.

**Results:** There are several treatment options, including pharmacological therapy, physical rehabilitation, psychological therapies, and surgical interventions, for chronic pain management. Magnesium has been FDA-approved for several indications including hypomagnesemia, arrhythmia, prevention of seizures in eclampsia/preeclampsia, and constipation. Magnesium has been used for numerous off-label uses, notably for acute and chronic pain

management. The mechanism of magnesium in pain management is primarily through its action as a voltage-gated antagonist of NMDA receptors, which are involved in pain transduction.

**Conclusions:** This narrative review will focus on the current evidence and data surrounding the utilization of magnesium as a treatment option for chronic pain.



## A Comprehensive Review and Update of Post-surgical Cutaneous Nerve Entrapment

Charipova, K., Gress, K., Berger, A.A., Kassem H., Schwartz R., Herman J., Miriyala S., Paladini A., Varrassi G., Kaye A.D., Urts I.

*Curr Pain Headache Rep* 25, 11 (2021).

DOI: 10.1007/s11916-020-00924-1

**Purpose of Review:** This is a comprehensive review of the literature regarding post-surgical cutaneous nerve entrapment, epidemiology, pathophysiology, and clinical presentation.

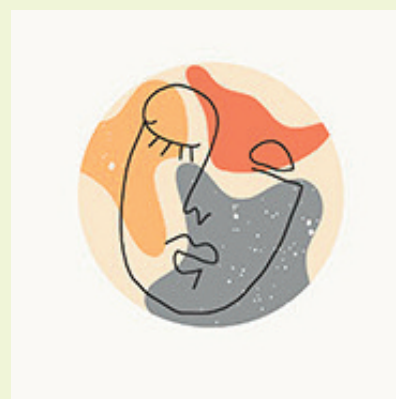
It focuses mainly on nerve entrapment leading to chronic pain and the available therapies.

**Recent Findings:** Cutaneous nerve entrapment is not an uncommon result (up to 30% of patients) of surgery and could lead to significant, difficult to treat chronic pain. Untreated, entrapment can lead to neuropathy and damage to enervated structures and musculature, and significant morbidity and financial loss. Nerve entrapment is defined as pressure neuropathy from chronic compression. It causes changes to all layers of the nerve tissue.

It is most significantly associated with hernia repair and other procedures employing a Pfannenstiel incision. The initial insult is usually incising of the nerve, followed by formation of a neuroma, incorporation of the nerve during closing, or

constriction from adhesions. The three most commonly involved nerves are the iliohypogastric, ilioinguinal, and genitofemoral nerves. Cutaneous abdominal nerve entrapment could occur during thoracoabdominal surgery. The presentation of nerve entrapment usually involved post-surgical pain in the territory innervated by the trapped nerve, possibly with radiation that tracks the nerve course. Once a suspected neuropathy is identified, it can be diagnosed with relief in pain after a nerve block has been instilled. Treatment is usually started with pharmaceutical solutions, topical first and oral if those fail. Most patients require escalation to a second line of treatment and see good result with injection therapy. Those that require further escalation can choose between ablation and surgical therapies.

**Summary:** Post-surgical nerve entrapment is not uncommon and causes serious morbidity and financial loss. It is underdiagnosed and thus undertreated. Preventing nerve entrapment is the best treatment; when it does occur, options include topical and oral analgesics, nerve blocks, ablation therapy, and repeat surgery.



## Role of Inhaled Methoxyflurane in the Management of Acute Trauma Pain

Fabbri A., Ruggiano G., Garcia Collado S., Ricard-Hibon A., Restelli U., Sbrana G., Marinangeli F., Farina A., Coffey F.

*J Pain Res.* 2020;13:1547-1555

DOI: 10.2147/JPR.S252222

**Abstract:** Adequate treatment of trauma pain is an integral part of the management of trauma patients, not just for ethical reasons but also because undertreated pain can lead to increased

morbidities and worse long-term outcomes. Trauma pain management presents challenges in the pre-hospital setting, particularly in adverse or hostile environments as well as in busy emergency departments (EDs). Inhaled methoxyflurane, administered at analgesic doses via a disposable inhaler, has recently become available in Europe for the emergency treatment of moderate to severe pain in conscious adult trauma patients. A growing body of evidence demonstrates that inhaled methoxyflurane is well tolerated and effective in providing a rapid onset of analgesia. In this paper, we discuss the rationale for methoxyflurane use in trauma pain management, data from clinical trials recently conducted in Europe, its efficacy and safety profile compared to current standard treatments, its place in therapy and organizational impact. We conclude that inhaled methoxyflurane represents an effective treatment option in the different settings where trauma patients require rapid and flexible pain resolution, with potential organizational advantages.



## Comparison between Acupuncture and Nutraceutical Treatment with Migratens® in Patients with Fibromyalgia Syndrome: A Prospective Randomized Clinical Trial

Schweiger V., Secchettin E., Castellani C., Martini A., Mazzocchi E., Picelli A., Polati E., Donadello K., Valenti M.T., Dalle Carbonare, L.

*Nutrients* 2020, 12, 821

DOI: 10.3390/nu12030821

**Objectives:** Fibromyalgia syndrome (FMS) is a chronic clinical condition characterized by pain,

fatigue, altered sleep, and cognitive disturbances. The purpose of this study was to compare two alternative treatments (nutraceutical and acupuncture) in FMS patients through a randomized clinical trial.

**Research Methods:** A total of 60 FMS female patients were randomized for treatment with a nutritional combination containing coenzyme Q10, vitamin D, alpha-lipoic acid, magnesium, and tryptophan (Migratens® Group) or acupuncture treatment (Acupuncture Group) performed according the principles of traditional Chinese medicine (TCM), both for 3 months. Changes in pain and in quality of life (QoL) measured with a Fibromyalgia Impact Questionnaire Score-Revised (FIQ-R) and the Fibromyalgia Severity Scale (FSS) were performed at 1, 3, and 6 months after the start of treatments.

**Results:** A total of 55 patient completed the study (21 in the Migratens® Group and 34 in the Acupuncture Group). Migratens® treatment shows a statistically significant reduction of pain 1 month after the start of therapy (T1,  $p = 0.025$ ), strengthened after 3 months with maintenance of treatment ( $p = 0.012$ ). The efficacy in reducing pain was apparent in the Acupuncture Group at all post-treatment determinations and at follow-up (T1 and T2  $p = <0.001$ ). Regarding QoL, improvement in FIQ-R and FSS values was revealed in both groups.

**Conclusion:** The nutraceutical approach with Migratens® seems to be an effective option to for patients with FMS. Our experience confirmed also the validity of acupuncture in these patients.

Considering the complexity of the management of FMS patients, our results suggest a cyclical and sequential, or even concurrent treatment with different approaches, to improve the efficacy and the compliance of patients to long-term treatment.

## Personalizing Cancer Pain Therapy: Insights from the Rational Use of Analgesics (RUA) Group

Varrassi G., Coluzzi, F., Guardamagna V.A., Puntillo F., Sotgiu G., Vellucci R., & Rational Use of Analgesics (RUA) Group

*Pain Ther* (2021)

DOI: /10.1007/s40122-021-00248-x

**Introduction:** A previous Delphi survey from the Rational Use of Analgesics (RUA) project involving Italian palliative care specialists revealed some discrepancies between current guidelines and clinical practice with a lack of consensus on items regarding the use of strong opioids in treating cancer pain. Those results represented the basis for a new Delphi study addressing a better approach to pain treatment in patients with cancer.

**Methods:** The study consisted of a two-round multidisciplinary Delphi study. Specialists rated their agreement with a set of 17 statements using a 5-point Likert scale (0=totally disagree and 4=totally agree). Consensus on a statement was achieved if the median consensus score (MCS) (expressed as value at which at least 50% of participants agreed) was at least 4 and the interquartile range (IQR) was 3-4.

**Results:** This survey included input from 186 palliative care specialists representing all Italian territory. Consensus was reached on seven statements. More than 70% of participants agreed with the use of low dose of strong opioids in moderate pain treatment and valued transdermal route as an effective option when the oral route is not available. There was strong consensus on the importance of knowing opioid pharmacokinetics for therapy personalization and on identifying immediate-release opioids as key for tailoring therapy to patients' needs. Limited agreement was reached on items regarding breakthrough pain and the management of opioid-induced bowel dysfunction.

**Conclusion:** These findings may assist clinicians in applying clinical evidence to routine care settings and call for a reappraisal of current pain treatment recommendations with the final aim of optimizing the clinical use of strong opioids in patients with cancer.

## Pathophysiology of musculoskeletal pain: a narrative review

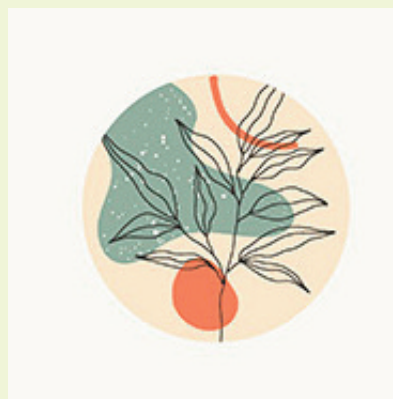
Puntillo F, Giglio M, Paladini A, et al.

*Therapeutic Advances in Musculoskeletal Disease*. January 2021

doi:10.1177/1759720X21995067

**Abstract:** Musculoskeletal pain (excluding bone cancer pain) affects more than 30% of the global population and imposes an enormous burden on patients, families, and caregivers related to functional limitation, emotional distress, effects on mood, loss of independence, and reduced quality of life.

The pathogenic mechanisms of musculoskeletal pain relate to the differential sensory innervation of bones, joints, and muscles as opposed to skin and involve a number of peripheral and central nervous system cells and mediators. The interplay of neurons and non-neural cells (e.g. glial, mesenchymal, and immune cells) amplifies and sensitizes pain signals in a manner that leads to cortical remodeling. Moreover, sex, age, mood, and social factors, together with beliefs, thoughts, and pain behaviors influence the way in which musculoskeletal pain manifests and is understood and assessed. The aim of this narrative review is to summarize the different pathogenic mechanisms underlying musculoskeletal pain and how these mechanisms interact to promote the transition from acute to chronic pain.



## Anesthetic Considerations for Cesarean Delivery After Uterine Transplant

Shehata I, Barsoumv S, Elhass A, Varrassi G., Paladini A., Myrcik D, Urits I., Kaye A.D., Viswanath O  
 March 16, 2021. *Cureus* 13(3): e13920  
 doi:10.7759/cureus.13920

**Abstract:** Infertility has many etiologies and can have devastating consequences for young couples attempting to bring children into the world.

Uterine factor for infertility is related to either uterine agenesis (Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome), unexpected hysterectomy, or presence of a nonfunctioning uterus. In this review, a patient with MRKH syndrome underwent donor uterus transplantation at the Cleveland Clinic, conceived, and delivered the first healthy baby in the United States and the second worldwide. Additionally, we review the pertinent literature on anesthesia problems.

Donor-related uterine transplant is a recent medical innovation requiring multidisciplinary expertise. In patients who deliver successfully, according to the current literature, the transplanted uterus can be used for one more pregnancy only if the mother so desires, otherwise cesarean hysterectomy (C-Hyst) should be performed. In the observed case, C-Hyst was performed because the patient developed placenta accreta and the couple desired no further pregnancy. In summary, with our limited data, careful management of these patients is required to ensure the best outcome for the mother and the newborn fetus.



## Improved Pain Control with Combination Spinal Cord Stimulator Therapy Utilizing Sub-perception and Traditional Paresthesia Based Waveforms: A Pilot Study

Berger A.A., Urits I., Hasoon J., Gill J, Aner M., Yazdi C.C., Viswanath O., Cornett E.M., Kaye A.D., Imani F., Imani F., Varrassi G., Simopoulos T.T.  
*Anesth Pain Med. Online ahead of Print ; 11(1):e113089*  
 doi: 10.5812/aapm.113089

**Background:** Chronic back and neck pain affects 20% of Americans. Spinal cord stimulation (SCS) is an effective therapy for otherwise refractory chronic pain. Traditional SCS relies on low-frequency stimulus in the 40 - 60 Hz range causing robust paresthesia in regions overlapping with painful dermatomes.

**Objective:** This study aims to determine the effect of superimposing sub-perception stimulation in patients who previously had good long-term relief with paresthesia.

**Methods:** This is a prospective observational trial examining patients who had previously been implanted with paresthesia based SCS for failed back surgery syndrome (FBSS) or complex regional pain syndrome (CRPS). These patients presented for implantable pulse generator (IPG) replacement based on battery depletion with an IPG capable of combined sub-perception and paresthesia based SCS therapy. Patients were assessed immediately following the exchange and four weeks later using a telephone survey.

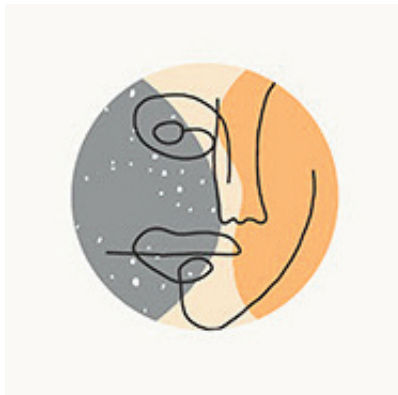
Their pain was assessed on each follow up using a Numerical Rating scale (NRS); the primary outcome was the change in NRS after four weeks from the exchange day. Secondary outcomes included paresthesia changes, which included the subjective quality of sensation generated, the overall subjective coverage of the painful region, subjective variation of coverage with positional changes, and global perception of the percentage improvement in pain.

**Results:** Based on our clinic registry, 30 patients were eligible for IPG exchange, 16 were consented for follow up and underwent an exchange, and 15 were available for follow up four weeks following. The average NRS decreased from 7.47 with traditional SCS to 4.5 with

combination therapy. 80% of patients reported an improvement in the quality of paresthesia over traditional SCS therapy, and in most patients, this translated to significantly improved pain control.

**Conclusions:** Our findings suggest improved pain relief in patients who had previously had good results with paresthesia based therapy and subsequently underwent IPG exchange to a device capable of delivering combined sub-perception stimulation. The mechanism of action is unclear though there may be an additive and/or synergistic effect of the two waveforms delivered.

Larger studies with long-term follow-up are needed to elucidate the durability of pain relief and the precise mechanism by which combined sub-perception and paresthesia based SCS may improve overall patient outcomes.



## Neuromodulation for Pain Management in the Inpatient Setting: A Narrative Review

Abd-Elseyed A., Tang T., Karri J., Hughes M., Urits I, Gupta M., Pasqualucci A., Myrcik D., Varrassi G., Viswanath O.

March 15, 2021

Cureus 13(3): e13892

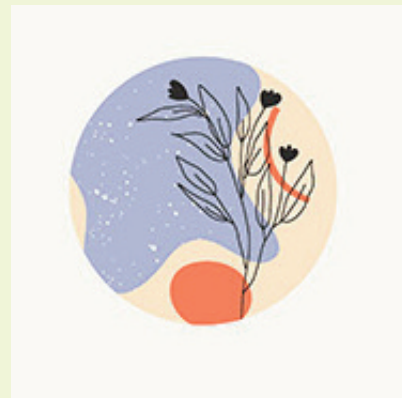
doi:10.7759/cureus.13892

**Abstract:** Pain is highly prevalent and pharmacological therapy is not always efficacious. There are a few pathophysiological reasons to believe that neuromodulation would increase the rate of success of pain management.

This review article is focused on that aspect, discussing non-invasive or minimally invasive neuromodulation techniques in both the inpatient

and outpatient setting.

This article provides an in-depth discussion of the multiple neuromodulation techniques available over time to be suitable and effective when used as analgesic therapies for chronic pain. We reviewed the literature and discussed all available neuromodulation options that were tested in the inpatient and outpatient setting. Neuromodulation plays a very important role in treating chronic pain in both inpatient and outpatient setting.



## Dealing With COVID-19 Patients: A Moderated Mediation Model of Exposure to Patients' Death and Mental Health of Italian Health Care Workers

Portoghese I, Galletta M, Meloni F, Piras I, Finco G, D'Aloja E, Campagna M.

Frontiers in Psychology 2021: 12: Article 622415

DOI=10.3389/fpsyg.2021.622415

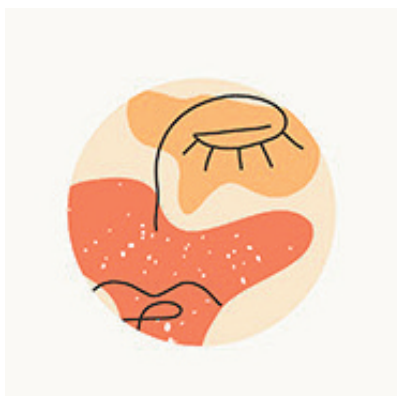
**Introduction:** The COVID-19 pandemic is asking health care workers (HCWs) to meet extraordinary challenges. In turn, HCWs were experiencing tremendous psycho-social crisis as they have had to deal with unexpected emotional requirements (ERs) arising from caring for suffering and dying patients on a daily basis. In that context, recent studies have highlighted how HCWs working during the COVID-19 outbreak manifested extreme emotional and behavioral reactions that may have impacted their mental health, increasing the risk for developing post-traumatic stress symptoms.

**Purpose:** The aim of the study was to investigate

post-traumatic stress symptoms, such as intrusion symptoms, as a potential mediator of the link between ERs and crying at work, and whether rumination moderates the relationship between ERs and intrusion-based PTS symptoms among HCWs who have had to deal with patients dying from COVID-19.

**Methods:** An online cross-sectional study design was performed. A total of 543 Italian HCWs (physicians and nurses) participated in the study. Participation was voluntary and anonymous. We used the SPSS version of bootstrap-based PROCESS macro for testing the moderated mediation model. Results: ERs had an indirect effect on crying at work through the mediating role of intrusion symptoms. Results from the moderated mediation model showed that rumination moderated the indirect effect of ERs on crying at work via intrusion symptoms, and this effect was significant only for high rumination. Furthermore, when we tested for an alternative model where rumination moderates the direct effect of ERs on crying at work, this moderation was not significant.

**Conclusions:** As the second wave of the COVID-19 pandemic is ongoing, there is an urgent need for decision-makers to rapidly implement interventions aimed at offering timely psychological support to HCWs, especially in those contexts where the risk of emotional labor associated to patients dying from COVID-19 is higher.



## Deciphering the state of immune silence in fatal COVID-19 patients

Bost, P., De Sanctis, F., Canè, S., Ugel S., Donadello K., Castellucci M., Eyal D., Fiore A., Anselmi C., Barouni R.M., Trovato R., Caligola S., Lamolinara A., Iezzi M., Facciotti F., Mazzariol A., Gibellini D., De Nardo P., Tacconelli E., Gottin L., Polati E., Schwikowski B., Amit I., Bronte V. Viswanath O. *Nature Commun* 12, 1428 (2021). DOI: 10.1038/s41467-021-21702-6

**Abstract:** Since the beginning of the SARS-CoV-2 pandemic, COVID-19 appeared as a unique disease with unconventional tissue and systemic immune features. Here we show a COVID-19 immune signature associated with severity by integrating single-cell RNA-seq analysis from blood samples and broncho-alveolar lavage fluids with clinical, immunological and functional ex vivo data. This signature is characterized by lung accumulation of naïve lymphoid cells associated with a systemic expansion and activation of myeloid cells. Myeloid-driven immune suppression is a hallmark of COVID-19 evolution, highlighting arginase-1 expression with immune regulatory features of monocytes. Monocyte-dependent and neutrophil-dependent immune suppression loss is associated with fatal clinical outcome in severe patients. Additionally, our analysis shows a lung CXCR6+ effector memory T cell subset is associated with better prognosis in patients with severe COVID-19. In summary, COVID-19-induced myeloid dysregulation and lymphoid impairment establish a condition of 'immune silence' in patients with critical COVID-19.

## The efficacy of balneotherapy, mud therapy and spa therapy in patients with osteoarthritis: an overview of reviews

D'Angelo, D., Coclite, D., Napoletano, A., Fauci A.J., Latina R., Gianola S., Castellini G., Salomone K., Gambalunga F., Sperati F., L Iacorossi L., Iannone P.

*Int J Biometeorol* (2021)

doi.org/10.1007/s00484-021-02102-3

**Abstract:** Osteoarthritis is a degenerative disease considered a leading cause of functional disability. Its treatment is based on a combination of pharmacological and non-pharmacological interventions, but the role of these latter is still debated. This overview of systematic reviews aimed at evaluating the short-term efficacy of different thermal modalities in patients with osteoarthritis. We searched PubMed, Scopus, CINHAL, Web of Science, ProQuest and the Cochrane Database of Systematic Reviews from inception until October 2020, with no language restrictions. We selected the following outcomes a priori: pain, stiffness and quality of life. Seventeen systematic reviews containing 27 unique relevant studies were included. The quality of the reviews ranged from low to critically low. Substantial variations in terms of interventions studied, comparison groups, population, outcomes and follow-up between the included SRs were found. From a re-analysis of primary data, emerged that balneotherapy was effective in reducing pain and improving stiffness and quality of life, mud therapy significantly reduced pain and stiffness, and spa therapy showed pain relief.

However, the evidence supporting the efficacy of different thermal modalities could be seriously flawed due to methodological quality and sample size, to the presence of important treatment variations, and to the high level of heterogeneity and the absence of a double-blind design. There is some encouraging evidence that deserves clinicians' consideration, suggesting that thermal modalities are effective on a short-term basis for treating patients with AO.



## Assessment of Pain and Associated Comorbidities: A Survey of Real Life Experiences Among Nurses in Italy

Angeletti C., Angeletti P.M., Paesani M., Guetti C., Gyra A., Perseo G., Ciccozzi A., Marinangeli F., Altobelli E.

*J Pain Res.* 2021;14:107-115

DOI: 10.2147/JPR.S245792

**Purpose:** Pain is a symptom that should be evaluated along with its comorbidities in order to plan an effective holistic treatment strategy involving specific pharmacological interventions, side effect management, psychological support, control of therapeutic effects over time, and dialogue with the patient and their relatives. In this holistic process of caring for patients with pain, nurses play a central role as they deal with suffering patients directly and continuously. The purpose of this study was to evaluate the types of pain identified by nurses in their daily clinical practice and the associated comorbidities (anamnestic history taking) by geographical region and to evaluate the pharmacological strategies used.

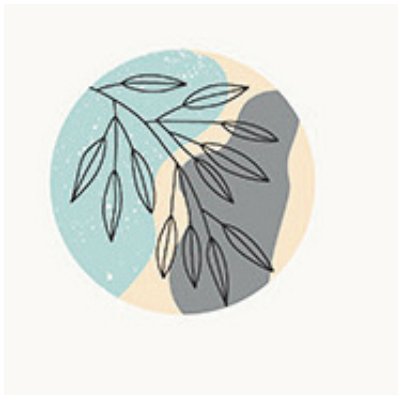
**Methods:** A cross-sectional survey was performed among 696 registered nurses in Italy. Data were collected using an online questionnaire.

**Results:** There was a significant difference between geographical regions in terms of reports of acute and chronic pain: acute pain was more frequently reported in the South (63.5%), while chronic pain was more frequent in the Central region (32.3%;  $p=0.0008$ ). Additionally, chronic oncological pain was more frequent in the



Northeast (29.6%), while chronic non-oncological pain was more frequently reported in the Central region (33.9%;  $p=0.0001$ ). The underlying pain disorders reported were also different between geographical regions; rheumatic pain (21.8%) and neurological pain (18.6%) were more frequent in the Central region, while musculoskeletal pain was significantly more frequent in the South (43.4%;  $p=0.004$ ). Anxiety, sleep disorders and somatization were found in acute pain (60.82%, 43.56% and 53.12%), while depression and mood disorders were more frequently detected in chronic pain condition ( $p < 0.001$ ).

**Conclusions:** Our study showed differences among Italian regions in pain assessment. Specific education on pain management nursing is essential for nurses. Promotion of optimal nursing care for people affected by pain is the main focus of pain management nursing. Nowadays, nurses should focus on personalized complex care and research in order to improve the patient's quality of life.





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Grazie a un accordo tra l'Associazione Italiana Studio Dolore e l'editore della rivista Signa Vitae, Journal of Anaesthesia, Intensive Care, Emergency and Pain Medicine, i soci AISD potranno pubblicare usufruendo di uno sconto del 20% sui costi di pubblicazione.

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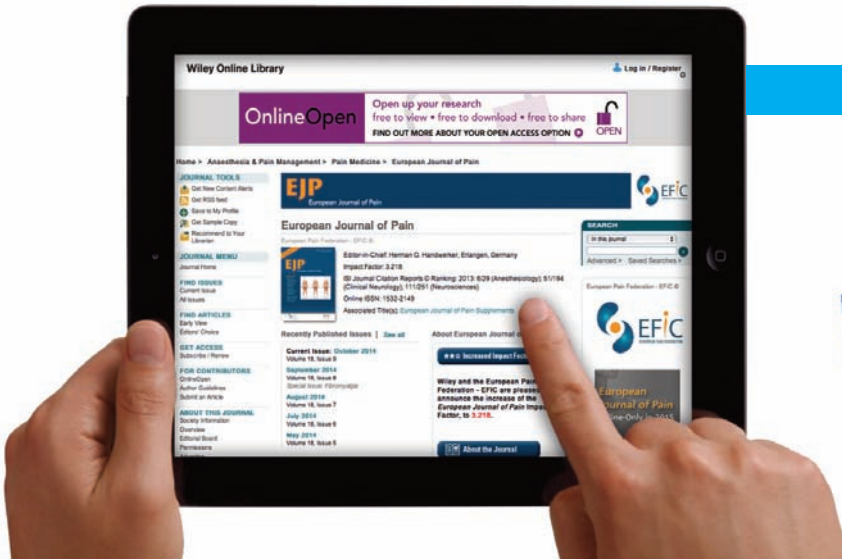
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